CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125388Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

NDA/BLA#: 125388/0 | Supplement Number: N/A | NDA Supplement Type (e.g. SE5): N/A

Division Name: | PDUFA Goal Date: | Stamp Date: 2/25/2011

Division of Hematology Products | August 30, 2011

Proprietary Name: N/A

Established/Generic Name: Brentuximab Vedotin

Dosage Form: Injection

Applicant/Sponsor: Seattle Genetics

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: Treatment of patients with relapsed or refractory Hodgkin lymphoma

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.)

ection 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):

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

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

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

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

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

Not feasible:

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

Not meaningful therapeutic benefit:

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

pediatric patients in this/these pediatric subpopulation(s).

- Ineffective or unsafe:
  - ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling*)
  - ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
  - ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Δ Formulation failed:
  - ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

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

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

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

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

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

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

* Other Reason: _____

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

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

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

Pediatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __mo.	__ wk. __mo.	Yes ☐	No ☐
☐	Other	__yr. __mo.	__yr. __mo.	Yes ☐	No ☐
☐	Other	__yr. __mo.	__yr. __mo.	Yes ☐	No ☐
☐	Other	__yr. __mo.	__yr. __mo.	Yes ☐	No ☐
☐	Other	__yr. __mo.	__yr. __mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

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

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

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __mo.	__ wk. __mo.
☐	Other	__yr. __mo.	__yr. __mo.
☐	Other	__yr. __mo.	__yr. __mo.
☐	Other	__yr. __mo.	__yr. __mo.
☐	Other	__yr. __mo.	__yr. __mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

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

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

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

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

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

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

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

This page was completed by:

{See appended electronic signature page} 8/8/11

Regulatory Project Manager

(Revised: 6/2008)

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

1.3.3 DEBARMENT CERTIFICATION

On behalf of Seattle Genetics, Inc. ("Seattle Genetics"), I hereby certify that Seattle Genetics 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.

Kirk Schumacher
Vice President
Legal Affairs and Compliance and General Counsel
Seattle Genetics, Inc.

February 16, 2011
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # N/A BLA # 125388/0	NDA Supplement # N/A BLA STN # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Adcetris Established/Proper Name: Brentuximab Vedotin Dosage Form: Injection		Applicant: Seattle Genetics, Inc. Agent for Applicant (if applicable): N/A
RPM: Lara Akinsanya		Division: Division of Hematology Products

NDAs:
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 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

N/A

Provide a brief explanation of how this product is different from the listed drug.

N/A

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ 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.

❖ Actions	
• Proposed action • User Fee Goal Date is August 30, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☒ Received

[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): N/A

☒ 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

BLAs: Subpart E
☒ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☒ Yes, dates August 9, 2011
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☒ Yes ☐ No
Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• 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 BURST

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. 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
• NDAs 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 # N/A 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 # N/A 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 # N/A 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 # N/A 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 # N/A 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). *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*).* *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.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	August 19, 2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) August 19, 2011
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	August 16, 2011
• Original applicant-proposed labeling	February 28, 2011
• Example of class labeling, if applicable	N/A

[3] Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of 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 draft labeling	
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 June 8, 2011 June 8, 2011
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM April 5, 2011 ☒ DMEPA July 29, 2011, August 17, 2011 ☐ DRISK N/A ☒ DDMAC August 17, 2011 ☐ CSS N/A ☐ Other reviews PM (OBP) - August 18, 2011; PMHT-July 13, 2011; QT-IRT - June 8, 2011

Administrative / Regulatory Documents

❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	03/30/2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs 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 is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan Designation • Pediatric Page/Record *(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

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

❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	August 12, 2011; August 10, 2011; August 10, 2011; August 5, 2011; August 2, 2011; August 2, 2011, July 29, 2011; July 29, 2011; July 13, 2011; July 8, 2011; July 1, 2011; June 30, 2011; June 28, 2011; June 28, 2011; June 27, 2011; June 27, 2011; June 24, 2011; June 23, 2011; June 22, 2011; June 20, 2011; June 15, 2011; June 14, 2011; June 1, 2011; May 23, 2011; May 17, 2011; May 13, 2011; May 13, 2011; May 12, 2011; May 6, 2011; May 4, 2011; April 29, 2011; April 19, 2011; April 8, 2011; March 18, 2011; March 17, 2011; March 14, 2011; March 2, 2011
❖ Internal memoranda, telecons, etc.	August 15, 2011; August 5, 2011; July 29, 2011; July 26, 2011
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg December 7, 2010; November 18, 2010; August 12, 2010
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Label Negotiation - August 15, 2011; Post ODAC - July 21, 2011; CMC - January 19, 2010; SPA - October 1, 2009; Non-Clinical - March 27, 2009; EOP1 - July 24, 2008
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	July 14, 2011
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None August 19, 2011
Division Director Summary Review *(indicate date for each review)*	☐ None August 18, 2011
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None August 8, 2011
PMR/PMC Development Templates *(indicate total number)*	☐ None 10
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	August 1, 2011
• Clinical review(s) *(indicate date for each review)*	August 1, 2011

[5] Filing reviews should be filed with the discipline reviews.

• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	see clinical review page 16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested July 25, 2011
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None July 28, 2011
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None July 28, 2011
Statistical Review(s) *(indicate date for each review)*	☐ None July 28, 2011
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 August 3, 2011
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None August 3, 2011
❖ 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 August 8, 2011
• Supervisory Review(s) *(indicate date for each review)*	☐ None August 5, 2011
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None August 5, 2011
❖ 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 August 16, 2011; August 5, 2011
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None August 5, 2011; August 1, 2011
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None August 2, 2011; August 1, 2011
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☒ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed August 8, 2011; August 5, 2011
❖ 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)*	August 3, 2011
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: August 19, 2011 ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125388 and 125399

MEETING MINUTES

Seattle Genetics, Inc.
Attention: Elaine Waller
Senior Vice President, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Waller:

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

We also refer to the teleconference between representatives of your firm and the FDA on August 15, 2011. The purpose of the meeting was to discuss pending PDA proposed changes to the package insert for brentuximab vedotin.

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

If you have any questions, call Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC,
Clinical Team Leader
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Category:	**BLA**
Meeting Date and Time:	August 15, 2011; 1:30 PM to 2:00 PM (EST)
Meeting Location:	Teleconference
Application Number:	125388/125399
Product Name:	brentuximab vedotin
Indication:	for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates and the treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.
Applicant Name:	Seattle Genetics, Inc.
Meeting Chair:	Virginia Kwitkowski
Meeting Recorder:	Lara Akinsanya

FDA PARTICIPANTS

Office of Oncology Drug Products (OODP)
Richard Pazdur, M.D., Office Director

Division of Hematology Products (DHP)
Ann T. Farrell, M.D., Acting Division Director
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Acting Clinical Team Leader
Karen McGinn, M.S.N., C.R.N.P., Senior Clinical Analyst
R. Angelo de Claro, MD, Medical Officer
Haleh Saber, Ph.D., Supervisory Pharmacologist
Lara Akinsanya, M.S., Regulatory Health Project Manager

Study Endpoints and Labeling Division (SEALD)
Laurie Burke, R.Ph., M.P.H.

SPONSOR PARTICIPANTS

Seattle Genetics, Inc

Lynn Courtney, MS, Associate Director, Regulatory Affairs
Bruce Hart, PhD, Senior Director, Regulatory Affairs
Naomi Hunder, MD, Medical Director
Tom Reynolds, MD, PhD, Chief Medical Officer
Elaine Waller, PharmD, Senior Vice President, Regulatory Affairs

1.0 BACKGROUND

Seattle Genetics, Inc. is developing brentuximab vedotin for the treatment of relapsed or refractory Hodgkins lymphoma (HL) and relapsed or refractory systemic anaplastic large cell lymphoma. On August 14, 2011 the FDA contacted Seattle Genetics, Inc. to request a teleconference to discuss the resolution of pending FDA proposed comments/changes to the draft package insert (PI).

2. DISCUSSION

The meeting began with the Agency asking the Applicant for the status of their response to the outstanding 483s issued to the drug manufacturing sites. The Sponsor indicated they are fully aware of the outstanding 483 issues and committed to responding to them by August 15, 2011.

The FDA discussed with the Applicant, all the outstanding comments and changes to the FDA proposed PI dated August 15, 2011.

After discussions, the Applicant and FDA agreed on all of the changes that were proposed in the revised PI.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues identified which required further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Revised PI per discussions at the meeting will be forwarded to Applicant for review	FDA	August 15, 2011
Provide update regarding the status of Applicant's response to the outstanding 483s issued to the manufacturing sites	Applicant	August 15, 2011

6.0 ATTACHMENTS AND HANDOUTS

The attached draft PI dated August 15, 2011 was discussed at the meeting.

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

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, August 12, 2011 12:46 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request: Clinical/ STN 125388 - regarding PMR frontline HL trial

Dear Lynn,

Please respond with any proposed changes to your PMR trial description.

We note that you are proposing double-blind, placebo-controlled trials for the Hodgkin lymphoma front-line confirmatory trial. Given the pulmonary monitoring requirements for bleomycin, be aware that both arms will need to undergo the same monitoring and evaluation procedures in order to maintain the blind.

Alternatively, you could remove the placebo control, but lose the patient reported outcomes data. Patient reported outcomes are not evaluable in open label trials for regulatory purposes.

Please respond **as soon as possible.**

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125388 and 125399

MEETING MINUTES

August 11, 2011

Seattle Genetics, Inc.
Attention: Elaine Waller
Senior Vice President, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Waller:

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

We also refer to the teleconference between representatives of your firm and the FDA on August 5, 2011. The purpose of the meeting was to discuss CMC issues discovered during review.

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

If you have any questions, call me at (301) 796-2017.

Sincerely,

Joel Welch, Ph.D.
Regulatory Health Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Category:	BLA
Meeting Date and Time:	August 8, 2011; 1:30 PM to 2:30 PM (EST)
Meeting Location:	Teleconference
BLA Number:	125388/125399
Product Name:	brentuximab vedotin
Received Briefing Package:	Not Applicable
Sponsor Name:	Seattle Genetics
Meeting Requestor:	Not Applicable
Meeting Chair:	Marjorie Shapiro
Meeting Recorder:	Joel Welch

FDA ATTENDEES
Office of Pharmaceutical Science
Office of Biotechnology Products
Division of Monoclonal Antibodies

Marjorie Shapiro, PhD	Laboratory Chief MS 9-9-11
Joel Welch, PhD	CMC Regulatory Project Manager

SPONSOR ATTENDEES

Vaughn Himes	Executive VP, Technical Operations
Chuck Foerder	Director, Bioanalytical Development
Nathan Ihle	Executive Director, Process Chemistry
Chuck Smith	Executive Director, Quality Assurance
Bruce Hart	Senior Director, Regulatory Affairs
Robert Mills	Associate Director, Regulatory Affairs

1.0 BACKGROUND

Seattle Genetics, Inc. is developing brentuximab vedotin for the treatment of relapsed or refractory Hodgkins lymphoma (HL) and relapsed or refractory systemic anaplastic large cell lymphoma. On August 5, 2011, the FDA contacted Seattle Genetics, Inc. to request a teleconference to discuss CMC issues encountered during review.

2.0 DISCUSSION

The purpose of the discussion was to discuss the timeframe of post-marketing commitments already communicated to the Sponsor. Three commitments were discussed:

1) Harmonization of the BLA with the drug master file
2) Revision of the intermediate, drug product, and drug substance specifications
3). Discussion of an immunogenicity study evaluating interference of sCD30

For PMC 1 an agreement was previously reached between the Agency and the Sponsor to harmonize the documents within 3 months of the action date. The Sponsor agreed to provide a specific date to the Agency for this commitment.

Regarding PMC 2, the Sponsor had previously agreed to revise the specifications after additional manufacturing data is obtained. The Sponsor committed to revising the specifications after ≥25 lots of antibody and ≥10 lots of drug had been manufactured. The Sponsor inquired if the PMC would reflect a date to revise the specifications, or if it instead reflects the number of lots to be manufactured. The Agency stated that an actual date is required, and would be willing to consider a date that is a year and quarter in lieu of a year and a month to provide extra flexibility given potential difficulty in forecasting a manufacturing schedule.

With respect to PMC 3, the Agency had not previously communicated to the Sponsor of the need to perform a study evaluating the interference of soluble CD30 on the formation of Anti-Product Antibodies. The Agency noted that the sensitivity of their immunogenicity assay is good, relative to assays for other monoclonal antibody products. The Sponsor agreed to consider how long it will take to complete the study and provide a time frame or date for completion of the study to the Agency.

For each PMC, the Sponsor agreed to provide the required date by email to regulatory project manager, Lara Akinsaya during the week of August 15.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues identified which required further discussion.

4.0 ACTION ITEMS

There were no outstanding action items.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts.

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, August 10, 2011 10:38 AM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: BLAs 125388 and 125399_ FDA Revised PI -Revisions DUE Aug 12
Attachments: adcetris_USPI_FDA proposed_Aug09_2011.doc; Explanations for Prescribing Information Changes_FDA Responses.doc

Dear Lynn,

Please see attached revised draft of the FDA proposed PI for BLAs 125388 and 125399. Also attached is the FDA's responses to your specific questions and comments.

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

· Accept any changes that you agree with

· Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed

After you have made the changes, please send me the revised tracked change before you make your official submission via the gateway.

Please provide a revised PI to me by Friday, **August 12, 2011.**

Thank You.
Lara

From: Lynn Courtney [mailto:lcourtney@seagen.com]
Sent: Friday, August 05, 2011 7:09 PM
To: Akinsanya, Lara
Subject: RE: BLAs 125388 and 125399_ FDA Proposed PI -Revisions DUE Aug 5 - Request for teleconference

Dear Lara,

Thank you for your patience in allowing extra time for us to prepare our response. Our revised label with specific comments and questions is attached. Also note that we have prepared a separate document outlining specific issues and questions for FDA. Seattle Genetics welcomes a teleconference with FDA early next week to discuss any of the proposed changes.

Regards,
Lynn

From: Akinsanya, Lara [mailto:Lara.Akinsanya@fda.hhs.gov]
Sent: Wednesday, August 03, 2011 10:26 AM
To: Lynn Courtney
Subject: RE: BLAs 125388 and 125399_ FDA Proposed PI -Revisions DUE Aug 5 - Request for teleconference

Akinsanya, Lara

.om: Akinsanya, Lara
Sent: Wednesday, August 10, 2011 10:15 AM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: STN 125388 & 125399 : PMCs and PMRs

Attachments: ADCETRIS PMRs and PMCs 080911.doc

Dear Lynn,

Attached is the final list of all the FDA's post-marketing requirements (PMRs) and post-marketing commitments (PMCs) for brentuximab vedotin.

ADCETRIS PMRs
and PMCs 080911...

Please note that successful completion of post-marketing requirement trials 1, 2, OR 3 could be considered to convert your accelerated approval to regular approval pending review of the submission of the safety results (with clinical study report) of AETHERA (see PMR #4). **Please notify us of which trial (# 1, 2 or 3) you select as your confirmatory trial.**

.ease provide an official response with your choice regarding your confirmatory trial and provide your timetable for PMR #5. Please respond by **noon tomorrow, August 11, 2011.**

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Brentuximab vedotin (Adcetris ™) Post-Marketing Requirements and Commitments

Background: Under Subpart E, approval may be based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity ("Surrogate") [21 CFR 601.41]. The development plan for brentuximab vedotin included single-arm, Phase 2 trials with Objective Response Rate as the primary endpoint. The single-arm design of these small trials did not permit an adequate assessment of the risk benefit ratio.

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefits or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Post marketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

Although an approval of a CD30 companion in-vitro diagnostic test for the current indications is not required at this time, subsequent development of this drug in the proposed trials (see PMR # 1, 2 and 3) and development in other tumor types will require development of a CD30 companion *in vitro* diagnostic test. Consult with CDRH to facilitate your development.

The following post-marketing trials are being requested to verify and describe the clinical benefit of brentuximab vedotin. The use of one of these trials to convert to regular approval would be contingent upon the demonstration of a favorable risk benefit evaluation resulting in a supplemental BLA approval.

Successful completion of post-marketing requirement trials 1, 2, OR 3 could be considered to convert your accelerated approval to regular approval pending review of the submission of the safety results (with clinical study report) of AETHERA (see PMR #4). **Please notify us of which trial (# 1, 2 or 3) you select as your confirmatory trial.**

Post-Marketing Requirements

1. PMR BLA 125388 for Hodgkin Lymphoma under accelerated approval

Randomized Phase 3 Trial of Brentuximab Vedotin (SGN-35) in Patients with Hodgkin Lymphoma who are at high risk of relapse but are in complete remission at day 60 after autologous stem cell transplantation. Patients at high risk of relapse and who are in Complete Remission (CR) at Day 60 evaluation following ASCT will be randomized to receive treatment with brentuximab vedotin or placebo for up to 16 cycles.

The primary endpoint of the trial will be PFS determined by an independent blinded review facility. Trial size to be proposed by Sponsor.

Schedule Milestones:

Phase 3 Trial Protocol Submitted:	12/31/2012
Phase 3 Trial Completed:	06/30/2018
Final Phase 3 Clinical Study Report Submitted:	06/30/2019

2. PMR BLA 125388 for Hodgkin Lymphoma under accelerated approval

A randomized phase 3 trial of SGN-35 (brentuximab vedotin) in combination with AVD versus ABVD as frontline therapy in patients with advanced Hodgkin Lymphoma. Enrollment of approximately 880 patients is planned with a primary endpoint of progression free survival determined by an independent blinded review facility. Overall survival is a key secondary endpoint.

Schedule Milestones:

Final Protocol Submission:	9/30/2012
Study/Trial Completion:	6/30/2018
Final Report Submission:	6/30/2019

3. PMR BLA 125399 for Anaplastic Large Cell Lymphoma under accelerated approval

A randomized phase 3, double-blind, placebo-controlled trial of SGN-35 (brentuximab vedotin) in combination with CH-P versus CHOP as frontline therapy in patients with CD30-positive mature T- and NK-cell lymphomas and systemic ALCL (sALCL). Enrollment of approximately 300 patients is planned with a primary endpoint of progression free survival as determined by an independent blinded review facility. Overall survival is a key secondary endpoint.

Schedule Milestones:

Final Protocol Submission:	12/31/2012
Study/Trial Completion:	6/30/2018
Final Report Submission:	6/30/2019

4. PMR BLA 125388 for Hodgkin Lymphoma under accelerated approval

In order to provide additional safety data, the results of the randomized, placebo-controlled trial (AETHERA) will assist the Agency in clarifying the safety profile of brentuximab vedotin. Due to trial design limitations, the trial results will not support a new clinical indication with the current design.

AETHERA Trial: SGN035-005
Title: A Phase 3 Study of Brentuximab Vedotin (SGN-35) in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant (The AETHERA Trial)

Description: A randomized, double-blind, placebo-controlled phase 3 study of SGN-35 (brentuximab vedotin) and best supportive case (BSC) versus placebo and BSC in the treatment of patients at high risk of residual Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT). Enrollment of 322 patients is planned with a primary endpoint of progression free survival determined by independent review facility.

Status: Ongoing

Timetable:
Phase 3 Trial Completion Date: 2013
Phase 3 Trial Final Report Submission Date: 2014

5. For Both BLA 125388 & 125399:

Reversibility/Resolution of drug-induced peripheral neuropathy

Sponsor to characterize the duration and reversibility of treatment emergent neuropathy in a prospective trial.

Timetable:
Final Protocol Submission Date:
Phase 3 Trial Completion Date:
Phase 3 Trial Final Report Submission Date:

POST-MARKETING COMMITMENTS *
Non-Clinical Trials

*These studies would not be required to convert to regular approval.

1. Perform additional experimental work to understand the impact of soluble CD30 in serum samples on the determination of anti-drug antibodies.

Final Report Submission Date: 09/30 2012

2. Provide summary data for validating all in-process product intermediate maximum hold times for the cAC10 manufacturing process at scale in a CBE0.

Final Report Submission Date: 12/31/2012

3. Perform the bacteriostasis/fungistasis testing for the bioburden test of the bulk drug substance using three batches of BDS samples stored under routine sample storage conditions at 2-8°C.

Summary Data in Annual Report: 12/31/2012

4. Commit to reassess brentuximab vedotin drug substance and drug product specifications based on the combination of Intermediate lots used to manufacture SGN-35 BDS and DP when the total number of BDS and DP lots include ≥25 lots cAC10 and ≥10 lots of SGD-1006 as input intermediates and, as part of your annual Product Quality Review for brentuximab vedotin.

Final Report Submission Date: 03/31/2016

5. Harmonize all CMC information contained in your application with that contained in DMF (b) (4).

Final Report Submission Date: 11/30/2011

6. Reevaluate the Limit of Detection (LOD) of methylene blue using standard curve with different concentrations of dye that include concentrations below the LOD. Results of the LOD determination will be appended to the method validation report and communicated to the FDA.

Final Report Submission Date: 12/31/2011

7. The CDRH guidance referenced for biological indicator (BI) incubation time has been superseded by the CDRH Guidance on BI Premarket Notification 510(k) Submissions. The guidance refers to BIs used to monitor sterilization processes in health care facilities. BIs intended for use in a manufacturing setting are excluded. The (b) (4) Test BIs used for (b) (4) validation studies should be (b) (4) to confirm that all BIs are negative. This change should be made to the (b) (4) validation protocols at (b) (4) and reported in the next annual report.

Final Report Submission Date: 12/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125388 and 125399

MEETING MINUTES

August 9, 2011

Seattle Genetics, Inc.
Attention: Elaine Waller
Senior Vice President, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Waller:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 29, 2011. The purpose of the meeting was to discuss CMC issues discovered during review.

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

If you have any questions, call me at (301) 796-2017.

Sincerely,

Joel Welch, Ph.D.
Regulatory Health Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Category:	BLA
Meeting Date and Time:	July 29, 2011; 1:30 PM to 2:30 PM (EST)
Meeting Location:	Teleconference
BLA Number:	125388/125399
Product Name:	brentuximab vedotin
Received Briefing Package:	Not Applicable
Sponsor Name:	Seattle Genetics
Meeting Requestor:	Not Applicable
Meeting Chair:	Marjorie Shapiro
Meeting Recorder:	Joel Welch

FDA ATTENDEES
Office of Pharmaceutical Science
Office of Biotechnology Products
Division of Monoclonal Antibodies

Marjorie Shapiro, PhD	Laboratory Chief MS 8/4/11
Joel Welch, PhD	CMC Regulatory Project Manager

SPONSOR ATTENDEES
Seattle Genetics, Inc.

Morris Rosenberg	Executive VP, Development
Shan Jiang	Director, Formulations
Nathan Ihle	Executive Director, Process Chemistry
Phil Tsai	Senior Director, Bioprocess Development
Chuck Smith	Executive Director, Quality Assurance
Oscar Salas-Solano	Director, Analytical Development
Kevin Anderson	Principal Scientist, Analytical Development
Bruce Hart	Senior Director, Regulatory Affairs
Robert Mills	Associate Director, Regulatory Affairs

Millennium Pharmaceuticals:

Karen Quinn	Associate Director, Regulatory Affairs-CMC
Csanad Varga	Associate Director, Sterile Formulations

1.0 BACKGROUND

Seattle Genetics, Inc. is developing brentuximab vedotin for the treatment of relapsed or refractory Hodgkins lymphoma (HL) and relapsed or refractory systemic anaplastic large cell lymphoma. On July 27, 2011, the FDA contacted Seattle Genetics, Inc. to request a teleconference to discuss CMC issues encountered during review.

2.0 DISCUSSION

Prior to the meeting, the Agency provided four topics for discussion to the Sponsor:

Topic 1.

A follow up to a discussion at the (b) (4) Inspection regarding how Seattle Genetics will report to the Agency when a new product is brought into the manufacturing suite.

Discussion During Meeting:

The Agency began by summarizing the background of the issue. The Agency stated that if the approved facility were manufacturing a single product, the second product added to the facility would typically require submission of a prior-approval supplement prior to beginning manufacture. However, as (b) (4) is already a multi-product facility, a CBE-0 would typically be filed for introduction of subsequent products. The Agency also noted that the exception to this policy is for the addition of "high risk" products, which would still require a PAS. As an example, a high risk product could include a new drug not previously manufactured at the site, or a different conjugation platform for a drug-antibody conjugate. The Agency also suggested that (b) (4) could submit a Drug Master File and in it include the risk assessments necessary upon introduction of new products to their facility. The Sponsor indicated they currently have procedures in place to be notified in case of the introduction of a new product in this manufacturing facility. The Agency suggested that the Sponsor could request a meeting if a PAS is required. The Sponsor accepted this feedback.

Topic 2.

Glass lamella formation.

Discussion During Meeting:

The Agency stated that the presence of glass lamella is an emerging issue for all biotechnology products. The Agency noted that the Sponsor currently uses a HIAC method for the evaluation of sub-visible particulates which might also be useful for the evaluation of lamella. The Agency noted that a large of body literature is available that summarizes the potential risk factors for the presence of glass lamella and that citrate buffer (used by the Sponsor) is one such risk factor. However, the Agency mentioned that other factors, including the pH of the formulation and the fact that the product is lyophilized decreases the risk. The Sponsor indicated they are aware of this potential issue, and agreed with the Agency regarding the risk factors as reported in literature. They noted they are already working on the issue. The Agency stated this issue does not necessarily rise to the level of a post-marketing commitment, and that a summary of the

work performed to date in an annual report would be sufficient. The Sponsor agreed with this feedback.

Topic 3.
Discussion of commitments to re-assess the release specifications for the intermediates, DS and DP.

Discussion During Meeting:
The Agency stated that it understands the Sponsor's position that they do not want to reassess specifications for intermediates, drug product, and drug substance until after the completion of additional batch manufacture to generate process understanding. The Agency said it would accept the current specifications with the understanding that a reassessment of each specification after a certain number of batches would become a post-marketing commitment.

Topic 4
FMEA analysis for product quality criticality assessment – the determination of high, mid or low criticality.

Discussion During Meeting:
The Agency began by noting that these BLAs were not intended as a Quality by Design submission. Nevertheless, the Agency wanted some discussion regarding the Sponsor's classification of the criticality of attributes. The Sponsor stated that an interdisciplinary team utilized a risk-ranking tool and assigned the potential risk to both safety and efficacy for each attribute (b) (4) . The result is a risk priority score which was grouped into low (<25), medium (25-49), or high (> 50). The Sponsor did not consider process controls or in-process capabilities in their assessment. The Sponsor noted that of the (b) (4) quality attributes it evaluated, that (b) (4) fell into either the "medium" or "high" classification. Moreover, they felt this large percentage of attributes reflects the conservative nature of their approach. The Agency stated it understood this approach and highlighted the decision to include "medium" risk as a sound one. No further action was indicated on this topic.

3.0 ISSUES REQUIRING FURTHER DISCUSSION
There were no issues identified which required further discussion.

4.0 ACTION ITEMS
There were no outstanding action items.

5.0 ATTACHMENTS AND HANDOUTS
There were no attachments or handouts.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125388 and 125399

MEETING MINUTES

August 9, 2011

Seattle Genetics, Inc.
Attention: Elaine Waller
Senior Vice President, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Waller:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 26, 2011. The purpose of the meeting was to discuss resolution of deficiencies in DMF (b) (4).

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

If you have any questions, call me at (301) 796-2017.

Sincerely,

Joel Welch, Ph.D.
Regulatory Health Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Category:	BLA
Meeting Date and Time:	July 26, 2011; 2:00 PM to 3:00 PM (EST)
Meeting Location:	Teleconference
BLA Number:	125388/125399
Product Name:	brentuximab vedotin
Received Briefing Package:	Not Applicable
Sponsor Name:	Seattle Genetics
Meeting Requestor:	Not Applicable
Meeting Chair:	Xiao-Hong Chen
Meeting Recorder:	Joel Welch

FDA ATTENDEES
Office of Pharmaceutical Science
Office of Biotechnology Products
Division of Monoclonal Antibodies

Kathleen Clouse, PhD	Division Director
Marjorie Shapiro, PhD	Laboratory Chief
Joel Welch, PhD	CMC Regulatory Project Manager

Office of Pharmaceutical Science
Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I

Xiao-Hong Chen, PhD	Quality Reviewer
Richard Lostritto, PhD	Division Director
Sarah Pope Miksinski, PhD	Branch Chief Sarah Pope Miksinski 8/9/11

SPONSOR ATTENDEES
Seattle Genetics, Inc.

Nathan Ihle	Executive Director Process Chemistry,
Morris Rosenberg	Executive VP Development
Wendel Doubleday	Director Process Chemistry
Robert Mills, Associate	Director Regulatory Affairs

Millennium Pharmaceuticals:

Karen Quinn	Associate Director, Regulatory Affairs-CMC
Csanad Varga	Associate Director, Sterile Formulations

1.0 BACKGROUND

Seattle Genetics, Inc. is developing brentuximab vedotin for the treatment of relapsed or refractory Hodgkins lymphoma (HL) and relapsed or refractory systemic anaplastic large cell lymphoma. On July 25, 2011, the FDA contacted Seattle Genetics, Inc. to request a teleconference to discuss the resolution of deficiencies in DMF (b) (4).

2.0 DISCUSSION

The meeting began with the Agency asking for clarification of Sponsor's understanding of the nature of the deficiencies that had been communicated for DMF (b) (4). The Sponsor indicated they are fully aware of each issue and committed to resolving them. The Agency stated it preferred all issues be addressed prior to taking an action on the application. The Sponsor stated they wished to discuss the issue further with the DMF holder but indicated they had some ability to expedite changes that are necessary. The Agency inquired if the changes needed were only administrative / editorial or if additional experimental work was required. The Sponsor stated while much of the work is administrative reconciliation of the DMF with the BLA, some experimental work was necessary as one deficiency required additional characterization data to be submitted. This data still needs to be generated.

The FDA noted that the resolution of these issues would require either a post-marketing commitment or post-marketing requirement. The Agency noted that a PMC is preferable as a PMR applies traditionally to safety issues and contains far more regulatory oversight. The Sponsor indicated they understood this.

The Sponsor committed to harmonizing the BLA and DMF within three months of approval of the BLA. At that time, the Sponsor agreed to provide general correspondence to the BLA indicating the BLA and DMF are consistent, and to notify the participants in this teleconference. The sponsor also agreed to include a commitment in the BLA to submit additional characterization data as requested by the Agency within three months of action. The Sponsor clarified if the raw data was required in the BLA or if merely the data table could be updated with test methods and a reference to the updated DMF provided. The Agency agreed the latter approach was acceptable.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues identified which required further discussion.

4.0 ACTION ITEMS

There were no outstanding action items.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts.

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, August 05, 2011 6:56 PM
To: 'Lynn Courtney'
Subject: RE: URGENT Information Request : Clinical/BLAs 125388 and 125399 - SGEN response

Its ok. Thanks Lynn.

From: Lynn Courtney [mailto:lcourtney@seagen.com]
Sent: Friday, August 05, 2011 5:17 PM
To: Akinsanya, Lara
Subject: RE: URGENT Information Request : Clinical/BLAs 125388 and 125399 - SGEN response
Importance: High

Dear Lara,

Our apologies for running a few minutes late. The response to your request is below:

HL:

- 106 patient lymphoma specimens were submitted for CD30 screening
- All 106 were positive for CD30 expression by central review and 102 were enrolled on the pivotal trial

sALCL:

- 65 patient lymphoma specimens were submitted for CD30 screening
- 7 screen failures were CD30 positive
- 57 enrolled were CD30 positive
- 1 enrolled did not have an unstained slide available for CD30 testing

Bottom line: All samples evaluated for CD30 were positive for expression.

Regards,
Lynn

From: Akinsanya, Lara [mailto:Lara.Akinsanya@fda.hhs.gov]
Sent: Friday, August 05, 2011 11:59 AM
To: Lynn Courtney
Subject: URGENT Information Request : Clinical/BLAs 125388 and 125399

Dear Lynn,

Would you please provide me with this information by 5pm EST?

How many patients (both screened and enrolled) turned out to have CD30-negative test results after being diagnosed with HL or ALCL morphologically?

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, August 02, 2011 5:29 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: BLAs 125388 and 125399_ FDA Proposed PI -Revisions DUE Aug 5

Attachments: adcetris_USPI_FDA proposed_Aug02_2011.doc

Dear Lynn,

Please see attached revised draft of the FDA proposed PI for BLAs 125388 and 125399. Please review the changes/comments and do the following to the same draft:

adcetris_USPI_FDA proposed_Aug...

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed

er you have made the changes, please send me the revised tracked change before you make your official submission via the gateway.

Please provide a revised PI to me by Friday, **August 5, 2011**.

Thank you

Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, August 02, 2011 2:17 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: STN 125388 & 125399 : Additional FDA comments/Carton and Container Labels - DUE Aug 5

Dear Lynn,

1. Container
   a. Please indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60.
   b. Remove the storage conditions for the reconstituted solution and provide the storage temperature range and conditions for the vial to prevent confusion.
   c. Add the statement, "See Prescribing Information for dosage and dilution." to comply with 21 CFR 201.5 and 21 CFR 201.55.

2. Carton label
   a. Add the required statement, "No Preservative" to the side panel per 21 CFR 610.61(e) near the vial contents listing.
   b. Add the required statement, "No U.S. Standard of Potency" to panel per 21 CFR 610.61.
   c. Please add the statement, "Store vial at 2-8°C (36-46°F) in the original carton to protect from light." per 21 CFR 610.61(i).

3. Carton and Container
   a. Revise the manufacturer listing per the definition of manufacturer per 21 CFR 600.3(t) from (b) (4) to "Manufactured by: ..."

Please respond to the above information request before **Friday, August 5**, 2011, if possible.

Please let me know if you have any questions.

Thank You

Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

n: Akinsanya, Lara
Sent: Friday, July 29, 2011 2:14 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: STN 125388 & 125399 : FDA comments/Carton and Container Labels - DUE Aug 5

Dear Lynn,

Please respond to the following information request from the Division of Medication Error Prevention and Analysis:

A. *Container Label*

1. Increase the prominence of the proper name to at least ½ the size of the proprietary name taking into account typography, layout, contrast, and other printing features to ensure it has prominence commensurate with the proprietary name per 21 CFR 201.10(g)(2).
2. Revise the presentation of the strength statement to read, '50 mg per vial' or '50 mg/vial'.
3. Revise the statement (b) (4) to read, 'Single-use vial. Discard unused portion.' and relocate this statement to appear below the strength statement rather than appearing next to the strength statement.
4. Delete the vertical line on the principal display panel which appears between the strength statement, '50 mg' and the 'single-use vial' statement.

B. Carton Labeling

1. See comments A1 through A4 and revise the carton labeling accordingly.
2. Relocate the NDC number to appear in the upper 1/3 portion of the principal display panel as required in 21 CFR 207.35(3)(i).
3. Revise the vial content statement on the side panel to omit the portion which reads, '. (b) (4)
4. Revise the reconstitution statement on the side panel to read, 'After reconstitution...the concentration of Adcetris (brentuximab vedotin) is 5 mg/mL', instead of the current presentation of "... (b) (4)
5. Revise the recommended dosage statement on the side panel to read, 'See Prescribing Information'.

Please respond to the above information request before **Friday, August 5**, 2011, if possible.

Please let me know if you have any questions.

Thank You

Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, July 29, 2011 11:01 AM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request: Clinical/ STN 125388/99 - DUE by August 5, 2011

Dear Lynn,

Please provide a response to the following information request:

Please provide (or identify the location in the submission of) details of the central pathology confirmation of CD30 positivity for tumor samples in both the ALCL and HL trials. Please provide information as to the techniques used to conduct the central testing.

Please respond before **Friday, August 5, 2011 if possible.**

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125388/99

MEETING MINUTES

Seattle Genetics, Inc.
Attention: Elaine Waller,
Senior Vice President, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Waller:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for brentuximab vedotin (SGN-35).

We also refer to the meeting between representatives of your firm and the FDA on July 21, 2011. The purpose of the meeting was to obtain feedback from the Division on your proposed confirmatory trial plan for BLA 125388 (for relapsed or refractory Hodgkin Lymphoma) and BLA 125399 (for relapsed or refractory systemic Anaplastic Large Cell Lymphoma).

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 Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

/ Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC/
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC
Clinical Team Leader
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	Post-ODAC
Meeting Date and Time:	July 21, 2011; 2:00PM – 3:00PM
Meeting Location:	White Oak Campus, Building 22
Application Number:	BLA 125388 BLA 125399
Product Name:	Brentuximab vedotin (SGN-35)
Indication:	For the treatment of patients with relapsed or refractory Hodgkin lymphoma and for the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma
Sponsor/Applicant Name:	Seattle Genetics, Inc.
Meeting Chair:	Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C
Meeting Recorder:	Lara Akinsanya, M.S.

FDA ATTENDEES

Office of Oncology Drug Products (OODP)

Anthony Murgo, M.D., M.S., Associate Director of Regulatory Science

Division of Hematology Products (DHP)

Lara Akinsanya, M.S., Regulatory Health Project Manager
R. Angelo de Claro, M.D., Medical Officer
Ann T. Farrell, M.D., Acting Division Director
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader
Karen McGinn, M.S.N., C.R.N.P., Senior Clinical Analyst

SPONSOR ATTENDEES

Seattle Genetics, Inc

Lynn Courtney, MS, Associate Director, Regulatory Affairs
David Gray, PhD, Senior Manager, Biostatistics
Bruce Hart, PhD, Senior Director, Regulatory Affairs
Naomi Hunder, MD, Medical Director
Tom Reynolds, MD, PhD, Chief Medical Officer
Eric Sievers, MD, Executive Medical Director
Elaine Waller, PharmD, Senior Vice President, Regulatory Affairs

Millennium Pharmaceuticals, Inc

Ray Lubecki, RPh, Director, Regulatory Affairs

1.0 BACKGROUND

Seattle Genetics requested a Post-ODAC meeting with FDA on July 18, 2011, to obtain feedback from the Division on Seattle Genetics' proposed confirmatory trial plan for BLA 125388 (relapsed or refractory HL) and BLA 125399 (relapsed or refractory systemic ALCL). On July 18, 2011, FDA communicated with Seattle Genetics by phone that the meeting was granted.

2. DISCUSSION

The FDA had a wide ranging discussion with Seattle Genetics, Inc. regarding their proposed post-approval confirmatory studies.

The Applicant described plans for a protocol amendment to the AETHERA trial that may include requiring that patients have no evidence of disease progression by comparing baseline CT scan to pre-transplant CT scan AND no symptoms of lymphoma, in order to be eligible for randomization.

A broad overview was provided for three possible trials:

- Mature CD30+ T-cell and NK-cell neoplasms: Phase 3, randomized, double-blind, placebo-controlled trial of CH-P + SGN-35 versus CHOP in the treatment of patients with newly-diagnosed, mature CD30 positive T-cell and NK-cell neoplasms including systemic anaplastic large cell lymphoma (sALCL) in approximately 300 patients. The primary endpoint would be PFS as determined by an independent review facility. The Applicant indicated that a Special Protocol Assessment would be requested for this trial.

- CD30-positive Hodkin Lymphoma frontline trial of ABVD versus AVD+ SGN-35. Randomized, phase 3 trial of approximately 880 patients with a primary endpoint of PFS as determined by an independent review facility.

The Applicant posed one question to the Division:

If one of the agreed upon confirmatory studies completes before the others and the results are positive, does FDA agree that a submission and approval of supplemental BLAs based on this study would result in conversion to regular approval in both HL and systemic ALCL BLAs at that time?

FDA Response: Yes. One randomized clinical trial that is well designed, adequately conducted, internally consistent, and provides statistically persuasive, clinically meaningful efficacy findings with a favorable risk-benefit profile may support conversion of both accelerated approvals.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

Seattle Genetics Inc. will submit their proposed studies to be in the post marketing requirements (PMR) for both applications.

5.0 ATTACHMENTS AND HANDOUTS

- Seattle Genetics Inc.'s handouts and slide presentation discussed at the meeting.

7 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, July 13, 2011 10:37 AM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - CMC: STN 125388/99 - DUE by July 20, 2011

Dear Lynn,

Please respond to the information request below:

- Please provide summary data for three most recent decontamination (sanitizing) revalidation runs for the (b) (4). In addition, provide validation data demonstrating package integrity of the microbiological testing materials (b) (4).

Please respond by **July 20, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, July 08, 2011 3:21 PM
To: 'Lynn Courtney'
Cc: Robert Mills; Akinsanya, Lara
Subject: FDA Response to Seattle Genetics, Inc Information Request: STN 125388/99

Dear Lynn,

Please see below for the Agency's response to your questions:

1. Does the FDA agree the microorganisms, the proposed inoculation level and test duration/timepoints selected for the study are appropriate to support and establish the hold time for use in the proposed label claims of brentuximab vedotin?

   FDA response: The microbial challenge study design appears to be appropriate for establishing the hold time for reconstituted drug product.

2. Seattle Genetics seeks FDA's guidance for interpreting results in which growth may be seen for some microorganisms but not other microorganisms.

   FDA response: Please report the microbial count data collected for each challenge organism at each time point of the study. Interpretation of the data will be a review issue.

3. Should the results of the study be submitted by 5 August and support a hold time of greater than 4 hours and $\leq$ 24 hours, will FDA consider these results for inclusion in the product label?

   FDA response: Due to application review deadlines, please submit a report containing the study protocol and data by 1-Aug-2011 so that the results can be considered for inclusion in the product labeling.

Thanks
Lara

From: Lynn Courtney [mailto:lcourtney@seagen.com]
Sent: Friday, July 08, 2011 2:56 PM
To: Akinsanya, Lara
Cc: Robert Mills
Subject: RE: Teleconference Date and Time - Product Quality Microbiology: STN 125388/99 - DUE by July 15, 2011

Hi Lara,

I will be flying out to the WDC area on Monday to prepare for the ODAC meeting next week. Since I will be in transit, could you please copy Rob Mills on the response?

Thanks,
Lynn

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, July 01, 2011 1:10 PM
To: 'Lynn Courtney'
Subject: RE: Information Request - Product Quality Microbiology: STN 125388/99 - DUE by July 12, 2011

Dear Lynn,

There are a 9 additional questions that were supposed to go with this information request when I sent them initially- would you please add them questions below to this request?

1. Regarding the (b) (4) stoppers, please provide the vendor's acceptance criteria for bioburden and endotoxin in terms of CFU/stopper and EU/stopper.

2. Regarding the biological indicators (BIs) used during (b) (4) requalification:
   a. Provide validation information for the (b) (4) Test capsules and describe the positive and negative controls used for requalification studies.
   b. Describe population verification procedures for the (b) (4) Test capsules and the spore strips.

3. Please provide the following information regarding requalification of the (b) (4) used to sterilize equipment and components for workshop ATM3:
   a. Clarify whether all maximum loads (equipment, stoppers, and overseals) are requalified each year. If not, describe the requalification schedule for each load type.
   b. Provide summary reports and data for the three most recent requalification studies. Describe the types of loads tested and provide the heat penetration (minimum F_0) and bacterial challenge results.

4. Please provide the controlled temperature ranges for the (b) (4) loads of SGN-35 fill equipment, stoppers, and overseals in terms of the variability around the temperature set point (for example, (b) (4)).

5. Please provide the following information regarding (b) (4) processes:
   a. Heat penetration (minimum F_0) and bacterial challenge results from the three most recent (b) (4) validation studies for the filling machine.
   b. Heat penetration (minimum F_0) and bacterial challenge results from the three most recent (b) (4) validation studies for the lyophilizer.
   c. Clarify whether any portion of the product transfer line contacts sterile product. If it does, then provide the heat penetration (minimum F_0) and bacterial challenge results from the three most recent (b) (4) validation studies for the transfer line.

6. Please provide the following information regarding sterility testing and sterility test method qualification:
   a. Describe how the media used for sterility testing is tested for growth promotion.
   b. State the acceptance criteria for the sterility test method qualification study.
   c. For each batch tested for the sterility test method qualification study, provide the recovery data for the test samples and controls (CFU recovered) and calculate the % recovery for each challenge organism.

7. The endotoxin specification for the drug product is listed as (b) (4) in section 3.2.P.5.1 of the BLA. The endotoxin limit for the drug product is listed as (b) (4) in the endotoxin method validation report. Please clarify.

8. Please provide the following data regarding endotoxin method qualification for the drug product:
   a. Amount of CSE detected in drug product dilutions compared to amount of CSE detected in dilutions with (b) (4) only.
   b. The geometric mean endpoints.
   c. The MVD calculation.

9. Please provide the following information regarding environmental monitoring:
   a. The footnotes (a) to (f) for Table 8 of section 3.2.A.1.
   b. The specifications for particulates (b) (4) shown in Table 10 in section 3.2.P.3.5 do not match the (b) (4) specifications shown in Table 8 of section 3.2.A.1. Please clarify.

I truly apologize for the initial omission. I am still workign on settign up the teleconference call that you requested with the reviewers and I will get back to you regarding that.

Thanks for understanding.
Lara

From: Lynn Courtney [mailto:lcourtney@seagen.com]
Sent: Thursday, June 30, 2011 10:59 AM
To: Akinsanya, Lara
Subject: RE: Information Request - Product Quality Microbiology: STN 125388/99 - DUE by July 12, 2011

Dear Lara,

Seattle Genetics requests a teleconference (proposed dates Thursday, 7 July or Friday, 8 July at a time that works best for the FDA participants) to obtain feedback on our proposed protocol and timing to receipt of data in preparation for finalizing our response to Question 1 below, received 28 June and due to FDA by 12 July. Review materials for the call will be provided the day before the teleconference.

We would request the participation of the Microbiology Reviewer and Dr. Shapiro for this call.

Q1: The proposed labeling claims that reconstituted drug product may be stored for up to 24 hours at 2-8°C. Please submit microbiological studies in support of the 24-hour post-reconstitution storage time at 2-8°C. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during reconstitution. The test should be run at the label's recommended storage conditions and be conducted for 48 hours (twice the recommended storage period) and using the label-recommended diluent. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-reconstitution storage period is not more than 4 hours at 2-8°C.

Please let me know if you have any questions regarding this request.

Regards,
Lynn

From: Akinsanya, Lara [mailto:Lara.Akinsanya@fda.hhs.gov]
Sent: Tuesday, June 28, 2011 2:24 PM
To: Lynn Courtney
Cc: Akinsanya, Lara
Subject: Information Request - Product Quality Microbiology: STN 125388/99 - DUE by July 12, 2011

Dear Lynn,

Please respond to the information request below:

1. The proposed labeling claims that reconstituted drug product may be stored for up to 24 hours at 2-8°C. Please submit microbiological studies in support of the 24-hour post-reconstitution storage time at 2-8°C. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during reconstitution. The test should be run at the label's recommended storage conditions and be conducted for 48 hours (twice the recommended storage period) and using the label-recommended diluent. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-reconstitution storage period is not more than 4 hours at 2-8°C.

2. Please provide the following information for each media fill performed to validate SGN-35 production:
   a. The media fill duration.
   b. A summary of the environmental monitoring results.
   c. Clarify whether the lyophilization step was simulated under sterile air or nitrogen, and state the length of time that vials are held in the lyophilizer during media fills.
   d. The line speed for the SGN-35 fill process is (b) (4). The media fill procedure indicates that initial qualification evaluates minimum, normal, and maximum line speeds where applicable. Clarify whether the (b) (4) line speed was used for all of the media fills performed to validate SGN-35 production, and justify choice of the line speed for simulation of worst-case conditions.

3. Please describe the vial washing procedure. Provide summaries of the validation reports and data for the three most recent requalification runs for the vial washer in workshop ATM3. Compare the conditions used for validation to those used for routine production.

4. Please provide summaries of the validation reports and data for the three most recent requalification runs for the depyrogenation tunnel in workshop ATM3, including the following information:
   a. Describe the endotoxin spiking and recovery procedures.
   b. Provide the following endotoxin reduction data for each requalification run: the amount of endotoxin applied, the amount of endotoxin recoverable (positive control vials), the amount of endotoxin recovered (challenge vials) and the endotoxin log reduction.
   c. State the number of vials and the vial size (5 ml, 10 ml, etc.) tested during each requalification run. Compare the loads used for requalification to those used for routine production, and explain why the requalification loads are considered worst-case.

Please respond by **July 12, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, June 30, 2011 3:31 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - CMC: STN 125388/99 - DUE by July 14, 2011

Dear Lynn,

Please respond to the information request below regarding the drug product and two general comments:

SGN-35 DP Questions

1. We note that in section 3.2.P.2.3.2 describing the comparability assessment between Process B and Process C that you propose to utilize this standard analytical package for post-marketing comparability studies. In general, the analytical methods are acceptable for comparability studies, but we have the following comments.
   a. We recommend that you also include an assessment of sub-visible particles (b) (4) We note that the Small Volume Sub-Visible Particle method (TM-107) assesses particles between (b) (4). We request that you also include a method that can qualitatively assess (b) (4) particles.
   b. Post-marketing comparability studies should include predefined acceptance criteria based on a statistical analysis of all previously manufactured lots.
   c. A comparability protocol may become obsolete and need revision should new regulatory requirements, safety issues, scientific issues arise or if there have been advances in methodology.
   d. The comparability protocol should include process comparability.
   e. We note that there was not a similar statement regarding post-marketing comparability for cAC10 or SGN-35 BDS. Please comment.

2. Section 3.2.P.2.3.4 describes the process characterization for SGN-35 DP.
   a. (b) (4) are considered to be of high criticality and are controlled for cAC10 and SGN-35 BDS as well as SGN-35 DP, we are not sure that the data support the proposed AOR. Please comment.
   b. Have any manufacturing scale lots been outside the NOR but within the AOR for mixing rate and mixing time?
   c. The tank hold time for the (b) (4). For the material compatibility study samples were held in (b) are also considered to be of high criticality. We are not sure that the data support the proposed AOR. Please comment

d. Have any manufacturing scale lots been outside the NOR but within the AOR for hold time?

3. Section 3.2.P.2.6 describes compatibility and in-use stability studies. We note that for the studies using IV bags of different materials, the % cAC10 was essentially the same across the three concentrations of diluted SGN-35 DP except for DP diluted in polyethylene bags. (b) (4) This discrepancy is unlikely to be related to assay sensitivity for diluted product, since this was not a trend for IV bags of other materials. We are concerned that SGN-35 DP diluted to a low concentration may not be compatible with polyethylene IV bags. Please comment.

Questions Pertaining to cAC10, SGN-35 BDS and SGN-35 DP

4. You are not claiming to manufacture cAC10, SGN-35 BDS or SGN-35 DP using an enhanced approach, but we note that you follow the principles presented in ICH Q8, Q9, Q10 and Q11. We also note that for cAC10, SGN-35 BDS and SGN-35 DP, you state that the process is controlled within the NORs or at setpoints which fall at or within the established AORs. The NORs or setpoints are defined in the Batch Records and operating outside of the NOR or setpoint will result in an investigation. Please clarify the conditions that would allow you to change a NOR or setpoint within a Batch Record and how this would be reported to the Agency.

5. We note that the stability update submitted on June 24, 2011 contained data only for SGN-35 DP. Please comment on your intention to provide updated stability data for cAC10 and SGN-35 BDS.

Please respond by **July 14, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, June 28, 2011 11:34 AM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical: STN 125388 - DUE by July 1, 2011

Dear Lynn,

Please respond to the information request below:

According to section 5.4.6.2 of the independent review charter, CT+PET response of PR (partial response) requires CR or PR based on CT evaluation and at least one (1) previously involved site should be FDG-positive.

- Patient SG035-0003-10006-0047 is listed as having Partial Response (PR) as the best response per IRF. However, this patient had stable disease on CT evaluation at the timepoints assessed as Partial Response (Cycle 4 and Cycle 7). FDA Adjudication: Change best response from PR to SD for patient SG035-0003-10006-0047.

- Patient SG035-0003-39001-0070 is listed as having Partial Response (PR) as the best response per IRF. However, this patient had stable disease on CT evaluation at the timepoint assessed as Partial Response (Cycle 4).
  FDA Adjudication: Change best response from PR to SD for patient SG035-0003-39001-0070.

Please respond by **July 1, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, June 28, 2011 5:24 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - Product Quality Microbiology: STN 125388/99 - DUE by July 12, 2011

Dear Lynn,

Please respond to the information request below:

1. The proposed labeling claims that reconstituted drug product may be stored for up to 24 hours at 2-8°C. Please submit microbiological studies in support of the 24-hour post-reconstitution storage time at 2-8°C. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during reconstitution. The test should be run at the label's recommended storage conditions and be conducted for 48 hours (twice the recommended storage period) and using the label-recommended diluent. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-reconstitution storage period is not more than 4 hours at 2-8°C.

2. Please provide the following information for each media fill performed to validate SGN-35 production:
   a. The media fill duration.
   b. A summary of the environmental monitoring results.
   c. Clarify whether the lyophilization step was simulated under sterile air or nitrogen, and state the length of time that vials are held in the lyophilizer during media fills.
   d. The line speed for the SGN-35 fill process is (b) (4). The media fill procedure indicates that initial qualification evaluates minimum, normal, and maximum line speeds where applicable. Clarify whether the (b) (4) line speed was used for all of the media fills performed to validate SGN-35 production, and justify choice of the line speed for simulation of worst-case conditions.

3. Please describe the vial washing procedure. Provide summaries of the validation reports and data for the three most recent requalification runs for the vial washer in workshop ATM3. Compare the conditions used for validation to those used for routine production.

4. Please provide summaries of the validation reports and data for the three most recent requalification runs for the depyrogenation tunnel in workshop ATM3, including the following information:
   a. Describe the endotoxin spiking and recovery procedures.

b. Provide the following endotoxin reduction data for each requalification run: the amount of endotoxin applied, the amount of endotoxin recoverable (positive control vials), the amount of endotoxin recovered (challenge vials) and the endotoxin log reduction.
c. State the number of vials and the vial size (5 ml, 10 ml, etc.) tested during each requalification run. Compare the loads used for requalification to those used for routine production, and explain why the requalification loads are considered worst-case.

Please respond by **July 12, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, June 27, 2011 3:32 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical: STN 125388 - DUE by July 1, 2011

Dear Lynn,

Please respond to the information request below:

- Please provide a dataset containing the Hodgkin Lymphoma histological subtypes from each patient enrolled to SG035-0003 from initial diagnosis and at time of relapse (if available).

Please respond by **July 1, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, June 27, 2011 3:40 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request for BDS and immunogenicity - CMC/Microbiology: STN 125388/99 - DUE by July 11, 2011

Dear Lynn,

Please respond to the information request below:

SGN-35 BDS Questions

1. Your plan for concurrent validation of the [redacted] (b) (4) for SGN-35 BDS is acceptable. However, you do not provide information as to whether [redacted] (b) (4) lots will be placed on stability. We request that you commit to placing the first three lots of [redacted] (b) (4) material on stability.

2. Regarding the comparability of SGN-35 BDS across processes (Section 3.2.S.2.6.4)
   a. Please clarify whether cAC10 lot NGH002 listed in Table 14 is really lot NGY002.

[redacted] (b) (4)

3. Regarding Characterization of SGN-35: Even though SGN-35 does not have significant, if any, CDC or ADCC activity has its ability to bind C1Q and FcγR been evaluated? We note SGN-35 has ADCP activity.

4. We acknowledge that even though some SGN-35 BDS and DP release specifications are justified based on an analysis of as many as 33 or 25 lots, respectively, the number of combinations of cAC10 and SGD-1006 Intermediate lots used to manufacture BDS is much smaller. However, there are several release specifications that are broader than the manufacturing history, predicted Tolerance Interval or a ± 3 Standard Deviation approach.
   a. Tolerance Intervals will narrow as the number of lots analyzed increases. For those methods where the predicted Tolerance Interval does not match, and is broader than the range determined by the ± 3 Standard Deviation approach (e.g. Binding ELISA for BDS and Moisture for DP), the ± 3 Standard Deviation approach is better at this time for establishing release specifications.
   b. For BDS the specifications for icIEF, Binding ELISA, HIC, CE-SDS and SEC should be

reassessed and tightened to better reflect the historical batch data, Tolerance Interval or ± 3 Standard Deviation range.

c. For DP the specifications for icIEF, HIC and [redacted] (b) (4) should be reassessed and tightened to better reflect the historical batch data, Tolerance Interval or ± 3 Standard Deviation range.

d. Purity by HIC is also monitored by comparing the chromatographic profile to that of a reference standard, but no numerical acceptance limits have been established. Propose numerical acceptance limits for drug loading distribution to better control the purity by HIC.

e. Typically it is reasonable to reassess release specifications when ~ 30 lots of drug substance or drug product have been manufactured. Given that several SGN-35 BDS or DP lots can be manufactured from the same combination of cAC10 and SGD-1006 lots, these BDS and DP lots will not be representative of typical lot-to-lot variability. Submit a proposal for the re-evaluation of all SGN-35 BDS and DP specifications that will reflect lot-to-lot variability based on the combination of Intermediate lots used to manufacture SGN-35 BDS.

5. Regarding stability studies for SGN-35 BDS and DP:
   a. Neither the stability protocols nor the stability data tables specify the stability acceptance criteria. Provide tables showing the relevant stability acceptance criteria for lots currently on stability.

Immunogenicity Questions

6. Regarding the electrochemiluminescent assay to detect antibodies to SGN-35 in human serum:
   a. No details were provided describing the anti-ID30 anti-idiotype antibody. Provide information regarding the generation and purification of this antibody. Is it polyclonal or monoclonal and was avidity assessed after the purification process?
   b. Regarding the assay cut point:
      i. The Grubb's outlier test was used for the calculation of outliers. For the ECL method, 5 out of 30 serums were outliers (table 2 of the report), while only 1 outlier out of 20 serums were outliers in the ELISA method. Please comment on the differences in the outlier number detected between these two protocols and whether the same serum samples were used in both studies.
      ii. The Draft Guidance for Industry Assay Development for Immunogenicity Testing of Therapeutic Proteins recommends that assay validation with a sample of 50-100 is statistically more reliable for determining the variability of the assay to effectively define the cut point. We note that you used serum from 30 samples. Please comment.
      iii. The assay cut point was determined to be [redacted] (b) (4) RLU. Please define RLU.
   c. For the confirmatory assay, please explain the rationale for using [redacted] (b) (4) signal reduction for the determination of positive samples used to establish the assay cut point. Please comment [redacted] (b) (4)
   d. We note that there was no medium positive QC sample in the study assessing precision. FDA recommends including positive samples with dilutions representative of low, medium and high values within the assay dynamic range. Please comment.
   e. We note that the study of specificity and free drug tolerance (interference) only used [redacted] (b) (4) that was described in the validation of the ELISA assay. Please comment.
   f. For bridging assays, FDA recommends that the labeling of the detection antigen (biotinylated SGN-35) does not significantly obscure critical antigenic determinants. Please comment.
   g. Robustness and stability were not assayed in this validation protocol. For example, small

changes in temperature, pH, buffer or incubation times can impact results. Freezing and thawing samples may also affect assay results and those parameters should be evaluated. Please comment.

h. It is not clear how you distinguish anti-drug antibodies (ADA) against cAC10 versus ADA against the vc-MMAE drug linker. Please comment.

7. Regarding the cell-based bioassay for the detection of neutralizing antibodies to SGN-35 in human serum:
   a. We note that the [redacted] (b) (4) was removed from revision 2 of the test method. Please provide a rationale.
   b. During the study assessing selectivity of the assay, we note that Figure 6 and Table 11 (page 28 of the report) do not specify which samples are from normal human serum or from Hodgkin's lymphoma patients. The last three samples seem to be more positive when they are spiked with the [redacted] (b) (4) compared with the first nine samples. Please comment.
   c. We note in the validation report that data from the [redacted] (b) (4) linearity runs were used for determining sensitivity. It is stated that five QC's (NC, PC, LC, MC, and HC) and additional [redacted] (b) (4) were tested for assay sensitivity. However, in Table 12 and Figure 7 not all the QC's are depicted, and the HC is missing. Please comment.
   d. Regarding the assay cut point:
      i. We note that the determination of the assay cut point was validated with and without extraction, while the rest of parameters were validated without the extraction step. Please comment.
      ii. Please define RFU (relative fluorescence unit).

8. The presence of high levels of soluble CD30 in the serum of patients with Hodgkin's Lymphoma has been extensively documented in the literature. The role that high levels of soluble CD30 in the serum may have in the determination of anti-drug antibodies, including neutralizing antibodies, from patients treated with Brentuximab Vedotin should be addressed.

9. It appears that the electrochemiluminescent assay does not distinguish ADA directed against cAC10 or the vc-MMAE drug linker. Ideally the assay should be designed to distinguish ADA directed against both and the levels of ADA against both cAC10 and vc-MMAE should be reflected in the Package Insert.

Please respond by **July 11, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, June 24, 2011 9:15 AM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical: Brentuximab Vedotin - DUE by June 28, 2011

Dear Lynn,

Please respond to the information request below regarding container closure integrity:

1. We requested you to submit a dataset including patients with Hodgkin lymphoma who did not have a prior autologous stem cell transplant in SG035-0001 and SG035-0002 . Please explain why the following two patients are not included in the dataset ADSLASCT.XPT submitted in Serial 0020:

   Patient 1: PTNO 001-0014 from Study SG035-0001
   Patient 2: USUBJID SG035-0002-001-0007 from Study SG035-0002

   Alternatively, you can submit an updated dataset ADSLASCT.XPT which includes the above two patients.

2. Please submit the datasets ADAEPNR1 and ADAEPNR2 used to derive Table 5.2.3 and Table 12 in the 120-day safety update (Serial 0021). Please include a DEFINE.PDF file.

Please respond by **June 28, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, June 23, 2011 4:51 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - Office of Compliance: STN 125388 - DUE by July 07, 2011

Dear Lynn,

Please respond to the information request below regarding container closure integrity:

- Please calculate the Limit of Detection (LOD) of methylene blue using a standard curve with different concentrations of dye that include concentrations below the LOD. Additions of minute volume (b) (4) of dye result in intrinsic high variability of your assay. In addition, the calculated LOD corresponds to the smallest volume of dye assayed and it is not known if a smaller volume will be detected.

Please respond by **July 07, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, June 22, 2011 9:36 AM
To: Akinsanya, Lara; 'Lynn Courtney'
Subject: Additional Information Request - CMC: STN 125388 & 125399 - DUE by July 05, 2011

Dear Lynn,

I have one more request to add to the list. See below:

Regarding the generation of the CHO cell line expression cAC10 (b) (4)

(b) (4)

Thanks
Lara

From: Akinsanya, Lara
Sent: Monday, June 20, 2011 5:13 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - CMC: STN 125388 & 125399 - DUE by July 05, 2011

Dear Lynn,

Please respond to the information request below regarding cAC10:

Questions 1-10 are related to the manufacturing process (Section 3.2.S.2.2) and the studies reported in Section 3.2.S.2.6 Manufacturing Process Development.

1. (b) (4)
2.

4 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, June 15, 2011 5:18 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical: STN 125388 & 125399 - DUE June 22

Dear Lynn,

Please respond to the information request below:

A. When can we expect your 4-month safety update for SG035-0003 and SG035-0004?

B. Please submit a dataset containing the following information for Hodgkin Lymphoma patients who did not receive an autologous stem cell transplant for clinical trials SG035-0001 and SG035-0002.
    1. Study Number
    2. Patient Number or USUBJID Number
    3. Diagnosis (HL?)
    4. Gender
    5. Age (in years)
    6. Race
    7. Primary Refractory Disease (Y or N or Unknown)
    8. Relapsed or Refractory to Last Systemic Therapy (Y or N or Unknown)
    9. ASCT (Y or N)
    10. Number of Prior Systemic Chemotherapy Regimens
    11. Baseline B Symptoms (Y or N or Unknown)
    12. Stage of HL at Initial Diagnosis
    13. Baseline Bone Marrow Involvement (Y or N or Unknown)
    14. Brentuximab vedotin Dose and Schedule (i.e., 1.8 mg/kg q3 weeks)
    15. Number of Cycles of Brentuximab vedotin
    16. Best Response per IRF
    17. Best Response per Investigator

Please respond by **June 22, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, June 14, 2011 3:58 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - CMC: STN 125388 & 125399 - DUE June 28

Dear Lynn,

Please respond to the issues listed below regarding SGD-1006:

1. CMC information for SGD-1006 intermediate is submitted in both BLA and DMF (b) (4). Submit a summary of the major differences between the BLA and DMF with appropriate explanations and/or justifications.

2. Differences are noted between the BLA and the DMF in specifications, manufacturing process and controls, etc. When the information in the release specification for SGD-1006 intermediate are different, it is understood that information in the BLA is the regulatory submission for the to be marketed product. Revise SGD-1006 intermediate specifications in DMF (b) (4) so that they are consistent with the specifications in the BLA.

3. Provide structural characterization results for isolated intermediates in each of the (b) (4) manufacturing process (b) (4). Provide data (b) (4) in each stage of the manufacturing process. It is recommended that you include additional testing (b) (4).

4. Tighten the proposed acceptance criteria for specific rotation to better reflect historical batch analysis data.

5. Tighten the proposed acceptance criteria for assay to better reflect historical batch analysis data.

6. Tighten the proposed acceptance criteria for purity and total related substances based on the commercial process batch release data.

7. Tighten the proposed acceptance criteria for (b) (4) based on the commercial process batch release data.

8. Provide justification for not performing release and stability testing for bacterial endotoxins or microbial limits.

9. Batch data provided is insufficient to support the exclusion of testing for [redacted (b) (4)], as only two lots were tested for those [redacted (b) (4)] historically. [redacted (b) (4)]

10. Submit revised SGD-1006 intermediate specification table that reflects all the changes you propose based on the Agency's comments.

11. Clarify which tests you will routinely perform as acceptance testing for SGD-1006 intermediate and which tests will be per DMF holder's COA.

Please respond by **June 28, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

BLA 125388
BLA 125399

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Seattle Genetics, Inc.
21823 30th Drive Southeast
Bothell, Washington 98021

JUN 8 2011

ATTENTION: Elaine Waller, PharmD, MBA
Senior Vice President, Regulatory Affairs

Dear Dr. Waller:

Please refer to your Biologics License Applications (BLA) dated February 25, 2011, received February 28, 2011, submitted under section 351 of the Public Health Service Act, for Brentuximab Vedotin for Injection, 50 mg per vial.

We also refer to your March 17, 2011, correspondence, received March 18, 2011, requesting review of your proposed proprietary name, Adcetris. We have completed our review of the proposed proprietary name, Adcetris and have concluded that it is acceptable.

The proposed proprietary name, Adcetris, will be re-reviewed 90 days prior to the approval of the BLAs. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 17, 2011 submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lara Akinsanya at (301) 796-9634.

Sincerely,

Carol Holquist

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, June 01, 2011 5:15 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical: STN 125388 - DUE June 9

Hi Lynn,

Please respond to the issues listed below regarding best response assessments made by the independent review facility (IRF):

1. **Best response assessment of CR for SG035-0003-11002-0086**

	C2	C4	C7
Timepoint Response CT+CDR	PR	PD	PD
Timepoint Response CT+CDR+PET		CR	PD

FDA Adjudication: Patient did not achieve CR in Cycle 4. Patient developed new FDG-positive tumor in Cycle 4 (TUCODE 300: L axillary node, GTD 2.1 cm). Reclassify best response as PR in Cycle 2, with progression date at Cycle 4 assessment.

2. **Best response assessment of CR for SG035-0003-10011-0074**

	BL	C2	C4	C7	C10	UV	C
PR CT+CDR		CR	CR	CR	CR	PR	C
PR CT+CDR+PET			PR	PR		PR	
TUCODE: 003 FDG-PET	POS	n.d.	POS	POS	n.d.	POS	n
TUCODE: 003 GTD (cm.)	2.7	1.2	0.9	1	1.3	1.5	1

(BL baseline; UV unscheduled visit; n.d. not done; GTD greatest transverse diameter)

FDA Adjudication: Patient did not achieve CR. Patient had persistently FDG-positive tumor (TUCODE: 003, L axillary node), even at lowest GTD measurement of 0.9 to 1 cm. Reclassify best response as PR in Cycle 2, with progression date at Cycle 16 assessment.

3. **Best response assessment of PR for SG035-10004-0019**

Please provide explanation why this patient cannot be classified as CR for best response.

4. **Best response assessment of PR for SG035-39001-0073**

Please provide explanation why this patient cannot be classified as CR for best response.

Please respond by **June 9, 2011**.

Thank You
Lara

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, May 23, 2011 3:21 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical: STN 125388 - DUE June 1

Dear Lynn Courtney,

Please respond to the below information request for STN 125388:

The SAE narratives for the patients (-0013, -0074, -0067, -0022) are absent. Submit narratives discussing the following SAEs. Describe the circumstances surrounding and the clinical course of each SAE.

1. USUBJID: SG035-0003-10002-0013
   SAE: PLEURAL EFFUSION

2. USUBJID: SG035-0003-10011-0074
   SAE: WRIST FRACTURE

3. USUBJID: SG035-0003-10013-0067
   SAE: HAEMOPTYSIS

4. USUBJID: SG035-0003-10015-0022
   SAE: ABDOMINAL PAIN UPPER, NAUSEA, DIARRHEA

The SAE narrative for the patient -0075 does not have adequate information. Submit details of the SAEs, if further information is available. Patient -0075 died in (b) (6). Submit the post-mortem report if an autopsy was conducted.

5. USUBJID: SG035-0003-10016-0075
   SAE: ABDOMINAL PAIN, INTESTINAL PERFORATION, DIFFUSE LARGE B CELL LYMPHOMA

Please respond by **June 01, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, May 17, 2011 2:33 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical & Biostatistics: STN 125388 & 125399 DUE 5/25

Dear Lynn Courtney,

Please respond to the below information request regarding the durability update for STN 125388 and STN 125399:

1. Submit updated analysis datasets (ADEFF, ADSL, ADRS, ADTUMOR, ADRSIR, ADTRIR) as well as SAS programs used to derive these datasets.

2. Submit the data-cut dates for the updated datasets.

3. Submit an efficacy report discussing the update.

Please respond by **May 25, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, May 13, 2011 3:31 PM
To: 'Lynn Courtney'
Subject: Information Request: STN 125388 & STN 125399 - Response to clinical pharmacology question 1

Dear Lynn,

The Clinical Pharmacology reviewers have the following additional request in response to your submission:

The subject level dataset "adsl", located in module 5 under the iss-hI sub-folder, should include a variable indicating grade 3/4 thrombocytopenia. Currently, the "adsl" dataset provides information only for grade 4 thrombocytopenia. Please update this dataset to include grade 3/4 thrombocytopenia status of patients enrolled in phase 1 and 2 trials.

Thanks
Lara

From: Lynn Courtney [mailto:lcourtney@seagen.com]
Sent: Thursday, May 05, 2011 12:08 PM
To: Akinsanya, Lara
Subject: RE: STN 125388 & STN 125399 - Filable (Filing Letters)_Response to clinical pharmacology question 1

Dear Lara,

We have responded to the following request for information from the 29 April 2011 filing letters for both BLA 125388 (SN 0008) and 125399 (SN 0008). The datasets were submitted through the gateway last night.

Clinical Pharmacology
1. The subject level dataset "adsl", located in module 5 under the iss-hI sub-folder, has missing data regarding peripheral neuropathy, grade 4 thrombocytopenia, and grade 3/4 neutropenia for the phase 1 studies. Please update the "adsl" dataset by providing the peripheral neuropathy, grade 4 thrombocytopenia, and grade 3/4 neutropenia status of patients in the phase 1 trials.

Please let me know if you have any questions.

Best regards,
Lynn

From: Akinsanya, Lara [mailto:Lara.Akinsanya@fda.hhs.gov]
Sent: Friday, April 29, 2011 9:19 AM
To: Lynn Courtney
Subject: STN 125388 & STN 125399 - Filable (Filing Letters)

Dear Lynn,

Please see attachment for the Filing Letters for STN 125388 & 125399. Hard copies are also been sent and you shodul receive them within a week.

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, May 12, 2011 11:41 AM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - CMC Microbiology: STN 125388 & 125399

Dear Lynn Courtney,

Please respond to the below information request for STN 125388 and STN 125399:

cAC10 manufacturing at (b) (4)

1. The reject limits for the in-process bioburden samples for the (b) (4) processes are unacceptably high. Please remove these reject limits. Any bioburden results exceeding the action limits should be investigated, the impact on the product evaluated, and the lot disposition determined.

2. Provide information and summary microbiology validation data in support of the maximum hold times for all process intermediates at scale.

3. Please provide summary validation data for the shipping of cAC10 and BDS, and include the temperature profiles and summary data from the TOQ, POQ, and PQ studies.

4. Please provide bioburden sample volumes used to test for the cell culture samples.

Brentuximab vedotin BDS manufacturing at (b) (4)

1. With regard to the manufacturing of brentuximab vedotin at (b) (4) the in-process bioburden sample for the pooled cAC10 is taken (b) (4), which does not provide for a meaningful assessment of the bioburden level in the pool after hold. Please monitor the bioburden of the pooled cAC10 (b) (4).

2. Please provide microbiology validation data supporting the maximum hold times (Table 69, Section 3.2.S.2.6) for the bulk drug substance process intermediates at scale.

3. Please provide test volumes used for the in-process bioburden samples from the brentuximab vedotin bulk drug substance manufacturing process.

4. You indicated in your report FC2126/BV/06R, "Qualification Report for bioburden", that the BDS samples used for the qualification studies were store at (b) (4) prior to testing. It is not clear if the bacteriostasis/fungistasis effect of the samples was impacted by the storage condition or the (b) (4) process. Please qualify the bioburden test using BDS samples stored under routine sample storage conditions.

Please respond by **May 23, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, May 06, 2011 3:10 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - QT/IRT : STN 125388 & 125399

Attachments: HighlightsofClinicalPharmacology.doc

Dear Lynn Courtney,

Please respond to the below information request from the Division of Cardiovascular and Renal Products for STN 125388 and STN 125399:

- Please complete the attached ClinPharm table and submit the completed table to your BLAs by **COB on Friday May 13, 2011**.

HighlightsofClinicalPharmacolo...

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, May 04, 2011 3:02 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - Clinical: STN 125388 & 125399

Dear Lynn Courtney,

Please respond to the below information request from the clinical reviewers for STN 125388 and STN 125399:

According to 21CFR314.50(f)(2), Sponsors must submit CRFs for any patient who died during a clinical trial.

Please provide narratives and CRFs for all patients who died during the clinical trial, if not already included with the submission: 13 deaths in SG035-0003 and 12 deaths in SG035-0004.
You need to submit additional sets of narratives and CRFs for patients who died during the clinical trial: 10 for Study -0003 and 5 for Study -0004.

	USUBJID of Patients who Died during the Clinical Trial	Narratives and CRFs Submitted?
Study SG035-0003 (Hodgkin Lymphoma)		
1	SG035-0003-10001-0033	No
2	SG035-0003-10002-0013	No
3	SG035-0003-10002-0055	No
4	SG035-0003-10003-0046	No
5	SG035-0003-10004-0027	Yes
6	SG035-0003-10004-0069	Yes
7	SG035-0003-10005-0005	No
8	SG035-0003-10006-0018	No
9	SG035-0003-10017-0075	No
10	SG035-0003-10018-0056	No
11	SG035-0003-10020-0058	Yes
12	SG035-0003-11002-0083	No
13	SG035-0003-39001-0049	No
Study SG035-0004 (sALCL)		
14	SG035-0004-10002-0011	Yes
15	SG035-0004-10004-0025	No
16	SG035-0004-10004-0057	Yes
17	SG035-0004-10009-0007	No
18	SG035-0004-10012-0034	Yes
19	SG035-0004-10013-0053	Yes
20	SG035-0004-10015-0001	No
21	SG035-0004-10016-0013	Yes
22	SG035-0004-10018-0017	No
23	SG035-0004-10018-0023	No
24	SG035-0004-33001-0015	Yes
25	SG035-0004-33001-0020	Yes

Please respond by **COB on Wednesday May 11, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125388/0

FILING ISSUES
April 29, 2011

Seattle Genetics, Inc.
Attention: Elaine Waller
Senior Vice President, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Waller:

Please refer to your biologics license application (BLA) dated February 25, 2011, received February 28, 2011, submitted under section 351 of the Public Health Service Act for brentuximab vedotin.

We also refer to your submissions dated March 14, 2011; March 17, 2011; March 22, 2011 and March 25, 2011.

We have completed an initial review of your application for brentuximab vedotin to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today. The user fee goal date is August 30, 2011. 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.

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 August 9, 2011.

We request that you submit the following information:

Clinical Pharmacology

1. The subject level dataset "adsl", located in module 5 under the iss-hl sub-folder, has missing data regarding peripheral neuropathy, grade 4 thrombocytopenia, and grade 3/4 neutropenia for the phase 1 studies. Please update the "adsl" dataset by providing the peripheral neuropathy, grade 4 thrombocytopenia, and grade 3/4 neutropenia status of patients in the phase 1 trials.

Product Quality Microbiology

2. Please provide the following information for the microbial ingress challenge test:
    a. Species and concentration of the microorganism at the beginning and the end of the test
    b. Critical test parameters such as immersion time, temperature and pressure
    c. Positive and negative controls, including preparation of the positive controls
    d. Growth promotion test of the media
    e. Incubation conditions of challenged vials
    f. Method of detection

3. Please provide the concentration of the methylene blue solution used in the dye ingress test.

4. Please provide the rationale for using additions (b) (4) methylene blue dye to the reconstituted sample to determine the limit of detection of the dye as opposed to larger volumes of sequentially diluted dye.

5. Please indicate the interval of crimp force used to test worst-case scenario of container closure integrity. If no samples have been validated outside the normal operating range, please validate the method using worst-case scenario conditions.

6. Please indicate the speed of the capping line and if worst-case scenarios for speed have been used to validate container closure integrity.

7. Regarding the (b) (4) stoppers:
    g. Please provide a copy of the vendor's certificate of analysis listing the bioburden and endotoxin specifications for the (b) (4) stoppers.
    h. Please provide a summary report and data for the supplier's validation of the (b) (4) process or provide a letter of authorization for review of this information in the supplier's DMF. The letter of authorization should refer to a DMF provided to the CDER Central Document Room and should refer to specific sections of the DMF.

8. Regarding [redacted]:
   a. Please state which of the two [redacted] is the [redacted]. Describe the actions that are taken in case of [redacted] failure.
   b. Please clarify whether the [redacted].
   c. Please provide a summary and the validation report for the product [redacted].

9. Please provide microbiological testing data to support the 24 hour hold time for reconstituted vials at 2-8°C.

10. Please provide information and summary data for the rabbit pyrogen test of brentuximab vedotin in conformance to 21CFR610.13(b) or provide justification for not performing the test. Unless a meaningful rabbit pyrogen test cannot be performed with this product, the test should be done at least once to demonstrate that the product does not contain pyrogenic substances other than bacterial endotoxin.

Please respond only to the above requests for 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.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

/Ann Farrell, M.D./
Ann Farrell, M.D.
Acting Division Director
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Tuesday, April 19, 2011 2:14 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Biostatistics Information Request: STN 125388 & 125399

Dear Lynn Courtney,

Please respond to the below information request from the Biostatistics reviewers for STN 125388 and STN 125399:

1. Please provide data on time to objective response and time to complete response along with censored times for the non-responders.

2. Please provide data define pdf files.

Please respond by **COB on Tuesday April 26, 2011**.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, April 08, 2011 9:59 AM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: DSI Information Request: STN 125388 & 125399

Dear Lynn Courtney,

Please respond to the below information request from the Division of Scientific Investigations (DSI):

1. Are all study records for both studies targeted for audit (SG035-0003 and SG035-0004) maintained at the Seattle Genetics location?

2. Regarding the CRO (b) (4), that was contracted to provide the function of Independent Review Facility (IRF) for reading CT and PET scans for both studies; please confirm the location of all study records (SG035-0003 and SG035-0004) related to the IRF function, as we intend to audit the CRO.

Please respond by COB **on Tuesday April 12, 2011.**

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Friday, March 18, 2011 12:42 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: RE: Information Request: STN 125388 & 125399 - SGN-35 AE datasets

Dear Lynn,

The clinical review team has considered your proposal, and recommend Seattle Genetics submit two datasets:

- Dataset 1: ISS "AE" raw dataset updated with MedDRA code for Preferred Term and System Organ Class
- Dataset 2: ISS "ADAE" ADaM (analysis) dataset updated with MedDRA code for Preferred Term and System Organ Class

Thank You
Lara

From: Lynn Courtney [mailto:lcourtney@seagen.com]
Sent: Thursday, March 17, 2011 2:44 PM
To: Akinsanya, Lara
Subject: RE: Information Request: STN 125388 & 125399 - SGN-35 AE datasets
Importance: High

Dear Lara,

This request could apply to both SDTM and ADaM (analysis) datasets for studies: SG035-0001, SG035-0002, SG035-0003, SG035-0004, SGN35-007, SGN35-008 and the ISS.

We propose that we add the MedDRA code for Preferred Term and System Organ Class to the ISS "ADAE" ADaM (analysis) dataset which contains AEs for all studies and submit this one dataset.

Is this acceptable?

Bests regards,
Lynn

From: Akinsanya, Lara [mailto:Lara.Akinsanya@fda.hhs.gov]
Sent: Thursday, March 17, 2011 10:59 AM
To: Lynn Courtney
Cc: Akinsanya, Lara
Subject: Information Request: STN 125388 & 125399 - SGN-35 AE datasets

Dear Lynn Courtney,

The clinical reviewers have requested the following:

- For BLAs, 125388 & 125399, please resubmit the AE datasets to include the numerical **MedDRA Code** for each row (event).

Please provide the revised dataset by **Noon on Thursday March 24, 2011**.

Please let me know if you have any questions.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
ent: Thursday, March 17, 2011 1:59 PM
.o: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request: STN 125388 & 125399 - SGN-35 AE datasets

Dear Lynn Courtney,

The clinical reviewers have requested the following:

- For BLAs, 125388 & 125399, please resubmit the AE datasets to include the numerical **MedDRA Code** for each row (event).

Please provide the revised dataset by **Noon on Thursday March 24, 2011**.

Please let me know if you have any questions.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
:01) 796-9849 (fax)

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, March 14, 2011 3:37 PM
To: 'Lynn Courtney'
Cc: Akinsanya, Lara
Subject: Information Request - STN 125388 & 125399- SGN-35 AOP meeting- 03/21/11

Dear Lynn Courtney,

The clinical reviewers have requested that the following be included in your upcoming applicant orientation presentation:

- the confirmatory studies (brief description and timeline for completion) for both Hodgkin's Lymphoma and Anaplastic Large Cell Lymphoma.

Thank You
Lara

Lara Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125388/0

BLA ACKNOWLEDGEMENT
March 2, 2011

Seattle Genetics, Inc.
Attention: Elaine Waller
Senior Vice President, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Waller:

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: brentuximab vedotin

Date of Application: February 25, 2011

Date of Receipt: February 28, 2011

Our Submission Tracking Number (STN): BL 125388/0

Proposed Use: Relapsed or refractory Hodgkin's Lymphoma

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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains **BLA 125388/0** submitted on February 25, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

If you have any questions, call me at (301) 796-9634.

Sincerely,

/Lara Akinsanya/
Lara Akinsanya, M.S.
Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 71634

MEETING MINUTES

Seattle Genetics
Attention: Ms. Lynn Courtney
Associate Director, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Courtney:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for brentuximab vedotin (SGN-35, CAC10-vcMMAE(4)).

We also refer to the meeting between representatives of your firm and the FDA on Tuesday, December 7, 2010. The purpose of the meeting was to discuss Chemistry, Manufacturing and Controls (CMC) plans in support of BLA submission.

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) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Sr. Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA, Chemistry, Manufacturing and Controls
Meeting Date and Time:	Tuesday, December 07, 2010, 1000 – 1100 ET
Meeting Location:	White Oak Building 22, Room 1315
Application Number:	IND 071634
Product Name:	brentuximab vedotin (SGN-35, CAC10-vcMMAE(4))
Indication:	Relapsed or refractory Hodgkin lymphoma (HL); relapsed or refractory systemic anaplastic large cell lymphoma (ALCL)
Sponsor/Applicant Name:	Seattle Genetics/Millennium Pharmaceuticals, Inc.
Meeting Chair:	Marjorie Shapiro, Ph.D.
Meeting Recorder:	Scott N. Goldie, Ph.D.

FDA ATTENDEES

Francisco Borrego	OBP/DMA, Reviewer
Debasis Ghosh, Ph.D.	ONDQA, Quality Reviewer
Scott N. Goldie, Ph.D.	ONDQA, Sr. Regulatory Health Project Manager for Quality
Patricia Hughes,	OC/DMPQ/BMT, Team Leader
Sarah Pope Miksinski, Ph.D.	ONDQA, Branch Chief
Marjorie Shapiro, Ph.D.	OBP/DMA, Chief, Laboratory of Molecular and Developmental Immunology
Qing (Joanna) Zhou	OBP/DMA, Reviewer

SPONSOR ATTENDEES

Seattle Genetics

Kevin Anderson, PhD,	Principal Scientist, Analytical Biochemistry
Bruce Hart, PhD,	Senior Director, Regulatory Affairs
Vaughn Himes, PhD,	Executive Vice President, Technical Operations
Nathan Ihle, PhD,	Executive Director, Process Chemistry
Robert Mills, MA,	Associate Director, Regulatory Affairs
Morris Rosenberg, PhD, DSc,	Executive Vice President Process Science
Chuck Smith,	Executive Director, Quality
Phil Tsai, PhD,	Senior Director, BioProcess Development
Elaine Waller, PharmD,	Senior Vice President, Regulatory Affairs

Millennium Pharmaceuticals, Inc.

Csanad Varga, PhD,	Associate Director, Sterile Formulation

1.0 BACKGROUND

Brentuximab vedotin (SGN-35), an antibody-drug conjugate, consists of a chimeric IgG1 (anti-CD30 antibody [cAC10]) chemically conjugated to the drug-linker intermediate SGD-1006. This synthetic intermediate is made up of both the drug component monomethyl auristatin E (MMAE) and a peptidic linker.

The strength and dosage form is a 50 mg/vial sterile, preservative free, white to off-white lyophilized powder for solution for IV infusion, proposed for the treatment of relapsed or refractory Hodgkin lymphoma (HL); relapsed or refractory systemic anaplastic large cell lymphoma (ALCL)

In the original IND submission (IND 071364, submitted on 27 June 2006), Seattle Genetics described the production of brentuximab vedotin drug product using the manufacturing process termed "Process A". As part of ongoing development for the manufacture of brentuximab vedotin, Seattle Genetics submitted an amendment to the IND on 17 March 2009 (serial number 0075) to introduce drug product manufactured via a process (Process B) reflecting changes to the (b) (4) On 2 September 2009, Seattle Genetics submitted an amendment (serial number 0105) to introduce material manufactured by a process (Process C) (b) (4) at the commercial scale in preparation for process validation (conformance manufacturing), (b) (4)

On 19 January 2010, a Type B meeting was held with FDA to obtain feedback on the proposed control and validation strategies for the intended commercial process (Process C), the comparability plan for evaluation of Process C with previous process versions and the proposed format for Module 3. The guidance received has been incorporated into these strategies.

On 12 August 2010, a teleconference held with the FDA provided feedback clarifying the format for CTD Module 3 content. Module 3 will contain three separate 3.2.S. sections (one each for the drug-linker, monoclonal antibody, and drug substance); and references and cross-references will be hyper-linked to provide reviewers with sufficient paths for navigation.

On 22 September 2010, the Office of Combination Products (OCP) communicated its decision that brentuximab vedotin as a combination product would be regulated as a biologic within CDER. It is the goal of Seattle Genetics to submit a Biological License Application (BLA), per 21 CFR 601.2, in Q1 2011 for approval in patients with relapsed or refractory Hodgkin lymphoma and relapsed or refractory anaplastic large cell lymphoma.

The purpose of the 7 December 2010 Type B pre-BLA meeting is to solicit final agency comment, in preparation for the submission for registration, on the:

- Adequacy of the rationales for establishing the specifications for drug-linker, antibody, bulk drug substance and drug product;

- Acceptability of the control strategy for the (b) (4) additional GMP starting materials used in the manufacture of SGD-1006;
- Acceptability of the proposed timing during the review period of the application for a stability update and the content of the stability update to be used in support of the expiry dating for drug product (DP);
- Maintenance of equivalency between Process C, and the conformance lots and post-conformance commercial manufacture;
- Acceptability of any pre-approval inspection activities within the constraints of the current Contract Manufacturing Organization (CMO) production schedules; and
- Acceptability of the proposed categorical exclusion for an Environmental Assessment, as an outcome of the determination by Office of Combination Products (OCP) that brentuximab vedotin will be regulated under a BLA.

Meeting Chronology: Meeting requested 20 September 2010 (SD-284); Meeting granted 14 October 2010; Meeting request replaced in EDR 02 November 2010 (SD-285) Briefing package submitted (EDR) 05 November 2010. (SD-311); Preliminary responses sent 24 November 2010; Face to face meeting with altered agenda held as scheduled on 07 December 2010.

2.0 DISCUSSION

Briefing Package Question 1: Does the Agency agree that the rationales for establishing the specifications, as proposed in this package, are adequate to support registration?

FDA Response to Question 1: The establishment of release specifications and the adequacy of the justification is a review issue however, your approach appears reasonable. Specific comments for the SGN-35 intermediates, drug substance and drug product are below.

a. cAC10 Intermediate

FDA Response to Question 1a: Specifications such as "conforms to reference standard" or "comparable to reference standard" are acceptable provided that the reference standard is well defined for that quality attribute. For example for icIEF as an identity method, the number of peaks and PI range in the reference standard should be well characterized.

It is not clear why the specifications for CE-SDS (b) (4) are proposed to be (b) (4)

The anti-HCP antiserum needs to be qualified for its ability to detect potential HCP impurities. These data should include 2D SDS-PAGE gels of the range of HCPs detected by a sensitive protein stain, such as silver stain, compared to the range detected by western blot analysis (or another similarly sensitive assay) using the antiserum employed in the assay. It is the agency's experience that analysis of HCP coverage by a 1-dimensional SDS-PAGE gel method is not sufficiently sensitive for this purpose.

For the Binding ELISA potency assay, have lots with potency results at the upper and lower limits of the proposed range been used to manufacture drug substance and tested in the cytotoxicity assay?

While there may be no specific requirements for intermediates, we recommend that bioburden action limits for in-process testing and the release specification for cAC10 be set as if cAC10 was manufactured as the bulk drug substance. See additional comment 5.

b. SGD-1006 Intermediate

FDA Response to Question 1b: No further comment at this time. Adequacy will be determined during BLA review.

c. Bulk Drug Substance (BDS) and Drug Product (DP)

FDA Response to Question 1c: Since the SGN-35 BDS and DP manufacturing processes do not contain steps (b) (4), these impurities should be well characterized for BDS and DP. For example are the (b) (4) primarily dimers or larger aggregates? If they are dimers, are they reversible? What is the nature of the fragments and what is their potential for toxicity due to SGN-1006?

With respect to BDS, DP and cAC10, using Tolerance Intervals to justify specifications is acceptable however, as the number of lots manufactured increases, the Tolerance Intervals should decrease. We note that in all the examples provided, the Tolerance Intervals are broader than your manufacturing experience and the proposed specifications are based on the Tolerance Intervals. We recommend that you continue to analyze lots and reevaluate specifications as additional lots of cAC10 and SGN-35 drug substance and product are manufactured.

Discussion: Seattle Genetics acknowledged receipt of FDA's response and agreed that the final specifications are a review issue based on the data included in the BLA. Meeting participants agreed that there is limited data based on analytical and manufacturing experience to draw from to support the determination of acceptance criteria that would ensure product quality and patient performance at this time. While tolerance intervals may be the primary driver for the establishment of some specifications, other considerations may be more important for release criteria for certain methods.

To date there are only limited data for CE-SDS and SEC, for which there is more experience, is an orthogonal method that captures similar information regarding purity.

Regarding the Binding ELISA potency assay for cAC10, there have been no lots to date with results at the upper and lower limits of the proposed acceptance criteria, but among the lots manufactured to date, those with the highest and lowest result in the Binding ELISA (NGY003 and NGY008) also have reasonable results when tested as SGN-35 drug substance (NGY008) or drug product (NGY003) in the cytotoxicity assay.

Meeting participants agreed that appropriate scientific justification be included in the application to support the choice of the specifications and associated acceptance criteria.

Seattle Genetics stated that they planned to reevaluate specifications as additional lots of cAC10 and SGN-35 drug substance and product are manufactured.

Briefing Package Question 2: Does FDA agree that the designations and controls for the 3 additional GMP starting materials, as proposed, are adequate to support registration?

FDA Response to Question 2: The proposed designations and controls for the three additional starting materials appear to be acceptable to support the registration. However, the adequacy of the information will be decided at the time of BLA review. Please see additional comments included in Section 3.0.

Discussion: Seattle Genetics acknowledged receipt of FDA's response. No further discussion occurred during the meeting.

Briefing Package Question 3: Does FDA agree that submission of the updated Drug Product stability data within the planned timeframe will not extend the PDUFA review date of the application?

FDA Response to Question 3: It is acceptable to provide a simple stability update within the review period. A "simple stability update" is defined as stability data and analyses performed under the same conditions, and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. Furthermore, the "simple stability update" will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA. Simple stability updates are not essential for the establishment of BLA approvability. Rather, simple stability updates are useful for extending the proposed shelf-life to a more commercially advantageous duration. Simple stability updates submitted up to month seven (7) for a standard submission and month four (4) for a priority submission will be reviewed and considered in shelf life determinations. If there is any deviation from the stability protocol as described in the original submission, or if additional CMC information not related to a simple stability update is included, the amendment will not be considered as a "simple stability update."

Discussion: Seattle Genetics acknowledged receipt of FDA's response. No further discussion occurred during the meeting.

Briefing Package Question 4: Does the Agency agree that no further assessment of comparability is needed, based on the assessments of the minor changes pre- and post-validation, supporting the claim that commercial manufacturing is representative of Process C and supports registration?

FDA Response to Question 4: At the 19 January 2010, meeting we were unaware that the (b) (4) process would be moved to a new suite in the facility. However, provided that the equipment in Downstream Suite 6 is the same or equivalent to that used in Downstream Suite 1, additional comparability studies would not be required. The data from all comparability studies should be included in the BLA. The specific facility changes will be evaluated during the pre-approval inspection

Discussion: Seattle Genetics acknowledged receipt of FDA's response. Seattle Genetics committed to include in the application data demonstrating the comparability of the product from the three manufacturing processes and the two manufacturing suites including manufacturing methods and extended characterization data at the time of submission. FDA also recommended that Seattle Genetics include standard operating procedures for well defined, significant changes in manufacturing processes (such as manufacture of new cell banks (MCB and WCB), qualification of a new reference standard or reprocessing of material due to filter integrity test failure) in the application for review so as to not need a prior approval supplement in the future.

Briefing Package Question 5: If a pre-approval inspection of a production facility is determined to be needed but cannot be scheduled during the production window, would an inspection of the facility without the product in production be sufficient to meet the Agency's needs?

FDA Response to Question 5: We acknowledge that a tentative schedule of production activities was provided in the meeting package in Table 33. The inspections will be scheduled when the facilities are in operation. Generally, inspections of drug substance manufacturing facilities should occur when the specific product under review is being manufactured. Drug product (b) (4) facilities should be in operation for a meaningful inspection, but are not required to be manufacturing the specific product. See additional comment 4.

Discussion: Seattle Genetics acknowledged receipt of FDA's response. No further discussion occurred during the meeting.

Briefing Package Question 6: Does FDA agree that brentuximab vedotin, as a combination product, qualifies for a categorical exclusion from the requirement for an Environmental Assessment based on the criteria set forth in 21CFR §25.15 and 25.31(b) and (c)?

FDA Response to Question 6: The categorical exclusion from the requirements of Environmental Assessment will be reviewed by the Agency at the time of BLA filing.

IND 071634
Meeting Minutes

Office of New Drug Quality Assessment, Division of New Drug Quality Assessment I
Office of Biotechnology Products, Division of Monoclonal Antibodies
Office of Compliance, Division of Manufacturing Product Quality

Type B Pre-NDA Chemistry, Manufacturing and Controls (CMC)

Discussion: Seattle Genetics acknowledged receipt of FDA's response. No further discussion occurred during the meeting.

Additional FDA Comments:

1. Provide the source, brief description of synthesis, and certificate of analysis for the proposed starting materials for SGD-1006.

2. Provide the grade and purity of all the chemicals and reagents used in the production of SGD-1006, Bulk Drug Substance and Drug Product.

3. The adequacy of Type II DMF (b) (4) describing the manufacturing of SGD-1006 should be based on the information contained in the DMF only. If the DMF holder is different from the BLA applicant then a LOA (Letter of Authorization) should be submitted during the time of BLA filing.

4. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. We note that the briefing package did not list the FEI number for Seattle Genetics, Inc. Manufacturing schedules at all the drug substance and drug product sites should be provided in the BLA submission to facilitate the planning of the pre-license inspections.

5. The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control for both the cAC10 intermediate and the brentuximab vedotin BDS. The provided information should include, but not be limited to the following:

   - Monitoring of bioburden and endotoxin levels at critical manufacturing steps using validated bioburden and endotoxin tests. The pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
   - Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
   - (b) (4) and storage validation (3.2.S.2.5).
   - Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
   - Data summaries of shipping validation studies (3.2.S.2.5).
   - Drug substance bioburden and endotoxin release specifications. The bioburden limit should be < 1 CFU/10 mL for bulk materials allowed to be stored for extended periods of time at refrigerated temperatures (3.2.S.4).

6. The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) operations. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products". Test methods and validation data summaries for the container closure integrity test and preservative effectiveness test (if applicable) should be submitted in Section 3.2.P.2.5 of the submission. Provide the study protocols and validation data summaries in Section 3.2.P.3.5 for the following:

   - Bacterial filter retention study for the sterilizing filter,
   - Sterilization and depyrogenation of sterile product-contact equipment and components, and equipment requalification program,
   - In-process controls and hold times,
   - Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs,
   - A description of the routine environmental monitoring program, and
   - The lyophilization process, if applicable. The application should include Lyophilizer sterilization validation data and information.

7. It is recommended that a container closure integrity test be performed in lieu of the sterility test for stability samples at initial time and every 12 months (annually) until expiry.

Discussion: Seattle Genetics acknowledged receipt of FDA's response and requested further discussion on Additional Comment 5. Meeting participants agreed that the controls and procedures to address the bioburden and endotoxin control strategy are subject to the review and inspection by FDA reviewers and investigators and need to be included in the application. The microbial control strategy should be based on process understanding and risk assessments of the individual steps of the manufacturing process prone to microbial contamination. Particular attention should be given to process intermediate and (b) (4) hold conditions. Hold conditions should validated to ensure manufacturing scale process consistency and product quality. FDA recommended that the application contain a summary of the microbial controls used in each of the manufacturing facilities. Specifically, FDA recommended a summary of the bioburden and endotoxin data obtained during process validation with appropriate cross referencing links in the BLA when necessary. FDA also recommended that the results of the shipping validation study demonstrating adequate control when exposed to worst-case environmental conditions be included in the application.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

FDA recommended that Seattle Genetics complete the application process for an FEI number for their facility prior to application submission. FDA also recommended that all FEI numbers and other contact information for each manufacturing site be verified and included in the application. Seattle Genetics committed to include a manufacturing and testing schedule for all facilities to facilitate the scheduling of the site inspections.

Meeting participants also discussed the existence of a warning letter issued by the Office of Compliance to the proposed drug product manufacturer and the potential impact on the application. This discussion also included risk mitigation and next steps with respect to the Seattle Genetics application. FDA stated that a re-inspection is necessary and the re-inspection could occur as part of the pre-approval inspection of the application.

4.0 ACTION ITEMS

There were no other action items other that those discussed in Section 2.0 (above).

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Sr. Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

{See appended electronic signature page}

Marjorie Shapiro, Ph.D.
Chief, Laboratory of Molecular and Developmental Immunology
Division of Monoclonal Antibodies
Office of Biotechnology Products
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments, handouts or slides distributed for the meeting.

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

/s/

SCOTT N GOLDIE
12/08/2010

MARJORIE A SHAPIRO
12/08/2010

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	pre-BLA (Clinical)
Meeting Date and Time:	November 18, 2010
Meeting Location:	FDA White Oak Campus
Application Number:	IND 71634
Product Name:	brentuximab vedotin
Indication:	treatment of relapse or refractory Hodgkin lymphoma
Sponsor/Applicant Name:	Seattle Genetics
Meeting Chair:	Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Clinical Team Leader (Acting), DHP
Meeting Recorder:	Alberta Davis-Warren, BS, RPM

FDA ATTENDEES

Ann Farrell, M.D., Division Director, DHP
Edvardas Kaminskas, M.D., Deputy Division Director, DHP
Virginia Kwitkowski, M.S., R.N., ACNP-BC, Clinical Team Leader (Acting), DHP
Karen McGinn, CRNP, MSN, Clinical Analyst, DHP
R. Angelo De Claro, M.D., Medical Officer, DHP
Qin Ryan, M.D., Ph.D., Clinical Team Leader (Acting), DHP
Mark Rothmann, Ph.D., Team Leader, Mathematical Statistician, DB3
Kallappa Koti, Ph.D., Mathematical Statistician, DB3
Bahru Habtemariam, Ph.D., Clinical Pharmacologist, OTS/OCP/DCP5
Marjorie Shapiro, Ph.D., Team Leader, Division of Monoclonal Antibodies, OPS/OBP/DMA
Francisco Borrego, Ph.D., Senior Staff Fellow, OPS/OBP/DMA
Alberta Davis-Warren, BS, Regulatory Project Manager, DDOP

SPONSOR ATTENDEES

Seattle Genetics
Robert Bader, PharmD, Associate Director, Pharmacovigilance and Risk Management
Lynn Courtney, MS, Associate Director, Regulatory Affairs
David Gray, PhD, MBA, Senior Manager, Biostatistics
Bruce Hart, PhD, Senior Director, Regulatory Affairs
Dana Kennedy, PharmD, BCOP, Medical Director
Tom Reynolds, MD, PhD, Chief Medical Officer
Eric Sievers, MD, Executive Medical Director
Elaine Waller, PharmD, Senior Vice President, Regulatory Affairs

External Clinical Experts
Seattle Genetics has invited a leading expert in lymphoma (b) (4)

(b) (4)

Millennium Pharmaceuticals, Inc.
Note that Seattle Genetics is developing brentuximab vedotin in collaboration with Millennium Pharmaceuticals, Inc. and the following representatives from the collaborator will be present at the meeting.
Antonio Gualberto MD, PhD, Senior Medical Director
Ray Lubecki, RPh, Director, Worldwide Regulatory Affairs Oncology

1.0 BACKGROUND

Seattle Genetics had stated in the pre-submission planning meeting held on 12 August 2010 that they are planning on a BLA submission (No. 125388) in the first Quarter of 2011. The BLA submission will seek approval of brentuximab vedotin for 2 indications: treatment of relapsed or refractory HL and treatment of relapsed or refractory systemic ALCL.

On September 3, 2010, Seattle Genetics requested a pre-submission meeting with FDA to discuss the registrational strategy for brentuximab vedotin based on the efficacy and safety data obtained in the phase 2 clinical trials in HL (SG035-0003) and systemic ALCL (SG035-0004). The efficacy results presented in the meeting briefing package submitted October 19, 2010 were final and will be placed in the planned BLA submission.

Seattle Genetics requested a Type B pre-NDA Clinical meeting to discuss key elements of NDA compilation to facilitate assembly of a submission that meets FDA standards and expectations. FDA submitted preliminary comments to Seattle Genetics on November 15, 2010; on November 16, 2010, Seattle Genetics requested for the meeting to focus on the FDA responses to the following specific questions: #1a and #4a (these are related questions for HL and ALCL); #2c and #5c (these are related questions for HL and ALCL); and questions #3, 6, and 10. The following captures the meeting discussions held November 18, 2010.

2. DISCUSSION

HL Questions

1. a) Does the FDA agree that data from study SG035-0003 along with supporting safety and activity data from phase 1 studies are sufficient to enable a filable submission for brentuximab vedotin?

   FDA response to Question #1a: The entire BLA submission for study SG035-0003 will have to be reviewed in order to make a filing determination.

   Given your report regarding the hepatic metabolism and fecal elimination of MMAE, your intention to not include information from the hepatic impairment study in your BLA submission may be a filing issue given the potential safety concerns with use in this

special population. You should propose a time-line to FDA for submitting these data. This should not extend beyond 72 days from submission.

Meeting Discussion to Question #1a: (b) (4) **FDA suggested that the Sponsor consider partnering with NCI for the hepatic impairment study.** (b) (4) **If inadequate data for hepatic impairment is submitted with the BLA, a post marketing requirement would be necessary.**

b) Does the FDA agree that the submission supports brentuximab vedotin for the treatment of relapsed or refractory HL as an indication?

FDA response to Question #1b: The indication will be determined based upon the subjects you enrolled in your pivotal study.

2. a) Does FDA agree that an ORR of 75% with median durability of greater than 6 months constitutes evidence of clinical benefit?

FDA response to Question #2a: Generally, response rate in a single-arm trial is not adequate for regular approval. Whether a high response rate with an acceptable duration will be considered a surrogate for clinical benefit (and acceptable for accelerated approval) will be a review issue.

b) Does FDA agree that achievement of CR in 34% of patients with durability as presented in this package constitutes evidence of clinical benefit?

FDA response to Question #2b: Please see our response to Question #2a.

c) Does FDA agree that a median PFS of 34.0 weeks observed with brentuximab vedotin versus a median PFS of 17.9 weeks observed with the most recent prior treatment provides supportive evidence of clinical benefit?

FDA response to Question #2c: No, historical controls and non-pre-specified endpoints are not likely to be accepted for regulatory action.

Meeting Discussion to Question #2c: The Sponsor stated that the PFS analysis a pre-specified secondary efficacy endpoint in both studies. FDA reiterated that PFS is not an acceptable efficacy endpoint in a single arm trial. Whether the PFS analysis is utilized for regulatory action will be a review issue.

d) Does FDA agree that enablement of consolidative allogeneic SCT in 7% of patients following treatment with brentuximab vedotin provides supportive evidence of clinical benefit?

FDA response to Question #2d: No, please provide the evidence that this is clinical benefit. Since enablement of consolidative allogeneic SCT was not a pre-specified endpoint, this finding, if supported by the data, would be exploratory.

3. What criteria would FDA apply to determine if the data support a regular vs. accelerated approval in the relapsed or refractory HL indication?

FDA response to Question #3: FDA would apply the following criteria:

- **Regular approval of an oncologic new molecular entity (NME) usually requires two adequate and well-controlled clinical trials establishing that the NME provides clinical benefit and has an acceptable benefit to risk ratio.**
- **Under Subpart E 21 CFR 601.40-46 Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses may be applicable to brentuximab vedotin and would take into account magnitude and durability of response, and require a confirmatory trial for regular approval.**

Meeting Discussion to Question #3: Following accelerated approval a confirmatory study (per indication) would be required to confirm and describe the clinical benefit. The Sponsor stated that phase 1 safety study is planned for the untreated ALCL population combining CHOP with SGN 35. A global phase 3 HD trial with a primary endpoint of PFS after auto transplant is ongoing. The confirmatory study for conversion to regular approval does not necessarily have to be in that exact indication that holds accelerated approval.

Systemic ALCL Questions

4. a) Does the FDA agree that data from study SG035-0004 along with supporting safety and activity data from phase 1 studies are sufficient to enable a filable submission for brentuximab vedotin?

FDA response to Question #4a: The entire BLA submission for study SG035-0004 will have to be reviewed in order to make a filing determination.

Given your report regarding the hepatic metabolism and fecal elimination of MMAE, your intention to not include information from the hepatic impairment study in your BLA submission may be a filing issue given the potential safety concerns with use in this special population. You should propose a time-line to the FDA for submitting these data. This should not extend beyond 72 days from submission.

Meeting Discussion to Question #4a: (b) (4) **FDA suggested that the Sponsor consider partnering with NCI for the hepatic impairment study.** (b) (4) **If inadequate data for hepatic impairment is submitted with the BLA, a post marketing requirement would be necessary.**

b) Does the FDA agree that the submission supports brentuximab vedotin for the treatment of relapsed or refractory systemic ALCL as an indication?

FDA response to Question #4b: The indication will be determined based upon the subjects you enrolled in your pivotal study.

5. a) Does FDA agree that achievement of an ORR in 86% of patients constitutes evidence of clinical benefit?

FDA response to Question #5a: Generally, response rate in a single-arm trial is not adequate for regular approval. Whether a high response rate with an acceptable duration will be considered a surrogate for clinical benefit (and acceptable for accelerated approval) will be a review issue.

b) Does FDA agree that achievement of CR in 53% of patients constitutes evidence of clinical benefit?

FDA response to Question #5b: Please see our response to Question #5a.

c) Does FDA agree that demonstrating a median PFS of 41.1 weeks observed with brentuximab vedotin versus a median PFS of 25.9 weeks observed with the most recent prior treatment provides supportive evidence of clinical benefit?

FDA response to Question #5c: No, historical controls and non-pre-specified endpoints are not likely to be accepted for regulatory action.

Meeting Discussion to Question #5c: The Sponsor stated that the PFS analysis a pre-specified secondary efficacy endpoint in both studies. FDA reiterated that PFS is not an acceptable efficacy endpoint in a single arm trial. Whether the PFS analysis is utilized for regulatory action will be a review issue.

d) Does FDA agree that enablement of consolidative autologous or allogeneic SCT in 24% of patients following treatment with brentuximab vedotin provides supportive evidence of clinical benefit?

FDA response to Question #5d: No, please provide the evidence that this is clinical benefit. Since enablement of consolidative autologous or allogeneic SCT was not a pre-specified endpoint, this finding, if supported by the data, would be exploratory.

6. What criteria would FDA apply to determine if the data support a regular vs. accelerated approval in the relapsed or refractory systemic ALCL indication?

FDA response to Question #6: FDA would apply the following criteria:

- **Regular approval of an oncologic new molecular entity (NME) usually requires two adequate and well-controlled clinical trials establishing that the NME provides clinical benefit and has an acceptable benefit to risk ratio.**
- **Under Subpart E 21 CFR 601.40-46 Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses may be applicable to brentuximab vedotin and would take into account magnitude and durability of response, and require a confirmatory trial for regular approval.**

Meeting Discussion to Question #6: Please refer to our discussion of Question #3.

7. Does the FDA agree with the proposed plan to submit a single update for response duration in SG035-0004 during the submission review, prior to three months of the PDUFA date, without extending the review cycle?

FDA response to Question #7: Yes, this plan is acceptable.

Safety Question

8. Based on the safety profile and the intended use of brentuximab vedotin in oncology indications, a Risk Evaluation and Mitigation Strategy is not warranted. Does the FDA agree?

FDA response to Question #8: Determination of the need for a Risk Evaluation and Mitigation Strategy will be a review issue.

Administrative Questions

9. Seattle Genetics intends to request a priority review of the submission for the HL and systemic ALCL indications. Does the FDA anticipate granting a priority review for both indications?

   FDA response to Question #9: Priority Review Status will be made at the time of FDA filing determination.

10. Seattle Genetics offers to provide an Applicant Orientation Presentation of the high level contents of the submission to the FDA after submission and prior to FDA's decision to file the submission. Does the FDA anticipate requesting such a presentation?

    FDA response to Question #10: Yes, FDA anticipates requesting such a presentation.

    Meeting Discussion to Question #10: FDA stated that the Sponsor presentations are usually conducted within 30 days of submission of the BLA.

11. Does the FDA anticipate brentuximab vedotin would be the subject of an ODAC meeting? When can Seattle Genetics anticipate being notified of FDA's decision for an ODAC hearing?

    FDA response to Question #11: Yes, FDA anticipates that brentuximab vedotin will be the subject of an ODAC meeting. FDA will schedule the ODAC meeting after the BLA submission is received.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

None.

5.0 ATTACHMENTS AND HANDOUTS

None.

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

/s/

LISA M SKARUPA
02/04/2011

VIRGINIA E KWITKOWSKI
02/04/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 71634

MEETING MINUTES

Seattle Genetics
Attention: Lynn Courtney
Associate Director, Regulatory Affairs
21823 30th Drive SE
Bothell, WA 98021

Dear Ms. Courtney:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Brentuximab vedotin (SGN-35).

We also refer to the teleconference between representatives of your firm and the FDA on August 12, 2010. The purpose of the meeting was to Seattle Genetics requests a preliminary dialogue with FDA to obtain clarity on agency expectations on key elements of the NDA compilation that are not dependent on the outcome of the pivotal trial. This early feedback would greatly facilitate the timely compilation of an NDA submission that meets FDA standards and expectations.

A copy of the official minutes of the telecon 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) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa, R.N., M.S.N., A.O.C.N.
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B Meeting
Meeting Category:	pre-NDA Meeting (Clinical and E-Submission)
Meeting Date and Time:	August 12, 2010 2pm
Meeting Location:	Teleconference
Application Number:	IND 71634
Product Name:	Brentuximab vedotin (SGN-35)
Indication:	Treatment of relapsed or refractory Hodgkin lymphoma (HL).
Sponsor/Applicant Name:	Seattle Genetics
Meeting Chair:	Edvardas Kaminskas, M.D.
Meeting Recorder:	Lisa Skarupa, RN, MSN, Regulatory Project Manager

FDA ATTENDEES

Edvardas Kaminskas, M.D., Deputy Director, DHP
Karen McGinn, M.D., Clinical Reviewer, DHP
Qin Ryan, M.D., Clinical Team Leader, DHP
Kimberly Ringgold, Ph.D, PharmTox Reviewer, DHP
Mark Rothmann, Ph.D., Statistician Team Leader, DHP
Kallappa Koti, Statistician Reviewer, DHP
Joseph Grillo, Ph.D., Clinical Pharmacology, DCP5
Marjorie Shapiro, Ph.D., Division of Monoclonal Antibodies, ONDQA
Douglas Warfield, Regulatory Information Specialists
Valerie Gooding, Regulatory Information Specialists

SPONSOR ATTENDEES

Seattle Genetics
Debbie Bellinghausen, Senior Manager, Regulatory Affairs (Operations)
Lynn Courtney, MS, Associate Director, Regulatory Affairs
Bruce Hart, PhD, Senior Director, Regulatory Affairs
Linda MacKeen, Director, Medical Writing
Stephen Pearce, Senior Manager, Clinical Programming
Marie Anne Stager, RN BSN, Director, Clinical Operations
Eric Sievers, MD, Executive Medical Director

Millennium Pharmaceuticals, Inc.
Ray Lubecki, RPh, Director, Worldwide Regulatory Affairs Oncology
Ellen Bolotin, Associate Medical Director, Clinical Research

BACKGROUND

Seattle Genetics is targeting a NDA submission in the first quarter of 2011 seeking accelerated approval of brentuximab vedotin for patients with relapsed or refractory HL. Seattle Genetics requests a preliminary dialogue with FDA to obtain clarity on agency expectations on key elements of the NDA compilation that are not dependent on the outcome of the pivotal trial. This early feedback would greatly facilitate the timely compilation of a NDA submission that meets FDA standards and expectations. Pre-NDA meetings based on clinical and CMC data will be requested at a later date once mature data from the pivotal trial and manufacturing campaigns become available. The preliminary responses from FDA were sent to Seattle Genetics on August 4, 2010; Seattle Genetics accepted most of the FDA responses. The following are the remaining questions which Seattle Genetics would like further discussion with FDA: Questions #1, #4, #11, #12, #13, and #20. The meeting discussions were captured for these questions.

DISCUSSION

Clinical Content

1. Seattle Genetics plans to submit CDISC transport files for SDTM and ADaM datasets in addition to study specific listings included in Appendix 16.2 of the clinical study report (CSR). Therefore, the CSR folders "Data Listing Datasets" and "Patient Profiles" will not be populated. Does the FDA agree? (See section 3.1)

FDA Response to Question #1: **You have to submit reviewable data: Data Listing Datasets, Patient Profiles including narratives are essential for adequate review. The guidance documents, as referenced in Section 3.1, do not indicate that SDTM dataset submissions remove the requirement for Data Listing Datasets and Patient Profiles.**

Meeting Discussion: **The Sponsor will submit datasets that meet the SDTM requirements and the ADaM datasets requirements. See meeting discussion under Question #13.**

2. Seattle Genetics does not plan to include radiographic images for the phase 2 study SG035-0003 in the NDA, but rather have them available to FDA upon request. Does the FDA agree? (See section 3.2)

FDA Response to Question #2: **The Division no longer accepts radiographic images.**

3. If radiographic images will be requested by FDA during the NDA review, Seattle Genetics or (b) (4) (the independent review facility) intends to provide them as PDF files. Does the FDA agree? (See section 3.2)

FDA Response to Question #=3: **The Division no longer accepts radiographic images.**

4. Seattle Genetics proposes to provide a summary listing for each patient where there is discordance between the investigator and the independent review facility assessment of best clinical response in the SG035-0003 clinical study report. Does the FDA agree with this approach? (See section 3.3)

FDA Response to Question #4: **In addition to the summary listing please provide an explanation for the discordance in each case.**

Meeting Discussion: **The Sponsor will provide the best effort to provide an explanation for the discordance in each case.**

5. All literature references cited in the clinical summaries in Module 2 (2.5, 2.7) and study reports in Module 5 will be provided in 5.4 Literature References, with the exception of literature references cited in analytical method validation study reports in 5.3.1.4 Reports of Bioanalytical and Analytical Methods, which will be available upon request. Does the FDA agree?

FDA Response to Question #5: **We do not agree. Please provide literature references cited in analytical method validation.**

Nonclinical Content

6. All literature references cited in the nonclinical summaries in Module 2 (2.4, 2.6) will be provided in Module 4.3 Literature References, whereas the majority of literature references cited in study reports in Module 4 will not be included in the NDA, but will be available upon request. Does the FDA agree?

FDA Response to Question #6: **Your approach is acceptable. However, literature references pivotal to the safety decision making or supporting statements in the label should be included with the NDA. In addition, please provide literature references cited in study reports related to metabolism and CYP/transporter induction and inhibition.**

Regulatory Content

7. Seattle Genetics proposes to submit financial interest disclosure/certification for only the phase 2 pivotal study SG035-0003. Does the FDA agree that financial interest disclosure/certification is not required for the phase 1 studies, including the clinical pharmacology studies? (See section 3.4)

FDA Response to Question #7: **If there is any chance that Phase I data will be necessary to support the efficacy or safety of your drug, financial interest disclosure/certification would be required. We encourage you to provide financial interest disclosure/certification in support of an NDA.**

Operational Issues

The following questions seek clarity on specific operational aspects necessary for compilation of the NDA; therefore a sponsor position is not presented.

Module 1

8. Signed documents (i.e., Forms 356h, 3397, 3454, 3455 and cover letter) will be provided as scanned PDFs in Module 1. Original signed forms will not be submitted. Does the FDA agree?

FDA Response to Question #8: **Yes. However, in the event of an audit, the original signed documents may be requested by the auditor. You may use electronic signatures which include scanned signed documents if you submitted letters of the Non-Repudiation Agreement (http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm113964.htm). For additional information regarding electronic signatures, please refer to the Electronic Signature web page located at http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm113223.htm.**

Please assure that scanned PDF's (including embedded tables) are formatted so that they are searchable (i.e., OCR).

9. Seattle Genetics proposes to submit the draft label in Structured Product Label (SPL) format, negotiate versions of the label in PDF format, and then submit the approved label in SPL format post-approval. Does the FDA agree?

FDA Response to Question #9: **No, we do not agree. Please submit both the Word version and PDF version.**

Meeting Discussion: **Sponsor agrees.**

Module 3

10. Brentuximab vedotin is an antibody-drug conjugate. Three separate Module 3.2.S.4 Control of Drug Substance sections will be provided in Module 3, one each for the drug substance, monoclonal antibody, and drug linker. One Module 2.3.S. Drug Substance section of the Quality Overall Summary will reference all three 3.2.S sections. Does the FDA agree?

FDA Response to Question #10: **Yes, this is an acceptable format for the proposed NDA.**

11. When applicable, clearly defined cross references will be provided, but not hyperlinked, between Module 3 granules. Does the FDA agree?

FDA Response to Question #11: **All references and cross references should be hyperlinked to provide sufficient navigation. Please refer to page 8 in the Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications (PDF - 132KB) (June 2008) and page 4 in the Portable Document Format Specifications (PDF - 57KB) (6/4/2008) .**

Meeting Discussion: **FDA requires that the Sponsor to provide the hyperlinks.**

Module 5

12. The Integrated Summary of Safety (ISS) will discuss safety data for ~300 patients. The narrative portion of the ISS (including incorporated tables and figures) will reside in Module 2 (2.7.4 Summary of Clinical Safety) and will comply with the overall page requirement (~50-400 pages) for section 2.7. Appendices of supporting tables and figures, as well as analysis datasets used in the integrated safety analyses will reside in Module 5 (5.3.5.3 Reports of Analyses of Data from More than One Study). Does the FDA agree?

FDA Response to Question #12: **Only the summaries should be placed in Module 2 (2.7.3 and 2.7.4) but complete study reports and the actual ISE and ISS should be placed in Module 5. Please also refer to the Final Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (PDF - 98KB) (April 2009). Both raw and derived datasets are required to support any summaries provided in the submission.**

Meeting Discussion: **The Sponsor will provide the summaries in Module 2 and the ISE, ISS, and complete study reports (CSR) in Module 5.**

13. The dataset for SG035-0001 (a phase 1, first-in-man study) was originally set up in non-CDISC format. SDTM data tabulations in CDISC format and analysis datasets in legacy format will be provided for this study. Does the FDA agree?

FDA Response to Question #13: **We do not agree. Please provide both analysis and SDTM data tabulations in CDISC format for SG035-0001.**

Meeting Discussion: **The Sponsor will submit datasets that meet the SDTM requirements and the ADaM datasets requirements except dataset for SG035-0001. For study SG035-0001, the Sponsor will provide the raw datasets (in SDTM format) per Study Data Specifications Version 1.5.1.**

14. Data tabulations and analysis datasets/programs for all other clinical studies will be provided in CDISC format (per SDTM v1.2 IG v3.1.2, ADaM v2.1 IG 1.0, respectively). Does the FDA agree?

FDA Response to Question #14: **We agree; however, please note that datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.**

15. The define.xml file and style sheet, plus the cascading style sheet and 3 '.gif' images for an enhanced define.xml will be provided for all clinical studies. Does the FDA agree?

FDA Response to Question #15: **We agree.**

16. Information regarding supplemental qualifier data will be provided in the SDTM define.xml file instead of in a separate 'SupplementalDataDefs.pdf' file. Does the FDA agree?

FDA Response to Question #16: **We agree.**

17. Integrated individual parent study ADaM datasets are being provided for the ISS/Integrated Summary of Effectiveness. SDTM data tabulations will not be provided. Does the FDA agree?

FDA Response to Question #17: **No, your approach is unacceptable. You should provide SDTM data tabulations for the ISE and ISS. The guidance calls for data listings and subject profiles.**

18. Annotated case report forms (blankcrf.pdf) will be provided for each clinical study with variable displays in SDTM format. Does the FDA agree?

FDA Response to Question #18: **We agree.**

19. Programs will be provided for ADaM datasets only. Does the FDA agree?

FDA Response to Question #19: **Yes, programs should be provided for both the derivation of the ADaM datasets and the analysis of those ADaM datasets.**

20. ADaM dataset programs are intended for reference only and can not be compiled. Does the FDA agree?

FDA Response to Question #20: **Aside from the data locations, the programs should be executable.**

Meeting Discussion: **The Sponsor will provide all SAS program listings in text form for all listings, tables, and figures where they computed values to perform analysis.**

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

None

ATTACHMENTS AND HANDOUTS

None

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/s/

EDVARDAS KAMINSKAS
10/23/2010

MEETING MINUTES

Meeting Type:	**Type B**
Meeting Category:	**Chemistry, Manufacturing and Controls (CMC)**
Meeting Date and Time:	**January 19, 2010**
Meeting Location:	**White Oak Building 22**
Application Number:	**IND 71634**
Product Name:	**Brentuximab vedotin (SGN-35)**
Indication:	**For the treatment of patients at high risk of residual Hodgkin lymphoma following autologous stem cell transplant**
Sponsor/Applicant Name:	**Seattle Genetics, Inc.**
Meeting Chair:	**Sarah Pope Miksinski, Ph.D.**
Meeting Recorder:	**Althea Cuff**

FDA ATTENDEES

Sarah Pope Miksinski, Ph.D., Branch Chief, Division of Pre-Marketing Assessment III, ONDQA
Terrance Ocheltree, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment III, ONDQA
Debassis Ghosh, Ph.D., Clinical Reviewer, Division of Pre-Marketing Assessment III ONDQA,
Marjorie Shapiro, Ph.D., Chief, Laboratory of Molecular and Developmental Immunology, DDOP

SPONSOR ATTENDEES

Bruce Hart, Ph.D., Senior Director, Regulatory Affairs
Nathan Ihle, PhD, Senior Director, Process Chemistry
Morris Rosenberg, DSc, Executive Vice President, Development
Vaughn Himes, PhD, Executive Vice President, Technical Operations
Philip Tsai, PhD, Senior Director, Bioprocess Development
Chuck Smith, Senior Director, Quality Assurance/Quality Control
Shan Jiang, PhD, Associate Director, Formulations
Michael Sun, PhD, Associate Director, Process Chemistry
Kevin Anderson, PhD, Principle Scientist, Analytical Biochemistry & Formulations
Michael Glacken, PhD, Senior Director, Biologics Process Development, Millennium Pharmaceuticals
Colleen Costello, Ph.D, Director, Regulatory Affairs, Millennium Pharmaceuticals

BACKGROUND

On November 9, 2009, Seattle Genetics submitted a meeting packaged to discuss the following:

- Seattle Genetics is planning for an NDA submission in the first half of 2011 seeking accelerate approval of brentuximab vedotin for patient with relapsed/refractory HL.
- Seattle Genetics is seeking agency comment on the proposed commercial process (Process C) control and validation strategies for NDA submission and commercial launch.

The Sponsor submitted a subsequent background package on December 11, 2009, which contained questions for FDA consideration. On January 12, 2010, FDA communicated their preliminary responses to the posed questions.

Seattle Genetics wanted to focus on Questions 1, 3, 5 and 7.

DISCUSSION

1. Does FDA agree that the proposed control strategy for GMP intermediate SGD-1006, including raw materials, in-process controls, and release testing is acceptable for commercial manufacture?

FDA Response:

Raw materials:

Your designation of the proposed starting materials is incomplete. Based on your proposed synthetic scheme, there are (b) (4) potential starting materials. (b) (4) starting materials (b) (4) and the remaining (b) (4) starting materials (b) (4) are (b) (4) available from various suppliers.

- For the (b) (4) starting materials, provide at least two methods of identification, assay, impurity profile, chiral purity, diastereomer content (if applicable), acceptance criteria, test methods and certificates of analysis from the supplier and the applicant.

- For (b) (4) starting materials, provide a brief description of synthesis and literature reference (if available) or refer to DMF including the letter of authorization from the DMF holder to use such information (if applicable), purging studies to show the removal of carryover impurities in the (b) (4), and all of the attributes mentioned above for the (b) (4) available starting materials. In addition, report any possible changes in the process and the supplier before the implementation of such changes.

  Provide a specification for reagents, solvents, and auxiliary materials. List all tests to which the material will conform and the associated acceptance criteria in the specification and include a reference to the analytical procedure that will be used to perform each test. When contamination with viral adventitious agents or transmissible spongiform encephalopathy (TSE) agents is a concern, additional information may be warranted. The adequacy of the information will be determined during the NDA review process.

In-process Controls:

Your proposed In-Process controls appear to be reasonable. However, identify critical process parameters and discuss how these affect critical quality attributes of SGD-1006.

Release testing:

Revise your proposed lot release testing attributes. Consider the following:

- (b) (4)
- Report any Organic Impurities and residual solvent as per ICHQ3A(R2).

The adequacy of the information to support commercial manufacture will be determined during the NDA review process.

MEETING DISCUSSION:

- ***The sponsor asked for some clarification on the designation of three hitherto undefined compounds as the starting materials. FDA stated that*** (b) (4) ***significantly contribute to the structure of the drug substance and might be considered as more appropriate starting materials. The sponsor agreed to consider this proposal.***
- ***The sponsor agreed to provide additional information as described in FDA response on raw materials including the six proposed starting materials.***
- ***The sponsor agreed to provide additional information as described in FDA response in the above "in-process controls."***
- ***The sponsor agreed to include*** (b) (4) ***. The acceptability of this proposal will depend on the Sponsor's demonstrated process understanding and justification as provided in the NDA.***
- ***The sponsor agreed to report any organic and residual solvents as per ICHQ3A(R2).***

2. Does FDA agree that the proposed control strategy for GMP antibody intermediate cAC10, including raw materials, in-process controls, release and stability testing is acceptable for commercial manufacture?

FDA Response:

Raw-materials and process solutions: The control strategy appears acceptable at this time, but a final determination will be made during the NDA review.

- The SOP for acceptance of each raw material should include additional testing by Seattle Genetics or your contract manufacturers and not rely solely on the Certificate of Analysis provided by the vendor.

In-process Controls: The in-process controls appear acceptable at this time, but a final determination will be made during the NDA review.

- Provide alert, action and reject limits that are appropriately justified.

Release and stability testing: The proposed release and stability testing for the cAC10 intermediate appear acceptable at this time, but a final determination will be made during the NDA review.

- It is acceptable to remove testing of (b) (4) from lot release testing provided that their removal to acceptable levels is appropriately validated.
- We support your use of the new assay for host cell proteins as product specific reagents are more sensitive than those provided commercially. It is not clear how much data will be available to establish a limit for host cell protein since it appears that the new assay will be implemented for the conformance lots. We recommend a retrospective analysis of previous Process A, B and C lots of cAC10 lots if they are available.
- Acceptance criteria listed as "determined by comparison to reference material" are acceptable provided that the reference material is well defined, e.g. the number of peaks and pI range for icIEF.
- The extinction coefficient used to determine protein concentration must be determined specifically for cAC10

3. Does FDA agree that the proposed control strategy for brentuximab vedotin bulk drug substance (BDS), including raw materials, in-process controls, release, and stability testing is acceptable for commercial manufacture?

FDA Response:

Raw-materials and process solutions: The control strategy appears acceptable at this time, but a final determination will be made during the NDA review.

In-process Controls: The in-process controls appear acceptable at this time, but a final determination will be made during the NDA review.

- Provide alert, action and reject limits that are appropriately justified.

Release and stability testing: The proposed release and stability testing for brentuximab vedotin BDS appear acceptable at this time, but a final determination will be made during the NDA review.

- Acceptance criteria listed as "determined by comparison to reference material" are acceptable provided that the reference material is well defined.

We note that cytotoxicity testing is not included as part of brentuximab vedotin BDS release. This may be acceptable provided that the BDS is homogeneous at the time of fill. Provide information on how this will be demonstrated.

MEETING DISCUSSION: There was discussion on where in the process to show homogeneity. Seattle Genetics stated that samples could be taken from different areas of the pooling tank prior to fill to demonstrate homogeneity. FDA stated this appears to be acceptable.

4. Does FDA agree that the proposed control strategy for brentuximab vedotin drug product (DP), including raw materials, in-process controls, release, and stability testing is acceptable for commercial manufacturing?

FDA Response:

Raw-materials: The control strategy appears acceptable at this time, but a final determination will be made during the NDA review.

- Provide a description of the Dot blot test. Since there will be a limited number of CMOs with adequate facilities to fill cytotoxic drugs, it is conceivable that additional antibody-drug conjugates may already be filled at this facility, or will be filled here in the future. The identity test should readily distinguish brentuximab vedotin from other antibody-drug conjugates.

In-process Controls: The in-process controls appear acceptable at this time, but a final determination will be made during the NDA review.

- Provide alert, action and reject limits that are appropriately justified.
- Based on the information provided in the meeting package, the proposed control strategy appears to be acceptable from a sterility assurance standpoint.
- The removal of the bulk sterility test (specified by 21 CFR 610.12) as was performed for the clinical batches is acceptable for the commercial manufacturing process.

Release and stability testing: The proposed release and stability testing for brentuximab vedotin DP appear acceptable at this time, but a final determination will be made during the NDA review.

- Acceptance criteria listed as "determined by comparison to reference material" are acceptable provided that the reference material is well defined.
- The release specification for sterility should be "Sterile" or "No Growth" and not reported as "NMT limit"

5. Does FDA agree that the characterization plan for cAC10 intermediate, BDS and DP is adequate to support filing of an NDA for brentuximab vedotin?

FDA Response:

The characterization plan for cAC10 intermediate, BDS and DP appears adequate to support a filing.

- Regarding the determination of product related substances and impurities, please describe which assays in Table 22 will be used for this assessment.
- Regarding the proposed testing to assess the effects of conjugation on cAC10, will the extremes of the conjugation steps be assessed?

MEETING DISCUSSION: HIC will be used (b) (4) ***for testing in the cytotoxicity assay. SEC will be used*** (b) (4) ***. Regarding the conjugation process, principles of QbD will be applied and the effects of conjugation on cAC10 will be assessed using a range of process parameters during conjugation.***

6. Does the FDA agree that no further assessment of comparability is required prior to commercial launch of brentuximab vedotin?

FDA Response:

Based on the information submitted in the briefing package, your proposal appears to be reasonable. Submit comparability data with the NDA. Final determination will be made during the NDA review process.

7. Does FDA agree that the process validation plan is acceptable?

FDA Response:

Based on the information provided in the briefing package, the adequacy of the plan can't be determined.

Provide additional details of the cAC10 lots that will be used for the DP validation process. It is acceptable to use lots that were not conformance lots, but three different cAC10 lots should be used.

Provide a more detailed genealogy of the cAC10 and SGD-1006 lots that will be used in the manufacture of the BDA and DP conformance lots.

Provide more details to justify your proposal to manufacture one DP conformance lot at (b) (4). What impact would the smaller scale have on product quality?

MEETING DISCUSSION: Seattle Genetics provided an additional figure clarifying Figure 12 in the meeting package and the 2010 Conformance plan. It was agreed to include this figure as part of the meeting minutes. See attached. The difference between "Process C", "Pre-conformance" and "Conformance" lots of cAC10, SGD1006 and BDS is that the Pre-conformance lots include additional testing and that, while the "Pre-conformance" and

"Conformance" processes are essentially the same as "Process C", there may be slight changes in the Master Batch Record reflecting optimized procedures.

From an antibody and drug linkage perspective, these lots are acceptable. Data will be evaluated when submitted.

Any proposed post-approval strategies must be included in the NDA and will become a part of the NDA review.

8. Does FDA agree that brentuximab vedotin qualifies for a categorical exclusion from the requirement for an Environmental Assessment based on the criteria set forth in 21CFR §25.15 and 25.31(b)?
FDA Response:
Based on the information submitted in the briefing package, your proposal appears to be reasonable. However, the adequacy of the information will be determined during the NDA review process.

9. Does FDA accept the structure of Module 3 utilized during clinical development, with cAC10 and SGD-1006 described as intermediates in the manufacture of brentuximab vedotin bulk drug substance, as the preferred organization for Module 3 of the planned NDA submission?
FDA Response:
Your proposal is acceptable. The section describing the development, manufacture, characterization/comparability, testing and stability of cAC10 should essentially be a stand alone unit within Module 3, containing all the information that is expected for a BLA describing a monoclonal antibody.

Additional Comments:
Provide in a single location (either in the NDA itself or prior to submission), all manufacturing facilities associated with this NDA, including the address, FEI, and specific manufacturing responsibilities for each site.

2.0 ISSUES REQUIRING FURTHER DISCUSSION

Meeting Discussion: Seattle Genetics discussed timing of Pre-NDA Meeting and what should be included in the package. The Agency indicated that the following are some of the items that should be included:

- *stability protocol*
- *site specific – commercial launch and clinical sites*
- *specification*
- *final designation of starting material*
- *vial/container changes*
- *comparability*

Meeting Minutes
Type B Meeting held January 19, 2010

3.0 CONCURRENCE:

{See appended electronic signature page}

Althea Cuff
Regulatory Health Project Manager for Quality
Division of Post-Marketing Assessment
Office of New Drug Quality Assessment

{See appended electronic signature page}

Sarah Pope Miksinski, PhD
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-71634	GI-1	SEATTLE GENETICS INC	SGN-35

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/s/

Sarah Pope Miksinski
02/24/2010

Meeting Minutes
Type A Meeting held October 1, 2009

MEETING MINUTES

Meeting Type:	**Type A**
Meeting Category:	**Guidance**
Meeting Date and Time:	**October 1, 2009**
Meeting Location:	**White Oak Building 22, Room 1311**
Application Number:	**IND 71634**
Product Name:	**SGN35**
Indication:	**For the treatment of patients at high risk of residual Hodgkin lymphoma following autologous stem cell transplant**
Sponsor/Applicant Name:	**Seattle Genetics, Inc.**
Meeting Chair:	**Ann Farrell, MD**
Meeting Recorder:	**Lisa Skarupa**

FDA ATTENDEES
Robert Justice, M.D., Director, DDOP
Ann Farrell, M.D., Deputy Director, DDOP
Edvardas Kaminskas, M.D., Clinical Team Leader, DDOP
Karen McGinn, M.D., Clinical Reviewer, DDOP
Kun He, Ph.D., Biostatistics Team Leader, OTS/OB/DBV
Gwynn Ison, M.D., Clinical Reviewer, DDOP
Iordanis Gravanis, M.D., Scientific Administrator, EMEA

SPONSOR ATTENDEES
Thomas C. Reynolds, M.D., Ph.D., Chief Medical Officer
Eric Sievers, M.D., Senior Medical Director
Dana Kennedy, Pharm.D., BCOP, Associate Medical Director
David Gray, Ph.D., M.B.A., Senior Manager, Biostatistics
Bruce Hart, Ph.D., Senior Director, Regulatory Affairs
Lynn Courtney, M.S., Associate Director, Regulatory Affairs

(b) (4)

[redacted]

BACKGROUND
On July 27, 2009 Seattle Genetics, Inc. submitted a meeting request to discuss the FDA response to the Special Protocol Assessment Request for protocol SGN35-005: "A randomized, double-blind, placebo-controlled Phase 3 study of SGN-35 and best supportive care (BSC) versus placebo and BSC in the treatment of patients at high risk of residual Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT)", submitted on April 30, 2009. The Sponsor submitted a subsequent background package on August 17, 2009 which contained questions for FDA consideration. On September 22, 2009 FDA communicated their preliminary responses to the posed questions.

Meeting Minutes
Type A Meeting held October 1, 2009

DISCUSSION

Protocol

1. a) Does FDA agree that with the proposed modifications, PFS is an appropriate primary endpoint for SGN35-005 (see Section 2.1.1)?

FDA RESPONSE: No. The clinical study as defined appears to be enrolling a heterogeneous population with up to 40% of patients being in PR/CRu and 60% in CR. We recommend that you design the trial focusing on a single population. We do not recommend PFS as an endpoint in a trial with patients who are already in CR as the study would be a maintenance trial in patients who may not need additional therapy. Additionally, we question whether achieving stable disease for those patients who are in PR/CRu would represent a clinical benefit. Lastly, we do not believe you would be able to blind this study given the side effects associated with SGN-35.

MEETING DISCUSSION: The Agency again expressed concerns about the potential enrollment of a heterogeneous population which could impact the ability of the trial to show a benefit at the end. The Agency recommended that the Sponsor carefully write the exclusion /inclusion criteria to avoid enrollment of patients who are less than a PR. The Agency also indicated that depending on the patient population proposed for the trial preferred endpoints may differ. The Sponsor's proposal to use PFS as the primary endpoint and OS as a key secondary endpoint may be acceptable.

The Agency recommends that if the Sponsor wishes to use PFS as the primary endpoint that the scans be reviewed by an independent review committee.

b) Does FDA agree that SGN35-005 with PFS as a primary endpoint could be considered a confirmatory study for full approval of brentuximab vedotin?

FDA RESPONSE: No. See response to Question 1 (a).
Whether the Agency would consider results from a single arm trial for accelerated approval will be a review issue. Please see the minutes of the Sept 1, 2009 ODAC meeting.

2. Does FDA agree that the proposed frequency of radiologic assessments is adequate to characterize PFS (see Section 2.2.1)?

FDA RESPONSE: No. See response to Question 1 (a).

3. Does FDA agree that an ad hoc radiologic assessment triggered as a result of clinical findings adequately captures progression events that occur between regularly scheduled surveillance scans (see Section 2.2.2)?

FDA RESPONSE: No. See response to Question 1 (a).

Meeting Minutes
Type A Meeting held October 1, 2009

4. Does FDA agree that frequent adequate lymphoma assessments occurring every 3 weeks during therapy and every 3 months for 1 year in follow-up thereafter are appropriate to monitor for progression in a consistent manner between the study arms (see Section 2.2.2)?

FDA RESPONSE: No. See response to Question 1 (a).

5. Would a sample size designed to demonstrate a six-month difference in median PFS between brentuximab vedotin and placebo (18 months vs. 12 months) as statistically significant be acceptable for the confirmatory study (see Section 2.3)?

FDA RESPONSE: No. See response to Question 1 (a).

Statistical Analysis Plan

6. Does FDA agree that the proposed interim analysis for futility and efficacy is acceptable (see Section 3.1)?

FDA RESPONSE: No. See response to Question 1 (a).

7. Does FDA agree that provision of unblinded treatment assignment to treating oncologists (upon request) at the time of lymphoma progression is acceptable (see Section 3.2)?

FDA RESPONSE: No, cross-over to treatment with SGN-35 is not recommended.

MEETING DISCUSSION: The Agency agrees that patients may be unblinded at progression. The Sponsor is not proposing a cross-over to SGN-35.

ACTION ITEMS
None

ATTACHMENTS AND HANDOUTS
None

Application ype/Number	Submission Type/Number	Submitter Name	Product Name
IND-71634	GI-1	SEATTLE GENETICS INC	SGN-35

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/s/

ANN T FARRELL
10/15/2009

IND 71634 Clinical Pharmacology
and Non-Clinical Meeting SGN-35
March 27, 2009 Teleconference

MEETING MINUTES

MEETING DATE: March 27, 2009 **TIME:** 1:00pm to 2:00pm **LOCATION:** Teleconference
IND 71634
Meeting Request Receipt Date: January 23, 2009
Briefing Document Receipt Date: February 25, 2009
Drug: SGN-35 {cAC10-vcMMAE(4)}
Sponsor: Seattle Genetics
Type of Meeting: Type B Meeting, Clinical Pharmacology and Non-Clinical Meeting

PARTICIPANTS:
FDA Attendees:
Ann Farrell, M.D., Deputy Director, DDOP
Karen McGinn, M.D. Clinical Reviewer, DDOP
Haleh Saber, Ph.D., Pharmacology Toxicology Reviewer, DDOP
Sophia Abraham, Ph.D. Clinical Pharmacology Reviewer, OTS/OCP/DCP5
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, OTS/OCP/DCP5
Suchitra Balakrishnan, Ph.D., Reviewer IRT, OTS/OCP/PS
Christine Garnett, Ph.D. Team Leader IRT, OTS/OCP/PS
Huifang Chen, Ph.D. Statistician fellow, OTS/OB/DBVI
Joanne Zhan, Ph.D. Statistician, OTS/OB/DBVI
Lisa Skarupa, RN, MSN, Regulatory Project Manager, DDOP

Sponsor Attendees:
Bruce Hart, PhD, Senior Director, Regulatory Affairs
Lynn Courtney, MS, Associate Director, Regulatory Affairs
Carmel Lynch, PhD, Director, Non-Clinical Development and Clinical Pharmacology
Jonathan Drachman, MD, Vice President, Translational Medicine
Nancy Whiting, PharmD, Associate Medical Director
Aileen Murphy, Director of Biostatistics
Zhihong Ping, Senior Biostatistician

Background:
As per meeting request, SGN-35 {cAC10-vcMMAE(4)} is being studied for the proposed indications: treatment of relapsed or refractory Hodgkin lymphoma and treatment of relapsed or refractory systemic anaplastic large cell lymphoma. Seattle Genetics submitted a meeting request dated January 22, 2009 to obtain FDA's comments regarding the proposed clinical pharmacology and non-clinical development strategies to support continued clinical development and NDA submission/commercial launch of SGN-35. Seattle Genetics submitted meeting background materials dated February 24, 2009. FDA submitted preliminary responses to Seattle Genetics on March 19, 2009. Below is the meeting discussion on March 27, 2009 teleconference between Seattle Genetics and the Division of Drug Oncology Products.

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List of specific questions:

Non-Clinical Questions

1. Does the FDA agree that the proposed genotoxicity study with MMAE is sufficient to describe the genotoxicity (if any) of SGN-35?

   FDA Response: We agree with your proposal to conduct the genetic toxicology studies with the free MMAE. However, the battery of studies as described in ICH S2, should be conducted. For the proposed indications, we expect the results to be submitted with your NDA.

2. Does the FDA agree that the design of the proposed single chronic toxicity study conducted in cynomolgus monkeys is sufficient to address the chronic toxicity of SGN-35? Does the FDA agree that weekly dosing for 3 months duration is appropriate?

   FDA Response: Yes, the design of your toxicology study appears to be acceptable. We concur with your proposal to conduct the chronic toxicology study of 3-month duration in Cynomolgus monkeys only.

3. Does the FDA agree that the proposed single embryo-fetal development (Segment II) study conducted in rats is sufficient to address the reproductive toxicity of SGN-35?

   FDA Response: Considering that toxicities associated with SGN-35 were mainly related to MMAE, your proposal to conduct an embryo-fetal toxicity study in rats is acceptable. To adequately assess toxicities associated with the product, we expect 3 dose levels of SGN-35 in your study, in addition to the control arm. Please also include an arm consisting of the free MMAE. If the drug (SGN-35 or MMAE) is shown to be positive for embryofetal lethality or teratogenicity, a study in a second species will not be required.

   For additional information, please see the ICH S9 DRAFT Guidance "Nonclinical Evaluation for Anticancer Pharmaceuticals," currently under discussion, posted at http://www.fda.gov/cder/guidance/8681dft.pdf.

4. Does the FDA agree that carcinogenicity studies are not required for approval of SGN-35?

   FDA Response: Yes, we agree that for the proposed indications (relapsed or refractory HL and relapsed or refractory ALCL) carcinogenicity studies will not be required.

5. Does the FDA agree that additional safety pharmacology studies are not required for approval of SGN-35?

FDA Response: Yes. Your GLP safety pharmacology study conducted with SGN-35 in Cynomolgus monkeys (CV, CNS, and respiratory effects) appears to be sufficient. A final decision will be made after review of data submitted with your NDA.

6. Does the FDA have any additional comments or considerations regarding the non-clinical plan for SGN-35?

FDA Response: Not at this time.

Clinical Pharmacology Questions

1. (b) (4)

Meeting Discussion: The sponsor proposes to collect MMAE and metabolites in urine and feces of healthy subjects. This plan may be acceptable provided the Agency concurs with the dose and the results of genetic toxicology and safety pharmacology studies. The Agency requested that the sponsor submit the protocol for review.

The Agency referred the sponsor to the referenced guidances under question #5.

2. Does the FDA agree that the proposed pharmacokinetics plan is sufficient to characterize SGN-35?
FDA Response: The proposed pharmacokinetic plan appears acceptable.

3. Does the FDA agree with the following proposals?
   a. Intensive ECG monitoring in a subset of patients treated with SGN-35 as a single-agent will adequately address the potential for QT/QTc prolongation.

FDA Response: The proposed ECG sub-study is adequate to characterize large effects on the QT interval due to SGN-35 although there is going to be significant confounding due to co-morbidities, previous anthracycline exposure, prior chemotherapy or stem-cell transplant.

   b. If the results of this monitoring do not show a signal of QT/QTc prolongation, additional studies evaluating QT/QTc will not be required for approval of SGN-35.

FDA Response: If there is no QTc signal in this assessment, performing screening ECGs and repeat ECGs as clinically indicated in future clinical studies for safety assessments is reasonable.

4. Does the FDA agree that clinical drug-drug interaction studies are not required for approval of SGN-35?

FDA Response: No, we do not agree. The clinical drug-drug interactions studies should be conducted during drug development and be included in the NDA when it is filed to provide important safety information on the use of your drug. Drug-drug interaction studies of SGN-35 with a strong CYP3A4 inhibitor (e.g., ketoconazole), a strong CYP3A4 inducer (e.g., rifampin), and a sensitive CYP 3A4 substrate (e.g., midazolam) should be conducted. We refer you to the FDA Guidance for Industry http://www.fda.gov/cder/guidance/6695dft.pdf for more information.
Meeting Discussion: Sponsor queried whether a study in healthy subjects can be conducted. FDA responded that results of the three genetic toxicology studies and the safety pharmacology studies need to be submitted for review and FDA concurrence prior to initiating the studies.
The sponsor queried whether they need to conduct all three drug-drug interaction (DDI) studies mentioned above, the Agency stated yes. The sponsor needs to submit all DDI protocols for review.

5. Does the FDA agree that studies in special populations are not required for approval of SGN-35?

FDA Response: No, we do not agree. The special populations studies should be conducted during drug development and be included in the NDA when it is filed to provide important safety information on the use of your drug. If you choose the population PK approach to assess the impact of renal or hepatic impairment on the PK of SGN-35, cAC10, and MMAE, we recommend that you enroll a sufficient number of patients with a wide range of hepatic and renal function in your studies and get enough PK samples to characterize their PK. You should pre-plan the analysis and power the study to get precise estimates (relative standard error ≤ 20%) of the mean clearance parameter in renal and hepatic impaired patients. For further information, see hepatic and renal impairment guidances at http://www.fda.gov/cder/guidance/3625fnl.pdf and http://www.fda.gov/cder/guidance/1449fnl.pdf.

6. Does the FDA have any additional comments or considerations regarding the clinical pharmacology plan for SGN-35?

FDA Response: In addition, you should address the following issues:

1. **We recommend that you conduct in vitro studies to determine whether SGN-35 and MMAE is a substrate and/or an inhibitor of the efflux transporter, P-glycoprotein.**

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2. **We recommend that you submit the following datasets in your anticipated NDA submission to support your population PK analysis:**
   - **All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
   - **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**

Additional FDA comments regarding the QTc evaluation plan:

1. **We do not agree with your null hypothesis. The sample size for an ECG sub-study is mainly determined by: (1) the distance between the non-inferiority margin (20 ms for most of oncology products) and the true mean difference to be detected; (2) the variability of the study; (3) the number of time points; (4) the shape of the true mean difference to be detected over time; (5) type I error; (6) type II error and (7) correlation of the data. Assume: (1) the data are independent; (2) type I error rate is 0.05 and (3) type II error rate is 0.15 (=power 85%). With 24 subjects, you can detect a difference of 5 ms between post-dose and baseline assuming SD = 15 ms and the non-inferiority margin of 20 ms. If the true mean difference is greater than 5 ms, your proposed sample size will not have enough power to detect that difference.**

   Meeting Discussion: The FDA clarified that the type I error rate is 0.05. The sponsor can look at the one sided 95% (or two sided 90%) upper bound of the confidence interval and compare the upper bound with the non-inferiority margin.

2. **We recommend you incorporate the following elements into your assessment of the ECGs recorded during this study:**
   a. **Use of a central ECG laboratory employing a limited number of skilled readers, to control variability in interpretation,**
   b. **Blinding of ECG readers to treatment, time, and day (i.e., Day -1; Day 1) identifiers.**
   c. **Review of all ECGs from a particular subject by a single reader on one day, and**
   d. **Pre-specify the lead for interval measurements.**
   e. **Baseline and on-treatment ECGs should be based on the same lead.**

3. **When you submit your ECG sub-study report, please include the following items:**
   a. **Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed**
   b. **Electronic copy of the study report**
   c. **Electronic or hard copy of the clinical protocol**
   d. **Electronic or hard copy of the Investigator's Brochure**
   e. **Annotated CRF**

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f. **A Define file which describes the contents of the electronic data sets**
g. **Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes for the primary statistical analyses**
h. **Please make sure that the ECG raw data set includes at least the followings: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate HR, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.). Lead, ECG ID (link to waveform files if applicable).**
i. **Data set whose QT/QTc values are the average of the above replicates at each nominal time point.**
j. **Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis**
k. **Narrative summaries and case report forms for any**
    i. **Deaths**
    ii. **Serious adverse events**
    iii. **Episodes of ventricular tachycardia or fibrillation**
    iv. **Episodes of syncope**
    v. **Episodes of seizure**
    vi. **Adverse events resulting in the subject discontinuing from the study**
l. **ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)**
m. **A completed Highlights of Clinical Pharmacology Table**

Additional Questions during the Meeting:
Seattle Genetics stated that to enroll all subjects (n=24 proposed) from the pivotal trial will be challenging as this study will enroll only 100 patients in total and enrollment has already commenced. There were 3 potential alternatives proposed to FDA in order to obtain the necessary number of patients for the QT study.

1. Would it be acceptable to enroll patient from other single-agent studies where SGN-35 is given at the same dose and schedule (1.8 mg/kg q3wk) as on the pivotal study? These other studies would potentially include patients with other CD30+ hematologic malignancies (in particular ALCL) and would have similar inclusion and exclusion criteria.

2. We are also planning a retreatment protocol where patients with Hodgkin Lymphoma or ALCL who achieved and objective response to therapy, discontinued treatment and then subsequently progressed will be enrolled to receive retreatment with SGN-35. Would it be acceptable to include patients from this retreatment protocol provided that the patients have all washed out from their last dose of SGN-35 by at least 5 half-lives?

3. Finally, would it be acceptable to enroll patients into the QT study who have already received one or more doses of SGN-35 (for example, enrolling a patient at Cycle 2+) if a baseline ECG were obtained prior to initiating treatment in the same manner with the same equipment?

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FDA response:
All three scenarios may be acceptable depending on the design of the QT study. Please submit the study protocol for review so that the clinical and IRT teams can comment.

Seattle Genetics requested the table IRT/QT team was referring to.
Table: Sample sizes for constant mean effect over time (4 time points, independent, α = 0.05, β= 0.15)

	Distance (non-inferiority margin, true mean difference to be detected)		
σ	5 (20, 15)	10 (20, 10)	15 (20, 5)
9	75	19	9
11	112	28	13
13	157	40	18
15	208	52	24
17	267	67	30
19	334	84	38

For instance, if one wants to detect a distance of 5 ms (with the non-inferiority margin of 20 ms and a true mean difference to be detected of 15 ms), a sample size of 208 per arm is needed for SD = 15 ms. On the other hand, if one wants to detect a distance of 15 ms (with the non-inferiority margin of 20 ms and a true mean difference to be detected of 5 ms), a sample size of 24 subjects per arm is needed for SD = 15 ms.

Note:
(1) With 24 subjects, you can detect a difference of 5 ms between post-dose and baseline assuming SD = 15 ms and the non-inferiority margin of 20 ms. If the true mean difference is greater than 5 ms, your proposed sample size will not have enough power to detect that difference.
(2) If the number of time points is less (greater) than 4, the sample sizes needed will be smaller (larger) than those provided in the table above. If data are correlated or if the true mean difference is a hill shape instead of a constant shape, the sample size will be reduced too.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 71634	SEATTLE GENETICS INC	SGN-35

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/s/

ANN T FARRELL
03/31/2009

MEETING MINUTES

Date: July 24, 2008 Time: 3:00pm to 4:00pm Location: FDA White Oak

IND#: 71, 634
End of Phase 1 Meeting Request Submission Date: May 22, 2008
Briefing Document Submission Date: June 23, 2008
Drug: SGN-35
Sponsor: Seattle Genetics

FDA ATTENDEES:

Robert Justice, M.D., Director, DDOP
Bhupinder Mann, M.D., Clinical Reviewer, DDOP
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCP5
Aakanksha Khandelwal, Ph.D., Clinical Pharmacology, DCP5
Jian Wang, Ph.D., Clinical Pharmacology, DCP5
Chris Holland, M.S., Statistical Reviewer, OTS/OB/DBV

SPONSOR ATTENDEES:

Eric Sievers, MD, Senior Medical Director
Dana Kennedy, PharmD, BCOP, Assistant Medical Director
Thomas C. Reynolds, MD, PhD, Chief Medical Officer
Carmel Lynch, PhD, Director, Non-Clinical Development
Nathan Ihle, PhD, Senior Director, Process Chemistry
(b) (4)
Bruce Hart, Ph.D., RAC, Senior Director, Regulatory Affairs
Aileen Murphy, MPH, Associate Director, Biometrics
Sponsor Attendees via teleconference:
Lynn Courtney, MS, Associate Director, Regulatory Affairs
Zhihong Ping, PhD, Senior Biostatistician
Rema Assaf, Senior Project Manager

Background:

On May 22, 2008 Seattle Genetics submitted a meeting request to discuss their proposed registrational Phase 2 single-agent studies in patients with relapsed or refractory HL and relapsed or refractory sALCL. The sponsor submitted a subsequent background package on June 23, 2008 which contained questions for FDA consideration. On July 21, 2008 FDA communicated their preliminary responses to the posed questions.

QUESTIONS FOR DISCUSSION

End-of-Phase 1/pre-pivotal meeting clinical questions:

Proposed Registrational Strategy for SGN-35 in Relapsed HL

Single-Arm Phase 2 Pivotal Trial

Q1 Does the FDA agree that patients who have previously received autologous stem cell transplant (ASCT) with subsequent progressive or relapsed HL represent an unmet medical need (see Section 5.2.4)?

FDA response: Yes.

Q2 Does the FDA agree that one single-arm, open-label, Phase 2 study is acceptable for accelerated approval under Subpart H for patients who have previously received ASCT with subsequent progressive or relapsed HL (see Section 5.2.5 and Appendix B)?

FDA response: A controlled randomized trial is preferred. Highly superior response rate in favor of SGN35 may support an accelerated approval with possibility of conversion to full approval if continued safety and efficacy are demonstrated favoring SGN35.

A single arm trial may be acceptable provided there is sufficient evidence of efficacy, i.e. high response rate with prolonged duration, for SGN35 with acceptable safety.

Meeting Discussion: Sponsor understands response above.

Q3 Does the FDA agree that overall objective response rate (ORR), confirmed at 5 weeks, as assessed by Cheson 2007 response criteria per independent review represents an acceptable surrogate endpoint for establishing evidence of clinical benefit in patients with relapsed or progressive HL after ASCT (see Section 5.2.6)?

FDA response: No, the confirmation at 5 weeks criterion only defines a response. In HL five weeks of response cannot be considered a clinical benefit. A response rate combined with a meaningful duration may predict clinical benefit. Note that SD is not evaluable in a single arm trial, and the clinical benefit of a partial response (PR) in patients with HL relapsed after ASCT is not established.

Meeting Discussion: Sponsor clarified that the 5 weeks criterion is for confirmation of response. Sponsor believes that durable PR represents clinical benefit. FDA agreed that the durability of the PRs is important and will be a review issue.

Q4 Seattle Genetics understands that the study results for efficacy will be a review issue in an NDA filing. With the justification provided in this briefing package, does the FDA agree that an ORR ≥ 20% represents a clinical benefit and that a one-sided 97.5% confidence interval of ORR excluding 20% in the planned single-arm study can be considered as the basis for accelerated approval under Subpart H (see Section 5.2.6 and Appendix B)?

FDA response: No, we do not agree that a 20% response rate represents clinical benefit. Note that in a patient population similar to your proposed study population, CALGB reported response rate of 75% (95% CI 57.8 to 87.9%) and CR of 17% (95% CI of 6.4 to 32.8%). Please see Bartlett, et al. *Annals of Oncology 18: 1071-1079, 2007.*

Meeting Discussion: Sponsor clarified that the 20% response rate was the lower bound of the confidence interval. They anticipate a response rate of 30-40% with a significant proportion of CRs and durable responses with acceptable safety profile. The sponsor asks whether such results would support accelerated approval. FDA stated that this would be review issue but warned that available therapy is determined at the time of regulatory action.

Q5 Does the FDA agree that the proposed secondary endpoints, including duration of response, are appropriate to support the primary endpoint of confirmed ORR (see Appendix B)?

FDA response: Please see also response to Question 4. While duration of response in the responders is important, it needs to be considered in view of the total number of responders. Note that all the patients entering your proposed trial will be exposed to the study treatment and its risks. Time-to-event endpoints such as PFS, event-free survival (EFS), and OS are not interpretable in single-arm trials.

Meeting Discussion: Sponsor agrees.

Confirmatory Study: Relapse Prevention Trial

Q6 Does the FDA agree that a randomized, double-blinded, placebo-controlled, Phase 3 study of SGN-35 vs. placebo for the prevention of relapse after ASCT, with progression-free survival (PFS) as the primary endpoint, is an appropriate confirmatory study for full approval (see Section 5.2.5 and 5.4)?

FDA response: Please clarify why the preferred endpoint for study in patients who are at high risk of relapse and death following ASCT should not be OS. What will be the control in this trial? Given the toxicities/AEs associated SGN35, how will you ensure the blinding? If SGN35 is already approved, will it be feasible to conduct the proposed confirmatory study at all, or in a reasonable time frame with due diligence.

Meeting Discussion: Sponsor clarified that progression-free survival is preferable as the primary endpoint because of confounding of OS by subsequent therapies.

The control in the trial is placebo.
The sponsor clarified that the toxicity profile of SGN-35 allows comparison with the placebo.

The sponsor plans to complete enrollment onto the confirmatory study prior to approval.

Proposed Registrational Strategy for SGN-35 in Relapsed sALCL

Q7 Does the FDA agree that patients with sALCL who have relapsed or refractory disease after first-line CHOP (or equivalent anthracycline-based multi-agent chemotherapy) therapy represent an unmet medical need (see Section 6.2.3)?

FDA response: Defining an unmet medical need is difficult in NHL. Please refer to the ODAC meeting for Marqibo.

Patients who attained a CR with CHOP or CHOP-like chemotherapy had a favorable outcome with ASCT in a reported series of 64 patients. Patients with ALK positive disease seem to have more favorable outcome in other series. Patients who are refractory to upfront CHOP or CHOP-like chemotherapy or have ALK negative ALCL can be considered to represent an unmet medical need. What will be the patients' status with regard to Rituxan, Zevalin, and Bexxar?

Meeting Discussion: (handout attached) FDA agrees this population represents an unmet medical need.

Q8 Does the FDA agree that one single-arm, open-label, Phase 2 study is acceptable for registration for patients with relapsed or refractory sALCL (see Section 6.2.3 and Appendix C)?

FDA response: No. One single-arm, open-label, Phase 2 study in the proposed patient population is not likely to be sufficient to support approval.

Meeting Discussion: A single-arm Phase 2 study may support accelerated approval depending on the response rate, including proportion of CRs, duration of response, and the risk-benefit ratio.

Q9 Does the FDA agree that the rarity of the sALCL patient population does not allow for a large randomized confirmatory study and that full approval would be granted based on the Phase 2 study (see Section 6.2)?

FDA Response: The rarity of a disease does not necessarily preclude one from performing a randomized trial.

Meeting Discussion: sponsor will consider options for confirmatory trials, e.g. a Hodgkin's study, ALCL patient post transplant, and requests a telecon to discuss them. A sufficiently large CR rate and duration might support full approval.

Q10 Does the FDA agree that overall ORR, confirmed at 5 weeks, as assessed by Cheson 2007 response criteria per independent review represents an acceptable endpoint for establishing evidence of clinical benefit in patients with relapsed or refractory sALCL (see Section 6.2.4 and Appendix C)?

FDA Response: No, the confirmation at 5 weeks criterion only defines a response, by itself it cannot be considered a clinical benefit. A response rate combined with a meaningful duration may predict clinical benefit in an appropriately defined patient population.

Meeting Discussion: See discussion under Q#3.

Q11 Seattle Genetics understands that the study results for efficacy will be a review issue in an NDA filing. However, with the justification provided in this briefing package, does FDA agree that an ORR ≥ 20% represents a clinical benefit and that a one-sided 97.5% confidence interval of ORR excluding 20% in the planned single-arm study can be considered clinically meaningful and acceptable for FDA approval (see Section 6.2.4, and Appendix C)?

FDA: See responses to questions 8 and 9 above. No, we do not agree that a 20% response rate represents clinical benefit. CR associated with a meaningful duration may be considered a clinical benefit in some populations. Clinical benefit of obtaining SD or PR while continuing a treatment is questionable; it may have some clinical value if there are no or minimal toxicities.

Can you provide us any data or literature to support the assertion that a PR in patients with ALCL is of any clinical benefit outside the context of proving that the patient has chemotherapy sensitive disease which may benefit from further high dose chemotherapy supported by ASCT?

Meeting Discussion: See discussion under Q#4.

Q12 Does the FDA agree that the proposed secondary endpoints, including duration of response, are appropriate to support the primary endpoint of confirmed ORR (see Appendix C)?

FDA response: Time-to-event endpoints such as PFS, EFS, and OS are not interpretable in single-arm trials. Please also see our responses to questions 8, 9, and 11 above.

Meeting Discussion: See discussion under Q#5.

Proposed SGN-35 Dosing Regimen and Registrational Safety Database

Q13 Does the FDA agree that the dose and schedule of SGN-35 proposed (1.8 mg/kg, every 3 weeks) is appropriate for future single-agent development (see Sections 3.2.6.6 and 4)?

FDA: Yes.

Meeting Discussion: Sponsor agrees.

Q14 Does the FDA agree that the proposed safety database of at least 175 patients treated with SGN-35 as a single agent is sufficient for registrational purposes in the intended indications (see Section 3.2.6)?

FDA: Yes.

Meeting Discussion: Sponsor agrees.

Other

Q15 Does the FDA have any additional comments or considerations regarding the clinical registrational strategy for SGN-35 in the target indications?

FDA: Recommend SPA.

Meeting Discussion: Sponsor agrees. FDA requested only the protocol, SAP, and questions for the SPA. Inclusion of patients aged 12 and above are allowed in planned pivotal studies with appropriate safety monitoring and rationale for dose. Sponsor will submit PK data to support dosing for pediatric patients.

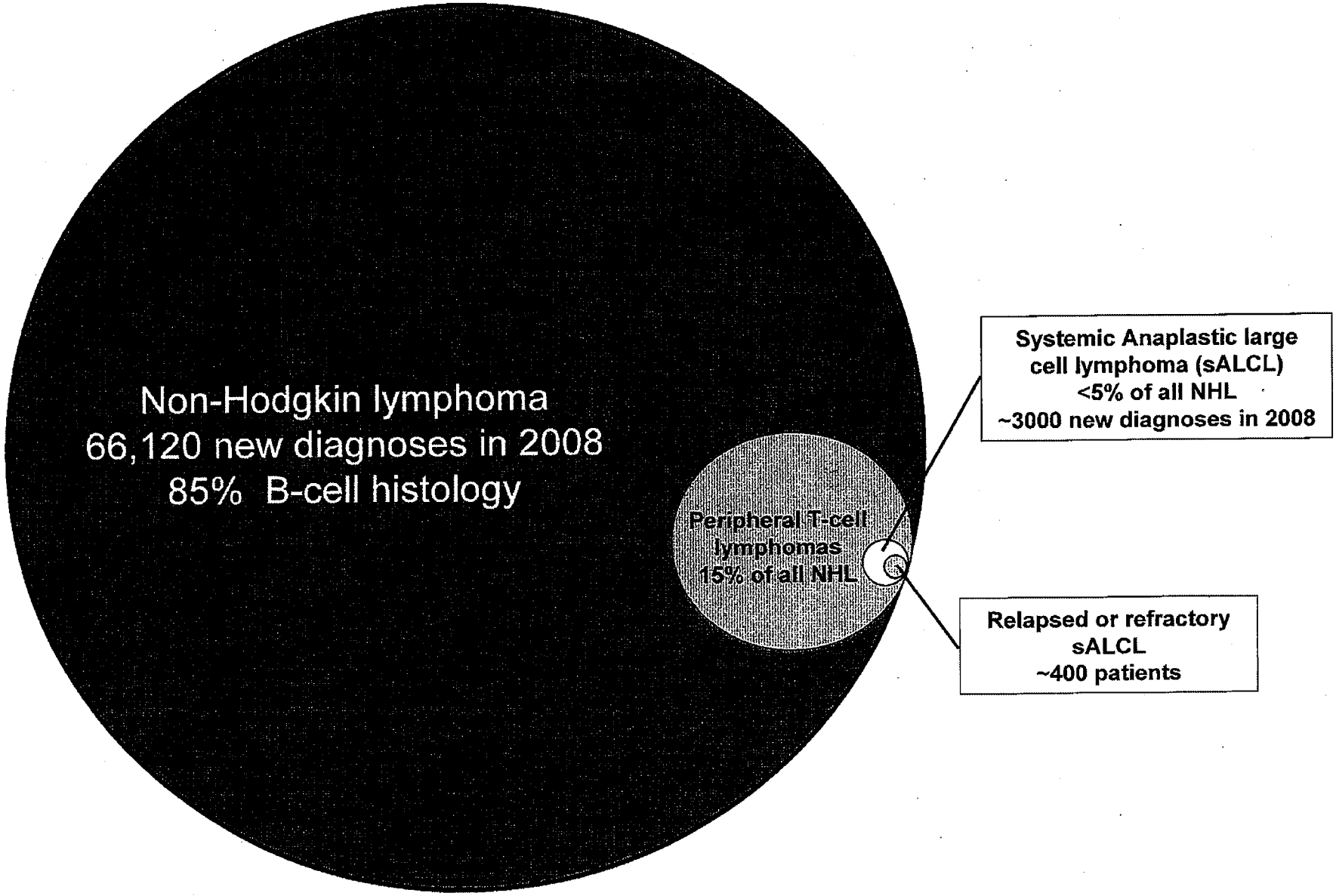
Additional Clinical Pharmacology Comments

1. **In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development. Please submit an ECG evaluation plan for review.**

2. **We remind you of the clinical pharmacology responses and comments conveyed during the pre-IND meeting dated 23-Mar-2005.**
3. **Please submit the overall clinical pharmacology plan for SGN-35.**

Meeting Discussion: Sponsor acknowledges Clinical Pharmacology Comments and will commit to scheduling meeting with clinical pharmacology.

2008 American Cancer Society Statistics



Linked Applications	Sponsor Name	Drug Name
IND 71634	SEATTLE GENETICS INC	SGN-35

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/s/

LISA M SKARUPA
08/08/2008