CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761040Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

BLA#: 761040 Supplement Number: NA NDA Supplement Type (e.g. SE5): _

Division Name:DHP PDUFA Goal Date: 8/20/17 Stamp Date: 12/20/17

Proprietary Name: Besponsa

Established/Generic Name: Inotuzumab Ozogamicin

Dosage Form: Lyophilized (b) (4) powder

Applicant/Sponsor: Wyeth Pharmaceuticals,a subsidiary of Pfizer Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) None
(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: Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

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 failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

Not feasible:

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

* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

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

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

Δ Formulation failed:

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

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the 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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

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

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

* Other Reason: _____

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

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

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

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

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

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

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

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

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

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

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

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

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

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

requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

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

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

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

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

If there are additional indications, please 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 failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

☐ Justification attached.

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

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

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

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

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

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

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

* Other Reason: _____

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

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

(Revised: 6/2008)

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

/s/

RACHEL S MCMULLEN
08/11/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 761040	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Besponsa Established/Proper Name: inotuzumab ozogamicin Dosage Form: Lyophilized (b) (4) powder		Applicant: Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc. Agent for Applicant (if applicable): Alison Russell
RPM: Rachel McMullen		Division: Division of Hematology Products (DHP)

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☒ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action **August 20, 2017** • User Fee Goal Date is **August 20, 2017**	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

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

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Announcement for distribution to ASCO members
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval: August 17, 2017
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Conditionally Acceptable letters: July 31, 2017; May 17, 2016 DMEPA Reviews: July 28, 2017; May 16, 2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ PLR format review: March 10, 2017 DMEPA: ☒ June13, 2017; May 8, 2017 DMPP/PLT (DRISK): ☒ None OPDP: ☒ May 30, 2017 SEALD: ☒ None CSS: ☒ None Product Quality: August 8, 2017 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	August 7, 2017 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☐ Completed (Do not include)

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

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC NA If PeRC review not necessary, explain: Orphan designation on March 25, 2013	Pediatric Page: August 11, 2017
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Breakthrough Therapy Granted letter: October 15, 2015 (IND 065658)
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	October 8, 2015
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	August 11, 2017 (3) August 10, 2017 August 7, 2017 (2) August 3, 2017 August 2, 2017 July 27, 2017 July 24, 2017 (2) July 21, 2017 (2) July 18, 2017 July 12, 2017 July 6, 2017 June 26, 2017 June 19, 2017 June 16, 2017 June 12, 2017 June 6, 2017 (2) June 2, 2017 June 1, 2017 May 17, 2017 May 11, 2017 May 9, 2017 May 3, 2017 April 28, 2017 April 19, 2017 March 28, 2017(2) March 14, 2017 March 7, 2017 March 3, 2017 March 2, 2017 (3)

	March 1, 2017 (2) February 27, 2017 February 16, 2017 February 6, 2017 January 31, 2017 (2) January 30, 2017 January 24, 2017 January 9, 2017 January 3, 2017 September 22, 2016 August 5, 2016 July 27, 2016 July 5, 2016 June 16, 2016 May 13, 2016 (2) May 10, 2016 (2) May 5, 2016 April 25, 2016 April 18, 2016 April 6, 2016 March 18, 2016
❖ 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)	MPC communication to Division indicating concurrence with the Applicant's BTDR and indicating that an MPC discussion is not needed. Email dated October 7, 2017 Teleconferences: August 9, 2017; May 26, 2016; May 11, 2016
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	November 10, 2014
• EOP2 meeting *(indicate date of mtg)*	October 20, 2014
• Mid-cycle Communication *(indicate date of mtg)*	April 5, 2017
• Late-cycle Meeting *(indicate date of mtg)*	June 23, 2017
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	CMC Meeting: May 3, 2017 CMC specific EOP2 meeting: May 30, 2007

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	Page 235 of multidisciplinary review dated August 17, 2017
Division Director Summary Review *(indicate date for each review)*	Page 234 of multidisciplinary review dated August 17, 2017
Cross-Discipline Team Leader Review *(indicate date for each review)*	Page 18-23 of multidisciplinary review dated August 17, 2017
PMR/PMC Development Templates *(indicate total number)*	1 PMR template 1 PMC template
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	Section 7 of multidisciplinary review dated August 17, 2017
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Pages 199-201 of the multidisciplinary review dated August 17, 2017
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	CDRH Reviews: August 14, 2017; June 6, 2017
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	Evaluation of need for a REMS (DRISK review): May 19, 2017
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Letters: June 20, 2017 (2) Clinical Inspections Summary: May 26, 2017

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

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	
Clinical Microbiology Review(s) *(indicate date for each review)*	
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review Co-signed multidisciplinary review dated August 17, 2017
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Section 7 of multidisciplinary review dated August 17, 2017
Statistical Review(s) *(indicate date for each review)*	Section 7 of multidisciplinary review dated August 17, 2017
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review Co-signed multidisciplinary review dated August 17, 2017
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Section 6 of multidisciplinary review dated August 17, 2017
Clinical Pharmacology review(s) *(indicate date for each review)*	Section 6 of multidisciplinary review dated August 17, 2017 QT Study Review: May 5, 2017
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review Co-signed multidisciplinary review dated August 17, 2017
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review Section 5 of multidisciplinary review dated August 17, 2017
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Section 5 of multidisciplinary review dated August 17, 2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	CMC Executive Summary: July 3, 2017 Integrated Quality Assessment: July 3, 2017 OBP Review: June 28, 2017 Facilities Assessment: June 12, 2017 DMA Review: May 26, 2017 Quality Assessment-DS: May 19, 17 Product Quality- Micro: March 21, 2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Page 6 of OBP review dated June 28, 2017
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

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

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

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/s/

RACHEL S MCMULLEN
08/21/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix _ FDA Response
Date:	Friday, August 11, 2017 11:10:58 AM
Attachments:	image016.png image017.png image018.png image002.png
Importance:	High

Good morning Alison,

With reference to your query regarding the nonproprietary name suffix, the team has provided the following response:

FDA response:

(b) (4) Should your 351(a) BLA be approved during this review cycle, Inotuzumab ozogamicin will be the proper name designated in the license and this proper name should be reflected in your proposed labels and labeling accordingly. (b) (4), please be advised that FDA has noted in the Nonproprietary Naming Guidance that we are continuing to consider the process for implementation of this naming convention for previously licensed biological products.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]

Sent: Tuesday, August 01, 2017 2:19 PM
To: McMullen, Rachel
Subject: RE: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Rachel

As mentioned below, in order to avoid delaying the approval of the application and in the interest of public health, FDA agreed to approve the proper name (BESPONSA) as designated without a suffix.

(b) (4)

Can you let me know if FDA consider this timeframe to be acceptable?

Alison

Alison Russell, PhD
Inotuzumab ozogamicin (BESPONSA) Global Regulatory Lead
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: Russell, Alison
Sent: Tuesday, March 28, 2017 11:44 AM
To: 'McMullen, Rachel'
Subject: RE: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Rachel – I confirm receipt
Txs, Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Tuesday, March 28, 2017 10:54 AM
To: Russell, Alison
Subject: RE: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Good afternoon Alison,

With reference to your email and query, please note the following response from the team:

Your 351(a) BLA is within the scope of our recently issued guidance for industry, Nonproprietary Naming of Biological Products. However, FDA issued the final guidance at a point in our review of your application that does not allow sufficient time for FDA to designate a proper name that includes a suffix as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your 351(a) BLA be approved during this review cycle.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Wednesday, March 22, 2017 2:46 PM
To: McMullen, Rachel
Subject: RE: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Rachel

By way of follow-up to your telephone call on 17 March 2017, I have become aware of feedback received today from FDA project manager Kris Kolibab to another Pfizer team (Mylotarg)

"Your 351(a) BLA is within the scope of our recently issued guidance for industry, Nonproprietary Naming of Biological Products. However, FDA issued the final guidance at a point in our review of your application that does not allow sufficient time for FDA to designate a proper name that includes a suffix as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your 351(a) BLA be approved during this review cycle."

For planning purposes, can I assume that the same guidance may be applied to inotuzumab

ozogamicin?

Sorry to bother you again so soon, but the Pfizer team will need some guidance on this matter very soon.

Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: Russell, Alison
Sent: Wednesday, March 15, 2017 9:02 AM
To: 'McMullen, Rachel'
Subject: RE: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Rachel – Txs; I confirm receipt and the team will proceed accordingly.
Alison

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Wednesday, March 15, 2017 8:33 AM
To: Russell, Alison
Cc: McMullen, Rachel
Subject: RE: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Hi Alison,

With reference to your query below, (b) (4) .

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Tuesday, March 14, 2017 7:49 PM
To: McMullen, Rachel
Subject: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Rachel

With reference to the attached FDA labeling guidance document "Nonproprietary Naming of Biological Products" issued in January 2017 (see excerpt below), I am interested to know if inotuzumab ozogamicin will be required to have a suffix (4 lowercase letters) included in the proper name designated by FDA at the time of licensure.

I look forward to hearing from you in this regard.

Alison

A. Prospective Naming of Biological Products Submitted Under Section 351(a) of the PHS Act

An applicant should propose a suffix composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at the time of licensure (see section VI of this guidance). Such submissions can be made during the investigational new drug application (IND) phase16 or at the time of BLA submission. An applicant should submit up to 10 proposed suffixes, as described in this section, in the order of the applicant's preference. We recommend including any supporting analyses of the proposed suffixes for FDA's consideration based on the factors described in this guidance.

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

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/s/

RACHEL S MCMULLEN
08/14/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040/Inotuzumab _ Final FDA Proposed Labeling: USPI _Please Respond by Monday, August 14th
Date:	Friday, August 11, 2017 3:09:33 PM
Attachments:	BLA 761040_USPI_BESPONSA_inotuzumab ozogamicin_Pfizer_FINAL Proposed USPI_8-11-17.docx image008.png
Importance:	High

Good afternoon Alison,

With reference to BLA 761040/inotuzumab ozogamicin, we are in agreement with Pfizer's proposed labeling. Please review and provide your concurrence to the attached FDA proposed labeling for the **USPI.**

Please update the revision date and provide Pfizer's confirmation regarding final FDA proposed labeling via email by **COB on Monday, August 14, 2017.** Following that, please submit the information formally to your BLA file.

Please ***confirm*** receipt of this email.

Thank you,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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

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/s/

RACHEL S MCMULLEN
08/11/2017

From: McMullen, Rachel
To: Russell, Alison
Cc: McMullen, Rachel
Subject: BLA 761040/Inotuzumab _ Agreed Upon PMR/PMC (Submit by August 15, 2017)
Date: Friday, August 11, 2017 2:58:05 PM
Attachments: image002.png
Importance: High

Good afternoon Alison,

With reference to BLA 761040 for Besponsa, please see below for the agreed upon PMRS and PMCS along with the timelines for study start dates and submission of protocols, etc. As long as this information is correct, please provide Pfizer's commitment by official submission to the BLA **no later than noon (ET) on Tuesday, August 15th.**

PMR #1:

BLA #	761040
Product Name:	Inotuzumab Ozogamicin
PMR Description:	Characterize toxicity after hematopoietic stem cell transplantation (HSCT) in adult and pediatric patients who receive inotuzumab ozogamicin. Include hepatic veno-occlusive disease, transplant related mortality (non-relapse mortality), and non-transplant related mortality. Conduct an analysis of registry data (for example the Center for International Blood and Marrow Transplantation Research registry) to evaluate safety at least through day 180 after transplantation. The number of available patients in the database will determine the sample size. Include details of all prior therapies. The minimum duration of the study is to be no less than five years.

PMR Schedule Milestones:	Draft Protocol Submission:	11/2017
	Final Protocol Submission:	02/2018
	Interim Report Submission:	02/2019
	Interim Report Submission:	02/2020
	Interim Report Submission:	02/2021
	Interim Report Submission:	02/2022
	Final Report Submission:	02/2023

PMR #2:

BLA #	761040
Product Name:	Inotuzumab Ozogamicin
PMR Description:	Conduct a randomized trial of at least 2 dose levels of inotuzumab ozogamicin in patients with relapsed or refractory acute lymphoblastic leukemia who are potential candidates for HSCT and at high risk for

	developing veno-occlusive disease (VOD). High risk is defined as patients with prior hematopoietic stem cell transplantation (HSCT), ongoing or prior liver disease, older patients (b) (4) 55 years), or later salvage line (Salvage (b) (4) 2). Safety parameters will include hepatic VOD, transplant related mortality (non-relapse mortality), and non-transplant related mortality. Descriptive analyses of safety and efficacy (including achievement of minimal residual disease [MRD]-negativity) will be conducted for the intent-to-treat population and the per-protocol population that excludes patients who do not proceed to HSCT. The study will include sufficient clinical pharmacokinetic sampling to analyze the exposure-response relationship for efficacy and safety. Submit complete clinical study report and datasets.	
PMR Schedule Milestones:	Draft Protocol Submission:	02/2018
	Final Protocol Submission:	05/2018
	Trial Completion:	04/2023
	Final Report Submission:	11/2023

Justification for timelines

- The proposed study is designed to determine the risk of VOD in patients who are potential candidates for HSCT (b) (4) (b) (4)
- (b) (4)
- Based on the above, the following timeline is assumed:
  - May 2018:
    - Final (FDA-agreed) protocol
  - September 2018:
    - First subject first visit (FSFV) (i.e., 4 months after final protocol)
  - January 2022:
    - Last subject first visit (LSFV); assumes enrollment rate of 2.5 patients /month [100 patients in 40 months])
  - April 2023:
    - Last subject last visit (LSLV [trial completion]); assumes 3 months of treatment (3

cycles) + 12 months follow-up after last dose

- November 2023:
  - Final report submission (i.e., 7 months after LSLV)

-
-

PMC: Product Quality (CMC)

BLA #	761040
Product Name:	Inotuzumab ozogamicin (Besponsa®)
PMC #1 Description:	Conduct the bioburden and endotoxin test method qualification of inotuzumab ozogamicin drug substance using two additional batches.

PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	11/30/2017

PMC #2 Description:	Conduct the sterility and endotoxin test method qualification of inotuzumab ozogamicin drug product using two additional batches.

PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	11/30/2017

PMC #3 Description:	Implement bioburden and endotoxin monitoring of the (b) (4) used to manufacture inotuzumab ozogamicin drug product.

PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	N/A
	Other: Implementation	11/30/2017

Please *confirm* receipt.

Kind regards,

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
08/11/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	Inotuzumab Ozogamicin/BLA 761040_ Information Request (Response DUE: ASAP or COB today)
Date:	Thursday, August 10, 2017 9:52:19 AM
Attachments:	image001.png
Importance:	High

Good morning Alison,

In follow up to yesterday's teleconference to discuss MRD for BLA 761040, please note the following information request from the FDA review team:

Information Request:

Response DUE: ASAP or by COB today, Thursday, August 9th

It is our understanding that there is no minimum requirement for total number of viable cells or number of leukemic cells for an MRD-positive or MRD-negative result. A requirement for 0.01% positive cells is required for MRD-positivity. However, the hematopathologist determines the final result and only requires 0.01% for a MRD-positive result, even if the total number of events collected is 100k or less.

Please use data only from the post-treatment samples.
Each data point included in the bars should represent one patient post-treatment sample. If multiple patient samples were tested from the same timepoint, please only include one.
The y-axis should be labeled and represent % post-treatment samples "MRD-positive".
The x-axis should have five groups of two bars (one bar should represent the treatment arm and one bar should represent the placebo arm). Each bar should indicate how many patient samples (n) are represented in the bar.

1st group: % samples MRD-positive from samples with =10K viable cells

2nd group: % samples MRD-positive from samples with >10K AND =100K viable cells

3rd group: % samples MRD-positive from >100K AND = 250K viable cells

4th group: % samples MRD-positive from >250K viable cells AND = 1000K viable cells

5th group: % samples MRD-positive from >1000K viable cells

Please provide a response to me at your earliest conveniece and no later than COB today, Thursday, August 9th, followed by an official submission to your BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products

Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
08/10/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: August 9, 2017

Application Number: BLA 761040
Product Name: Inotuzumab Ozogamicin
Sponsor/Applicant Name: Wyeth Pharmaceuticals, a subsidiary of Pfizer Inc.

Subject: Discuss MRD Analysis

FDA Participants
Division of Hematology Products (DHP)
Ann Farrell, MD; Director
Angelo de Claro, MD ; Clinical Team Lead
Tanya Wroblewski, MD ; Clinical Reviewer
Rachel McMullen, MPH, MHA ; Senior Regulatory Project Manager

Division of Biometrics:
Thomas Gwise, PhD ; Deputy Director
Qing Xu, PhD ; Statistics Reviewer

CDRH/OIR/DIHD :
Doug Jeffery, PhD ; Acting Branch Chief
Kelly Oliner, PhD ; Deputy Director
Lea Carrington, MS, MBA, MT(ASCP); Division Director
Cortez McBerry, PhD ; Scientific Reviewer

Sponsor/Applicant Participants
Pfizer Inc.
Amber Donahue, PhD, Biomarker Assay Specialist, Oncology Clinical Assay Group
Iman Jilani, PhD, Oncology Clinical Assay Group Lead
Philip Johnson; BS, MBA, Asset Team Lead
Caroline Henesey; PhD, Hematology Global Regulatory Portfolio Lead
Steffan Ho, PhD, Translational Oncology
Douglas Laird; PhD, Translational Oncology Lead
Alison Russell, PhD, Regulatory Lead
Erik Vandendries; MD, PhD, Clinical Lead

(b) (4)

1.0 BACKGROUND:

On August 9, 2017, the Agency had a teleconference with Wyeth/Pfizer to discuss and clarify the MRD analysis for BLA 761040.

2.0 DISCUSSION:

The discussion was focused on Pfizer's responses to four comments that CDRH provided regarding the MRD assay that was employed during the clinical trial.

1. Discussion of CDRH Comment 1:

   CDRH comment: Please provide the sample acceptance criteria, i.e., that each sample must have one million events collected, and the positive result criteria, i.e., that MRD is defined as >100 events clustered in the expected manner

   Sponsor Response: the goal was to collect at least one million events (live WBCs) with MRD being defined as 100 blasts for a sensitivity of 10^{-4}. Samples were accepted with as few as 250,000 events but were flagged as questionable in the report. There is no lower limit for either minimum number of total events or blasts and some samples were accepted with as few as 100,000 events and some less than 100,000 events. Samples were only considered positive if $\geq 0.01\%$ blasts were present. For some post-treatment BM samples it was difficult to obtain one million live WBCs. All results were reviewed and approved by a hematopathologist. Most of the study was reviewed by one hematopathologist, however approximately three were involved over the course of the study.

   CDER follow-up question: Were the hematopathologists blinded to the patient data?

   Sponsor Response: Yes, we believe so

   CDER Comment: Please provide in writing that the hematopathologists were blinded to the patient data.

   CDRH post-meeting comment: even if the hematopathologist was blinded to the patient data, the lack of CD22+ cells in the treated population could potentially "unblind" the hematopathologist to the patient status.

2. Discussion of CDRH Comment 2 (note this is comment A for question 3 in the document "CDRH.Additional.Comments..2017.08.08.doc"):

   CDRH Comment: Please clarify what the acceptance criteria were for the time allowed between collection and testing of bone marrow samples.

   Sponsor Response: The Sponsor acknowledged that the NY State Department of Health recommendation is to test bone marrow samples within 48 hours of collection. Due to the number of sites and geographical location, not all samples could be collected, shipped, and tested within 48 hours. Sample stability was tested at days 1, 3, 5, and 7. Acceptance criteria for sample stability were that the loss of normal B cells from the patient samples must be <30% compared to Day 1. Data demonstrated that samples were

stable up to five days post-collection. 65% of bone marrow samples were tested within 48 hours, 35% were tested within 2–5 days, and two samples were tested after five days. The results from the samples that were tested after more than five days did not affect any of the outcome data.

3. Discussion of CDRH Comment 3 (note this is comment B for question 3 in the document "CDRH.Additional.Comments..2017.08.08.doc")

   CDRH Comment: Please explain your rationale for comparing the accuracy of the MRD assay used in the clinical trial (the (b) (4) assay) to the "CLIA lab" assay. Please also explain why you think a < ±30% difference between the two assays is acceptable.

   Sponsor Response: The CLIA lab assay was all that was available to compare to the trial assay ((b) (4) assay). The markers in the CLIA lab assay are not identical to the trial assay, but the markers are appropriate to detect MRD in B-ALL samples. The CLIA lab assay was not designed to collect enough events to detect MRD at 10^{-4} so the results of the comparison between the two assays do not meet acceptance criteria in samples with low levels of blasts. The Sponsor cited a 2011 scientific paper for justification of acceptance criteria < ±30% between the two assays.

4. Discussion of CDRH Comment 4 (note this is comment C for question 3 in the document "CDRH.Additional.Comments..2017.08.08.doc"):

   CDRH Comment: Please clarify the gating strategy that you employed when comparing baseline and post-treatment samples, if the sample types were different or no MRD results existed at baseline.

   Sponsor Response: The gating strategy for peripheral blood and bone marrow samples is identical for the detection of B-ALL, so there is no concern about using the gating strategy for a baseline peripheral blood sample to assess MRD status of a post-treatment bone marrow sample. For post-treatment samples that did not have a baseline MRD result, a "historical normal" sample was used to determine the gating strategy. The same "historical normal" sample was used for all samples that did not have a baseline MRD result.

3.0 ACTION ITEMS:

Pfizer agreed to provide the following items requested by the Agency:

- Written statement regarding the blinding of the hematopathologist
- CDRH asked the Sponsor to provide written summary comments from the teleconference
- CDRH Comment to CDER: Although false positive and false negative results are possible with these sample acceptance criteria we are mostly concerned about false

negative results, i.e., samples that are called MRD negative with <100k-250k events collected but that are actually MRD positive.

- CDRH Request for Sponsor:

  It is our understanding that there is no minimum requirement for total number of viable cells or number of leukemic cells for an MRD-positive or MRD-negative result. A requirement for 0.01% positive cells is required for MRD-positivity. However, the hematopathologist determines the final result and only requires 0.01% for a MRD-positive result, even if the total number of events collected is 100k or less.

  Please use data only from the post-treatment samples.

  Each data point included in the bars should represent one patient post-treatment sample. If multiple patient samples were tested from the same timepoint, please only include one. The y-axis should be labeled and represent % post-treatment samples "MRD-positive". The x-axis should have five groups of two bars (one bar should represent the treatment arm and one bar should represent the placebo arm). Each bar should indicate how many patient samples (n) are represented in the bar.

  1st group: % samples MRD-positive from samples with ≤10K viable cells
  2nd group: % samples MRD-positive from samples with >10K AND ≤100K viable cells
  3rd group: % samples MRD-positive from >100K AND ≤ 250K viable cells
  4th group: % samples MRD-positive from >250K viable cells AND ≤ 1000K viable cells
  5th group: % samples MRD-positive from >1000K viable cells

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

/s/

RACHEL S MCMULLEN
08/10/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	Inotuzumab Ozogamicin/BLA 761040_ FDA Proposed Labeling (Response DUE: August 8, 2017)
Date:	Monday, August 07, 2017 1:38:55 PM
Attachments:	image001.png BLA 761040_USPI_BESPONSA_inotuzumab ozogamicin_FDA Proposed Edits_8-7-17.docx
Importance:	High

Good afternoon Alison,

In follow up to our conversation today, the FDA team has provided an additional edit/comment on the labeling (USPI) for **BLA 761040 (inotuzumab).** Since the proposed edit is minor, the team is requesting a revised labeling response by COB tomorrow.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your labels and submit your revised labeling response to me via email by **COB tomorrow, Tuesday, August 8, 2017 or earlier if possible,** followed by an official submission of the label to the BLA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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

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/s/

RACHEL S MCMULLEN
08/07/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040/Inotuzumab Ozogamicin_Draft PMR2 (Response DUE: August 9, 2017)
Date:	Monday, August 07, 2017 1:46:42 PM
Attachments:	image013.png image014.png image020.png image021.png BLA 761040_PMR2 Draft_8-7-17_ FDA Proposed Edits.docx image002.png
Importance:	High

Good afternoon Alison,

With reference to BLA 761040, please refer to the attached document for the Agency's comment/revision regarding PMR #2 for inotuzumab.

Please submit all PMRs, along with their milestones to the BLA.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Friday, August 04, 2017 3:02 PM
To: McMullen, Rachel
Subject: RE: BLA 761040/Inotuzumab Ozogamicin _Draft PMR2 _Response DUE: COB, Friday, August 4th

Rachel

Per FDA's request below, please find attached:

- Revised PMR #2 with Pfizer's proposed revisions .

I plan to follow-up with submission of this document officially to BLA 761040.

Txs, Alison

Alison Russell, PhD
Inotuzumab ozogamicin (BESPONSA) Global Regulatory Lead
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: Russell, Alison
Sent: Thursday, August 3, 2017 3:26 PM
To: 'McMullen, Rachel'
Subject: RE: BLA 761040/Inotuzumab Ozogamicin _Draft PMR2 _Response DUE: COB, Friday, August 4th

Rachel

I plan to discuss with the Pfizer team tomorrow and hope to send you a response via email then. This would followed by an official notification to BLA 761040.

Can you let me know if that is considered acceptable?

Alison

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Thursday, August 3, 2017 3:10 PM
To: Russell, Alison
Cc: McMullen, Rachel
Subject: [EXTERNAL] BLA 761040/Inotuzumab Ozogamicin _Draft PMR2 _Response DUE: COB, Friday, August 4th
Importance: High

Good evening Alison,

Thank you for your response. Please find below the Agency's revision to the PMR #2 description.

PMR #2:

Conduct a randomized trial of at least 2 dose levels of inotuzumab ozogamicin in patients with relapsed or refractory acute lymphoblastic leukemia at high risk for developing veno-occlussive disease (VOD). High risk is defined as patients with prior hematopoietic stem cell transplantation (HSCT), ongoing or prior liver disease, older patients [redacted (b) (4)], later salvage line [redacted (b) (4)] [redacted (b) (4)] Safety parameters will include hepatic VOD, transplant related mortality (non-relapse mortality), and non-transplant related mortality. Descriptive analyses of safety and efficacy (including achievement of minimal residual disease[MRD]-negativity) will be conducted for the intent-to-treat population and the per-protocol population that excludes patients who do not proceed to HSCT [redacted (b) (4)] The study will include sufficient clinical pharmacokinetic sampling to analyze the exposure-response relationship for efficacy and safety. Submit the complete clinical study report and datasets.

Please submit all PMRs, along with their milestones to the BLA.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Thursday, July 27, 2017 10:14 AM
To: McMullen, Rachel
Subject: RE: BLA 761040/Inotuzumab Ozogamicin _Draft PMRs & PMCs _Response DUE: COB, Thursday, July 27, 2017

Rachel

Please find the following documents attached for FDA's consideration:

- PMR #1
- PMR #2
- PMC (accepted all FDA's revisions - some minor formatting changes)

I will follow-up with an official submission to BLA 761040.

Txs, Alison

Alison Russell, PhD
Inotuzumab ozogamicin (BESPONSA) Global Regulatory Lead
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: Russell, Alison
Sent: Monday, July 24, 2017 2:56 PM
To: Erik.Vandendries@pfizer.com; Khosravan, Reza; Parivar, Kourosh; Johnson, Philip; Henesey, Caroline; Mayer, Stephen; Subashi, Ann K; Dimitrov, Svetoslav; Ataher, Quazi
Subject: FW: BLA 761040/Inotuzumab Ozogamicin _Draft PMRs & PMCs _Response DUE: COB, Thursday, July 27, 2017

For URGENT discussion tomorrow

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Monday, July 24, 2017 2:38 PM
To: Russell, Alison
Cc: McMullen, Rachel
Subject: [EXTERNAL] BLA 761040/Inotuzumab Ozogamicin _Draft PMRs & PMCs _Response DUE: COB, Thursday, July 27, 2017
Importance: High

Good evening Alison,

Please refer to BLA 761040 for inotuzumab ozogamicin, received December 20, 2016, which provides for the proposed indication " treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)."

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies 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 requirements (PMRs) and post-marketing commitments (PMCs), based on the data available to date. 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. We are available to discuss by teleconference if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that

has already received full concurrence by FDA.

A copy of the draft PMR and PMC documents is attached. Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation number will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMRs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. 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. 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.

b. It is critical that you advise, prominently, both with the email and 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.

Please provide a response to me via email by COB on Thursday, July 27th or earlier if possible. Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

Inotuzumab ozogamicin (Besponsa)
Postmarketing requirement (PMR) # 2

PMR #2

BLA #	761040
Product Name:	Inotuzumab Ozogamicin
PMR Description:	Conduct a randomized trial of at least 2 dose levels of inotuzumab ozogamicin in patients with relapsed or refractory acute lymphoblastic leukemia who are potential candidates for HSCT and at high risk for developing veno-occlusive disease (VOD). High risk is defined as patients with prior hematopoietic stem cell transplantation (HSCT), ongoing or prior liver disease, older patients (≥ 55 years), or later salvage line (Salvage ≥ 2). Safety parameters will include hepatic VOD, transplant related mortality (non-relapse mortality), and non-transplant related mortality. Descriptive analyses of safety and efficacy (including achievement of minimal residual disease [MRD]-negativity) will be conducted for the intent-to-treat population and the per-protocol population that excludes patients who do not proceed to HSCT. The study will include sufficient clinical pharmacokinetic sampling to analyze the exposure-response relationship for efficacy and safety. Submit complete clinical study report and datasets.

PMR Schedule Milestones:	Draft Protocol Submission:	02/2018
	Final Protocol Submission:	06/2018
	Trial Completion:	06/2024
	Final Report Submission:	01/2025

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Comment [A1]: To Applicant (Aug 7): Provide justification for the proposed timeline. Include sample size considerations in your justification.

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Deleted: 2

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/s/

RACHEL S MCMULLEN
08/07/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040/Inotuzumab Ozogamicin _Draft PMR2 _Response DUE: COB, Friday, August 4th
Date:	Thursday, August 03, 2017 6:10:29 PM
Attachments:	image020.png image021.png image001.png
Importance:	High

Good evening Alison,

Thank you for your response. Please find below the Agency's revision to the PMR #2 description.

PMR #2:

Conduct a randomized trial of at least 2 dose levels of inotuzumab ozogamicin in patients with relapsed or refractory acute lymphoblastic leukemia at high risk for developing veno-occlussive disease (VOD). High risk is defined as patients with prior hematopoietic stem cell transplantation (HSCT), ongoing or prior liver disease, older patients (b) (4) later salvage line (b) (4) (b) (4). Safety parameters will include hepatic VOD, transplant related mortality (non-relapse mortality), and non-transplant related mortality. Descriptive analyses of safety and efficacy (including achievement of minimal residual disease[MRD]-negativity) will be conducted for the intent-to-treat population and the per-protocol population that excludes patients who do not proceed to HSCT (b) (4). The study will include sufficient clinical pharmacokinetic sampling to analyze the exposure-response relationship for efficacy and safety. Submit the complete clinical study report and datasets.

Please submit all PMRs, along with their milestones to the BLA.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Thursday, July 27, 2017 10:14 AM
To: McMullen, Rachel
Subject: RE: BLA 761040/Inotuzumab Ozogamicin _Draft PMRs & PMCs _Response DUE: COB, Thursday, July 27, 2017

Rachel

Please find the following documents attached for FDA's consideration:

- PMR #1
- PMR #2
- PMC (accepted all FDA's revisions - some minor formatting changes)

I will follow-up with an official submission to BLA 761040.

Txs, Alison

Alison Russell, PhD
Inotuzumab ozogamicin (BESPONSA) Global Regulatory Lead
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: Russell, Alison
Sent: Monday, July 24, 2017 2:56 PM
To: Erik.Vandendries@pfizer.com; Khosravan, Reza; Parivar, Kourosh; Johnson, Philip; Henesey, Caroline; Mayer, Stephen; Subashi, Ann K; Dimitrov, Svetoslav; Ataher, Quazi
Subject: FW: BLA 761040/Inotuzumab Ozogamicin _Draft PMRs & PMCs _Response DUE: COB, Thursday, July 27, 2017

For URGENT discussion tomorrow

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Monday, July 24, 2017 2:38 PM
To: Russell, Alison
Cc: McMullen, Rachel
Subject: [EXTERNAL] BLA 761040/Inotuzumab Ozogamicin _Draft PMRs & PMCs _Response DUE: COB, Thursday, July 27, 2017
Importance: High

Good evening Alison,

Please refer to BLA 761040 for inotuzumab ozogamicin, received December 20, 2016, which provides for the proposed indication " treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)."

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies 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 requirements (PMRs) and post-marketing commitments (PMCs), based on the data available to date. 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. We are available to discuss by teleconference if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

A copy of the draft PMR and PMC documents is attached. Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation number will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMRs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. 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. 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.

b. It is critical that you advise, prominently, both with the email and 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.

Please provide a response to me via email by COB on Thursday, July 27th or earlier if possible. Please

confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
08/03/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	Inotuzumab Ozogamicin/BLA 761040 _ FDA Proposed Labeling (Response DUE: August 4, 2017)
Date:	Wednesday, August 02, 2017 3:09:50 PM
Attachments:	BLA 761040_USPI_BESPONSA_inotuzumab ozogamicin_FDA Proposed Edits_8-2-17.docx image001.png
Importance:	High

Good afternoon Alison,

In follow up to our conversation today, the FDA team has provided some current edits/comments on the labeling (USPI) for **BLA 761040 (inotuzumab).**

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your labels and submit your revised labeling response to me via email no later than **1pm ET on Friday, August 4, 2017 or earlier if possible,** followed by an official submission of the label to the BLA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
08/02/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

ATTENTION: Alison Russell
Director, Worldwide Safety and Regulatory

Dear Ms. Russell:

Please refer to your Biologics License Application (BLA) dated and received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for Inotuzumab Ozogamicin, 0.9 mg/vial.

We also refer to your correspondence, dated and received June 22, 2017, requesting review of your proposed proprietary name, Besponsa.

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

If any of the proposed product characteristics as stated in your June 22, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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 Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Rachel McMullen, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4574.

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/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
07/31/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	Inotuzumab Ozogamicin/BLA 761040 _ FDA Proposed Labeling (Response DUE: July 28, 2017)
Date:	Thursday, July 27, 2017 2:47:33 PM
Attachments:	USPI_BESPONSA_inotuzumab ozogamicin_FDA Proposed Edits_7-27-17.docx image002.png
Importance:	High

Good afternoon Alison,

With reference to **BLA 761040** for **Inotuzumab**, FDA's current edits/comments on the labeling (**USPI)** are attached. Since the proposed change is minor, we request a response by noon tomorrow, Friday, July 28th.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your label and submit your revised USPI to me via email by **noon tomorrow, Friday, July 28, 2017,** followed by an official submission of the label to the BLA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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

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/s/

RACHEL S MCMULLEN
07/28/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040/Inotuzumab Ozogamicin _Draft PMRs & PMCs _Response DUE: COB, Thursday, July 27, 2017
Date:	Monday, July 24, 2017 5:37:49 PM
Attachments:	image001.png BLA 761040_PMR1_Revised_7-24-17.docx BLA 761040_PMR2 Draft_7-24-17.docx Supporting Document_PMR 2.doc BLA 761040_Post marketing Commitments_CMC.docx
Importance:	High

Good evening Alison,

Please refer to BLA 761040 for inotuzumab ozogamicin, received December 20, 2016, which provides for the proposed indication " treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)."

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies 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 requirements (PMRs) and post-marketing commitments (PMCs), based on the data available to date. 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. We are available to discuss by teleconference if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

A copy of the draft PMR and PMC documents is attached. Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation number will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMRs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. 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. 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.

b. It is critical that you advise, prominently, both with the email and 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.

Please provide a response to me via email by COB on Thursday, July 27th or earlier if possible. Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

PMR #1

BLA #	761040
Product Name:	Inotuzumab Ozogamicin

PMR Description: Characterize toxicity after hematopoietic stem cell transplantation (HSCT) in adult and pediatric patients who receive inotuzumab ozogamicin. Include hepatic veno-occlusive disease, transplant related mortality, and non-transplant related mortality. Conduct an analysis of registry data (for example the Center for International Blood and Marrow Transplantation Research registry) to evaluate safety at least through day 180 after transplantation. The number of available patients in the database will determine the sample size. Include details of all prior therapies. The minimum duration of the study is to be no less than five years.

PMR Schedule Milestones:		
	Draft Protocol Submission:	11/2017
	Final Protocol Submission:	02/2018
	Interim Report Submission:	02/2019
	Interim Report Submission:	02/2020
	Interim Report Submission:	02/2021
	Interim Report Submission:	02/2022
	Final Report Submission:	02/2023

PMR #2

BLA #	761040
Product Name:	Inotuzumab Ozogamicin
PMR Description:	Conduct a randomized, (b) (4) trial (b) (4) of inotuzumab ozogamicin (b) (4) Include hepatic veno-occlusive disease, transplant related mortality, and non-transplant related mortality. (b) (4) Include sufficient clinical pharmacokinetic sampling to (b) (4) analyze the exposure- (b) (4) relationship. Submit complete clinical study report and datasets.

PMR Schedule Milestones:	Draft Protocol Submission:	MM/YYYY
	Final Protocol Submission:	MM/YYYY
	Trial Completion:	MM/YYYY
	Final Report Submission	MM/YYYY

Supporting Document for PMR 2

FDA Assessment of Sponsor Response to FDA Proposal for Dose Optimization Study (Received from Sponsor on June 27, 2017)

The FDA acknowledges the updated exposure-response (ER) analysis to support the selected inotuzumab ozogamicin dose of 1.8 mg/m^2. However, the rates of VOD and non-relapse mortality are high at the selected dose. (b) (4) . Data obtained at the lower doses were not sufficient to rule out the possibility that a lower dose may provide a better balance of safety and efficacy.

Your ER analysis for CR/CRi is primarily based on data derived from a single dose level (B1931022), which may not be sufficient to characterize the true ER relationship. Ideally, multiple dose levels can help establish a true ER relationship. Additionally, the concentration of calicheamicin, which may be correlated with the occurrence of VOD, was not included in the exposure-response analysis.

In addition to conducting ER analyses with variable concentrations under a single dose, your calculation of the Clinical Utility Index (CUI) is based on the most responsive population of patients (CD22+ > 90%), which maximizes the value of CUI. Your CUI analysis does not consider non-relapse mortality, which is likely due to drug induced toxicity.

The analysis based on average dose per cycle assumes that dose is the only factor affecting response, with no consideration for other patient factors. Furthermore, the analysis could be biased. Responders are more likely to receive only one or two cycles of treatment compared to non-responders, who are more likely to receive more treatment cycles and are subject to dose reductions and dose delays resulting in lower average dose per cycle.

Although your analysis of safety did not identify a correlation between average dose per cycle and VOD, prior experience with the similar drug, Mylotarg, demonstrated that the pivotal trial did not reflect the high rate of VOD observed in the post-marketing phase. In addition, the body of data available for Mylotarg indicates that dose reduction from 9 mg/m^2 to ≤ 6 mg/m^2 substantially reduces the incidence of VOD.

To address these concerns, we recommend PMR 2.

Post marketing Commitment (PMC): Product Quality (CMC)

BLA # 761040
Product Name: Inotuzumab ozogamicin (Besponsa®)

PMC #1 Description: Conduct the bioburden and endotoxin test method qualification of inotuzumab ozogamicin drug substance using two additional batches.

PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	11/30/2017

PMC #2 Description: Conduct the sterility and endotoxin test method qualification of inotuzumab ozogamicin drug product using two additional batches.

PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	11/30/2017

PMC #3 Description: Implement bioburden and endotoxin monitoring of the (b) (4) used to manufacture inotuzumab ozogamicin drug product.

PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	N/A
	Other: Implementation	11/30/2017

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/s/

RACHEL S MCMULLEN
07/24/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	Inotuzumab Ozogamicin/BLA 761040 _ FDA Proposed Labeling (Response DUE: July 26, 2017)
Date:	Monday, July 24, 2017 6:14:44 PM
Attachments:	USPI - BESPONSA- inotuzumab ozogamicin_FDA Proposed Edits_7-24-17.docx BLA 761040 Container Carton Comments July 21, 2017.docx image001.png
Importance:	High

Good evening Alison,

With reference to **BLA 761040** for **Inotuzumab**, FDA's current edits/comments on the labeling (**USPI and Carton Container labels**) are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your labels and submit your revised labeling response to me via email no later than **3pm ET on Wednesday, July 26, 2017,** followed by an official submission of the label to the BLA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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

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/s/

RACHEL S MCMULLEN
07/24/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040 _ Clinical Information Request (Response DUE: July 25, 2017)
Date:	Friday, July 21, 2017 1:48:19 PM
Attachments:	image001.png
Importance:	High

Good afternoon Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following information request from the review team.

Clinical Information Request:

Submit a dataset(1 patient per row) that includes the ITT population(N=326) for Study B1931022. Include the following information in the dataset:

- USUBJID
- Treatment arm
- Flag for ITT 218
- Complete Response(CR)- yes or no
- Complete remission with partial hematological recovery(CRh)- yes or no
- Complete remission with incomplete count recovery(CRi)- yes or no
- MRD positivity- yes or no
- Specify the assessor(EAC or Investigator)

CRh is defined as ANC> 500/microliter and platelet count > 50,000/microliter with <5% blasts in bone marrow
CRi defined as ANC < 1000/microliter and Platelet count < 100/microliter and blasts < 5% blasts in bone marrow

Please submit a response to me promptly via email by **3pm ET on Tuesday July 25, 2017** followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
07/21/2017

Vora, Neil

From: Russell, Alison <Alison.Russell@pfizer.com>
Sent: Friday, July 21, 2017 12:00 PM
To: Vora, Neil
Cc: McMullen, Rachel
Subject: RE: BLA 761040/Proprietary Name review

Neil – I confirm receipt.
Thanks for your timely response.
Alison

From: Vora, Neil [mailto:Neil.Vora@fda.hhs.gov]
Sent: Friday, July 21, 2017 8:58 AM
To: Russell, Alison
Cc: McMullen, Rachel
Subject: [EXTERNAL] RE: BLA 761040/Proprietary Name review

Hi Alison,

The Proprietary Name goal date is 9/20/17. We understand that this Proprietary Name goal date may be past the application goal date however, we will try to provide a response prior to the application goal date.

Thanks,
Neil

Neil Vora, PharmD, MBA, PMP
Safety Regulatory Project Manager (SRPM)

Center for Drug Evaluation and Research (CDER)
Office of Surveillance and Epidemiology (OSE)
U.S. Food and Drug Administration
Tel: 240-402-4845
Neil.Vora@fda.hhs.gov

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Thursday, July 20, 2017 5:59 PM
To: Vora, Neil
Cc: McMullen, Rachel
Subject: BLA 761040/Proprietary Name review

Neil

With reference to the letter dated 06 July 2017 (received via mail today), I noted the following “The user feel goal date will be September 20, 2017.” According to the filing communication letter received from FDA on 02 March 2017, the current user date is 20 August 2017.

Can I ask if this is an error or has the user fee date actually changed to September 20, 2017 due to the ongoing Proprietary Name review?

Alison

Alison Russell, PhD
Inotuzumab ozogamicin (BESPONSA) Global Regulatory Lead
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

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/s/

NEIL VORA
07/21/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040/Inotuzumab Ozogamicin _Draft PMR#1 _Response DUE: July 25, 2017
Date:	Tuesday, July 18, 2017 1:42:46 PM
Attachments:	image002.png
Importance:	High

Good afternoon Alison,

Please refer to BLA 761040 for inotuzumab ozogamicin, received December 20, 2016, which provides for the proposed indication " treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)."

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trial is necessary as a post-marketing requirement (PMR), based on the data available to date. 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. We are available to discuss by teleconference if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation number will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMRs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. 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. 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.

b. It is critical that you advise, prominently, both with the email and 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.

PMR #1

BLA #	761040
Product Name:	Inotuzumab Ozogamicin
PMR Description:	Characterize toxicity after hematopoietic stem cell transplantation (HSCT) in adult and pediatric patients who receive inotuzumab ozogamicin. Include hepatic veno-occlusive disease, transplant related mortality, and non-transplant related mortality. Conduct an analysis of registry data (for example the Center for International Blood and Marrow Transplantation Research registry) to evaluate safety at least through day 180. The number of available patients in the database will determine the sample size. Include details of all prior therapies. The minimum duration of the study is to be no less than five years.

PMR Schedule Milestones:	Draft Protocol Submission:	MM/YYYY
	Final Protocol Submission:	MM/YYYY
	Interim Report (annually):	MM/YYYY
	Final Report Submission	

MM/YYYY

Provide the protocol for FDA review and concurrence before initiating the trial. Thank you and please do not hesitate to contact us if you have any questions.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
07/18/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	Inotuzumab Ozogamicin/BLA 761040 _ FDA Proposed Labeling (Response DUE: July 17, 2017)
Date:	Wednesday, July 12, 2017 1:02:33 PM
Attachments:	BLA 761040__inotuzumab ozogamicin_USPI_7-17-17.docx BLA 761040 Container Carton Comments_7-12-17.docx image019.png image002.png
Importance:	High

Good afternoon Alison,

With reference to **BLA 761040** for **Inotuzumab**, the FDA team has reviewed Pfizer's labeling response and has provided additional edits/comments on the labeling (**USPI and Carton Container labels**).

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

Please update your labels and submit your revised labeling response via email by **5pm ET on Monday, July 17th** followed by an official submission of the label to the BLA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: McMullen, Rachel
Sent: Thursday, June 01, 2017 2:19 PM
To: Russell, Alison
Cc: McMullen, Rachel
Subject: Inotuzumab Ozogamicin/BLA 761040 _ FDA Proposed Labeling (Response DUE: June 14, 2017)
Importance: High

Good afternoon Alison,

With reference to **BLA 761040** for **Inotuzumab**, FDA's current edits/comments on the labeling (**USPI and Carton Container labels**) are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your labels and submit your revised labeling response to me via email by **1pm ET on Wednesday, June 14, 2017,** followed by an official submission of the label to the BLA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
07/12/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

PROPRIETARY NAME ACKNOWLEDGEMENT

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

ATTENTION: Alison Russell
Director, Worldwide Safety and Regulatory

Dear Ms. Russell:

Please refer to your Biologics License Application (BLA) dated and received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for Inotuzumab Ozogamicin (b)(4) mg/vial.

We acknowledge receipt of your correspondence, dated and received June 22, 2017, requesting a review of your proposed proprietary name, Besponsa.

The user fee goal date will be September 20, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Rachel McMullen, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Neil Vora, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

NEIL VORA
07/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB: June 28, 2017.

Please provide the manufacturers of components of the container closure system of (b) (4) the inotuzumab ozogamicin Drug Substance and Drug Product. Provide references to all relevant Drug Master Files.

If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber -S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=0014262141
Date: 2017.06.26 11:33:54 -04'00'

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

Vora, Neil

From: Russell, Alison <Alison.Russell@pfizer.com>
Sent: Tuesday, June 20, 2017 9:12 AM
To: Vora, Neil
Subject: RE: Proprietary Name, BLA 761040

Follow Up Flag: Follow up
Flag Status: Flagged

Hi Neil – Thanks for your reply. We plan to submit the document week.
Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: Vora, Neil [mailto:Neil.Vora@fda.hhs.gov]
Sent: Tuesday, June 20, 2017 6:06 AM
To: Russell, Alison
Subject: Re: Proprietary Name, BLA 761040

Hi Alison,

This will be a standard 90 day PNR review cycle, however, we understand Pfizer expects application approval this August and will aim to meet that goal date.

Please try and submit ASAP due to the upcoming OND PDUFA date.

Thanks so much,

Neil

From: Russell, Alison
Sent: Monday, June 19, 2017 6:54 PM
To: Vora, Neil
Subject: RE: Proprietary Name, BLA 761040

Hi Neil

Thanks for the clarification; very helpful. We plan to submit this document to BLA 761040 in the next few days. Is it possible for you to estimate the expected review time after you receive it?

Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: Vora, Neil [mailto:Neil.Vora@fda.hhs.gov]
Sent: Monday, June 19, 2017 3:52 PM
To: Russell, Alison
Subject: RE: Proprietary Name, BLA 761040

Hi Alison,

We request you to resubmit the proprietary name request submission for the proposed name, Besponsa, BLA 761040 based on the revised BLA amendment (revised USPI, Carton, and Container labels) submitted to FDA on May 26, 2017. Per the Proprietary Name Request Conditionally Acceptable Letter "If any of the proposed product characteristics as stated in your March 30, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review."

Thanks so much,
Neil

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Monday, June 19, 2017 3:00 PM
To: Vora, Neil
Subject: RE: Proprietary Name, BLA 761040

Neil

Sorry, just to clarify my question, is your request for me to update the proprietary name submission for the proposed name, Besponsa, based on the revised version of the labeling submitted to FDA (BLA 761040) on 25 June?

Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: Russell, Alison
Sent: Monday, June 19, 2017 10:02 AM
To: 'Vora, Neil'

Cc: Quinlan, Michael C.
Subject: RE: Proprietary Name, BLA 761040

Neil

Thanks for your message.

Can you please elaborate on what you are referring to by this part?

- What has changed regarding the product characteristics?
- Are you expecting a resubmission of the document previously submitted to BLA 761040 Module 1 Section 1.2?

Alison

From: Vora, Neil [mailto:Neil.Vora@fda.hhs.gov]
Sent: Monday, June 19, 2017 9:37 AM
To: Russell, Alison
Subject: Proprietary Name, BLA 761040
Importance: High

Hi good afternoon Alison,

Reference is made to the March 30, 2016 proprietary name submission for the proposed name, Besponsa. Given that the product characteristics for BLA 761040 Besponsa have changed, we are kindly requesting Pfizer to submit a proprietary name request because of the change. If you have any questions, please do not hesitate to reach out.

Kind regards,
Neil

Neil Vora, PharmD, MBA, PMP
Safety Regulatory Project Manager (SRPM)

Center for Drug Evaluation and Research (CDER)
Office of Surveillance and Epidemiology (OSE)
U.S. Food and Drug Administration
Tel: 240-402-4845
Neil.Vora@fda.hhs.gov

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/s/

NEIL VORA
06/20/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	RE: Inotuzumab Ozogamicin/BLA 761040 _Clarification re: Information Request
Date:	Monday, June 12, 2017 3:08:48 PM
Attachments:	image020.png image021.png image007.png
Importance:	High

Good afternoon Alison,

With reference to the email below, please note the following clarification provided by the FDA review team:

CLARIFICATION: All the responses that contain page numbers are from the Study B1931022 original clinical study report (sCSR). We understand from your comments that pages referenced from the Study B1931022 original clinical study report (sCSR) are for CD22 expression. It is unclear how the measurement of CD22 expression is used in the study. Please provide your responses to the questions for CD22 expression.

You have not provided any information for the MRD measurements. It is unclear if bone marrow samples were used for all MRD measurements. Please provide a detailed description of the assay, data, and assay validations for review of the flow cytometry procedures, including the gating strategy used in the assessment of MRD.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Tuesday, June 06, 2017 6:45 PM
To: McMullen, Rachel
Subject: RE: Inotuzumab Ozogamicin/BLA 761040 _ Information Request (DUE: Noon on June 26th)

Rachel – See below some questions regarding the FDA IR received 06 Jun 2017. Can you pls provide some clarification?

Thanks for your continued support.
Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda hhs.gov]
Sent: Tuesday, June 6, 2017 2:22 PM
To: Russell, Alison
Cc: McMullen, Rachel
Subject: Inotuzumab Ozogamicin/BLA 761040 _ Information Request (DUE: Noon on June 26th)
Importance: High

Good evening Alison,

With reference to BLA 761040, the team is requesting a prompt response to the following information request regarding the flow cytometry device used as part of the B1931022 study:

Information request:

1. Please provide the # leukocyte events captured. In order to evaluate the 10-4 claim for MRD used in the analysis, please provide the total number of events collected on each sample.

2. The MRD results are intended to be sampled from bone marrow aspirates. On page 70, the sponsor stated that "A peripheral blood sample was provided to the central vendor if a patient had an inadequate BM aspirate at screening". Given that the study was designed to be performed use bone barrow samples, does this change in matrix type introduce bias or potential errors? I assume FDA means Study B1931022 original clinical study report (sCSR) Section 9.5.2.2.2 on page 66. Pls can you confirm?

3. The B1931022 Report indicated on page 69 that there is "data on file" and "Details regarding assay validation and bioanalytical methods will be reported separately." Please provide the assay validation for review of the flow cytometry procedures, including the gating strategy used in the assessment of MRD. I assume FDA means page 69 of the original clinical study report (sCSR) for

Study B1931022? If so, these sentences refer to evaluation of CD22 expresssion, not MRD. Can you pls clarify the Agency's request?

4. On page 70, you stated "The leukemic phenotype and/or genotype could also be evaluated by other test methods at the discretion of the Sponsor." Please provide justification for any changes made to the assay during the course of the study and provide a summary of the number of samples used for the MRD assay and a description of any missing and discordant samples. I assume FDA means page 70 of the original clinical study report (sCSR) for Study B1931022? If so, these sentences refer to evaluation of CD22 expresssion, not MRD. Can you pls clarify the Agency's request?

Please submit a response to the above request via email to me by noon ET on Monday, June 26th and also follow up with an official submission to your BLA file.

Please *confirm* receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
06/12/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	Inotuzumab Ozogamicin/BLA 761040 _ Information Request (DUE: Noon on June 26th)
Date:	Tuesday, June 06, 2017 5:21:58 PM
Attachments:	image002.png
Importance:	High

Good evening Alison,

With reference to BLA 761040, the team is requesting a prompt response to the following information request regarding the flow cytometry device used as part of the B1931022 study:

Information request:

1. Please provide the # leukocyte events captured. In order to evaluate the 10-4 claim for MRD used in the analysis, please provide the total number of events collected on each sample.

2. The MRD results are intended to be sampled from bone marrow aspirates. On page 70, the sponsor stated that "A peripheral blood sample was provided to the central vendor if a patient had an inadequate BM aspirate at screening". Given that the study was designed to be performed use bone barrow samples, does this change in matrix type introduce bias or potential errors?

3. The B1931022 Report indicated on page 69 that there is "data on file" and "Details regarding assay validation and bioanalytical methods will be reported separately." Please provide the assay validation for review of the flow cytometry procedures, including the gating strategy used in the assessment of MRD.

4. On page 70, you stated "The leukemic phenotype and/or genotype could also be evaluated by other test methods at the discretion of the Sponsor." Please provide justification for any changes made to the assay during the course of the study and provide a summary of the number of samples used for the MRD assay and a description of any missing and discordant samples.

Please submit a response to the above request via email to me by noon ET on Monday, June 26th and also follow up with an official submission to your BLA file.

Please *confirm* receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
06/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB: June 14, 2017.

Regarding your IR response dated May 24, 2017 to question 6 about the ECL method used to detect anti-product antibodies in human serum:

1. The sensitivity of the confirmatory ECL method is unclear. In order to assess the likelihood of false negative samples in the confirmatory assay, provide the number of ALL patient samples that were positive in the screening assay, but were negative in the confirmatory assay. For those samples that were confirmed positive, provide the end point titers obtained in the tier 3 analysis.

2. Based on your response to question 6c, our understanding is that every assay run includes a titrated positive control, with a ±1 dilution factor of the titration as an assay acceptance criterion. Please confirm or provide clarification. In addition, since Figure 2 provides the log10 titers of the serum-based unpurified Positive Controls, explain how the log10 titer was calculated for the affinity purified antibody sample, and provide the level or fold purification that was achieved.

If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber -S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=0014262141
Date: 2017.06.06 09:11:06 -04'00'

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

Andrew Shiber

Digitally signed by Andrew Shiber
Date: 6/06/2017 01:03:07PM
GUID: 508da6dc000266f39bb039bf6ed30638

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040 _ Clinical Information Request (Response DUE: June 8, 2017)
Date:	Friday, June 02, 2017 11:42:18 AM
Attachments:	image002.png
Importance:	High

Good morning Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following information request from the review team.

Clinical Information Request:

Analysis of the laboratory data for platelet counts demonstrates a delayed recovery of platelet count to normal values in the inotuzumab ozogamicin arm compared to the investigator choice arm. Submit the following data for Study B1931022:

1. Time(median and range) to platelet recovery to 25K, 50K and 100K from baseline for C1, C2 and C3, end of treatment and follow-up visit for both treatment arms
2. Number of patients who had platelet recovery to 25K, 50K and 100K from baseline for C1, C2 and C3 for both treatment arms.
3. Include the number of patients with thrombocytopenia with platelet count < 50,000/mm^3 persisting for 45 days after starting therapy for responding patients(CR and CRi)
4. The protocol recommended a dose reduction of inotuzumab ozogamicin of 25% for patients who achieved a CRi but did not have recovery of platelet counts to the values obtained at previous cycle. How many patients received a 25% dose reduction for this protocol dosing recommendation?
5. In patients who achieved CRi, how many achieved CRp for both arms in Study B1931022(achieved ANC> 1000/microl but platelet < 100,000/mm^3)?
6. Number of patients who achieved CRh (ANC> 500micromol and platelet count > 50,000/mm^3) in the inotuzumab ozogamicin arm and the investigator choice arm.

Please submit a response to me promptly via email by **3pm ET on Thursday, June 8, 2017** followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
06/12/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	Inotuzumab Ozogamicin/BLA 761040 _ FDA Proposed Labeling (Response DUE: June 14, 2017)
Date:	Thursday, June 01, 2017 2:19:23 PM
Attachments:	BLA 761040_USPI_FDA Proposed Labeling-6-1-17.docx BLA 761040 Container Carton Comments.docx BLA 761040_General Comment.docx image002.png
Importance:	High

Good afternoon Alison,

With reference to **BLA 761040** for **Inotuzumab**, FDA's current edits/comments on the labeling (**USPI and Carton Container labels**) are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your labels and submit your revised labeling response to me via email by **1pm ET on Wednesday, June 14, 2017,** followed by an official submission of the label to the BLA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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

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RACHEL S MCMULLEN
06/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB **May 24, 2017.**

We acknowledge your response to question 1 submitted in amendment 0049.

(b) (4)

[redacted]

If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber -S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=0014262141
Date: 2017.05.17 11:59:21 -04'00'

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

Andrew Shiber

Digitally signed by Andrew Shiber
Date: 5/17/2017 12:02:39PM
GUID: 508da6dc000266f39bb039bf6ed30638

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	Henesey, Caroline; Young, Michael; McMullen, Rachel
Subject:	BLA 761040 (inotuzumab ozogamicin) _ Clinical INFORMATION REQUEST (Due: May 18, 2017)
Date:	Thursday, May 11, 2017 2:48:39 PM
Attachments:	image001.png
Importance:	High

Good afternoon Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following information request from the team.

Clinical Information Request
Due Date: May 18, 2017

For Study B1931022 for the full ITT population(N=326), conduct exploratory analysis for EFS based on the following definition:

- Date of randomization until death due to any cause,
- Date of randomization until relapse from CR/CRi, or
- Date of Cycle 1 Day 1 until treatment failure after 2 cycles.

If a patient meets more than one criteria, the EFS event should be set at the earliest timepoint.

Please submit a response to me promptly via email by 4 pm EDT on May 18, 2017 and also follow up with an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
05/11/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB of **May 24, 2017.**

In your IR response dated April 7, 2017:

1. You provided a list of compounds considered as potential leachables, rather than the requested extractables study. Provide the data for the extraction studies that were performed on the stopper material for volatile, semi-volatile, and non-volatile compounds as well as (b) (4) impurities, using polar and non-polar solvents under accelerated temperature conditions, as referenced in the submission. In addition, provide the results of the extraction study conducted on the amber glass vials using water, acid and base, also referenced in the submission.
2. The incorrect file was uploaded in the response provided to our request for the (b) (4) for the Drug Substance. Provide the relevant information.
3. With regard to your compatibility studies for the infusion system, you provided the results of a single study describing the (b) (4) mg/mL concentration evaluated in three infusion bags, whereas a total of 8 compatibility studies were mentioned in BLA. Provide all the study sets demonstrating infusion system compatibility.
4. With regard to your proposed Drug Product release and stability specifications for moisture content, the data provided do not justify the proposed release and stability specification of (b) (4) % moisture content. Data were only provided for the developmental Drug Product lot, which assessed (b) (4).

[redacted] (b) (4) You should modify the release specification for moisture content based on the data you have, or perform [redacted] (b) (4)

5. No validation report for viral clearance was provided in the BLA. Provide the complete virus removal study report. In addition, provide data demonstrating that the manufacturing process [redacted] (b) (4) used in the virus removal study were representative of the product.
6. Regarding the ECL method used to detect anti-product antibodies in human serum:
    a. Justify the selection of 200-fold as the minimum required sample dilution. FDA recommends that dilutions not exceed 100-fold; for higher dilutions the overall effect on assay sensitivity and immunogenicity risk assessment should be considered (Draft guidance for industry, Assay development and validation for immunogenicity testing of therapeutic products, https://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf)
    b. Provide the mass-based sensitivity of the confirmatory assay. FDA's expectation is that the confirmatory assay is at least as sensitive as the screening assay, but with higher specificity (ibid).
    c. Justify the concentration of the anti-inotuzumab low positive control which, based our calculations, contains 2.76 µg/ml anti-product antibodies. Note that FDA recommends a low positive control containing a concentration of anti-product antibodies slightly above the sensitivity of the assay, to ensure consistent assay sensitivity across runs (ibid).
    d. Provide the mass-based sensitivity of the assay for the anti-calicheamicin positive control. As calicheamicin may be immunogenic, it is important to assess that the assay is able to sensitively detect antibodies against calicheamicin. In addition, justify in relation to the mass-based sensitivity of the assay, that the anti-calicheamicin low positive control is used at an appropriate concentration (see note to question 6c).
    e. No justification was provided regarding the concentrations of spiked inotuzumab ozogamicin, inotuzumab and CMC-BSA chosen for the tier 2 confirmatory analysis. We note that inotuzumab is spiked at a particularly high concentration, potentially leading to non-specific effects. Provide a rationale indicating that the concentrations of the spiked proteins are appropriate to confirm the presence of antibodies throughout and above the range of the assay.
    f. Provide a complete description and evaluation of the tier 3 End Point Titer analysis.

If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber -S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=4014262141
Date: 2017.05.09 10:45:14 -04'00'

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

Andrew
Shiber

Digitally signed by Andrew Shiber
Date: 5/09/2017 10:46:43AM
GUID: 508da6dc000266f39bb039bf6ed30638

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEETING MINUTES

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to the meeting between representatives of your firm and the FDA on May 3, 2017.

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

If you have any questions please contact the Regulatory Business Project Manager, Andrew Shiber at 301-796-4798.

Sincerely,

{See appended electronic signature page}

Marjorie A. Shapiro, Ph.D.
Chief, Laboratory of Molecular and Developmental Immunology
Division of Biotechnology Review and Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEETING MINUTES

Meeting Type: C
Meeting Category: CMC Only
Meeting Date and Time: May 3, 2017 12:00 P.M. Eastern Standard Time
Format: Teleconference

FDA, CDER, and the Office of Product Quality ATTENDEES:

Office of Biotechnology Products

Marjorie Shapiro, Ph.D.	Chief, Laboratory of Molecular and Developmental Immunology
Sarah Kennett, Ph.D.	Review Chief
Joel Welch, Ph.D.	Review Chief
Gerald Feldman, Ph.D.	Chief, Laboratory of Immunobiology
Mate Tolnay, Ph.D.	Product Quality
Antonina Aydanian, Ph.D.	Product Quality
Vicky Borders-Hemphill, Pharm.D.	Quality Labeling

Pfizer, Inc.

1.0 BACKGROUND

Purpose of meeting: To discuss two BLA submissions from the applicant where there is a discrepancy in the extractable volume claims within both labeling presentations and the actual extractable volume after reconstitution.

2.0 DISCUSSION

Agency:

The applicant submitted labeling within BLA 761040 Besponsa (inotuzumab ozogamicin) and BLA 761060 Mylotarg (gemtuzumab ozogamicin) for extractable volume after reconstitution that does not accurately represent the deliverable amount of product. This is inconsistent with 21 CFR 201.51(g) and the 2015 Guidance for Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products.
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389069.pdf

The Agency stated that the easiest remedy is for Pfizer to change all labels and labeling for the entire product presentation (vial labels, carton labeling, and prescribing information) for both products to reflect the accurate strength of the product per vial, the final concentration after reconstitution, the amount of diluent used to reconstitute, and the minimum deliverable volume after reconstitution.

BLA 761040 Besponsa (inotuzumab ozogamicin)
For BLA 761040, per the labeling claim, after reconstitution the final concentration should be (b) (4) mg (b) (4) mL with a deliverable volume of (b) (4) mL. Data submitted in the BLA do not reflect that a deliverable volume of (b) (4) mL can be withdrawn from the vial; therefore all labeling for the entire product presentation (vial labels, carton labeling, and prescribing information) should be changed to the accurate amount contained in the vial and the amount that can be extracted after reconstitution. The data submitted to BLA 761040 may be sufficient for the Agency to determine the appropriate amount to state on the label, but if additional information is available, it should be submitted to the BLA.

BLA 761060 Mylotarg (gemtuzumab ozogamicin)
For BLA 761060, per the labeling claim, after reconstitution the final concentration should be (b) (4) mg (b) (4) mL with a deliverable volume of (b) (4) mL. No data were submitted to the BLA other than the statement in 3.2.P.2.2.1 "The average extractable volume was (b) (4) ml." All labeling for the entire product presentation (vial labels, carton labeling, and prescribing information) should be changed to the accurate amount contained in the vial and the amount can be extracted after reconstitution. Submit sufficient data to the BLA that will help the Agency determine the appropriate amount to state on the label.

Pfizer:
Pfizer agreed that additional data regarding the extractable volume after reconstitution will be officially submitted to BLA 761060, and all labels and labeling claims for the entire product presentation will be changed to accurately reflect the amount contained in the vial and the extractable volume after reconstitution.

In addition, it is also agreed that the extractable volume after reconstitution data already submitted within BLA 761040 may be used to determine an accurate labeling claim, but additional extractable volume after reconstitution data may be submitted to BLA 761040. Pfizer agreed that all labels and labeling for the entire product presentation will be changed to accurately reflect the amount contained in the vial and the extractable volume after reconstitution that can be achieved as reflected by the data.

Action items:
Pfizer should submit information regarding extractable volume after reconstitution to both BLAs as soon as possible, but the Agency agreed that Pfizer should focus on BLA 761040, since this BLA has an earlier PDUFA deadline.

The Agency noted that the Division of Hematology Products, OHOP, has not yet communicated with Pfizer for either BLA regarding labeling and stated that Pfizer could expect Agency recommendations for these changes to the labels when DHP communicates proposed changes to the labels.

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/s/

MARJORIE A SHAPIRO
05/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB **May 8, 2017.**

(b) (4)

1. (b) (4)

2.

3.

4. (b) (4)

5.

INOTUZUMAB OZOGAMICIN DRUG SUBSTANCE

6. (b) (4)

7.

8.

INOTUZUMAB OZOGAMICIN DRUG PRODUCT

9. Clarify the endotoxin test method used during the Low Endotoxin Recovery (LER) studies conducted with RSE described under section 3.2.P.5.3 of the BLA.

If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber -S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=0014262141
Date: 2017.05.03 15:11:03 -04'00'

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

Andrew Shiber

Digitally signed by Andrew Shiber
Date: 5/03/2017 03:13:29PM
GUID: 508da6dc000266f39bb039bf6ed30638

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040 and 761060

GENERAL ADVICE

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:
Please refer to your original Biologics License Applications received December 20, 2016 and November 2, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin and gemtuzumab ozogamicin.

The Agency identified that inotuzumab ozogamicin (IO) (b)(4)mg/vial does not permit withdrawal of (b)(4)mg after reconstitution in 4 mL Sterile Water for Injection. In addition, the Agency identified that gemtuzumab ozogamicin (GO) (b)(4)mg/vial does not permit withdrawal of (b)(4)mg after reconstitution in 5 mL Sterile Water for Injection. Although GO is dosed at 3 mg/m2/dose, we note that it is dosed to a maximum of (b)(4)mg.

The Agency has scheduled a teleconference to discuss our concerns regarding extractable volume for both BLA 761040 and 761060.

Date: May 3, 2017
Time: 12:00 P.M. (Eastern Standard Time)

Submit a teleconference number to accept the request for a meeting.

If you have any questions, contact me.

Sincerely,

Andrew Shiber -S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=0014262141
Date: 2017.04.28 09:58:04 -04'00'

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

Andrew Shiber

Digitally signed by Andrew Shiber
Date: 4/28/2017 01:29:34PM
GUID: 508da6dc000266f39bb039bf6ed30638

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB **April 25, 2017.**

(b) (4)

1. (b) (4)

2.

INOTUZUMAB OZOGAMICIN DRUG SUBSTANCE

3. The bioburden method qualification was conducted with three replicates of the same batch, which does not consider batch to batch variability. Repeat the bioburden method qualification using two additional batches of drug substance.
4. Amendment 0035 summarizes the sample volumes used in the bioburden test method for (b) (4) (b) (4) Clarify if the indicated volumes refer to the sample volume tested per media type and if the bioburden qualification was conducted using the sample volumes used for the routine test.
5. Report 812-10-002-R.0 indicates that the (b) (4) for drug substance release was qualified (b) (4) (b) (4) for the drug substance method qualification.

If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber -S Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=0014626141
Date: 2017.04.19 14:59:38 -04'00'

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

Andrew
Shiber

Digitally signed by Andrew Shiber
Date: 4/19/2017 04:42:12PM
GUID: 508da6dc000266f39bb039bf6ed30638

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

MID-CYCLE COMMUNICATION

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Attention: Alison Russell, PhD
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Inotuzumab Ozogamicin (PF-05208773; CMC-544); lyophilized (b) (4) powder; (b) (4) mg/vial.

We also refer to the teleconference between representatives of your firm and the FDA on April 5, 2017. 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 Rachel McMullen, Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
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: April 5, 2017; 1:00PM-2:00PM

Application Number: BLA 761040
Product Name: Inotuzumab Ozogamicin (PF-05208773; CMC-544)

Proposed Indication: Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Applicant Name: Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.

Meeting Chair: R. Angelo de Claro, MD; Clinical Team Leader
Meeting Recorder: Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Division Director
R. Angelo de Claro, MD, Clinical Team Leader
Tanya Wroblewski, MD, Medical Officer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Michael Manning, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V,
Bahru Habtemariam, Pharm D, Clinical Pharmacology Team Leader
Salaheldin Hamed, PhD, Pharmacology Reviewer

Office of Product Quality
Gerald Feldman, PhD, Team Leader
Steven Fong, MS, PhD, Reviewer
Mate Tolnay, PhD, Product Quality Reviewer

Office of Biostatistics/Division of Biometrics V
Yuan Li Shen, PhD, Statistical Team Leader
Qing Xu, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology
Nicole Garrison, PharmD, Reviewer
Mei-Yean Chen, PharmD, Risk Management Analyst
Neil Vora, PharmD, MBA, Project Manager

APPLICANT ATTENDEES
Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Simon Jenkins, PhD (Asset Team Lead)
Jane Liang White, PhD (Statistical Lead)
Tao Wang, PhD (Statistics)
Svetoslav Dimitrov, MD (Safety Lead)
Reza Khosravan, PhD (Clinical Pharmacology Lead)
Marque Todd, PhD (Nonclinical toxicology)
Stephen Mayer, BA (Regulatory CMC)
David Wright. PhD (Nonclinical toxicology)
Theodore Johnson, PhD (Nonclinical ADME)
Bitha Narayanan, PhD (Nonclinical pharmacology)
Gretchen Jimenez, BS (Nonclinical pharmacology)
Caroline Henesey, PhD (Regulatory)
Alison Russell, PhD (Global Regulatory Lead)
Barbara Sleight, MD (Clinical)
Douglas Laird, PhD (Translational oncology)
Leena Das-Young, PharmD (Head; Late Phase Development for Oncology)
Allan Safferman, MD (Safety)
Norah Slattery, BS MBA (Regulatory CMC)
Nathalie Hayduk, MS (CMC)
Erik Vandendries, MD PhD (Global Clinical Lead)
Iain Webb, MD (Clinical)

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

Statistics:
Issues of interpretation of OS results are identified:

1. The OS result was confounded by HSCT.
    a. There was no difference seen between treatments in subjects not receiving HSCT
    b. For those subjects receiving HSCT, there were fewer early deaths in the control arm, but the subjects receiving inotuzumab ozogamicin have a better survival

outcome than the control group after 18 months.

2. In competing risk analysis, when we consider death attributed only to disease, there are fewer cumulative deaths over time in the inotuzumab ozogamicin arm than the control arm; but when we consider death attributed to causes other than disease, the trend was reversed.

Clinical Pharmacology:

3. We have persisting concern that the proposed inotuzumab ozogamicin dose of 1.8 mg/m^2 may not be optimal in balancing safety and efficacy. We are especially concerned with a relatively high rate of VOD adverse events. (b) (4) was not informed by a robust dose finding study, a post marketing requirement may be issued in order to identify a dose of inotuzumab ozogamicin that favorably balances safety and efficacy.

3.0 INFORMATION REQUESTS

We have the following information requests:

Clinical:

1. The mortality of hepatic veno-occlussive disease (VOD) with multi-organ failure (MOF) is > 80% and describing the frequency of VOD with MOF is important to characterize. Submit a summary based on the HEAB adjudication of the number of cases of VOD with multi-organ failure. Please provide a response within two-four weeks of the date of this communication.

2. You provided a financial disclosure summary for all the clinical investigators in the covered studies. Submit separate summaries of the financial disclosure information for the investigators for Study 1022 and Study 1010. Include how many investigators had no financial interests or arrangements and how many investigators had disclosable financial interests or arrangements with any sponsor of the covered clinical study.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The major safety concern with the use of inotuzumab ozogamicin in patient with relapsed or refractory precursor B-Cell ALL is the increased risk of post-transplantation non-relapse mortality and hepatotoxicity to include hepatic veno-occlussive disease (VOD). We recommend the following risk management strategies:

1. Include box warning in the USPI for VOD/SOS, hepatotoxicity and increased risk of post-transplant non-relapse mortality. Submit a revised USPI by April 19, 2017.

2. Post Marketing Requirement: (b) (4)
(b) (4)

(b) (4)

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late-Cycle Meeting between you and the review team is currently scheduled for June 23, 2017. We intend to send the briefing package to you approximately 5 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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 June 1, 2017.

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/s/

ROMEO A DE CLARO
04/06/2017

From: McMullen, Rachel
To: Russell, Alison
Subject: RE: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix
Date: Tuesday, March 28, 2017 1:54:00 PM
Attachments: image001.png
image002.png

Good afternoon Alison,

With reference to your email and query, please note the following response from the team:

Your 351(a) BLA is within the scope of our recently issued guidance for industry, Nonproprietary Naming of Biological Products. However, FDA issued the final guidance at a point in our review of your application that does not allow sufficient time for FDA to designate a proper name that includes a suffix as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your 351(a) BLA be approved during this review cycle.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Wednesday, March 22, 2017 2:46 PM
To: McMullen, Rachel
Subject: RE: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Rachel

By way of follow-up to your telephone call on 17 March 2017, I have become aware of feedback received today from FDA project manager Kris Kolibab to another Pfizer team (Mylotarg)

"Your 351(a) BLA is within the scope of our recently issued guidance for industry, Nonproprietary

Naming of Biological Products. However, FDA issued the final guidance at a point in our review of your application that does not allow sufficient time for FDA to designate a proper name that includes a suffix as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your 351(a) BLA be approved during this review cycle."

For planning purposes, can I assume that the same guidance may be applied to inotuzumab ozogamicin?

Sorry to bother you again so soon, but the Pfizer team will need some guidance on this matter very soon.

Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: Russell, Alison
Sent: Wednesday, March 15, 2017 9:02 AM
To: 'McMullen, Rachel'
Subject: RE: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Rachel – Txs; I confirm receipt and the team will proceed accordingly.
Alison

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Wednesday, March 15, 2017 8:33 AM
To: Russell, Alison
Cc: McMullen, Rachel
Subject: RE: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Hi Alison,

With reference to your query below, (b) (4) .

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products

Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Tuesday, March 14, 2017 7:49 PM
To: McMullen, Rachel
Subject: BLA 761040 (inotuzumab ozogamicin)/query regarding nonproprietary name suffix

Rachel

With reference to the attached FDA labeling guidance document "Nonproprietary Naming of Biological Products" issued in January 2017 (see excerpt below), I am interested to know if inotuzumab ozogamicin will be required to have a suffix (4 lowercase letters) included in the proper name designated by FDA at the time of licensure.

I look forward to hearing from you in this regard.

Alison

A. Prospective Naming of Biological Products Submitted Under Section 351(a) of the PHS Act

An applicant should propose a suffix composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at the time of licensure (see section VI of this guidance). Such submissions can be made during the investigational new drug application (IND) phase16 or at the time of BLA submission. An applicant should submit up to 10 proposed suffixes, as described in this section, in the order of the applicant's preference. We recommend including any supporting analyses of the proposed suffixes for FDA's consideration based on the factors described in this guidance.

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,

San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

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/s/

RACHEL S MCMULLEN
08/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040 **INFORMATION REQUEST**

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB **April 3, 2017.**

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

a) (b) (4)

b) Modify Table 3.2.P.3.4 -2 updated in amendment 0035 to reflect action limits with the sign ≥.

2. Section 3.2.P.3.5, Process Validation and Evaluation

a) (b) (4)

b)

c)

3. Section 3.2.P.5.3, Validation of Analytical Procedures

The sterility and endotoxin method qualifications were conducted with three replicates of the same batch and do not consider batch to batch variability. Repeat the sterility and endotoxin methods qualification with 2 more batches of drug product.

4. Section 3.2.S.4.3, Validation of Analytical Procedures

Conduct the endotoxin method verification with 2 more batches (b) (4) in addition to the data for one drug substance lot provided in the BLA.

If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber -S

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

Andrew Shiber

Digitally signed by Andrew Shiber
Date: 3/28/2017 07:47:46AM
GUID: 508da6dc000266f39bb039bf6ed30638

From: McMullen, Rachel
To: Russell, Alison
Cc: McMullen, Rachel
Subject: BLA 761040/ Inotuzumab Ozogamicin _ Information Request (Response DUE: March 20th)
Date: Tuesday, March 14, 2017 9:43:28 AM
Importance: High

Good morning Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following request from the team.

Clinical Information Request:

1. Provide the rationale for the early termination of Study B1931006: Open-label, randomized Phase 3 Study of Inotuzumab Ozogamicin Administered in Combination with Rituximab Compared to Defined Investigator's Choice Therapy in Subjects with relapsed or refractory CD22 positive, Follicular B cell NHL.

2. In Study 1022, the last bilirubin prior to HSCT was identified in the univariate analysis(N=79) as a potential factor in the development of VOD. Clarify if the this the last bilirubin prior to the preparative regimen or the transplantation(infusion of stem cells).

Please submit a response via email to the information request below by 12pm (ET) on March 20th, followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
03/14/2017

From: McMullen, Rachel
To: Russell, Alison
Cc: McMullen, Rachel
Subject: BLA 761040/ Inotuzumab Ozogamicin _ Information Request (Response DUE: March 13th)
Date: Tuesday, March 07, 2017 11:19:56 AM
Importance: High

Good morning Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following request from the team.

Information Request:

For patients in the inotuzumab ozogamicin arm who proceeded to transplantation(N=77) in Study 1022, submit the following information:

- Number of patients who developed VOD with time interval of ≤ 42 days between last dose of inotuzumab and VOD onset
- Number of patients who developed VOD with time interval of > 42 days between last dose of inotuzumab and VOD onset.

Please submit a response via email to the information request below by 2pm (ET) on March 13th, followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
03/07/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Wyeth Pharmaceuticals, Inc.,
a subsidiary of Pfizer, Inc.
Attn: Allison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for Inotuzumab Ozogamicin.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB **March 10, 2017.**

[redacted] (b) (4) **DRUG SUBSTANCE (DS)**

1. Provide a diagram of the [redacted] (b) (4) inotuzumab ozogamicin DS manufacturing processes indicating the following for each step:
   a. [redacted] (b) (4)
   b. [redacted]
   c. [redacted]
   d. [redacted]
2. [redacted] (b) (4)
3. [redacted]

4. (b) (4)

5.

6.

7.

8.

9.

DRUG PRODUCT (DP)

1. **Section 3.2.P.2.5, Microbiological Attributes. Container Closure Integrity**
   Refer to Table 3.2.P.2.5-1 and clarify if the validation of CCIT was performed (b) (4)

2. **Section 3.2.P.3.2, Batch Formula**
   Provide the maximum and minimum proposed commercial batch size for the drug product.

3. **Section 3.2.P.3.4, Control of Critical Steps and Intermediates**
   a) (b) (4)

b) (b) (4)

c)

d)

4. Section 3.2.P.3.5, Process Validation and Evaluation

a) (b) (4)

b)

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

a) (b) (4)

b)

c)

d) Refer to the data provided in sequence 0008 regarding the rabbit pyrogen test and clarify the type of distress that caused the death of two rabbits.

If you have any questions, please contact me.

Sincerely,

Andrew Shiber -S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=0014262141
Date: 2017.03.03 07:35:04 -05'00'

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Attention: Alison Russell, PhD
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application (BLA) dated December 20, 2016, received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for Inotuzumab Ozogamicin (PF-05208773; CMC-544); lyophilized (b) (4) powder; (b) (4) mg/vial.

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 August 20, 2017. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 1, 2017.

In addition, the planned date for our internal mid-cycle review meeting is March 21, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Rachel McMullen, Senior Regulatory Project Manager, at (240) 402-4574.

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
03/02/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin _ Information Request _ DUE: March 7th
Date:	Thursday, March 02, 2017 11:05:14 AM
Importance:	High

Good afternoon Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please submit a response via email to the information request below by COB on Tuesday, March, 7th followed by an official submission to the BLA file.

Information Request:

Provide clarification regarding the 3 additional patients(Patient 11031002, Patient 10471009 and patient 10471014) reported in SCS as having VOD after the data cut-off date of 8 March 2016 and the inclusion of only one additional patient as having VOD/SOS in the 120 day safety update. Include a narrative summary and HEAB adjudication report for the additional patient reported in 120 day safety update as having VOD.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
03/07/2017

From: McMullen, Rachel
To: Russell, Alison
Cc: McMullen, Rachel
Subject: RE: BLA 761040/ Inotuzumab Ozogamicin _ Information Request _ Clarification
Date: Thursday, March 02, 2017 8:04:14 AM
Importance: High

Good morning Alison,

In follow up to your email below, please note the following clarifications (in blue text) from the team:

Regarding below, the Sponsor assumes that what the FDA wants is the number of patients who proceeded to CR/CRi and proceeded directly to HSCT after receiving inotuzumab ozogamicin (ie, not including patients who may have achieved CR/CRi, relapsed, received follow-up therapy and then went to HSCT). *Can you pls confirm that this assumption is correct?*
FDA Response: Yes, this is correct. Number of patients who achieved CR/CRI and proceeded directly to HSCT(not including those who attained CR/CRI, relapsed and received follow-up therapy and then went to HSCT).

Regardless, we will need to perform additional data programming to address this request and propose sending a response by COB Friday 10 March. *Is this acceptable to the Agency?* ***FDA Response: yes***

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Wednesday, March 01, 2017 6:45 PM
To: McMullen, Rachel
Subject: RE: BLA 761040/ Inotuzumab Ozogamicin _ Information Request _ DUE: March 7th

Rachel

Regarding below, the Sponsor assumes that what the FDA wants is the number of patients who proceeded to CR/CRi and proceeded directly to HSCT after receiving inotuzumab ozogamicin (ie, not including patients who may have achieved CR/CRi, relapsed, received follow-up therapy and then went to HSCT). *Can you pls confirm that this assumption is correct?*

Regardless, we will need to perform additional data programming to address this request and propose sending a response by COB Friday 10 March. *Is this acceptable to the Agency?*

Thanks

From: Russell, Alison
Sent: Wednesday, March 1, 2017 9:05 AM
To: 'McMullen, Rachel'
Subject: RE: BLA 761040/ Inotuzumab Ozogamicin _ Information Request _ DUE: March 7th

I confirm receipt

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda hhs.gov]
Sent: Wednesday, March 1, 2017 8:40 AM
To: Russell, Alison
Cc: McMullen, Rachel
Subject: BLA 761040/ Inotuzumab Ozogamicin _ Information Request _ DUE: March 7th
Importance: High

Good morning Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please submit a response via email to the information request below by COB on Tuesday, March, 7th followed by an official submission to the BLA file.

Information Request:

Submit the following information for patients on the inotuzumab ozogamicin arm from Study 1022:

- The median number of cycles of inotuzumab(median and range) for patients who achieved CR/CRi and went to post-study transplantation.
- The number of investigator reported cases of VOD for patients who achieved CR/CRi and went to post- study transplantation.
- The median number of cycles of inotuzumab(median and range) for patients who did not achieve CR/CRi and MRD negativity and did not proceed to transplantation.
- For the investigator reported events of VOD in patients who proceeded to post study transplantation, the median number of days(median and range) from last dose of inotuzumab to date of onset of VOD

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
03/07/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin _ Information Request _ DUE: March 7th
Date:	Wednesday, March 01, 2017 11:39:51 AM
Importance:	High

Good morning Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please submit a response via email to the information request below by COB on Tuesday, March, 7th followed by an official submission to the BLA file.

Information Request:

Submit the following information for patients on the inotuzumab ozogamicin arm from Study 1022:

- The median number of cycles of inotuzumab(median and range) for patients who achieved CR/CRi and went to post-study transplantation.
- The number of investigator reported cases of VOD for patients who achieved CR/CRi and went to post- study transplantation.
- The median number of cycles of inotuzumab(median and range) for patients who did not achieve CR/CRi and MRD negativity and did not proceed to transplantation.
- For the investigator reported events of VOD in patients who proceeded to post study transplantation, the median number of days(median and range) from last dose of inotuzumab to date of onset of VOD

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
03/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Wyeth Pharmaceuticals, Inc.,
a subsidiary of Pfizer, Inc.
Attn: Allison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for Inotuzumab Ozogamicin.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB **March 24, 2017.**

Questions related to the (b) (4)

1. (b) (4)

2. Regarding the manufacturing process and process controls,
   a. (b) (4)

b. [redacted]

c. [redacted]

d. [redacted]

3. [redacted]

4. [redacted]

Questions related to Inotuzumab ozogamicin Drug Substance:

1. No information was provided regarding the [redacted]
2. [redacted]
3. Regarding the reference materials,
   a. [redacted]
   b. [redacted]
   c. [redacted]
4. The response to FDA's information request provided on May 24, 2016, regarding the [redacted] study was incomplete. Provide a completed [redacted] study, with appropriate sign off by Quality Control.
5. Regarding the DS container closure system, provide the size and manufacturer of the [redacted]

Questions related to Inotuzumab ozogamicin Drug Product:

1. Your overfill study provided on May 24, 2016 that assessed extractable volume indicated extractable volumes of [redacted] ml from all four analyzed batches (Table 3.2.P.2.2-3). Clarify how the values for all four batches could be exactly [redacted] ml. If the results of measurements were rounded up or down, provide further details in

order to assure that a nominal volume of (b) (4) ml can be routinely removed from the vials.

2. Regarding your extractable studies for Drug Product, no results were provided. Provide a sufficiently detailed summary of the results, allowing verification of the conclusions.
3. Regarding your studies to determine compatibility with the infusion system, no results were provided. Provide a sufficiently detailed summary of the results, allowing verification of the conclusions.
4. Regarding your shipping validation studies, no results were provided for the (b) (4) studies. Provide a sufficiently detailed summary of the results, allowing verification of the conclusions.
5. Regarding the non-compendial analytical methods "appearance of lyophile" and "reconstitution time", provide detailed method descriptions and validation reports.
6. Regarding Drug Product release and stability specifications,
    a. To justify the proposed specification for moisture content (lyophilized drug product), provide the results of the development studies that concluded that moisture content of (b) (4) % has no impact on product quality.
    b. (b) (4)
    c.

Questions related to the (b) (4) Inotuzumab ozogamycin Drug Substance and Drug Product, as applicable:

1. For <u>all</u> release and stability specifications where the specification is set wider than the calculated tolerance interval, provide assay-specific justifications that the proposed specification provides adequate control over the product quality attribute.
2. Regarding the downstream manufacturing process:
    a. (b) (4)
    b.
    c.

If you have any questions, please contact me.

Sincerely,

Andrew Shiber -S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=0014262141
Date: 2017.03.01 09:37:36 -05'00'

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

Andrew Shiber

Digitally signed by Andrew Shiber
Date: 3/01/2017 03:47:56PM
GUID: 508da6dc000266f39bb039bf6ed30638

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	RE: BLA 761040 (inotuzumab ozogamicin) _ FDA response
Date:	Monday, February 27, 2017 6:13:59 PM
Attachments:	image001.png
Importance:	High

Good evening Alison,

In follow up to the email below and Pfizer's proposals regarding submission of this updated OS analysis to BLA 761040, please note the response from the FDA review team:

FDA Response:
Regarding the updated overall survival submission for Study B1931022, we request that you submit the tables, listings, figures(TLFs) and associated e-sub datasets(SDTM and ADAM) by April 21, 2017. A delay in submission of this information may be considered as a major amendment.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Friday, February 24, 2017 2:26 PM
To: McMullen, Rachel
Subject: BLA 761040 (inotuzumab ozogamicin)

Rachel

Update of Study B1931022 Overall Survival (OS) data

- For Study B1931022, the primary readout of final overall survival (OS) analysis, with data cutoff date of 08 March 2016, was presented in the supplemental clinical study report (sCSR) included in BLA Roll 3 (BLA 761040 SN 0016) submitted on 28 November 2016. Per the study protocol and statistical analysis plan, 248 deaths were required for the final OS analysis. The primary readout reflected mature OS data with 252 deaths (77.3%) observed in 326 patients randomized to the study.
- According to the Study B1931022 protocol, follow-up for OS was to continue until 2 years after the last patient was randomized; this timepoint occurred on 04 January 2017. Therefore, after cleaning the clinical database (ie, addressing outstanding queries), the Sponsor locked the clinical database for Study B1931022 on 22 February 2017 and plans to perform an updated analysis of OS based on data in the locked clinical database. With 267 deaths at the database lock, the event rate for OS will increase from 77.3% (at the time of the primary readout) to 81.9%.

The Sponsor is seeking FDA's agreement on the following proposals regarding submission of this updated OS analysis to BLA 761040:

- Submit tables, listings, figures (TLFs) and associated e-sub datasets (SDTM and ADAM) by mid-May 2017.
- Submit a supplemental clinical study report (sCSR) by end-September 2017 (ie, post-approval).

Can you let me know if this is acceptable to the Agency?

Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

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/s/

RACHEL S MCMULLEN
02/27/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

PRIORITY REVIEW DESIGNATION

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Attention: Alison Russell, PhD
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application (BLA) dated December 20, 2016, received December 20, 2016, submitted under section 351(a) of the Public Health Service Act for Inotuzumab Ozogamicin (PF-05208773; CMC-544); lyophilized (b) (4) powder (b) (4) mg/vial.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 601.2(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is August 20, 2017.

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 June 1, 2017.

If you have any questions, call Rachel McMullen, Regulatory Project Manager, at (240) 402-4574.

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
02/16/2017

From: McMullen, Rachel
To: Russell, Alison
Cc: McMullen, Rachel
Subject: BLA 761040/ Inotuzumab Ozogamicin _ Information Request _ DUE: February 9th
Date: Monday, February 06, 2017 3:31:48 PM

Good afternoon Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please submit a response to the information request below by COB on Thursday, February 9, 2017, followed by an official submission to the BLA file.

Information Request:

Please provide the correction factors of QTcS for Study PMR533 of BLA761040, and update the analysis dataset pkecg0.xpt by adding QTcS (currently empty field), PR, QRS and their baselines and deltas.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
02/06/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin _ Information Request _ Please Provide Study Report (Response Due: COB, Feb 1st)
Date:	Tuesday, January 31, 2017 3:34:46 PM
Importance:	High

Good afternoon Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following request from the team:

Information Request:

Please provide the study report for Study pmar-332 Inotuzumab ozogamicin concentration QT analysis for study B1931007 [0001 (2) 03/30/2016]. We are unable to access the referenced study report, which should be in module 5.3.4.2.

Please submit the final study report for Study B1931007pmar-332. The link provided in your submission dated 03/30/2016 does not contain any valid information.

Please submit a response to me via email by COB tomorrow, February 1st, followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993
Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
01/31/2017

From:	McMullen, Rachel
To:	"Russell, Alison"
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin _ Information Request (Response Due: COB, Friday, Feb 3rd)
Date:	Tuesday, January 31, 2017 3:04:56 PM
Attachments:	Highlights_ClinPharm_and_Cardiac_Safety.doc
Importance:	High

Good afternoon Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please complete the attached Clin Pharm and Cardiac Safety Table and submit a response to me via email by COB on Friday, February 3, 2017, followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993
Rachel.McMullen@fda.hhs.gov | 240-402-4574

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) 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	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• 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 *in vitro* and *in vivo* 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/

RACHEL S MCMULLEN
01/31/2017

From:	McMullen, Rachel
To:	"Russell, Alison"
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin _CLINICAL Information Request (Response Due: Friday, Feb 3rd)
Date:	Monday, January 30, 2017 3:24:31 PM
Importance:	High

Good afternoon Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following information request from the review team.

Clinical Information Request:

Submit an updated table of adverse drug reactions as displayed in the Summary of Clinical Safety, page 84, table 12 that includes the number of events and the percentages. Use the same grouped terms as in the footnotes.

Include edema(using grouped terms- edema, peripheral edema, peripheral swelling)
Include hypokalemia(include group terms- hypokalemia, blood potassium decreased).

Please submit a response to me via email by 2pm EST, on Friday February, 3, 2017, followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993
Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
01/30/2017

From:	McMullen, Rachel
To:	"Russell, Alison"
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin _CLINICAL Information Request (Response Due: Noon on Monday, Jan 30)
Date:	Tuesday, January 24, 2017 2:07:20 PM
Importance:	High

Good afternoon Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following information request from the review team.

Clinical Information Request:

Submit two analyses datasets that include the safety population for 1) patients who developed VOD and 2) patients with hepatotoxicity(cluster term) on Study 1022.

1. Submit an analysis dataset that includes the safety population for patients with VOD(pre and post study HSCT) and the following variables: treatment duration in weeks, total exposure, total exposure in cycle 1, actual treatment duration(cycles) , total exposure, actual total dose intensity and relative total dose intensity and corresponding analysis values. Include USUBJID, age, sex, SAFFL, ARM, treatment group.

2. Submit an analysis dataset that includes the safety population for patients with hepatotoxicity(cluster term) and the following variables: treatment duration in weeks, total exposure, total exposure in cycle 1, actual treatment duration(cycles) , total exposure, actual total dose intensity and relative total dose intensity and corresponding analysis values. Include USUBJID, age, sex, SAFFL, ARM, treatment group. Include the preferred term and SOC, grade of AE, TEAE in the dataset.

Please submit a response to me via email by noon on Monday, January 30, 2017, followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993
Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
01/24/2017

From:	McMullen, Rachel
To:	Russell, Alison
Cc:	McMullen, Rachel
Subject:	BLA 761040 (inotuzumab ozogamicin) _ Clinical Information Request (DUE: Thursday January 12, 2017)
Date:	Monday, January 09, 2017 4:12:08 PM
Importance:	High

Good afternoon Alison,

With reference to BLA 761040, please note the following information request from the FDA review team.

Clinical Information Request:

For Study B1931022

1. Submit an analysis dataset for the following sites: 1013, 1047, 1058, 1063, 1086, 1151, 1052, 1180, 1189, 1094, 1135, 1009, 1020, 1066, 1089, 1107 and 1130, 1131, 1263 and 1002 that includes the following variables USUBJID, protocol violations, discontinuations, serious adverse events, response(CR/CRi). Include flags for ITT, mITT, safety population flags and arm of study.

2. Send an analysis dataset for all causality adverse events that began on or after Cycle 1 day 1 but within 42 days of the last dose that include a flag for subjects who receive new anti-cancer treatment(including prior therapy for a subsequent HSCT).

Please submit a response to me promptly via email by **COB on Thursday January 12, 2017** followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
01/09/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA761040

BLA ACKNOWLEDGMENT

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Attention: Alison Russell, PhD
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

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: Inotuzumab Ozogamicin (PF-05208773; CMC-544); Lyophilized (b) (4) powder; (b) (4) mg/vial.

Date of Application: December 20, 2016

Date of Receipt: December 20, 2016

Our Reference Number: BLA 761040

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 February 18, 2017, 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. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RACHEL S MCMULLEN
01/03/2017

From:	McMullen, Rachel
To:	"Russell, Alison"
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin _CLINICAL Information Request (Response Due: With submission of CSR)
Date:	Thursday, September 22, 2016 1:44:00 PM
Importance:	High

Good afternoon Alison,

With reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following information request from the review team.

Clinical Information Request:

Submit the following analyses at the time of the submission of the CSR. Include the description of analysis methods, analysis datasets and SAS codes.

1. Perform analyses of survival (overall survival, Day 100 and Day + 180) in patients who underwent hematopoietic stem cell transplantation (HSCT) from the time of HSCT. Compare the baseline characteristics (including demographics, patient- and disease-related factors, transplantation treatment) between the treatment arms for this subgroup of patients who underwent HSCT.

2. Perform analyses of survival in patients who did not undergo HSCT. Compare the baseline characteristics (including demographics, patient- and disease-related factors,) between the treatment arms for this subgroup of patients who did not undergo HSCT.

3. Conduct additional analyses to better describe the treatment effect of inotuzumab ozogamicin. Submit analysis of the following parameters:
    a. Red cell transfusions
    b. Platelet transfusions
    c. Incidence and time to transfusion independence (provide definition for transfusion independence that includes platelet and RBC independence)
    d. Grade 3 and 4 bleeding events
    e. Grade ≥ 3 infections
    f. Use of filgrastim or pegfilgrastim support
    g. Length of hospitalization from time of randomization
    h. Intubation/ventilatory support in the intensive care unit

In general, summarize number of patients per arm who meet the above events, and total number of events per arm (e.g. number of transfused RBC units). For hospitalization and ICU data, summarize based on number of days.

Because several of the above items may occur as multiple events per patient, conduct time to recurrent-event analysis (items 3a, 3b, 3d, 3e, 3g). Conduct time to first-event analysis for items 3d, 3e, 3g, 3h.

Regarding the timing, the submission of these items can occur at the time of the submission of the CSR. Please submit a response to me via email followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993
Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
09/22/2016

From:	McMullen, Rachel
To:	"Russell, Alison"
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin/Qs re Death Narratives, D120 SU, and Module 2 Nonclinical _ FDA Response
Date:	Friday, August 05, 2016 11:42:55 AM
Attachments:	image001.png
Importance:	High

Good morning Alison,

With reference to your email inquiry below for BLA 761040, please note the response from the FDA review team (**in bolded blue text**).

Please confirm receipt of this correspondence.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993
Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Thursday, August 04, 2016 1:54 PM
To: McMullen, Rachel
Subject: BLA 761040/ Inotuzumab Ozogamicin/Qs re Death Narratives, D120 SU, and Module 2 Nonclinical

Rachel

This communication is being sent in reference to BLA 761040 Rolls 3 and 4 (see IND 65,658 SN 0707 dated 24 May 2016).

Efficacy (prose) narratives for patients who died and contributed to the analysis of OS in Study B1931022:

Example narrative

- Reference is made to FDA's 10 May 2016 request for efficacy narratives for patients who died and contributed to the analysis of OS in Phase 3 Study B1931022 and to the 26 May 2016 teleconference where FDA clarified that a complete description of events around the hematopoietic stem cell transplant (HSCT) period should be provided.
- To ensure FDA is in agreement with the content of the efficacy narratives, 2 examples of completed efficacy narratives for inotuzumab ozogamicin are being provided (note, in Roll 3, efficacy narratives from control treated patients will also be provided):
    - Patient # 10141010: Patient who proceeded to HSCT after receiving inotuzumab ozogamicin and developed venoocclusive disease (VOD) post-HSCT
    - Patient # 10181001: Patient who did not proceed to HSCT after receiving inotuzumab ozogamicin
    - A list of abbreviations used in the narratives are also provided for reference
- Please note: The efficacy narrative includes hyperlinks to applicable CIOMS or Hepatic Event Adjudication Board (HEAB) narratives (prose) for those hepatic events adjudicated by the HEAB, i.e., additional information will be available to FDA when the efficacy narratives are formally submitted as part of the eCTD.

Please can you confirm that the FDA review team consider the type of information included in the efficacy narratives to be acceptable?

FDA Response: The information included in the efficacy narratives appears acceptable. We note extensive use of abbreviations. Ensure consistent use of abbreviations throughout the narratives and study report.

Proposed presentation of data in BLA:

With regards presentation of information regarding these efficacy prose narratives for all deaths from Study B1931022 in the BLA Rolls 3 and 4:

- In Roll 3, efficacy narratives and an assessment document will be included in Module 5 Section 5.3.5.1
- In Roll 4, the key findings from the analysis of these narratives will be summarized in the Clinical Overview

Is this acceptable to FDA?

FDA Response: Yes

Day 120 Safety Update (D120 SU):

I would like to clarify that the D120 SU will include data that was in clinical database as of the beginning of September 2016, which enables writing of the D120 to initiate by approximately end of November 2016 (i.e., all data will be approximately 6 months old when submitted to the FDA by end of February 2017). As of the data cutoff date of 08 March 2016 (used for the supplemental clinical study report), a total of 54/307 treated patients were still in follow-up on study; 39 patients were in the inotuzumab ozogamicin arm and 15 patients were in the control arm. Therefore, the change to the safety data between September and November 2016 is likely to be minimal.

Is this acceptable to FDA?

FDA Response: Your proposed cutoff and submission dates are acceptable. Include datasets in the submission of the Day 120 safety update. Provide a list of datasets that you will submit with the Day 120 safety update.

Module 2 Nonclinical Documents (Module 2 Sections 2.4 and 2.6):

I would like to inform FDA that following a recent analysis of updated population pharmacokinetic (POPPK) data from Study B1931022, we have determined that the updated PK parameters for inotuzumab ozogamicin will result in revisions to some of the nonclinical components in Module 2. Therefore, Pfizer intends to submit the following updated nonclinical components in Roll 3: Module 2 Section 2.4, 2.6.4, 2.6.5, 2.6.6, and 2.6.7.

Will this require an update to the rolling review schedule previously submitted under IND 65,658 SN 0707 dated 24 May 2016?

FDA Response: No update is required.

Thanks,
Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

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/s/

RACHEL S MCMULLEN
08/05/2016

From:	McMullen, Rachel
To:	"Russell, Alison"
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin _Stats Information Request (RESPONSE DUE: Friday, July 29, 2016) _ FDA Response (Clarification)
Date:	Wednesday, July 27, 2016 10:52:16 AM
Attachments:	image001.png
Importance:	High

Good morning Alison,

With reference to your email below requesting further clarification, please note the team's response:

FDA RESPONSE:

Please see our response in RED. For this request, FDA intends to explore the confounding effect of SCT and MRD for the OS results and recognize the effect of SCT and MRD are time-dependent. Due to the multiple MRD assessment records over time for each patient, the time-dependent feature of MRD assessment will be complicated. Therefore, FDA made some revisions of this request. At the first run-through, we may only consider the most current MRD level when SCT occurs, otherwise set the MRD level as the last MRD assessment. Those without MRD assessment will be assigned as missing.

FDA would also like to have a separated MRD dataset to be submitted. This dataset will have one record per subject and with all the MRD assessments displayed horizontally (e.g. MRD1-MRDxx), the corresponding time of the MRD assessment (e.g. end of experimental treatment, end of intervening induction therapy, etc.), date of the corresponding period for each MRD (e.g. Date 1-Datexx). This data can be submitted one week after the Part A and Part B are submitted.

For Part A and B:

- In the initial part of the IR, FDA is requesting data for OS (see below); however, in the subsequent part of the IR, OS and PFS is mentioned (see below). Can you pls clarify if only OS data is required? Only OS is requested.

For Part A:

- **For "time from the first CR to SCT":**
  - we propose deriving data for patients who achieved either CR or CRi (per Investigator assessment) since either patient can proceed to SCT : YES
  - for patients who went to SCT without achieving CR/CRi, patients who achieved

CR/CRi but didn't go to SCT, patients who did not achieve CR/CRi and didn't go to SCT, we will indicate this data as "missing" : YES

- **For "the most current MRD level prior to transplant":**
  - we would propose deriving data for MRD status prior to SCT for those patients who went to SCT (with no intervening induction therapy [ie treatment that the patients might have received subsequent to study therapy {eg. blinatumomab}]); for those patients who went to SCT after receiving an intervening induction therapy, we will indicate this data as "missing"; is this acceptable?

We would like to request the MRD level to be included for both patients who went to SCR with no intervening induction therapy and after receiving an intervening induction therapy. However, please provide an indicator variable to indicate when the corresponding MRD is from (e.g. after the experimental or after subsequent therapy).

  - for patients who did not go to SCT, we will indicate this data as "missing"; is this acceptable?

For those patients who did not have the SCT, one record of LAST MRD level (e.g. maybe including the assessment right after the experimental treatment as well as after the additional intervening induction therapies, etc.) should also be provided.

- **For MRD status (negative or positive):**
  - please note that we don't have MRD status on all patients e.g., patients with known resistant/progressive disease may not have an MRD assessment

This request is for all patient who had available MRD assessments.

- **For "time from randomization to the corresponding MRD assessment prior to transplant":**
  - for patients who achieve MRD-negativity, does FDA want the first time to achieve MRD-negativity after start treatment or the last MRD assessment prior to SCT? The last MRD assessment prior to SCT
  - for patients who are MRD-positive, please clarify what FDA want (this is unclear to Pfizer): Actually, we like to have the actual value of the MRD assessment, not MRD positive and negative status.
  - for patients with MRD status missing, this data will be indicated as "missing" Yes

This is the corresponding time from randomization to the MRD assessment time that we requested in #3. For patients who had SCT, time of the most current MRD assessment prior

to SCT will be used. For patients who did not have SCT, time of the LAST MRD assessment (e.g. after the experimental treatment or after the additional intervening induction therapies) can be provided.

- **For "time from first CR to the corresponding MRD assessment":** Please see the MRD assessment described in #3 for this corresponding MRD assessment .
  - we propose deriving data for patients who achieved either CR or CRi (per Investigator assessment) Yes
  - for patients who first achieved CRi and then achieved CR, we propose using the first CR date; is this acceptable? If the decision of MRD assessment is strictly based on CR response, then this is YES.
  - With regards to "corresponding MRD assessment":
    - for patients who achieve MRD-negativity, does FDA want the first time to achieve MRD-negativity after start treatment or the last MRD assessment prior to SCT? The last MRD assessment prior to SCT
  - for patients who are MRD-positive, please clarify what FDA want (this is unclear to Pfizer) Actually, we like to have the actual value of the MRD assessment, not MRD positive and negative status.
    - for patients with MRD status missing, this data will be indicated as "missing" Yes

Please confirm receipt of this correspondence.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993
Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Tuesday, July 26, 2016 2:38 PM
To: McMullen, Rachel
Subject: RE: BLA 761040/ Inotuzumab Ozogamicin _Stats Information Request (RESPONSE DUE:

Friday, July 29, 2016)

Rachel

With regards FDA IR (statistics) received 25 July 2016, Pfizer would like clarification on the points below and would be amenable to a teleconference to discuss further if FDA consider this would be useful.

For Part A and B:

- In the initial part of the IR, FDA is requesting data for OS (see below); however, in the subsequent part of the IR, OS and PFS is mentioned (see below). Can you pls clarify if only OS data is required?

For Part A:

- **For "time from the first CR to SCT":**
  - we propose deriving data for patients who achieved either CR or CRi (per Investigator assessment) since either patient can proceed to SCT
  - for patients who went to SCT without achieving CR/CRi, patients who achieved CR/CRi but didn't go to SCT, patients who did not achieve CR/CRi and didn't go to SCT, we will indicate this data as "missing"
- **For "the most current MRD level prior to transplant":**
  - we would propose deriving data for MRD status prior to SCT for those patients who went to SCT (with no intervening induction therapy [ie treatment that the patients might have received subsequent to study therapy {eg. blinatumomab}]); for those patients who went to SCT after receiving an intervening induction therapy, we will indicate this data as "missing"; is this acceptable?
  - for patients who did not go to SCT, we will indicate this data as "missing"; is this acceptable?
- **For MRD status (negative or positive):**
  - please note that we don't have MRD status on all patients e.g., patients with known resistant/progressive disease may not have an MRD assessment
- **For "time from randomization to the corresponding MRD assessment prior to transplant":**
  - for patients who achieve MRD-negativity, does FDA want the first time to achieve MRD-negativity after start treatment or the last MRD assessment prior to SCT?
  - for patients who are MRD-positive, please clarify what FDA want (this is unclear to Pfizer)
  - for patients with MRD status missing, this data will be indicated as "missing"
- **For "time from first CR to the corresponding MRD assessment":**

- we propose deriving data for patients who achieved either CR or CRi (per Investigator assessment)
- for patients who first achieved CRi and then achieved CR, we propose using the first CR date; is this acceptable?
- With regards to "corresponding MRD assessment":
  - for patients who achieve MRD-negativity, does FDA want the first time to achieve MRD-negativity after start treatment or the last MRD assessment prior to SCT?
  - for patients who are MRD-positive, please clarify what FDA want (this is unclear to Pfizer)
  - for patients with MRD status missing, this data will be indicated as "missing"

Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: Russell, Alison
Sent: Monday, July 25, 2016 2:24 PM
To: 'McMullen, Rachel'
Subject: RE: BLA 761040/ Inotuzumab Ozogamicin _Stats Information Request (RESPONSE DUE: Friday, July 29, 2016)

Rachel – I confirm receipt of your information request.
Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Monday, July 25, 2016 2:15 PM
To: Russell, Alison
Cc: McMullen, Rachel
Subject: BLA 761040/ Inotuzumab Ozogamicin _Stats Information Request (RESPONSE DUE: Friday, July 29, 2016)
Importance: High

Good evening Alison,

In reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following information request from the review team.

Statistical Information Request:

Please submit time-to-event data for OS (one record per subject) including the following variables :

- cause of death;
- time to death or censoring;
- time from randomization to SCT;
- time from the first CR to SCT;
- the most current MRD level prior to transplant ;
- MRD status (negative or positive)
- time from randomization to the corresponding MRD assessment prior to transplant ;
- time from first CR to the corresponding MRD assessment.
- demographics, baseline status, and other important prognostic variables

Please also convert the above mentioned time-to-event (OS/PFS) data with time-varying-covariate (Stem Cell Transplantation) using counting process format (i.e. [start, stop) as shown in the SAS PROC PHREG manual). The counting process method has multiple records for each patient ; with each record corresponding to an interval of time (start, stop) during which all covariates remain constant. If the interval does not end in an event, code it as censored. This data will contain one record per subject for patients with no transplant and two records per subject for patients with transplant with cause of death the MRD level, timing of SCR or MRD timing to be kept as constant across the multiple records.

Please note variable names should be the consistent for all datasets in different submissions for the same study so that sets can be combined or sorted as needed. It is confusing if the same variable has different names in the same dataset with different submission. For example, variable name for transplantation type in ADSL dataset submitted on 3/30/2016 was coded as SCTTYPE, however, the transplantation type in ADSL dataset submitted on 5/16/2016 was coded as TRANTYP.

Please submit a response to me promptly via email by **COB on Friday, July 29, 2016** followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products

Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993
Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
07/27/2016

From:	McMullen, Rachel
To:	"Russell, Alison"
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin _Stats Information Request (RESPONSE DUE: Friday, July 29, 2016)
Date:	Monday, July 25, 2016 5:15:02 PM
Importance:	High

Good evening Alison,

In reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following information request from the review team.

Statistical Information Request:

Please submit time-to-event data for OS (one record per subject) including the following variables :

- cause of death;
- time to death or censoring;
- time from randomization to SCT;
- time from the first CR to SCT;
- the most current MRD level prior to transplant ;
- MRD status (negative or positive)
- time from randomization to the corresponding MRD assessment prior to transplant ;
- time from first CR to the corresponding MRD assessment.
- demographics, baseline status, and other important prognostic variables

Please also convert the above mentioned time-to-event (OS/PFS) data with time-varying-covariate (Stem Cell Transplantation) using counting process format (i.e. [start, stop) as shown in the SAS PROC PHREG manual). The counting process method has multiple records for each patient ; with each record corresponding to an interval of time (start, stop) during which all covariates remain constant. If the interval does not end in an event, code it as censored. This data will contain one record per subject for patients with no transplant and two records per subject for patients with transplant with cause of death the MRD level, timing of SCR or MRD timing to be kept as constant across the multiple records.

Please note variable names should be the consistent for all datasets in different submissions for the same study so that sets can be combined or sorted as needed. It is confusing if the same variable has different names in the same dataset with different submission. For example, variable name for transplantation type in ADSL dataset submitted on 3/30/2016 was coded as SCTTYPE, however, the transplantation type in ADSL dataset submitted on 5/16/2016 was coded as TRANTYP.

Please submit a response to me promptly via email by **COB on Friday, July 29, 2016** followed by an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993
Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
07/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

GENERAL ADVICE

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:
Please refer to your original Biologics License Application received January 21, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

The Agency will not conduct an inspection of the Pearl River site that was planned for July 18-22, 2016. A future communication will be sent regarding the Agency's plan for an inspection of the Pearl River site.

If you have any questions, contact me.

Sincerely,

Andrew Shiber -S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=0014262141
Date: 2016.07.05 14:27:37 -04'00'

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received January 21, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by June 24, 2016 in order to continue our evaluation of your application.

Based on the teleconference held on May 26, 2016 between Pfizer and OHOP, the final component of the inotuzumab ozogamicin BLA will be submitted in December 2016. In addition, Pfizer indicated that the gemtuzumab ozogamicin BLA will be submitted in October 2016. The Agency is exploring the feasibility of coordinating the pre-approval inspections for inotuzumab ozogamicin and gemtuzumab ozogamicin. Therefore, provide a side-by-side comparison of the drug substance and drug product manufacturing processes for both inotuzumab ozogamicin and gemtuzumab ozogamicin. Furthermore, provide the planned manufacturing schedule for the gemtuzumab ozogamicin drug substance and drug product at the Pearl River, NY site.

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

Sincerely,

Melinda J. Bauerlien -S

Digitally signed by Melinda J. Bauerlien -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300178565, cn=Melinda J. Bauerlien -S
Date: 2016.06.16 12:27:46 -04'00'

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

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 26, 2016

Application Number: BLA 761040
Product Name: Inotuzumab Ozogamicin
Sponsor/Applicant Name: Pfizer

Subject: Discuss Applicant's Revised Rolling Review Schedule

FDA Participants:
Ann Farrell, MD, Division Director
Albert Deisseroth, MD, PhD, Clinical Team Lead
Angelo de Claro, MD, Clinical Team Lead
Tanya Wroblewski, MD, Clinical Reviewer
Joslyn Brunelle, PhD, Product Quality Team Lead
Michelle Dougherty, PhD, Branch Chief
Yuan Li Shen, PhD, Biostatistics Team Lead
Qing Xu, PhD, Biostatistics Reviewer
Rachel McMullen, MPH, MHA, Regulatory Project Manager

Sponsor/Applicant Participants :
Joseph Boni, PhD, Clinical Pharmacology Lead
Leena Das-Young, PharmD, Late Phase Development Head; Oncology
Ramzi Dagher, MD, Oncology Regulatory Head
Svetoslav Dimitrov, MD, Safety Risk Lead
Caroline Henesey, PhD, Hematology Global Regulatory Portfolio Lead
Rebecca Hintze, Data Programming Lead
Jane Liang, PhD, Statistical Lead
Mace Rothenberg, MD, Head, Global Product Development, Oncology
Cindy Ru, PhD, Asset Team Lead
Alison Russell, PhD, Global Regulatory Lead
Paul Wissel, MD, Clinical
Erik Vandendries, MD PhD, Global Clinical Lead

1.0 BACKGROUND:

This teleconference is in reference to Pfizer's new BLA 761040, for Inotuzumab Ozogamicin. The application is under a rolling review and the 2nd wave submission was received on March 30, 2016.

This application has breakthrough status and qualifies for a priority review. However, the FDA review team noted at the Application Orientation Meeting that the BLA appears to be missing critical and significant data. Towards this end, the FDA team had a previous teleconference with Pfizer on May 11, 2015 to identify missing data components and timelines for submission of

these items. An information request listing the missing data items (Stats, Clinical pharmacology, Pharmacology toxicology, and Product Quality) and timelines for submission was sent to Pfizer on May 10, 2016.

2.0 DISCUSSION:

This teleconference is in follow up to the Sponsor's revised rolling review schedule which was provided by Pfizer on May 18, 2016.

The Agency stated that the revised rolling submission plan proposed by the Applicant is acceptable (roll3: November 2016 and roll4: December 2016). The Agency discussed timelines of submission of the 120-day safety update. The Sponsor agreed with the Agency's recommendation to submit the 120-day safety update end of February 2017, with a data cutoff date of end November 2016.

The Agency recommended that the BLA submission include revised versions of the SCE, SCS, and SCP.

The Agency agreed that the BLA will not include the clinical study report or data for the MD Anderson trial.

The Agency noted that we continue to receive multiple SPI requests each week for the drug and asked the Applicant for their plans for an expanded access program. Pfizer noted that they had not explored this in further detail. The Agency noted that having an intermediate or expanded access program is beneficial for identifying the patient populations and evaluating safety in the future.

The Agency noted that death narratives for patients who undergo transplantation should include information from time of transplantation to death, not just the 30 day period immediately prior to death. Additional details to include regarding transplantation would be details on conditioning regimen (reduced intensity vs myeloablative), details on the graft (marrow/peripheral blood, HLA-matching), comorbidities, VOD, and GVHD.

3.0 ACTION ITEMS:

The Agency will provide a written response to the Sponsor regarding the revised rolling review submission plan.

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/s/

RACHEL S MCMULLEN
05/26/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761040

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
10646 Science Center Drive
San Diego, CA 92121

ATTENTION: Alison Russell, PhD
Director, Worldwide Safety and Regulatory

Dear Dr. Russell:

Please refer to your Biologics License Application (BLA) dated and received March 30, 2016, submitted under section 351(a) of the Public Health Service Act for Inotuzumab Ozogamicin, (b) (4) mg per vial.

We also refer to your correspondence, dated and received March 30, 2016, requesting review of your proposed proprietary name, Besponsa.

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

If any of the proposed product characteristics as stated in your March 30, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Rachel McMullen, Regulatory Project Manager in the Office of New Drugs at (240) 402-4574.

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
05/17/2016

From:	McMullen, Rachel
To:	"Russell, Alison"
Cc:	McMullen, Rachel
Subject:	RE: BLA 761040 (inotuzumab ozogmicin)/clarification regarding submission plan items _ FDA Statistical Comments
Date:	Friday, May 13, 2016 2:09:15 PM
Attachments:	image001.png
Importance:	High

Good afternoon Alison,

In reference to Pfizer's request for clarification, please note the following additional comments provided by the team.

Statistical Comments:

Your proposed competing risk analysis methods appear to be acceptable. However, due to interpretation difficulties of the results based on competing risk analysis, we have the following additional requests:

1. The analysis results described in Haesook Kim, et. al. and/or James Dignam, et. al. (see below) using both regular KM (censoring competing event; with log rank test) and competing risk approach to calculate the cumulative incidence of an event of interest in the presence of competing risk should be provided. Both results should be compared and explained.
2. A competing risk analysis incorporating potential prognostic variables (e.g. disease status, age) as described in Fine and Gary (see below), should also be performed. The interpretation of the results should consider the issues described in Haesook, et. al, Boris Freidlin, et. al. or James Dignam, et. al (shown below]) (i.e. about differential impact on each competing event based on a potential prognostic factor).
3. Provide the SAS codes and derived datasets that are used to perform these analyses.

References:

- *James J. Dignam,Qiang Zhang, and Maria N. Kocherginsky, The Use and Interpretion of Competing Risks Regression Models, Clin Cancer Res. 2012 April 15; 18(8): 2301–2308*
- *Boris Freidlin and Edward L. Korn, Testing treatment effects in the presence of competing risks, Statist. Med. 2005; 24:1703–1712*
- *Haesook Kim, Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis, Clinical Cancer Research, Clin Cancer Res 2007;13:559-565*
- *Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509*

Please *confirm* receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: McMullen, Rachel
Sent: Friday, May 13, 2016 10:57 AM
To: 'Russell, Alison'
Cc: McMullen, Rachel
Subject: RE: BLA 761040 (inotuzumab ozogmicin)/clarification regarding submission plan items _ FDA Response
Importance: High

Good morning Alison,

In response to your email below, requesting clarification of the items requested by the team, please note the following responses:

1. Your plan for submission of the efficacy narratives as well as your proposed approach to collect any additional details pertaining to the deaths of subjects in your trial appears reasonable. Be sure to include in prose description narratives of the events at time or around the time of death and events preceding death that may have contributed to the patient's death**.**
2. With regard to the competing risk analyses for OS, the primary event of interest is death due to leukemia (relapse or progression) and the competing risk is death due to other causes than relapse or progression. Conduct competing risk analyses for the ITT population and the subgroup of patients who proceeded to allogeneic hematopoietic stem cell transplantation.
3. The Division recommends that you submit narratives for all cases of hepatic veno-occlusive disease across the entire inotuzumab ozogamicin development program(Study B1931010, MDACC study, and from all nine of the Non-Hodgkin Lymphoma Studies).

Please *confirm* receipt of this correspondence.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Friday, May 13, 2016 10:11 AM

To: McMullen, Rachel
Subject: RE: BLA 761040 (inotuzumab ozogmicin)/clarification regarding submission plan items

Rachel
Thanks so much for your kind support
Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Thursday, May 12, 2016 3:45 PM
To: Russell, Alison
Subject: RE: BLA 761040 (inotuzumab ozogmicin)/clarification regarding submission plan items

Hi Alison,

Thank you for the email. I have shared it with our team and will follow up as soon as I have a response.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Thursday, May 12, 2016 3:04 PM
To: McMullen, Rachel
Subject: BLA 761040 (inotuzumab ozogmicin)/clarification regarding submission plan items

Rachel

With reference to the document provided from FDA regarding the 'essential items' for BLA 761040 (BLA 761040_IR_Submission Plan_DHP_May 10.doc), Pfizer would like clarification regarding the items below. With reference to the email from FDA dated May 11, requesting that Pfizer submit the revised schedule for rolling review by 1 pm EDT May 18, is it possible for the FDA review team to provide a response to the items below, and in particular Item #1, to Pfizer by Friday May 13 COB.

Alison

1. **Regarding: Narratives for all deaths in the inotuzumab arm and the investigator choice arm. The narratives should be detailed and include cause of death as listed on death certificate, autopsy reports or any other pertinent details and provide prose description of (a) events at time or around the time of death, and (b) events preceding death that may have contributed to the patient's death.**

Pfizer will provide efficacy narratives. The efficacy narratives will contain all the available efficacy information, as well as the data surrounding the patient deaths that are available in the safety and clinical databases. In addition, we will attempt to obtain as much information as we can from clinical sites. With respect to the death information, we currently have the causes of death for all patients as reported by the Investigator. This may include multiple causes if a patient had multiple contributing factors to the death (such disease progression, infection, liver toxicity, etc.). We have also captured whether this information is from an autopsy and/or death certificate (we don't have the actual death certificates). For fatal SAEs, which includes all fatal hepatic events, we have additional information included in SAE narratives. We have hepatic biopsy reports for all patients with serious hepatic toxicity. We will also attempt to provide all autopsy reports from the sites (currently, 8 patients are known to have autopsies). All patients who died during the study reporting period or with VOD will have SAE reports. Beyond the reporting period, patient who died may not have SAE reports, especially if the cause of death is disease progression. If the disease progression occurred without other complications, the only information we will have is 'disease progression'. For a patient died of disease progression with other complications, we will have the other complications listed. Is this acceptable?

2. **Regarding: Include a competing risk analyses (relapse, death due to other causes than relapse or progression) for all patients who achieve a CR/CRi.**

Questions:

- Since you recommend to conduct this competing risk analysis for OS, does "relapse" mean "death due to relapse"?
- If so, is "death due to relapse" the event of interest and "death due to other causes than relapse or progression" the competing risk?

The methods for the competing risk analyses for OS we propose to use are from the following literature references:

1. Gray, R. (1988), A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. The Annals of Statistics, 16, 1141–1154.
2. Gooley, TA; Leisenring, W; Crowley, J; Storer, BE, "Estimation of failure probabilities in the presence of competing risks: new representations of old estimators" Statistics in Medicine 1999 pp. 695-706
3. Lin, G., So, Y., and Johnston, G. (2012), “Analyzing Survival Data with Competing Risks Using SAS Software,” in Proceedings of the SAS Global Forum 2012 Conference.

Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

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/s/

RACHEL S MCMULLEN
05/13/2016

From: McMullen, Rachel
To: "Russell, Alison"
Cc: McMullen, Rachel
Subject: RE: BLA 761040 (inotuzumab ozogmicin)/clarification regarding submission plan items _ FDA Response
Date: Friday, May 13, 2016 10:57:18 AM
Attachments: image001.png
Importance: High

Good morning Alison,

In response to your email below, requesting clarification of the items requested by the team, please note the following responses:

1. Your plan for submission of the efficacy narratives as well as your proposed approach to collect any additional details pertaining to the deaths of subjects in your trial appears reasonable. Be sure to include in prose description narratives of the events at time or around the time of death and events preceding death that may have contributed to the patient's death**.**
2. With regard to the competing risk analyses for OS, the primary event of interest is death due to leukemia (relapse or progression) and the competing risk is death due to other causes than relapse or progression. Conduct competing risk analyses for the ITT population and the subgroup of patients who proceeded to allogeneic hematopoietic stem cell transplantation.
3. The Division recommends that you submit narratives for all cases of hepatic veno-occlusive disease across the entire inotuzumab ozogamicin development program(Study B1931010, MDACC study, and from all nine of the Non-Hodgkin Lymphoma Studies).

Please *confirm* receipt of this correspondence.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Friday, May 13, 2016 10:11 AM
To: McMullen, Rachel
Subject: RE: BLA 761040 (inotuzumab ozogmicin)/clarification regarding submission plan items

Rachel
Thanks so much for your kind support
Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Thursday, May 12, 2016 3:45 PM
To: Russell, Alison
Subject: RE: BLA 761040 (inotuzumab ozogmicin)/clarification regarding submission plan items

Hi Alison,

Thank you for the email. I have shared it with our team and will follow up as soon as I have a response.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Thursday, May 12, 2016 3:04 PM
To: McMullen, Rachel
Subject: BLA 761040 (inotuzumab ozogmicin)/clarification regarding submission plan items

Rachel

With reference to the document provided from FDA regarding the 'essential items' for BLA 761040 (BLA 761040_IR_Submission Plan_DHP_May 10.doc), Pfizer would like clarification regarding the items below. With reference to the email from FDA dated May 11, requesting that Pfizer submit the revised schedule for rolling review by 1 pm EDT May 18, is it possible for the FDA review team to provide a response to the items below, and in particular Item

#1, to Pfizer by Friday May 13 COB.

Alison

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2. **Regarding: Include a competing risk analyses (relapse, death due to other causes than relapse or progression) for all patients who achieve a CR/CRi.**

Questions:

- Since you recommend to conduct this competing risk analysis for OS, does "relapse" mean "death due to relapse"?
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2. Gooley, TA; Leisenring, W; Crowley, J; Storer, BE, "Estimation of failure probabilities

in the presence of competing risks: new representations of old estimators" Statistics in Medicine 1999 pp. 695-706

3. Lin, G., So, Y., and Johnston, G. (2012), “Analyzing Survival Data with Competing Risks Using SAS Software,” in Proceedings of the SAS Global Forum 2012 Conference.

Alison

Alison Russell, PhD
Director, Global Regulatory Strategy
Pfizer Inc,
10646 Science Center Drive,
San Diego, CA 92121.
Phone (858) 344 4473
Email alison.russell@pfizer.com

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/s/

RACHEL S MCMULLEN
05/13/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 11, 2016

Application Number: BLA 761040
Product Name: Inotuzumab Ozogamicin
Sponsor/Applicant Name: Pfizer

Subject: Discuss Plan for Outstanding Data Components

FDA Participants:
Angelo de Claro, MD, Clinical Team Lead
Tanya Wroblewski, MD, Clinical Reviewer
Joslyn Brunelle, PhD, Product Quality Team Lead
Bahru Habtemariam, Pharm D, Clinical Pharmacology Team Lead
Salaheldin Hamed, PhD, Clinical Pharmacology Reviewer
Yuan Li Shen, PhD, Biostatistics Team Lead
Qing Xu, PhD, Biostatistics Reviewer
Rachel McMullen, MPH, MHA, Regulatory Project Manager

Sponsor/Applicant Participants :
Rebecca Hintze
Cindy (Qinhua) Ru
Erik Vandendries
Jane Liang White
Caroline Henesey
Barbara Sleight
Douglas Laird
Ramzi Dagher
Mace Rothenberg
Leena Das-Young
Svetoslav Dimitrov
Alison Russell

1.0 BACKGROUND:

This teleconference is in reference to Pfizer's new BLA 761040, for Inotuzumab Ozogamicin and is in follow up to the Application Orientation Meeting held on May 9, 2016. The application is under a rolling review and the 2nd wave submission was received on March 30, 2016.

2.0 DISCUSSION:

The application has breakthrough status and qualifies for a priority review. However, upon initial review, it appears that the application is missing critical and significant data. The FDA review

team noted this at the Application Orientation Meeting and the team discussed the timelines of submission of additional clinical data and analyses with Pfizer in this follow up teleconference.

The Agency noted that there are components of sections for Stats, Clinical pharmacology, Pharmacology toxicology, and Product Quality which are as yet incomplete. A list of these missing data items, and timelines for submission was sent as an information request to Pfizer on May 10, 2016.

The Clinical team recommended that the sponsor submit the updated datasets by May 16, 2016, updated CSR and safety/efficacy narratives by mid-June, and updated labeling/clinical overview/SCE/SCS/ISE/ISS by mid-July. The Agency emphasized that Pfizer obtain MD Anderson data for inclusion in the submission (PK data) and that this is a required component of the BLA review.

Since this data will constitute re-writing major portions of the application, it would impact the review timelines and as such it would not be prudent for the Agency to undertake the review without having a complete application.

As such the Agency notified the Sponsor that the Agency will re-issue the rolling review agreement and the components discussed will constitute the applicant's final submission.

The Agency will issue an amended acknowledgment letter.

3.0 ACTION ITEMS:

1. Pfizer agreed to submit datasets (all SDTM, and subset of ADAM: ADSL, ADEX, ADTTE, ADAE) on Monday, May 16th.

2. Pfizer will provide a list of data components and proposed submission timelines to the Agency for review and commitment by May 18th.

3. Pfizer should obtain MD Anderson data for inclusion in the submission (including PK data) _required component.

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/s/

RACHEL S MCMULLEN
05/11/2016

From:	McMullen, Rachel
To:	"Russell, Alison"
Cc:	McMullen, Rachel; Shiber, Andrew J
Subject:	BLA 761040/ Inotuzumab Ozogamicin _ Product Quality INFORMATION REQUEST (Due: May 18, 2016)
Date:	Tuesday, May 10, 2016 6:00:34 PM

Good evening Alison,

In reference to BLA 761040 for Inotuzumab Ozogamicin, please note the following information request for product quality.

Product Quality Information Request
Due Date: May 18, 2016

1. Provide the study reports for preparation and testing of Master Cell Bank, Working Cell Bank, and End of Production cell testing, including study reports for all viral and adventitious agent testing.

2. Provide the following information for the (b) (4), Inotuzumab Ozogamicin Drug Substance, and/or Inotuzumab Ozogamicin Drug Product. Note that study reports can be submitted under Section 3.2.R Regional Information:
   a. All Process Validation reports
   b. (b) (4)
   c. Validation reports for all analytical methods
   d. Protocols for (b) (4)
   e. Study Reports to support (b) (4)
   f. Protocols for the (b) (4)
   g. Shipping validation reports
   h. Study Reports and risk assessment on extractables and/or leachables from all container closure systems

3. For Drug Product, provide extractable volume data to support the end-user can withdraw the labeled amount of reconstituted solution (b) (4) mL (b) (4) mg).

Please submit a response to me promptly via email by **5pm EDT on May 18, 2016** and also follow up with an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
05/10/2016

From:	McMullen, Rachel
To:	"Russell, Alison"
Cc:	McMullen, Rachel
Subject:	BLA 761040/ Inotuzumab Ozogamicin _ CLINICAL & STATS INFORMATION REQUEST
Date:	Tuesday, May 10, 2016 2:10:57 PM
Attachments:	BLA 761040_IR_Submission Plan_DHP_May_10.doc
Importance:	High

Good afternoon Alison,

In reference to BLA 761040 for Inotuzumab Ozogamicin, please refer to the attached information request for clinical and statistical items. Please submit a response to me promptly via email by the due dates noted in the attached document and also follow up with an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

BLA 761040 Inotuzumab Ozogamicin
DHP Clinical Recommendations for Sponsor Submission of Additional Data, Narratives, and Reports

Due Date: May 13, 2016

Submit updated datasets for all 326 patients with data cutoff of 8 March 2016. Include SDTM datasets, ADAM datasets, and SAS codes used to generate ADAM datasets.

Due Date: June 15, 2016:

Submit an updated CSR for Study B1931022 with data cutoff of 8 March 2016. The CSR should contain the following:

Efficacy

a. Explain why the treatment effect on complete remissions and achievement of MRD-negative status did not translate into a similar magnitude of effect on overall survival for patients who received inotuzumab ozogamicin. Include analyses of published literature to support your rationale.

b. Include PFS analysis based on standard definition of PFS(death and progressive death)

c. Include a competing risk analyses (relapse, death due to other causes than relapse or progression) for all patients who achieve a CR/CRi.

d. Include subgroup analyses for overall survival endpoint

e. For the patients in both arms who proceed to transplantation, submit data that includes the type of transplantation, conditioning regimen, GVHD prophylaxis, donor (related, unrelated), and outcomes following transplantation (including deaths, GVHD, and hepatic VOD)

f. Provide for both arms, the number of patients who died due to relapse or progression of original disease or experience death from other causes [Non-relapse mortality (NRM)/ transplant related mortality (TRM)]. Provide cumulative incidence curves/calculations for each competing risk (e.g. relapse, non-relapse mortality) for the patients who proceeded to transplantation. For deaths due to other causes than progression, provide causes for death (e.g. VOD, GVHD, infections, etc.)

g. Include rationale on the proposed cut-off for MRD assessments of 0.01% or 1×10^{-4}; use literature to support your rationale.

h. Narratives for all deaths in the inotuzumab arm and the investigator choice arm. The narratives should be detailed and include cause of death as listed on death certificate,

autopsy reports or any other pertinent details and provide prose description of (a) events at time or around the time of death, and (b) events preceding death that may have contributed to the patient's death.

Safety

i. Updated safety information for all 326 patients with data cut-off of 8 March 2016

j. Include detailed analysis for the patients who developed hepatic VOD that includes the following:

(1) Exposure to inotuzumab ozogamicin (include total dose, number of cycles)

(2) Interval between last dose of inotuzumab ozogamicin and diagnosis of VOD

(3) Treatment received for hepatic VOD and outcomes (death, resolution, etc.)

k. Narratives for all the patients who developed hepatic VOD (any grade) that includes a description of preparative regimen(for patients that proceeded to HSCT), description of the hepatic VOD diagnosis, day of diagnosis[related to study day and transplantation day (if applicable], include laboratory values(total bilirubin, hepatic ultrasounds if available, biopsies if performed), treatment received and description of outcome.

l. Safety narratives for the following treatment-emergent adverse events regardless of attribution: serious adverse events (SAE), discontinuations due to adverse events, deaths. If leukemia progression or persistence are the adverse events coded as the reason for the SAE, discontinuation, or death, describe the documentation for leukemia progression or persistence.

Due Date: July 15, 2016

1. Updated summary documents: clinical overview, ISS and ISE, SCE and SCS based on a data cutoff date of 8 March 2016

2. Exposure-response and dose-response analyses for efficacy and safety based on a data cutoff date of 8 March 2016

3. Updated labeling based on 8 Mar 2016 data cutoff date for Study B1931022

STATISTICAL INFORMATION REQUEST

Due Date: June 15, 2016

1. Resubmit Clinical Study Report (CSR) for Study B1931022, because all the hyperlinks for this report do not work.

2. Please provide the definition of the truncation time for the Restrict Mean Survival Time (RMST) calculation, including the justification of the truncation time selection. Please also submit the analysis program for the RMST calculation.

3. Please provide the analysis of censoring distribution for OS, including the reason of the censoring.

4. For the primary efficacy analysis CR/CRi, please provide the reasons for the patients not being assessed for the primary efficacy analysis.

5. For the interim analysis, please clarify which method you used for the alpha spending. We can't find this information in your protocol and SAP.

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/s/

RACHEL S MCMULLEN
05/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received January 21, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB: **May 12, 2016.**

1. Regarding ***Section 3.2.P.2.6***, *Compatibility*:

   Provide summary data from the microbial challenge study conducted to support product in-use storage time after reconstitution (1) and dilution (2). This information should be submitted to Section 3.2.P.2.6, Compatibility. (b) (4) (b) (4) a bracketing approach should be used in the microbial challenge studies. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, and use the label-recommended diluent. Periodic intermediate sample times are recommended. The inoculum size should be measurable and repeatable. Please refer to the following publication: John Metcalfe, Microbiological Quality of Drug Products after Penetration of the Container System for Dose Preparation Prior to Patient Administration, American Pharmaceutical Review, February 01, 2009.

2. (b) (4)

3. Some of the information related to microbial control and [redacted] provided in ***Section 3.2.P.3.5*** should also be provided in ***Section 3.2.P.3.3*** and/or ***3.2.P.3.4*** of the submission. Please update the appropriate sections with the following missing information:

- [redacted]

4. Regarding ***Section 3.2.P.3.5***, *Validation of* [redacted]:

- [redacted]

5. Regarding ***Section 3.2.P.3.5***, Media Fills, please provide the following additional information regarding the Media Fill runs:

- The [redacted], fill line, and the type of filling equipment.
- The media fill volume.
- The total time for each media fill.

- (b) (4)

6. **Regarding *Section 3.2.P.5.2,* *Analytical Procedures***, please include the following information:

- (b) (4)

7. Provide summary data from the qualification of the bioburden, sterility, and endotoxin test methods performed for (b) (4) and with three representative DP lots to ***Section 3.2.P.5.3***, *Validation of Analytical Procedures*. For the endotoxin test method qualification, please provide summary data on the recovery of the endotoxin with different DP dilutions tested within MVD. Provide summary data from Low endotoxin recovery (LER) studies including justification of the maximum hold time of (b) (4) hours.

8. Please provide the protocol report and summary data for the Rabbit Pyrogen Test for three DP lots tested, including: the justification for the administered dose based on the maximum dose of DP per day per kg of body weight of a human and the data on the temperature rise in rabbits compare to temperature baseline.

9. Provide summary data on the Container Closure Integrity Testing (CCIT) method qualification in ***Section 3.2.P.5.3***, Validation of Analytical Procedures and a detailed CCIT method description in ***Section 3.2.P.5.2*** of the BLA.

10. The allowed commercial dose of the diluted DP stated in a Label is 0.5 - 0.8mg/m^2/1 hour. Please provide a justification for the endotoxin release specification of the drug product (b) (4) (b) (4) (b) (4) We recommend a 2-fold safety margin to be implemented in the release specification.

If you have any questions, please contact me at 301-796-4798.

Sincerely,

Andrew Shiber -S

Digitally signed by Andrew Shiber -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -S, 0.9.2342.19200300.100.1.1=0014262141
Date: 2016.06.05 12:03:24 -04'00'

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

PROPRIETARY NAME ACKNOWLEDGEMENT

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
10646 Science Center Drive
San Diego, CA 92121

ATTENTION: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory

Dear Dr. Russell:

Please refer to your Biologics License Application (BLA) dated and received March 30, 2016, submitted under section 351(a) of the Public Health Service Act, for Inotuzumab Ozogamicin, (b) (4) mg per vial.

We acknowledge receipt of your correspondence, dated and received March 30, 2016, requesting a review of your proposed proprietary name, Besponsa.

If the application is filed, the user fee goal date will be June 28, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Rachel McMullen, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Kevin Wright, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KEVIN WRIGHT
04/25/2016

BLA 761040 **INFORMATION REQUEST**

Pfizer, Inc.
Attention: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your original Biologics License Application received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for Besponsa (inotuzumab ozogamicin)

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your supplement. Please submit your response prior to COB April 29, 2016.

1) (b) (4)

2) Your submission states that the Wyeth Pharmaceutical facility (FEI 2410662) proposed for inotuzumab ozogamicin drug substance and drug product manufacture supports production of (b) (4) Please submit your risk assessment for cross contamination mitigation for highly toxic or potent products.

If you have any questions, please contact me.

Sincerely,

Andrew Shiber -A

Digitally signed by Andrew Shiber -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -A, 0.9.2342.19200300.100.1.1=4001426214
Date: 2016.04.18 11:53:52 -04'00'

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA761040

BLA ACKNOWLEDGMENT

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Attention: Alison Russell, PhD
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

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: Inotuzumab Ozogamicin (PF-05208773; CMC-544); Lyophilized (b) (4) powder (b) (4) mg/vial.

Date of Application: March 30, 2016

Date of Receipt: January 21, 2016

Our Reference Number: BLA 761040

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 May 29, 2016, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Rachel McMullen, MPH, MHA
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

RACHEL S MCMULLEN
04/06/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

INFORMATION REQUEST

Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application 761040 received January 21, 2016, submitted under section 351(a) of the Public Health Service Act for inotuzumab ozogamicin.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your responses to questions 1 to 6 prior to COB: Friday, March 25, 2016 and the response to question 7 as soon as possible.

Module 3.2.P of the BLA is incomplete because critical product quality microbiology information was not provided. Module 1.4 of the BLA is incomplete because some of the required Drug Master File Letters of Authorization were not provided. Please provide the following missing information which is required for review of drug product quality.

1. Provide the Drug Master File (DMF) Letter(s) of Authorization (LOA) referencing depyrogenation and sterilization data for the (b) (4) stoppers. The LOA should reference a CDER DMF, should clearly identify the relevant stopper, should list all of the applicable depyrogenation and sterilization sites, and should clearly identify the location of the information in the DMF.

2. Sterilization and depyrogenation validation data (b) (4) Provide the following information and validation data summaries in Section 3.2.P.3.5 of the BLA.

    a. (b) (4)

i. (b) (4)

ii.

iii.

b. (b) (4)

i. (b) (4)

ii.

iii.

iv.

v. If the information requested in (2.b) is located in DMFs, provide the relevant LOAs in Module 1.4 of the BLA. The LOAs should reference CDER DMFs.

c. (b) (4), provide validation data analogous to that requested for (b) (4) in section 3.2.P.3.5 of the BLA.

3. (b) (4) sterilization validation data was not provided. In section 3.2.P.3.5 of the BLA, provide summary data for the three most recent

(b) (4)

4 (b) (4)

5. Vial depyrogenation data was not provided. Provide the following information in section 3.2.P.3.5:

   a. The depyrogenation (b) (4) used for routine manufacturing of the drug product.

   b. (b) (4)

   c. (b) (4)

6. Some of the information provided in the Appendix (3.2.A) should be provided in Module 3.2.P instead. Please make the following changes:

   a. Move "Environmental Monitoring of Media Simulation Validation Runs" from the Appendix to Section 3.2.P.3.5 of the BLA.

   b. Move "Environmental Qualification and Monitoring" from the Appendix to Section 3.2.P.3.3 of the BLA and add the environmental monitoring limits.

7. To facilitate pre-license inspection planning of the manufacturing facilities, please confirm the scheduled manufacturing dates for (b) (4) inotuzumab ozogamicin drug substance. (b) (4) In addition, provide the schedule for the drug

(b) (4)

If you have any questions, please contact me at 301-796-4798.

Sincerely,

{See appended electronic signature page}

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

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/s/

ANDREW J SHIBER
03/18/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 065658

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Attention: Alison L. Russell, PhD
Director, Worldwide Safety and Regulatory, WR&D
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for inotuzumab ozogamicin; CMC-544; WAY 207294.

We also refer to your August 18, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that inotuzumab ozogamicin; (CMC-544; WAY 207294) for Acute Lymphoblastic Leukemia (ALL) 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 inotuzumab ozogamicin; (CMC-544; WAY 207294) for Acute Lymphoblastic Leukemia (ALL) to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[1]

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics,* Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting[2]. Please refer to the *Guidance for Industry: Formal Meetings*

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf
[2]http://www fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default htm.

between FDA or Sponsors and Applicants[3] for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for inotuzumab ozogamicin; (CMC-544; WAY 207294) for Acute Lymphoblastic Leukemia (ALL) is rescinded, submission of portions of the BLA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Rachel McMullen, Regulatory Project Manager, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

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

[3] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

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/s/

ANN T FARRELL
10/15/2015

CDER Breakthrough Therapy Designation Determination Review

IND/NDA/BLA #	IND 65658
Request Receipt Date	August 18, 2015
Product	Inotuzumab Ozogamicin
Indication	Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia(ALL)
Drug Class/Mechanism of Action	Antibody-drug conjugate(ADC) of humanized anti-CD22 antibody covalently bound to semi-synthetic derivative of calicheamicin
Sponsor	Wyeth Pharmaceuticals Inc. A, Subsidiary of Pfizer Inc.
ODE/Division	CDER/OHOP/DHP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	October 17, 2015

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). ***Note:*** *Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):** Inotuzumab ozogamicin is indicated for the treatment of relapsed or refractory B-Cell acute lymphoblastic leukemia (ALL).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Brief Description of the Drug

Inotuzumab ozogamicin is an antibody-drug conjugate(ADC) comprised of humanized anti-CD22 antibody covalently bound to N-acetyl-gamma calicheamicin dimethylhydrazide, a semi-synthetic derivate of calicheamicin. CD22 is expressed on normal mature B cells and malignant cells to include B-cell ALL. Inotuzumab ozogamicin binds to CD22 receptors at the cell surface of malignant cells and is internalized to the lysosomal compartment where the cytotoxic payload, N-acetyl-gamma calicheamicin dimethylhydrazide is related into the lysosome. The cytotoxin intercalates in DNA leading to double-strand DNA break formation leading to apoptosis and cell death.

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[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Brief Description of the disease and intended population

Acute Lymphoblastic Leukemia(ALL) is a disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs leading to abnormal hematopoiesis, organ failure and death if untreated. Relapsed or refractory ALL is a life-threatening condition. CD22 expression has been observed in up to 100% of subjects studied with relapsed or refractory ALL(Shah et al, 2015), thus making CD22 an attractive target.

Relapsed or refractory B-cell ALL is often a fatal disease with a median survival time in adults of approximately 3-6 months(O'Brien S. et al, 2008, Thomas DA et al, 1999). Five year OS is approximately 33% with HSCT in second CR, 8% with HSCT for patients without a CR and 4% with chemotherapy alone.

The goal of treatment of relapsed or refractory ALL is to induce complete remission(CR) and proceed to allogeneic hematopoietic stem cell transplantation(HSCT). Factors that affect achievement of CR include age, time to first relapse and number of prior relapses.

Factors associated with survival after relapse of ALL include age, time to first relapse, reinduction response(CR vs no response) and treatment with allogenic HSCT. Given the relatively low CR rates overall, long-term outcome is poor for patients with ALL who relapse, especially for those relapse less than 1-2 years from the first CR.

7. Information related to endpoints used in the available clinical data:

a. Endpoints considered by the Sponsor as supporting breakthrough therapy designation:

- CR and CRi(CR with incomplete blood count recovery, platelets ≤100,000/mcl and/or neutrophils ≤ 1000/mcl.
- Duration of Response(DoR), Duration of CR and MRD

b. Endpoint accepted by the Division as a clinically significant endpoint(outcome measure) for patients with the disease:

- Durable CR
- Overall survival(in a controlled trial)

c. Any other biomarkers the division would consider likely to predict a clinical benefit even if not yet a basis for accelerated approval.

Minimal Residual Disease(MRD)- The FDA held a workshop on MRD in ALL in 2012 and it was discussed that the presence of MRD at the end of primary induction or intensification was associated with a significant increase in relapse for both children and adults with ALL. MRD positivity after reinduction has negative prognostic significance even for patients who go on to HSCT.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- FDA-approved drugs for the treatment of ALL include doxorubicin, daunorubicin, vincristine, asparaginase, and cytarabine with approvals for treatment in general or for induction specifically and cyclophosphamide, methotrexate and 6-mercaptopurine for maintenance in remission. In practice, none of these agents are used as s ingle agent for reinduction of relapsed or refractory ALL.
- Marqibo(vincristine sulfate liposome injection) received accelerated approval in 2012 for the treatment of adult patients with Ph-ALL in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. Approval was based on CR rate in a single-arm trial(CR 5%, CRi 11%, ORR 15% , and the median duration of CR was 56 days).
- Gleevec(Imatinib) received accelerated approval in 2006 based on CHR rate in a single arm trial in 4 patients with relapsed or refractory Ph+ ALL with CHR rate of 19% and mediation duration of CHR of 3.4 months.
- Sprycel(Dasatanib) received approval in 2006 based on single arm trial of 40 patients with relapsed or refractory Ph+ all with MHR rate of 38% and mediation duration of MHR of 4.6 months
- Iclusig(ponatinib) received accelerated approval for adult patients with Ph+ ALL for whom no other TKI therapy is indicated based on single arm trial with 32 adults with MHR of 41% with mediation duration of 3.2 months.
- Blincyto(blinatumomab) received accelerated approval in 2014 for the treatment of Ph- patients with relapsed or refractory B-cell precursor ALL. Approval was based on CR/CRi rate in single arm trial of 185 adults(CR 32%, CRh 9% OR 42%) and median duration was 5.9 months. The MRD negativity was 75% and the HSCT rate among those who achieved CR/CRh was 39%.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

- Blincyto(blinatumomab), a bispecific anti-CD3/CD19 monoclonal antibody was granted breakthrough therapy designation in 2014 for the indication " treatment of adult patients with Philadelphia-negative relapsed or refractory B-precursor acute lymphoblastic leukemia." The preliminary clinical evidence demonstrated a response rate of 38% which is more than expected for any single-agent therapy and the responses were fairly durable. The control of minimal residual disease demonstrated the depth of these responses.

- Blinatumomab received accelerated approval on December 3, 2014 for the indication stated above.

10. Information related to the preliminary clinical evidence:

Overview of clinical development program for relapsed or refractory B cell ALL in adults

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Overview of Clinical Development Plan for Inotuzumab Ozogamicin n Relapsed/Refractory ALL in adults

Study	Phase	Population	Endpoints
Study B1931022	Phase 3 trial	Adult patients with relapsed or refractory CD22-positive ALL due to receive Salvage 1 or	Primary:CR/CRi per Endpoint Adjudication

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

		2 therapies	Committee and Overall Survival
Study B1931010	Phase 1 /2 Study	Relapsed/Refractory CD22-positive B-cell ALL	P1 Primary: RP2D dose of weekly inotuzumab P2 Primary: CR/CRi

Phase 3 Study B1931022 is the main source of data to support the request. The study is a multicenter, global, open-label, randomized Phase 3 study in adult patients with relapsed or refractory CD22-positive B-cell ALL due to receive Salvage 1 or Salvage 2 therapy. Patients were randomized(1:1) to receive inotuzumab ozogamicin monotherapy or Investigator's choice of chemotherapy.

Randomization was stratified by 3 factors: duration of first remission(CR1D; < 12 months versus ≥ 12 months), line of salvage(Salvage 1 versus 2), and patient age at randomization(< 55 versus ≥ 55 years).

The primary endpoints were CR/CRi per the Endpoint Adjudication Committee(EAC) and overall survival(OS). The secondary endpoints included MRD, DoR, PFS, HSCT rate.

The primary endpoint of CR/CRi was to be evaluated on the first 218 patients randomized. As of the data cutoff date of 2 October 2014 used for assessment of the CR/Cri primary endpoint, a total of 279 patients were randomized. The ITT population included all 279 patients randomized as of the data cutoff date. The ITT218 population a subset of the IT population including the initial 218 patients randomized was pre-specified primary population for the final analysis of CR/CRi.

The dose schedule is as follows: inotzumab IV 0.8mg/m^2 for Cycle 1, Day 1, then Inotuzumab 0.5mg/m^2 on Cycle1 Day 5, then Inotuzumab 0.5mg/m^2 IV on Cycle 1, Day 15. Cycle 2 and cycles beyond C2 – Inotuzumab at a dose of 0.5mg/m^2 IV on Days 1, 8 and 15 of each cycle.

Overall, the key demographic and baseline characteristics were balanced between both study arms. Table 3 shows the demographic characteristics of the subjects evaluated.

Table 3. Phase 3 Study B1931022: Key Demographic and Baseline Characteristics – ITT and ITT218 Population

Characteristic	Inotuzumab Ozogamicin		Investigator's Choice of Chemotherapy[a]	
	ITT (N=141)	ITT218 (N=109)	ITT (N=138)	ITT218 (N=109)
Age (years)				
Median (range)	47.0 (18-78)	47.0 (18-78)	47.5 (18-79)	47.0 (18-79)
<55 years [n (%)]	87 (61.7)	66 (60.6)	87 (63.0)	69 (63.3)
≥55 years [n (%)]	54 (38.3)	43 (39.4)	51 (37.0)	40 (36.7)
Men [n(%)]	79 (56.0)	61 (56.0)	89 (64.5)	73 (67.0)
Race [n(%)]				
White	101 (71.6)	76 (69.7)	103 (74.6)	79 (72.5)
Black	3 (2.1)	1 (0.9)	3 (2.2)	2 (1.8)
Asian	20 (14.2)	17 (15.6)	18 (13.0)	17 (15.6)
Other/unspecified	17 (12.1)	15 (13.8)	14 (10.1)	11 (10.1)
ECOG performance status [n (%)]				
0	53 (37.6)	43 (39.4)	53 (38.4)	45 (41.3)
1	68 (48.2)	50 (45.9)	67 (48.6)	53 (48.6)
2	19 (13.5)	15 (13.8)	17 (12.3)	10 (9.2)
Missing	1 (0.7)	1 (0.9)	1 (0.7)	1 (0.9)
Salvage status [n (%)]				
1	95 (67.4)	73 (67.0)	91 (65.9)	69 (63.3)
2	45 (31.9)	35 (32.1)	46 (33.3)	39 (35.8)

- Measures of efficacy outcomes for treatment which include CR/CRi(and CR and CRi alone), MRD, DoR, DoCR and duration of CRi are shown in Table **4. The CR rate for inotuzumab was 36% compared to 17% in the Investigator Choice Arm. The ORR was 81% versus 30% in the investigator choice arm. The MRD negativity in patients with CR/CR was 78% and 90% in the subjects with CR. The median duration of response was 5.4 months for patients with a CR.**

Table 4. Phase 3 Study B1931022: Efficacy Outcomes

Assessment/ Analysis Population		CR/CRi		CR		CRi	
		Inotuzumab Ozogamicin	Investigator Choice[a]	Inotuzumab Ozogamicin	Investigator Choice[a]	Inotuzumab Ozogamicin	Investigator Choice[a]
EAC; ITT-218	n (%) [95% CI]	88/109 (80.7) [72.1, 87.7]	32/109 (29.4) [21.0, 38.8]	39/109 (35.8) [26.8-45.5]	19/109 (17.4) [10.8-25.9]	49/109 (45.0) [35.4-54.8]	13/109 (11.9) [6.5-19.5]
	Difference, % [97.5% CI]	51.4 [38.4, 64.3]		18.3 [5.2-31.5]		33.0 [20.3-45.8]	
	1-sided p-value[b]	<0.0001		0.0011		<0.0001	
MRD-negativity[c]							
EAC[d]	n1/n2[e] (%) [95% CI]	69/88 (78.4) [68.4-86.5]	9/32 (28.1) [13.7-46.7]	35/39 (89.7) [75.8-97.1]	6/19 (31.6) [12.6-56.6]	34/49 (69.4) [54.6-81.7]	3/13 (23.1) [5.0-53.8]
	1-sided p-value[b]	<0.0001		<0.0001		0.0034	
DoR[f]							
Inv[g]	Median, months [95% CI]	4.6 [3.9-5.4]	3.1 [1.4-4.9]	5.4 [4.2-9.5]	3.3 [1.4-7.7]	4.2 [3.0-5.3]	1.7 [0.3-5.6]
	HR [95% CI]	0.546 [0.309-0.962]		0.403 [0.153-0.1060]		0.509 [0.214-1.212]	
	1-sided p-value[h]	0.0169		0.0292		0.0609	
DoCR[i] / DoCRi[j]							
Inv[k]	Median, months [95% CI]	NA	NA	4.9 [3.4-8.5]	3.3 [2.2-7.7]	4.2 [3.0-5.3]	1.7 [0.3-5.6]
	HR [95% CI]	NA		0.609 [0.230-1.611]		0.509 [0.214-1.212]	
	1-sided p-value[h]	NA		0.1571		0.0609	

Source: Study B1931022 CSR Table 14.2.1.1.4 (CR/CRi), Table 14.2.1.5.2 (MRD), Table 14.2.4.1 (DoR, DoCR, and DoCRi)

- Analysis of OS: A second interim analysis of OS was conducted based on a data cutoff of 19 Jan 2015 when 163 OS events had occurred in 326 randomized patients. The External Data Monitoring Committee for the study reviewed the results on 11 March 2015 and recommend the study continue as planned. No information regarding the interim OS analysis was submitted in the briefing package and the final OS analysis is projected to occur around the 1-2 Q 2016.

- Safety Data: The most common (> 20% all-causality TEAEs in the Inotuzumab ozogamicin arm included neutropenia(48%), thrombocytopenia(45%), nausea(32%), anemia(30%), headaches(28%), leukopenia(27%), febrile neutropenia(27%), pyrexia(27%), fatigue(22%), and AST increase(205). These were similar or less than TEAEs in the Investigator's Choice arm.

Table 5. Phase 3 Study B1931022: Summary of All-Causality All Grades and Grade 3 or Higher TEAEs Reported in ≥20% of Subjects (by Decreasing Order of Frequency of All Grade TEAEs in Inotuzumab Ozogamicin Arm)

	Inotuzumab Ozogamicin (n=139)		Investigator's Choice of Chemotherapy[b] (n=120)	
Preferred Term	All Grades n (%)	Grade 3 or Higher n (%)	All Grades n (%)	Grade 3 or Higher n (%)
Any AEs, n (%)	136 (97.8)	126 (90.6)	119 (99.2)	114 (95.0)
Neutropenia	67 (48.2)	64 (46.0)	53 (44.2)	50 (41.7)
Thrombocytopenia	**62 (44.6)**	**51 (36.7)**	**73 (60.8)**	**71 (59.2)**
Nausea	**44 (31.7)**	3 (2.2)	**56 (46.7)**	0
Anemia	**42 (30.2)**	**26 (18.7)**	**64 (53.3)**	**48 (40.0)**
Headache	39 (28.1)	2 (1.4)	33 (27.5)	0
Leukopenia	**38 (27.3)**	**35 (25.2)**	**47 (39.2)**	**47 (39.2)**
Febrile neutropenia	**37 (26.6)**	**33 (23.7)**	**62 (51.7)**	**59 (49.2)**
Pyrexia	**37 (26.6)**	5 (3.6)	**50 (41.7)**	6 (5.0)
Fatigue	31 (22.3)	4 (2.9)	17 (14.2)	2 (1.7)
AST increased	**28 (20.1)**	7 (5.0)	**12 (10.0)**	4 (3.3)
Diarrhea	**25 (18.0)**	1 (0.7)	**48 (40.0)**	1 (0.8)
Vomiting	24 (17.3)	1 (0.7)	28 (23.3)	0
Lymphopenia	**24 (17.3)**	**22 (15.8)**	**34 (28.3)**	**34 (28.3)**
Constipation	23 (16.5)	0	28 (23.3)	0

Source: Study B1931022 CSR; Table 14.3.1.2.9.1 file generation 24 March 2015
Data cutoff date: 02 October 2014

The notable safety finding associated with inotuzumab ozogamicin is the increase frequency of patients who develop hepatic VOD/SOS during study therapy and in follow-up post-HSCT compared to the Investigator's choice therapy.

The frequency of VOD/SOS was highest for subjects who received inotuzumab ozogamicin following HSCT. The Sponsor is conducting an assessment of risk factors including age, prior HSCT, salvage status, prior history of liver disease, baseline ECOG performance status, duration of inotuzumab treatment and the use of prophylactic agents on the incidence of VOD/SOS**. Table 9 below describes the incidence of VOD occurring in both study arms.**

Table 9. Phase 3 Study B1931022: Summary of All-Causality and Treatment Related VOD/SOS SAEs Occurring in All Subjects Up to 2 Years Post-Dose

	Inotuzumab Ozogamicin (N=139); n (%)	Investigator's Choice of Chemotherapy[a] (N=120); n (%)
VOD/SOS[b]:	15	1
VOD/SOS during study therapy without intervening HSCT	5 (3.6)	0
VOD/SOS in follow-up post HSCT[c]	10 (20.8)	1 (5.0)

Secondary Studies

- Phase 1/ 2 Study B1931010: Open-label, multiple dose study of single-agent inotuzumab ozogamicin administered as 2-3 weekly doses during a 28-day cycle in patients with relapsed/refractory CD22-pisitive B cell ALL. The phase 1 portion was designed to determine the recommended Phase 2 dose of weekly inotuzumab ozogamicin and the Pahse2 portion of the study as to determine the safety and efficacy of the RP2Dof inotuzuymab ozogamcin in patients with CD22 positive B-cell ALL who were due to receive Salvage 2 therapy. The primary efficacy endpoint was CR/CRi and secondary efficacy endpoints included MRD, DoR , PFS, post-treatment HSCT rate and OS.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT : Grant Breakthrough Designation for " Treatment of patients with of relapsed or refractory B-Cell acute lymphoblastic leukemia(ALL). The indication (b) (4) adult patients with ALL."

Rationale: Relapsed and/or refractory ALL is a serious condition and substantial clinical evidence demonstrates a response rate of 80.7% and a CR rate of 35.8% which are more than expected for any single-agent therapy and the responses are fairly durable. The control of minimal residual disease demonstrates the profound depth of these responses.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

- Sponsor's plan: A pre-BLA meeting was held in July 2015 with plans to submit the BLA Q4 2015 for regular approval.
- FDA Advice
  - Submit OS data for at time of BLA submission

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

O'Brien S, Thomas D, Ravandi F, et al. Outcome of Adults with Acute Lymphoblastic Leukemia after Second Salvage Therapy. Cancer 2008; 113(11):186-91.

Shah, N, Stetler-Stevenson, M, Yuan, C et al. Characterization of CD22 expression in acute lymphoblastic leukemia: CD22 Expression in ALL. Pediatr Blood and Cancer 2015;62(6): 964-9

Thomas DA, Faderl S, Kantarjian H, Smith TL, et al. Primary Refractory and Relapsed Adult Acute Lymphoblastic leukemia: Characteristics, Treatment Results, and Prognosis with Salvage Therapy. Cancer 1999; 86:1216-1230.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation	X
Deny Breakthrough Therapy Designation	☐

Reviewer Signature:	{See appended electronic signature page}
Team Leader Signature:	{See appended electronic signature page}
Division Director Signature:	{See appended electronic signature page}

APPEARS THIS WAY ON ORIGINAL

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

/s/

TANYA M WROBLEWSKI
10/08/2015

ROMEO A DE CLARO
10/08/2015

ANN T FARRELL
10/08/2015

Benton, Sandra J

From: Benton, Sandra J
Sent: Wednesday, October 07, 2015 11:42 AM
To: Jarow, Jonathan; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa; Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Wedlake, Lauren; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; McMullen, Rachel; De Claro, R. Angelo; Kaminskas, Edvardas; Farrell, Ann T; Wroblewski, Tanya
Subject: RE: October 9, 2015 Medical Policy Council – Breakthrough Therapy Designation - IND 065658

As the Council agrees with DHP's recommendation to grant Wyeth Pharmaceuticals' breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the October 9, 2015 meeting agenda.

Please let me know if you have any questions. Thanks!

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

From: Benton, Sandra J
Sent: Tuesday, September 29, 2015 2:31 PM
To: Jarow, Jonathan; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa; Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Wedlake, Lauren; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; McMullen, Rachel; De Claro, R. Angelo; Kaminskas, Edvardas; Farrell, Ann T; Wroblewski, Tanya
Subject: October 9, 2015 Medical Policy Council – Breakthrough Therapy Designation - IND 065658

Hi! OMP has scheduled a Medical Policy Council discussion on October 9, 2015 regarding the breakthrough therapy designation request from Wyeth Pharmaceuticals Inc. for its IND 065658, PF-05208773 (inotuzumab ozogamicin) for the treatment of patients with relapsed or refractory B-cell ALL.

DHP recommends that this breakthrough therapy request be granted. Attached is DHP's background on the breakthrough therapy designation with its rationale for granting the request.

DHP has asked if this request can be reviewed by email.

Would you please review DHP's recommendation and let me know by COB Tuesday, October 6 if –

- You agree with DHP's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DHP's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.
- You disagree with DHP's recommendation regarding this breakthrough therapy request.

If the Council agrees with bullet 1, I will cancel the discussion for this IND.

Please let me know if you have any questions. Thank you.

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

<< File: CDER MPC BTD Review Template.doc Inotuzumab_ADC (2).doc >> << File: Inotuzumab presentation Breakthrough OHOP rounds.ppt >> << File: req-comm-ind.pdf >>

APPEARS THIS WAY ON ORIGINAL

CDER Breakthrough Therapy Designation Determination Review

IND/NDA/BLA #	IND 65658
Request Receipt Date	August 18, 2015
Product	Inotuzumab Ozogamicin
Indication	Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia(ALL)
Drug Class/Mechanism of Action	Antibody-drug conjugate(ADC) of humanized anti-CD22 antibody covalently bound to semi-synthetic derivative of calicheamicin
Sponsor	Wyeth Pharmaceuticals Inc. A, Subsidiary of Pfizer Inc.
ODE/Division	CDER/OHOP/DHP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	Octobr 17, 2015

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). ***Note:*** *Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):** Inotuzumab ozogamicin is indicated for the treatment of relapsed or refractory B-Cell acute lymphoblastic leukemia (ALL).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒ NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒ YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Brief Description of the Drug

Inotuzumab ozogamicin is an antibody-drug conjugate(ADC) comprised of humanized anti-CD22 antibody covalently bound to N-acetyl-gamma calicheamicin dimethylhydrazide, a semi-synthetic derivate of calicheamicin. CD22 is expressed on normal mature B cells and malignant cells to include B-cell ALL. Inotuzumab ozogamicin binds to CD22 receptors at the cell surface of malignant cells and is internalized to the lysosomal compartment where the cytotoxic payload, N-acetyl-gamma calicheamicin dimethylhydrazide is related into the lysosome. The cytotoxin intercalates in DNA leading to double-strand DNA break formation leading to apoptosis and cell death.

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Brief Description of the disease and intended population

Acute Lymphoblastic Leukemia(ALL) is a disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs leading to abnormal hematopoiesis, organ failure and death if untreated. Relapsed or refractory ALL is a life-threatening condition. CD22 expression has been observed in up to 100% of subjects studied with relapsed or refractory ALL(Shah et al, 2015), thus making CD22 an attractive target.

Relapsed or refractory B-cell ALL is often a fatal disease with a median survival time in adults of approximately 3-6 months(O-Brien S et al, 2008, Thomas DA et al, 1999). Five year OS is approximately 33% with HSCT in second CR, 8% with HSCT for patients without a CR and 4% with chemotherapy alone.

The goal of treatment of relapsed or refractory ALL is to induce complete remission(CR) and proceed to allogeneic hematopoietic stem cell transplantation(HSCT). Factors that affect achievement of CR include age, time to first relapse and number of prior relapses.

Factors associated with survival after relapse of ALL include age, time to first relapse, reinduction response(CR vs no response) and treatment with allogenic HSCT. Given the relatively low CR rates overall, long-term outcome is poor for patients with ALL who relapse, especially for those relapse less than 1-2 years from the first CR.

7. Information related to endpoints used in the available clinical data:

a. Endpoints considered by the Sponsor as supporting breakthrough therapy designation:

- CR and CRi(CR with incomplete blood count recovery, platelets ≤100,000/mcl and/or neutrophils ≤ 1000/mcl.
- Duration of Response(DoR), Duration of CR and MRD

b. Endpoint accepted by the Division as a clinically significant endpoint(outcome measure) for patients with the disease:

- Durable CR
- Overall survival(in a controlled trial)

c. Any other biomarkers the division would consider likely to predict a clinical benefit even if not yet a basis for accelerated approval.

Minimal Residual Disease(MRD)- The FDA held a workshop on MRD in ALL in 2012 and it was discussed that the presence of MRD at the end of primary induction or intensification was associated with a significant increase in relapse for both children and adults with ALL. MRD positivity after reinduction has negative prognostic significance even for patients who go on to HSCT.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- FDA-approved drugs for the treatment of ALL include doxorubicin, daunorubicin, vincristine, asparaginase, and cytarabine with approvals for treatment in general or for induction specifically and cyclophosphamide, methotrexate and 6-mercaptopurine for maintenance in remission. In practice, none of these agents are used as s ingle agent for reinduction of relapsed or refractory ALL.
- Marqibo(vincristine sulfate liposome injection) received accelerated approval in 2012 for the treatment of adult patients with Ph-ALL in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. Approval was based on CR rate in a single-arm trial(CR 5%, CRi 11%, ORR 15% , and the median duration of CR was 56 days).
- Gleevec(Imatinib) received accelerated approval in 2006 based on CHR rate in a single arm trial in 4 patients with relapsed or refractory Ph+ ALL with CHR rate of 19% and mediation duration of CHR of 3.4 months.
- Sprycel(Dasatanib) received approval in 2006 based on single arm trial of 40 patients with relapsed or refractory Ph+ all with MHR rate of 38% and mediation duration of MHR of 4.6 months
- Iclusig(ponatinib) received accelerated approval for adult patients with Ph+ ALL for whom no other TKI therapy is indicated based on single arm trial with 32 adults with MHR of 41% with mediation duration of 3.2 months.
- Blincyto(blinatumomab) received accelerated approval in 2014 for the treatment of Ph- patients with relapsed or refractory B-cell precursor ALL. Approval was based on CR/CRi rate in single arm trial of 185 adults(CR 32%, CRh 9% OR 42%) and median duration was 5.9 months. The MRD negativity was 75% and the HSCT rate among those who achieved CR/CRh was 39%.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

- Blincyto(blinatumomab), a bispecific anti-CD3/CD19 monoclonal antibody was granted breakthrough therapy designation in 2014 for the indication " treatment of adult patients with Philadelphia-negative relapsed or refractory B-precursor acute lymphoblastic leukemia." The preliminary clinical evidence demonstrated a response rate of 38% which is more than expected for any single-agent therapy and the responses were fairly durable. The control of minimal residual disease demonstrated the depth of these responses.

- Blimatumomab received accelerated approval on December 3, 2014 for the indication stated above.

10. Information related to the preliminary clinical evidence:

Overview of clinical development program for relapsed or refractory B cell ALL in adults

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Overview of Clinical Development Plan for Inotuzumab Ozogamicin n Relapsed/Refractory ALL in adults

Study	Phase	Population	Endpoints
Study B1931022	Phase 3 trial	Adult patients with relapsed or refractory CD22-positive ALL due to receive Salvage 1 or	Primary:CR/CRi per Endpoint Adjudication

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

		2 therapies	Committee and Overall Survival
Study B1931010	Phase 1 /2 Study	Relapsed/Refractory CD22-positive B-cell ALL	P1 Primary: RP2D dose of weekly inotuzumab P2 Primary: CR/CRi

Phase 3 Study B1931022 is the main source of data to support the request. The study is a multicenter, global, open-label, randomized Phase 3 study in adult patients with relapsed or refractory CD22-positive B-cell ALL due to receive Salvage 1 or Salvage 2 therapy. Patients were randomized(1:1) to receive inotuzumab ozogamicin monotherapy or Investigator's choice of chemotherapy.

Randomization was stratified by 3 factors: duration of first remission(CR1D; < 12 months versus ≥ 12 months), line of salvage(Salvage 1 versus 2), and patient age at randomization(< 55 versus ≥ 55 years).

The primary endpoints were CR/CRi per the Endpoint Adjudication Committee(EAC) and overall survival(OS). The secondary endpoints included MRD, DoR, PFS, HSCT rate.

The primary endpoint of CR/CRi was to be evaluated on the first 218 patients randomized. As of the data cutoff date of 2 October 2014 used for assessment of the CR/Cri primary endpoint, a total of 279 patients were randomized. The ITT population included all 279 patients randomized as of the data cutoff date. The ITT218 population a subset of the IT population including the initial 218 patients randomized was pre-specified primary population for the final analysis of CR/CRi.

The dose schedule is as follows: inotzumab IV 0.8mg/m^2 for Cycle 1, Day 1, then Inotuzumab 0.5mg/m^2 on Cycle1 Day 5, then Inotuzumab 0.5mg/m^2 IV on Cycle 1, Day 15. Cycle 2 and cycles beyond C2 – Inotuzumab at a dose of 0.5mg/m^2 IV on Days 1, 8 and 15 of each cycle.

Overall, the key demographic and baseline characteristics were balanced between both study arms. Table 3 shows the demographic characteristics of the subjects evaluated.

Table 3. Phase 3 Study B1931022: Key Demographic and Baseline Characteristics – ITT and ITT218 Population

Characteristic	Inotuzumab Ozogamicin		Investigator's Choice of Chemotherapy[a]	
	ITT (N=141)	ITT218 (N=109)	ITT (N=138)	ITT218 (N=109)
Age (years)				
Median (range)	47.0 (18-78)	47.0 (18-78)	47.5 (18-79)	47.0 (18-79)
<55 years [n (%)]	87 (61.7)	66 (60.6)	87 (63.0)	69 (63.3)
≥55 years [n (%)]	54 (38.3)	43 (39.4)	51 (37.0)	40 (36.7)
Men [n(%)]	79 (56.0)	61 (56.0)	89 (64.5)	73 (67.0)
Race [n(%)]				
White	101 (71.6)	76 (69.7)	103 (74.6)	79 (72.5)
Black	3 (2.1)	1 (0.9)	3 (2.2)	2 (1.8)
Asian	20 (14.2)	17 (15.6)	18 (13.0)	17 (15.6)
Other/unspecified	17 (12.1)	15 (13.8)	14 (10.1)	11 (10.1)
ECOG performance status [n (%)]				
0	53 (37.6)	43 (39.4)	53 (38.4)	45 (41.3)
1	68 (48.2)	50 (45.9)	67 (48.6)	53 (48.6)
2	19 (13.5)	15 (13.8)	17 (12.3)	10 (9.2)
Missing	1 (0.7)	1 (0.9)	1 (0.7)	1 (0.9)
Salvage status [n (%)]				
1	95 (67.4)	73 (67.0)	91 (65.9)	69 (63.3)
2	45 (31.9)	35 (32.1)	46 (33.3)	39 (35.8)

- Measures of efficacy outcomes for treatment which include CR/CRi(and CR and CRi alone), MRD, DoR, DoCR and duration of CRi are shown in Table **4. The CR rate for inotuzumab was 36% compared to 17% in the Investigator Choice Arm. The ORR was 81% versus 30% in the investigator choice arm. The MRD negativity in patients with CR/CR was 78% and 90% in the subjects with CR. The median duration of response was 5.4 months for patients with a CR.**

Table 4. Phase 3 Study B1931022: Efficacy Outcomes

Assessment/ Analysis Population		CR/CRi		CR		CRi	
		Inotuzumab Ozogamicin	Investigator Choice[a]	Inotuzumab Ozogamicin	Investigator Choice[a]	Inotuzumab Ozogamicin	Investigator Choice[a]
EAC; ITT-218	n (%) [95% CI]	88/109 (80.7) [72.1, 87.7]	32/109 (29.4) [21.0, 38.8]	39/109 (35.8) [26.8-45.5]	19/109 (17.4) [10.8-25.9]	49/109 (45.0) [35.4-54.8]	13/109 (11.9) [6.5-19.5]
	Difference, % [97.5% CI]	51.4 [38.4, 64.3]		18.3 [5.2-31.5]		33.0 [20.3-45.8]	
	1-sided p-value[b]	<0.0001		0.0011		<0.0001	
MRD-negativity[c]							
EAC[d]	n1/n2[e] (%) [95% CI]	69/88 (78.4) [68.4-86.5]	9/32 (28.1) [13.7-46.7]	35/39 (89.7) [75.8-97.1]	6/19 (31.6) [12.6-56.6]	34/49 (69.4) [54.6-81.7]	3/13 (23.1) [5.0-53.8]
	1-sided p-value[b]	<0.0001		<0.0001		0.0034	
DoR[f]							
Inv[g]	Median, months [95% CI]	4.6 [3.9-5.4]	3.1 [1.4-4.9]	5.4 [4.2-9.5]	3.3 [1.4-7.7]	4.2 [3.0-5.3]	1.7 [0.3-5.6]
	HR [95% CI]	0.546 [0.309-0.962]		0.403 [0.153-0.1060]		0.509 [0.214-1.212]	
	1-sided p-value[h]	0.0169		0.0292		0.0609	
DoCR[i] / DoCRi[j]							
Inv[k]	Median, months [95% CI]	NA	NA	4.9 [3.4-8.5]	3.3 [2.2-7.7]	4.2 [3.0-5.3]	1.7 [0.3-5.6]
	HR [95% CI]	NA		0.609 [0.230-1.611]		0.509 [0.214-1.212]	
	1-sided p-value[h]	NA		0.1571		0.0609	

Source: Study B1931022 CSR Table 14.2.1.1.4 (CR/CRi), Table 14.2.1.5.2 (MRD), Table 14.2.4.1 (DoR, DoCR, and DoCRi)

- Analysis of OS: A second interim analysis of OS was conducted based on a data cutoff of 19 Jan 2015 when 163 OS events had occurred in 326 randomized patients. The External Data Monitoring Committee for the study reviewed the results on 11 March 2015 and recommend the study continue as planned. No information regarding the interim OS analysis was submitted in the briefing package and the final OS analysis is projected to occur around the 1-2 Q 2016.

- Safety Data: The most common (> 20% all-causality TEAEs in the Inotuzumab ozogamicin arm included neutropenia(48%), thrombocytopenia(45%), nausea(32%), anemia(30%), headaches(28%), leukopenia(27%), febrile neutropenia(27%), pyrexia(27%), fatigue(22%), and AST increase(205). These were similar or less than TEAEs in the Investigator's Choice arm.

Table 5. Phase 3 Study B1931022: Summary of All-Causality All Grades and Grade 3 or Higher TEAEs Reported in ≥20% of Subjects (by Decreasing Order of Frequency of All Grade TEAEs in Inotuzumab Ozogamicin Arm)

	Inotuzumab Ozogamicin (n=139)		Investigator's Choice of Chemotherapy[b] (n=120)	
Preferred Term	All Grades n (%)	Grade 3 or Higher n (%)	All Grades n (%)	Grade 3 or Higher n (%)
Any AEs, n (%)	136 (97.8)	126 (90.6)	119 (99.2)	114 (95.0)
Neutropenia	67 (48.2)	64 (46.0)	53 (44.2)	50 (41.7)
Thrombocytopenia	**62 (44.6)**	**51 (36.7)**	**73 (60.8)**	**71 (59.2)**
Nausea	**44 (31.7)**	3 (2.2)	**56 (46.7)**	0
Anemia	**42 (30.2)**	**26 (18.7)**	**64 (53.3)**	**48 (40.0)**
Headache	39 (28.1)	2 (1.4)	33 (27.5)	0
Leukopenia	**38 (27.3)**	**35 (25.2)**	**47 (39.2)**	**47 (39.2)**
Febrile neutropenia	**37 (26.6)**	**33 (23.7)**	**62 (51.7)**	**59 (49.2)**
Pyrexia	**37 (26.6)**	5 (3.6)	**50 (41.7)**	6 (5.0)
Fatigue	31 (22.3)	4 (2.9)	17 (14.2)	2 (1.7)
AST increased	**28 (20.1)**	7 (5.0)	**12 (10.0)**	4 (3.3)
Diarrhea	**25 (18.0)**	1 (0.7)	**48 (40.0)**	1 (0.8)
Vomiting	24 (17.3)	1 (0.7)	28 (23.3)	0
Lymphopenia	**24 (17.3)**	**22 (15.8)**	**34 (28.3)**	**34 (28.3)**
Constipation	23 (16.5)	0	28 (23.3)	0

Source: Study B1931022 CSR; Table 14.3.1.2.9.1 file generation 24 March 2015
Data cutoff date: 02 October 2014

The notable safety finding associated with inotuzumab ozogamicin is the increase frequency of patients who develop hepatic VOD/SOS during study therapy and in follow-up post-HSCT compared to the Investigator's choice therapy.

The frequency of VOD/SOS was highest for subjects who received inotuzumab ozogamicin following HSCT. The Sponsor is conducting an assessment of risk factors including age, prior HSCT, salvage status, prior history of liver disease, baseline ECOG performance status, duration of inotuzumab treatment and the use of prophylactic agents on the incidence of VOD/SOS**. Table 9 below describes the incidence of VOD occurring in both study arms.**

Table 9. Phase 3 Study B1931022: Summary of All-Causality and Treatment Related VOD/SOS SAEs Occurring in All Subjects Up to 2 Years Post-Dose

	Inotuzumab Ozogamicin (N=139); n (%)	Investigator's Choice of Chemotherapy[a] (N=120); n (%)
VOD/SOS[b]:	15	1
VOD/SOS during study therapy without intervening HSCT	5 (3.6)	0
VOD/SOS in follow-up post HSCT[c]	10 (20.8)	1 (5.0)

Secondary Studies

- Phase 1/ 2 Study B1931010: Open-label, multiple dose study of single-agent inotuzumab ozogamicin administered as 2-3 weekly doses during a 28-day cycle in patients with relapsed/refractory CD22-pisitive B cell ALL. The phase 1 portion was designed to determine the recommended Phase 2 dose of weekly inotuzumab ozogamicin and the Pahse2 portion of the study as to determine the safety and efficacy of the RP2Dof inotuzuymab ozogamcin in patients with CD22 positive B-cell ALL who were due to receive Salvage 2 therapy. The primary efficacy endpoint was CR/CRi and secondary efficacy endpoints included MRD, DoR , PFS, post-treatment HSCT rate and OS.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT : Grant Breakthrough Designation for " Treatment of patients with of relapsed or refractory B-Cell acute lymphoblastic leukemia(ALL). The indication (b) (4) adult patients with ALL."

Rationale: Relapsed and/or refractory ALL is a serious condition and substantial clinical evidence demonstrates a response rate of 80.7% and a CR rate of 35.8% which are more than expected for any single-agent therapy and the responses are fairly durable. The control of minimal residual disease demonstrates the profound depth of these responses.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

- Sponsor's plan: A pre-BLA meeting was held in July 2015 with plans to submit the BLA Q4 2015 for regular approval.
- FDA Advice
  - Submit OS data for at time of BLA submission

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

References

Shah, N, Stevenson, M, Yuan,C et al. Characteriziation of CD22 Expression in Acute Lymphoblastic Leukemia, Pediatr Blood Cancer 2015:62:964

4-6-15/M. Raggio

Breakthrough Therapy Designation Inotuzumab Ozogamicin

Treatment of Patients with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia(ALL)
IND 065658

Tanya Wroblewski, MD
Division of Hematology Products
Office of Hematology and Oncology Products

Reference ID: 3831418

Inotuzumab Ozogamicin

- Humanized IgG antibody that targets CD22
- CD22 is expressed on both normal cells of the mature B-cell lineage and malignant cells of B-cell cancers
- CD22 expressed nearly 100% in B-Cell ALL

FDA Approved Therapies for ALL

Salvage therapies: CR rate 40-46%

- DFS of 2-7.5 months
- CR rate lower for early relapse, better for late relapse
- Single agents response rates 7-12%
- No standard of care for induction regimen in relapsed/refractory setting

- Doxorubicin, daunorubicin, vincristine and cytarabine with approvals for treatment in general and specifically for induction. Cyclophosphamide, methotrexate and 6-MP for maintenance in remission.

FDA Approved Therapies

- Marquibo: received accelerated approval in 2012 for adult patients with Ph-ALL in second or greater relapse
  - CR in a single arm trial- CR 5%, CRi- 11%, OR-15%.
- Blincyto (Blinatumomab)- granted AA in 2014 for treatment of R/R B-cell ALL
  - CR/CRh: 41.6%
  - CR: 32.4%
  - MRD: 75%
  - Median DoR: 5.9 months

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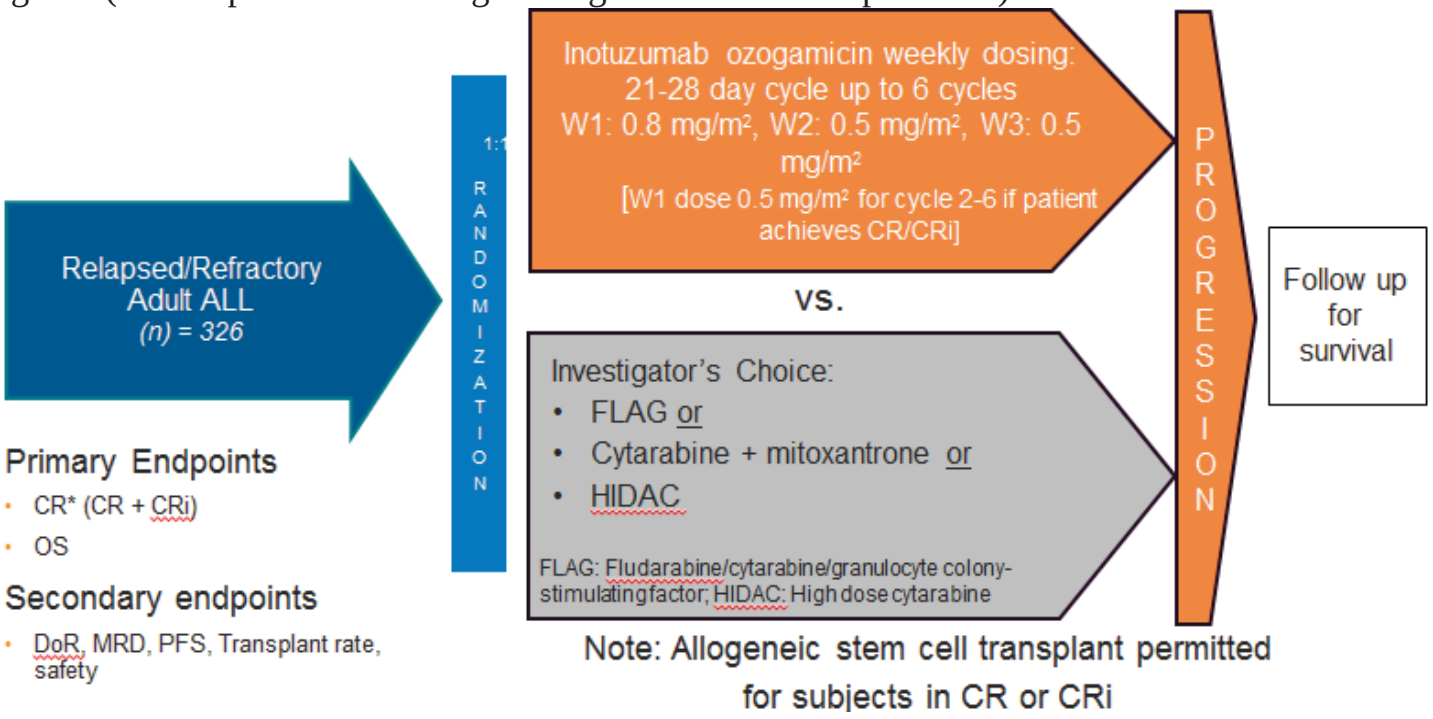
Study B1931022-Phase 3 Randomized, Open-Label Study

Figure 1(From Sponsor's Meeting Package submitted 22 April 2015)



Reference ID: 3831418

Study B1930122

Stratification Factors

- Duration of first remission(< 12 months or ≥ 12 months)
- Salvage treatment that patient will receive on Study(salvage 1 or 2)
- Salvage 1: Relapse after initial treatment or resistant disease(No CR/CRi) after initial treatment
- Salvage 2: Relapse after salvage 1 therapy or resistant disease after salvage 1
- Patient age at randomization(< 55 or ≥ 55)

Endpoints

- Primary endpoint Overall Survival and **CR(CR Plus CRi)**
- OS- A second interim analysis of OS conducted based on data cutoff of 19 Jan 2015 when 163 OS events occurred in 326 randomized subjects. DMC recommended continuing study. Final analysis OS is projected to occur 1st quarter 2016.
- ITT analysis set: all 279 patients randomized
- ITT218 Analysis set: initial 218 subjects randomized was pre-specified in SAP for final analysis of CR/CRi

Demographics

Characteristic	Inotuzumab Ozogamicin		Investigator's Choice of Chemotherapy[a]	
	ITT (N=141)	ITT218 (N=109)	ITT (N=138)	ITT218 (N=109)
Age (years)				
Median (range)	47.0 (18-78)	47.0 (18-78)	47.5 (18-79)	47.0 (18-79)
<55 years [n (%)]	87 (61.7)	66 (60.6)	87 (63.0)	69 (63.3)
≥55 years [n (%)]	54 (38.3)	43 (39.4)	51 (37.0)	40 (36.7)
Men [n(%)]	79 (56.0)	61 (56.0)	89 (64.5)	73 (67.0)
Race [n(%)]				
White	101 (71.6)	76 (69.7)	103 (74.6)	79 (72.5)
Black	3 (2.1)	1 (0.9)	3 (2.2)	2 (1.8)
Asian	20 (14.2)	17 (15.6)	18 (13.0)	17 (15.6)
Other/unspecified	17 (12.1)	15 (13.8)	14 (10.1)	11 (10.1)
ECOG performance status [n (%)]				
0	53 (37.6)	43 (39.4)	53 (38.4)	45 (41.3)
1	68 (48.2)	50 (45.9)	67 (48.6)	53 (48.6)
2	19 (13.5)	15 (13.8)	17 (12.3)	10 (9.2)
Missing	1 (0.7)	1 (0.9)	1 (0.7)	1 (0.9)
Salvage status [n (%)]				
1	95 (67.4)	73 (67.0)	91 (65.9)	69 (63.3)
2	45 (31.9)	35 (32.1)	46 (33.3)	39 (35.8)

Efficacy Results

Assessment/ Analysis Population		CR/CRi		CR		CRi	
		Inotuzumab Ozogamicin	Investigator Choice[a]	Inotuzumab Ozogamicin	Investigator Choice[a]	Inotuzumab Ozogamicin	Investigator Choice[a]
EAC; ITT-218	n (%) [95% CI]	88/109 (80.7) [72.1, 87.7]	32/109 (29.4) [21.0, 38.8]	39/109 (35.8) [26.8-45.5]	19/109 (17.4) [10.8-25.9]	49/109 (45.0) [35.4-54.8]	13/109 (11.9) [6.5-19.5]
	Difference, % [97.5% CI]	51.4 [38.4, 64.3]		18.3 [5.2-31.5]		33.0 [20.3-45.8]	
	1-sided p-value[b]	<0.0001		0.0011		<0.0001	
MRD-negativity[c]							
EAC[d]	n1/n2[e] (%) [95% CI]	69/88 (78.4) [68.4-86.5]	9/32 (28.1) [13.7-46.7]	35/39 (89.7) [75.8-97.1]	6/19 (31.6) [12.6-56.6]	34/49 (69.4) [54.6-81.7]	3/13 (23.1) [5.0-53.8]
	1-sided p-value[b]	<0.0001		<0.0001		0.0034	
DoR[f]							
Inv[g]	Median, months [95% CI]	4.6 [3.9-5.4]	3.1 [1.4-4.9]	5.4 [4.2-9.5]	3.3 [1.4-7.7]	4.2 [3.0-5.3]	1.7 [0.3-5.6]
	HR [95% CI]	0.546 [0.309-0.962]		0.403 [0.153-0.1060]		0.509 [0.214-1.212]	
	1-sided p-value[h]	0.0169		0.0292		0.0609	
DoCR[i] / DoCRi[j]							
Inv[k]	Median, months [95% CI]	NA	NA	4.9 [3.4-8.5]	3.3 [2.2-7.7]	4.2 [3.0-5.3]	1.7 [0.3-5.6]
	HR [95% CI]	NA		0.609 [0.230-1.611]		0.509 [0.214-1.212]	
	1-sided p-value[h]	NA		0.1571		0.0609	

Treatment Emergent Adverse Events

Preferred Term	Inotuzumab Ozogamicin (n=139)		Investigator's Choice of Chemotherapy[b] (n=120)	
	All Grades n (%)	Grade 3 or Higher n (%)	All Grades n (%)	Grade 3 or Higher n (%)
Any AEs, n (%)	136 (97.8)	126 (90.6)	119 (99.2)	114 (95.0)
Neutropenia	67 (48.2)	64 (46.0)	53 (44.2)	50 (41.7)
Thrombocytopenia	**62 (44.6)**	**51 (36.7)**	**73 (60.8)**	**71 (59.2)**
Nausea	**44 (31.7)**	3 (2.2)	**56 (46.7)**	0
Anemia	**42 (30.2)**	**26 (18.7)**	**64 (53.3)**	**48 (40.0)**
Headache	39 (28.1)	2 (1.4)	33 (27.5)	0
Leukopenia	**38 (27.3)**	**35 (25.2)**	**47 (39.2)**	**47 (39.2)**
Febrile neutropenia	**37 (26.6)**	**33 (23.7)**	**62 (51.7)**	**59 (49.2)**
Pyrexia	**37 (26.6)**	5 (3.6)	**50 (41.7)**	6 (5.0)
Fatigue	31 (22.3)	4 (2.9)	17 (14.2)	2 (1.7)
AST increased	**28 (20.1)**	7 (5.0)	**12 (10.0)**	4 (3.3)
Diarrhea	**25 (18.0)**	1 (0.7)	**48 (40.0)**	1 (0.8)
Vomiting	24 (17.3)	1 (0.7)	28 (23.3)	0
Lymphopenia	**24 (17.3)**	**22 (15.8)**	**34 (28.3)**	**34 (28.3)**
Constipation	23 (16.5)	0	28 (23.3)	0

Deaths: Inotuzumab: all causality 15(11%) versus 11(9.2) in IC

Safety Results(VOD)

Table 9. Phase 3 Study B1931022: Summary of All-Causality and Treatment Related VOD/SOS SAEs Occurring in All Subjects Up to 2 Years Post-Dose

	Inotuzumab Ozogamicin (N=139); n (%)	Investigator's Choice of Chemotherapy[a] (N=120); n (%)
VOD/SOS[b]:	15	1
VOD/SOS during study therapy without intervening HSCT	5 (3.6)	0
VOD/SOS in follow-up post HSCT[c]	10 (20.8)	1 (5.0)

Regulatory Recommendation

- The Sponsor has met the two key requirements for BT Designation:
  1. **Serious and life threatening condition**
  2. **Preliminary clinical evidence demonstrates substantial improvement over existing therapies(single agents) on one or more clinically significant endpoints:**
     - **CR 36% versus 17%**
     - **CRi 45% versus 12%**
     - **CR/CRi 81% versus 39%**
     - **MRD negativity 78% versus 28%**
     - **Duration of Response: median 4.6 months versus 3.1**

Regulatory Recommendation

- Grant BT designation request
  - Sponsor plans to submit the BLA by the end of this year
    - OS data will be submitted 1st quarter 2016 to the BLA.
  - Sponsor conducting analysis of risk factors for VOD/SOS and will be submitted with BLA.

Back-up

Characteristic	Inotuzumab Ozogamicin		Investigator's Choice of Chemotherapy[a]	
	ITT (N=141)	ITT218 (N=109)	ITT (N=138)	ITT218 (N=109)
Other	1 (0.7)	1 (0.9)	1 (0.7)	1 (0.9)
Duration of First Remission [n (%)]				
< 12 months	81 (57.4)	62 (56.9)	89 (64.5)	71 (65.1)
≥ 12 months	60 (42.6)	47 (43.1)	49 (35.5)	38 (34.9)
Karyotype				
Normal	39 (27.7)	27 (24.8)	30 (21.7)	23 (21.1)
Abnormal	84 (59.6)	66 (60.6)	86 (62.3)	70 (64.2)
Unknown/Missing	18 (12.8)	16 (14.7)	22 (15.9)	16 (14.7)
Chromosomal Abnormalities [n(%)]				
Ph+[b]	19 (13.5)	14 (12.8)	24 (17.4)	18 (16.5)
t(4;11)	5 (3.5)	3 (2.8)	7 (5.1)	5 (4.6)
Other	59 (41.8)	49 (45.0)	55 (39.9)	46 (42.2)
Response to prior regimen #1				
Complete response	116 (82.3)	93 (85.3)	111 (80.4)	90 (82.6)
Other	25 (17.7)	16 (14.7)	26 (18.8)	18 (16.5)
Unknown	0	0	1 (0.7)	1 (0.9)
Response to prior regimen #2				
Complete response[c]	23 (51.1)	15 (42.9)	24 (50.0)	19 (46.3)
Other[c]	21 (46.7)	19 (54.3)	24 (50.0)	22 (53.7)
Unknown[c]	1 (2.2)	1 (2.9)	0	0
Peripheral blast count ($10^3/mm^3$)				
N	140	108	135	108
Median	113.7	175.4	30.0	39.3

Phase ½ Study B1931010

Table 10. Phase 1/2 Study B1931010: Efficacy Results

	Phase 2 (N=35) 1.8 mg/m^2	Total (N=72) All Doses
CR/CRi, n (%) (95% CI; %)[a]	24 (68.6) (50.7-83.2)	49 (68.1) (56.0-78.6)
CR, n (%)	10 (28.6)	23 (31.9)
CRi, n (%)	14 (40.0)	26 (36.1)
Median time to CR/CRi, months (range)	0.84 (0.49-2.99)	0.89 (0.49-2.99)
Median DoR, months (95% CI)	3.81 (2.16-5.78)	4.63 (3.82-6.60)
Median PFS, months (95% CI)	3.68 (2.60-4.74)	3.91 (2.85-5.43)
Post-treatment HSCT rate; n (%)[b]	8 (22.9)	24[b] (33.3)
MRD-negativity[c] in patients who achieved a CR/CRi, n (%)	18 (75.0)	41(83.7)
Number of deaths, n (%)	29 (82.9)	54 (75.0)
Number of censored subjects, n (%)	6 (17.1)	18 (25.0)
Median OS, months (95% CI)	6.41 (4.51-7.89)	7.36 (5.68-9.21)

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

/s/

SANDRA J BENTON
10/08/2015

ANN T FARRELL
10/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 065658

MEETING MINUTES

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.
Attention: Alison L. Russell, PhD
Director, Worldwide Safety and Regulatory, WR&D
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-05208773 (inotuzumab ozogamicin).

We also refer to the teleconference between representatives of your firm and the FDA on November 10, 2014. The purpose of the meeting was to seek agreement with the Agency regarding the proposed content and format of the original BLA for inotuzumab ozogamicin.

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

If you have any questions, call Amy Chi, Regulatory Project Manager at (240) 402-0992.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center of Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Guidance
Meeting Date and Time:	November 10, 2014 at 3:00 PM – 4:00 PM (EST)
Meeting Location:	Teleconference
Application Number:	065658
Product Name:	PF-05208773 (inotuzumab ozogamicin)
Indication:	Treatment of patients with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL)
Sponsor/Applicant Name:	Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Meeting Chair:	R. Angelo de Claro, MD
Meeting Recorder:	Amy Chi, MSN

FDA ATTENDEES

CDER Participants:

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products (DHP)
Edvardas Kaminskas, MD, Deputy Director
R. Angelo de Claro, MD, Clinical Team Leader
Karen McGinn, MS, CRNP, Senior Clinical Analyst
Amy Chi, MSN, Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Yuan Li Shen, PhD, Team Leader

Office of Clinical Pharmacology/Division of Clinical Pharmacology
Bahru Habtemariam, PharmD, Team Leader
Young-Jin Moon, PhD, Reviewer

Office of Clinical Pharmacology/Division of Pharmacometrics
Jee Eun Lee, PhD, Reviewer

Office of Clinical Pharmacology/Genomics and Targeted Therapy
Rosane Charlab Orbach, PhD, Acting Team Leader
Sarah Dorff, PhD, Reviewer

Office of Business Informatics/Division of Data Management Services & Solutions
Lisa Lin, Project Manager Officer, eData Team Project Manager

Center for Devices and Radiological Health (CDRH)

Office of In vitro Diagnostics and Radiological Health (OIR)
Division of Molecular Genetics and Pathology
Donna Roscoe, PhD, Genetic Disorders Branch Team Leader
Xueying Sharon Liang, MD, PhD, Regulatory Scientist

SPONSOR ATTENDEES

Erik Vandendries, MD, PhD, Clinical
Stephanie Green, PhD, Statistics
Joseph Boni, PhD, Clinical Pharmacology
Craig Davis, PhD, Translational Oncology (Pharmacogenomics)
David Postma, BS, Data Programming
Stuart Pearce, BS, Data Programming
Sharayu Nadkarni, M Phil, Data Programming
Alison Russell, PhD, Regulatory
Caroline Henesey, PhD, Regulatory
Ramzi Dagher, MD, Regulatory
Leena Das-Young, PharmD, Project Management
Tatyana Nisan, BS, Asset Team Leader
Cindy Ru, PhD, Asset Team Leader
(b) (4)

1.0 BACKGROUND

Inotuzumab ozogamicin consists of a recombinant, humanized IgG4 antibody covalently bonded to a fully-characterized semi-synthetic derivative of γ-calicheamicin. γ-Calicheamicin is a cytotoxic antibiotic (natural product) produced by microbial fermentation. (b) (4) Inotuzumab ozogamicin drug product is a sterile, preservative-free, lyophilized dosage form.

The purpose of the meeting is to seek agreement with the Agency regarding the proposed content and format of the original BLA for inotuzumab ozogamicin.

2. DISCUSSION

2.1. Content and Format

Question 1: Does the Agency agree with the proposed list of clinical studies to be included in the BLA and the Sponsor's approach regarding MDACC IIR Study 2009-0872 and other IIR studies?

FDA Response to Question 1:
Yes. This appears acceptable.

Discussion:
No discussion occurred.

Question 2: Does the Agency agree with the types and format of datasets and programs to be included in the BLA?

***FDA Response to Question 2*:**
Define.xml files should be submitted for those data with CDISC format, in addition to define.pdf files. Please also indicate which CDISC/SDTM and/or CDISC/ADaM version(s) you have used. If the SDTM data is converted from original raw CRF data, both raw CRF data and SDTM data need to be submitted to provide traceability.

Please also submit 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 for Study B1931010 in the BLA submission.

Discussion:
The sponsor agreed with the Agency recommendations regarding types and format and datasets to be included. The Agency provided clarification regarding traceability of SDTM data based on submission of annotated CRF that include SDTM variables.

Question 3: Does the Agency concur with the proposed table of contents for the BLA?

FDA Response to Question 3:
Yes. The proposed Table of Contents for the planned BLA appears acceptable. However, please see additional comments below:

- **Please use leaf titles to differentiate between Drug Substance documents in m2 and m3 by indicating the file's true content (e.g. "(b) (4)-general-information", or something similar)**
- **The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5**
- **Global Regulatory Health Authority Meeting Minutes document should be placed in m1.6.3. (not m5.4), with a clear leaf title indicating the content.**

Include a summary of the important dates and revised items during the development (i.e. database unblinding date, interim analyses or interim locked/unblinding dates for the DSMB, SAP [including amendment] sign-off dates, protocol [including amendment] sign-off dates, etc). Also please make sure the protocol, SAP and amendments are included in Module 5.

Discussion:
No discussion occurred.

2.2. Efficacy

Question 4: The Sponsor proposes to split the content of the Integrated Summary of Efficacy (ISE) between Modules 2 (text) and 5 (listings, tables, figures, and datasets), as per the Guidance for Industry entitled, "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" dated April 2009, Section V.D – Example 4, for the SCE to meet the requirements of the ISE.

Does the Agency concur with the proposals for the SCE?

FDA Response to Question 4:

(b) (4)

We recommend submission of interim OS analysis at the time of BLA submission. This may require adjustment of alpha spending if the timing of the interim OS analysis does not coincide with the pre-specified timing at 60% of OS events. Absence of OS data poses challenges with the benefit:risk analysis. The Agency considers OS as an important safety and efficacy endpoint.

Discussion:
The Agency reiterated recommendations for submission of interim or final OS analysis at the time of BLA submission.

2.3. Safety

Question 5: The Sponsor proposes to split the text, listings, tables, figures, and datasets of the Integrated Summary of Safety (ISS) between Modules 2 and 5, as per the Guidance for Industry entitled, "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" dated April 2009, Section V.D – Example 4, for the SCS to meet the requirements of the ISS.

Does the Agency concur with the proposals for the SCE?

FDA Response to Question 5:
This appears to be acceptable; however, it will be a review issue.

Discussion:
No discussion occurred.

Question 6: Does the Agency concur with the proposed analysis to assess the effect of inotuzumab ozogamicin on hepatic injury, including VOD?

FDA Response to Question 6:
This appears to be acceptable; however, it will be a review issue.

Discussion:
No discussion occurred.

Question 7: Does the Agency concur with the proposed analysis to assess the effect of Inotuzumab ozogamicin on platelets and neutrophils?

FDA Response to Question 7:
This appears to be acceptable; however, it will be a review issue.

Discussion:
No discussion occurred.

Question 8: Does the Agency concur with the proposal regarding patient safety narratives and CRFs?

FDA Response to Question 8:
This appears to be acceptable; however, it will be a review issue.

Discussion:
No discussion occurred.

Question 9: Does the Agency concur that a REMS will not be required?

FDA Response to Question 9:
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of inotuzumab ozogamicin outweigh its risks, and, if a REMS is needed, what the required REMS elements would be. Should you decide to submit a REMS, refer to the FDA Guidance for Industry, "*Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf.

Discussion:
No discussion occurred.

Question 10: Does the Agency concur with the proposals for the 120-day Safety Update?

FDA Response to Question 10:
This appears to be acceptable; however, it will be a review issue.

Discussion:
No discussion occurred.

2.4. Bioanalytical Methods and Validation

Question 11: Does the Agency concur with the proposed data content for inclusion in the bioanalytical reports?

FDA Response to Question 11:
For a trial with potential for registration of a drug that depends on a companion diagnostic device, studies of the kind described by sponsor (i.e., for "selectivity, linearity, accuracy and precision of bioanalytical methods") are best conducted before testing of trial specimens begins.

If it is ultimately determined that a companion diagnostics for CD22 measurements is essential to the safe and effective use of the therapeutic, a regulatory submission to CDRH will be needed to establish the performance of the test with the drug for a contemporaneous approval of the two products. The specifics of the analytical studies and statistical analyses required to support approval of a PMA can be discussed in greater detail in a Pre-submission from sponsor to CDRH. Additional analytical validation studies (i.e., beyond those proposed in the sponsor's briefing package) will be required in a PMA submission. These include, and are not limited to, the following:

- **Analytical Sensitivity and Specificity**
- **Lot-to-lot and instrument to instrument reproducibility**
- **Interference and carryover.**

We note changes to Inclusion Criterion #1 in your protocol. Provide a history of changes to Inclusion Criterion #1, and number of subjects enrolled per amendment.

Discussion:
See discussion to Question #16.

2.5. Clinical Pharmacology

Question 12: Does the Agency concur with the proposals for the SCP and will the Agency require ECG waveforms to be submitted to the ECG warehouse?

FDA Response to Question 12:
Overall, your plan appears to be reasonable. However, the adequacy of the population PK analysis and the covariate analyses for hepatic/renal impairment would be review issues. For PK/safety analysis, include the changes in measures for liver function, e.g., AST, ALT, Total Bilirubin, for analysis to evaluate the effect of exposure on potential hepatotoxicity.

Moreover, we recommend that PK/safety and PK/efficacy analyses include both total calicheamicin (conjugated and unconjugated) and unconjugated calicheamicin as exposure measures.

Discussion:
The Sponsor agreed to provide PK/safety analysis for liver function as part of the application submission. The Sponsor will provide available data for unconjugated calicheamicin.

ECG waveforms from inotuzumab ozogamicin studies in patients with relapsed/refractory ALL (B1931022 and B1931010) should be submitted to the ECG warehouse for all studies.

Question 13: Does the Agency concur that the Sponsor plans regarding assessment of inotuzumab ozogamicin drug-drug interactions are appropriate?

FDA Response to Question 13:
In order to determine the need for further DDI evaluation, you should also evaluate the relationship between unconjugated calicheamicin and important safety endpoints.

In addition, you should include R value for each enzyme in order to determine whether in vivo human DDI studies are not needed. Refer to the Drug Interaction Studies Guidance.

Discussion:
See discussion to Question #12.

Question 14: Does the Agency concur that the Sponsor plans regarding assessment of renal and hepatic impairment are appropriate?

FDA Response to Question 14:
It is our expectation that the BLA submission should provide complete information in order to write a complete Package Insert with dosing recommendations for all patients, including those with hepatic and renal impairment. See the response to question 12.

Discussion:
No discussion occurred.

2.6. Evaluation of QTC Interval Prolongation and Proarrhythmic Potential

Question 15: Does the Agency concur with these proposals for QTc evaluation and PK/QTc?

***FDA Response to Question 15*:**
Yes, your proposals for QTc evaluation and PK/QTc analysis are acceptable. We are also interested in the effects of the inotuzumab ozogamicin on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes. When you submit your cardiac safety report, please include the following items:

a. **Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed**
b. **Electronic copy of the study report**
c. **Electronic or hard copy of the clinical protocol**
d. **Electronic or hard copy of the Investigator's Brochure**

e. Annotated CRF
f. A data definition file which describes the contents of the electronic data sets
g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
j. Narrative summaries and case report forms for any
  i. Deaths
  ii. Serious adverse events
  iii. Episodes of ventricular tachycardia or fibrillation
  iv. Episodes of syncope
  v. Episodes of seizure
  vi. Adverse events resulting in the subject discontinuing from the study
k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com). If you use Holter recording and select 10-second segments to measure, submit either the entire Holter recording or at least the entire analysis windows
l. A completed Highlights of Clinical Pharmacology Table
Advancing in this field – and possibly reducing the burden of conducting QT studies depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at www.cardiacsafety.org/library.

Discussion:
No discussion occurred.

2.7. Analysis of CD22 and Clinical Outcomes

Question 16: Does the Agency concur with the proposed analysis to determine the need for a companion diagnostic for the safe and effective use of inotuzumab ozogamicin?

FDA Response to Question 16:
If results from both bone marrow and peripheral blood samples will be used in determining need, specifications or performance characteristics of a companion diagnostic CD22 test, the sponsor should ensure that results from both sample types are validated for their intended use.

In addition, please provide clarification of the following:

- **Definition of CD22 positivity by the test and the range of CD22 expression levels.**
- **Percentage of patients who are CD22 negative as defined by local tests, and percentage of patients who are CD22 negative as defined by the central test.**
- **Percentage of CD22 positive patients in the screened population (i.e., percentage of tested patients who are included in the trial).**

Discussion:
The Sponsor provided clarification that approximately 5 % of the patients had been excluded based on CD22 testing performed by the local laboratories. The Sponsor also clarified that they had not found a correlation between CD22 expression and CR/CRi rates. Based on this information, the Agency considers the requirement for a companion diagnostic to be unlikely for the application.

2.8. Pharmacogenomics

Question 17: Does the Agency concur with the Sponsor's proposed pharmacogenomic analysis?

FDA Response to Question 17:
In principle we concur with your approach of conducting exploratory pharmacogenomic analyses as laid out in pages 64-65 of the meeting package. However, based on the submitted materials, we do not have enough information to comment on your specific plan at this time. Please refer to the FDA Guidance for Industry entitled "*Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling*" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf.

Discussion:
No discussion occurred.

2.9. Nonclinical

Question 18: Module 4 of Appendix 1 (Section 14) shows the nonclinical study reports that the Sponsor proposes to include in Module 4 of the eCTD.

Does the Agency concur that the proposed content of Module 4 is appropriate?

FDA Response to Question 18:
Yes, the content appears to be acceptable.

Discussion:
No discussion occurred.

2.10. Pediatrics

Question 19: Since inotuzumab ozogamicin is designated as an Orphan Drug for the "treatment of B-cell ALL", the Sponsor considers that submission of a pediatric assessment for inotuzumab ozogamicin for the treatment of adult patients with relapsed/refractory B-cell ALL is not required.

Does the Agency concur?

FDA Response to Question 19:
Yes. See Section 3.0.

Discussion:
No discussion occurred.

3.0 OTHER MEETING INFORMATION

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION
None.

5.0 ACTION ITEMS
None.

6.0 ATTACHMENTS AND HANDOUTS
None.

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/s/

ROMEO A DE CLARO
11/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 065658

MEETING MINUTES

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.
Attention: Alison L. Russell, PhD
Director, Worldwide Safety and Regulatory, WR&D
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-05208773 (inotuzumab ozogamicin).

We also refer to the teleconference between representatives of your firm and the FDA on October 20, 2014. The purpose of the meeting was to discuss the proposals for the planned analysis for the primary endpoint in the ongoing pivotal study Phase 3 Study B1931022 in patients with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL).

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

If you have any questions, call Amy Chi, Regulatory Project Manager at (240) 402-0992.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Ongoing Pivotal Phase 3 Study
Meeting Date and Time:	October 20, 2014 at 2:00 PM – 3:00 PM (EDT)
Meeting Location:	Teleconference
Application Number:	IND 065658
Product Name:	PF-05208773 (inotuzumab ozogamicin)
Indication:	Acute Lymphoblastic Leukemia (ALL)
Sponsor/Applicant Name:	Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.
Meeting Chair:	R. Angelo de Claro, MD
Meeting Recorder:	Amy Chi, MSN

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products (DHP)
Ann Farrell, MD, Director
R. Angelo de Claro, MD, Clinical Team Leader
Karen McGinn, MS, CRNP, Senior Clinical Analyst
Donna Przepiorka, MD, PhD, Clinical Reviewer
Amy Chi, MSN, Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Yuan Li Shen, PhD, Team Leader
Xin Gao, PhD, Reviewer

SPONSOR ATTENDEES

Stephanie Green, PhD, Statistics
Kongming Wang, PhD, Statistics
Tanya Nisan, BS, Asset Team Leader
Erik Vandendries, MD, Clinical
Alison Russell, PhD, Regulatory
Caroline Henesey, PhD, Regulatory
Mace Rothenberg, MD, Oncology Medical Officer
Rolf Linke, MD, Clinical
Robert Benedetto, MBA, President

1.0 BACKGROUND

Inotuzumab ozogamicin consists of a recombinant, humanized IgG4 antibody covalently bonded to a fully-characterized semi-synthetic derivative of γ-calicheamicin. γ-Calicheamicin is a cytotoxic antibiotic (natural product) produced by microbial fermentation. (b) (4) Inotuzumab ozogamicin drug product is a sterile, preservative-free, lyophilized dosage form.

During the May 19, 2014 meeting between the Sponsor and FDA, the Agency requested that the Sponsor provide their proposals for the planned analysis for the primary endpoint in the ongoing pivotal Phase 3 Study B1931022 in patients with relapsed/refractory B-cell ALL. The purpose of this meeting is to obtain feedback from the Agency on the proposed analysis.

2. DISCUSSION

Question 1:

In pivotal Phase 3 Study B1931022, to account for some patients refusing treatment post-randomization to Arm B, the Sponsor amended the protocol to increase the sample size from 194 to 218 for assessment of the primary endpoint of CR/CRi and from 292 to 325 for assessment of the key secondary endpoint of overall survival (OS). As described in the current version of the statistical analysis plan (SAP; version 2 dated 30 May 2014), the primary efficacy analysis for pivotal Phase 3 Study B1931022 includes an analysis of all patients according to assigned arm assuming that patients with no study treatment, or who started treatment but did not have a response assessment, are non-responders. The Sponsor plans to maintain the primary analysis as currently described in the SAP and proposes the following sensitivity analyses for CR/CRi:

- *Comparison excluding patients who did not receive study treatment and assuming patients without response assessment are non-responders, with and without adjustment for baseline factors;*
- *Comparison including all patients using logistic regression multiple imputation*
- *(missing at random [MAR] and missing not at random [MNAR]); and Comparison including all patients according to assigned arm and assuming patients with no study treatment are responders.*

Does the Agency concur with these proposals?

FDA Response to Question 1:

1. The Agency maintains the position that the ITT population should be used for the primary efficacy analysis in general. However, Study B1931022 illustrates an extreme case that all the early drop-out patients discontinued from the study prior to receiving therapy were in one arm only. In such cases, the efficacy analysis still using an ITT population may either overestimate or underestimate treatment effects when the early drop-out patients were treated as non-responders or responders respectively.

Due to the lack of a well-accepted method in such situations, the Agency may consider a modified ITT population for the primary efficacy analysis of response rate. However, the analyses results based on the ITT population (assuming either responders or non-responders for all the patients who discontinued from the study early without receiving any study treatment and who started treatment but did not have a response assessment) should also be submitted for review.

The modified ITT population should include all randomized patients who received therapy at least once. However, as the statistical properties of randomization may not be maintained through a modified ITT population, the Agency requests that you should perform extensive sensitivity analyses to evaluate the robustness of efficacy findings. Whether or not the efficacy findings from a modified ITT population may support the approval of the investigated therapy will be a review issue.

2. In addition to what have been proposed in this submission, the Agency requests an additional sensitivity analysis of response rate. This sensitivity analysis should use a modified ITT population. For the patients randomized to the treatment group, estimate their probabilities of dropping out if they were randomized to the control group. Then perform hypothesis testing and estimate treatment effects after assigning each patient in the treatment group a weight based on the probability of drop out from the previous step. Please refer to the following papers:

   Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized studies. *J. Educ. Psychol.* 1974; 66:668-701.

   Robins J, Richardson T, Spirtes P. On identification and inference for direct effects. *Epidemiology* 2009.

   Robins J, Richardson T. Alternative graphical causal models and the identification of direct effects. *Technical Report 100*, Center for Statistics and the Social Sciences, University of Washington 2010.

3. The Agency recommends that ITT population should be used for the primary efficacy analysis of overall survival. Sensitivity analyses based on different methods of handling early drop-outs should be proposed.

4. The Agency also recommends comparisons between the patients who dropped out the study and those who did not with respect to their demographic characteristics and other important baseline variables.

5. The experimental arm must demonstrate a clinically meaningful CR rate and duration of response. For OS to be included in the prescribing information, you must first win on the primary endpoint, and OS must be statistically significant in the experimental arm.

6. You will need to provide justification that modified CR endpoints such as CRi and CRp are reasonably likely to predict for clinical benefit in your proposed indication. The

acceptability of CRi will be a review issue. We recommend you provide MRD data to support the acceptability of CRi.

In addition, based upon your changes to the SAP:

- We agree with your proposed increase in sample size for CR/CRi and OS.
- We agree with your proposal to cap patients with Ph+ ALL to approximately 20%.
- We agree with removal of TTP as an endpoint.
- We agree with your definition of the per-protocol population, but analyses will be considered exploratory.

Discussion on FDA comment #5:
The Agency noted inconsistent descriptions of the endpoints of CR/CRi and OS between the statistical sections and the protocol. The Sponsor proposal to test CR/CRi at alpha 0.0125 one sided and test OS at alpha 0.0125 one sided is acceptable to the Agency. The Sponsor clarified that there will be no recycling of alpha between the two endpoints. The Agency recommended that the Sponsor submit a revised SAP that identifies CR/CRi and OS as multiple primary endpoints and that the analysis plan in the revised SAP will supersede previous versions of the protocol and SAP.

3.0 OTHER MEETING INFORMATION

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

None.

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

/s/

ROMEO A DE CLARO
10/24/2014

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 30, 2007
TIME: 3:00 PM
LOCATION: Room 1415, WO
APPLICATION: IND 65,658, Wyeth (b) (4)
DRUG NAME: inotuzumab ozogamicin (CMC-544)
TYPE OF MEETING: Type B, CMC-specific EOP2 meeting

MEETING CHAIR: Ravi Harapanhalli, Ph.D.

MEETING RECORDER: Kim Robertson *for* Carl Huntley, R. Ph., MBA

FDA ATTENDEES:

Robert Kane, MD, Medical Reviewer, DODP (invited)
Ravi Harapanhalli, Ph.D., Branch Chief, ONDQA
Xiao Chen, Ph.D., Senior Reviewer, ONDQA
Marjorie Shapiro, MD, Reviewer, OBP/DMA
Kim Robertson, Regulatory Project Manager, DDOP

EXTERNAL CONSTITUENT ATTENDEES:

Justin Moran	Associate Director Bioprocess development
Victor Gangi	Director, Global Regulatory Affairs
Tish Weber	Senior Manager
Maureen McLaughlin	Director, Development Quality Unit

BACKGROUND:

Inotuzumab ozogamicin is an antibody-drug conjugate developed by Wyeth. Inotuzumab ozogamicin consists of a recombinant, humanized IgG4 antibody covalently bonded to a semi-synthetic derivative of calicheamicin. Calicheamicin is a cytotoxic natural product produced by microbial fermentation. Inotuzumab Ozogamicin for Injection (b) (4) mg/vial) is a sterile, preservative-free, freeze-dried dosage form. (b) (4)

Summary of Manufacturing Changes:

- (b) (4)
- (b) (4) and other changes) and manufacturing site change
- Drug substance change in storage condition (b) (4)
- Drug product fill volume change from (b) (4) mg/vial to (b) (4) mg/vial

MEETING OBJECTIVES:

In preparation for the start of the Phase 3 clinical development program, a meeting with the Agency is necessary to review information on the plans for changes in chemistry, manufacturing, and controls information. The meeting is intended to provide an overview of changes planned from the initial manufacturing of Phase 3 supplies through transition to commercial sites of manufacture and to discuss the appropriateness of the stability protocols to support Phase 3 studies and the planned NDA.

LIST OF SPECIFIC QUESTIONS, ANSWERS AND DISCUSSION:

Q1 Does the Agency agree that the proposed data package supports a commercial expiry period for the (b) (4)

FDA:

(b) (4)

Discussion Point: ***Provided comparability is established between commercial and clinical lots, your proposal to include two clinical batches and one commercial batch is acceptable for the assessment of the expiration date.***

Q2 Does the Agency agree that data from one development lot of drug product (b) (4)

FDA:

Your approach to (b) (4) using one developmental batch of the drug substance is acceptable. However, note that at least three primary batches of the drug substance need to be submitted in the NDA for the assessment of expiration dating period. The adequacy of the generated stability data to support your proposed expiry will depend on the degree of similarity between the primary stability and proposed commercial batches.

Discussion Point: It was agreed that based (b) (4) ***This data will be submitted in the NDA.***

Q3 Does the Agency agree that the stability data (b) (4) for the drug product supply produced at the commercial site of manufacture?

FDA:
It appears that during the Phase 3 clinical stage, changes will be mad (b) (4) Therefore, clinical batches used for Phase 3 studies should be the basis for primary stability studies. (b) (4) are not adequate for considering stability data from Phase 1 as being representative of Phase 3 batches. Therefore, stability data from three registration batches will be considered primary data and all other stability data from Phase1/2 studies would be considered supportive data, if justified. Also, as discussed in the answer to question #1, granting an expiry is a review issue.

Discussion Point: ***The FDA agreed that the sponsor's approach appears acceptable, provided adequate comparability is established. We would expect a timely stability update during the review period. Expiration dating period will be based on the assessment of the available data.***

FDA Additional Comments:

Develop a specification for (b) (4) for the drug substance and the drug product.

Define the quality attribute (b) (4)

Discussion Point: The sponsor clarified that the (b) (4) **.**

Revise the stability protocol (Table 6-6) to include the testing of the following quality attributes at each time point:
(b) (4)
Isoelectric Focusing
Particulate matter
SDS-PAGE Nonreduced

Discussion Point: ***It was agreed that particulate testing will be retained at all time points in the primary stability protocol.***

Revise the stability protocol for (b) (4) the drug substance to include bioburden and endotoxins.

Discussion Point: ***The sponsor will consider incorporating bio-burden and endotoxins*** (b) (4) ***for drug substance manufacturing. This point requires further discussion.***

(b) (4)

Discussion Point: ***No discussion was necessary.***

We note that the commercial manufacturing sites (b) (4) for inotuzumab ozogamicin for injection have not yet been identified. We recommend that you discuss your plane for demonstrating comparability between the clinical and commercial processes prior to filing an NDA.

<u>Discussion Point:</u> The Agency recommends that the sponsor uses both pilot source reference material and ADF lots of reference materials in the proposed clinical to commercial comparability studies.

<u>ACTION ITEMS:</u>

- **Further discussion is needed with regard to endotoxin testing and bio-burden testing for the (b) (4) drug substance stability monitoring.**

- **The sponsor will inform the Agency of the measures taken with regard to the CMC comments from the original IND review.**

Meeting Adjourned: 4:30 PM

Meeting Chair: Ravi Harapanhalli, Ph.D.
PM: Kim Robertson for Carl Huntley

Submitted by:

_____
Carl Huntley, R.Ph., MBA
Regulatory Project Manager

Concurrence Chair:

_____
Ravi Harapanhalli, Ph.D.
Branch Chief

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/s/

Ravi Harapanhalli
6/14/2007 03:06:50 PM

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/s/

Carl Huntley

6/14/2007 06:34:32 PM

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

LATE-CYCLE MEETING MINUTES

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Attention: Alison Russell, PhD
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Inotuzumab Ozogamicin (PF-05208773; CMC-544); lyophilized (b) (4) powder; (b) (4) mg/vial.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 23, 2017. Per your request, this meeting was converted to a teleconference.

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 Rachel McMullen, Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Lead
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

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time:	June 23, 2017; 11:00AM-12:00PM (ET)
Meeting Location:	Teleconference
Application Number:	BLA 761040
Product Name:	Inotuzumab Ozogamicin (PF-05208773; CMC-544)
Indication:	Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia (ALL)
Applicant Name:	Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Meeting Chair:	R. Angelo de Claro, MD
Meeting Recorder:	Rachel McMullen, MPH, MHA

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Richard Pazdur, MD, Office Director

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Division Director
R. Angelo de Claro, MD, Clinical Team Leader
Tanya Wroblewski, MD, Medical Officer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Chris Sheth, PhD, Pharmacology/Toxicology Team Leader
Michael Manning, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V,
Bahru Habtemariam, Pharm D, Clinical Pharmacology Team Leader
Salaheldin Hamed, PhD, Pharmacology Reviewer

Office of Product Quality
Gerald Feldman, PhD, Product Quality Team Leader
Mate Tolnay, PhD, Product Quality Reviewer
Charles Jewell, PhD, Product Quality Reviewer
María José López Barragán, PhD; Microbiology Reviewer
Vicky Borders-Hemphill, Pharm D, Labeling Review Specialist
Thuy Nguyen, MPH , Quality Assessment Lead

Office of Biostatistics/Division of Biometrics V
Yuan Li Shen, PhD, Statistical Team Leader
Qing Xu, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology
Nicole Garrison, PharmD, Reviewer
Mei-Yean Chen, PharmD, Risk Management Analyst
Neil Vora, PharmD, MBA, Project Manager

APPLICANT ATTENDEES

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.

Kofi Asomaning, MD ScD, Epidemiology Lead
Ramzi Dagher, MD, Oncology Global Regulatory Portfolio Head
Leena Das-Young, PharmD; Head, Late Phase Development Oncology
Svetoslav Dimitrov, MD; Safety Lead
Philip Johnson, BS, MBA; Asset Team Lead
Caroline Henesey, PhD; Hematology Global Regulatory Portfolio Lead
Alison Russell, PhD; Regulatory Lead
Kim Kelso, MA; Project Management
Reza Khosravan, PhD; Clinical Pharmacology Lead
Douglas Laird, PhD; Translational Oncology Lead
Kourosh Parivar, M.Pharm, Head, Clinical Pharmacology
Jane Liang White, PhD; Statistical Lead
Fausto Loberiza, MD, MS; Medical Affairs Lead
Stephen Mayer, BA; Regulatory, CMC
Allan Safferman, MD; Safety
Ann Subashi, MS, Regulatory, CMC
Erik Vandendries, MD, PhD; Clinical Lead
Tao Wang, PhD; Statistics
Iain Webb, MD; Hematologic Malignancies Clinical Lead

1.0 BACKGROUND

BLA 761040/SDN 25 was submitted on December 20, 2016 for Inotuzumab Ozogamicin (PF-05208773; CMC-544).

Proposed indication(s): Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia (ALL)

PDUFA goal date: August 20, 2017

FDA issued a Background Package in preparation for this meeting on June 16, 2017.

2.0 DISCUSSION

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

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Information Requests – 5 minutes

Clinical

The administration of inotuzumab ozogamicin demonstrates a delayed recovery of platelet counts. Applicant conducting analysis to assess time to platelet recovery based on baseline platelet counts and platelet nadirs.

Discussion: ***There was no discussion.***

3. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

The review teams are considering the following:

Clinical Pharmacology

PMR: The proposed inotuzumab ozogamicin dose of 1.8 mg/m^2 may not be optimal in balancing safety and efficacy. The relatively high rate of VOD adverse events is a significant concern. (b) (4) was not informed by robust dose-response data, we are uncertain whether the proposed dose of 1.8 mg/m^2 balances the safety and efficacy of inotuzumab ozogamicin. There is a possibility that a lower dose may provide a more favorable balance of safety and efficacy. Therefore, we recommend a dose-finding study. The study should investigate at least (b) (4) dose levels with sufficient number of patients to assess the response rate at each dose level. (b) (4)

Discussion: ***The Sponsor stated that exposure-response analyses for safety and efficacy, including analysis for CR/Cri, MRD negativity, and VOD support the proposed starting dose. Lower doses of IO lead to lower rates of CR/Cri, MRD-negativity, and same rates of VOD. The Agency accepts the Sponsor's proposal to submit additional documentation on the exposure-response analyses. The Agency notes limitations with the narrow range of dose levels and availability of corresponding exposure levels.***

Post-Meeting Note: The Sponsor submitted the additional analysis to support the proposed dose on June 26, 2017.

Clinical

PMR: (b) (4)
(b) (4)

Discussion: ***The Agency recommended a minimum of 5 year follow-up for this proposed PMR. The Agency advised the Sponsor that final concurrence would occur upon submission of the protocol and synopsis. The Sponsor agreed to broaden the inclusion criteria to include pediatric patients. The Agency clarified that the sample size would be primarily driven by number of available patients in CIBMTR database.***

Chemistry Manufacturing and Controls

PMC-1: Conduct the bioburden and endotoxin test method qualification of inotuzumab ozogamicin drug substance using two additional batches.

PMC Schedule Milestones: Study Completion: 11/2017

PMC-2: Conduct the sterility and endotoxin test method qualification of inotuzumab ozogamicin drug product using two additional batches.

PMC Schedule Milestones: Study Completion: 11/2017

PMC-3: Implement bioburden and endotoxin monitoring of the (b) (4) used to manufacture inotuzumab ozogamicin drug product.

PMC Schedule Milestones: Implementation: 11/2017

Discussion: ***There was no discussion.***

4. Major labeling issues – 20 minutes

Refer to the prescribing information sent to you on June 1, 2017 for labeling recommendations. The Agency expects to receive back the labeling from you on or before June 19, 2017. Prior to the late cycle meeting, please inform the Agency of labeling-related issues that you wish to discuss at the late cycle meeting.

Discussion: ***The Agency provided feedback on FDA recommended labeling approaches to address overfill and deliverable amounts. The Agency referred the Sponsor to FDA Guidance on Allowable Excess Volume (June 2015) available at https://www.fda.gov/downloads/drugs/guidances/ucm389069.pdf.***

The Agency will provide recommendations in the labeling (USPI, Carton and Container)to be sent back to the Sponsor.

The Agency disagrees with the definition of PFS and hence does not recommend including PFS claims in Section 14 of the USPI.

5. Review Plans – 10 minutes

The Agency anticipates meeting the PDUFA timelines for the application review. During the remaining review time, the Agency will work with the Applicant to reach labeling agreement.

Discussion: ***The following issues were discussed.***

- ***Pediatric Development: The Sponsor does not plan to submit a PPSR at the moment. The Sponsor provided an update on the pediatric development plans in Europe and in the US. The Agency recommended that the Sponsor discuss a PPSR submission with the Agency.***

- ***Facilities: Additional information regarding the Pearl River facilities inspection is pending from Pfizer. The Sponsor will follow up.***

6. Wrap-up and Action Items – 10 minutes

Discussion: ***The Sponsor noted that the anticipated date for launching drug supplies is July 2017.***

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/

ROMEO A DE CLARO
06/26/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

LATE CYCLE MEETING
BACKGROUND PACKAGE

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Attention: Alison Russell, PhD
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Inotuzumab Ozogamicin (PF-05208773; CMC-544); lyophilized (b) (4) powder; (b) (4) mg/vial.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 23, 2017. Per your request, this meeting is being converted to a teleconference. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at rachel.mcmullen@fda.hhs.gov, at least one week prior to the meeting.

If you have any questions, call Rachel McMullen, Regulatory Project Manager, at (240) 402-4574.

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

ENCLOSURES:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	June 23, 2017; 11:00AM-12:00PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	BLA 761040
Product Name:	Inotuzumab Ozogamicin
Indication:	Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia (ALL)
Applicant Name:	Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.

FDA ATTENDEES (tentative)

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Division Director
R. Angelo de Claro, MD, Clinical Team Leader
Tanya Wroblewski, MD, Medical Officer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Chris Sheth, PhD, Pharmacology/Toxicology Team Leader
Michael Manning, PhD, Pharmacology/Toxicology Reviewer

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Salaheldin Hamed, PhD, Pharmacology Reviewer

Office of Product Quality
Gerald Feldman, PhD, Product Quality Team Leader
Mate Tolnay, PhD, Product Quality Reviewer

Office of Biostatistics/Division of Biometrics V
Yuan Li Shen, PhD, Statistical Team Leader
Qing Xu, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology
Nicole Garrison, PharmD, Reviewer
Mei-Yean Chen, PharmD, Risk Management Analyst
Neil Vora, PharmD, MBA, Project Manager

APPLICANT ATTENDEES

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.

Leena Das-Young, PharmD; Head, Late Phase Development Oncology
Svetoslav Dimitrov, MD; Safety Lead
Philip Johnson, BS, MBA; Asset Team Lead
Ted Johnson, PhD Nonclinical, ADME
Caroline Henesey, PhD; Hematology Global Regulatory Portfolio Lead
Nathalie Hayduk, PhD; Pharmaceutical Sciences
Reza Khosravan, PhD; Clinical Pharmacology Lead
Douglas Laird, PhD; Translational Oncology Lead
Jane Liang White, PhD; Statistical Lead
Fausto Loberiza, MD, MS; Medical Affairs Lead
Stephen Mayer, BA; Regulatory, CMC
Alison Russell, PhD; Regulatory Lead
Allan Safferman, MD; Safety
Ann Subashi, MS, Regulatory, CMC
Erik Vandendries, MD, PhD; Clinical Lead
Tao Wang, PhD; Statistics
Iain Webb, MD; Hematologic Malignancies Clinical Lead
David Wright, PhD; Nonclinical, Toxicology

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

No substantive review issues have been identified to date/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 – 5 minutes

Clinical

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(b) (4)

(b) (4)

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PMC Schedule Milestones: Study Completion: 11/2017

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5. Review Plans – 10 minutes

The Agency anticipates meeting the PDUFA timelines for the application review. During the remaining review time, the Agency will work with the Applicant to reach labeling agreement.

6. Wrap-up and Action Items – 10 minutes

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/s/

ANN T FARRELL
06/16/2017