

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125326

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125326/0

Supplement Number: _____

NDA Supplement Type (e.g. SE5): _____

Division Name: DBOP

PDUFA Goal Date: July 30, 2009

Stamp Date: 1/30/2009

Proprietary Name: ARZERRA

Established/Generic Name: Ofatumumab

Dosage Form: 100 mg/5 mL single-use vial (IV)

Applicant/Sponsor: _____

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

- (1) _____
- (2) _____
- (3) _____
- (4) _____

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

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: indicated for treatment of patients with chronic lymphocytic leukemia who have received prior therapy

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 ^a	Not meaningful therapeutic benefit ^a	Ineffective or unsafe [†]	Formulation failed ^Δ
☐ Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

Justification):*** Not feasible:**

☐ Necessary studies would be impossible or highly impracticable because:

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

*** Not meaningful therapeutic benefit:**

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

] Justification attached.

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

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

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

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

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

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

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

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

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

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

- ☐ Yes: (Complete Section A.)
☐ No: Please check all that apply:
☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
☐ Completed for some or all pediatric subpopulations (Complete Sections D)
☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

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

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

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

☐ Justification attached.

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

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

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

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

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

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

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

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

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

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

* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

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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.

Action 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)

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

CONFIDENTIAL

m1.3.3 Debarment Certification

DEBARMENT CERTIFICATION

GlaxoSmithKline certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (BLA 125326).



Craig Wozniak

November 2008

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125326	NDA Supplement # BLA STN # 0	If NDA, Efficacy Supplement Type:
Proprietary Name: Arzerra Established/Proper Name: Ofatumumab Dosage Form: 100mg/ 5mL single-use vial		Applicant: Glaxo Group Limited d/b/a GlaxoSmithKline Agent for Applicant (if applicable):
RPM: Raymond Chiang		Division: DBOP
NDA: NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review. ☐ No changes ☐ Updated Date of check: 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. On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.
♦ User Fee Goal Date Action Goal Date (if different)		October 31, 2009
♦ Actions		
• Proposed action		☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions (specify type and date for each action taken)		☒ None
♦ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm062265.pdf). If not submitted, explain _____		☐ Received

¹ The Application Information section is (only) a checklist. The Contents of Action Package section (beginning on page 5) lists the documents to be included in the Action Package.

Application Characteristics ²	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): ☒ Fast Track ☐ Rolling Review ☒ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC BLAs: Subpart E ☒ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies Comments: _____	
♦ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: <u>orphan indication</u>	orphan indication
♦ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	☒ Yes, date 10.13.09
♦ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☒ No
♦ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other FDA Press Release

² All questions in all sections pertain 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)	☐ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire _____
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
♦ Copy of this Action Package Checklist³	Yes
Officer/Employee List	
♦ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
♦ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 10.26.09
Labeling	
♦ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	10.26.09
• Original applicant-proposed labeling	yes, dated 1.30.09
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
♦ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 3/26/09

Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
Original applicant-proposed labeling	1.30.09
Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent division proposal for (only if generated after latest applicant submission)	
Most recent applicant-proposed labeling	10.16.09
- Proprietary Name - Review(s) (indicate date(s)) - Acceptability/non-acceptability letter(s) (indicate date(s))	May 15, 2009, September 22, 2009 Acceptability letter dated May 19, 2009
Labeling reviews (indicate dates of reviews and meetings)	☒ RPM 10.5.09; 3.31.09 ☒ DMEDP addendum 8.25.09; 7.31.09 ☒ DRISK 5.12.09 ☒ DDMAC 8.19.09 ☐ CSS ☒ Other reviews SEALD 7.14.09; MHT 5.6.09; OBP 10.27.09, 6.17.09
Administrative / Regulatory Documents	
Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (indicate date of each review)	2.27.09
NDA only: Exclusivity Summary (signed by Division Director)	☐ Included
Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant in on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (indicate date) - If yes, OC clearance for approval (indicate date of clearance communication)	☐ Yes ☒ No ☐ Not an AP action
Pediatric Page (approvals only, must be reviewed by PERC before finalized)	☒ Included
Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	☒ Verified, statement is acceptable
Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	10.8.09 IR email 10.1.09 IR email 9.28.09 IR email 9.25.09 IR email 9.21.09 IR tcon 9.15.09 IR email 9.11.09 IR email 9.9.09 IR email

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	9.8.09 IR email 9.4.09 IR tcon 8.27.09 IR email 8.19.09 IR email 8.12.09 IR tcon 8.11.09 IR email 8.5.09 AI email 8.3.09 IR email 8.3.09 IR email 7.23.09 IR email 7.23.09 IR email 7.14.09 IR tcon 7.14.09 IR email 7.13.09 IR email 7.1.09 IR tcon 6.30.09 IR tcon 6.23.09 IR tcon 6.19.09 IR ltr 6.18.09 IR email 6.12.09 IR ltr 5.21.09 Advice/IR tcon 5.19.09 IR tcon 5.19.09 Advice Ltr 5.11.09 IR ltr 4.20.09 Advice F2F mtg 4.14.09 IR ltr 4.8.09 Advice/IR tcon 3.30.09 Filing ltr 3.27.09 IR email 3.12.09 IR email 3.12.09 Advice/IR tcon 3.9.09 IR tcon 3.6.09 IR ltr 3.4.09 IR tcon 3.3.09 IR tcon 2.25.09 IR tcon 2.18.09 IR tcon 2.18.09 Ack ltr 2.12.09 IR tcon 2.12.09 Advice/IR tcon 2.10.09 IR tcon 2.9.09 IR tcon 2.6.09 IR tcon 2.2.09 Advice/IR tcon
♦ Internal memoranda, telecons, etc.	6.15.09 team meeting 5.19.09 team meeting 5.4.09 team meeting 4.21.09 team meeting 4.6.09 mid-cycle meeting 4.2.09 team meeting 3.25.09 review designation memo 3.12.09 team meeting 2.27.09 filing meeting 2.13.09 first committee meeting
Minutes of Meetings	
• PeRC (indicate date of mtg; approvals only)	☒ Not applicable

• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	☐ Not applicable 7.22.09
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 10.28.08; 11.21.08
• EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg 8.9.07
• Other (e.g., EOP2a, CMC pilot programs)	12.21.05 Pre-Phase 2; 9.30.05 Type C Mtg.; 9.25.03 Type C Mtg.
◆ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	5.29.09
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	6.29.09
Decisional and Summary Memos	
◆ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None 10.26.09
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 10.20.09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 9.21.09 addendum 10.9.09
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 17
Clinical Information⁵	
◆ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	please see CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	9.21.09; 2.23.09 (filing review)
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☐ None
◆ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	Included in Section 7 of clinical review
◆ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Located in Section 3.3 of clinical review
◆ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
◆ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not needed
◆ Risk Management • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo (<i>indicate date</i>) • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☐ None 10.6.09 DMEPA review 5.12.09 DRISK review
◆ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☐ None requested 7.2.09
Clinical Microbiology ☐ None	
◆ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☒ None

⁵ Filing reviews should be filed with the discipline reviews.

Biostatistics ☐ None	
♦ Statistical Division Director Review(s) (indicate date for each review)	☒ None
Statistical Team Leader Review(s) (indicate date for each review)	☐ None 9.18.09
Statistical Review(s) (indicate date for each review)	☐ None integrated with clinical review; 2.25.09 (filing review)
Clinical Pharmacology ☐ None	
♦ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☐ None 7.13.09
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 7.13.09; 7.13.09; 7.7.09; 4.21.09; 2.27.09 (filing review)
♦ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☒ None
Nonclinical ☐ None	
♦ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ None
• Supervisory Review(s) (indicate date for each review)	☐ None 9.2.09
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 8.10.09; 2.20.09 (filing review)
♦ 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 Included in P/T review, page
♦ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☒ None requested
Product Quality ☐ None	
♦ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☒ None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☐ None 8.17.09
• Product quality review(s) (indicate date for each review)	☐ None 8.17.09
• ONDQA Biopharmaceutics review (indicate date for each review)	N/A
• BLAs only: Facility information review(s) (indicate dates)	☐ None 8.20.09; 3.5.09 (filing review)
♦ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	☐ Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
♦ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (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)	8.17.09 on page 7 of Product Quality Review
☐ Review & FONSI (indicate date of review)	N/A

☐ Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Facilities Review/Inspection	9.2.09; 8.20.09; 8.11.09
• NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date)	Date completed: ☐ Acceptable ☐ Withhold recommendation
• BLAs: ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (date completed must be within 60 days prior to AP)	Date completed: 8.7.09 ☒ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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Order: FDA/Apl, Then Date Ascending

THIS REPORT MAY CONTAIN CONFIDENTIAL INFORMATION

STN: L 125326/0

Applicant: Glaxo Group Limited d/b/a GlaxoSmithKline #1809

Product: Ofatumumab

Short Summary: treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab

Date	Elec	Post	Description	FDA Recd Date	Login ID
02-FEB-2009			Telecon. Advice / Information Request (CHIANG, RAYMOND)		
06-FEB-2009			Telecon. Information Request (CHIANG, RAYMOND)		
09-FEB-2009			Telecon. Information Request (CHIANG, RAYMOND)		
10-FEB-2009			Telecon. Information Request (CHIANG, RAYMOND)		
12-FEB-2009			Memo. Review Committee Assigned Memorandum (CHIANG, RAYMOND)		
12-FEB-2009			Telecon. Advice / Information Request (CHIANG, RAYMOND)		
12-FEB-2009			Telecon. Information Request (CHIANG, RAYMOND)		
13-FEB-2009			Meeting Summary. First Committee Meeting (CHIANG, RAYMOND)		
18-FEB-2009			Letter. Acknowledgement Letter - STN Assignment - Application (CHIANG, RAYMOND)		
18-FEB-2009			Telecon. Information Request (CHIANG, RAYMOND)		
25-FEB-2009			Telecon. Information Request (CHIANG, RAYMOND)		
27-FEB-2009			Meeting Summary. Filing Meeting Summary (CHIANG, RAYMOND)		
03-MAR-2009			Telecon. Information Request (CHIANG, RAYMOND)		
04-MAR-2009			Telecon. Information Request (CHIANG, RAYMOND)		
06-MAR-2009			Letter. Information Request (CHIANG, RAYMOND)		
09-MAR-2009			Telecon. Information Request (CHIANG, RAYMOND)		
10-MAR-2009			Memo. Other - Orphan Designation Letter uploaded on behalf of Timothy Cote (CHIANG, RAYMOND)		
12-MAR-2009			Telecon. Advice / Information Request (CHIANG, RAYMOND)		
12-MAR-2009			Telecon. Information Request (CHIANG, RAYMOND)		
27-MAR-2009			Telecon. Information Request (CHIANG, RAYMOND)		
30-MAR-2009			Letter. Filing Notification Letter (CHIANG, RAYMOND)		
08-APR-2009			Telecon. Advice / Information Request (CHIANG, RAYMOND)		
14-APR-2009			Letter. Deficiencies Identified - Filing Issues Letter (CHIANG, RAYMOND)		
20-APR-2009			Telecon. Advice (CHIANG, RAYMOND)		
21-APR-2009			Memo. Other - QT-IRT review uploaded on behalf of Suchitra Balakrishnan (CHIANG, RAYMOND)		
11-MAY-2009			Letter. Information Request (CHIANG, RAYMOND)		
11-MAY-2009			Memo. Other - Uploaded Risk Management Plan (RMP) review memo on behalf of Claudia Karwoski (CHIANG, RAYMOND)		
19-MAY-2009			Letter. Other / PNR Acceptance - proprietary name granted (CHIANG, RAYMOND)		
19-MAY-2009			Telecon. Information Request (CHIANG, RAYMOND)		
21-MAY-2009			Telecon. Advice / Information Request (CHIANG, RAYMOND)		
12-JUN-2009			Letter. Major Amendment Acknowledgement (CHIANG, RAYMOND)		
18-JUN-2009			Telecon. Information Request (CHIANG, RAYMOND)		
19-JUN-2009			Letter. Information Request (CHIANG, RAYMOND)		
23-JUN-2009			Telecon. Information Request (CHIANG, RAYMOND)		
30-JUN-2009			Telecon. Information Request (CHIANG, RAYMOND)		
01-JUL-2009			Telecon. Information Request (CHIANG, RAYMOND)		
02-JUL-2009			Memo. Inspection Memo - DSI Memo (GERSHON, SHARON)		
07-JUL-2009			Memo. Other - Clinical Pharmacology Review (YANG, JUN)		
13-JUL-2009			Memo. Other / Assign Schedule Type - Clinical Pharmacology Team Leader Review (ZHAO, HONG)		

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Order: FDA/Appl, Then Date Ascending

THIS REPORT MAY CONTAIN CONFIDENTIAL INFORMATION

STN: L 125326/0

Applicant: Glaxo Group Limited d/b/a GlaxoSmithKline #1809

Product: Ofatumumab

Short Summary: treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab

Date	Elec	Post	Description	FDA Recd Date	Login ID
13-JUL-2009			Memo. Other - Clinical Pharmacology Genomics Review uploaded on behalf of Mike Pacanowski (CHIANG, RAYMOND)		
13-JUL-2009			Memo. Other - Clinical Pharmacology: Pharmacometric Review uploaded on behalf of Justin Earp (CHIANG, RAYMOND)		
13-JUL-2009			Telecon. Information Request (CHIANG, RAYMOND)		
14-JUL-2009			Telecon. Advice / Information Request (CHIANG, RAYMOND)		
14-JUL-2009			Telecon. Information Request (CHIANG, RAYMOND)		
23-JUL-2009			Telecon. Information Request (CHIANG, RAYMOND)		
23-JUL-2009			Telecon. Information Request (CHIANG, RAYMOND)		
03-AUG-2009			Telecon. Information Request (CHIANG, RAYMOND)		
03-AUG-2009			Telecon. Labeling via FAX/e-mail / Labeling Target Closure (CHIANG, RAYMOND)		
05-AUG-2009			Telecon. Advice / Information Request / PMC Target Closure - Proposed clinical and clinical pharmacology PMRs/PMCs (CHIANG, RAYMOND)		
07-AUG-2009			Memo. Establishment Inspection Report - EER report (STOCK, MARISA)		
10-AUG-2009			Memo. Committee Memo/Pharm-tox Review (MCDUGAL, ANDREW)		
11-AUG-2009			Memo. Other - Facilities Drug Substance Review (CHI, BO)		
11-AUG-2009			Telecon. Advice / Information Request - Proposed CMC PMCs (CHIANG, RAYMOND)		
12-AUG-2009			Telecon. Information Request (CHIANG, RAYMOND)		
17-AUG-2009			Memo. Other - Product Quality Review (MUTHUKKUMAR, SUBRAMANIAN)		
17-AUG-2009			Memo. Other - Product Quality Team Leader Review (RELAHAN, BARBARA)		
19-AUG-2009			Telecon. Advice / Information Request - Proposed clinical, clinical pharmacology, and CMC PMRs/PMCs (CHIANG, RAYMOND)		
20-AUG-2009			Memo. Other - Facilities Team Leader Review (HUGHES, PATRICIA)		
27-AUG-2009			Telecon. Labeling via FAX/e-mail (CHIANG, RAYMOND)		
02-SEP-2009			Memo. Other - Uploaded Associate Director for Pharmacology Review on behalf of John Leighton (CHIANG, RAYMOND)		
02-SEP-2009			Memo. Other - Facilities Drug Product Review (OBENHUBER, DONALD)		
04-SEP-2009			Telecon. Advice (CHIANG, RAYMOND)		
08-SEP-2009			Telecon. Advice / Information Request - Proposed revisions to package insert, carton and container labels (CHIANG, RAYMOND)		
09-SEP-2009			Telecon. Advice / Information Request - Comment concerning package insert label (CHIANG, RAYMOND)		
11-SEP-2009			Telecon. Advice / Information Request - Comments concerning package insert, carton and container labels (CHIANG, RAYMOND)		
15-SEP-2009			Telecon. Information Request (CHIANG, RAYMOND)		
21-SEP-2009			Memo. Committee Memo/Clinical Review (LEMERY, STEVEN)		
21-SEP-2009			Telecon. Information Request (CHIANG, RAYMOND)		
25-SEP-2009			Telecon. Information Request - Request for additional PMRs (CHIANG, RAYMOND)		
28-SEP-2009			Telecon. Information Request - Request additional PMR (CHIANG, RAYMOND)		
01-OCT-2009			Telecon. Information Request - Request additional PMR (CHIANG, RAYMOND)		
06-OCT-2009			Memo. Other - Healthcare Practitioner Survey Review Memo (ARNWINE, KRISTINA)		
08-OCT-2009			Telecon. Labeling via FAX/e-mail (CHIANG, RAYMOND)		

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Order: FDA/Appl, Then Date Ascending

THIS REPORT MAY CONTAIN CONFIDENTIAL INFORMATION

STN: L 125326/0

Applicant: Glaxo Group Limited d/b/a GlaxoSmithKline #1809

Product: Ofatumumab

Short Summary: treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab

Date	Elec	Post	Description	FDA Recd Date	Login ID
26-OCT-2009			Telecon. Information Request - Arzerra approval notification (CHIANG, RAYMOND)		
26-OCT-2009			Letter. Approval (CHIANG, RAYMOND)		
30-JAN-2009	Y		Original Application. treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab	30-JAN-2009	60008320
12-FEB-2009	Y		Amendment # 1. Unsolicited amendment to replace SAS transport files to include immunogenicity data	13-FEB-2009	60008431
13-FEB-2009	Y		Amendment # 2. Response to February 6, 2008 IR to submit Request for Proprietary Review as amendment to BLA	17-FEB-2009	60008450
19-FEB-2009	Y		Amendment # 3. Response to February 18, 2009 IR for SAS programs and datasets	19-FEB-2009	60008480
26-FEB-2009	Y		Amendment # 4. Response to February 12, 2009 IR for production schedules of DS and DP	26-FEB-2009	60008538
27-FEB-2009	Y		Amendment # 5. Response to February 25, 2009 IR for sterilization filter validation info and Barnard Castle manufacturing site diagrams	27-FEB-2009	60008556
06-MAR-2009	Y		Amendment # 7. Response to FDA questions concerning CMC facilities	06-MAR-2009	60008631
11-MAR-2009	Y		Amendment # 8. Completed "Highlights of Clinical Pharmacology" form	12-MAR-2009	60008663
17-MAR-2009	Y		Amendment # 9. Response to March 6, 2009 IR request	17-MAR-2009	60008708
18-MAR-2009	Y		Amendment # 10. Response to March 12, 2009 electronic mail IR	18-MAR-2009	60008721
03-APR-2009	Y		Amendment # 11. Response to March 27, 2009 electronic mail IR from statistical reviewer	03-APR-2009	60008835
17-APR-2009	Y		Amendment # 12. Available therapy briefing document in response to FDA request in 3.12.09 tcon	20-APR-2009	60008921
20-APR-2009	Y		Amendment # 13. Revised label in response to 74 day letter	20-APR-2009	60008925
30-APR-2009	Y		Amendment # 14. 90-Day Safety Update	01-MAY-2009	60009013
14-MAY-2009	Y		Amendment # 15. Responses to FDA Day 74 Requests	15-MAY-2009	60009122
18-MAY-2009	Y		Amendment # 16. Response to question 4 from FDA Day 74 Request IRC discrepancies	19-MAY-2009	60009142
20-MAY-2009	Y		Amendment # 17. Response to FDA Statistical Request to include dataset with DOR, date of progression and censoring times for Investigator response analysis in 5.19.09 tcon	21-MAY-2009	60009171
22-MAY-2009	Y		Amendment # 18. CMC Notification of Out of Specifications results for sub-visible particles	22-MAY-2009	60009192
05-JUN-2009	Y		Amendment # 19. Response to FDA request for additional CMC information in 5.11.09 letter and F/U to question 14 in 74-day letter	05-JUN-2009	60009271
22-JUN-2009	Y		Amendment # 20. Response to FDA request for additional CMC information in 6.18.09 electronic communication	22-JUN-2009	60009380
02-JUL-2009	Y		Amendment # 21. Response to FDA request for additional CMC information in 6.19.09 letter	02-JUL-2009	60009477
20-JUL-2009	Y		Amendment # 22. Response to FDA information requests in 7.13.09 and 7.14.09 electronic communications.	20-JUL-2009	60009576
20-JUL-2009	Y		Amendment # 23. Response to FDA's information requests in 6.30.09 and 7.1.09 tcons	21-JUL-2009	60009578
28-JUL-2009	Y		Amendment # 24. Response to July 23, 2009 FDA information request for submission of SAE report to BLA	28-JUL-2009	60009647
30-JUL-2009	Y		Amendment # 25. Response to July 23, 2009 FDA information request	30-JUL-2009	60009663
06-AUG-2009	Y		Amendment # 26. Response to August 3, 2009 FDA information request	06-AUG-2009	60009709
10-AUG-2009	Y		Amendment # 27. Revised package insert label in response to August 3, 2009 FDA information request	11-AUG-2009	60009739

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Order: FDA/AppI, Then Date Ascending

THIS REPORT MAY CONTAIN CONFIDENTIAL INFORMATION

STN: L 125326/0

Applicant: Glaxo Group Limited d/b/a GlaxoSmithKline #1809

Product: Ofatumumab

Short Summary: treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab

Date	Elec	Post	Description	FDA Recd Date	Login ID
20-AUG-2009	Y		Amendment # 28. Post-marketing Requirements and Post-Marketing Commitments in response to August 11, 2009, August 12, 2009, August 19, 2009 FDA information requests	20-AUG-2009	60009810
15-SEP-2009	Y		Amendment # 29. Revised package insert, carton and container labels in response to August 27, 2009, September 8, 2009, and September 11, 2009 FDA advice and information requests.	16-SEP-2009	60009992
25-SEP-2009	Y		Amendment # 30. Response to September 21, 2009 FDA request for risk mitigation assessment for 20 vial dosage	28-SEP-2009	60010096
29-SEP-2009	Y		Amendment # 31. Response to September 25, 2009 and September 28, 2009 FDA request for additional post-marketing requirements	30-SEP-2009	60010118
06-OCT-2009	Y		Amendment # 32. Revised Post-marketing Requirements in response to October 1, 2009 FDA information request.	06-OCT-2009	60010170
12-OCT-2009	Y		Amendment # 33. Copies of presentations from February 20, 2009 technical walk-through meeting, April 20, 2009 meeting, and May 29, 2009 ODAC meeting for reference	13-OCT-2009	60010204
13-OCT-2009	Y		Amendment # 34. GSK submission revised package insert in response to October 8, 2009 FDA information request	13-OCT-2009	60010211
16-OCT-2009	Y		Amendment # 35. GSK response to September 15, 2009 FDA request for enlarged vial label and amended OMB110911 clinical trial	16-OCT-2009	60010227
26-OCT-2009	Y		Amendment # 36. Revised proposed prescribing information and revised vial and carton labels	26-OCT-2009	60010272
30-OCT-2009	Y		Amendment # 37. Final printed prescribing information and final vial and carton labels	30-OCT-2009	60010323

Chiang, Raymond

From: Philip.A.Witman@gsk.com
Sent: Monday, October 26, 2009 4:29 PM
To: Chiang, Raymond
Subject: Re: Approval of STN BL 125326/0 Arzerra (ofatumumab)
Importance: High

Hi, Ray,

I most gladly confirm that I have received this e-mail. We thank the Division for all your dedication to complete this review by the Action Date.

Have a great evening.

Best regards,

Philip

Philip A. Witman
Associate Director
Global Regulatory Affairs - Oncology

Trade secret and/or confidential commercial information contained in this message (including any attachments) is exempt from public disclosure to the full extent provided under law. If you are not the intended recipient of this message, or if you are not responsible for delivering it to the intended recipient(s), do not use, disclose, reproduce, or distribute this message (including any attachments). If you have received this message in error, please erase all copies (including any attachments) and notify me immediately. Thank you.

"Chiang, Raymond" <Raymond.Chiang@fda.hhs.gov>

26-Oct-2009 16:04

Please respond to "Chiang, Raymond"
<Raymond.Chiang@fda.hhs.gov>

To Philip.A.Witman@gsk.com

cc

Subject Re: Approval of STN BL 125326/0 Arzerra (ofatumumab)

Phillip,

FDA has today approved your BLA application, STN BL 125326/0, for Arzerra (ofatumumab). Please find attached the approval letter and approved package insert and carton and container labels. We will provide you with a hard copy by US mail. Please confirm receipt of this electronic message by return email.

Raymond S. Chiang, M.S.
Consumer Safety Officer/ Regulatory Project Manager

10/27/2009

Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Email: Raymond.Chiang@fda.hhs.gov

phone: 301-796-1940

<<ScannedFINALAPLTR(email).pdf>> [attachment "ScannedFINALAPLTR(email).pdf" deleted by Philip A Witman/PharmRD/GSK]

10/27/2009

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To submit a final report for ongoing clinical trial OMB110911, entitled, "A Phase III, Open-label, Randomized, Multicenter Trial of Ofatumumab Added to Chlorambucil versus Chlorambucil Monotherapy in Previously Untreated Patients with Chronic Lymphocytic Leukemia" which is intended to verify the clinical benefit of Arzerra (ofatumumab) through demonstration of a clinically meaningful effect on progression-free survival. The protocol for clinical trial OMB110911 was submitted to FDA on October 24, 2008 and began patient accrual on December 22, 2008. We also acknowledge receipt of the amended protocol submitted August 21, 2009.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>N/A</u>
	Study/Clinical trial Completion Date:	<u>10/14/2013</u>
	Final Report Submission Date:	<u>06/30/2014</u>
	Other: Patient Accrual 50% (222 patients)	<u>08/30/2010</u>
	Patient Accrual 75% (333 patients)	<u>03/30/2011</u>
	Patient Accrual completed	<u>11/30/2011</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☒ Unmet need

- ☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

This is a PMR because the drug is to be approved under Subpart E of 21 CFR 601.41. The drug was studied for a life-threatening condition in a patient population with unmet medical need. Approval requires that postmarketing studies verify and describe the clinical benefit of ofatumumab.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- Which regulation?

- ☒ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)

The PMR is a clinical trial to verify the clinical benefit of ofatumumab.

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*



(signature line for BLAs)

10/22/09

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To develop a validated, sensitive, and accurate assay for the detection of an immune response (binding antibodies) to Arzerra (ofatumumab) including procedures for accurate detection of antibodies to Arzerra (ofatumumab) in the presence of Arzerra (ofatumumab) levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>N/A</u>
	Study/Clinical trial Completion Date:	<u>N/A</u>
	Final Report Submission Date:	<u>03/31/2010</u>
	Other: <u>N/A</u>	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

This approval is for a life-threatening condition in a patient population with unmet medical need. Additional immunogenicity information is needed to assess any safety risks due to anti-product antibodies. This PMR is necessary for the completion of Postmarketing Requirement Number 3 described in the Approval Letter.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Immunogenicity risk related to anti-product antibodies.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR is required in order to satisfy the requirements for PMR number 3 described in the Approval Letter. See template related to PMR number 3 entitled:

"To conduct an assessment of anti-drug antibody (ADA) response to Arzerra (ofatumumab) with a validated assay (required in PMR 2) capable of sensitively detecting ADA responses in the presence of Arzerra (ofatumumab) levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 patients, including Arzerra (ofatumumab)-treated patients enrolled in clinical trial OMB110911. The final report will include information on the level of Arzerra (ofatumumab) in each patient's test sample at each sampling time point."

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

 10/22/09
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To conduct an assessment of anti-drug antibody (ADA) response to Arzerra (ofatumumab) with a validated assay (required in PMR 2) capable of sensitively detecting ADA responses in the presence of Arzerra (ofatumumab) levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 patients, including Arzerra (ofatumumab)-treated patients enrolled in clinical trial OMB110911. The final report will include information on the level of Arzerra (ofatumumab) in each patient's test sample at each sampling time point.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>N/A</u>
	Study/Clinical trial Completion Date:	<u>N/A</u>
	Final Report Submission Date:	<u>12/31/2013</u>
	Other: <u>Patient accrual completed</u>	<u>11/30/2011</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

This approval is for a life-threatening condition in a patient population with unmet medical need. Additional immunogenicity information is needed to assess any safety risks due to anti-product antibodies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Assessing immunogenicity of the this biological product as a marker of safety.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The applicant has agreed to submit immunogenicity results from ongoing study OMB110911 and any other ongoing or completed trials to satisfy this requirement. Study OMB110911 is required as a confirmatory study under accelerated approval regulations.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☒ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

 10/2/09

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To conduct clinical trial OMB112855, a trial of QTc intervals in patients who have been administered Arzerra (ofatumumab): QTc assessments will be performed in patients who have failed at least one fludarabine-containing regimen (at least two cycles) and failed at least one alemtuzumab-containing regimen (a minimum of at least 12 administrations) or who are considered inappropriate for treatment with alemtuzumab due to lymphadenopathy with at least one lymph node > 5 cm and requiring therapy and who receive the dose and schedule of Arzerra (ofatumumab) per the approved prescribing information. The number of patients evaluated for QTc interval changes will be at least 12. For the QTc assessments, ECGs will be collected in triplicate at baseline, at steady-state Arzerra (ofatumumab) concentrations, periodically on-therapy (e.g., every 3 months), and at the end of treatment. The final report will be a comprehensive combined report of the results (including primary data) of clinical trial OMB112855 and of the sub-trial assessing QTc intervals in OMB110911 (see below).

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>01/31/2010</u>
	Study/Clinical trial Completion Date:	<u>06/30/2012</u>
	Final Report Submission Date:	<u>12/31/2012</u>
	Other: <u>Patient Accrual completed</u>	<u>06/30/2011</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Assessing the potential effect of this biological product on QT interval as a marker of cardiac safety

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☒ **Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☒ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

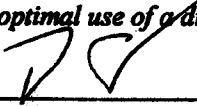
☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*



(signature line for BLAs)

10/22/09

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To conduct an assessment of QTc intervals as a sub-trial in clinical trial OMB110911. The total number of patients in OMB110911 with evaluable ECG measurements will be at least 50 (25 per treatment arm). For the QTc assessments, ECGs will be collected in triplicate at baseline, at steady-state Arzerra (ofatumumab) concentrations, periodically on-therapy (e.g., every 3 months), and at the end of treatment. The final report will be a comprehensive combined report of the results (including primary data) of the sub-trial assessing QTc intervals in OMB110911 and of clinical trial OMB112855.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>01/31/2010</u>
	Study/Clinical trial Completion Date:	<u>06/30/2012</u>
	Final Report Submission Date:	<u>12/31/2012</u>
	Other: <u>Patient Accrual completed</u>	<u>06/30/2011</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Assessing the potential effect of this biological product on QT interval as a marker of cardiac safety

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☒ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

 10/22/09

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To submit the final report for clinical trial Hx-CD20-406 entitled "A single-arm international, multi-center trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell Chronic Lymphocytic Leukemia who have failed fludarabine and alemtuzumab" which shall include results of objective response rates according to the IRC and according to the clinical investigators. The final report will provide summary analyses and primary data. Accrual to this trial has been completed.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>N/A</u>
	Study/Clinical trial Completion Date:	<u>06/30/2011</u>
	Final Report Submission Date:	<u>12/31/2011</u>
	Other: Patient accrual completed	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The interim results of the proposed study were submitted in support of the BLA. Thus the issue is not appropriate for a pre-approval requirement (the submitted results support an accelerated approval in a life-threatening condition in a patient population with unmet medical need). This PMC will provide confirmation of the treatment effects (i.e., effects on the surrogate endpoint of durable objective response rates) observed in the small patient population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Additional data on objective response rates from clinical trial already submitted as a BLA

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

 10/22/09
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To reassess release and stability specifications for ofatumumab drug substance and drug product through August 31, 2011. The assessment will be submitted in the 2011 Annual Report.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>MM/DD/YYYY</u>
	Other: 2011 Annual Report.	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

An assessment of release and stability specifications requires long-term data. This is a standard post-approval assessment that needs to be done as part of the life cycle approach to manufacturing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

An assessment of specification is part of the normal life-cycle approach to manufacturing. However, for specific reasons as described below an assessment of specifications after 2 years is further warranted

- a. Relatively, there was a consistent decrease in potency during storage.
- b. The specification for icIEF was set based on the statistical analysis of the release data presented and assessment of the method variability identified in the validation. GSK indicated that there was only a limited amount of data was available for this assay.
- c. For drug substance stability and drug product release and stability, the specification for 7 / 8 to reflect the minimal data set currently available.

b(4)

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

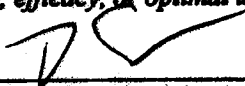
- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*



(signature line for BLAs)

10/22/09

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To develop and implement a quantitative specification for the icIEF assay used in the drug substance and drug product stability programs. The assessment will be submitted as a Change Being Effected-30 (CBE-30) to the BLA by October 31, 2011.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>10/31/2011</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Establishment of a stability specification for the icIEF assay requires the acquisition of long term stability data from more product lots and was not feasible prior to approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The icIEF assay is a newly implemented analytical assay. During the review, GSK was requested to set quantitative release and stability specifications that controlled for all major product charge isoforms. Release specifications were established but GSK stated that there was not enough information from stability studies to establish similar specifications for the stability program. They agreed to establish specifications however after more data was available.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Will provide long term product stability data.
 - ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
 - ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

 10/22/09

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To develop and validate a semi-quantitative assay for measurement of visible particulates. The test method and specification should be incorporated into drug substance and drug product lot release and stability programs and submitted as a CBE-30 supplement by October 31, 2011.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>10/31/2011</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

This PMC involves the development of a new product release and stability method. It was not feasible to have this method developed and validated prior to approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Drug substance and drug product release and stability data indicates that visible particles may be present in this product. Currently the level of visible particulates is controlled using non-quantitative, descriptive acceptance criteria. Therefore, a validated semi-quantitative assay method which can accurately quantitative the number of visible particulates is needed. Such an assay will provide a more accurate level of control over the presence of visible particles in ofatumumab drug product.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
Development of a product release assay.
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.



(signature line for BLAs)

10/22/09

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To submit a Prior Approval Supplement (PAS) for the introduction of a / ✓
mg ofatumumab single-use vial, 20 mg/mL, to reduce the number of vials
needed for the 2000 mg dose. b(4)

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>12/31/2010</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

This PMC concerns the development of a new vial size for the drug product and it was not feasible for this to be accomplished prior to approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

During ofatumumab administration, the contents of 20 vials needs to be combined for a single dose. There was concern on the part of the clinical team that having to combine this many vials may lead to dosing errors due to events such as vial break, mis-calculation of vial usage etc. Increasing the vial size or developing a more concentrated formulation would reduce the number of vials required for a dose and therefore reduce the potential for dosing errors.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-
- Development of a new drug product presentation (larger vial size)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

 10/22/09

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To revise the system suitability criteria for the robotic format of the complement-mediated antibody cytotoxicity potency assay so that the coefficient of variation (CV) (%) for duplicates is consistent with validation limits and is less than or equal to 25%. A final report including details of the system suitability criteria will be submitted and a revised potency assay SOP will be submitted in the annual report. Alternatively, the robot format of the potency assay will be removed from the BLA.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u> </u>
	Final Report Submission Date:	<u>03/31/2010</u>
	Other: 2010 Annual Report	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Information on the SOP of the potency assay was not provided to the Agency until late in the review cycle. The system suitability requirement for the amount of variation allowed between duplicates did not meet the range used for assay validation and therefore needed to be revised. Due to the limited amount of time left in the review clock, and the fact that this deficiency would be unlikely to impact product quality, it was felt the revision could be done post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The criterion specified is part of the system suitability acceptance criteria (SSAC) for the product's release and stability potency assay. It does not conform to the parameter used for assay validation and therefore needs to be revised.

Upon seeing the requested PMC, GSK revised the PMC to include removal of the robotic form of the assay from the BLA. The BLA itself contained validation information on both a manual as well as the robotic format. The manual assay format was fully validated and found to be suitable for its intended purpose. The manual format of the assay was used for product testing throughout clinical development. Removal of the robotic format and use of the manual method format, therefore, will not adversely affect product release or stability testing.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-
- Revision of system suitability requirement for the potency assay.
-

Agreed upon:

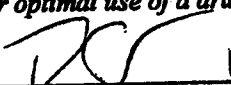
- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*



(signature line for BLAs)

10/22/09

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To perform leachables studies to characterize the potential presence of volatile leachables from the elastomeric stopper and the presence of ^ under accelerated conditions (25°C) for 6 months and at the recommended storage temperature for 24 months as outlined in the June 5, 2009 submission. The results of these studies will be submitted in the annual report.

b(4)

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u> </u>
	Final Report Submission Date:	<u> </u>
	Other: 2012 Annual Report	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

This is a long-term study to monitor the presence of two potential drug product leachates that were identified by the sponsor as being of concern. The occurrence of these potential leachates will be monitored during storage at the recommended storage temperature for the duration of the drug product shelf-life.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

In addition to the extractable study, GSK stated in their response IR that they have initiated a leachable study to cover the highest risk areas for the Ofatumumab drug product and also critically examined its extractable studies and information supplied from its supplier. From this analysis GSK has created leachable studies to further study two areas; the potential volatiles leachables from the elastomeric stopper and the presence of / as a leachable.

The volatiles have been chosen for further study since the extractable study outlined may not adequately predict their presence in the drug product due to volatile nature of potential leachables and the limited scope of the GCMS method employed. The extractable results also indicated a source of , therefore GSK commissioned a leachable study to investigate this further. GSK submitted planned protocols for these studies. It will include material stored at 5°C (up to 24m) and 25°C (up to 6m) for both volatile and leachates.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

 10/22/09

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To establish permanent control action limits for purification step yields and analyze 30 in-control points. The permanent control action limits and the results of the analysis of 30 in-control points will be submitted in the annual report.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	
	Final Report Submission Date:	<u>2010 Annual Report</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
☒ Long-term data needed
☒ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

While step yields for the purification process were recorded in the batch record, no control limits had been established. In response to the Agency's inquiry about control of step yields, GSK established temporary control limits based on the average ± 3 standard deviations of 20 lots. In the May 14, 20009 response, GSK committed to establish permanent control limits after a minimum of 30-in-control points had been analyzed. It is only feasible to do this as a post-approval commitment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

21 CFR 211.105 requires yield to be determined at the conclusion of each appropriate phase of manufacturing.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
Establishment of step yields for the manufacturing process after more experience has been gained.
-

Agreed upon:

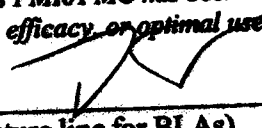
- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.


(signature line for BLAs)

10/2/09

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To conduct a study or studies to identify the composition of visible particles observed in drug substance lots when particles are observed during ongoing stability studies of the drug substance conformance lots. The results of these studies will be submitted in the annual report.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	
	Final Report Submission Date:	<u>2010 Annual Report</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The study is only feasible to conduct post-approval since it entails further characterization of visible particulates in commercial lots.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

One common pathway of degradation for the ofatumumab is the appearance of visible and sub-visible particles. Information was available on the composition of sub-visible particles but not for the composition of the visible particles. GSK committed to investigate the composition of visible particles from drug substance lots when particles are observed during ongoing stability studies of the drug substance

Information on the composition of particles can aid in the identification of the basis for their formation which may lead to measures that better control their appearance. In addition, information on particle composition can provide information on possible safety issues associated with the particles. If deemed appropriate, this information can be used to require the development of strategies to better monitor, control and/or limit particle formation.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

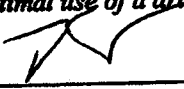
- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

 10/22/09

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: To confirm the lack of deleterious effect on the stability of drug substance of reprocessing at the / step by monitoring the real-time stability of drug substance lot 09P01105 and performing accelerated stability studies on this lot at 25°C for 6 months and at 40°C for 3 months. The real time and accelerated studies will include the licensed drug substance stability program's tests and acceptance criteria. Real time stability data and results of the accelerated stability studies will be submitted in the annual report. b(4)

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	<u>MM/DD/YYYY</u>
Study/Clinical trial Completion Date:	<u> </u>
Final Report Submission Date:	<u> </u>
Other: Accelerated data submitted in the 2010 Annual Report. Data from real-time studies to be submitted in the applicable Annual Report..	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The issue involves investigating the long term stability of drug substance lots that have undergone / Sufficient information was available from one drug substance lot to allow re-processing, but this addition study will provide additional support and information from a more extensive stability study. b(4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The ofatumumab BLA allows for

b(4)

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ **Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*



(signature line for BLAs)

10/22/09

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Developing an improved bioburden test method for cell culture, primary recovery, and purification samples

PMR/PMC Schedule Milestones: Final protocol Submission Date: MM/DD/YYYY
 Study/Clinical trial Completion Date: MM/DD/YYYY
 Final Report Submission Date: 3/31/2010
 Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

GSK needs to validate the new bioburden test method. This is appropriate for a PMC because it does not affect the safety of the product. The process is generally under good microbial control.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Qualify the membrane filtration method for the bioburden test to allow using larger sample volumes. The current bioburden test for cell culture, primary recovery, and purification samples uses small sample volumes.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

To update the bioburden test for cell culture, primary recovery, and purification samples from /
/ to filtration method. A study will be performed to establish the appropriate volume of
each sample in the test. The validation information and data for the updated bioburden test will be
provided at the end of the study by March 31, 2010.

b(4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

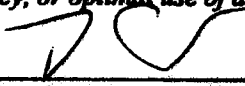
- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☐ Are the objectives clear from the description of the PMR/PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*



(signature line for BLAs)

10/22/09

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Validate drug substance intermediate hold times for microbial control at commercial scale

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>12/31/2010</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

GSK needs to conduct intermediate hold time validation at scale. This is appropriate for a PMC because this PMC does not affect safety of the product. The risk of microbial contamination is also mitigated by other microbial controls in place during manufacturing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The product intermediate hold times need to be validated at scale for microbial control. The hold times have been validated for chemical stability only.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- Which regulation?

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

To validate drug substance intermediate hold times for microbial control at commercial scale. Validation data will be submitted at the end of the study by December 31, 2010.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
 - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - ☐ Thorough Q-T clinical trial
 - ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

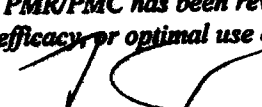
- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☐ Are the objectives clear from the description of the PMR/PMC?
 - ☐ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*


(signature line for BLAs)

10/22/09



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

Memorandum

Date: October 13, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: Financial Disclosure: STN BL 125326/0 ofatumumab

Financial Disclosure Review can be found in section 3.3 of the clinical review.



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

Memorandum

Date: October 8, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: FDA's proposed package insert revisions: BL STN 125326/0- Arzerra
(ofatumumab)

FDA's proposed revisions to the package insert for Arzerra (ofatumumab) BL STN 125326/0 sent to GlaxoSmithKline on October 8, 2009.

Chiang, Raymond

From: Chiang, Raymond
Sent: Thursday, October 08, 2009 5:57 PM
To: 'Charles.C.Depew@gsk.com'; Philip.A.Witman@gsk.com
Subject: RE: FDA proposed ofatumumab label (10.8.09)
Importance: High
Attachments: 10 08 09 FDA draft Arzerra label to be sent to GSK.doc

Philip and Charles,

As per conversation with Phillip, attached is FDA's proposed ofatumumab package label dated 10.8.09. Please submit your response by email and formally to the BLA by noon, Tuesday, October 13, 2009. Please submit a tracked changes and clean copy.

Further review of your proposed indication statement will be required by FDA upper management.

thanks,
ray

10/9/2009

14 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 1

From: Arnwine, Kristina
To: Jones-Smith, Tselaine; Chiang, Raymond;
cc: Toyer, Denise P; Holquist, Carol A; Gootenberg, Joseph; Lemery, Steven;
Keegan, Patricia; Jones, Karen;
Subject: RE: BLA #125326- Arzerra Proprietary Name Review
Date: Friday, October 09, 2009 3:09:48 PM

Ray,

To follow up, the presentation of Arzerra in title case on the container and carton labeling and in all caps in the insert labeling does not affect the acceptability of the proprietary name from DMEPA's perspective. However, as Tselaine stated, DBOP should contact SEALD with regard to the presentation of Arzerra in all caps in the insert labeling from a formatting perspective.

Let us know if you have any additional questions. Thanks.

Kristina

From: Jones-Smith, Tselaine
Sent: Friday, October 09, 2009 3:02 PM
To: Chiang, Raymond; Arnwine, Kristina
Cc: Toyer, Denise P; Holquist, Carol A; Gootenberg, Joseph; Lemery, Steven; Keegan, Patricia; Jones, Karen
Subject: RE: BLA #125326- Arzerra Proprietary Name Review
Importance: High

In an email dated September 30, 2009, DMEPA management recommended that you consult with SEAL with regards to the presentation of the proprietary name, Arzerra, in all caps in the insert labeling.

Thanks,
Tselaine

Tselaine Jones Smith, PharmD
Safety Evaluator
Office of Surveillance and Epidemiology

*Division of Medication Error Prevention and Analysis
Food & Drug Administration
10903 New Hampshire Avenue
CDER Building #22, Room 4406
Silver Spring, MD 20993
Office: 301-796-0566
Fax: 301-796-9865
Tselaine.Jones-Smith@fda.hhs.gov*

From: Chiang, Raymond
Sent: Friday, October 09, 2009 2:51 PM
To: Jones-Smith, Tselaine; Arnwine, Kristina
Cc: Toyer, Denise P; Holquist, Carol A; Gootenberg, Joseph; Lemery, Steven; Keegan, Patricia; Jones, Karen
Subject: RE: BLA #125326- Arzerra Proprietary Name Review
Importance: High

Tselaine and Kristina,

Dr. Keegan wanted me to follow up with you concerning this issue. GSK wants that the proprietary name be in all caps (ARZERRA) in the package insert. However, GSK wants the proprietary name be in mixed letters (Arzerra) in the carton and container labels. Please advise whether this changes your decision to accept proprietary name as per your review dated 9.22.09. When you reply, please reply to all.

thanks,
ray

From: Keegan, Patricia
Sent: Wednesday, September 30, 2009 9:49 AM
To: Jones-Smith, Tselaine; Chiang, Raymond; Lemery, Steven
Cc: Arnwine, Kristina; Toyer, Denise P; Holquist, Carol A; Griffith, Sandra J; Campbell, Cheryl; Gootenberg, Joseph
Subject: RE: BLA #125326- Arzerra Proprietary Name Review

The sponsor wants the name to be in all caps (ARZERRA). Does this constitute a change that voids this review or is it OK

From: Jones-Smith, Tselaine

Sent: Tue 9/29/2009 1:16 PM

To: Chiang, Raymond; Keegan, Patricia; Lemery, Steven

Cc: Arnwine, Kristina; Toyer, Denise P; Holquist, Carol A; Jones-Smith, Tselaine; Griffith, Sandra J; Campbell, Cheryl

Subject: BLA #125326- Arzerra Proprietary Name Review

Hello Ray and Team,

DMEPA has completed our re-assessment of the proprietary name Arzerra in response to a notification that BLA #125326 may be approved within 90 days. I am attaching a copy of the signed review. Please let me know if you have any questions.

Thank you,
Tselaine

Tselaine Jones Smith, PharmD

Safety Evaluator

Office of Surveillance and Epidemiology

Division of Medication Error Prevention and Analysis

Food & Drug Administration

10903 New Hampshire Avenue

CDER Building #22, Room 4406

Silver Spring, MD 20993

Office: 301-796-0566

Fax: 301-796-9865

Tselaine.Jones-Smith@fda.hhs.gov



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

Memorandum

Date: September 28, 2009

From: Raymond Chiang, DBOP/ODDP/CDER

Subject: FDA's requests concerning additional Arzerra PMR: BL STN 125326/0-Arzerra (ofatumumab)

FDA's requests concerning additional Arzerra PMR concerning immunogenicity issues.

Chiang, Raymond

From: Chiang, Raymond
Sent: Monday, September 28, 2009 2:22 PM
To: 'Charles.C.Depew@gsk.com'
Cc: Philip.A.Witman@gsk.com
Subject: RE: Additional post-marketing request
Importance: High

Charles,

In addressing your email (dated 9.28.09 @ 10:27AM) below, please see the following modification (in bold) to the possible PMR:

Possible PMR

To conduct an assessment of anti-drug antibody (ADA) response to ofatumumab with a validated assay capable of sensitively detecting ADA responses in the presence of ofatumumab levels that are expected to be present at the time of patient sampling. This will be evaluated in at least 300 patients, **including ofatumumab-treated patients enrolled in study 911**. The final study report should include information on the level of ofatumumab in each patient's test sample at each sampling timepoint.

The timetable you submitted on XXXX, 2009 states that you will conduct this assessment according to the following milestones:

- **Final Protocol Submission** by XXXXXXXX
- **Patient Accrual Completed** by XXXXXXXX
- **Trial Completion Date:** by XXXXXXXX
- **Final Report Submission:** by XXXXXXXX

thanks,
ray

From: Charles.C.Depew@gsk.com [mailto:Charles.C.Depew@gsk.com]
Sent: Monday, September 28, 2009 10:27 AM
To: Chiang, Raymond
Cc: Philip.A.Witman@gsk.com
Subject: Additional post-marketing request

Hi Ray,

Thanks for taking my call this morning in reference to the Division's additional post-marketing request (appended below). ~~For your request, we have the following question: Study 911, our agreed confirmatory trial under a PMC, will deliver approximately 220 patients. The ADA and PK sampling scheme in 911 is already set up to meet this~~ PMC request with respect to ofatumumab exposure. Will 220 patients be sufficient to provide the level of data

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9/29/2009

necessary for an appropriate assessment of the potential for ofatumumab to induce the development of anti-drug antibodies?

With respect to your question regarding NDC codes on the carton, I will look into and get back to you later today.

thanks,
chuck

Philip,

FDA has identified a need for an additional post-marketing requirement, including time milestones, to conduct additional assessment of anti-drug antibodies. We request you make a proposal for fulfilling this post-marketing requirement. Such studies do need to be conducted in CLL.

We request that it be provided by COB, Tuesday, September 29, 2009.

Below is a general outline of some elements that would be desirable:

Possible PMR

To conduct an assessment of anti-drug antibody (ADA) response to ofatumumab with a validated assay capable of sensitively detecting ADA responses in the presence of ofatumumab levels that are expected to be present at the time of patient sampling. This will be evaluated in at least 300 patients. The final study report should include information on the level of ofatumumab in each patient's test sample at each sampling timepoint.

The timetable you submitted on XXXX, 2009 states that you will conduct this assessment according to the following milestones:

- **Final Protocol Submission** by XXXXXXXX
- **Patient Accrual Completed** by XXXXXXXX
- **Trial Completion Date:** by XXXXXXXX
- **Final Report Submission:** by XXXXXXXX

Note: If you are going to need to develop an assay that is more sensitive, then the protocol should have provisions for banking samples for analysis by the new assay.

Possible PMR (if a new assay is to be developed)

To develop a validated, sensitive and accurate assay for the detection of an immune response (binding antibodies) to ofatumumab, including procedures for accurate detection of antibodies to ofatumumab in the presence of _____ ofatumumab that are expected to be present at the time of the patient sampling. The assay methodology and validation report will be submitted by XXXXXXXX.

~~The timetable you submitted on XXXX, 2009 states that you will conduct this assessment according to:~~

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9/29/2009

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the following milestones:

- **Assay and Methodology Report** by **XXXXXXXX**

Chuck Depew, Pharm.D.
GSK Regulatory Affairs
GlaxoSmithKline
Office (919) 483-6065
Cell (919) 961-1009

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9/29/2009

From: Masucci, Iris
To: Chiang, Raymond;
cc: Gootenberg, Joseph; Lemery, Steven; Jones, Karen;
Subject: RE: Re: Please make any necessary changes/
comments to most current version of Arzerra label
Date: Tuesday, August 25, 2009 1:13:32 PM
Attachments: Iris 25AUG09 edits to 8 24 09 Arzerra label (JG SL and RC edits) -not clean.
doc

Ray et al. -

Attached is my mark-up of the 8/24 Arzerra label. It's looking great. But there were a few comments and questions, and some format changes.

Ray - I already fixed the cross-ref in the Highlights I&U section that you mentioned in your message.

Thanks,
Iris

From: Chiang, Raymond
Sent: Monday, August 24, 2009 1:45 PM
To: Masucci, Iris
Cc: Gootenberg, Joseph; Lemery, Steven; Jones, Karen
Subject: Re: Please make any necessary changes/comments to most current version of Arzerra label
Importance: High

Iris,

We are going through negotiations with GSK concerning their Arzerra (ofatumumab) package insert label. Please review label and make any necessary changes/comments to the attached Arzerra (ofatumumab) package insert label. Also, please address specific comments addressed to you. This label will be sent to initiate the second round of negotiations. Hopefully, GSK will agree to most of our proposed changes.

thanks,
ray

Raymond S. Chiang, M.S.
Consumer Safety Officer/ Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Email: Raymond.Chiang@fda.hhs.gov

phone: 301-796-1940

<< File: 8 24 09 Arzerra label (JG, SL and RC edits) -not clean.doc >>



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

Memorandum

Date: September 25, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: FDA's requests concerning additional Arzerra PMR; BL STN 125326/0-Arzerra (ofatumumab)

FDA's requests concerning additional Arzerra PMR concerning immunogenicity issues.

Chiang, Raymond

From: Chiang, Raymond
Sent: Friday, September 25, 2009 4:51 PM
To: 'Philip.A.Witman@gsk.com'
Subject: RE: Need for additional post-marketing requirement for Arzerra
Importance: High

Philip,

FDA has identified a need for an additional post-marketing requirement, including time milestones, to conduct additional assessment of anti-drug antibodies. We request you make a proposal for fulfilling this post-marketing requirement. Such studies do need to be conducted in CLL.

We request that it be provided by COB, Tuesday, September 29, 2009.

Below is a general outline of some elements that would be desirable:

Possible PMR

To conduct an assessment of anti-drug antibody (ADA) response to ofatumumab with a validated assay capable of sensitively detecting ADA responses in the presence of ofatumumab levels that are expected to be present at the time of patient sampling. This will be evaluated in at least 300 patients. The final study report should include information on the level of ofatumumab in each patient's test sample at each sampling timepoint.

The timetable you submitted on XXXX, 2009 states that you will conduct this assessment according to the following milestones:

• Final Protocol Submission	by XXXXXXXX
• Patient Accrual Completed	by XXXXXXXX
• Trial Completion Date:	by XXXXXXXX
• Final Report Submission:	by XXXXXXXX

Note: If you are going to need to develop an assay that is more sensitive, then the protocol should have provisions for banking samples for analysis by the new assay.

Possible PMR (if a new assay is to be developed)

To develop a validated, sensitive and accurate assay for the detection of an immune response (binding antibodies) to ofatumumab, including procedures for accurate detection of antibodies to ofatumumab in the presence of 1 ofatumumab that are expected to be present at the time of the patient sampling. The assay methodology and validation report will be submitted by XXXXXXXX.

The timetable you submitted on XXXX, 2009 states that you will conduct this assessment according to the following milestones:

• Assay and Methodology Report	by XXXXXXXX

9/29/2009

b(4)



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

Memorandum

Date: September 21, 2009
From: Raymond Chiang, RPM DBOP/ODDP/CDER/FDA
Subject: Teleconference to discuss GSK's proposed external risk assessment associated with use of 20 vials: BL STN 125326\0- Arzerra (ofatumumab)

GlaxoSmithKline Attendees:

Philip Witman

FDA Attendees:

Tselaine Jones-Smith
Kristina Arnwine
Raymond Chiang

Discussion:

On Monday, September 21, 2009, a teleconference was held between FDA and GlaxoSmithKline (GSK) to discuss GSK's external risk assessment protocol associated with use of 20 vials. FDA requested GSK provide this protocol in order to address any safety concerns associated with the necessity of 20 vials. GSK stated that a protocol has not been created. FDA requested GSK submit this protocol by Friday, September 25, 2009. GSK agreed.

Tcon concluded.

Post-meeting addendum:

GSK communicated by email (dated September 22, 2009) that in lieu of a formal protocol, a detailed survey for pharmacists to complete will be submitted.



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

Memorandum

Date: September 15, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: FDA request for enlarged vial label and amended clinical trial protocol
OMB110911-information request

FDA requested enlarged vial label and amended clinical trial protocol OMB110911.

From: Chiang, Raymond
To: "Philip.A.Witman@gsk.com";
cc: tiffany.m.kenney@gsk.com; Jones, Karen;
Subject: RE: ARZERRA BLA125326 - FDA Comments that Require Clarification
Date: Friday, September 11, 2009 6:14:33 PM

Philip,

Please see our responses in dark blue font below.

As a FYI, I will be out of town next Monday- Wednesday. If you have any questions, please contact Karen Jones.

thanks,
ray

From: Philip.A.Witman@gsk.com [mailto:Philip.A.Witman@gsk.com]
Sent: Wednesday, September 09, 2009 2:24 PM
To: Chiang, Raymond
Cc: tiffany.m.kenney@gsk.com
Subject: ARZERRA BLA125326 - FDA Comments that Require Clarification
Importance: High

Good afternoon, Ray,

Our labelling group requests some clarification to some of the comments you provided yesterday for the vial/carton/label. I have forwarded the e-mail so nothing gets lost in my translation to you.

Please forward this to your appropriate team members so we can get a rapid response in order to comply with the deadline in your e-mail from yesterday.

Thanks in advance.

Best regards,

Philip

Philip A. Witman
Associate Director
Global Regulatory Affairs - Oncology

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----- Forwarded by Philip A Witman/PharmRD/GSK on 09/09/2009 02:21 PM -----

Tiffany M Kenney/PharmRD

Strategic Product Labeling, Global Regulatory Affairs
RTP 5.4724 919-483-6503

09-Sep-2009 11:02

To Philip A Witman/PharmRD/GSK@GSK

CC Melissa H Beaman/PharmRD/GSK@GSK

Subject: Arzerra comments that require clarification

Hi Philip,

We have the following questions on the FDA comments. FDA comment in bold, GSK request for clarification in regular font.

3. **To comply with 21 CFR 600.3, 21 CFR 610.62 and 21 CFR 201.57(a)(2), please revise the Prescribing Information title to following presentation.**

**Arzerra
Ofatumumab
Injection, for Intravenous Infusion**

14. **To comply with 21 CFR 600.3, and 21 CFR 201.57(a)(2), please revise the Prescribing Information title to following presentation. The agency is working to standardize the presentation of the Product title and prefers the following presentation:**

**Arzerra (ofatumumab)
injection, for intravenous infusion**

Is the FDA requesting that we add "for Intravenous Infusion" to both the carton and vial label, or is Comment #3 referring to the Prescribing Information only?

FDA response: We request that you include "for Intravenous Infusion" for both the carton and vial label as stated in Comment #3 above

Does the FDA prefer the parentheses around the established name as in Comment #14 or without parentheses as in Comment #3? We believe the parentheses are appropriate around ofatumumab, but we request clarification.

FDA response: We prefer parentheses around the established names in all presentations.

Does the FDA prefer the dosage form and route of administration initial-capped as in Comment #3 or all lower case as in Comment #14? We believe that "ofatumumab" and "Injection" are intended rather than "Ofatumumab" and "injection" but we again request clarification.

Please note that we prefer the following product title for the cartons and vial label:

Arzerra
(ofatumumab)
Injection

FDA response: We prefer the following product title for carton and vial label:

Arzerra
(ofatumumab)
Injection, for Intravenous Infusion

We prefer that the following product title for the prescribing information:

Arzerra (ofatumumab)
Injection, for Intravenous Infusion
Are the presentations acceptable to FDA?

FDA response: We prefer the following for the package insert label:

Arzerra (ofatumumab)
Injection, for intravenous infusion

10. Please revise the inactive ingredients (buffering agents) to

alphabetical order per the United States Pharmacopeia, 5/1/09-8/1/09, USP 32/ NF27, General Chapter, Labeling of Inactive Ingredients <1091>.

The cartons submitted for review list the inactive ingredients in the following order: "0.195 mg/mL citric acid monohydrate, 5.85 mg/mL sodium chloride, 8.55 mg/mL sodium citrate, Water for Injection, USP." Would the FDA please provide clarification on the revised order that is being requested, since we have already listed these ingredients in alphabetical order?

FDA response: The current order is acceptable

Kind regards,
Tiffany

Tiffany M. Kenney
Labeling Coordinator
Internal Phone: 8-703-6503



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

Memorandum

Date: September 11, 2009

From: Raymond Chiang, DBOP/ODDP/CDER

Subject: FDA's comments concerning Arzerra package insert, carton and container labels: BL STN 125326/0-Arzerra (ofatumumab)

FDA's comments concerning Arzerra package insert, carton and container labels sent to GlaxoSmithKline on September 11, 2009.

From: Chiang, Raymond
To: "Philip.A.Witman@gsk.com";
cc: tiffany.m.kenney@gsk.com; Jones, Karen;
Subject: RE: ARZERRA BLA125326 - FDA Comments that Require Clarification
Date: Friday, September 11, 2009 6:14:33 PM

Philip,

Please see our responses in dark blue font below.

As a FYI, I will be out of town next Monday- Wednesday. If you have any questions, please contact Karen Jones.

thanks,
ray

From: Philip.A.Witman@gsk.com [mailto:Philip.A.Witman@gsk.com]
Sent: Wednesday, September 09, 2009 2:24 PM
To: Chiang, Raymond
Cc: tiffany.m.kenney@gsk.com
Subject: ARZERRA BLA125326 - FDA Comments that Require Clarification
Importance: High

Good afternoon, Ray,

Our labelling group requests some clarification to some of the comments you provided yesterday for the vial/carton/label. I have forwarded the e-mail so nothing gets lost in my translation to you.

Please forward this to your appropriate team members so we can get a rapid response in order to comply with the deadline in your e-mail from yesterday.

Thanks in advance.

Best regards,

Philip

Philip A. Witman
Associate Director
Global Regulatory Affairs - Oncology

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----- Forwarded by Philip A Witman/PharmRD/GSK on 09/09/2009 02:21 PM -----

Tiffany M Kenney/PharmRD

Strategic Product Labeling, Global Regulatory Affairs
RTP 5.4724 919-483-6503

09-Sep-2009 11:02

To Philip A Witman/PharmRD/GSK@GSK

cc Melissa H Beaman/PharmRD/GSK@GSK

Subject Arzerra comments that require clarification

Hi Philip,

We have the following questions on the FDA comments. FDA comment in bold, GSK request for clarification in regular font.

3. **To comply with 21 CFR 600.3, 21 CFR 610.62 and 21 CFR 201.57(a)(2), please revise the Prescribing Information title to following presentation.**

**Arzerra
Ofatumumab
Injection, for Intravenous Infusion**

14. **To comply with 21 CFR 600.3, and 21 CFR 201.57(a)(2), please revise the Prescribing Information title to following presentation. The agency is working to standardize the presentation of the Product title and prefers the following presentation:**

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injection, for intravenous infusion**

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FDA response: We request that you include "for Intravenous Infusion" for both the carton and vial label as stated in Comment #3 above

Does the FDA prefer the parentheses around the established name as in Comment #14 or without parentheses as in Comment #3? We believe the parentheses are appropriate around ofatumumab, but we request clarification.

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Does the FDA prefer the dosage form and route of administration initial-capped as in Comment #3 or all lower case as in Comment #14? We believe that "ofatumumab" and "Injection" are intended rather than "Ofatumumab" and "injection" but we again request clarification.

Please note that we prefer the following product title for the cartons and vial label:

Arzerra
(ofatumumab)
Injection

FDA response: We prefer the following product title for carton and vial label:

Arzerra
(ofatumumab)
Injection, for Intravenous Infusion

We prefer that the following product title for the prescribing information:

Arzerra (ofatumumab)
Injection, for Intravenous Infusion
Are the presentations acceptable to FDA?

FDA response: We prefer the following for the package insert label:

Arzerra (ofatumumab)
Injection, for intravenous infusion

10. Please revise the inactive ingredients (buffering agents) to

**alphabetical order per the United States Pharmacopeia, 5/1/09-8/1/09, USP 32/
NF27, General Chapter, Labeling of Inactive Ingredients <1091>.**

The cartons submitted for review list the inactive ingredients in the following order: "0.195 mg/mL citric acid monohydrate, 5.85 mg/mL sodium chloride, 8.55 mg/mL sodium citrate, Water for Injection, USP." Would the FDA please provide clarification on the revised order that is being requested, since we have already listed these ingredients in alphabetical order?

FDA response: The current order is acceptable

Kind regards,
Tiffany

Tiffany M. Kenney
Labeling Coordinator
Internal Phone: 8-703-6503



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

Memorandum

Date: September 9, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: FDA's comment concerning Arzerra package insert: BL STN 125326/0-
Arzerra (ofatumumab)

FDA's comment concerning package insert label for Arzerra (ofatumumab) BL STN 125326/0 sent to GlaxoSmithKline on September 9, 2009.

Chiang, Raymond

From: Chiang, Raymond
Sent: Wednesday, September 09, 2009 1:29 PM
To: 'Philip.A.Witman@gsk.com'
Subject: Proposed language to Section 12.1 of Arzerra label as per 9.4.09 tcon
Importance: High

Philip,

Please see FDA's proposed language to Section 12.1 of Arzerra label as per the 9.4.09 tcon. Also, please send your proposed package insert label by noon, Thursday, September 10, 2009.

12.1 Mechanism of Action

Ofatumumab binds specifically to both the small and large extracellular loops of the CD20 molecule. The CD20 molecule is expressed on normal B lymphocytes (pre-B to mature B-lymphocyte) and on B-cell CLL. The CD20 molecule is not shed from the cell surface and is not internalized following antibody binding.

The Fab domain of ofatumumab binds to the CD20 molecule and the Fc domain mediates immune effector functions to result in B-cell lysis *in vitro*. Data suggest that possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent, cell-mediated cytotoxicity.

thanks,
ray

9/9/2009



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

Memorandum

Date: September 8, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: FDA's proposed carton and container label revisions: BL STN 125326/0-
Arzerra (ofatumumab)

FDA's proposed revisions to the package insert, carton and container labels for Arzerra (ofatumumab) BL STN 125326/0 sent to GlaxoSmithKline on September 8, 2009.

Comments to the Licensee (9.8.09):

Comments concerning both the carton and container labels

1. The total drug content is listed as 100 mg without the corresponding volume. Per USP recommendations (USP 32-NF 27), the strength per total volume should be the prominent and primary expression of strength on the principal display panel, followed in close proximity by strength per milliliter in parenthesis. Additionally, the statement of drug concentration appears adjacent to the statement of total drug content. Revise the strength statement in accordance with USP and position the expression of drug concentration directly below the statement of total drug content. For example:

**100mg/5mL
(20 mg/mL)**

2. Please revise established name and proprietary name as per 21 CFR 201.10(g)(2). Please note that the established name should be printed at least half as large as letters comprising the proprietary name, and that the established name should have a prominence commensurate with the prominence of the proprietary name, e.g., established name and proprietary name presented with same font color.
3. To comply with 21 CFR 600.3, 21 CFR 610.62 and 21 CFR 201.57(a)(2), please revise the Prescribing Information title to following presentation.

**Arzerra
Ofatumumab
Injection, for Intravenous Infusion**

Comments concerning container label

4. Please remove the text below "100 mg (20 mg/mL)" to comply with 21 CFR 610.61 (c) and to provide space for revision requested in comment #.1.
5. Please revise the container label to display the manufacturer per 21 CFR 610.60(2). Please note: as per 21 CFR 600.3 (t), the "manufacturer is defined as any person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards, including all steps in the manufacture of the products under the license.
6. Please indicate how the label is affixed to the vial and where the visual area of inspection is located as per 21 CFR 610.60 (e). Please provide an explanation.

7. If space permits, include the following statements on the principal display panel.
- 'Single Use Vial, Discard Unused Portion'
 - 'For Intravenous Infusion Only'
8. Please consider decreasing the space utilized for the bar code to provide space for requested revisions.

Comments concerning carton labeling

9. Please add the statement "No U.S. standard of potency" to comply with 21 CFR 610.61(r).
10. Please revise the inactive ingredients (buffering agents) to alphabetical order per the United States Pharmacopeia, 5/1/09-8/1/09, USP 32/NF27, General Chapter, Labeling of Inactive Ingredients <1091>.
11. Please remove the statement, / from the carton labels per 21 CFR 201.10. This statement is duplicative and the removal of this statement will provide room for other important information as noted above. b(4)
12. Despite being presented in a yellow bar, the route of administration statement 'For Intravenous Infusion Only' is difficult to read due to the use of all capital letters. Consider presenting the route of administration in mixed case letter presentation to improve readability.
13. The current presentation of the statement, 'Contains XX single use vials of Ofatumumab concentrate (20 mg/mL) for dilution and 2 filters' presents the net quantity, the expression of drug concentration and the 'single use vials' statement on the same line rather than as distinct pieces of information. Revise the presentation to include three separate statements as follows.
- a. Per 21 CFR 201.51(d) revise the net quantity statement to read 'Contains XX vials' and 'Contains 2 filters.'
 - b. Relocate the 'Single Use vial' statement directly below the net quantity statement and revise it to read as 'Single Use Vials-Discard Unused Portion'. For example:

Contains XX vials
Contains 2 filters
Single Use Vials- Discard Unused Portion

- c. Remove the phrase ' / ' from the statement as it is a duplicative of the drug concentration statement.

b(4)

Comments concerning package insert label

14. To comply with 21 CFR 600.3, and 21 CFR 201.57(a)(2), please revise the Prescribing Information title to following presentation. The agency is working to standardize the presentation of the Product title and prefers the following presentation:

Arzerra (ofatumumab)
injection, for intravenous infusion

15. We request that you revise the "HOW SUPPLIED/STORAGE AND HANDLING" in the prescribing information to a chart format for clarity.

Vials per carton	NDC
3 single use vials with 2 filters	NDC 0173-0808-02
10 single use vials with 2 filters	NDC 0173-0808-05



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

Memorandum

Date: September 4, 2009
From: Gina M. Davis, RPM DBOP/ODDP/CDER/FDA
Subject: Teleconference with Arzerra to discuss label revisions: BL STN 1253260

GlaxoSmithKline Attendees:

Jeffrey Bloss
Geoffrey Chan
Charles Depew
Ira Gupta
Thomas Lin
Kathy Rouan
Philip Witman
Carlo Russo
Tiffany Davis
Michael Arning
Paolo Paoletti
Michael Bauer
Trine Osterby

FDA Attendees:

Patricia Keegan	Division Director, DBOP
Joseph Gootenberg	Associate Division Director, DBOP
Steven Lemery	Medical Officer, DBOP
Barbara Rellahan	CMC, Reviewer, DMA
Jenny Zhang	Statistical Reviewer, OB/DBV
Andrew McDougal	Nonclinical Reviewer, DBOP
Hong Zhao	Clinical Pharmacology, Team Leader, DCP5/OCF
Gina Davis	Regulatory Project Manager, DBOP

Discussion:

On Friday, September 4, 2009, a teleconference was held between FDA and GlaxoSmithKline (GSK) to discuss FDA Arzerra (ofatumumab) label revisions sent to GSK on August 27, 2009. Section 1, Indications and Usage; Section 12.1, Mechanism of Action; and Section 14, Clinical Studies were discussed at the teleconference.

Section 14 - Clinical Studies

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b(4)

Section 1 - Indications and Usage

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b(4)

Section 12.1 Mechanism of Action

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b(4)

Action Items:

FDA will discuss any action items internally. Any possible changes to the label will be sent to GSK by September 11, 2009, with two additional administrative comments previously discussed with GSK.



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

Memorandum

Date: August 27, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: FDA's proposed label revisions: BL STN 125326/0- Arzerra (ofatumumab)

FDA's proposed revisions to the PLR package insert for Arzerra (ofatumumab) BL STN 125326/0 sent to GlaxoSmithKline on August 27, 2009.

13 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative-2



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

Memorandum

Date: August 19, 2009

From: Raymond Chiang, DBOP/OODP/CDER

Subject: Email: STN BL 125326/0 ofatumumab- Information Request

FDA emailed proposed clinical, clinical pharmacology, and CMC postmarketing commitments.
FDA requested a response to postmarketing commitments.

From: Chiang, Raymond
To: "Philip.A.Witman@qsk.com";
Subject: RE: Attached revised PMRs and PMCs for BL STN 125326/0 Arzerra (ofatumumab)
Date: Wednesday, August 19, 2009 1:12:24 PM
Attachments: Arzerra PMRs and PMCs (8 19 09).doc

Phillip,

Please see attached revised PMRs and PMCs for BL STN 125326/0 Arzerra (ofatumumab). If you agree to the proposed PMRs and PMCs, please submit commitments as an email and as an official response to the BLA no later than noon, Thursday, August 20, 2009. Please note: only editorial and format changes were made. In addition PMR #2 concerning QTc assessment was split up into 2 PMRs, but the original commitment is the same.

thanks,
ray

Arzerra PMRs and PMCs (8.19.09)

POSTMARKETING REQUIREMENTS for ARZERRA BLA STN 125326

1. To submit a final study report for ongoing study OMB110911, entitled, "A Phase III, Open-label, Randomized, Multicenter Trial of Ofatumumab Added to Chlorambucil versus Chlorambucil Monotherapy in Previously Untreated Patients with Chronic Lymphocytic Leukemia" which is intended to verify the clinical benefit of ofatumumab through demonstration of a clinically meaningful effect on progression-free survival. Study OMB110911 was submitted to FDA on October 24, 2008 and as amended (Amendment 2) with submission to FDA on August 21, 2009; and began patient accrual on December 22, 2008.

The timetable you submitted on August 20, 2009 states that you will conduct this trial according to the following milestones:

- **Patient Accrual 50% Completed (222 patients)** **August 30, 2010**
- **Patient Accrual 75% Completed (333 patients)** **March 30, 2011**
- **Patient Accrual Completed** **November 30, 2011**
- **Trial Completion Date:** **October 14, 2013**
- **Final Report Submission:** **June 30, 2014**

2. To conduct clinical trial OMB112855, a study of QTc intervals in patients who have been administered ofatumumab: QTc assessment will be performed in patients who have failed at least one fludarabine-containing regimen (at least two cycles) and failed at least one alemtuzumab-containing regimen (a minimum of at least 12 administrations) or who are considered inappropriate for treatment with alemtuzumab due to lymphadenopathy with at least one lymph node > 5 cm and requiring therapy and who receive the dose and schedule of ofatumumab per the approved prescribing information. The number of subjects evaluated for QTc interval changes will be at least 12. For the QTc assessments, ECGs will be collected in triplicate at baseline, at steady-state ofatumumab concentrations, periodically on-therapy (e.g., every 3 months), and at the end of treatment. The final report will be a comprehensive combined report of the results (including primary data) of clinical trial OMB112855 and of the substudy assessing QTc intervals in OMB110911 (see below).

The timetable you submitted on August 20, 2009 states that you will conduct study OMB112855 according to the following milestones:

- **Final Protocol Submission:** **January 31, 2010**
- **Patient Accrual Completed:** **June 30, 2011**
- **Trial Completion Date:** **June 30, 2012**
- **Final Report Submission:** **December 31, 2012**

3. To conduct assessment of QTc intervals as a substudy of clinical trial OMB110911. The total number of subjects in OMB110911 with evaluable ECG measurements will be at least 50 (25 per treatment arm). For the QTc assessments, ECGs will be collected in triplicate at baseline, at steady-state ofatumumab concentrations, periodically on-therapy (e.g., every 3 months), and at the end of treatment. The final report will be a comprehensive combined report of the results (including primary data) of the substudy assessing QTc intervals in OMB110911 and of clinical trial OMB112855.

The timetable you submitted on August 20, 2009 states that you will conduct the QTc substudy in OMB110911 according to the following milestones:

• Final Protocol Submission:	January 31, 2010
• Patient Accrual Completed:	June 30, 2011
• Trial Completion Date:	June 30, 2012
• Final Report Submission:	December 31, 2012

POSTMARKETING COMMITMENT

4. To submit the final study report for Hx-CD20-406 entitled "A single-arm international, multi-center trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell Chronic Lymphocytic Leukemia who have failed fludarabine and alemtuzumab" to include objective response rates according to the IRC and objective response rates according to the clinical investigators. The final study report will provide summary analyses and primary data. Accrual to this study has been completed.

The timetable you submitted on August 20, 2009 states that you will conduct this trial according to the following milestones.

• Trial Completion Date:	June 30, 2011
• Final Report Submission:	December 31, 2011

CMC POSTMARKETING COMMITMENTS for ARZERRA (Ofatumumab) BLA STN 125326

5. To reassess release and stability specifications for ofatumumab drug substance and drug product through August 31, 2011. The assessment will be submitted in the 2011 annual report.

6. To develop and implement a quantitative specification for the icIEF assay used in the drug substance and drug product stability programs. The assessment will be submitted as a Changes Being Effectuated-30 (CBE-30) supplement by October 31, 2011.
7. To develop and validate a semi-quantitative assay for measurement of visible particulates. The test method and specification will be incorporated into drug substance and drug product lot release and stability programs and a CBE-30 supplement submitted by October 31, 2011.
8. To submit a Prior Approval Supplement (PAS) for the introduction of ~~of~~ ofatumumab single-use vial, 20 mg/mL, to reduce the number of vials needed for the 2000 mg dose by December 31, 2010. b(4)
9. To revise the system suitability criteria for the robotic format of the complement-mediated antibody cytotoxicity potency assay so that the coefficient of variation (CV) (%) for duplicates is consistent with validation limits and is less than or equal to 25%. A final report including details of the system suitability criteria revisions will be submitted by March 2010 and a revised potency assay SOP will be submitted in the 2010 annual report. Alternatively, the robot format of the potency assay will be removed from the BLA.
10. To perform leachables studies to characterize the potential presence of volatile leachables from the elastomeric stopper and the presence of ~~the~~ ~~the~~ under accelerated conditions (25°C) for 6 months and at the recommended storage temperature for 24 months as outlined in the June 5, 2009 submission. The results of these studies will be submitted in the 2012 annual report. b(4)
11. To establish permanent control action limits for purification step yields and analyze 30 in-control points. The permanent control action limits and the results of the analysis of 30 in-control points will be submitted in the 2010 annual report.
12. To conduct a study or studies to identify the composition of visible particles observed in drug substance lots when particles are observed during ongoing stability studies of the drug substance conformance lots. The results of these studies will be submitted in the 2010 annual report.
13. To confirm the lack of a deleterious effect on the stability of drug substance of reprocessing at the ~~the~~ ~~the~~ step by monitoring the real-time stability of drug substance lot 09P01105 and performing accelerated stability studies on this lot at 25°C for 6 months and at 40°C for 3 months. The real time and accelerated studies will include the licensed drug substance stability program's tests and acceptance criteria. Real time stability data and results of the accelerated stability studies will be submitted in the 2010 annual report. b(4)
14. To update the bioburden test for cell culture, primary recovery, and purification samples from ~~the~~ ~~the~~ to filtration method. A study will be performed b(4)

to establish the appropriate volume of each sample in the test. A final study report including the validation information and data for the updated bioburden test will be submitted by March 31, 2010.

15. To validate drug substance intermediate hold times for microbial control at commercial scale. A final report containing the validation data will be submitted by December 31, 2010.



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

Memorandum

Date: August 12, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: Teleconference with GSK/Genmab concerning proposed QTc studies

FDA Participants:

Steve Lemery
Jeff Summers
Raymond Chiang
Hong Zhao
Jun Yang
Michael Axelson
Karen Jones
Grace Carmouze

GSK:

Michael Arning
Charles Depew
John Finkle
Ira Gupta
Roxanne Jewell
Kathy Rouan
Phillip Witman
Sreeni Yalamanchili

Genmab:

Anne Christine Korsgaard

This call was held between GSK and FDA to discuss post-marketing requirements for QTc studies. FDA stated that GSK proposed in their January 30, 2009, submission to evaluate QTc at two dose levels, one with monotherapy at 2000 mg dose in 12 patients (Clinical Trial 112855)

/ FDA stated that GSK was now proposing Clinical Trial OMB110911 to replace Clinical Trial

b(4)

FDA requested that GSK conduct the following clinical trials with ofatumumab to assess QTc intervals: 1) a sub-trial in clinical trial OMB110911 with at least 50 patients (25 per treatment arm) at the 1000 mg dose with chemotherapy and 2) a clinical trial OMB112855 at the monotherapy dose of 2000mg with at least 12 patients.

GSK agreed to conduct the clinical trials as requested.

FDA also requested that GSK propose new dates for completion of the clinical trials and submission of the final study reports.

GSK agreed.

Tcon concluded.



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

Memorandum

Date: August 11, 2009
From: Raymond Chiang, DBOP/ODP/CDER
Subject: Email: STN BL 125326/0 ofatumumab- Information Request

FDA emailed proposed CMC postmarketing commitments. FDA requested a response to CMC postmarketing commitments.

From: Chiang, Raymond
To: "Philip.A.Witman@qsk.com";
Subject: RE: Ofatumumab; PMCs (CMC)
Date: Tuesday, August 11, 2009 12:22:09 PM
Attachments: Ofatumumab Postmarketing Commitments 8-11-09.doc

Phillip,

Please see the attached list of proposed CMC postmarketing commitments. We request that you respond with a formal letter of commitment via both email and formal submission to the BLA.

A response by this Friday, COB is requested.

Please confirm receipt of this email.

thanks,
ray

2 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative- 3

Chi, Bo

From: Stock, Marisa
Sent: Friday, August 07, 2009 10:06 AM
To: Chi, Bo
Cc: CDER-TB-EER
Subject: RE: EER for BLA 125326/0

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the original request below to find the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of BLA 125326/0 at this time.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Chi, Bo
Sent: Friday, July 24, 2009 3:26 PM
To: Hoyt, Colleen; Stock, Marisa
Subject: EER for BLA 125326/0

Hi, could you provide Establishment evaluation in support of approving GSK's new BLA 125326/0? The sites involved are:

DS manufacturer, Testing for Visual Inspection, pH, Osmolality, Protein Concentration, icIEF, GP HPLC, SDS-PAGE, Endotoxin and Bioburden for DS, release and stability testing of DS, cell bank storage, release and stability testing of DP for Protein Concentration, Particles, Osmolality, icIEF, SDS PAGE, GP HPLC
Lonza Biologics plc
228 Bath Road
Slough
Berkshire
SL1 4DX
UK

b(4)

FEI: 1000583959

Inspected May 4-9, 2009 and classified VAI. The (b) profile was covered and is acceptable.

Additional cell bank storage

Lonza Biologics Inc.,
101 International Drive,
Portsmouth,
NH 03801
USA.
FEI: 3001451441

Chiang, Raymond

From: Chi, Bo
Sent: Friday, August 07, 2009 12:48 PM
To: Chiang, Raymond
Cc: Laughner, Erik
Subject: FW: EER for BLA 125326/0

Ray and Erik,
Here is the updated response to TB-EER (compliance check).

Bo

From: Stock, Marisa
Sent: Friday, August 07, 2009 10:06 AM
To: Chi, Bo
Cc: CDER-TB-EER
Subject: RE: EER for BLA 125326/0

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the original request below to find the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of BLA 125326/0 at this time.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Chi, Bo
Sent: Friday, July 24, 2009 3:26 PM
To: Hoyt, Colleen; Stock, Marisa
Subject: EER for BLA 125326/0

Inspected September 18-28, 2007 and classified VAI. The (b) profile was covered and is acceptable.

b(4)

DP manufacturer, Secondary packaging of DP, and testing, including stability testing for Visual Inspection, Osmolality, Extractable Volume, Endotoxin and Sterility, approval for release
Glaxo Operations UK Limited
(Trading as Glaxo Wellcome Operations),
Harmire Road, Barnard Castle,
Co. Durham DL12 8DT,
United Kingdom
FEI: 3003722390

A pre-approval inspection for BLA 125236/0 was conducted May 18-22, 2009 and initially classified (b) (4) and (b) profiles were covered, however a final district decision has not yet been made.

Testing for _____ and release testing of DP for Protein Concentration, Particles, icIEF, SDS PAGE, GP HPLC
Lonza Biologics plc
515 Eskdale Road
Winnersh Triangle
Wokingham
Berkshire
RG41 5TU
UK
FEI: 3007518488

b(4)

Inspected May 4-9, 2009 and classified VAI. The (b) profile was covered and is acceptable.

Thank you.

Bo

Hi, could you provide Establishment evaluation in support of approving GS' new BLA 125326/0? The sites involved are:

DS manufacturer, Testing for Visual Inspection, pH, Osmolality, Protein Concentration, icIEF,

GP HPLC, SDS-PAGE, Endotoxin and Bioburden for DS, release and stability testing of DS, cell bank storage, release and stability testing of DP for Protein Concentration, Particles, Osmolality, icIEF, SDS PAGE, GP HPLC ^{b(4)}

Lonza Biologics plc

228 Bath Road

Slough

Berkshire

SL1 4DX

UK

FEI: 1000583959

Inspected May 4-9, 2009 and classified VAI. The (b) profile was covered and is acceptable.

Additional cell bank storage

Lonza Biologics Inc.,

101 International Drive,

Portsmouth,

NH 03801

USA.

FEI: 3001451441

Inspected September 18-28, 2007 and classified VAI. The (b) profile was covered and is acceptable.

b(4)

b(4)

DP manufacturer, Secondary packaging of DP, and testing, including stability testing for
Visual Inspection, Osmolality, Extractable Volume, Endotoxin and Sterility, approval for release
Glaxo Operations UK Limited
(Trading as Glaxo Wellcome Operations),
Harmire Road, Barnard Castle,
Co. Durham DL12 8DT,
United Kingdom

FEI: 3003722390

A pre-approval inspection for BLA 125236/0 was conducted May 18-22, 2009 and initially classified NAI. The (b) (4) profiles were covered, however a final district decision has not yet been made.

Testing for / and release testing of DP for Protein Concentration, Particles,
icIEF, SDS PAGE, GP HPLC

b(4)

Lonza Biologics plc
515 Eskdale Road
Winnersh Triangle
Wokingham
Berkshire
RG41 5TU
UK

FEI: 3007518488

Inspected May 4-9, 2009 and classified VAI. The (b) (4) profile was covered and is acceptable.

Thank you.

Bo



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

Memorandum

Date: August 5, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: Email: STN BL 125326/0 ofatumumab- Advice/Information Request

FDA emailed proposed clinical and clinical pharmacology postmarketing requirements/commitments. FDA requested a response to proposed clinical and clinical pharmacology postmarketing requirements/commitments.

From: Laughner, Erik
To: Philip.A.Witman@gsk.com;
cc: Chiang, Raymond;
Subject: Ofatumumab; PMRs/PMCs (Clinical and Clin Pharm)
Date: Wednesday, August 05, 2009 1:24:08 PM
Attachments: Ofatumumab Postmarketing Requirements-Commitment 8-5-09.doc

Hello Philip,

Please see the attached list of proposed clinical and clinical pharmacology postmarketing requirements/commitment. We request that you respond with a formal letter of commitment via both email and formal submission to the BLA. Please insert dates in the listed requirements/commitment where indicated.

A response by this Friday, mid-day is requested.

FDA CMC commitments will be sent in a later correspondence.

Please confirm receipt of this email.

Thanks

Erik

Erik S. Laughner, M.S.
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/cder/Offices/OODP/about.htm>

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and notify me immediately. Thank you.



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

Memorandum

Date: August 3, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: Tcon and email: STN BL 125326/0 ofatumumab- Information Request

FDA requested CMC information in a tcon and by email.



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

Memorandum

Date: August 3, 2009

From: Erik Laughner, DBOP/OODP/CDER

Subject: Tcon with GSK concerning BLA STN 125326 (Ofatumumab); CMC

FDA Participants:

Rashmi Rawat, DMA
Barbara Rellahan, DMA
Subramanian Muthukkumar, DMA
Karen Jones, DBOP
Erik Laughner, DBOP
Steve Lemery, DBOP

GSK:

Mary Stawicki, Manager, Biopharm Regulatory Affairs
Philip Witman, Associate Director, Global Regulatory Affairs
Narendra Bam, Vice President, Biopharm Process Development
Thomas Hartman, Vice President, GMP Operations
Lee Olszewski, Director, Biopharm Analytical Sciences
Jennifer Elliott, Manager, Quality Control
Bibi Tee, Director, Quality Control
Amol Ketkar, Manager, Biopharmaceutical Technologies
David Paoella, Manager, Department of Downstream Process Development
John Erickson, Director, Department of Downstream Process Development
Nilesh Shah, Manager, Department of Microbial & Cell Culture Development (Upstream Process Development)
Pramthesh Patel, Director, Department of Microbial & Cell Culture Development (Upstream Process Development)
Jan Thirkettle, Medicines Product Development, Biopharm Team Leader
Ben Thompson, Regulatory Project Manager, CMC Regulatory, EU
Rebecca Street, Medicines Product Development Manager, Biopharm Team UK
Robert Clemmitt, Biopharm Technical Manager, Ofatumumab

DISCUSSION:

The product review team in DMA informed GSK that they had reviewed the recent July 30, 2009, communication which mentioned that a recent DS lot that has undergone reprocessing. FDA noted that they were considering allowing the step prior to BLA approval, but would need a commitment from GSK to look at stability. FDA stated that they

b(4)

would provide something in writing on email and request feedback within in a couple of days. GSK acknowledged.

FDA also noted that GSK would need to provide information to support shipment of DP from the manufacturing site to the distributor and from the distributor to the pharmacy. This information should include information/data that demonstrates product quality is controlled during shipping, a description of the shipping containers and summary information on validation studies performed on the shipping containers and the results of those studies. FDA stated that this request would also be provided in writing via email. GSK acknowledged and agreed to provide the needed information within a couple of days.

The teleconference concluded.

From: Laughner, Erik
To: "Phillip.A.Witman@gsk.com";
cc: Chiang, Raymond; Jones, Karen;
Subject: BLA 125326; CMC information request
Date: Monday, August 03, 2009 2:29:35 PM

Philip,

Per today's telecon, please see our information requests. Please confirm receipt of this email.

1. Provide information to support shipment of DP from the manufacturing site to the distributor and from the distributor to the pharmacy. This should include information/data that demonstrates product quality is controlled during shipping, a description of the shipping containers and summary information on validation studies performed on the shipping containers and the results of those studies.

2. Provide a commitment in regard to the most recent drug substance lot that has undergone \ \ reprocessing:

b(4)

To place drug substance lot [indicate lot number] into the real-time drug substance stability program and to perform accelerated stability studies on this lot at 25°C for 6 months and at 40°C for 3 months. The real time and accelerated studies will include the licensed drug substance stability program's tests and acceptance criteria. Real time stability data will be submitted in the Annual Report and the accelerated stability studies will be completed by [indicate date] and submitted in the [indicate year] Annual Report.

Sincerely,

Erik Laughner, RPM



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

Memorandum

Date: August 3, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: FDA's proposed label revisions: BL STN 125326/0- Arzerra (ofatumumab)

FDA's proposed revisions to the PLR package insert for Arzerra (ofatumumab) BL STN 125326/0 sent to GlaxoSmithKline on August 3, 2009.

14 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative- 4



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

Memorandum

Date: July 23, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: Email: STN BL 125326/0 ofatumumab- Information Request

FDA requested the report of a SAE related to hepatitis and subsequent death be submitted to STN BL 125326/0. The initial safety report for this event was submitted to IND 11719 on July 9, 2009 and a follow-up report was submitted on July 22, 2009.



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

Memorandum

Date: July 23, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: Email: STN BL 125326/0 ofatumumab- Information Request

Information request was sent to Philip Witman by email.

From: Chiang, Raymond
To: "Philip.A.Witman@gsk.com";
Subject: RE: CMC Information Request concerning ofatumumab
Date: Thursday, July 23, 2009 9:54:24 PM
Attachments: DMA IR Letter-5.doc

Philip,

Please see attached Information Request from our CMC review team concerning ofatumumab.
Please provide a response no later than July 30, 2009. As usual, please respond to this email to confirm receipt.

thanks,
ray

Date: July 23, 2009

b(4)

1. Revise the stability specifications for ofatumumab reference standards to include the _____ assay with appropriate acceptance criteria. Submit revised specifications to the BLA.

2.

b(4)

3. In regard to the proposed drug product stability specification for sub-visible particles, please note the following. Information has not been provided that robustly demonstrates that the quality of Arzerra drug product with levels of particles that exceed USP limits is not compromised. (Amend the BLA with an updated table for drug product stability specifications for Arzerra which includes USP <788> limits for the sub-visible particle assay.

b(4)

4. The current drug substance and drug product release and stability specification for the non-reduced SDS-PAGE assay / does not appear to be supported by clinical experience as recommended by ICH Q6B. Clinical experience to date appears to support an acceptance criterion of ^ / Please revise the acceptance criterion and update the BLA, or provide additional justification to support your proposal.

5. Data from drug substance (DS) and drug product (DP) stability studies indicate that there is a reproducible decrease in product potency over time at the recommended storage temperature. While not all DS and DP lots show a decrease, a notable number of the lots demonstrate a significant decrease which raises concerns that lots released with values at the lower end of the specification would fail the potency specification prior to the end of the shelf-life. Revise the potency assay specification to provide increased confidence that the specification is sufficiently narrow to ensure lots remain within the stability specification limit over the established shelf-life. As stated in ICH Q6B, the concept of release limits vs. shelf-life limits may be applied where justified.

6. After review of the stability data we concur with the proposed DS shelf-life of 24 months at 2-8°C. Review of the stability data for the DP validation lots however, indicates there is a significant change in the charge profile of lots stored under accelerated conditions at both 3 and 6 months. Therefore, per ICH Q1E, the accelerated stability data cannot be used for extrapolation of DP shelf-life. Since the submission contains 6 months of real-time stability data from the validation lots with 24 months of supportive real-time data from clinical DP lots, we find the data support a 12 month DP shelf-life at 2-8°C.



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Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 23, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: Email: STN BL 125326/0 ofatumumab- Information Request

FDA requested the report of a SAE related to hepatitis and subsequent death be submitted to STN BL 125326/0. The initial safety report for this event was submitted to IND 11719 on July 9, 2009 and a follow-up report was submitted on July 22, 2009.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Center for Drug Evaluation and Research

Memorandum

Date: July 22, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: STN BL 125326 original BLA 125326/0: Internal wrap-up meeting held July 22, 2009

The internal wrap-up meeting was held on this date.

From: Philip.A.Witman@gsk.com
To: Chiang, Raymond;
Subject: Projections for Enrollment of Subjects into ARZERRA Protocol OMB110911
Date: Wednesday, July 15, 2009 4:50:29 PM

Dear Ray,

Per our teleconference yesterday afternoon, our Clinical Operations team in the UK for the 911 study has sent me the following projections for enrollment of subjects into the ofatumumab + chlorambucil vs. chlorambucil study:

- 25% (111) subject randomisation estimated to be achieved = Jan-2010
- 50% (222) subject randomisation estimated to be achieved = Aug-2010
- 75% (333) subject randomisation estimated to be achieved = Mar-2011
- 100% (444) subject randomisation estimated to be achieved = Nov-2011

Please forward these to Drs. Lemery and Gootenberg per their request.

Have a good evening.

Best regards,

Philip

Philip A. Witman
Associate Director
Global Regulatory Affairs - Oncology

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From: Philip.A.Witman@ask.com
To: Chiang, Raymond;
Subject: Amended Protocol OMB110911 - For Possible Review by Dr. Lemery
Date: Monday, July 13, 2009 5:11:21 PM
Attachments: OMB110911 Amendment 2 Final 13Jul2009.doc

Good afternoon, Ray,

Per our discussion earlier this afternoon, attached is the Microsoft Word version of the amended Protocol OMB110911. As I mentioned, we feel that this revised version incorporates the FDA's comments and concerns from the written correspondence dated 18 December 2008 and from the additional comments and suggestions provided during our teleconference on 23 June 2009.

If possible, would Dr. Lemery be able to look at this version in the next few days so he is comfortable that we have made the requested and appropriate changes? This way, we can minimize further amendments to the protocol. Although there is a summary of the changes on Pages 2 and 3, the detailed record of modifications found on Pages 124-142 probably will be more useful to review.

Obviously, as we propose to make this the clinical trial to confirm clinical benefit, then we would like agreement from the Division that the study will satisfy that purpose.

We need to get Amendment 2 of the protocol into publishing by the end of this week to comply with submitting the approved protocol and the Reporting and Analysis Plan to the Division by early next week as requested. Concurrently, we will send the amended protocol to the IRBs/ECs at the participating sites.

Thank you and Dr. Lemery in advance for your consideration.

Best regards,

Philip

Philip A. Witman
Associate Director
Global Regulatory Affairs - Oncology

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

Memorandum

Date: July 14, 2009

From: Raymond Chiang, DBOP/ODDP/CDER

Subject: Email: STN BL 125326/0 ofatumumab- Information Request

FDA requested GSK submit a copy and results of "risk assessment" that was conducted with pharmacist to investigate potential issues in order to mitigate the requirement of 20 vials until the larger vial size can be introduced.

From: Chiang, Raymond
To: "Philip.A.Witman@gsk.com";
Subject: RE: Amended Protocol OMB110911 - For Possible Review by Dr. Lemery
Date: Tuesday, July 14, 2009 11:11:12 AM

Philip,

Please see an information request below from our Safety Review Team. Please submit this requested information by July 20, 2009. In order to streamline submissions, please submit this information in the same amendment to the BLA as the information requested on July 13, 2009 concerning the Drug Substance.

As usual, please reply to this email to verify receipt.

thanks,
ray

On April 15, 2009, GSK submitted the following response to our safety concerns with 20 vials for one dose:

QUESTION 5

The requirement to use 20 vials for one dose (2000 mg) may lead to confusion and

medication errors thus presenting a safety concern. As you indicated in the

February 20, 2009 technical walk-through meeting, you plan to introduce a new vial

size or strength to mitigate potential medication errors with this product. Please

submit a written commitment (including timelines) for submission of a prior

approval supplement to support introduction of this new strength or vial size.

Response:

GSK intends to submit a Prior Approval Supplement in the 1st quarter of 2010 which will

include the introduction of a \ \ vial of Ofatumumab Injection, 20 mg/mL to reduce

b(4)

the number of vials needed per 2000 mg dose. This supplement will also introduce an

increase in manufacturing scale (and several consequential process changes). A change

of formulation will also be introduced at this point with the aim of reducing visible particles seen in the finished product.

GSK has completed a risk assessment with pharmacists to investigate potential issues in

order to mitigate the requirement for 20 vials until the larger vial size can be introduced.

Training will be provided for pharmacists, physicians and GSK representatives around

the importance of using the full dose, and systems will be in place for re-supply of vials

in the event of breakages. The pack provides the vials in dose-aligned units (3 for initial

dose plus 10 x 2 for follow on doses)...

Please submit a copy of the Licensee's 'risk assessment' (see yellow highlight above) that was conducted with pharmacist to investigate potential issues in order to mitigate the requirement of 20

vials until the larger vial size can be introduced'? We would also like to see the results of the risk assessment.



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Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 14, 2009

From: Raymond Chiang, DBOP/ODDP/CDER

Subject: Teleconference: STN BL 125326/0 ofatumumab- Advice/Information Request

FDA Participants:

Steve Lemery
Joe Gootenberg
Patricia Keegan
Mark Rothmann
Jenny Zhang

GSK:

Philip Witman
Michael Arning
William Bushnell
Geoffrey Chan
Charles Depew
Philip Witman
Randy Davis
Roxanne Jewell
Klaus Edvardsen
Yasser Kamel
Astrid McKeown
Oliver Wright

Genmab:

Michael Bauer
Trine Østerby

FDA expressed concerns whether the OMB119011 would accrue at rate that would allow the trial to be completed in a timely manner. FDA acknowledged receipt of GSK's July 13, 2009 email, indicating that 69 subjects had now been enrolled. FDA stated that the new data and targeted enrollment appear more encouraging than after the previous teleconference regarding post-marketing commitments. FDA requested that GSK provide projected timelines for patient accrual milestones for the OMB119011 study.

GSK stated that enrollment for the OMB119011 study is going well and are certain that all OMB119011 accrual timelines will be met. GSK plans to amend the OMB119011 protocol as soon as possible then open enrollment at additional clinical sites. GSK submitted the proposed

amendment informally to FDA for review. GSK stated that the last patient enrolled, or full OMB119011 study accrual, will be expected to occur by November 2011. FDA stated that they will try to re-review the OMB119011 study and provide comments as soon as possible.

FDA requested that GSK email the projected dates for 50% accrual, 75% accrual and 100% accrual.

GSK agreed to provide requested information by tomorrow.

Attachment: 1) Proposal with OMB119011 timelines sent by email July 15, 2009.
2) OMB119011 amendment sent by email July 13, 2009.



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

Memorandum

Date: June 23, 2009

From: Raymond Chiang, DBOP/OODP/CDER

Subject: Teleconference with GSK/Genmab concerning proposed PMCs/PMRs

FDA Participants:

Joe Gootenberg
Steve Lemery
Raymond Chiang
Jenny Zhang
Mark Rothmann
Grace Carmouze

GSK:

Michael Arning
Robert Watson
Philip Witman
Amol Ketkar
Randy Davis
Charles Depew
Roxanne Jewell
Catherine Bentley
Klaus Edvardsen
Rajni Fagg
Jan Thirkettle
Ben Thompson
Stephen Buckley
Geoffrey Chan
Ira Gupta

Genmab:

Michael Bauer
Nedjad Losic
Trine Østerby

This call was held between GSK and FDA to discuss post-marketing commitments (PMCs). FDA stated that during this call, FDA would listen to GSKs proposals but not make any formal agreements during this call pending further internal discussion. GSK proposed to replace protocol [redacted] with protocol OMB119011 as the confirmatory clinical study (for clinical benefit) if ofatumumab is granted accelerated approval. GSK stated that rituximab plus cyclophosphamide and fludarabine has become standard of care in the community, and

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/ / Accrual into the OMB119011 study has been more rapid and GSK stated that this study is feasible. GSK stated that FDA's prior recommendations regarding restricting the study population to patients less likely to tolerate FC are being incorporated into the protocol.

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GSK stated that enrollment for the pivotal study, study 406, will be completed in 1 month. FDA stated that a decision will be made whether the final results of this study will be requested as a PMC.

FDA stated that additional internal discussions are ongoing regarding additional PMC requests. Any additional requests will be discussed with GSK at a later date.

Tcon concluded.

Proposed Clinical Post-marketing Commitments for ARZERRA BLA 125326

Type of Commitment	Study Number	Title or Summary	Number of Subjects	Submission of Protocol	Completion Date	Submission to BLA
Clinical	Hx-CD20-406	A single-arm international, multi-centre trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell Chronic Lymphocytic Leukemia who have failed fludarabine and alemtuzumab	225	07-Mar-2006 and 19-Oct-2006	30-Jun-2011	31-Dec-2011
Clinical	OMB110911	A phase III, open label, randomized, multicenter trial of Ofatumumab-Chlorambucil combination vs. Chlorambucil Monotherapy in previously untreated patients with B-Cell Chronic Lymphocytic Leukemia	444	24-Oct-2008	14-Oct-2013	30-Jun-2014
Clinical	OMB112855	QTc assessment in subjects who have failed at least one fludarabine-containing regimen (at least two cycles) and failed at least one alemtuzumab-containing regimen (a minimum of at least 12 administrations) or considered inappropriate for treatment with alemtuzumab due to lymphadenopathy with at least one lymph node > 5 cm and requiring therapy and who receive the dose and schedule of ofatumumab per the approved prescribing information	12	Request for Comment and Advice submitted on 30-Jan-2009	15-Feb-2012	31-Aug-2012

Proposed CMC Post-marketing Commitments for ARZERRA BLA 125326

Type of Commitment	Study Number	Title or Summary		Submission to BLA
CMC	TBD	Assessment of release and stability specifications for ofatumumab drug substance and drug product		31-Oct-2011
CMC	TBD	Assessment of release and stability specifications for ofatumumab drug substance and drug product for icIEF		31-Oct-2011
CMC	TBD	Development of a semi-quantitative assay for measurement of visible particulates		31-Oct-2011
CMC	TBD	Post-approval submission with introduction of _____ vial size (i.e., _____)		31-Dec-2010

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125326/0

Glaxo Group Limited d/b/a GlaxoSmithKline
ATTENTION: Philip A. Witman, M.P.H., M.Phil.
Associate Director, Global Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

JUN 19 2009

Dear Mr. Witman:

This letter is in regard to your biologics license application for Arzerra (ofatumumab) submitted January 30, 2009, under Section 351 of the Public Health Service Act.

We refer to your BLA amendment of May 14, 2009, containing responses to our letter dated April 14, 2009, and to your BLA amendment of June 5, 2009, containing responses to our letter dated May 11, 2009.

We have determined that the following information is necessary to take a complete action on your application:

Chemistry, Manufacturing and Controls:

1. Submit a postmarketing commitment to develop and implement a quantitative specification for the icIEF assay used in the drug substance and drug product stability programs. Please incorporate the specification into the stability testing programs within 2 years from time of approval and reported in a changes being effected (CBE) request.
2. In your June 5, 2009 submission, you proposed to increase the sub-visible particle stability specification for particles / particles per vial. This specification is not supported by pre-clinical or clinical experience and it exceeds the limit established by USP <788> (USP 32) which no longer excludes products which are /
The proposal to revise the drug product stability specification for sub-visible particles / is therefore unacceptable. Please submit to the BLA an updated table for stability specification for ofatumumab drug product 20 mg/mL stating the original specification for this assay.
3. It does not appear that there is sufficient control over /

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- //
- b(4)
4. In your May 14, 2009 submission, you responded to question 6 of our April 14, 2009 letter with additional potency assay data from qualification of a new master reference standard. Clarify where these assays were performed (i.e. at Genmab or /). Provide the % CV between plates run for the experiments reported in Table 6 (relative potency data for the master reference standard).
 5. It is our understanding that qualification of new reference standards will require the reference standard to meet all the criteria outlined in Table 4 (m3.2.S.5) and all the commercial drug substance lot release criteria. Please confirm. / b(4)
reference standard acceptance criteria for the potency assay should be narrower than that used for release. Submit revised acceptance criteria for the potency assay that will be used for reference standard qualification.
 6. Provide information on the criteria that will be used to determine when a new reference standard will be established.
 7. Provide a reference standard stability protocol including the testing interval and methods (with acceptance criteria) that will be used.
 8. Provide accelerated stability data for drug substance lot 08P02024 to support / b(4)
Provide information on whether /
 9. / b(4)
 10. / b(4)
 11. / b(4)

12. You committed, in your last response on May 14th, 2009, to execute a protocol to formally verify microbial control (bioburden and endotoxin data) for drug substance during pool hold storage at commercial scale. Please submit the protocol to the BLA. In addition, Table 72 in Section m3.2.S.2.5. (Process Validation and/or Evaluation) contains two maximum hold times for each product intermediate at different temperatures. They are labeled as “maximum hold time” or “facility policy.” Please remove the referenced hold times that you do not plan to validate at Lonza, Slough and amend the BLA accordingly.
13. With regard to the bioburden test for the bulk drug substance, you stated that the

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Please submit the information requested above within two weeks of the date of receipt of this letter. We request that, to the extent possible, all information be provided in a single complete submission.

Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. Review of your application is continuing.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Raymond Chiang, at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



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

Memorandum

Date: June 18, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: Email: STN BL 125326/0 ofatumumab- Information Request

FDA requested GSK submit response to CMC information request.

From: Chiang, Raymond
To: "Philip.A.Witman@qsk.com";
Subject: RE: Request for CMC Information
Date: Thursday, June 18, 2009 1:20:21 PM

Phillip,

Please see information request from the CMC review team:

Submit the SOP for the robotic potency assay performed by [redacted], as previously requested or indicate where this information is located in the BLA. This should contain information on the system suitability requirements used for the potency assay. If the SOP does not explicitly state what the system suitability requirements are, those should also be provided.

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Please email and submit formally as an amendment to the BLA the requested information by Monday, June 22, 2009.

thanks,
ray



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125326/0

Glaxo Group Limited d/b/a GlaxoSmithKline
ATTENTION: Phillip A. Witman, M.P.H., M.Phil.
Associate Director, Global Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

JUN 12 2009

Dear Mr. Witman:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Arzerra (ofatumumab).

We also refer to our April 14, 2009 letter which included our plans to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 2, 2009.

On June 5, 2009, we received an amendment to this application that provided chemistry and manufacturing information responding to information request letters dated April 14, 2009 and May 11, 2009. We have classified this information as a major amendment. Therefore, we are extending the goal date by three months to provide time for a full review of the amendment. The extended user fee goal date is October 31, 2009.

Due to the extension of the user fee goal date, we now plan to communicate proposed labeling and any additional postmarketing commitment requests by September 30, 2009.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Raymond Chiang, at (301) 796-2320.

Sincerely,

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



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

Memorandum

Date: June 15, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: STN BL 125326 original BLA 125326/0: Team meeting held June 15, 2009

A team meeting was held on this date.

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # BLA# 125326/0	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Arzerra Established/Proper Name: Ofatumumab Dosage Form: 100mg/5 mL single-use vial Strengths:		
Applicant: GlaxoGroup Limited d/b/a GlaxoSmithKline Agent for Applicant (if applicable):		
Date of Application: January 30, 2009 Date of Receipt: January 30, 2009 Date clock started after UN:		
PDUFA Goal Date: July 30, 2009		Action Goal Date (if different):
Filing Date: March 1, 2009 Date of Filing Meeting: February 27, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication: Treatment of patients with chronic lymphocytic leukemia who have received prior therapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Refer to Appendix A for further information.		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		☐ Standard ☒ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☒ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☒ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 11719	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	X YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	☐ YES X NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	X YES ☐ NO
User Fee Status Comments: orphan indication	☐ Paid X Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i> If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i> Comments:	☐ YES ☐ NO ☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> Comments:	☐ YES # years requested: ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	X Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?	☒ Not applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? *Check the Electronic Orange Book at: <http://www.fda.gov/cder/ob/default.htm>*

☐ YES
☐ NO

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL).

Comments:

☐ All paper (except for COL)
☒ All electronic
☐ Mixed (paper/electronic)

XCTD

☐ Non-CTD
☐ Mixed (CTD/non-CTD)

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?

Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.

Comments:

X YES
☐ NO

If electronic submission, does it follow the eCTD guidance? (<http://www.fda.gov/cder/guidance/7087rev.pdf>)

X YES
☐ NO

If not, explain (e.g., waiver granted):

Form 356h: Is a signed form 356h included? <i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i> Are all establishments and their registration numbers listed on the form? Comments:	☒ YES ☐ NO ☒ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? Comments:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only) If no, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? Comments:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	☐ YES ☒ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? Comments: N/A	☐ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? <i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>	☒ YES ☐ NO

<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i> Comments:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>) <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☒ Not Applicable (<i>electronic submission or no CMC technical section</i>) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? <i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i> Comments:	☒ YES ☐ NO
Pediatrics	
PREA <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> Are the required pediatric assessment studies or a full waiver of pediatric studies included? If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? <i>If no, request in 74-day letter.</i> <i>If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</i> Comments: orphan indication	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request?	☐ YES ☐ NO
<i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	
Comments: N/A	
Prescription Labeling	
Check all types of labeling submitted.	☐ Not applicable ☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)
Comments:	
Is electronic Content of Labeling submitted in SPL format?	☒ YES ☐ NO
<i>If no, request in 74-day letter.</i>	
Comments:	
Package insert (PI) submitted in PLR format?	☒ YES ☐ NO
If no, was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request? <i>If no, request in 74-day letter.</i>	☐ YES ☐ NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	☒ YES ☐ NO
Comments: New indication & conversion to PLR format.	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (send WORD version if available)	☒ Not Applicable ☐ YES ☐ NO
Comments:	
REMS consulted to OSE/DRISK?	☒ Not Applicable ☐ YES ☐ NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	Not Applicable ☒ YES ☐ NO
Comments:	

OTC Labeling	
Check all types of labeling submitted. Comments:	X Not Applicable ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? <i>If no, request in 74-day letter.</i> Comments:	☒ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> Comments: N/A	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> Comments:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? Comments:	☒ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting.</i> Comments:	☒ YES Date(s): EOP2 CMC: 7/13/07; Comments on EOP2 meeting package 9/6/07
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i> Comments:	X YES Date: Pre-BLA Clinical: 9/29/08; Pre-BLA CMC 10/23/08 ☐ NO
Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i> Comments:	☐ YES Date(s): X NO No agreement letters 7/11/08 and 10/15/08 for protocol OMB119013

Chiang, Raymond

From: Chi, Bo
Sent: Tuesday, April 14, 2009 11:40 AM
To: Chiang, Raymond; CDER-TB-EER; Dillon, Laura; Stock, Marisa; Randazzo, Giuseppe
Cc: Obenhuber, Donald; Hughes, Patricia; Muthukkumar, Subramanian; Rawat, Rashmi; Rellahan, Barbara
Subject: RE: Re: Please conduct an establishment evaluation of the following facilities in the attached consult form form BL STN 125326/0.

Ray,

I have requested an establishment evaluation at the beginning of the review cycle to help us determine the sites that require inspection. I will request another one near the end of the review cycle. The next evaluation needs to include the outcome for our planned inspections for the drug substance, drug product manufacture sites and testing labs. I will forward you the response to the final EER after I get it.

Bo

From: Chiang, Raymond
Sent: Tuesday, April 14, 2009 11:29 AM
To: CDER-TB-EER; Dillon, Laura; Stock, Marisa; Randazzo, Giuseppe
Cc: Chi, Bo; Obenhuber, Donald; Hughes, Patricia; Muthukkumar, Subramanian; Rawat, Rashmi; Rellahan, Barbara
Subject: Re: Please conduct an establishment evaluation of the following facilities in the attached consult form form BL STN 125326/0.
Importance: High

To CDER-TB-EER

Please conduct an establishment evaluation of the following facilities in the attached consult form form BL STN 125326/0. I have cc'ed the chemistry reviewers from DMA and ONDQA if you have any site specific questions.

thanks,
ray

Raymond S. Chiang, M.S.
Consumer Safety Officer/ Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Email: Raymond.Chiang@fda.hhs.gov
phone: 301-796-1940
<< File: EER Consult.pdf >>

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 27, 2009

NDA/BLA #: 125326/0

PROPRIETARY/ESTABLISHED NAMES: Arzerra (ofatumumab)

APPLICANT: GlaxoGroup Limited d/b/a GlaxoSmithKline

BACKGROUND: Original BLA submission for human monoclonal antibody against CD20 indicated for Alemtuzumab and Fludarabine refractory chronic lymphocytic leukemia (CLL)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Raymond Chiang	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Joseph Gootenberg		Y
Clinical	Reviewer:	Steven Lemery	Y
	TL:	Joseph Gootenberg	Y
OSE	Reviewer:	Tselaine Jones-Smith	Y
	TL:	Kristina Arnwine	Y

Clinical Pharmacology	Reviewer:	Jun Yang/Justin Earp	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Jenny (Jing) Zhang	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Andrew McDougal	Y
	TL:	Anne Pilaro	Y
Product Quality (CMC)	Reviewer:	Subramanian Muthukkumar	Y

	TL:	Barbara Rellahan	Y
Facility (for BLAs/BLA supplements)	Reviewer:	Bo Chi	Y
	TL:	Patricia Hughes	Y
Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon	N
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues?	☒ Not Applicable
If yes, list issues:	☐ YES ☐ NO
Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO
If no, explain:	

Electronic Submission comments	☐ Not Applicable
List comments:	
CLINICAL	☐ Not Applicable
Comments: The clinical review team noted that only 59 patients were considered double refractory. The clinical team will have comments to be included in the 74-day letter	☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	☒ YES NO
If no, explain: Unlikely that any single site influenced the results. FDA has a good understanding of the safety profile.	
• Advisory Committee Meeting needed?	☒ YES Date if known:
Comments: sponsor requesting accelerated approval based on a single-arm study and objective response rate	☐ NO ☒ To be determined

If no, for an original NME or BLA application, include the reason. For example: ○ this drug/biologic is not the first in its class ○ the clinical study design was acceptable ○ the application did not raise significant safety or efficacy issues ○ the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease	Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments: The clinical pharmacology team stated that 2 datasets were missing and that comments will be included in the 74-day letter.	Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS Comments: The statistical team will request a summary of concordance/discordance from sponsor.	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Comments: The nonclinical review team will have comments to be included in the 74-day letter	
PRODUCT QUALITY (CMC) Comments: The CMC review team will have comments to be included in the 74-day letter, including a request for a Table of Contents (with hyperlinks) for every module.	Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? • Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	Not Applicable ☐ YES ☐ NO Not Applicable ☒ YES ☐ NO
• Sterile product? If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)	☒ YES ☐ NO ☐ YES ☐ NO
FACILITY (BLAs only) Comments: The facilities review team will have comments to be included in the 74-day letter.	Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, M.D.	
GRMP Timeline Milestones:	

First Committee Meeting- February 13, 2009
 Filing Meeting- February 27, 2009
 Mid-Cycle Meeting- April 6, 2009

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): ☐ Standard Review X Priority Review

ACTION ITEMS

☐	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
X	If BLA or priority review NDA, send 60-day letter.
☐	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.



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

Memorandum

Date: May 21, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: Teleconference: STN BL 125326/0 ofatumumab- Advice/Information Request

FDA Participants:

Patricia Hughes
Kristy Zielny
Don Obenhuber
Subramanian Muthukkumar
Barbara Rellahan
Patrick Swann

GSK:

Catherine Bentley
Jennifer Elliott
Ben Thompson
Jennifer Dally
Leonard (Lee) Olszewski
Philip Witman

GSK requested a teleconference to clarify information requests communicated by FDA in a May 11, 2009 information request letter. GSK emailed specific questions to be discussed in the May 21, 2009 teleconference.

Question 6: FDA has asked us to justify the current limits for release and stability GP HPLC testing with data. In the initial application we set the limits at \ because we didn't have enough stability data from our proposed commercial method to support a tighter limit. We still do not have enough stability data time points at this time. Would we be able to provide this as a commitment?

b(4)

Discussion during teleconference: FDA requested GSK provide the actual numerical results they used to set the specification. GSK asked whether FDA was requesting data for specifications. FDA stated yes. GSK agreed to provide the requested information.

Questions 7: FDA has asked us for a lower limit for osmolality. We currently have a lower limit set in accordance with pharmacopeia. Does FDA want us to introduce an upper limit?

Discussion during teleconference: FDA answered yes; FDA does want GSK to introduce an upper limit.

Question 19: FDA has asked us to put a quantitative spec for IEF in place for use in future stability studies. However, we have implemented icIEF in response to FDA's earlier request for a quantitative method with the intention that this replaces the IEF assay. Therefore we did not include IEF in the stability commitment and do not plan to continue performing IEF as part of the drug substance stability program. This approach was discussed in the EOPII meeting. Can we clarify that FDA will accept icIEF as the quantitative method in place of IEF.

Discussion during teleconference: FDA stated that the BLA does not contain a list of specifications that are to be used in the drug substance stability program (this has been requested). Data on DS stability only has data from the IEF. For this reason FDA assumed that the IEF has going to be run for stability. FDA stated that submitting a list of the DS stability specifications will help clarify this issue. GSK stated that they are replacing the IEF with the icIEF.

FDA asked whether GSK will provide data that indicates that the icIEF has the same or better stability indicating abilities as the IEF since currently there is no DS stability data using the icIEF. GSK stated yes. FDA also requested GSK refer FDA to information in the BLA that supports their comparability in regard to stability indicating properties. GSK agreed to provide requested information.

FDA requested, as communicated in question 16 of the May 11 information request letter, GSK update the BLA to indicate the accurate vial size ofatumumab is supplied in. GSK agreed to update the BLA to indicate the accurate vial size.



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

Memorandum

Date: May 19, 2009

From: Raymond Chiang, DBOP/OODP/CDER

Subject: Teleconference: STN BL 125326/0 ofatumumab- **Information Request**

FDA Participants:

Patricia Keegan
Raymond Chiang
Jenny Zhang
Mark Rothmann

GSK:

Charles Depew
Geoffrey Chan
Kathy Rouan
Michael Arning
Philip Witman
William Bushnell
Ira Gupta
Debasish Roychowdhury
Randy Davis
Mary Woessner

Genmab:

Charlotte Russell
Nedjad Losic
Trine Osterby
Joris Wilms

FDA requested GSK submit the Investigator-based duration of response (DOR) for ofatumumab. FDA also requested GSK submit the primary data associated with this DOR.

GSK will submit the requested information.

FDA stated that Investigator-based data from 8 subjects in the double-refractory (DR) group and 7 subjects in the bulky fludarabine refractory (BFR) group is missing from the BLA submission.

FDA requested GSK submit a dataset with the Investigator-based date of onset of response, Investigator-based date of progression, and censoring times for the Investigator response analysis.

GSK will submit the requested information.

Meeting concluded.

Attachment: Documents submitted by GSK on May 19, 2009 at 6:27 PM EST via email.

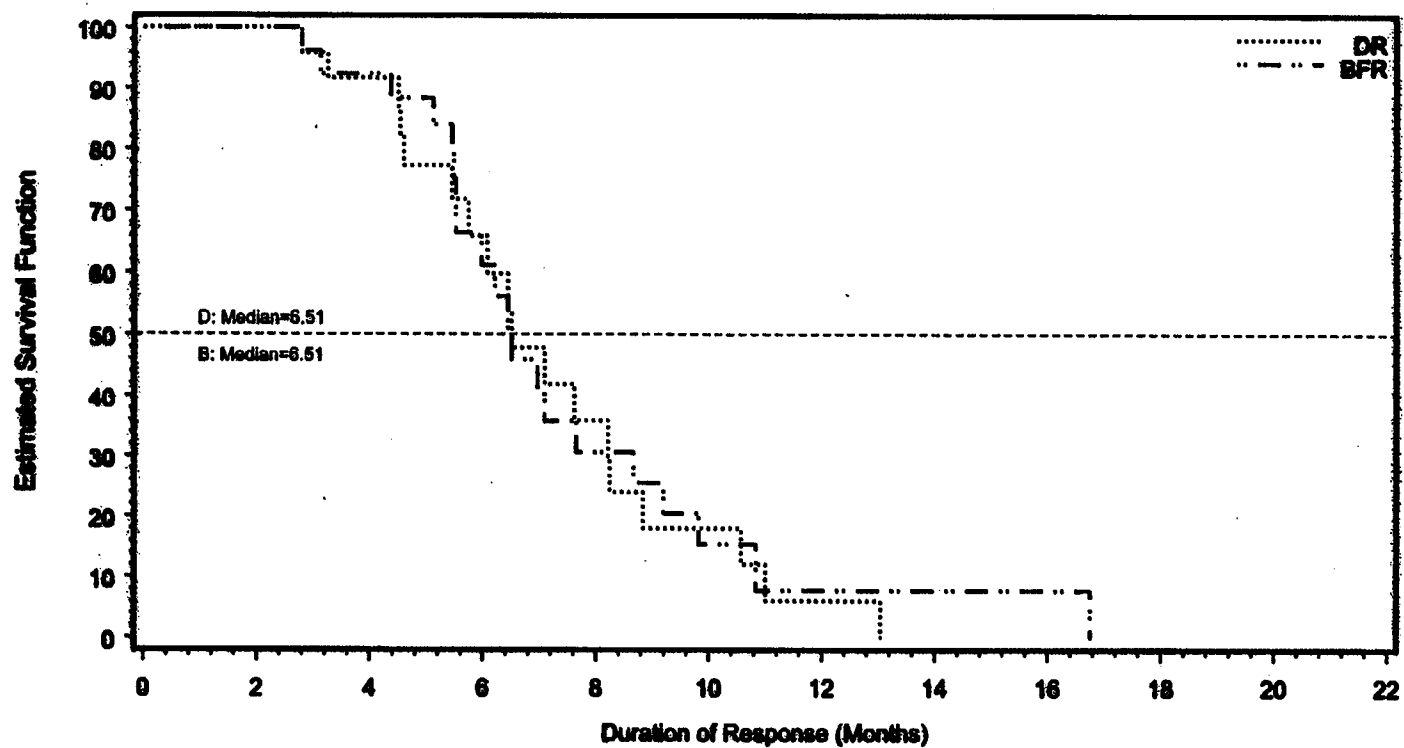
During a teleconference on 19 May 2009, the Division requested that the Sponsor submit a dataset with the date of onset of response, date of progression, and the censoring times for the Investigator response analysis. The FDA noted the analysis conducted by the Division included 8 censored patients in the DR group and 7 censored patients in the BFR group.

Sponsor Response:

The requested dataset (2.xpt) has been provided. The sponsor has identified 7 DR subjects (406128, 406205, 406222, 406233, 406248, 406254, 406260) and 7 BFR subjects (406107, 406120, 406194, 406238, 406252, 406255, 406256) for censoring. We cannot identify the eighth DR subject; we request that the Division verify that the 14 subject numbers identified match those of the Division and that the subject number of the eighth DR subject be provided. b(4)

The sponsor's analysis table (t_resp_inv_dur_surv_406.pdf) and figure (f_surv_inv_dur_no_406.pdf) have also been submitted in this response.

Figure 21.301
Duration of Investigator Response (Programmed Approach)



Number of Subjects at Risk:

DR	25	24	19	11	6	3	1	0	0	0	0	0
BFR	27	27	24	12	6	2	1	1	1	0	0	0

Table 21.301
Point Estimate of Duration (Months) of Investigator Response (Programmed Approach)

Group	n	Failed	Censored	Quartile	Point Estimate	95% CI	
						Lower Limit	Upper Limit
DR (N=59)	25	18	7	1st Quartile	5.45	4.50	6.51
				Median	6.51	5.75	8.25
				3rd Quartile	8.25	6.51	11.01
BFR (N=79)	27	20	7	1st Quartile	5.52	5.13	6.44
				Median	6.51	5.52	8.67
				3rd Quartile	9.20	6.51	10.84
Other (N=16)	10	8	2	1st Quartile	4.80	2.33	7.33
				Median	6.87	4.80	13.37
				3rd Quartile	7.36	6.87	
Total (N=154)	62	46	16	1st Quartile	5.45	4.60	6.08
				Median	6.51	5.98	7.36
				3rd Quartile	8.67	7.33	10.84



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

Memorandum

Date: May 19, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: STN BL 125326 original BLA 125326/0: Team meeting held May 19, 2009

A team meeting was held on this date.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125326/0

Glaxo Group Limited d/b/a GlaxoSmithKline
ATTENTION: Philip A. Witman, M.P.H., M.Phil.
Associate Director, Global Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

MAY 11 2009

Dear Mr. Witman:

This letter is in regard to your biologics license application for Arzerra (ofatumumab) submitted January 30, 2009, under Section 351 of the Public Health Service Act.

We also refer to your electronic mail transmission received April 28, 2009, notifying us of increased sub-visible particles in drug product lots produced at the Barnard Castle and facilities. We have determined that the following information is necessary to take a complete action on your application:

b(4)

Chemistry, Manufacturing and Controls:

1. Regarding the recent finding of increased sub-visible particles in drug product lots produced at Barnard Castle and facilities, please submit the following:

- a. An in-depth analysis of the composition of the sub-visible particles observed in drug product lots produced at Barnard Castle compared to those occurring in lots produced at
- b. An analysis that identifies the root cause for the significant increase in particulate formation in drug product lots filled at the Barnard Castle facility.

b(4)

c.

b(4)

4 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative-5

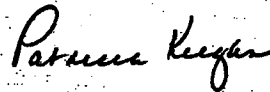
20. Submit a postmarketing commitment to develop and validate a semi-quantitative assay for measurement of visible particulates. The test method and specification should be incorporated into drug substance and drug product lot release and stability programs within two years from the time of approval.

Please submit the information requested above by June 5, 2009. We request that, to the extent possible, all information be provided in a single complete submission. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of your application is continuing.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Raymond Chiang, at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

¹ 1) Tyagi AK, Randolph TW, Dong A, Maloney KM, Hitscherich C Jr, Carpenter JF. 'IgG particle formation during filling pump operation: a case study of heterogeneous nucleation on stainless steel nanoparticles.' J Pharm Sci. 2009 Jan; 98(1):94-104.

2) Carpenter JF, Randolph TW, Jiskoot W, Crommelin DJ, Middaugh CR, Winter G, Fan YX, Kirshner S, Verthelyi D, Kozlowski S, Clouse KA, Swann PG, Rosenberg A, Cherney B. 'Overlooking subvisible particles in therapeutic protein products: gaps that may compromise product quality.' J Pharm Sci. 2009 Apr; 98(4):1201-5.



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

Memorandum

Date: May 4, 2009

From: Raymond Chiang, DBOP/ODDP/CDER

Subject: STN BL 125326 original BLA 125326/0: Team meeting held May 4, 2009

A team meeting was held on this date.



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

Memorandum

Date: April 21, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: STN BL 125326 original BLA 125326/0: Team meeting held April 21, 2009

A team meeting was held on this date.



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

Memorandum

Date: April 20, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: Face-to-Face meeting with GSK/Genmab concerning available therapies for CLL

FDA Participants:

Richard Pazdur
Patricia Keegan
Joe Gootenberg
Steve Lemery
Raymond Chiang
Karen Templeton-Somers
Anne Pilaro
Jenny Zhang
Ann Farrell
Rashmi Rawat
Subramanian Muthukkumar
Justin Earp
Hong Zhao
Jun Yang
Tselaine Jones-Smith
Kristine Arnwine

GSK:

Charles Depew
Geoffrey Chan
Kathy Rouan
Michael Arning
Philip Witman

Genmab:

Charlotte Russell
Trine Osterby

GSK provided a pdf copy of their briefing document by email on April 17, 2009 (attached).

FDA opened the Face-to-Face meeting with a statement that the purpose of the meeting was for GSK to demonstrate that ofatumumab is superior to available therapy. FDA stressed the importance of this issue since the pivotal trial (study 406) as a single-arm trial assumed that the enrolled subjects were not candidates for other available therapy. GSK stated understanding.

GSK presented a PowerPoint presentation that summarized the April 17, 2009 briefing document and that provided arguments to support the contention that ofatumumab is superior to available therapy.

FDA inquired regarding the source and relative population sizes for data provided in Table 3 of the briefing document. GSK stated that data included in Table 3 for fludarabine and alemtuzumab were from the approved labels; for FC, the population was 20 patients; for FCR, data were from the REACH trial; for rituximab, data were from the clinical trial for which Susan O'Brien was primary investigator.

GSK stated that, unlike ofatumumab, alkylating agents demonstrated decreased efficacy and increased toxicity with subsequent lines of therapy.

FDA asked whether the described responses were of similar durations. GSK explained that they were not.

GSK noted that limited data were available concerning bendamustine activity in patients refractory to fludarabine. Most available data for bendamustine were in the first line setting. Only 7 of the 22 patients from Germany enrolled in study 406 received bendamustine.

FDA stated that alkylating agents, including bendamustine, may be considered as a class when considering prior therapy.

FDA stated that the information presented will be considered during the ongoing review.

GSK agreed to submit the PowerPoint presentation as an amendment to the BLA.

Meeting concluded.

14 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

74-Day Letter

Our STN: BL 125326/0

Glaxo Group Limited d/b/a GlaxoSmithKline
ATTENTION: Phillip A. Witman, M.P.H., M.Phil.
Associate Director, Global Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

APR 14 2009

Dear Mr. Witman:

Please refer to your biologics license application (BLA), dated January 30, 2009, received January 30, 2009, submitted under section 351 of the Public Health Service Act, for Arzerra® (ofatumumab). Please also refer to our filing letter dated March 30, 2009 and our March 6, 2009, letter requesting additional information.

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 commitment requests by July 2, 2009.

Please address the following potential review issues within 30 days of receipt of letter unless specified otherwise:

CLINICAL/STATISTICAL:

1. Please provide audit certificates for study Hx-CD20-406 at study sites SE01, US01, and US02. Certificates for these sites were not provided in module 5.3.5.2 of the BLA.
2. In your define.pdf file for the statistical datasets, the derivations for the variables OS and OS01 in survival.xpt for the analysis of overall survival were described under "comments". However, we have been unable to replicate your overall survival analysis following those specified derivations from the raw data. Our results differ significantly from those presented in your submission, especially with regard to the censoring dates.

The relevant SAS program submitted (eff-surv.sas) uses variable names that are not found in any of the datasets in the BLA. Please submit a SAS program which derives the censoring dates for your overall survival analysis per the definition given in the "comments" column of OS01 in define.pdf, using variable names that can be found in the datasets.

3. The following inconsistencies with respect to death dates (DEATHDT in dataset eos.xpt) and time to death (OS in survival.xpt) were found:

patient ID	study entry	death date	OS (sponsor)	death date – study entry
406105	1-Aug-06	✓	25	
406168	6-Feb-07	✓	195	
406228	24-Jul-07	*	311	
406250	24-Oct-07	✓	131	

b(4)

*In the clinical study report, patient 406228 died on 11/24/07, which corresponds to OS of 311 days, however, the death date is missing in eos.xpt (see * above).

b(4)

Please address the above death date discrepancies by submitting revised datasets and a new analysis of survival.

4. Discrepancies were found for the following patients with respect to the IRC's overall response assessments. FDA derived the overall response assessments given in the table below (following the definitions in the protocol) for IRC reader 1, reader 2, and adjudicator (if applicable) from the individual by-visit patient IRC assessment dataset (vstresp.xpt) submitted in response to our information request letter dated March 6, 2009.

From the IRC charter and protocol, (i) if both initial readers' overall response assessments are in agreement, then their assessments would be the final IRC overall response, and (ii) in any case in which an adjudicator is needed, if the adjudicator's overall response assessment was in agreement with either of the two initial readers, then the overall IRC response would be that of the adjudicator and no consensus read would be necessary.

However, guideline (i) was not followed for the 10 patients "grayed out" in the table below and guideline (ii) was not adhered to for the remaining 5 patients listed. Please address these discrepancies between the IRC overall response assessment and the Charter criteria for response assessment by submitting new analyses which conform to the IRC

charter criteria or by providing an explanation why the current analyses/data should still be considered valid. Please also submit any related SAS programs.

group	patient ID	reader 1	reader 2	adjudicator	consensus	IRC (sponsor)	IRC (FDA)
DR	406118	3	4	4	Y	3	4
	406147	4	4	5	Y	3	4
	406158	5	5	3		3	5
	406195	3	4	4		3	4
	406199	4	4	NA		3	4
	406203	5	5	5		3	5
	406210	3	4	4	Y	3	4
	406218	4	4	3	Y	3	4
BFR	406108	4	4	5	Y	3	4
	406144	4	4	NA		3	4
	406162	4	5	5	Y	3	5
	406204	4	5	4	Y	3	4
	406223	5	5	NA		3	5
	406225	4	4	5		3	4
	406243	4	4	4		3	4

5. The requirement to use 20 vials for one dose (2000 mg) may lead to confusion and medication errors thus presenting a safety concern. As you indicated in the February 20, 2009 technical walk-through meeting, you plan to introduce a new vial size or strength to mitigate potential medication errors with this product. Please submit a written commitment (including timelines) for submission of a prior approval supplement to support introduction of this new strength or vial size.

CHEMISTRY, MANUFACTURING AND CONTROLS (CMC):

6. During validation of the potency assay for both the robotic and manual format, multiple validation parameters were not met. The potency assay will therefore need to be re-validated. There appears to be a particularly high degree of variability in assay precision (particularly with the robotic format) that might be resolved by inclusion of a greater number of replicates per plate. Submit the potency assay re-validation report (with an updated assay SOP and / / format, if applicable) to the BLA by June 1, 2009. b(4)
7. Submit the potency assay validation report which confirmed the assay's specificity and robustness. It is our understanding this study was performed by Genmab and is covered in report GMB3001-014.
8. For the / / cells used in the potency assay, provide information on the criteria used for maintenance of the cells once they have been thawed for use in the assay (for example, / / b(4)

4 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

42. Change  to “intravenous infusion” throughout label. b(4)
43. Relocate the horizontal line located between the Table of Contents and FPI to page 1.

Highlights Section:

44. Delete the white space between the major headings and the text underneath.
45. Do not use “TM” after the drug names in the Highlights section. Use “TM” only once in the content of the labeling (FPI).
46. For biologic products, the dosage form and route of administration are not part of the product name. Relocate the dosage form and route of administration to the line immediately below the product name.
47. If Arzerra is approved under accelerated approval, the INDICATIONS AND USAGE will need to be revised to include the following statement.

“Arzerra has been given accelerated approval for the treatment of chronic lymphocytic leukemia (CLL) based on studies that have investigated response rate, a surrogate endpoint for clinical benefit. Studies to determine whether Arzerra confers clinical benefit are ongoing.”

48. In the WARNINGS AND PRECAUTIONS, use bold font to identify each Warnings and Precaution subsection.

Full Prescribing Information (FPI):

49. If Arzerra is approved under accelerated approval, the INDICATIONS AND USAGE will need to be revised to include the following statement.

“Arzerra has been given accelerated approval for the treatment of chronic lymphocytic leukemia (CLL) based on studies that have investigated response rate, a surrogate endpoint for clinical benefit. Studies to determine whether Arzerra confers clinical benefit are ongoing.”

50. Because of the differences in administration schedules between studies Hx-CD20-406 and Hx-CD20-402, revise Table 3 in ADVERSE REACTIONS to include adverse event data from study Hx-CD20-406 only. Furthermore, please revise the Grade 3/4 columns in Table 3 so that the new columns show the incidence for all $\geq$ Grade 3 adverse reactions (including Grade 5 events).
51. Delete Table 6 from CLINICAL STUDIES. We consider this data to be supportive and will not allow this data to be included as marketing claims.

52. Revise the Adverse Reaction Section to include laboratory data as derived from the laboratory datasets (biochemistry and hematology) for the incidence of $\geq$ Grade 3 laboratory adverse reactions. We consider these objective findings to be more reliable than the reported assessments of investigators currently described in Table 3 of proposed label.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplement. Following a review of the supplement, we will advise you in writing of any action we have taken and request additional information if needed.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please call Raymond Chiang, Regulatory Project Manager, at (301) 796-1230.

Sincerely,



Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



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

Memorandum

Date: April 8, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: Tcon concerning Periodic Safety Update for BL STN 125326/0
(Ofatumumab)

FDA Participants:

Patricia Keegan
Steve Lemery
Raymond Chiang

GSK Participants:

Amy Calisto
Brian Natvig
Geoffrey Chan
Susan Cousounis
Ira Gupta
Theresa Nicholson
Christina Vleisides
Philip Witman
Michael Arning
Debasish Roychowdhury

Genmab Participants:

Michael Bauer

FDA stated the Briefing Document draft emailed on April 7, 2009 in preparation for the scheduled April 20, 2009 meeting was "on the right track".

In response to FDA request for clarification, GSK confirmed that the 90-day safety update would be submitted in lieu of the 120-day safety update. FDA reminded GSK that, in accordance with the September 29, 2008 pre-BLA meeting, only new information on serious adverse events (SAEs), deaths, and drop-outs should be submitted in the safety update. FDA requested confirmation that case report forms and case narratives, but not new/revised datasets, would be submitted with the safety update. GSK stated that the safety update would not contain case report forms and would contain datasets supporting a reanalysis of safety from the 406 study and other studies containing 2 additional months of safety information. GSK stated that CRFs are not available for deaths and dropouts. FDA stated that submission of case narratives alone would be acceptable provided that CRFs were submitted upon FDA request, as needed. GSK agreed to do so. FDA informed GSK that FDA may elect not to review or include general updates of safety in the package insert (PI). GSK acknowledged FDA's comment.

In response to FDA's question, GSK stated that safety update would contain new information for 32 patients enrolled in study 415. FDA asked GSK to identify whether any SAEs occurred in patients

enrolled in study sites in the United States for study 415 and if so, to identify the study site(s). GSK agreed to provide this information.

Addendum

GSK informed FDA that none of the 32 patients with new SAEs, deaths, or dropouts in study 415 were enrolled at US study sites.

Deaths Reported in Study GEN415

(Request by DBOP via teleconference on 08 April 2009)

Subject ID	Investigator Institution City, Country	Cause of Death	Relationship to Ofatumumab Per Investigator
415001 ^a	Prof. André Bosly Groupe d'Etude des Lymphomes de l'adulte Clin. Universitaires UCL de Mont-Godinne Service d'Hématologie Yvoir, Belgium	Disease progression	No
415004 ^b	Dr. Ka Lung Wu Ziekenhuis Stuivenberg Antwerpen, Belgium	Death ^c	Unknown
415009 ^b	Dr. Ka Lung Wu Ziekenhuis Stuivenberg Antwerpen, Belgium	Disease progression	No
415011	Dr. Olivier Casasnovas CHU de Dijon-Hôpital d'Enfants Dijon, France	Febrile neutropenia ^c	Yes
415012 ^b	Dr. Andrew Davies Southampton General Hospital Southampton, United Kingdom	Neutropenic sepsis ^c	Yes
415015 ^b	Dr. Didier Decaudin Hôpital de l'Institut Curie Paris Cedex 05, France	Sepsis ^c	No
415022	Dr. Alessio Perrotti Ospedale S. Eugenio Rome, Italy	Cardiac failure ^c	No
415027 ^b	Prof. André Bosly Groupe d'Etude des Lymphomes de l'adulte Clin. Universitaires UCL de Mont-Godinne Service d'Hématologie Yvoir, Belgium	Lymphoma ^c	No
415028	Dr. Maria Dolores Caballero Hospital Clínico de Salamanca Salamanca, Spain	Disease progression ^c	No

- a. Case reported as part of initial BLA application. Others post-BLA submission.
- b. Death reported during the extended follow-up phase of the study
- c. Death not recorded in clinical database, but reported to GSK Global Clinical Safety and Pharmacovigilance Database



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

Memorandum

Date: April 6, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: Mid-Cycle Meeting 125326/0

The Mid-cycle meeting for BL STN 125326/0 was conducted on April 6, 2009 at the Monday morning oncology meeting. The presenters were as follows:

CLINICAL: Steve Lemery-40 minutes
STATISTICS: Jenny Zhang—10 minutes
CLINICAL PHARMACOLOGY: Jun Yang-10 minutes
CMC: Subramanian Muthukkumar-5 minutes
FACILITIES: Bo Chi—5 minutes



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

Memorandum

Date: April 2, 2009

From: Raymond Chiang, DBOP/ODDP/CDER

Subject: STN BL 125326 original BLA 125326/0: Team meeting held April 2, 2009.

A meeting was held on this date.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

Our STN: BL 125326/0

Glaxo Group Limited d/b/a GlaxoSmithKline
ATTENTION: Phillip A. Witman, M.P.H., M.Phil.
Associate Director, Global Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

MAR 9 0 2009

Dear Mr. Witman:

This letter is in regard to your biologics license application (BLA), dated January 30, 2009, received January 30, 2009, submitted under section 351 of the Public Health Service Act, for Arzerra® (ofatumumab).

We have completed an initial review of your supplement to determine its acceptability for filing. Under 21 CFR 601.2(a), we filed your application today. The review classification for this application is Priority. Therefore, the user fee goal date is August 1, 2009. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before April 14, 2009.

We acknowledge your request to review this application under the provisions of 21 CFR 601 Subpart E – *Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please call Raymond Chiang, Regulatory Project Manager, at
(301) 796-2320.

Sincerely,

A handwritten signature in cursive script, appearing to read "Patricia Keegan".

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



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

Memorandum

Date: March 27, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: Email: STN BL 125326/0 ofatumumab- **Information Request**

FDA requested GSK submit response to statistical information request.

From: Chiang, Raymond
To: "Philip.A.Witman@gsk.com";
Subject: RE:Information request from statistical reviewer regarding ofatumumab BLA
Date: Friday, March 27, 2009 10:01:34 AM

Philip,

Please see Information request from statistical reviewer regarding ofatumumab BLA:

The analysis of duration of response was conducted only in the responder subset. However, the number of responders in the primary analysis of duration of response (DR=34; BFR=37) is different from the sensitivity analysis (DR=35; BFR=38).

a.) Provide an explanation of why there are two more responders in the sensitivity analysis of duration of response (patients 406145 and 406258 who were assessed to be NE and SD, respectively, in the primary analysis of response).

b.) Submit a revised sensitivity analysis (along with dataset) of duration of response or an explanation regarding why the current analysis/data should still be considered valid.

As per the statistical reviewer, this should be a quick issue to address. Please respond to this information request within a week.

thanks,
ray



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

Memorandum

DATE: March 25, 2009

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

SUBJECT: Designation of BLA application review status
Sponsor: GlaxoGroup Limited d/b/a GlaxoSmithKline
Product: Ofatumumab
Indication: BL STN 125326/0: treatment of patients with chronic lymphocytic leukemia who have received prior therapy.

TO: BLA 125326/0

The review status of this file submitted as a BLA application is designated to be:

☐ Standard (10 Months)

☒ Priority (6 Months)

Patricia Keegan, M.D.:

Patricia Keegan

Date: 3-25-2009



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

Memorandum

Date: March 12, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: Email: STN BL 125326/0 ofatumumab- Information Request

FDA requested GSK submit response to clinical information request. Please see request below:

Philip,

Pleased see information request from the medical officer:

Can you pass the following request onto GSK via email. They can respond by email or call me. However, If GSK does have additional data applicable to these questions, then they will have to submit this data to the BLA.

Patient 614 in study Hx-CD20-402 developed "cytolytic hepatitis" after his first infusion of ofatumumab. Was this patient's infectious hepatitis status (hepatitis B and C) assessed? Furthermore, since the time of data cut-off, have any cases of hepatitis B reactivation been reported (if so, can GSK identify the date that the safety report was submitted to the IND)? Finally, does GSK have data available regarding how many patients have received ofatumumab and who were carriers of hepatitis B?

thanks,

ray



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

Memorandum

Date: March 12, 2009

From: Raymond Chiang, DBOP/OODP/CDER

Subject: Tcon with GSK/Genmab BLA STN 125326/0

FDA Participants:

Patricia Keegan

Richard Pazdur

Anne Pilaro

Chris Tonroe

Jenny Zhang

Bo Chi

Steve Lemery

Bob Kane

Joseph Gootenberg

Raymond Chiang

Virginia Kwitkowski

Justin Earp

Michael Pacanowski

Barbara Rellahan

Subramanian Muthukkumar

Nicole Vesely

Tselaine Jones-Smith

Jun Yang

Hong Zhao

Kristina Arnwine

GSK:

Michael Arning

Catherine Bentley

William Bushnell

Amy Calisto

Geoffrey Chan

Randy Davis

Charles Depew

Richard Francovitch

Ira Gupta

Roxanne Jewell

Jeffrey Morrison

Paula Rogenes

Kathy Rouan

Debasish Roychowdhury

Geraldine Smith

Lakeisha Smith

Jan Thirkettle

Ben Thompson

Philip Witman

Genmab:

Ann Christine Korsgaard

Joris Wilms

The teleconference began at 12:00 PM EST.

FDA stated that FDA requested this teleconference to inform GSK of the need to meet requirements for accelerated approval for ofatumumab BLA (BLA STN 125326/0). FDA stated that accelerated approval requires demonstration that a drug to demonstrate meaningful therapeutic benefit over existing treatment, establishing that the drug meets an unmet medical need. GSK must provide evidence that ofatumumab is superior to available therapy including Treanda. FDA also stated that this issue would not be discussed at the May 29th ODAC meeting because it is a regulatory, rather than a scientific, issue. GSK stated understanding.

GSK requested clarification on the issue of presenting ofatumumab (Arzerra) as superior to available therapy. FDA stated that there were several ways to make this argument including superior efficacy, use in a patient population who no longer responds to available therapy, or improved safety profile and similar efficacy to available therapy. GSK asked whether Treanda could be grouped with other alkylating agents. FDA stated that since Treanda showed improved efficacy compared to chlorambucil, treating all alkylating agents as equivalent would not be appropriate.

FDA requested that GSK present the evidence to demonstrate that ofatumumab meets an unmet medical need at a meeting with FDA within the next 3-4 weeks. GSK agreed to meet with the FDA.

FDA stated that GSK should prepare a briefing document that is abbreviated and focused on the particular issue of whether ofatumumab (Arzerra) provides meaningful therapeutic benefit to patients over existing treatments. FDA also stated that the briefing document should be submitted as an amendment to the original BLA. In preparing for the meeting, FDA recommended that GSK consult the July 2004 FDA Guidance on Available Therapy.

Tcon concluded.



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

Memorandum

Date: March 12, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: STN BL 125326 original BLA 125326/0: Team meeting held March 12, 2009.

A meeting was held on this date.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

 **FILE COPY**

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MAR 10 2009

GlaxoSmithKline
One Franklin Square
P.O.Box 7929
Philadelphia, Pennsylvania 19101

Attention: Philip A. Witman, M.P.H., M. Phil.
Associate Director
Global Regulatory Affairs - Oncology

Re: Designation request # 09-2758

Dear Dr. Witman:

Reference is made to your request for orphan-drug designation submitted on January 22, 2009, of ofatumumab (trade name: Arzerra) for "treatment of chronic lymphocytic leukemia." Please also refer to our letter of January 26, 2009.

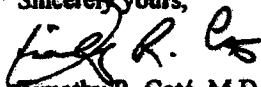
Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan-drug designation of ofatumumab is granted for *treatment of chronic lymphocytic leukemia*. Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (see 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you need further assistance in the clinical development of your drug, please feel free to contact Peter L. Vaccari, R.Ph., RAC, at (301) 827-3666. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,



Timothy R. Coté, M.D., M.P.H.

Director, Office of Orphan Products Development

GlaxoSmithKline

2

cc:

HF-35/OP File # 08-2758

HF-35/Chron

HF-35/PVaccari

jb 3/4/09

DESIGNATION GRANTED



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

Memorandum

Date: March 9, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: Information request re: completion of "Quality Assessment for NDA/BLA Submissions"

FDA asked for the following information email on March 9, 2009:

Philip,

Please see attached "Quality Assessment for NDA/BLA Submissions" form concerning BLA STN 125326. Please note that this will play no role in the final action taken on the review and is not to be used in dispute resolution. The primary purpose is for discussion during the post-action meeting (meeting between you and FDA after the action date). On this attached form, please focus on the Comments section, not the ratings section. Again, the purpose of the form is to only facilitate discussion during our post-action meeting.

thanks,
ray

From: Chiang, Raymond
To: "Philip.A.Witman@gsk.com";
Subject: RE: Quality Assessment for NDA/BLA Submissions
Date: Monday, March 09, 2009 2:30:27 PM
Attachments: Quality Assessment for NDA-BLA Submissions.pdf
Quality Assessment Criteria Checklist for NDA-BLA submissions.doc

Philip,

Please see attached "Quality Assessment for NDA/BLA Submissions" form concerning BLA STN 125326. Please note that this will play no role in the final action taken on the review and is not to be used in dispute resolution. The primary purpose is for discussion during the post-action meeting (meeting between you and FDA after the action date). On this attached form, please focus on the Comments section, not the ratings section. Again, the purpose of the form is to only facilitate discussion during our post-action meeting.

thanks,
ray

From: Philip.A.Witman@gsk.com [mailto:Philip.A.Witman@gsk.com]
Sent: Saturday, March 07, 2009 12:07 PM
To: Jones, Karen
Cc: Chiang, Raymond
Subject: Re: Letter/Information request/GSK Ofatumumab/STN 125326-0

Dear Dr. Jones,

Thank you for sending this request letter to me. I confirm that I have received it, and will forward it to our team. It looks like we'll be busy this week!

Have a great weekend and enjoy the weather.

Best regards,

Philip

Philip A. Witman
Associate Director

Global Regulatory Affairs - Oncology

Trade secret and/or confidential commercial information contained in this message (including any attachments) is exempt from public disclosure to the full extent provided under law. If you are not the intended recipient of this message, or if you are not responsible for delivering it to the intended recipient(s), do not use, disclose, reproduce, or distribute this message (including any attachments). If you have received this message in error, please erase all copies (including any attachments) and notify me immediately. Thank you.

"Jones, Karen" <Karen.Jones@fda.hhs.gov>

06-Mar-2009 17:07

To Philip.A.Witman@gsk.com

cc "Chiang, Raymond" <Raymond.Chiang@fda.hhs.gov>, "Philip.A.Witman@gsk.com" <IMCEAMAILTO-Philip+2EA+2EWitman+40gsk+2Ecom@fda.hhs.gov>

Subject Letter/Information request/GSK Ofatumumab/
STN 125326-0

Hello Mr. Witman,

On behalf of Raymond Chiang, please find attached an information request letter regarding your BLA for ofatumumab, assigned STN 125326/0:

<<kdj-20090306162104.pdf>>

A paper copy will follow by U.S. Mail.

Please respond via email confirming receipt of this message.

Thank you.

Karen D. Jones

Chief, Project Management Staff

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

301-796-1377; fax 301-796-9849 [attachment "kdj-20090306162104.pdf" deleted by Philip A Witman/PharmRD/GSK]



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125326/0

MAR 06 2009

Glaxo Group Limited d/b/a GlaxoSmithKline
ATTENTION: Philip A. Witman, M.P.H., M.Phil.
Associate Director, Global Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

Dear Mr. Witman:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed your biologics license application dated January 30, 2009, for Arzerra® (ofatumumab) and have determined that the following information is necessary to take a complete action on your application:

Chemistry, Manufacturing and Controls:

1. Provide a Table of Contents for Module 3 with links to all documents in this module.
2. In Section 3.2.S.2.5, Table 2, please insert links to the referenced sections.
3. For Section 3.2.S.2.3, please insert a table with links or bookmarks to all the major sections of this document.
4. In Section 3.2.S.2.3, Tables 3, 5 and 7, please insert links from the specified tests to the actual test reports.

5. / b(4)

6. / b(4)

7. / b(4)

1 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

21.

b(4)

NonClinical

22. In Module 4.2.3.2, nonclinical study #CD2007-01204 “GSK 1841157A: 2-dose subcutaneous and intravenous toxicity study in female cynomolgus monkeys followed by a 33-week off-dose period”, the pdf file does not load correctly; an error message “cannot find or create the font ‘AFDDKE+SimSun’ Some characters may not display or print correctly” appears. Tables 1-3 (pp 37-78), tables 5-7 (pp 85-103), Appendices 2-4 (pp 128-386) appear without data. Please resolve these issues. Please note that FDA reviewers have Adobe Acrobat Professional 8.0.

23. In Module 4.2.3.2, Study Hx-CD20-N-004 “HuMax-CD20: multiple dose toxicity study in Cynomolgus monkeys with a 6 month recovery period”, is not fully legible. The pdf file does not load correctly; an error message appears, “Cannot find or create the font ‘SymbolMT-Identity-H.’ Some characters may not display or print correctly.”

- a. Black boxes appear instead of signatures (p11, 12).
- b. Pages 358-408, 411-422 are not adequately legible (appearing as a mixture of obliterating black boxes, partially-readable text, and poor quality image capture).

Please resolve these issues.

24. In Module 4.3.3.2, study “Pilot and pharmacokinetic study in Cynomolgus monkeys using HuMax-CD20” is not fully legible.

- a. The pdf file does not appear to be loading correctly. Pages 274-313 have black boxes instead of graphs.
- b. Pages 314-359, 361-369, and the signatures on pp 5 and 394 are not adequately legible (poor-quality image capture).

Please resolve these issues.

25. All but one (study #CD2007-01024) of the GLP nonclinical studies state performance in accordance with the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice (GLP), but do not explicitly state compliance with 21CFR58.

Provide a brief statement for each GLP report, indicating either that it is fully in compliance with US FDA GLP or detailing each deviation beyond those already documented in the study reports. Also provide statements of compliance for each subreport (e.g. histology, PK).

For each GLP study conducted outside the U.S., indicate whether the test facility has been inspected by U.S. FDA and/or another U.S. regulatory agency.

- a. Study #25052 “HuMax-CD20: multiple dose intravenous toxicity study in Cynomolgus monkeys followed by a 6 month recovery period”
- b. Study #23542, “HuMax-CD20: multiple dose toxicity study in Cynomolgus monkeys with a 6 month recovery period”
- c. Study #28366, “HuMax-CD20: cycled repeat dose toxicity study in Cynomolgus monkeys with a 4 month recovery period”
- d. Study #231379 “HuMax-CD20: an immunohistochemical investigation of cross-reactivity in human tissues”
- e. Study “2148-010, “Intravenous embryo-fetal development study with HuMax-CD320 in the Cynomolgus monkey”

Clinical

- 26. Within 30 days of receipt of this letter, please submit source documentation for hematology labs in patients who were considered responders in the double refractory CLL population in study Hx-CD20-406.
- 27. Please submit an analysis of severe mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. This analysis should support inclusion (or failure to include) a statement in the Warnings and Precautions to be included in the label for severe mucocutaneous reactions.
- 28. The ——— dataset contains data for 148 subjects. Please submit a response to the BLA addressing the following requests:
 - a. Provide an explanation of why the / / dataset is not concordant with the 154 subjects contained in the / / dataset. b(4)
 - b. Submit a revised / / response dataset with all subjects or an explanation regarding why the current dataset should be considered valid. b(4)
- 29. We are unable to confirm the findings for number of prior therapies for the BFR subgroup in the Hx-CD20-406 study using the PRIORTH dataset. We identified 52 patients who received four or more prior regimens versus 51 for the GSK analysis. Furthermore, our review identified 42 patients in the BFR group who received 5 or more prior regimens versus 39 for the analysis in the BLA. Please repeat this analysis for the BFR subgroup and if the information in the BLA is incorrect, update the appropriate

sections of the application to correct this information. If the original results are confirmed, provide the program used to generate these results so that we can determine whether the program is valid and replicate the results.

30. Please submit audit certificates for all sites audited for studies Hx-CD20-406 and 402.
31. The following potential examples of miscoding using MedDRA are noted in the adverse event (AE) dataset. Please submit a revised AE dataset containing the following changes or provide adequate justification as to why revisions to the dataset are not indicated.
 - a. Patient number 406106: The verbatim term “neuropathy-motor (left sided weakness)” was coded to the preferred term “peripheral neuropathy.” It is unclear if left sided weakness should be considered a peripheral neuropathy (unilateral weakness typically related to the central nervous system).
 - b. Patient number 406133: The verbatim term “disease progression/sepsis” (Grade 5) was coded to the preferred term “disease progression”. This verbatim term describes two AEs and sepsis should have been coded as a separate Grade 5 AE.
 - c. Patient number 406213: The verbatim term “ataxia/disease progression” was coded to the preferred term “disease progression.” This verbatim term describes two AEs and ataxia should have been coded as a separate AE.
32. Multiple AEs were deleted from the CRF pages without explanation. In some instances, the explanation was obvious (the AE occurred prior to the first dose of study drug). However, in other instances, potentially important events were removed from the AE database without explanation. Please provide an explanation for the removal of the following selected AEs and determine whether the AEs should be included in a revised AE dataset.
 - a. Patient number 406147, AE number 21: Grade 3 hypotension was deleted as an AE, even though the page indicated that the ofatumumab infusion was temporarily interrupted.
 - b. Patient number 406234, AE number 18: An adverse event, fungus in mouth, was deleted. The patient received ofatumumab less than 30 days prior to the AE.
 - c. Patient number 406201, AE number 2: Grade 5 septic shock was deleted as an AE.
 - d. Patient number 406102, AE number 11: Grade 5 hemolytic anemia secondary to splenomegaly was deleted as an AE.
33. The following inconsistencies were noted in the datasets compared to annotations in the CRFs. Please submit to the file a revised AE dataset containing corrections to the

following, or provide adequate justification as to why changes in the dataset are not indicated.

- a. Patient number 406173: Adverse event 9, fever due to pneumonia, was Grade 4 in the CRF but was Grade 2 in the AE dataset.
 - b. Patient number 406238: In the CRF, adverse event number 18 described Grade 4 right eye infection. This Grade 4 AE was not included in the dataset for this patient (an early Grade 2 eye infection was included in the dataset).
 - c. Patient number 406176: AE number 8 in the CRF describes Grade 3 pneumonia. This AE is listed as Grade 2 in the dataset.
 - d. Patient number 406172: AE number 5 in the CRF describes Grade 2 fatigue. This AE is not included in the dataset.
34. The narrative summary for the death of patient number 406236 indicated that this patient had “gangrenes” on the left and right thigh. Gangrene was not included as an AE in the dataset for this patient. Please provide additional details regarding this patient’s clinical course. Specifically, provide a discussion regarding the cause of this patient’s gangrene and whether the gangrene occurred due to a mucocutaneous reaction after receiving ofatumumab.
 35. Please submit a statement to the BLA that provides a rationale for assuming the applicability of foreign data in this submission to the U.S. population, which addresses applicable FDA guidance and the requirements set out in 21 CFR 314.106.
 36. We cannot replicate your analysis for the derived shift tables using the BIOCHEM dataset for the Hx-CD20-406 study. Please provide the program used to derive the shift tables from the BIOCHEM dataset.
 37. The NCI CTCAE v3.0 defines Grade 3 uric acid elevation as greater than upper limit of normal (ULN) to 0.59 mmol/L (or 10 mg/dL) with physiologic consequences. State whether this criterion was used; if not, provide the definition used for uric acid elevation when designated as Grade 3 in the BIOCHEM dataset.
 38. Revise Table 3 of the proposed package insert label to include incidences of laboratory abnormalities that meet your pre-specified inclusion criteria for adverse reactions as derived from the BIOCHEM dataset.
 39. Revise Table 3 of the proposed package insert label to include two additional columns that describe the per-patient incidence of adverse reactions (one column for all grades and one column for AEs greater than or equal to Grade 3) for the DR population of CLL patients.

Biostatistics

40. Please submit (or direct to location of) data on individual IRC members' assessment of response (with adjudicator and consensus if applicable) for each subject by visit. Information content similar to that provided for investigator response in dataset / would be sufficient. Also, specify how an overall IRC response for each subject was determined from their visit assessments (i.e. was the algorithm used the same as for investigator response outlined in Section 3.1.2.1.4, page 42 of the Summary of Clinical Efficacy?). b(4)
41. In a February 18, 2009 electronic mail (email) communication, we requested the SAS programs and datasets pertaining to the sponsor sensitivity analysis outlined in Section 3.1.2.1.4 of the Summary of Clinical Efficacy. The information you submitted on February 19, 2009, included only the overall response derived dataset (resp_sp.xpt). Please also submit the derived dataset on algorithmic sponsor assessment of response for each subject by visit. Information content similar to that provided for investigator response in dataset / would be sufficient. b(4)

Please submit the information requested above within 10 calendar days, unless a different time-frame for response is requested in the specific item. We request that, to the extent possible, all information be submitted a single submission containing a complete response. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of your application is continuing.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Raymond Chiang, at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



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

Memorandum

Date: March 4, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: Information request re: please provide newest investigator's brochure and please complete and email back attached Clin Pharm form.

FDA asked for the following information via phone and email on March 4, 2009:

As per our phone conversation, please email the newest investigator's brochure (IB) by Friday, March 6, 2009 and submit it formally to the appropriate INDs by Monday, March 9, 2009. Also, complete and email back the attached Clin Pharm form.

From: Chiang, Raymond
To: "Philip.A.Witman@gsk.com";
cc: Kozeli, Devi;
Subject: Re: Submission of newest IB and completion of attached Clin Pharm form
Date: Wednesday, March 04, 2009 4:33:17 PM
Attachments: HighlightsofClinicalPharmacology.doc

Philip,

As per our phone conversation, please email the newest investigator's brochure (IB) by Friday, March 6, 2009 and submit it formally to the appropriate INDs by Monday, March 9, 2009. Also, complete and email back the attached Clin Pharm form.

thanks,
ray

Raymond S. Chiang, M.S.
Consumer Safety Officer/ Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Email: Raymond.Chiang@fda.hhs.gov
phone: 301-796-1940



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

Memorandum

Date: March 3, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: Information request re: completion of "Quality Assessment for NDA/BLA Submissions"

FDA asked for the following information email on March 3, 2009:

We would like to conduct the inspection at GSK at Barnard Castle, UK at the end of April if possible. Is the manufacturing process for the medically critical product similar to Ofatumumab?

Does the filling of that product use the same line as Ofatumumab?



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

Memorandum

Date: February 27, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: STN BL 125326 original BLA 125326/0: Filing meeting minutes from the filing meeting held February 27, 2009

This filing meeting for STN BL 125326/0 was a face-to-face, internal, FDA meeting. Attendees included Patricia Keegan, Joseph Gootenberg, Steve Lemery, Subramanian Muthukkumar, Barbara Rellahan, Rashmi Rawat, Karen Jones, Jenny Zhang, Justin Earp, Chris Tonroe, Anne Pilaro, Sharon Gershon, Bo Chi, Hong Zhao, Jun Yang, and Raymond Chiang.

Review Team:

Regulatory Project Manager
Medical Officer
Pharm/Tox Reviewer
Clinical Pharmacology Reviewer
Biostatistician
Quality Reviewer
Facilities Reviewer

Raymond Chiang
Steve Lemery
Andrew McDougal
Jun Yang/Justin Earp
Jenny (Jing) Zhang
Subramanian Muthukkumar/Rashmi Rawat
Bo Chi

ITEMS TO BE COVERED:

1. Team Introductions
2. Introduction of application, including important dates
 - a. First Committee Meeting Held: February 13, 2009
 - b. App Orient/ Tech Walk Through Held: February 20, 2009
 - c. PDUFA Action Date: July 30, 2009
 - d. Communicate Priority review designation: March 31, 2009 (Day 60)
 - e. Deficiencies Identified Letter Due: April 14, 2009 (Day 74)
 - f. Mid-Cycle Meeting Due (Priority): scheduled for April 6, 2009
 - g. ODAC/ASCO meeting in Orlando, FL: May 29, 2009
 - h. Complete Cross Discipline TL (CDTL) Review: July 7, 2009
 - i. Action Package and Action Letter to Dr. Keegan: July 7, 2009
 - j. Primary and Secondary Reviews due: June 30, 2009
 - k. Complete Division Director Review: July 15, 2009
 - l. Action Due Date (Priority): July 30, 2009
3. Overview of Application by Discipline

CHEMISTRY, MANUFACTURING AND CONTROLS:

- a. Discussion during meeting: The CMC team determined that application was fileable. CMC will have comments to be included in the information request (IR) letter, including requesting a Table of Contents (with hyperlinks) for every module)

NONCLINICAL:

- b. **Discussion during meeting:** The nonclinical team determined that application was fileable. NonClinical will have comments to be included in the IR letter. Pharm/Tox will follow up with OBPS concerning application issues.

CLINICAL PHARMACOLOGY:

- c. **Discussion during meeting:** The clinical pharmacology team determined that application was fileable. The clinical pharmacology stated that 2 datasets were missing and that comments will be included in the IR letter.

CLINICAL:

- d. **Discussion during meeting:** The clinical team determined that application was fileable. The clinical team noted that only 59 patients were considered double refractory. The clinical team will have comments to be included in the IR letter.

STATISTICAL:

- e. **Discussion during meeting:** The statistical team determined that application was fileable. The statistical team will request a summary of concordance/discordance from sponsor. The statistical team suggested that a joint statistics/clinical review be performed. The statistics and clinical reviewers will review the MAPP concerning joint reviews.

FACILITIES/INSPECTIONS:

- f. **Discussion during meeting:** The facilities team stated that the drug product (DP) site had been converted from Official Action Indicated (OAI) to Voluntary Action Indicated (VAI). DMPQ was not sure when inspections of sites would occur. DMPQ had 3 filing issues.

The review team agreed to send IR letter to GSK with a 10 day turn around from receipt of letter.

4. **Upcoming Internal Team Meetings:**

a.	Filing Meeting:	February 27, 2009
b.	Mid-Cycle Meeting: Scheduled for	April 6, 2009
c.	Team Meetings	
	• #1	3/12/09
	• #2	4/2/09
	• #3	4/21/09
	• #4	5/4/09

d. **Labeling Meetings**

Discussion during meeting: Ofatumumab review team agreed to initiate internal label meeting in mid-April 2009.

- e. ODAC planning meetings (please see Advisory Committee meet: Division's Timeline)
- f. ODAC practice sessions
- 5/18/09 (during regularly scheduled Monday Oncology Meeting)
 - 5/22/09 (during regularly scheduled Friday Clinical Rounds Meeting)
 - Practice session #3

• Practice session #4

5. **Upcoming External Meetings:**

- a. ODAC/ASCO meeting in Orlando, FL May 29, 2009

4. **Consults Requested:**

- a. DDMAC- requested February 11, 2009
- b. OSE
- DMEPA—Reviewer is Tselaine Jones-Smith (team leader is Kristina Arnwine). To review carton and container label and proprietary trade name review
 - DRISK—Reviewer and team leader is Mary Dempsey. To review RMP.
- c. DSI requested February 6, 2009— question from Steve Lemery to Sharon Gershon concerning the inclusion of 5 potential sites.

Discussion during meeting: Review team, with concurrence from DSI, agreed to inspect all 5 clinical sites requested on DSI consult form.

- d. MHT-requested Feb 9, 2009 for pregnancy label review
- e. Pediatric—scheduled on PeRC schedule for 3/25/09; orphan status designation application has been forwarded to Office Director for concurrence
- f. QT-IRT requested Feb 26, 2009
- g. CDRH

Discussion during meeting: Determined from review team that CDRH consult was not necessary.

- h. Combination Products

Discussion during meeting: Review team agreed to inform Office of Combination Products concerning this application.

5. **Reach agreement on filing decision**

Discussion during meeting: Ofatumumab review team concluded that this application would be considered a priority review application. This application is considered under accelerated approval.

The meeting concluded.

ACTION ITEMS:

6. Follow up with GSK concerning information requests from the Facilities review team.
7. Schedule labeling meetings.
8. Send consultation to Office of Combination Products.
9. Provide Joint Review MAPP to clinical and statistical reviewers.
10. Schedule more meetings as per 21st Century Desk Reference Guide.

11. Send IR letter to GSK by Friday, March 6, 2009, indicating a 10 day turnaround time to provide requested information.

POST MEETING ADDENDUM:

12. Email received from Pharmacometrics Reviewer on February 27, 2009 stating that the two datasets were received and that no comments will be included in the IR letter.
13. On March 3, 2009, GSK submitted formally to the BLA an amendment containing information regarding DMPQ requests. On March 4, 2009, an email was received from the facilities reviewer stating that the application was now fileable. The facilities reviewer gave her filing review to the RPM.
14. GSK acknowledged receipt of the IR letter on March 7, 2009.



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

Memorandum

Date: February 25, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: Information request re: please provide additional sterilization filter validation information as well as higher resolution facility diagrams for GSK Barnard Castle manufacturing site.

FDA asked for the following information via email on February 25, 2009:

Please provide additional sterilization filter validation information as well as higher resolution facility diagrams for GSK Barnard Castle manufacturing site.

From: Chiang, Raymond
To: "Philip.A.Witman@gsk.com";
Subject: RE: Filing issues for STN125326/0
Date: Wednesday, February 25, 2009 10:20:15 AM

Phillip,

Please address the 3 filing issues noted from manufacturing and quality quality reviewer. Please respond to this email to verify you have received it.

thanks,

ray

Ray, could you ask GSK for the following items for the filing of STN125326/0?

1. Provide the microbial retention validation summary report for the sterile filter.
2. Provide information and summary data on product specific determination for the sterile filter.
3. Provide facility diagrams with better resolution in BLA Section 3.2.A.1 for the GlaxoSmithKline facility in Barnard Castle. Alternatively, GSK can provide hard copies of the facility diagrams (enlarged bigger than 8 x 11).

b(4)

Thanks.

Bo

From: Philip.A.Witman@gsk.com [mailto:Philip.A.Witman@gsk.com]
Sent: Friday, February 20, 2009 4:10 PM
To: Chiang, Raymond
Subject: RE: Acknowledgement Letter for BLA Ofatumumab

Hi, Ray,

First, we had a productive meeting today, so thanks for setting it up.

Regarding the acknowledgement letter, we would prefer it via e-mail.

I'll have a few of those miscellaneous requests submitted next week. Have a great weekend.

Best regards,

Philip

Philip A. Witman
Associate Director
Global Regulatory Affairs - Oncology

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**"Chiang, Raymond" <Raymond.
Chiang@fda.hhs.gov>**

To Philip.A.Witman@gsk.com

cc

20-Feb-2009 12:02

Subject RE: Acknowledgement Letter for BLA
Ofatumumab

Philip,

I will be mailing you the acknowledgement letter for the Ofatumumab BLA.

Please advise whether you would like the letter by email or fax.

thanks,

ray

From: Philip.A.Witman@gsk.com [mailto:Philip.A.Witman@gsk.com]
Sent: Wednesday, February 18, 2009 6:24 AM
To: Chiang, Raymond
Subject: Telephone Information for Participants Who Need to Teleconference for ARZERRA Meeting

Good morning again, Ray,

As we have done for prior meetings, I will set up a teleconference line so some of your reviewers or other interested participants who cannot be in the room will be able to participate via telephone.

The call-in information follows. I have put the relevant information for the FDA in a bold and larger font.

Audio conference information:

GSK VPN number: 7 or 8 455-5000

US Toll Free: 888-643-3083

US toll call (Preferred): 857-207-4197

UK Freephone: 0808-101-2760

UK toll call (Preferred): 0203-024-9429

Denmark local call: 43682074

Denmark toll free: 80889501

Participant Passcode: 66529204

Several members of our team from remote sites in Denmark, the UK, and in RTP also will be on the call in the event of a question that is more appropriate for them.

We look forward to meeting with you and your review team on Friday.

Best regards,

Philip

**Philip A. Witman
Associate Director
Global Regulatory Affairs - Oncology**

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125326

BLA ACKNOWLEDGEMENT

Glaxo Group Limited d/b/a GlaxoSmithKline
ATTENTION: Phillip A. Witman, M.P.H., M.Phil.
Associate Director, Global Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

FEB 18 2009

Dear Mr. Witman:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Arzerra® (ofatumumab)

Date of Application: January 30, 2009

Date of Receipt: January 30, 2009

Our Submission Tracking Number (STN): BL 125326/0

Proposed Use: Treatment of patients with chronic lymphocytic leukemia

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/oc/datacouncil/spl.html>. 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 format and content requirements of revised 21 CFR 201.56-57.

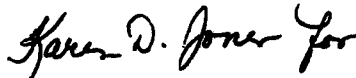
We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application.

This acknowledgement does not mean that this BLA has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Raymond Chiang, at (301) 796-2320. Thank you.

Sincerely,

A handwritten signature in black ink, appearing to read "Karen D. Jones for".

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



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

Memorandum

Date: February 18, 2009

From: Raymond Chiang, DBOP/OODP/CDER

Subject: Information request re: SAS programs and related datasets for the algorithm used in the Sponsor Sensitivity Analysis in Module 2.7.3, Section 3.1.2.1.4, Table 14 be provided to the BLA

FDA asked for the following information via email on February 18, 2009:

Please provide SAS programs and related datasets for the algorithm used in the Sponsor Sensitivity Analysis in Module 2.7.3, section 3.1.2.1.4, Table 14 be provided to the BLA.

From: Chiang, Raymond
To: "Philip.A.Witman@gsk.com";
Subject: RE: Friday meeting
Date: Wednesday, February 18, 2009 3:23:42 PM

Philip,

Please see the message I am relaying from the statistical review concerning your application:

The sponsor included in their clinical efficacy results a sensitivity analysis on the primary endpoint using their own algorithm. I took a closer look at their submission today and was not able to find the sas program for that algorithm. It would be helpful if the sponsor could provide the program for their sensitivity analysis (i.e. Section 3.1.2.1.4, Table 14 in their Summary of Clinical Efficacy). Please submit the program for the Technical Walk-Through? They do not need to spend any time during the meeting on it, only provide the sas files and any related datasets not already in the submission.

Also, you mentioned that GSK was willing to bring along a programmer for the Walk-Through. From my prospective, there is no need as long as all the programs are submitted.

Can you please address this issue during or before the technical walkthrough scheduled this Friday. Also, I am assuming that you are bringing your own laptop, so please come early so we can set up before the meeting. You can call me at my office upon your arrival.

thanks,

ray

From: Philip.A.Witman@gsk.com [mailto:Philip.A.Witman@gsk.com]
Sent: Wednesday, February 18, 2009 6:01 AM
To: Chiang, Raymond
Subject: Final Foreign Visitor Form for Meeting on Friday

Good morning, Ray,

Here is the final FDA Foreign Visitor Form, from Dr. Michael Arning at GSK.

Please note that Joris Wilms from Genmab will not be joining us in person, so no form is needed.

I will send you our list of participants in a few minutes.

Best regards,

Philip

Philip A. Witman
Associate Director
Global Regulatory Affairs - Oncology

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

Memorandum

Date: February 12, 2009

From: Raymond Chiang, DBOP/OODP/CDER

Subject: Information request re: requesting production schedules for the manufacture of ofatumumab drug substance and drug product and to provide FEI numbers for three facilities.

FDA asked for the following information via email on February 12, 2009:

Please provide production schedules for the manufacture of ofatumumab drug substance and drug product and to provide FEI numbers for three facilities.

From: Chi, Bo
To: "Philip.A.Witman@gsk.com";
cc: Hughes, Patricia; Chiang, Raymond;
Subject: Ofatumumab manufacturing schedules
Date: Thursday, February 12, 2009 12:25:31 PM

Dear Mr. Witman,

Please provide the production schedules for the manufacture of Ofatumumab drug substance and drug product at the following facilities:

Drug substance

Lonza Biologics plc
228 Bath Road
Slough
Berkshire
SL1 4DX
UK
FEI: 1000583959

Drug product

Glaxo Operations UK Limited
(Trading as Glaxo Wellcome Operations),
Harmire Road, Barnard Castle,
Co. Durham DL12 8DT,
United Kingdom
FEI: 3003722390

In addition, please provide the FEI numbers for the following facilities:

/

/

b(4)

l /

b(4)

b(4)

**Lonza Biologics plc
515 Eskdale Road
Winnersh Triangle
Wokingham
Berkshire
RG41 5TU
UK**

Thank you.

**Bo Chi
Biotech Manufacturing Team
Office of Compliance**



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

Memorandum

Date: February 12, 2009
From: Raymond Chiang, DBOP/OODP/CDER
Subject: teleconference

Teleconference on February 12, 2009:

1. FDA communicated to GSK that the meeting room was not Wi-Fi enabled so they would have to present from their hard drive.
2. GSK stated that the original "request for trademark assessment" will be deleted from the original BLA STN 125326 submission and resubmitted as an amendment to the original BLA no later than Friday, February 13, 2009.
3. FDA requested that GSK consult email from Nicole Vesely dated February 10, 2009, concerning the list of consultants to be provided to the FDA. GSK understood and agreed to provide list of consultants to FDA as advised in this email.
4. GSK stated that all the contact information, including phone numbers and email, for all the clinical sites included in the original BLA submission will be provided no later than Monday February 16, 2009. GSK provided contact information for site US01 and CZ02 over the phone.
5. GSK stated that they will provide in an email questions concerning question #11 from September 29, 2008 meeting and concerning whether a programmer from GSK will need to attend the technical walk-through meeting.
6. FDA advised GSK that approval of refund of their application fee would need to be approved 180 days from original BLA submission. FDA advised GSK to send letter requesting refund of their application fee pending orphan designation to Jane Axelrad. Her address is as follows: Associate Director for Policy; Center for Drug Evaluation and Research; 10903 New Hampshire Avenue; Building 51; Room 6140; Silver Spring, MD 20993-0002. GSK appreciated the advice and will submit letter as advised.



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

Memorandum

Date: February 10, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: teleconference

Teleconference on February 10, 2009:

1. FDA reminded GSK concerning the technical-walk-through meeting for this submission on February 20, 2009 at 9:30-10:30 AM EST. GSK understood. GSK asked whether the meeting room would be Wi-Fi enabled. FDA stated that they would get back to them concerning whether the meeting room was Wi-Fi enabled or not.
2. FDA requested GSK delete the original "request for trademark assessment" from the original BLA STN 125326 submission and resubmit the "request for trademark assessment" as an amendment to the original BLA. GSK understood and agreed. FDA advised GSK to submit all eCTD inquiries to esub@fda.hhs.gov.
3. GSK inquired what constitutes a consultant for ofatumumab. FDA stated that they would get back to them.
4. FDA requested GSK provide all the contact information, including phone numbers and email, for all the clinical sites included in the original BLA submission. GSK stated that they would consult Genmab and provide the requested information to FDA ASAP.



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

Memorandum

Date: February 9, 2009
From: Raymond Chiang, DBOP/ODP/CDER
Subject: teleconference

Teleconference on February 9, 2009:

1. FDA verified with GSK concerning the technical-walk-through meeting for this submission on February 20, 2009 at 9:30-10:30 AM EST. GSK understood.
2. FDA asked whether GSK was in the process of completing the Foreign Visitor Forms for the technical walk-through meeting on February 20, 2009. GSK stated that they were completing the forms.

tcon concluded



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

Memorandum

Date: February 6, 2009
From: Raymond Chiang, DBOP/ODDP/CDER
Subject: teleconference

Teleconference on February 6, 2009:

1. GSK asked which consultants FDA were seeking, as per the teleconference on February 2, 2009. FDA requested GSK send question as an email and this would be forwarded to the review team for a final decision. GSK agreed.
2. FDA requested GSK submit your "Request for Proprietary Trademark Review" as an amendment to the original BLA 125326. GSK agreed. GSK asked questions on the logistics of eCTD submission. FDA requested GSK send their question as an email and this would be forward to the eCTD team for advice. GSK agreed.
3. FDA requested GSK to have the technical-walk-through meeting for this submission on February 20, 2009 at 9:30-10:30 AM EST. GSK agreed.



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

Memorandum

Date: February 2, 2008

From: Raymond Chiang, DBOP/OODP/CDER

Subject: Tcon with GSK concerning BLA STN 125326 (Ofatumumab) to be discussed at ODAC/ASCO on May 29, 2009 in Orlando, Florida

FDA Participants:

Patricia Keegan	<i>Division Director</i>
Steve Lemery	<i>Clinical Reviewer</i>
Raymond Chiang	<i>Regulatory Project Manager</i>

GSK:

Michael Arning	<i>Clinical</i>
Geoff Chan	<i>Clinical</i>
Roxanne Jewell	<i>Clinical Pharmacology</i>
Kathy Rouan	<i>Medicines Development Leader</i>
Amy Calisto	<i>Project/Submission Manager</i>
Chuck Depew	<i>Regulatory Affairs</i>
Randy Davis	<i>Biostatistics</i>

The teleconference began at 12:00 PM. EST.

FDA informed GSK that their BLA STN 125326 (Ofatumumab) was tentatively scheduled to be discussed at ODAC/ASCO meeting on May 29, 2009 in Orlando, Florida as per the FDAAA Regulations. FDA stated that there was no red flags associated with this BLA. FDA also stated that more new molecular entities (NMEs) were being scheduled for Advisory Committee. GSK appreciated being informed. FDA stated that this will not be disclosed to the public. FDA informed them that Nicole Vesely will be contacting them concerning the logistics of the ODAC/ASCO meeting.

FDA requested a list of people who were consultants for GSK be provided to expedite the FDA's screening process for special government employees (SGEs). GSK agreed.

The teleconference concluded.



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

Memorandum

Date: February 13, 2008
From: Raymond Chiang, DBOP/OODP/CDER
Subject: STN BL 125326 original BLA 125326/0: First Committee meeting minutes from the first committee meeting held February 13, 2009

This first committee meeting for STN BL 125326 was a face-to-face, internal, FDA meeting.

REVIEW TEAM:

Regulatory Project Manager
Medical Officer
Pharm/Tox Reviewer
Clinical Pharmacology Reviewer
Biostatistician
Quality Reviewer
DMPQ Reviewer

Raymond Chiang
Steve Lemery
Andrew McDougal
Jun Yang/Justin Earp
Jenny (Jing) Zhang
Subramanian Muthukkumar/Rashmi Rawat
Bo Chi

MEETING DUE DATES:

• First Committee Meeting Held:	February 13, 2009
• Filing Meeting scheduled	February 27, 2009
• Filing Action Due	March 31, 2009
• Deficiencies Identified Meeting Due	April 14, 2009
• Mid-Cycle Meeting tentatively scheduled for	April 24, 2009 (tentative)
• Application Review Due Date (Priority)	August 1, 2009

DISCUSSION TOPICS:

1. **Review Status:** The team had no conclusion whether this application qualifies as a priority or standard review. Justification for the review decision will be provided in a memo to the file.
 - a. Clinical Review team: The clinical review team will continue review to assess whether OSE Consult is required for Pharmacovigilance Med Guide or proposed patient insert is required. Clinical Reviewer stated that Table 6 in label will probably be struck out.
 - b. The clinical pharmacology team had no major issues.
 - c. The biostatistics review team stated that a programmer from GSK during the technical walk-through meeting would be helpful.
 - d. The CMC review team will request that a table of contents for each module.
2. **Advisory Committee:** ODAC/ASCO is scheduled on May 29, 2009 in Orlando, Florida
3. **Labeling:** Labeling comments will be included in the filing letter.
4. **Consults:** DSI, DDMAC, OSE, CDRH and MHT will require independent consults. The

ofatumumab review team will need more time to assess whether CDRH consult is needed concerning in-line filter.

5. **Application Deficiencies:** The facilities review team noted that drug product (DP) is under official action indicated (OAI). This issue will need to be resolved with a completed 483 form and a change of status to voluntary action indicated (VAI). Language concerning this issue will be included in the filing letter. The CMC review team will requests a table of comments to be included for each module; this however is not mandatory.

The meeting concluded.

Action Items:

6. Provide checklist to GSK as per 21st Century GRMP guidelines.
7. Identify additional consults needed
8. Schedule labelling meetings.
9. Schedule team meetings every 2 weeks after filing meeting.
10. Obtain filing review memos from appropriate reviewers.
11. Invite 21st century staff to all major meetings for this application.

Post Meeting Addendum:

12. A review team was assigned from OSE. Still awaiting reviewer assignments from DDMAC, SEALD, DSI, Maternal Health Team, QT-IRT, and Pediatrics.



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

Memorandum

Date: **DEC 21 2005**

From: *Erik Laughner M.S, DBOP, OODP, CDER*

Subject: Pre-Phase 2 Meeting Minutes (Prior to the meeting, preliminary Agency comments to the Sponsor's questions were provided by fax on November 23, 2005. Genmab A/S provided responses by email on November 29, 2005 and are incorporated below. The actual meeting minutes, which were largely clarification points on the pre-meeting comments, are incorporated in *italics*).

Meeting Date and Time: 11/30/05; 10:30-11:30 AM

Meeting Requestor/Sponsor: B&H Consulting Services for Genmab A/S

Product: BB-IND 11719; Human Monoclonal Antibody (HuMax-CD20, 2F2) to CD20

Type of meeting: Type C/pre-Phase 2/Teleconference

Meeting Package Receipt date: October 31, 2005

Background: Reference is made to our December 10, 2004, letter designating as a Fast Track development program the investigation of HuMax-CD20 for use in combination with fludarabine for treatment of patients with previously untreated CLL to show an improvement in progression-free and overall survival as compared with fludarabine. Reference is also made to our August 26, 2005, meeting to discuss the acceptability and feasibility of the proposed trial intended to support accelerated approval and to briefly discuss the acceptability and feasibility of the design of a proposed confirmatory trial: combination therapy with HuMax-CD20 + fludarabine vs. fludarabine monotherapy, in previously untreated patients with CLL.

Meeting Purpose: To discuss the proposed clinical protocol Hx-CD20-404, titled "A double-blind, randomized, three-dose-arm, parallel group, international, multi-center, Phase II/III trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell Chronic Lymphocytic Leukemia refractory to fludarabine". The FDA acknowledges the upcoming December 9, 2005, teleconference to discuss the CMC development plans for this product.

Sponsor Submitted Questions:

- 1) **Does the FDA agree that the interim data found on the Interim Report for the chronic toxicology study in cynomolgus monkeys, and available safety data from previous clinical trials with HuMax-CD20 are adequate to allow initiation of the proposed clinical trial with HuMax-CD20 in CLL patients?**

FDA response faxed November 23, 2005: Yes, adequate information is available to support the initiation of the proposed Phase 2 clinical trial. Regarding the monkey toxicology study (study number 665493), FDA has concerns about the quality and organization of the study report that we would like to relay either during the scheduled teleconference or in an independent teleconference with the appropriate toxicologist. Moreover, please provide a complete study report as soon as possible, before an end-of-Phase 2 meeting or before discussion about further clinical trials to support licensure.

Genmab response emailed November 29, 2005: Genmab acknowledges the response and understand the concern about the quality of the interim report. This has been addressed and discussed with the CRO. A new updated and reformatted interim report will be provided before the end of the toxicology study, i.e. January 2006.

Discussion during teleconference: The FDA pointed out that there were errors such as duplicate tables and missing data and requested that the sponsor carefully review the toxicology reports before submission to the FDA. Genmab explained that the plan is to submit an updated interim report in January, an interim report in mid-March, and a final, unaudited report a few weeks later when the histopathology data would be available. Genmab also explained that the expected date for initiation of the clinical protocol would be April, 2006. The FDA requested that the interim report not be provided in January if a more complete report would be available in March. The FDA agreed to this schedule with the assumption that there will be 30 days between the time of submission of the toxicology report and the initiation of the clinical trial to allow for the review of the toxicology study.

- 2) Does the FDA agree with the suggested definition of refractory to fludarabine outlined below? Refractory to fludarabine (section 5 of the protocol) is defined as:

- a. failure to achieve partial remission (PR) or complete remission (CR) to at least one fludarabine-containing treatment regimen; or
- b. disease progression while on a fludarabine-containing treatment regimen; or
- c. disease progression in responders within 6 months of the last dose or a fludarabine-containing treatment regimen.

FDA response faxed November 23, 2005: Yes.

Genmab response emailed November 29, 2005: Acknowledged.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

- 3) Does the FDA agree with the proposed dose selection and dose criteria?

FDA response faxed November 23, 2005: No. There is not adequate justification for the 3 dose schedules chosen. In the CLL trial Hx-CD20-403 there was no evidence of activity in the subjects treated at the 100/500 mg x 4 weekly dose or the 300/1000 mg x 4 weekly dose. This trial proposes to use 2 similar dose schedules 300/500 mg and 300/1000 mg. Although there is speculation in the background section of the protocol that the expanded number of doses and length of treatment (8 weekly then q 4 week x 3 doses) will result in higher sustained antibody levels, this is theoretical and should be piloted to show proof of principle prior to embarking on this trial.

Genmab response emailed November 29, 2005: Genmab acknowledge the FDA response. As evidence of activity and safety has been shown with the 200mg dose we suggest to proceed using only this dose in the proposed clinical trial Hx-CD20-404 (See proposed update trial design in synopsis at the end of this document, as well as comment to FDA Q6).

Discussion during teleconference: Genmab acknowledged that they understood the FDA would not be providing comments regarding the proposed revised clinical protocol and the provided schema because the Agency did not have sufficient time to review the changes.

- 4) Does the FDA agree with the response criteria; definition of CR, nPR, PR, SD, and PD, section 8.1.14 of the protocol?

FDA response faxed November 23, 2005: Yes

Genmab response emailed November 29, 2005: Acknowledged.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

- 5) Does the FDA agree with the listed in- and exclusion criteria, section 5 of the protocol?

FDA response faxed November 23, 2005: Yes, for the purposes of a Phase 2 study, but not for purposes of a study intended to support accelerated approval. See detailed response to question 6.

Genmab response emailed November 29, 2005: See response to question 6.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

- 6) Does the FDA agree on the proposal of primary and secondary endpoints, section 4 of the protocol?

FDA response faxed November 23, 2005: The primary and secondary endpoints are appropriate endpoints for a Phase 2 dose finding study however, the proposed study is not adequate in design to support accelerated approval based on the population under the study and proposed endpoints and objectives. FDA recognizes durable objective responses as a surrogate endpoint reasonably likely to predict clinical benefit *where there is an unmet medical need*, i.e., no alternative therapy. In order for this trial to support accelerated approval, Genmab A/S would need to establish, at the time of submission of an application, that there is no alternative therapy available or, that based on the magnitude of the objective response rate and/or the durability of the responses observed in the clinical trial (i.e., very high response rates of prolonged durability), your product is superior to available therapy. The most convincing evidence for such an effect would require an internally controlled trial comparing HuMax-CD20 to available therapy. Alternatively, the study should be revised to limit enrollment to patients who are intolerant of, or whose disease is refractory to, alternative therapies.

The secondary efficacy endpoints, excluding duration of response, are extremely difficult to interpret in the context of a single arm trial and are highly unlikely to provide useful information in support of licensure.

Genmab response emailed November 29, 2005: Our current protocol outlines patients who are refractory to fludarabine. According to the inclusion criteria, patients may have received treatment regimens including fludarabine either as monotherapy or as combination therapy. In addition, patients may or may not have received alkylating agents prior to entering the trial.

However, in the FDA reply dated 23 November it is stated that the proposed study is not adequate in design to support accelerated approval based on the population under the study and the proposed endpoints and objectives.

Genmab therefore proposes an alternative patient population including patients who have failed both fludarabine and alemtuzumab. The definition of failure to fludarabine is the same as outlined under Question 2.

Failure to alemtuzumab is defined as refractory or intolerant (including ineligible) to alemtuzumab:

Refractory to alemtuzumab is defined as:

- Failure to achieve PR or CR to alemtuzumab; or
- Disease progression while on alemtuzumab; or
- Disease progression in responders within 12 months of the last dose of alemtuzumab

Intolerance to alemtuzumab is defined as:

- Discontinuation of therapy due to side effects/toxicity whether or not response occurred.
- Ineligible to treatment to alemtuzumab at the physician's discretion, due to concurrent medical conditions, such as previous severe or ongoing active autoimmune hemolysis, ongoing immune-mediated thrombocytopenia, and previous pneumocystis carinii pneumonia (PCP).

Does the FDA find that this population satisfies the requirements for an unmet medical need and therefore will be acceptable to support an accelerated approval?

As a consequence Genmab suggests an updated trial design (see synopsis at the end of this document) and proposes a single-arm, pivotal trial with 100 patients.

The expected response rate is 20%. The primary objective will be to show that the objective response rate $> 10\%$, by demonstrating that the lower limit of the two-sided 95% exact confidence interval for the objective response rate is $> 10\%$.

Is it acceptable to the FDA to support an accelerated approval in the suggested patient population with no alternative treatment options (see synopsis enclosed) under the assumption that an adequate duration of response is observed?

Discussion during teleconference: There was discussion about the requirement for prior therapy of subjects with alkylating agents in order to satisfy the criteria for the study subjects to constitute a population with an unmet medical need. The FDA stated that it would discuss with its outside consultant to determine what constituted current medical practice for this US patient population and recommended that Genmab also consult oncologists to determine current US medical practice.

Genmab requested clarification of their understanding that because Alemtuzumab is currently marketed under accelerated approval, it does not need to be considered an available therapy in the determination of unmet medical need. The FDA confirmed that although this is the current situation, it is possible that Alemtuzumab will be granted regular approval prior to submission of a marketing application for HuMax-CD20 and it would be prudent for Genmab to include Alemtuzumab as a prior therapy

The definition of refractory to Alemtuzumab was discussed; specifically the provision of disease progression within 12 months. The FDA questioned whether there was data to support the assumption that patients who progressed after 6 months from the last dose of Alemtuzumab would not respond to a second course of Alemtuzumab. Genmab stated that their consultants advised that physicians would not be willing to treat patients progressing within 12 months of previous Alemtuzumab therapy with a repeat course of Alemtuzumab due to the prolonged side effects associated with this therapy. The FDA stated that this would be discussed with the FDA external consultant; however, data on clinical experience with retreatment would make a more compelling argument.

The FDA also commented that the Sponsor would need to pre-specify which conditions would constitute ineligibility to receive Alemtuzumab and this information would need to be captured on a Case Report Form. Genmab acknowledged and agreed. The FDA noted that while they did not have any specific questions or comments regarding the proposed revised protocol schema provided by Genmab in their November 29, 2005, response at this time, the outside consultants may want to see a more complete protocol. Genmab replied that they believe the critical points are shown on the proposed schema.

- 7) Does the FDA agree with the proposed PK sampling schedule, section 8.2.9 of the protocol?

FDA response faxed November 23, 2005: This schedule is not clearly outlined, and additional information is needed for FDA to respond to this question.

Genmab response emailed November 29, 2005: The schedule will be clearly outlined in the updated protocol submission under the IND 11719.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

- 8) Does the FDA agree that:

- a. All patients must have a CT and bone marrow examination performed at Visit 1?

FDA response faxed November 23, 2005: Yes.

Genmab response emailed November 29, 2005: Acknowledged.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

- b. A confirmatory CT scan and bone marrow examination must be performed 8 weeks after the investigator observes the onset of a CR; i.e. item 1-4 in the definition of CR, section 8.1.14 of the protocol?

FDA response faxed November 23, 2005: Yes.

Genmab response emailed November 29, 2005: Acknowledged.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

- c. A CT scan is only to be performed of non-palpable lymph nodes in the chest and abdomen?

FDA response faxed November 23, 2005: Yes.

Genmab response emailed November 29, 2005: Acknowledged.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

9) Does the FDA agree that:

- a. Documentation for refractory to fludarabine is adequately addressed in the CRF pages "prior treatment regimens" (pages 5-7 of the CRF)?

FDA response faxed November 23, 2005: No. The case report forms do not capture adequate information regarding the dose or cumulative exposure of fludarabine, to permit confirmation that patients have received an adequate trial of fludarabine. The form should include foot note definitions of the abbreviations FCM, FCR, and FR.

Genmab response emailed November 29, 2005: The Case Report Form will be updated according to the FDA requirements in the updated protocol submission under IND 11719.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

- b. Documentation for physical lymph node assessment at baseline (CRF page 21) and during follow-up (CRF pages 30-31) is adequately addressed in these CRF pages?

FDA response faxed November 23, 2005: Yes.

Genmab response emailed November 29, 2005: This question was not addressed in the response.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

10) Does the FDA agree with the enclosed Statistical Analysis Plan (SAP), in particular:

a. Planned analysis of the primary endpoint (section 7.2 in SAP)?

FDA response faxed November 23, 2005: The primary analysis of objective tumor response should be based on exact confidence intervals.

Genmab response emailed November 29, 2005: The following procedure is proposed: exact confidence intervals will be presented for the primary endpoint, and p-values from exact two-sided tests will be calculated and multiplicity adjusted in accordance with the Hochberg's step-up procedure. Conclusions will be based in the multiplicity adjusted p-values.

Discussion during teleconference: The FDA agreed with this plan.

b. Definition of duration of response (section 7.3.1.1 in SAP): "The duration of response is defined as the time from the initial response (the first visit where response is observed) to progression or death and will be censored in the same way as progressive-free-survival?"

FDA response faxed November 23, 2005: The definition of duration of response is appropriate.

Genmab response emailed November 29, 2005: Acknowledged.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

c. Definition and analysis of progressive-free-survival, including censorings (section 7.3.1.1 SAP)?

FDA response faxed November 23, 2005: As discussed in FDA's response to question 6, analysis of PFS in a single-arm trial provides little useful information because of the highly variable natural history of the disease, although the information may be used to estimate effects in planning for adequately designed, comparative trials. In the context of adequately designed, internally controlled trials, FDA suggests that the analysis plan include proposals for pre-specified sensitivity analyses on PFS where changes to PFS and/or the PFS censoring status are made based on treatment discontinuation for undocumented progression, for toxicity or other reason, new anti-cancer started, or death or progression after more than one missed visit. In addition, patients who received additional treatment without objective, protocol-specified evidence of disease progression should continue to be monitored for tumor progression.

Genmab response emailed November 29, 2005: Acknowledged

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

d. Definition and analysis of clinical benefit (section 7.3.5 SAP)?

FDA response faxed November 23, 2005: No. See FDA's response to question 6. Acceptability of this protocol to support accelerated approval is contingent on revision of the stated objectives to define clinical benefit as demonstration of: effects on tumor (as reflected in both response rate and durability) that are superior to available therapy; a delay in time to progression (at least 4-6 months) in the overall population; and a reduction in disease-related sequelae (i.e., reduction in transfusion requirements, infection and autoimmune hemolysis or thrombocytopenia if present). The proposed analysis is to list the chosen measures as binary variables and summarize them. The proposed analysis does not include a method to demonstrate how these measures will be used to suggest that a response rate achieved in this study is associated with clinical benefit.

Genmab response emailed November 29, 2005: The objectives will be revised so that the primary endpoint will be objective response rate and that secondary endpoints will include duration of response and all other previously stated secondary endpoints, also including the ones that previously collectively were called clinical benefit. The latter ones will be split up into individual secondary endpoints and no longer be called clinical benefit.

Also, reduction in transfusion requirement, infection and autoimmune hemolysis or thrombocytopenia if present, will be added as secondary endpoints. For these new endpoints, reduction will be calculated by a comparison of the rate of the event during the trial, with the rate of the event during an appropriate time-interval just before screening. E.g. reduction in transfusion requirements will be calculated by comparing the rate of transfusions during the trial, with the rate of transfusions during the month just before screening.

Genmab would also like the FDA to clarify the last sentence: "The proposed analysis does not include a method to demonstrate how these measures will be used to suggest that a response rate achieved in this study is associated with clinical benefit."

Discussion during teleconference: The FDA agreed with the revised objectives. However, the FDA also stated it would not be appropriate to make comparisons of the secondary endpoints; the analysis would need to be limited to descriptive statistics. The FDA clarified that the clinical benefits that the response rate is purported to predict will need to be demonstrated in a confirmatory trial. Genmab stated that the confirmatory trial is the one described in the Fast track designation and that the clinical benefits would be verified in that trial.

- 11) Does the FDA agree with the proposed safety stopping rules and safety monitoring during the trial, sections 6.7, 6.8, 9.7, 11.3, and 12 of the protocol?

FDA response faxed November 23, 2005: Yes.

Genmab response emailed November 29, 2005: Acknowledged.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

- 12) Does the FDA agree with the interim analyses for futility and the proposed stopping rules, section 10.8 of the protocol?

FDA response faxed November 23, 2005: Yes.

Genmab response emailed November 29, 2005: Acknowledged.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

13) Does the FDA agree with the enclosed DMC charter?

FDA response faxed November 23, 2005: No. The Charter does not specifically indicate the number of members or the specific qualifications of members of the DMC. It should specifically define the type of expertise required of members, and preclude members with fiduciary interests, trial participants, or individuals who have contributed to protocol development. The document should outline the process that will allow data to be evaluated by the DMC without risk of unblinding of data to the company.

Genmab response emailed November 29, 2005: Acknowledged.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

14) Does the FDA agree with the enclosed IRC charter?

FDA response faxed November 23, 2005: No. The IRC Charter should be revised to address the following issues: How the determination of response, to be used in the primary efficacy analysis, will be derived should be clarified. Specifically, how will results of the radiologists', medical oncologist's, and hematopathologist's assessments be integrated to arrive at a final determination of response? Additional information regarding how the results of each response assessment will be captured and the algorithm for resolution of discrepancies between response assessments by the various medical specialists should be included in the IRC Charter. Will the 3 IRC reviewers be evaluating the data independently? The charter does not specify whether central review of hematopathology (bone marrow) will be conducted or how such a review will be conducted and recorded. The Imaging Manual that will be supplied to centers and the Independent Radiology Review Charter should be submitted for FDA review and comment.

FDA notes that the proposed trial design permits all subjects to receive investigational drug, therefore assessments of response by the IRC are masked only to treatment regimen but not the investigational agent.

Genmab response emailed November 29, 2005: The IRC charter will be revised to address the issues raised above by the FDA. The IRC Charter and the Independent Radiology Review Charter will be submitted for FDA review and comment before initiation of the Hx-CD20-404 trial.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

15) Does the FDA agree, based on rationale provided, that the current assay format for detection of HAHA in the proposed pivotal trial is adequate and that an alternative HAHA assay to detect neutralizing HAHA is not necessary?

FDA response faxed November 23, 2005: No. An alternate assay to detect neutralizing HAHA must be developed. Prior to analysis of patient samples from a trial intended to support licensure, the assay should be reviewed by FDA and determined to be acceptable and adequately qualified. The current assay format for the detection of HAHA in the proposed trial is not adequate because of the following reasons:

- a) To determine the HAHA positive response, the set limit of eight fold increase in titer versus pre-infusion appears to be too high. Please provide significant justification for this criteria, which should be based on assay results seen to date. The sponsor is referred to the *Journal of Immunological Methods*, 289: (2004) p 1-16 for further suggestions on setting appropriate criteria for a binding assay used to detect anti-product antibodies.
- b) The current assay does not detect antibodies generated against the Fc portion of HuMax-CD20. Therefore, an anti-product antibody response directed against the Fc portion of the product will not be detected. Please develop a more appropriate assay or develop an assay that can detect anti-Fc antibodies.

Genmab response emailed November 29, 2005: Genmab acknowledges the FDA response and we therefore aim to develop two assays: a two-sided assay and a neutralizing assay. The two-sided assay detects responses to the whole molecule, i.e. the Fc and F(ab) fragments. If a positive HAHA response is detected, the individual patient samples can be further analyzed in a Complement-Dependent Cytotoxic (CDC) based neutralization assay (i.e. the proposed potency assay, which is a CDC assay and to be discussed at the CMC meeting 9-Dec-2005).

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

Additional Statistical Comment:

- 16) Please provide the specific randomization method. The protocol should state what specific algorithm (e.g., randomly permuted blocks within strata or dynamic allocation) will be used for generating the random treatment assignments. (Block size should not be identified in the protocol.)

Genmab response emailed November 29, 2005: The protocol will state that the randomly permuted blocks within strata randomization procedure will be used.

Discussion during teleconference: Genmab acknowledged. There were no questions or comments.

FDA Attendees:

Erik Laughner, M.S., RPM
Amy Gomez, M.S., RPM
Karen Jones, CPMS
Pat Dinndorf, M.D., Clinical Reviewer
Joe Gootenberg, M.D., Clinical Team Leader
Iftekar Mahmood, Ph.D., Pharmacology Reviewer
Melanie Hartsough, Ph.D., Toxicology Reviewer
Kyung Lee, Ph.D., Statistical Reviewer
Mark Rothmann, Ph.D., Statistical Team Leader
Subramanian Muthkkumar, Ph.D., Product Reviewer
Patricia Keegan, M.D., Director DBOP

Genmab Attendees:

Mimi Folden Flensburg, International Clinical Project Leader
Hanne Damgaard Jensen, Vice President, Regulatory Affairs
Lene Jørgensen, Director, Process Development
Louise Ploug Larsen, Regulatory Affairs CMC Specialist
Nedjad Losic, Senior Statistician
Martin Munk, Senior Scientist
Thomas Oettinger, Associate Director, Project Management
Paul Parren, Vice President Research and Technology
Jørgen Petersen, Senior Medical Director
Lone E. Rasmussen, Director, Regulatory Affairs
Agneta Svedberg, Vice President, Clinical Development
Marie-Louise Valentin, Director of Corporate Drug Safety
Joris Wiel Jan Wilms, International Clinical Trial Manager
Marguerite Coleman, US Agent, Project Director, B&H Consulting Services

Background: Reference is made to our December 10, 2004, letter designating as a Fast Track development program the investigation of HbCD20 for use in combination with fludarabine for treatment of patients with previously untreated CLL to show an improvement in progression-free and overall survival as compared with fludarabine. Reference is also made to our August 26, 2005, meeting to discuss the acceptability and feasibility of the proposed trial intended to support accelerated approval and to briefly discuss the acceptability and feasibility of the design of a proposed confirmatory trial: combination therapy with HbCD20 + fludarabine vs. fludarabine monotherapy, in previously untreated patients with CLL.

Meeting Purpose: To discuss the proposed clinical protocol Hb-CD20-404, titled "A double-blind, randomized, three-dose-arm, parallel group, international, multi-center, phase II/III trial of HbCD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell Chronic Lymphocytic Leukemia refractory to fludarabine". The FDA acknowledges the upcoming December 9, 2005, teleconference to discuss the CMC development plans for this product.

Genmab acknowledges FDA's preliminary response of 23-Nov-2005, and in order to facilitate the discussion at the meeting 30-Nov-2005, we hereby provide our comments.

Spencer: Submitted Questions and FDA Response:

- Q Does the FDA agree that the interim data based on the Interim Report for the chronic toxicology study in myelomalignancies, and available safety data from previous clinical trials with HbCD20 are adequate to allow initiation of the proposed clinical trial with HbCD20 in CLL patients?

FDA RESPONSE: Yes, adequate information is available to support the initiation of the proposed phase 2 clinical trial. Regarding the chronic toxicology study (study number 000493), FDA has concerns about the quality and organization of the study report that we would like to rely either during the scheduled teleconference or in an independent teleconference with the appropriate toxicologist. Moreover, please provide complete study report as soon as possible, before an end-of-phase 2 meeting or before discussion about further clinical trials to support licensure.

Genmab acknowledges the response and understand the concern about the quality of the interim report. This has been addressed and discussed with the CRO. A new updated and reformatted interim report will be provided before the end of the toxicology study, i.e. January 2006.

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- 2) Does the FDA agree with the suggested definition of refractory to flutamide outlined below? Refractory to flutamide (section 4 of the protocol) is defined as:
- Failure to achieve partial remission (PR) or complete remission (CR) to at least one flutamide-containing treatment regimen; or
 - Disease progression while on a flutamide-containing treatment regimen; or
 - Disease progression in response within 6 months of the last dose of a flutamide-containing treatment regimen.

FDA RESPONSE: Yes.

Acknowledged.

- 3) Does the FDA agree with the proposed dose selection and dose criteria?

FDA RESPONSE: No. There is not adequate justification for the 3 dose schedules chosen. In the CLL trial Hx-CD20-403 there was no evidence of activity in the subjects treated at the 100/500 mg x 4 weekly dose or the 300/1000 mg x 4 weekly dose. This trial proposes to use 2 similar dose schedules 300/500 mg and 300/1000 mg. Although there is speculation in the background section of the protocol that the expanded number of doses and length of treatment (8 weekly then q 4 week x 3 doses) will result in higher sustained antibody levels, this is theoretical and should be piloted to show proof of principle prior to embarking on this trial.

Genmab acknowledge the FDA response. As evidence of activity and safety has been shown with the 2000mg dose we suggest to proceed using only this dose in the proposed clinical trial Hx-CD20-404 (See proposed update trial design in synopsis at the end of this document, as well as comment to FDA response to Q6).

- 4) Does the FDA agree with the response criteria: definition of CR, aPR, PR, SD, and PD, section 5.1.14 of the protocol?

FDA RESPONSE: Yes

Acknowledged

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5) Does the FDA agree with the listed inclusion and exclusion criteria, section 5 of the protocol?

FDA RESPONSE: Yes, for the purposes of a Phase 2 study, but not for purposes of a study intended to support accelerated approval. See detailed response to question 6.

See response to question 6.

6) Does the FDA agree on the proposed primary and secondary endpoints, section 4 of the protocol?

FDA RESPONSE: The primary and secondary endpoints are appropriate endpoints for a phase 2 dose finding study however, the proposed study is not adequate in design to support accelerated approval based on the population under the study and proposed endpoints and objectives. FDA recognizes certain objective responses as a surrogate endpoint reasonably likely to predict clinical benefit where there is an unmet medical need, i.e., no alternative therapy. In order for this trial to support accelerated approval, Genmab A/S would need to establish, at the time of submission of an application, that there is no alternative therapy available or, that based on the magnitude of the objective response rate and/or the durability of the responses observed in the clinical trial (i.e., very high response rates or prolonged durability), your product is superior to available therapy. The most convincing evidence for such an effect would require an internally controlled trial comparing HbCD20 to available therapy. Alternatively, the study should be revised to limit enrollment to patients who are intolerant of, or whose disease is refractory to, alternative therapies. The secondary efficacy endpoints, including duration of response, are extremely difficult to interpret in the context of a single arm trial and are highly unlikely to provide useful information in support of licensure.

Our current protocol outlines patients who are refractory to fludarabine. According to the inclusion criteria, patients may have received treatment regimens including fludarabine either as monotherapy or as combination therapy. In addition, patients may or may not have received alkylating agents prior to entering the trial.

However, in the FDA reply dated 23 November it is stated that the proposed study is not adequate in design to support accelerated approval based on the population under the study and the proposed endpoints and objectives.

Genmab therefore proposes an alternative patient population including patients who have failed both fludarabine and alemtuzumab. The definition of failure to fludarabine is the same as outlined under Question 2.

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Refractory to alemtuzumab is defined as:

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- Disease progression while on alemtuzumab; or
- Disease progression in responders within 12 months of the last dose of alemtuzumab

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- Discontinuation of therapy due to side effects/toxicity whether or not response occurred.
- Ineligible to treatment with alemtuzumab at the physician's discretion, due to concurrent medical conditions, such as previous severe or ongoing active autoimmune hemolysis, ongoing immune-mediated thrombocytopenia, and previous pneumocystis carinii pneumonia (PCP)

Does the FDA find that this population satisfies the requirements for an unmet medical need and therefore will be acceptable to support an accelerated approval?

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Is this acceptable to the FDA to support an accelerated approval in the suggested patient population with no alternative treatment options (see synopsis enclosed) under the assumption that an adequate duration of response is observed?

7) Does the FDA agree with the proposed PK sampling schedule, section 5.2.9 of the protocol?

FDA Response: This schedule is not clearly outlined, and additional information is needed for FDA to respond to this question.

The schedule will be clearly outlined in the updated protocol submission under the IND 11719.

8) Does the FDA agree that:

All patients must have a CT and bone marrow examination performed at Visit 17

FDA RESPONSE: Yes

Acknowledged.

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A confirmatory CT scan and bone marrow examination must be performed 8 weeks after the investigator observes the onset of a CR, i.e. Item 1-4 in the definition of CR, section 5.1.14 of the protocol?

DRAFT

DRAFT

FDA RESPONSE: Yes.

Acknowledged.

c. A CT scan is only to be performed if non-palpable lymph nodes in the chest and abdomen?

FDA RESPONSE: Yes.

Acknowledged.

9) Does the FDA agree that:

a. Documentation for refractory to flutamide is adequately addressed in the CRF pages "prior treatment regimen" (pages 5-7 of the CRF)?

FDA RESPONSE: No. The case report forms do not capture adequate information regarding the dose or cumulative exposure of flutamide, so permit confirmation that patients have received an adequate trial of flutamide. The form should include dose and definition of the abbreviations PCM, PCR, and FE.

The case Report Form will be updated according to the FDA requirements in the updated protocol submission under the IND 11719.

10) Does the FDA agree with the enclosed Statistical Analysis Plan (SAP), in particular:

a. Planned analysis of the primary endpoint (section 7.2 in SAP)?

FDA RESPONSE: The primary analysis of objective tumor response should be based on exact confidence intervals.

The following procedure is proposed: exact confidence intervals will be presented for the primary endpoint, and p-values from exact two-sided tests will be calculated and multiplicity adjusted in

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accordance with the Hochberg's step-up procedure. Conclusions will be based on the multiplicity adjusted p-values.

Definition of duration of response (section 7.3.1.1 SAP)? "The duration of response is defined as the time from the initial response (the first visit where response is observed) to progression or death and will be censored in the same way as progressive-free survival?"

FDA RESPONSE: The definition of duration of response is appropriate.

Acknowledged.

Definition and analysis of progressive-free survival, including censorings (section 7.3.1.1 SAP)?

FDA RESPONSE: As discussed in FDA's response to question 6, analysis of PFS in a single-arm trial provides little useful information because of the highly variable natural history of the disease, although the information may be used in estimate effects in planning for adequately designed, comparative trials. In the context of adequately designed, internally controlled trials, FDA suggests that the analysis plan include proposals for pre-specified sensitivity analyses on PFS where changes to PFS and/or the PFS censoring status are made based on treatment discontinuation for undocumented progression, for toxicity or other reason, new anti-cancer started, or death or progression after more than one intent visit. In addition, patients who received additional treatment without objective, protocol-specified evidence of disease progression should continue to be monitored for tumor progression.

Acknowledged.

Definition and analysis of clinical benefit (section 7.3.5 SAP)?

FDA RESPONSE: No. See FDA's response to question 6. Acceptability of this protocol to support accelerated approval is contingent on revision of the stated objectives to define clinical benefit as demonstration of effects on tumor (as reflected in both response rate and durability) that are superior to available therapy; a delay in time to progression (at least 4-6 months) in the overall population; and a reduction in disease-related sequelae (i.e., reduction in transfusion requirements, infection and spontaneous hemolysis or thrombocytopenia if present). The proposed analysis is to list the chosen measures as binary variables and summarize them. The proposed analysis does not include a method to demonstrate how these measures will be used to suggest that a response rate achieved in this study is associated with clinical benefit.

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The objectives will be revised so that the primary endpoint will be objective response rate and that secondary endpoints will include duration of response and all the other previously stated secondary endpoints, also including the ones that previously collectively were called clinical benefit. The latter ones will be split up into individual secondary endpoints and no longer be called clinical benefit.

Also, reduction in transfusion requirements, infection and autoimmune hemolysis or thrombocytopenia if present, will be added as secondary endpoints. For these new endpoints, reduction will be calculated by a comparison of the rate of the event during the trial, with the rate of the event during an appropriate time-interval just before screening. E.g. reduction in transfusion requirements will be calculated by comparing the rate of transfusions during the trial, with the rate of transfusions during the month just before screening.

Genmab would like FDA to clarify the last sentence: "The proposed analysis does not include a method to demonstrate how these measures will be used to suggest that a response rate achieved in this study is associated with clinical benefit".

- 11) Does the FDA agree with the proposed safety stopping rules and safety monitoring during the trial, sections 6.7, 6.8, 9.7, 11.3, and 12 of the protocol?

FDA RESPONSE: Yes.

Acknowledged.

- 12) Does the FDA agree with the interim analyses for efficacy and the proposed stopping rules, section 10.3 of the protocol?

FDA RESPONSE: Yes.

Acknowledged.

- 13) Does the FDA agree with the enclosed DMC charter?

FDA RESPONSE: No. The Charter does not specifically indicate the number of members or the specific qualifications of members of the DMC. It should specifically define the type of expertise required of members, and preclude members with fiduciary interests, trial participants, or individuals who have contributed to protocol development. The document should outline the process that will allow data to be reviewed by the DMC without risk of unblinding of data to the company.

Acknowledged.

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14) Does the FDA agree with the enclosed IRC charter?

FDA RESPONSE: No. The IRC Charter should be revised to address the following issues: How the determination of response, to be used in the primary efficacy analysis, will be derived should be clarified. Specifically, how will results of the radiologist, clinical oncologist's, and hematopathologist's assessments be integrated to arrive at a final determination of response? Additional information regarding how the results of each response assessment will be captured and the algorithm for resolution of discrepancies between response assessments by the various medical specialties should be included in the IRC Charter. Will the 3 IRC reviewers be evaluating the data independently? The charter does not specify whether central review of hematopathology (bone marrow) will be conducted or how such a review will be conducted and recorded. The Imaging Manual that will be supplied to centers and the Independent Radiology Review Charter should be submitted for FDA review and comment.

FDA notes that the proposed trial design permits all subjects to receive investigational drug, therefore assessments of responses by the IRC are needed only to treatment regimen but not the investigational agent.

The IRC charter will be revised to address the issues raised above by FDA. The IRC Charter and the Independent Radiology Review Charter will be submitted for FDA review and comment before initiation of the Hx-CD20-404 trial.

15) Does the FDA agree, based on rationale provided, that the current assay format for detection of HAHA in the proposed pivotal trial is adequate and that an alternative HAHA assay to detect neutralizing HAHAs is not necessary?

FDA RESPONSE: No. An alternate assay to detect neutralizing HAHA must be developed. Prior to analysis of patient samples from a trial intended to support licensure, the assay should be reviewed by FDA and determined to be acceptable and adequately qualified. The current assay format for the detection of HAHA in the proposed trial is not adequate because of the following reasons:

- a) To determine the HAHA positive response, the set limit of eight fold increase in their versus pre-infusion appears to be too high. Please provide significant justification for this criteria, which should be based on assay results seen to date. The sponsor is referred to the *Journal of Immunological Methods*, 289: (2004) p 1-16 for further suggestion on setting appropriate criteria for a binding assay used to detect anti-product antibodies.
- b) The current assay does not detect antibodies generated against the Fc portion of Hx-CD20. Therefore, an anti-product antibody response directed against the Fc portion of the product will not be detected. Please develop a more appropriate assay or develop an assay that can detect anti-Fc antibodies.

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Genmab acknowledges the FDA response and we therefore aim to develop two assays: a two-sided assay and a neutralizing assay. The two-sided assay detects responses to the whole molecule, i.e. the Fc and F(ab) fragments. If a positive HAHA response is detected, then individual patient samples can be further analysed in a Complement-Dependent Cytotoxic (CDC) based neutralization assay (i.e. the proposed potency assay, which is a CDC assay and to be discussed at the CMC meeting 9-Dec-2005).

Additional Statistical Comments:

- 1) Please provide the specific randomization method. The protocol should state what specific algorithm (e.g., randomly permuted blocks within strata or dynamic allocation) will be used for generating the random treatment assignments. (Block size should not be identified in the protocol.)

The protocol will state that the randomly permuted blocks within strata randomization procedure will be used.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

**Public Health Service
Food and Drug Administration
Rockville, MD 20857**

IND 11719

Glaxo Group Limited d/b/a GlaxoSmithKline
Attention: Philip A. Witman, M.P.H, M. Phil
Associate Director, US Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Mr. Witman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Human Monoclonal Antibody (HuMax-CD20, 2F2) to CD20 [Ofatumumab]."

We also refer to the meeting held on October 23, 2008, between representatives of your firm and this agency. A copy of the official minutes of the face-to-face meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Raymond Chiang, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

Meeting Type: Face-to-Face
Meeting Category: Pre-BLA
Meeting Date and Time: October 23, 2008; 2:00-3:30pm
Meeting Location: White Oak Bldg 22, conference room 1415
Application Number: 11719
Product Name: Ofatumumab [Human Monoclonal Antibody (HuMax-CD20, 2F2) to CD20]

Received Briefing Package September 23, 2008
Sponsor Name: GlaxoSmithKline
Meeting Requestor: Philip A. Witman
Meeting Chair: Patrick Swann
Meeting Recorder: Raymond Chiang

FDA Attendees

Office of Oncology Drug Products

Division of Biologic Oncology Products

Andrew McDougal	Pharmacology/Toxicology Reviewer
Raymond Chiang	Regulatory Project Manager
Mona Patel	Regulatory Project Manager
Vaishali Jarra	Regulatory Project Manager

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Division of Manufacturing & Product Quality/Biotech Manufacturing Team

Bo Chi	Microbiologist
Maan Abduldayem	Consumer Safety Officer
Patricia Hughes	Team Leader
Mary Farbman	Chemist

Office of Pharmaceutical Sciences

Office of Biotechnology Products

Division of Monoclonal Antibodies

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Subramanian Muthukkumar	CMC Reviewer
Barbara Rellahan	CMC Team Leader

Office of Clinical Pharmacology

Division of Clinical Pharmacology V

Jun Yang	Clinical Pharmacology Reviewer

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Nilesh Shah

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Biopharmaceutical Process Development

Biopharmaceutical Process Development

Biopharmaceutical Product Development

Biopharmaceutical Analytical Development

Global Regulatory Affairs

Global Biopharm CMC Regulatory Affairs

Sponsor Attendees

Genmab

Lene Joregensen

Louise Ploug Berth

Process Development

Regulatory Affairs

1.0 BACKGROUND

On August 8, 2008, GlaxoSmithKline (GSK) requested a type B pre-BLA meeting to discuss the CMC information in support of the Ofatumumab (HuMax-CD20) Biologics License Application (BLA).

On September 29, 2008, a face-to-face meeting was held between GSK and FDA to discuss the nonclinical and clinical portions in support of the Ofatumumab (HuMax-CD20) Biologics License Application (BLA).

Since the End-of-Phase-2 meeting on 13 July 2007 GSK has continued to review and revise the drug substance and drug product release specifications. GSK does not intend to discuss specific acceptance criteria at the Pre-BLA meeting, only to confirm the acceptability of the panel of tests.

Ofatumumab is a fully human immunoglobulin G1 monoclonal antibody directed against the human CD20 molecule expressed on B cells. Ofatumumab is expressed as a /
Drug substance contains / mg/mL ofatumumab / mM
sodium citrate, / M sodium chloride, pH 6.5. b(4)

Ofatumumab Injection, 20 mg/mL, is a clear, colorless, aqueous solution containing 20 mg/mL ofatumumab in / mM citrate buffer, mM sodium chloride, pH 6.5. It is supplied in a Type 1 glass vial sealed with a coated rubber stopper, which is secured with a / mm aluminum overseal and a flip-off cap. Each vial contains 5 mL of a solution intended for intravenous infusion. Prior to administration, the drug product is diluted into an infusion bag containing isotonic 0.9% Sodium Chloride Injection. b(4)

Drug substance for clinical and commercial supplies is manufactured under contract by Lonza Biologics at their facility in Slough UK. Initial drug product supplies, including those for the pivotal CLL study Hx-CD20-406, were manufactured under contract by / at their facility in / During 2007, drug product manufacture was transferred to the GSK site at Barnard Castle, UK and this is the proposed site for commercial manufacture. b(4)

2.0 DISCUSSION

Sponsor Submitted Questions and FDA Response:

1. Drug substance and drug product are manufactured on a campaign basis. Drug substance manufacture and certain testing are performed at contract manufacturers as described in Section 6 of Attachment 4. We anticipate that the FDA will conduct inspections of sites involved in the manufacture of ofatumumab

and we wish to schedule activities, especially with the CMOs, to ensure that appropriate parts of the process are in operation at time of inspection.

Can the Division provide advice on expectations for inspections, including sites and timings and manufacturing operations that you wish to review?

FDA RESPONSE: All facilities should be registered and ready for inspection at the time of the BLA submission. Please include a complete list of the manufacturing and testing sites in the BLA. Please provide a preliminary manufacturing schedule for both the drug substance and drug product at time of the pre-BLA meeting and in the original BLA submission to facilitate the planning of the pre-license inspection. Please provide the FEI numbers for / (and Lonza Biologics in Wokingham, UK at the time of the pre-BLA meeting.

b(4)

Discussion during meeting: FDA stated that Lonza Wokingham site should be registered with FDA and requested GSK/Genmab to provide the FEI number. GSK/Genmab agreed to provide the FEI number for the Wokingham site. FDA stated that internal meetings would determine the need for preapproval inspections for the manufacturing facilities and testing sites. FDA asked when GSK/Genmab planned on submitting the BLA. GSK/Genmab stated that the plan was to submit the BLA around December 23, 2008. GSK/Genmab also stated that a planned maintenance shutdown is planned by Lonza for the Slough, UK site. FDA stated that they will try to perform an inspection of the Slough, UK site before the planned shutdown. FDA asked if the filling process for the two other products on the same filling line at the GSK site at Barnard Castle, UK in March, 2009 is similar to the filling process of Ofatumumab. GSK/Genmab agreed to provide the information.

2. We consider that the changes highlighted in Table 6 of the supporting Briefing Document (Attachment 4) are minor and propose to include in the BLA data for those batches described in Table 7 of Attachment 4.

Does the Division agree that the data from the collection of batches included in Table 7 will be sufficient to demonstrate consistent product quality and stability and to support shelf-life claims for the commercial product?

FDA RESPONSE: Based on the limited information submitted in the briefing package, the FDA agrees with the proposal. A final decision of the adequacy of the data, however, will be BLA review issue.

Please note the following additional comments:

- a. With regard to the use of both a generic and a product specific Batch Manufacturing Record, please submit blank and executed copies of both types in the BLA.

Discussion during meeting: GSK understood and had no additional comments.

- b. The briefing package includes a summary of the amount and type of stability data that will be submitted in the BLA. Are there plans to submit updated stability data during BLA review cycle?

Discussion during meeting: GSK plans to provide sufficient stability data to support the proposed drug substance and drug product expiry dates at the time of the BLA submission.

- c. FDA recommends a container closure integrity test in lieu of sterility on the stability program.

Discussion during meeting: GSK understood and had no additional comments.

3. We consider that the ofatumumab process TSE and virus safety strategy described in Section 4 of the supporting Briefing Document (Attachment 4) provides sufficient control to ensure safety with respect to TSE and virus.

Does the Division agree with this proposal?

FDA RESPONSE: No. There was insufficient information submitted in the briefing package to determine the sufficiency of the characterization and testing scheme. Please see specific comments below:

- a. Please submit documentation in the BLA identifying the country of origin, and safety testing performed on all animal- and human-derived components used in the ofatumumab manufacturing process.

Discussion during meeting: GSK acknowledged this comment and will provide this information in the BLA.

- b. Viral safety information on the ofatumumab process will need to include data for testing of the master and working cell banks, and the end of production cells as outlined in ICH Q5A (R1) (<http://www.ich.org/cache/compo/276-254-1.html>), including results for pertinent species specific viral tests such as for bovine and murine specific viruses.

Discussion during meeting: GSK acknowledged this comment and will provide this information in the BLA.

4. Section 5 of the supporting Briefing Document (Attachment 4) describes the specifications for drug substance and drug product.

Does the Division concur that the tests included in the drug substance and drug

product release specifications are appropriate to ensure demonstration of identity, purity, safety, and potency of ofatumumab?

FDA RESPONSE: No. Drug Substance (DS) and drug product (DP) release specification tests and their acceptance criteria will be a critical BLA review issue. In general the proposed testing scheme is reasonable; however several deficiencies and issues were identified with both the DS and DP testing schemes as outlined below:

Drug Substance:

- a. To justify the removal of isoelectric focusing (IEF) and to establish the imaged capillary isoelectric focusing (icIEF) as a suitable replacement assay, please submit data from release and stability testing for both assays from all lots available in addition to assay validation information. If the IEF assay has stability indicating properties, information on the icIEF assay will need to demonstrate that it is equal to or better than the IEF at detecting product degradation.

Discussion during meeting: GSK/Genmab stated that data from release and stability testing for both assays from all available lots, in addition to assay validation information, will be submitted in the BLA. GSK/Genmab, however, stated that they do not have data for every batch. FDA asked GSK/Genmab whether all lots are currently being tested with both assays. GSK/Genmab stated that the lots were currently being tested with only icIEF assay. GSK/Genmab stated that they felt there would be data from a sufficient number of lots to demonstrate that the icIEF assay is a suitable replacement assay for the IEF assay. FDA asked how many lots have available data. Genmab stated more than 10.

- b. FDA does not agree with the proposal to remove /
/ from DS lot release testing at this time. Assays for these impurities should be included in the BLA DS lot release protocol until FDA review and concurrence with assay and process validation. b(4)

Discussion during meeting: GSK/Genmab stated that the testing methods for

- c. FDA is unclear whether a commercially available ELISA kit is being used to detect /
/ impurities in the manufacture of ofatumumab. Please clarify. Agency experience indicates the commercial kits can be insensitive b(4)

Therefore, data should be provided in the BLA that demonstrates that the

3 Page(s) Withheld

 X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Discussion during meeting: GSK/Genmab understood comment #6 and will provide this information in the BLA.

Linked Applications

Sponsor Name

Drug Name

IND 11719

GLAXO GROUP LTD
DBA GLAXOSMITHKLINE

Human Monoclonal Antibody (HuMax-
CD20, 2F2) to CD20

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

/s/

PATRICK G SWANN

11/21/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

**Public Health Service
Food and Drug Administration
Rockville, MD 20857**

IND 11719

Glaxo Group Limited d/b/a GlaxoSmithKline
Attention: Philip A. Witman, M.P.H, M. Phil
Associate Director, US Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Mr. Witman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Human Monoclonal Antibody (HuMax-CD20, 2F2) to CD20 [Ofatumumab]."

We also refer to the meeting held on September 29, 2008, between representatives of your firm and this agency. A copy of the official minutes of the face-to-face meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Raymond Chiang, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

Meeting Type:	Face-to-Face
Meeting Category:	Pre-BLA
Meeting Date and Time:	September 29, 2008; 2:00-3:30pm
Meeting Location:	White Oak Bldg 22, conference room 1415
Application Number:	11719
Product Name:	Ofatumumab [Human Monoclonal Antibody (HuMax-CD20, 2F2) to CD20]

Received Briefing Package	September 2, 2008
Sponsor Name:	GlaxoSmithKline
Meeting Requestor:	Philip A. Witman
Meeting Chair:	Jeff Summers
Meeting Recorder:	Raymond Chiang

FDA Attendees

Office of Oncology Drug Products

Division of Biologic Oncology Products

Patricia Keegan	Division Director
Joseph Gootenberg	Deputy Division Director
Steven Lemery	Medical Officer
Jeff Summers	Medical Team Leader
Andrew McDougal	Pharmacology/Toxicology Reviewer
Anne M. Pilaro	Pharmacology/Toxicology Supervisor
Karen D. Jones	Chief, Project Management Staff
Melanie Pierce	Regulatory Project Manager
Raymond Chiang	Regulatory Project Manager

Office of the Commissioner

Division of Scientific Investigations

Sharon Gershon	Pharmacologist

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Office of Biotechnology Products

Division of Monoclonal Antibodies

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Biostatistics and Programming

Regulatory Affairs

Corporate Drug Safety

Medical Director

Clinical expert:

Michael Keating

MD Anderson Cancer Center (Chair of IRC)

1.0 BACKGROUND

Study Hx-CD20-406 is the primary efficacy study intended to support the marketing application planned for late 2008. Study Hx-CD20-406 is a multicenter, single arm, open label trial of ofatumumab monotherapy in patients with refractory CLL. GlaxoSmithKline (GSK) states that the results from this trial will support accelerated approval based on the demonstration of durable objective tumor responses because there is an unmet medical need for the two populations enrolled in this study Hx-CD20-405. GSK identifies these two populations, which were analyzed separately as: 1) Double-Refractory (DR): subjects whose disease is refractory to both fludarabine and alemtuzumab and 2) bulky Fludarabine-Refractory (BFR): subjects whose disease is refractory to fludarabine and have lymphadenopathy > 5cm for whom GSK states alemtuzumab is inappropriate. Subjects in study Hx-CD20-406 were treated with 8 weekly infusions of ofatumumab, then infusions every 4 weeks for an additional 4 doses. The first infusion was 300 mg. Each subsequent infusion was 2000 mg. The primary endpoints are overall response rate at week 24 in the two study subpopulations (DR and BFR). At the interim analysis, GSK reports that the overall response rate in the DR group (n=59) was 59% with a duration of 7.1 months and the overall response rate in the BFR group (n= 79) was 48% with a duration of 5.6 months.

Efficacy data from study Hx-CD20-402, a single arm study that enrolled 33 subjects will be included in the proposed marketing application to provide additional supportive information for the activity of ofatumumab.

GSK proposes to confirm the clinical benefit of ofatumumab in clinical protocol OMB110913, which was submitted under a request for Special Protocol Agreement on August 20, 2008.

2.0 DISCUSSION

Sponsor Submitted Questions and FDA Response:

1. Does the Division agree that the proposed package of non-clinical studies is acceptable to support the registration of ofatumumab monotherapy for the treatment of patients with refractory CLL under the accelerated approval process?

FDA RESPONSE: FDA concurs that the nonclinical studies described in the briefing package appear appropriate to support registration; FDA has not identified and does not anticipate safety concerns based on the nonclinical studies. However, the adequacy of the resulting data to support licensure will be a review decision after the BLA is submitted, and the studies are fully reviewed in the context of all other information provided.

Discussion during meeting: GSK/Genmab had no additional comments.

2. Does the Division agree that the proposed package of clinical pharmacology data is acceptable to support the registration of ofatumumab monotherapy for the treatment of patients with refractory CLL under the accelerated approval process?

FDA RESPONSE: The proposed clinical pharmacology package appears to be acceptable. However, the adequacy of data will be determined during the BLA review. The impact of immunogenicity on PK, efficacy and safety should be evaluated. Please also provide all of the raw PK and immunogenicity data in .xpt format in your BLA submission.

Discussion during meeting: GSK/Genmab had no additional comments.

3. Clinical samples for the quantification of ofatumumab were collected over an extended period of time (up to six months after the last dose) in the clinical trials and were stored prior to bioanalysis. GSK is generating additional stability data to cover the longest duration of sample storage for the studies in the submission. GSK proposes to include a portion of the additional stability data in the submission, with data accumulation ongoing during the review time, and to provide updated stability data to the Division once they become available.

Does the Division agree with this proposal?

FDA RESPONSE: No. If the stability data is needed to interpret the PK results, the stability data should be provided at the time of BLA submission.

Discussion during meeting: GSK/Genmab agreed to provide the stability data.

4. Does the Division accept the proposal for reporting ongoing studies and studies from other (follicular lymphoma and non-oncology) indications?

FDA RESPONSE: Yes, assuming this proposal comprises all studies pertinent to the safety and effectiveness of ofatumumab.

Discussion during meeting: GSK/Genmab had no additional comments.

5. Does the Division agree that the bulky fludarabine-refractory CLL patients, in addition to the double refractory CLL patients, have an unmet medical need and would qualify for review under the accelerated approval process?

FDA RESPONSE: No, based on the results of the CAM307 study, patients with bulky lymphadenopathy who received first line chemotherapy demonstrated clinically meaningful responses to alemtuzumab. Accelerated approval regulations are based on the ability to provide meaningful therapeutic benefit to patients over existing treatments. Alemtuzumab is approved for first line treatment of CLL and therefore this clinical setting (alemtuzumab-naïve DBR) would not be considered to have an unmet medical need.

Discussion during meeting: GSK/Genmab contended that bulky fludarabine-refractory CLL patients have an unmet medical need based on medical literature. FDA reiterated that clinically meaningful treatment effect (response rates) and durable responses have been demonstrated with alemtuzumab in patients with bulky, fludarabine-refractory CLL. FDA referred to the CAM 307 study in which a reported 76% of patients with lymph nodes ≥ 5 cm in size responded to alemtuzumab. In addition, FDA stated that referring to a limited number of reports was not sufficient to make the argument that alemtuzumab is less effective than ofatumumab for treatment of this patient population. GSK/Genmab stated that fludarabine-refractory CLL patients do not tolerate alemtuzumab therapy, based on clinical experience (personal communication). FDA stated that regulatory decisions are based on data, not on expert clinical testimony regarding standard of care. FDA requested GSK/Genmab provide additional data in order to strengthen their argument that ofatumumab therapy demonstrates superior efficacy or similar efficacy with superior safety to alemtuzumab in the bulky, fludarabine-refractory CLL patient population. The ultimate decision regarding this issue will be a review issue. GSK/Genmab understood and agreed to provide the requested data.

6. It is acknowledged that clinical benefit needs to be confirmed in an additional study, such as the study OMBI0913 submitted as a Special Protocol Agreement (Serial No. 0173 on 23 May 2008) and currently under review by the Division, consistent with review under an accelerated approval process.

Does the Division agree that the package containing pivotal study HxD20- 406, supported by study Hx-eD20-406, and other data and information as described in this Pre-BLA meeting package will provide adequate basis to support the registration of ofatumumab monotherapy for the treatment of patients with refractory CLL under the accelerated approval process?

FDA RESPONSE: The proposal to provide data from study Hx-CD20-406 and other supportive studies is sufficient to enable review of a Biological License Application. However, the ability of data from these studies to support the registration of ofatumumab will be a review issue.

Discussion during meeting: GSK/Genmab had no additional comments.

7. Does the Division agree that the results from study Hx-eD20-406 indicate meaningful clinical activity?

FDA RESPONSE: The overall GlaxoSmithKline-reported response rate of 59% [99% CI: 42%, 75%] in the double-refractory population with a median duration response of 7.1 months described in the meeting package suggests that ofatumumab has clinical activity in patients with CLL. Accelerated approval, however, is not based on clinical activity but on improvement of a surrogate endpoint reasonably likely to predict clinical benefit. Approval of ofatumumab under accelerated approval regulations will be a review issue and will be based on the FDA analysis of the data.

Discussion during meeting: *GSK/Genmab had no additional comments.*

8. In addition to providing the assessment of response data by the Independent Response Committee, we propose to provide in the BLA further analyses of the response data for a more complete characterization of the results and understanding of the clinical benefit of ofatumumab. Section 6.2.1.1.2 of Attachment 5 provides details of this approach on response assessment.

Does the Division agree that the plan for sponsor evaluation of response is acceptable?

FDA RESPONSE: Yes, it is acceptable for GlaxoSmithKline to provide exploratory analyses of response data. Ensure that all aspects of the exploratory analyses are described and included in the BLA submission. FDA may conduct its own analyses to ensure robustness of data.

Note that FDA considers the Independent Response Committee assessment to be an audit of investigator-reported response determination because the committee utilized the tumor measurements made by the investigators.

Furthermore, GlaxoSmithKline should perform additional sensitivity analyses for duration of response. FDA is concerned that the protocol specified that the duration of response (DOR) analyses would be censored if a patient discontinued treatment due to toxicity or other reason rather than being followed for progression. Also note that the acceptance of your censoring plan for missing data for DOR may be contingent on the overall amount of missing data present in the study reports.

Discussion during meeting: *GSK disagreed with FDA's assessment that the Independent Response Committee (IRC) was an audit of investigator-reported response determination. FDA stated that the intent was not to impugn the IRC; however, the IRC reviewed laboratory-reported lymphocyte counts and investigator determined lymph node measurements. Thus there was no true independent review of lymph node size; FDA does not consider the IRC to have conducted a truly independent review of progression. GSK/Genmab stated that the IRC evaluation of response is standard clinical practice. GSK/Genmab also stated that consistency was maintained because each patient's response to therapy was assessed by three independent oncologists and/or hematologists. GSK/Genmab agreed to perform additional sensitivity analyses as requested by FDA. FDA stated that the proposal to conduct sensitivity analyses was acceptable, although the FDA's statements regarding IRC review as an audit process remained unchanged.*

9. Does the Division agree that the safety database of 362 oncology patients, supplemented by 269 patients from non-oncology studies, who have received ofatumumab is acceptable to support the proposed dosing and duration of exposure of ofatumumab monotherapy for the treatment of patients with refractory

CLL under the accelerated approval process?

FDA RESPONSE: Yes, the data appear sufficient to support the filing of a BLA; however, the ultimate decision regarding the adequacy of the data will be a review issue based on the dosing and exposure data that occurred during the clinical studies.

Discussion during meeting: *GSK/Genmab had no additional comments*

10. **Does the Division agree that it is acceptable to submit the QTc assessment as part of the efficacy and safety results from OMB110913 after the Division's review of the initial BLA submission?**

FDA RESPONSE: No. Since the ofatumumab dose used in the monotherapy is higher than the dose used in the combination therapy, the potential impact of ofatumumab on QT/QTc should be assessed at its highest clinical dose. Please submit a QTc assessment plan for FDA review.

Discussion during meeting: *GSK/Genmab stated that QTc studies will be performed as a sub-study within protocol OMB110913 providing ECG data for the combination with ofatumumab at a dose (1000mg) and without ofatumumab. GSK/Genmab proposed to conduct a QTc study for the 2000 mg monotherapy dose as a post marketing commitment (PMC). FDA stated that the QTc plan would need to be submitted with the original BLA submission. GSK/Genmab asked for references or guidance concerning the implementation of ECG monitoring in a clinical protocol to meet the objectives of a QTc assessment. FDA stated that ECGs should be performed at multiple time points including baseline, pre-dose, Cmax, steady state, and after treatment. FDA, however, also stated that if a safety signal is detected additional monitoring may be required. FDA reiterated that when GSK/Genmab submits their QTc plan as a component of the original BLA, the FDA QT-IRT team will review the plan and provide comments. GSK/Genmab agreed to submit their QTc plan in the original BLA submission. FDA requested that GSK/Genmab also provide all available ECG data in the original BLA at the proposed dose, noting that because ofatumumab will be given as monotherapy, GSK/Genmab will need to provide QTc data at the 2000 mg dose as well characterizing ECGs effects with the 1000 mg dose as a component of combination therapy. GSK/Genmab agreed to provide the information as requested in the original BLA submission.*

11. **The periodic safety update for the BLA will include updated safety information for the duration between the data cut-off date for the BLA (approximately 6 months prior to the date of the anticipated submission) and the BLA submission date. The safety update will also include an updated listing of SAEs from all ongoing studies of ofatumumab as of the date of submission of the BLA. We propose to submit this update approximately 90 days following the date of the BLA submission.**

Does the Division agree with this approach?

FDA RESPONSE: No. FDA requests that GlaxoSmithKline limit the submission of updated safety information to serious adverse events (SAEs), deaths, and drop-outs. However, FDA may request additional safety information if the FDA identifies new safety signals during the course of the review.

Discussion during meeting: *GSK/Genmab had no additional comments.*

12. **Section 6.3.4 of the Briefing Document (Attachment 5) describes the narratives that we propose to provide for serious adverse events and withdrawals due to adverse events. Based on prior advice from the Division, these adverse events of special interest for the populations under study are defined in Section 3.1.1.5.6 of the Briefing Document (Attachment 5).**

Does the Division agree with types, method of capturing, analysis, and reporting of the adverse events of special interest?

FDA RESPONSE: Insufficient information was provided to answer this question. In regard to narratives described in the background section of this question, FDA requests that subject narratives be submitted in the appropriate area of the ISS. FDA also requests that the following components be included in the narrative summaries:

- a. Subject age and gender
- b. Signs and symptoms related to the adverse event being discussed
- c. The specific toxicities that resulted in treatment discontinuation
- d. An assessment of the relationship of exposure duration to the development of the adverse event
- e. Pertinent medical history
- f. Concomitant medications with start dates relative to the adverse event
- g. Pertinent physical examination findings
- h. Pertinent test results (for example: lab data, ECG data, biopsy data)
- i. Discussion of the diagnosis as supported by available clinical data
- j. For events without a definitive diagnosis, a list of differential diagnoses
- k. Treatment provided
- l. Re-challenge results (if performed)

- m. Outcomes and follow-up information
- n. An informed discussion of the case, allowing a better understanding of what the subject experienced

Furthermore, FDA is concerned with the methods used to capture the adverse events of special interest. Because investigators were instructed not to report events known to be caused by CLL, it is unclear if the incidence of certain events including immune hemolytic anemia or infections were underreported during the conduct of study Hx-CD20-406. FDA suggests a random chart review of a proportion of patients (for example, a random 25% sample obtained from multiple sites) to determine the effect that this study provision had on the reporting of adverse events.

Discussion during meeting: *GSK/Genmab stated because GSK/Genmab audits case report form data for completeness by comparison with source documents, the safety database will be supplemented as appropriate to include all adverse events unless such events are clearly attributable to disease progression.*

13. **If the FDA's assessment of the safety of ofatumumab is consistent with that provided in the BLA, does the Division agree with the proposed general approach to risk management?**

FDA RESPONSE: A complete review of the full risk management plan after the BLA is submitted will be necessary to determine whether it is acceptable, since additional information regarding risks and safe product use may emerge during the review of your BLA.

Discussion during meeting: *GSK/Genmab had no additional comments.*

14. **Does the Division agree with the proposal to provide the Risk Management Plan in the BLA using the EU-RMP format?**

FDA RESPONSE: At this time, FDA does not have a defined format for risk management (other than a REMS) submitted with the original BLA application; therefore, your proposal to submit in the EU format is acceptable.

Discussion during meeting: *GSK/Genmab had no additional comments.*

15. **We propose to submit in the BLA case report forms (CRFs) and case narratives for deaths that occurred due to events other than disease progression, as well as CRFs and case narratives for patients whose adverse events resulted in discontinuation from the study within 30 days following the final dose of study medication from Study Hx-CD20-406. For patients in other studies, GSK proposes to provide CRFs and narratives for deaths that occurred due to events other than disease progression, as well as for patients whose adverse events resulted in discontinuation**

from the study within 30 days following the final dose of study medication to the FDA upon request.

Does the Division agree that this approach is acceptable?

FDA RESPONSE: No, FDA requests that CRFs, relevant pathology reports, and available radiology reports be submitted for all patients in study Hx-CD20-406 who achieved an objective tumor response. Note that CRFs for any patient must be made available if requested during the course of the review upon FDA request.

Discussion during meeting: FDA requested GSK/Genmab not to send CT scans unless FDA specifically requests them.

16. **Does the Division agree with the proposed plan for the Summary of Clinical Efficacy?**

FDA RESPONSE: Please see response to question 18.

17. **Does the Division agree with the proposed plan for the Summary of Clinical Safety?**

FDA RESPONSE: Please see response to question 18.

18. **Does the Division agree with the proposed plan to not include a separate Integrated Summary of Efficacy or Integrated Summary of Safety if the data contained in these sections is captured in Module 2 as part of the Clinical Summaries of Efficacy and Safety?**

FDA RESPONSE TO QUESTIONS #16 THROUGH #18: GlaxoSmithKline has provided insufficient information to allow FDA to formally agree with this plan. The proposed plan appears reasonable; however, if the text in Module 2 does not contain all the required elements of the ISS and ISE, FDA may refuse to file the BLA. Furthermore, FDA may refuse to file the application if Module 2 is not concise enough to meet recommended size limitations because of the inclusion of the ISE or ISS in this section of the BLA.

Discussion during meeting: GSK/Genmab understood and agreed to provide requested information.

19. **Does the Division agree with the proposed plan for submission of pharmacokinetic data?**

FDA RESPONSE: It appears to be acceptable. Please make sure to submit results from the ongoing study Hx-CD20-406.

Discussion during meeting: GSK/Genmab had no additional comments.

20. **Does the Division agree with the proposed specifications and file formats of the BLA?**

FDA RESPONSE: No, FDA requests that data be submitted to the agency in CDISC format. Since the current CDISC Study Data Tabulation Model does not call for all levels of the MedDRA hierarchy, an analysis Data Model dataset (ADAM-E) should be included with your data submissions. All datasets should be submitted to the FDA using standard SAS XPORT v5 because the specifications for creating such files (by an entity other than SAS) are in the public domain (required by law). The specifications for all subsequent SAS transport files are proprietary to SAS. Please provide the location of the SAS dataset, the names of the variables and the programs used to get every new value that will be appearing in the label. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the sBLA submission.

Discussion during meeting: GSK/Genmab stated that FDA previously stated that the BLA would not have to be submitted using CDISC format. FDA stated that this was a recommendation and not a requirement; however, FDA stated that submission of the BLA in the optimal format would more readily allow for a timely review.

21. **Does the Division agree that a full waiver from the conduct of separate pediatric studies for ofatumumab in the treatment of CLL may be granted?**

FDA RESPONSE: The FDA decision regarding acceptance of a pediatric waiver or deferral will be made at the time of the waiver request when the BLA is submitted. As part of the waiver request, submit a full review of the appropriate cancer statistics regarding CLL in the pediatric population.

Discussion during meeting: GSK/Genmab had no additional comments.

22. **GlaxoSmithKline has determined that pivotal study Hx-CD20-406 and supportive study Hx-CD20-402 are covered studies under 21 CFR Part 54. Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and, if applicable, Form 3455 (Disclosure Financial Interests and Arrangements of Clinical Investigators) will be included in the BLA submission for these studies.**

Does the Division agree with the proposal to provide Financial Disclosure information in this manner?

FDA RESPONSE: Yes, it is acceptable that financial disclosure information be limited to studies Hx CD20-406 and Hx-CD20-402. All financial disclosure information needs to be included in the original application in order for the application to be considered complete.

Discussion during meeting: GSK/Genmab had no additional comments.

Additional Nonclinical Comments:

23. The pre-BLA briefing package notes that four nonclinical studies (Studies #23542, #25052, #2138-010, and #283366), including the embryo fetal study have "Analytical data under review, may need recalculation of PK parameters in line with clinical data." The meaning of this statement is unclear; please clarify. Please provide a timeline for submission of these data to FDA. FDA interprets this statement to imply that GSK will re-evaluate the animal PK data, and compare the C_{max} and AUC values from these studies to the human PK experience with ofatumumab to date. Please provide clarification of this statement, as well as provide a timeline for submission of this information data to FDA.

***Discussion during meeting:** GSK/Genmab stated that FDA interpreted the statement correctly. GSK/Genmab stated that the planned submission date for the original BLA is December 2008. FDA requested that GSK/Genmab provide notification to the FDA project manager upon submission of the BLA. GSK/Genmab agreed to do this..*

Additional Clinical Comments (note that some of the analyses requested below may have been included in Attachment 14 of the BLA submission; time constraints prevented a page by page evaluation of all of your proposed analyses):

24. In the BLA submission, FDA requests that you provide the following:
- a. a detailed report of the data quality assurance activities and study monitoring and auditing activities
 - b. a detailed summary of protocol violations
 - c. a dataset that identifies each investigator with the respective medical institution to which they admitted patients into the study; please identify each subject enrolled by each investigator
 - d. a "treatment" dataset that contains subject visit number, visit date, and amount of ofatumumab administered
 - e. summary tables of the incidence of adverse events based on the cumulative dose and the average dose of ofatumumab administered
 - f. an adverse event dataset that includes verbatim terms and all levels of the MedDRA hierarchy including LLT, PT, HLT, HLGT, and SOC
 - g. an exploratory analysis to identify possible factors associated with a higher likelihood of study termination; including demographic variables, study site, and region

- h. an analysis summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment
- i. summary data on the per-patient incidence rate of adverse events
- j. data summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment
- k. summary tables of the incidence of adverse events based on the cumulative dose and average dose of ofatumumab administered
- l. minutes from all DMC meetings and minutes of classification meetings with detailed descriptions of analysis populations
- m. a dataset that describes all prior therapies; please include a column to describe whether the patient received prior alkylating agent therapy

Discussion during meeting: *GSK/Genmab had no additional comments.*

25. In the BLA submission, ensure that laboratory data are organized in the datasets in a standardized manner with consistent units and a single reference range for each laboratory variable. Define the range(s), with supporting documentation, that are used to identify severe toxicity.

Discussion during meeting: *GSK/Genmab had no additional comments.*

26. In the BLA submission, ensure that mapping of a preferred term to the MSSO defined primary SOC level is not changed.

Discussion during meeting: *GSK/Genmab had no additional comments.*

27. Additional guidance on a good safety review can be found on the following web link: www.fda.gov/cder/guidance/3580fnl.pdf.

Discussion during meeting: *GSK/Genmab had no additional comments.*

28. In the BLA submission, ensure that the package insert follows the regulatory requirements for the Physicians Labeling Rule. FDA recommends that wherever possible command language be used rather than passive tense when writing the label. Failure to write an adequate label may result in a refusal to file action. Available guidance

documents can be found at the following website:
<http://www.fda.gov/cder/regulatory/physlabel/default.htm>.

Discussion during meeting: *GSK/Genmab had no additional comments.*

ADDENDUM: PRE-BLA MEETING:

We have the following general comments regarding the content and organization of a BLA.

A. Information Required for Review

The sBLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at:
<http://www.fda.gov/cder/mapp/6010.3.pdf>.

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Exposure-Response Relationships - important exposure-response assessments.
3. Less common adverse events (between 0.1% and 1%).
4. Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Marked outliers and dropouts for laboratory abnormalities.
7. Analysis of vital signs focused on measures of central tendencies.
8. Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Overdose experience.
12. Explorations for dose dependency for adverse findings.

13. Explorations for time dependency for adverse findings.
14. Explorations for drug-demographic interactions.
15. Explorations for drug-disease interactions.
16. Explorations for drug-drug interactions.
17. Dosing considerations for important drug-drug interactions.
18. Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

B. Information Regarding Label in the Physician Labeling Rule (PLR) Format

Highlights:

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

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

8. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
9. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].
10. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
11. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
12. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
13. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

14. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)].
15. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
16. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
17. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
18. When a subsection is omitted, the numbering does not change.

[See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

19. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:
- “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI):

20. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
21. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
22. Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
23. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not *See Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
24. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
25. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]

26. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
27. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
28. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
29. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
30. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
31. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
32. Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

C. Information Regarding Submission of Electronic Data Sets

CDISC Data Requests to Sponsors: Quantitative Safety and Pharmacoepidemiology Group

Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC)

Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).

At a minimum the Safety Analysis Plan should address the following components:

1. Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).
2. Safety endpoints for Adverse Events of Special Interest (AERI)
3. Definition of Treatment Emergent Adverse Event (TEAE)
4. Expert adjudication process (Expert Clinical Committee Charter)
5. Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
6. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
7. When unanticipated safety issues are identified the QSAP may be amended.

Study Data Tabulation Model (SDTM) Issues

8. The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)
9. Domains:
 - a. There are additional domains listed below that are not included in the current SDTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains:
 - (1) (DV) Protocol deviations
 - (2) (DA) Drug Accountability
 - (3) (PC, PP) Pharmacokinetics
 - (4) (MB, MS) Microbiology
 - (5) (CF) Clinical Findings
 - b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains:

- (1) Tumor information
 - (2) Imaging Data
 - (3) Complex Inclusion/Exclusion Criteria
10. Variables:
 - a. All required variables are to be included.
 - b. All expected variables should be included in all SDTM datasets.
 - c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
 - d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
 - e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
 - f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.
11. Specific issues of note:
 - a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.
 - b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.
 - c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues:

12. Please specify which ADaM datasets you intend to submit.
13. Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
14. Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.

15. Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
16. Please indicate which core variables will be replicated across the different datasets, if any.
17. SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.

General Items

18. Controlled terminology issues
 - a. Please use a single version of MedDRA for a submission. Does not have to be most recent version
 - b. FDA recommends that the WHO drug dictionary be used for concomitant medications.
 - c. Please refer to the CDISC terminology for lab test names.
 - d. Issues regarding ranges for laboratory measurements should be addressed.

Linked Applications

Sponsor Name

Drug Name

IND 11719

GLAXO GROUP LTD
DBA GLAXOSMITHKLINE

Human Monoclonal Antibody (HuMax-
CD20, 2F2) to CD20

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

/s/

RAYMOND S CHIANG

10/28/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

**Public Health Service
Food and Drug
Administration
Rockville, MD 20857**

IND 11719

**Genmab A/S
Attention: Marguerite Coleman
B & H Consulting Services, Inc.
55 North Gaston Avenue
Somerville, NJ 08876**

Dear Ms. Coleman:

Please refer to your Investigational New Drug Application (IND) for "Human Monoclonal Antibody (HuMax-CD20, 2F2) to CD20." We also refer to the meeting held on July 13, 2007, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1393.

Sincerely,

{See appended electronic signature page}

**Erik S. Laughner
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research**



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

Meeting Type: B
Meeting Category: End of Phase 2
Meeting Date and Time: July 13, 2007; 10 AM ET
Meeting Location: Teleconference
Application Number: IND 11719
Product Name: Human Monoclonal Antibody (HuMax-CD20, 2F2) to CD20
Received Briefing Package: June 13, 2007

Sponsor Name: Genmab A/S

Meeting Requestor: Genmab A/S

Meeting Chair: Patricia Keegan
Meeting Recorder: Erik Laughner

FDA Attendees:

Division of Biologic Oncology Products

Kevin Shannon, M.D., Clinical Reviewer
Erik Laughner, M.S., Regulatory Project Manager
Jeff Summers, M.D., Medical Team Leader
Patricia Keegan, M.D., Director
Amy Gomez, R.N., M.S., Regulatory Project Manager

Division of Monoclonal Antibodies

Subramanian Muthukkumar, Ph.D., Product Reviewer
Patrick Swann, Ph.D., Deputy Director

Division of Clinical Pharmacology 5

Hong Zhao, Ph.D., Clinical Pharmacology Team Leader

Sponsor Attendees:

Torben Lund-Hansen	Vice President, Head of Manufacturing	Genmab
Tony Jørgensen	Vice President, QA and Regulatory Affairs	Genmab
Lene Jørgensen	Director, Process Development	Genmab
Patrick van Berkel	Director, Technology, Project Operations	Genmab
Anders Marcussen	CMC Coordinator, Aseptic Filling	Genmab
Narendra Bam	Vice President, Biopharmaceutical Development	GSK
Nigel Bell	Dose Form Technical Lead	GSK
Amol Ketkar	Manager, Biopharmaceutical Technologies	GSK
Catherine Bentley	Associate Director, CMC Regulatory	GSK
Ann Christine Korsgaard	Project Leader, Regulatory Affairs	Genmab
Louise Ploug Larsen	Project Leader (CMC), Regulatory Affairs	Genmab
Marguerite Coleman	US Agent, Project Director	B&H Consulting Services

Background and Purpose: HuMax-CD20 is a human monoclonal antibody targeted at the CD20 molecule in the cell membrane of B-cells, and is in clinical development for the treatment of rheumatoid arthritis, non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia (CLL).

HuMax-CD20 has been designated a Fast Track product by the FDA for use in combination with Fludarabine for treatment of patients with previously untreated CLL to show an improvement in progression-free and overall survival as compared with Fludarabine therapy.

In addition, Genmab has initiated a second development program which is distinct from the fast track development program referenced above. This program includes a Phase 1/2 study in 33 patients in Europe and the US with relapsed or refractory CLL (Hx-CD20-402) and a multicenter, single arm study (Hx-CD20-406) entitled, "A single-arm, international, multi-center trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell Chronic Lymphocytic Leukemia who have failed fludarabine and alemtuzumab". Genmab A/S, has indicated their intent to seek accelerated approval based on results of the trial, Hx-CD20-406, based on demonstration

of an objective response rate of substantial magnitude and durability, as discussed in the May 5, 2006, letter to Genmab and the May 23, 2006, teleconference with Genmab.

On May 11, 2007, Genmab A/S requested a formal FDA meeting to seek advice on their ongoing CMC development plans and data generated as it will relate to a future application for marketing approval under one or both of the clinical development programs

FDA Comments were provided to B&H Consulting Services (Authorized U.S. Agent) for Genmab A/S, on July 10, 2007. Genmab A/S provided written responses on July 12, 2007 (see attached at end of minutes). Actual FDA minutes are provided as "Discussion During the Teleconference."

Sponsor Submitted Questions and FDA Response:

***Introductory FDA Statement:** FDA is not able to provide definitive answers to several of Genmab's questions as additional information is needed. Genmab can either provide the requested information in a future Biological License Application (BLA) or in a submission in support of a future pre-BLA meeting when time is appropriate.*

Change in drug product manufacturer from / /to GSK, Barnard, UK

1. Does the Agency agree that the proposal to transfer drug product manufacture from (/ to GSK is acceptable provided that the GSK process qualification is successful and that the comparison between / and GSK manufactured batches is acceptable?

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007: Yes. However, a final determination of the acceptability of both the drug product fill process qualification and product comparability will be BLA review issues.

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion.

2. Does the Agency agree that it will be acceptable to remove the

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007:
Please provide data at the time of the BLA to show that the

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion.

3. Does the Agency agree to the proposal to reset the nominal fill volume based on validation at GSK provided that the extractable volume of _____, remains unchanged? b(4)

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007:

Genmab has not provided sufficient information to respond to this question. Please provide data and statistical analyses in the BLA to demonstrate that all vials will comply with USP requirements throughout the entire shelf life.

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion.

4. Does the Agency agree with the Company's proposal to use supportive stability data of drug product filled at _____ to justify _____ shelf life at 2-8°C for ofatumumab drug product manufactured at GSK, Barnard Castle? b(4)

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007: To support Genmab's proposal, adequate comparability data must be provided in the BLA, including accelerated/stress stability study for drug product batches that are manufactured at _____ and GSK. b(4)

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion.

Particle characterization

5. Is the planned data package to investigate particle formation in drug product acceptable to the Agency?

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007: FDA agrees that the planned data package is acceptable. FDA also suggests that Genmab consider additional techniques such as _____ for the characterization of particles. b(4)

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion.

Specification for ofatumumab drug substance

6. Does the Agency find the tests included in the drug substance specification appropriate for commercial use?

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007:No.
See FDA replies to question 8 and question 9. In addition, acceptance criteria of all tests included under drug substance specification will be a critical BLA review issue.

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion.

7. Does the Agency agree that the planned icIEF method is suitable as a quantitative determination of [redacted] as the identity test in the specification? b(4)

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007:Yes,
the method appears to be suitable as an identity test for studies providing the primary efficacy data in the BLA.

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion.

8. Does the Agency agree with the Company's proposal to discontinue routine [redacted] b(4)

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007: No.
FDA does not concur at this time. Specification [redacted]

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion. b(4)

9. Does the Agency agree with the Company's proposal not to include testing of the [redacted] profile of ofatumumab as a release test since the [redacted] b(4)

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007: No.
Genmab reports that varying [redacted] b(4)

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. FDA noted that Genmab's proposal to include a release specification with acceptance criteria set for the content of _____ will need to be reviewed in depth prior to concurrence.

b(4)

In vivo viral testing of unprocessed bulk

10. Does the Agency agree that it is not necessary to demonstrate ✓

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007: FDA agrees.

b(4)

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion.

Process validation for pyrogens

11. Does the Agency agree with the use of the LAL based test for bacterial endotoxins as the only test for pyrogens?

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007: No. Genmab has not provided sufficient information. As stated in 21 CFR 610.13, products should be tested for pyrogenic substances. Genmab may wish to pursue using the LAL method as an "Equivalent method..." as described in 21 CFR 610.9. In this case, evidence should be provided in the BLA that the LAL method is equal to or superior to the pyrogen test.

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion.

Specification for ofatumumab drug product

12. Does the Agency find the tests included in the drug product specification appropriate for commercial use?

PRELIMINARY FDA COMMENTS PROVIDED ON JULY 10, 2007: In general, FDA concurs with the list of tests. Please note that appearance should include assessment of a) color, b) clarity and c) visible particles. Acceptance limits of all tests included under drug product specification will be a critical BLA review issue.

DISCUSSION DURING THE TELECONFERENCE: See attached Genmab July 12, 2007, response at end of FDA minutes. There was no further discussion.

Genmab/GSK response to FDA preliminary comments 10-Jul-2007 to CMC EOPII meeting 13-Jul-2007

Introductory FDA Statement: FDA is not able to provide definitive answers to several of Genmab's questions as additional information is needed. Genmab can either provide the requested information in a future Biological License Application (BLA) or in a submission in support of a future pre-BLA meeting when time is appropriate.

Change in drug product manufacturer from / / to GSK, Barnard Castle, UK

1. Does the Agency agree that the proposal to transfer drug product manufacture from / / to GSK is acceptable provided that the GSK process qualification is successful and that the comparison between / / and GSK manufactured batches is acceptable?

b(4)

FDA RESPONSE: Yes. However, a final determination of the acceptability of both the drug product fill process qualification and product comparability will be BLA review issues.

Genmab/GSK response:

FDA response is acknowledged. To demonstrate product comparability drug product will be evaluated by the analytical methods included in the release specification plus testing for / . Results from stability studies at real time, accelerated and stress conditions will also be part of the product comparability evaluation.

2. Does the Agency agree that it will be acceptable to /

b(4)

FDA RESPONSE: Please provide data at the time of the BLA to show that the /

b(4)

Genmab/GSK response:

Acknowledged.

3. Does the Agency agree to the proposal to reset the nominal fill volume based on validation at GSK provided that the extractable volume of / / remains unchanged?

b(4)

FDA RESPONSE: Genmab has not provided sufficient information to respond to this question. Please provide data and statistical analyses in the BLA to demonstrate that all vials will comply with USP requirements throughout the entire shelf life.

Genmab/GSK response:

Acknowledged. Stability protocols for batches manufactured at Barnard Castle will include monitoring of extractable volume. In addition, supportive data for extractable fill volume at the end of the proposed shelf life for batches manufactured at / / will be included in the BLA. b(4)

4. Does the Agency agree with the Company's proposal to use supportive stability data of drug product filled at \ \ to justify a / - v shelf life at 2-8°C for ofatumumab drug product manufactured at GSK, Barnard Castle? b(4)

FDA RESPONSE: To support Genmab's proposal, adequate comparability data must be provided in the BLA, including accelerated/stress stability study for drug product batches that are manufactured at/ (and GSK. b(4)

Genmab/GSK response:

Acknowledged. Comparability will be demonstrated as described above (question 1).

Particle characterization

5. Is the planned data package to investigate particle formation in drug product acceptable to the Agency?

FDA RESPONSE: FDA agrees that the planned data package is acceptable. FDA also suggests that Genmab consider additional techniques such as / for the characterization of particles. b(4)

Genmab/GSK response:

Acknowledged.

Specification for ofatumumab drug substance

6. Does the Agency find the tests included in the drug substance specification appropriate for commercial use?

FDA RESPONSE: No. See FDA replies to question 8 and question 9. In addition, acceptance criteria of all tests included under drug substance specification will be a critical BLA review issue.

Genmab/GSK response:

Acknowledged, however please refer to response given for question 9.

7. Does the Agency agree that the planned icIEF method is suitable as a quantitative determination of / / as the identity test in the specification? b(4)

FDA RESPONSE: Yes, the method appears to be suitable as an identity test for studies providing the primary efficacy data in the BLA.

Genmab/GSK response:

Acknowledged. The icIEF method is currently being validated (finalized October 2007) and is introduced in release and stability specifications. The batches of ofatumumab used in the studies providing the primary efficacy data in the BLA have not been released using the icIEF method but the method will be included for the remaining testing time points in the stability program for these batches.

8. Does the Agency agree with the Company's proposal to discontinue routine /

b(4)

FDA RESPONSE: No. FDA does not concur at this time. Specification for /
should be included in the BLA under drug substance specifications until
FDA review and concurrence with assay validation.

b(4)

Genmab/GSK response:

Acknowledged.

9. Does the Agency agree with the Company's proposal not to include testing /

b(4)

FDA RESPONSE: No. Genmab reports that varying the

b(4)

Genmab/GSK response:

b(4)

In vivo viral testing of unprocessed bulk

10. Does the Agency agree that it is not necessary to demonstrate /

b(4)

FDA RESPONSE: FDA agrees.

Genmab/GSK response:

Acknowledged.

Process validation for pyrogens

11. Does the Agency agree with the use of the LAL based test for bacterial endotoxins as the only test for pyrogens?

FDA RESPONSE: No. Genmab has not provided sufficient information. As stated in 21 CFR 610.13, products should be tested for pyrogenic substances. Genmab may wish to pursue using the LAL method as an "Equivalent method..." as described in 21 CFR 610.9. In this case, evidence should be provided in the BLA that the LAL method is equal to or superior to the pyrogen test.

Genmab/GSK response:
Acknowledged.

Specification for ofatumumab drug product

12. Does the Agency find the tests included in the drug product specification appropriate for commercial use?

FDA RESPONSE: In general, FDA concurs with the list of tests. Please note that appearance should include assessment of a) color, b) clarity and c) visible particles. Acceptance limits of all tests included under drug product specification will be a critical BLA review issue.

Genmab/GSK response:
Acknowledged.

Linked Applications

Sponsor Name

Drug Name

IND 11719

GENMAB A/S

Human Monoclonal Antibody (HuMax-
CD20, 2F2) to CD20

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

/s/

ERIK LAUGHNER

08/09/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Our Reference: BB-IND 11719

Food and Drug Administration
Rockville, MD 20852

Genmab A/S
Attention: Marguerite Coleman
B & H Consulting Services, Inc.
55 North Gaston Avenue
Somerville, NJ 08876

DEC 21 2005

Dear Ms. Coleman:

Please refer to your Investigational New Drug Application (IND) for "Human Monoclonal Antibody (HuMax-CD20, 2F2) to CD20" and to the telephone conversation held on November 30, 2005, between representatives of your firm and this agency. As discussed, a copy of our memorandum of that meeting is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact me at (301) 796-1393.

Sincerely yours,

Erik Laughner, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures: FDA Meeting Summary and Sponsor Preliminary Comments



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

SEP 30 2005

Our Reference: BB-IND 11719

Genmab A/S
Attention: Marguerite Coleman
B & H Consulting Services, Inc.
55 North Gaston Avenue
Somerville, N.J. 08876

Dear Ms Coleman:

Please refer to your **Investigational New Drug Application (IND)** for "Human Monoclonal Antibody (HuMax-CD20, 2F2) to CD20," to the teleconference held on August 26, 2005, between Genmab A/S, and this agency and to the telephone conversation held on September 28, 2005, between you and Ms. Janet Condino regarding our teleconference summary issued September 23, 2005.

We have reviewed our August 23, 2005, teleconference, and, in order to provide greater clarity, we have revised the teleconference summary as follows: on page 6 we have revised item 9a, paragraph 2 to state "FDA responded that the tests need to be two-sided, but the one-sided study-wise type 1 error rate should be controlled at 0.025.

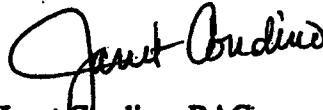
Please refer to the enclosed, revised meeting summary for these changes. This supersedes the meeting summary provided to you on September 23, 2005.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Biologic Oncology Products
5901-B Ammendale Road
Beltsville MD 20705-1266

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Janet Condino". The signature is fluid and cursive, with the first name "Janet" and last name "Condino" clearly distinguishable.

Janet Condino, RAC
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Meeting Summary



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

Memorandum

Date: **SEP 29 2005**
From: Janet Condino, OODP/DBOP, HFD 109
To: The file IND 11719
Subject: Type C Meeting Summary - Revised

Teleconference Date: Friday, August 26, 2005

Time: 3:00 - 4:00 pm

Location: WOC II 6FI-H

Meeting Requestor/Sponsor: B&H Consulting Services for Genmab A/S

Product: Human Monoclonal Antibody (HuMax-CD20) to CD20

Proposed Use: In combination with Fludarabine for treatment of patients with previously untreated CLL

Type of meeting: Type C, to discuss proposal for Fast Track

Meeting Purpose: The primary meeting purpose is to discuss the acceptability and feasibility of the proposed trial intended to support accelerated approval: monotherapy with HuMax-CD20 in patients with CLL who are refractory to fludarabine or cladribine. The secondary meeting purpose is to discuss briefly the acceptability and feasibility of the design of the proposed confirmatory trial: combination therapy with HuMax-CD20 + fludarabine vs. fludarabine monotherapy, in previously untreated patients with CLL.

FDA provided draft responses by facsimile transmission on August 25, 2005, to the questions submitted in the meeting package by Genmab, A/S.

An introductory statement containing the timing of projected submissions to FDA was presented by Hanne Jensen, Vice President of Regulatory Affairs, Genmab. A copy of this statement is attached to the meeting minutes as Appendix A.

Sponsor questions and FDA response:

1. *According to the Fast Track designation application approved on 10-Dec-2004, the*

pivotal trial proposed by Genmab is to investigate HuMax-CD20 as monotherapy in CLL patients who are refractory to fludarabine (2nd line therapy). In the confirmatory trial, HuMax-CD20 will be investigated in combination with fludarabine (1st line therapy). However according to the Fast Track approval letter dated 10-Dec-2004, Genmab is uncertain regarding the interpretation of paragraph two in the above mentioned letter, as it leaves some uncertainty as to whether Genmab and FDA are in agreement on the patient population for the pivotal trial:

From FDA correspondence 10-Dec-2004: We have reviewed your request and have concluded that it meets the criteria for the Fast Track designation. Therefore, we are designating as a Fast Track development program the investigation of HuMax-CD20 for use in combination with fludarabine for treatment of patients with previously untreated CLL to show an improvement in progression-free and overall survival as compared with fludarabine.

Does the FDA find the proposed monotherapy pivotal trial design in fludarabine/ cladribine refractory patients acceptable, in particular with regard to study population, for the development of HuMax-CD20 for CLL under the Fast Track designation?

FDA Faxed Response: The Fast Track development program for HuMax-CD20 in the treatment of CLL culminates with the trial intended to support regular approval. The proposed trial intended to support accelerated approval is an intermediate step in this development program and is considered to fall within the scope of the designation.

Discussion during the meeting: Genmab acknowledged the response and had no further questions on this issue.

2. *Does the FDA agree that the proposed monotherapy pivotal trial in fludarabine or cladribine refractory patients, followed by a post-approval confirmatory trial with combination therapy with HuMax-CD20+ fludarabine vs. fludarabine monotherapy in previously untreated patients with CLL, will fulfill the FDA requirements for filing a BLA for HuMax-CD20 for refractory CLL under the Fast Track designation? Please refer to the detailed synopsis for the pivotal trial in fludarabine or cladribine refractory patients and the synopsis for the post-BLA confirmatory trial enclosed in this information package.*

FDA Faxed Response: No. It is premature for GenMab to propose a trial intended to support accelerated approval for HuMax-CD20 for the treatment of CLL, pending identification of an active dose and preliminary characterization of activity and toxicity profile. Insufficient information has been provided in support of the proposed trial supporting accelerated approval. FDA strongly recommends the completion and analysis of the current Phase 1 study and as

well as the conduct of additional trials to investigate optimal dosing (including schedule) and to determine the scope of toxicity prior to proposing trials intended to support approval.

Discussion during the meeting: FDA reiterated their recommendation against combining a dose-finding study with a study to demonstrate clinical benefit in the same trial. They recommended that Genmab determine an optimal dose in a Phase 2 trial before commencing a trial designed to support accelerated or regular approval. Specifically, FDA is concerned with the fact that, based on the limited amount of data submitted to date, the two lower doses, given weekly for 4 weeks appear to be ineffective. There are no data in the premeeting package on the activity of any dose using the proposed 8-week schedule.

Genmab responded that additional data, including some on an expanded dosage schedule, exist from their phase 1 and phase 2 studies and will be available when their request for SPA is submitted (item 4, Appendix A). They also noted that the proposed study design is based on advice that was given during the December 6, 2004 meeting with FDA. FDA noted that the recommendation was given before the current data from the Phase 1 study were available.

Genmab asked if a phase 2, dose-finding study to determine minimum effective dose, conducted in a patient population for which no other treatment is available would be acceptable. FDA stated that the acceptability would depend on the design and goals of the study.

Agreement was not reached regarding the acceptability of Genmab's proposed trial to support accelerated approval.

Genmab requests that the Agency consider in particular the protocol-related questions below regarding the pivotal trial. For your convenience, these questions are demarcated within the text of the detailed synopsis for this trial.

Is the design of the pivotal trial acceptable to the Agency in terms of:

3. *Objectives, primary and secondary?*

FDA Faxed Response: No. A threshold response rate of 15% would not be sufficient to show that this product is likely to predict clinical benefit and provide an advantage over available therapy. The design of the trial supporting accelerated approval for alemtuzumab in a much more heavily pretreated group used a threshold response rate of 20% and the results of that trial demonstrated that alemtuzumab has a 33% response rate in patients who have failed fludarabine and an alkylating agent. A 15% response rate has been reported with rituximab as a single agent, and certainly in combination with other drugs.

Given these data, the proposed trial should be re-designed to demonstrate an effect in patients without available therapy or that is superior to available therapy.

In addition, the radiologic and clinical evidence of objective response rate with HuMax-CD-20 must be durable (duration at least 4-6 months) and associated with clear measures of clinical benefit including a reduction in transfusion requirements, infection rates and autoimmune hemolysis or thrombocytopenia, if present.

Discussion during meeting: In response to Genmab's proposed 20% threshold response rate as a surrogate for clinical benefit, FDA stated that acceptability of the 20% threshold would be dependent on the data and on the rationale provided to show that this provides a significant advance over available therapy and is likely to predict benefit.

4. *Endpoints, primary and secondary?*

FDA Response: Objective tumor response according to the NCIWG criteria over a 20 week period from start of treatment as assessed by an IRB may be an acceptable endpoint, depending on the specific objectives of the trial intended to support accelerated approval. FDA's response to question 3: above would also need to be satisfactorily addressed.

Discussion during the meeting: Genmab acknowledged FDA's response:

5. *Patient population, to be expanded to patients who are refractory to either fludarabine or cladribine? (Please see enclosed articles and abstracts)*

FDA Faxed Response: No. The Fast Track development program for HuMax-CD20 in the treatment of CLL seeks market approval in the United States and should demonstrate efficacy in populations whose prognosis and response to treatment is representative of patients with CLL treated in the United States. In the United States there is almost no use of cladribine as initial therapy for CLL and fludarabine has become the *de facto* standard of care. Therefore, demonstration of efficacy should be applicable to patients with CLL who are refractory to fludarabine. Although the response rates of fludarabine and cladribine are similar, it is not clear that cladribine-refractory and fludarabine-refractory patients are sufficiently similar in their responses and tolerability of subsequent therapy. Genmab should either restrict the study population to patients whose disease is refractory to fludarabine or provide evidence to support the assumption that patients with disease refractory to cladribine are sufficiently similar to patients with disease refractory to fludarabine, such that the results observed with HuMax-CD20 would be equally applicable to both populations.

Discussion during the meeting: Genmab acknowledged FDA's response and stated the proposed trial would not include cladribine refractory patients.

6. *Proposed doses and duration of treatment?*

FDA Faxed Response: No. There is not sufficient data to support the proposed dose, treatment schedule or length of therapy. Nonclinical toxicology studies, more detailed results of the Phase 1 study and pharmacokinetic and pharmacologic data supporting the proposed doses and schedule should be provided.

Discussion during the meeting: Genmab stated that this data will be submitted by the end of October (item 5, Appendix A)

7. *Is the definition of refractory* as proposed by Genmab in response to the FDA on 30-Nov-2004, acceptable to the agency in order to file for a BLA based on an interim analysis on objective response rate following 8 weekly doses?*

** refractory defined as progression of disease during treatment with fludarabine or within 12 months after cessation of previous treatment.*

FDA Faxed Response: No. The definition of refractory disease should be disease progression within 6 months of starting therapy.

Discussion during the meeting: Genmab requested clarification of the word "starting" and noted that in some cases the interval between starting therapy and disease progression under this definition would be quite short. Genmab stated the definition should be based on time from cessation of fludarabine therapy. Genmab stated that the definition of "refractory" as used for approval of alemtuzumab (Campath) included patients failing within 6 months of the last dose.

FDA indicated a willingness to consider the definition used for approval of alemtuzumab (Campath) in support Genmab's proposed definition.

8. *Inclusion and exclusion criteria?*

FDA Faxed Response: The appropriateness of inclusion and exclusion criteria would depend on the details of a specific trial proposed in the future.

With respect to the inclusion and exclusion criteria outlined in the proposed trial intended to support accelerated approval, the exclusion criteria indicate that patients with a previous autologous transplant more than 6 months prior to visit 1 are acceptable. Patients previously treated with autologous transplant should not be eligible.

Discussion during the meeting: Genmab acknowledged FDA's response.

9. *Statistical analyses?*

FDA Faxed Response: No. The statistical analysis plan is not acceptable. We have the following comments:

- a. The primary comparisons must maintain a one-sided study-wise type I error rate no greater than 0.025.

Discussion during the meeting: Genmab requested clarification of the use of a one-sided study-wise type I error rate no greater than 0.025 versus a two-sided study-wise type I error rate no greater than 0.05. FDA responded that the tests need to be two-sided, but the one-sided study-wise type I error rate should be controlled at 0.025.

- b. Please clarify the meaning of the statement on page 6 of the study synopsis, "An interim analysis will be performed when the primary endpoint data are available."

Discussion during the meeting: Genmab clarified that all patients that have a confirmed tumor response by week 20 will have their tumor response followed for four months or until loss of response. Those patients that did not have a confirmed tumor response by week 20 will not be followed thereafter for tumor response. When all patients satisfy one or the other of the two conditions described above, an analysis will be performed on tumor response.

- c. Descriptive statistics should be provided for the secondary endpoints.

Discussion during the meeting: Genmab stated that these will be provided.

Additional FDA Faxed Comments

Based on the information provided in the meeting submission, and our understanding of the current status of your drug development, we suggest that you carefully consider our comments regarding CMC, preclinical, clinical and statistical issues provided below.

CMC issues:

10. Before Genmab initiates a trial intended to support accelerated approval, the FDA will need to evaluate the CMC plans and associated protocols to ensure that the product utilized in these studies is adequately characterized for use in a trial intended to support a planned marketing application. As no CMC data were provided in the meeting package, FDA cannot make a meaningful assessment

as to the readiness of the product for a trial intended to support accelerated approval. FDA recommends that Genmab schedule a meeting or teleconference to discuss the CMC development plans for HuMax-CD20.

Discussion during the meeting: Genmab stated that complete CMC information will be submitted to this IND at the end of November (item 1, Appendix A)

11. No information regarding the immunogenicity of this agent is included in the meeting package. A validated assay (or assays) for the detection of immune responses to HuMax-CD20 must be in place prior to analysis of samples from a trial intended to support market approval

Discussion during the meeting: FDA also recommended that an assay to detect neutralizing antibodies should be developed, validated and in-place prior to analysis of samples from a trial intended to support market approval

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Discussion during the trial: Genmab acknowledged FDA's comment.

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FDA Attendees:

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Patricia Dimndorf, Clinical Reviewer
Patricia Keegan, Division Director
Melanie Hartsough, Toxicology Reviewer
Karen Jones, Chief, Project Management Staff
Mark Rothmann, Statistical Reviewer
Janet Condino, Regulatory Project Manager

Sponsor Attendees:

Agneta Svedberg, Vice President, Clinical Development
Jorgen Petersen, Senior Medical Director
Claus Moller, Executive Vice President, C.O.O.
Nedjad Losic, Senior Statistician
Mimi Folden Flensburg, International Clinical Project Leader
Joris Wilms, Clinical Trial Manager
Hanne Damgaard Jensen, Vice President, Regulatory Affairs
Thomas Oettinger, Associate Director, Project Manager,
Marguerite Coleman, US Agent, Project Director, B&H Consulting Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

SEP 23 2005

Our Reference: BB-IND 11719

Genmab A/S
Attention: Marguerite Coleman
B & H Consulting Services, Inc.
55 North Gaston Avenue
Somerville, N.J. 08876

Dear Ms Coleman:

Please refer to your Investigational New Drug Application (IND) for "Human Monoclonal Antibody (HuMax-CD20, 2F2) to CD20" and the telephone conversation held on August 26, 2005, between Genmab A/S, and this agency. A copy of our memorandum of that telephone conversation/meeting is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Biologic Oncology Products
5901-B Ammendale Road
Beltsville MD 20705-1266

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,

Janet L. Condino, RAC
Regulatory Project Manager
Office of Oncology Drug Products
Division of Biologic Oncology Drug Products
Center for Drug Evaluation and Research



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

Memorandum

Date: **SEP 23 2005**
From: Janet Condino, OODP/DBOP, HFD 109
To: The file IND 11719
Subject: Type C Meeting Summary

Teleconference Date: Friday, August 26, 2005

Time: 3:00 - 4:00 pm

Location: WOC II 6F1-H

Meeting Requestor/Sponsor: B&H Consulting Services for Genmab A/S

Product: Human Monoclonal Antibody (HuMax-CD20) to CD20

Proposed Use: In combination with Fludarabine for treatment of patients with previously untreated CLL

Type of meeting: Type C, to discuss proposal for Fast Track

Meeting Purpose: The primary meeting purpose is to discuss the acceptability and feasibility of the proposed trial intended to support accelerated approval: monotherapy with HuMax-CD20 in patients with CLL who are refractory to fludarabine or cladribine. The secondary meeting purpose is to discuss briefly the acceptability and feasibility of the design of the proposed confirmatory trial: combination therapy with HuMax-CD20 + fludarabine vs. fludarabine monotherapy, in previously untreated patients with CLL.

FDA provided draft responses by facsimile transmission on August 25, 2005, to the questions submitted in the meeting package by Genmab, A/S.

An introductory statement containing the timing of projected submissions to FDA was presented by Hanne Jensen, Vice President of Regulatory Affairs, Genmab. A copy of this statement is attached to the meeting minutes as Appendix A.

Sponsor questions and FDA response:

1. *According to the Fast Track designation application approved on 10-Dec-2004, the*

pivotal trial proposed by Genmab is to investigate HuMax-CD20 as monotherapy in CLL patients who are refractory to fludarabine (2nd line therapy). In the confirmatory trial, HuMax-CD20 will be investigated in combination with fludarabine (1st line therapy). However according to the Fast Track approval letter dated 10-Dec-2004, Genmab is uncertain regarding the interpretation of paragraph two in the above mentioned letter, as it leaves some uncertainty as to whether Genmab and FDA are in agreement on the patient population for the pivotal trial:

From FDA correspondence 10-Dec-2004: We have reviewed your request and have concluded that it meets the criteria for the Fast Track designation. Therefore, we are designating as a Fast Track development program the investigation of HuMax-CD20 for use in combination with fludarabine for treatment of patients with previously untreated CLL to show an improvement in progression-free and overall survival as compared with fludarabine.

Does the FDA find the proposed monotherapy pivotal trial design in fludarabine/ cladribine refractory patients acceptable, in particular with regard to study population, for the development of HuMax-CD20 for CLL under the Fast Track designation?

FDA Faxed Response: The Fast Track development program for HuMax-CD20 in the treatment of CLL culminates with the trial intended to support regular approval. The proposed trial intended to support accelerated approval is an intermediate step in this development program and is considered to fall within the scope of the designation.

Discussion during the meeting: Genmab acknowledged the response and had no further questions on this issue.

2. *Does the FDA agree that the proposed monotherapy pivotal trial in fludarabine or cladribine refractory patients, followed by a post-approval confirmatory trial with combination therapy with HuMax-CD20+ fludarabine vs. fludarabine monotherapy in previously untreated patients with CLL, will fulfill the FDA requirements for filing a BLA for HuMax-CD20 for refractory CLL under the Fast Track designation? Please refer to the detailed synopsis for the pivotal trial in fludarabine or cladribine refractory patients and the synopsis for the post-BLA confirmatory trial enclosed in this information package.*

FDA Faxed Response: No. It is premature for GenMab to propose a trial intended to support accelerated approval for HuMax-CD20 for the treatment of CLL, pending identification of an active dose and preliminary characterization of activity and toxicity profile. Insufficient information has been provided in support of the proposed trial supporting accelerated approval. FDA strongly recommends the completion and analysis of the current Phase 1 study and as

well as the conduct of additional trials to investigate optimal dosing (including schedule) and to determine the scope of toxicity prior to proposing trials intended to support approval.

Discussion during the meeting: FDA reiterated their recommendation against combining a dose-finding study with a study to demonstrate clinical benefit in the same trial. They recommended that Genmab determine an optimal dose in a Phase 2 trial before commencing a trial designed to support accelerated or regular approval. Specifically, FDA is concerned with the fact that, based on the limited amount of data submitted to date, the two lower doses, given weekly for 4 weeks appear to be ineffective. There are no data in the premeeting package on the activity of any dose using the proposed 8-week schedule.

Genmab responded that additional data, including some on an expanded dosage schedule, exist from their phase 1 and phase 2 studies and will be available when their request for SPA is submitted (item 4, Appendix A). They also noted that the proposed study design is based on advice that was given during the December 6, 2004 meeting with FDA. FDA noted that the recommendation was given before the current data from the Phase 1 study were available.

Genmab asked if a phase 2, dose-finding study to determine minimum effective dose, conducted in a patient population for which no other treatment is available would be acceptable. FDA stated that the acceptability would depend on the design and goals of the study.

Agreement was not reached regarding the acceptability of Genmab's proposed trial to support accelerated approval.

Genmab requests that the Agency consider in particular the protocol-related questions below regarding the pivotal trial. For your convenience, these questions are demarcated within the text of the detailed synopsis for this trial.

Is the design of the pivotal trial acceptable to the Agency in terms of:

3. *Objectives, primary and secondary?*

FDA Faxed Response: No. A threshold response rate of 15% would not be sufficient to show that this product is likely to predict clinical benefit and provide an advantage over available therapy. The design of the trial supporting accelerated approval for alemtuzumab in a much more heavily pretreated group used a threshold response rate of 20% and the results of that trial demonstrated that alemtuzumab has a 33% response rate in patients who have failed fludarabine and an alkylating agent. A 15% response rate has been reported with rituximab as a single agent, and certainly in combination with other drugs.

Given these data, the proposed trial should be re-designed to demonstrate an effect in patients without available therapy or that is superior to available therapy.

In addition, the radiologic and clinical evidence of objective response rate with HuMax-CD-20 must be durable (duration at least 4-6 months) and associated with clear measures of clinical benefit including a reduction in transfusion requirements, infection rates and autoimmune hemolysis or thrombocytopenia, if present.

Discussion during meeting: In response to Genmab's proposed 20% threshold response rate as a surrogate for clinical benefit, FDA stated that acceptability of the 20% threshold would be dependent on the data and on the rationale provided to show that this provides a significant advance over available therapy and is likely to predict benefit.

4. *Endpoints, primary and secondary?*

FDA Response: Objective tumor response according to the NCIWG criteria over a 20 week period from start of treatment as assessed by an IRB may be an acceptable endpoint, depending on the specific objectives of the trial intended to support accelerated approval. FDA's response to question 3. above would also need to be satisfactorily addressed.

Discussion during the meeting: Genmab acknowledged FDA's response.

5. *Patient population, to be expanded to patients who are refractory to either fludarabine or cladribine? (Please see enclosed articles and abstracts)*

FDA Faxed Response: No. The Fast Track development program for HuMax-CD20 in the treatment of CLL seeks market approval in the United States and should demonstrate efficacy in populations whose prognosis and response to treatment is representative of patients with CLL treated in the United States. In the United States there is almost no use of cladribine as initial therapy for CLL and fludarabine has become the *de facto* standard of care. Therefore, demonstration of efficacy should be applicable to patients with CLL who are refractory to fludarabine. Although the response rates of fludarabine and cladribine are similar; it is not clear that cladribine-refractory and fludarabine-refractory patients are sufficiently similar in their responses and tolerability of subsequent therapy. Genmab should either restrict the study population to patients whose disease is refractory to fludarabine or provide evidence to support the assumption that patients with disease refractory to cladribine are sufficiently similar to patients with disease refractory to fludarabine, such that the results observed with HuMax-CD20 would be equally applicable to both populations.

Discussion during the meeting: Genmab acknowledged FDA's response and stated the proposed trial would not include cladribine refractory patients.

6. *Proposed doses and duration of treatment?*

FDA Faxed Response: No. There is not sufficient data to support the proposed dose, treatment schedule or length of therapy. Nonclinical toxicology studies, more detailed results of the Phase 1 study and pharmacokinetic and pharmacologic data supporting the proposed doses and schedule should be provided.

Discussion during the meeting: Genmab stated that this data will be submitted by the end of October (item 5, Appendix A)

7. *Is the definition of refractory* as proposed by Genmab in response to the FDA on 30-Nov-2004, acceptable to the agency in order to file for a BLA based on an interim analysis on objective response rate following 8 weekly doses?*

** refractory defined as progression of disease during treatment with fludarabine or within 12 months after cessation of previous treatment.*

FDA Faxed Response: No. The definition of refractory disease should be disease progression within 6 months of starting therapy.

Discussion during the meeting: Genmab requested clarification of the word "starting" and noted that in some cases the interval between starting therapy and disease progression under this definition would be quite short. Genmab stated the definition should be based on time from cessation of fludarabine therapy. Genmab stated that the definition of "refractory" as used for approval of alemtuzumab (Campath) included patients failing within 6 months of the last dose.

FDA indicated a willingness to consider the definition used for approval of alemtuzumab (Campath) in support Genmab's proposed definition.

8. *Inclusion and exclusion criteria?*

FDA Faxed Response: The appropriateness of inclusion and exclusion criteria would depend on the details of a specific trial proposed in the future.

With respect to the inclusion and exclusion criteria outlined in the proposed trial intended to support accelerated approval, the exclusion criteria indicate that patients with a previous autologous transplant more than 6 months prior to visit 1 are acceptable. Patients previously treated with autologous transplant should not be eligible.

Discussion during the meeting: Genmab acknowledged FDA's response.

9. *Statistical analyses?*

FDA Faxed Response: No. The statistical analysis plan is not acceptable. We have the following comments:

- a. The primary comparisons must maintain a one-sided study-wise type I error rate no greater than 0.025.

Discussion during the meeting: Genmab requested clarification of the use of a one-sided study-wise type 1 error rate no greater than 0.025 versus a two-sided study-wise type 1 error rate no greater than 0.05. FDA responded that the test need to be two-sided, but the type 1 error rate should be controlled study-wise at 0.025.

- b. Please clarify the meaning of the statement on page 6 of the study synopsis, "An interim analysis will be performed when the primary endpoint data are available."

Discussion during the meeting: Genmab clarified that all patients that have a confirmed tumor response by week 20 will have their tumor response followed for four months or until loss of response. Those patients that did not have a confirmed tumor response by week 20 will not be followed thereafter for tumor response. When all patients satisfy one or the other of the two conditions described above, an analysis will be performed on tumor response.

- c. Descriptive statistics should be provided for the secondary endpoints.

Discussion during the meeting: Genmab stated that these will be provided.

Additional FDA Faxed Comments

Based on the information provided in the meeting submission, and our understanding of the current status of your drug development, we suggest that you carefully consider our comments regarding CMC, preclinical, clinical and statistical issues provided below.

CMC issues:

10. Before Genmab initiates a trial intended to support accelerated approval, the FDA will need to evaluate the CMC plans and associated protocols to ensure that the product utilized in these studies is adequately characterized for use in a trial intended to support a planned marketing application. As no CMC data were provided in the meeting package, FDA cannot make a meaningful assessment

as to the readiness of the product for a trial intended to support accelerated approval. FDA recommends that Genmab schedule a meeting or teleconference to discuss the CMC development plans for HuMax-CD20.

Discussion during the meeting: Genmab stated that complete CMC information will be submitted to this IND at the end of November (item 1, Appendix A)

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Jorgen Petersen, Senior Medical Director
Claus Moller, Executive Vice President, C.O.O.
Nedjad Losic, Senior Statistician
Mimi Folden Flensburg, International Clinical Project Leader
Joris Wilms, Clinical Trial Manager
Hanne Damgaard Jensen, Vice President, Regulatory Affairs
Thomas Oettinger, Associate Director, Project Manager,
Marguerite Coleman, US Agent, Project Director, B&H Consulting Services