CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125288Orig1s000

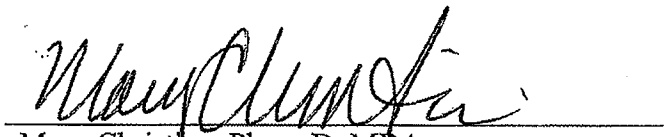
ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

BLA 125288/0/0

BELATACEPT (BMS-224818)

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.



4/22/2009
Certification Date

Mary Christian, PharmD, MBA
Director, Global Regulatory Strategy
ImmunoScience
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543
Mary.christian@bms.com
609-252-5281

Germain, June

From: Christian, Mary [mary.christian@bms.com]
Sent: Wednesday, June 01, 2011 2:39 PM
To: Germain, June
Subject: RE: PMC update: BLA 125288/belatacept

We acknowledge that the change reflects the expectation that we will re-evaluate the acceptance criteria and will submit a PMC final report. The report will include the specification, noting if a revision is warranted or not, with supportive data. If a revision to the specification is needed as a result of this data, this may require a supplement as well.

We're fine with this, June, and will revise the submission of PMCs today to reflect this accordingly. I'll let you know when the submission goes through the gateway.

-Thanks!
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Wednesday, June 01, 2011 1:42 PM
To: Christian, Mary
Subject: PMC update: BLA 125288/belatacept

Hi Mary,

Here is the updated PMC #5 wording:

Conduct a trend analysis of [redacted] (b) (4) profiles based on the results from 30 consecutively released future drug substance batches. Re-evaluate the acceptance criteria for this product attribute and submit a PMC final report. The submission should include the proposed specification and a justification that includes manufacturing data and data from lots used in the clinical trials.

Thanks
June

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BLA 125288
Belatacept
Bristol-Myers Squibb
REMS Information request

May 13, 2011

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009 and received July 1, 2009. We also refer to your resubmission of the BLA dated December 15, 2010. And also refer to your email submission of the REMS materials dated April 28, 2011.

In consultation with the Division of Epidemiology (Drug Utilization team) we have reviewed this submission and have the following comments on the REMS supporting document:

(b) (4)

2. Under the section (b) (4)

   The IMS Health, IMS National Sales Perspectives may be used to provide the volume of drugs in terms of sales (eaches, extended units, etc.) This database can be used to monitor sales and distribution data.

   (b) (4)

   The Belatacept Patient Registry, which will be a postmarketing requirement and which will attempt to enroll the vast majority of belatacept users, may yield data that can help answer the stated objective.

Please call me if you have any questions.

Sincerely,
June Germain, MS
Senior Regulatory Project Manager

BLA 125288
Belatacept
Bristol-Myers Squibb
REMS Document

April 22, 2011

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009 and received July 1, 2009. We also refer to your resubmission of the BLA dated August 16, 2010.

We have reviewed your August 16, 2010 submission which contains your proposed REMS and REMS supporting documents and we have the following comments/recommendations:

Attached is a clean version of the revised REMS document. The address of the company has been highlighted. Please revise the address with the appropriate number and street address (no PO Boxes).

Please call Ms. June Germain if you have any questions.

Sincerely,
Hyun Son, Pharm.D.
Regulatory Health Project Manager

Enclosure: Revised REMS document

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

STN: BLA 125288
Belatacept
Bristol-Myers Squibb

May 27, 2011

Dear Dr. Christian,

Enclosed please find the final REMS assessments, REMS document and PMR/PMCs. We have also reviewed your April 28 email containing the REMS attachments and your May 18 email response to the supporting document and agree with the changes.
Please submit all documents, except the REMS assessments to the BLA along with the package insert, medguide, and carton and container.

REMS assessment:

The REMS assessment plan should include, but is not limited to, the following:

1. The number of live webinars conducted and their dates.
2. The total number of unique participants at live webinars for the reporting period.
3. The date(s) of distribution of the Dear HCP Letter that occurred during the period
   a. The source(s) of the list of health care provider addresses
   b. The number of recipients at each distribution date
   c. The number of returned items
   d. A list of the documents included in each distribution
4. Journal information pieces published, including date and journal name, volume, and issue.
5. For each infusion center ordering Nulojix (belatacept) for the first time during the reporting period, the date of initial order, and the date of distribution of tear pads of pre-infusion checklists.
6. A survey of healthcare providers' and patients' understanding of the serious risks of Nulojix (belatacept).
7. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
8. A report on failures to adhere to distribution and dispensing of the Medication Guide, and corrective actions taken to address noncompliance.
9. A summary of all reported cases of PTLD and PML during the preceding reporting period.
10. An analysis of prescribers' compliance with the labeled contraindication regarding the use of Nulojix (belatacept) in EBV negative patients and patients in whom EBV-status is unknown.
11. A plan to monitor sales data to evaluate:
    a. A number of patients treated, reported by transplant organ received
    b. Number of units shipped, reported by year and type of healthcare setting (e.g., transplant center, infusion center, hospital)
12. Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical

trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the list above, the initial assessment should also include the following:

1. Launch date of Nulojix
2. The date the links to the full prescribing information, medication guide, and all approved REMS materials became available on the Nulojix REMS landing page.
3. Number of transplant centers visited within 90 days of launch and within 150 days of launch, and percentage of transplant volume covered by each transplant center visited.
4. The date(s) of distribution of the Dear Infusion Specialist Letter
    a. The source(s) of the list of infusion specialists
    b. The number of recipients
    c. The number of returned items
    d. A list of the documents included in the mailing

REMS public document:

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MANUFACTURING

4. Conduct a study to quantify at the end of the proposed [redacted] Provide a worst case risk assessment for those [redacted] including potential toxicity to humans, in your final report.

Final Report Submission: 12/2012

PMC:

5. [redacted]

6. Conduct a trend analysis for [redacted] content using an extended characterization [redacted] to generate informational data and based on the results from 30 consecutively released future drug substance batches, evaluate the need for introducing a validated release method and setting acceptance criteria for this product attribute, or provide justification for not requiring a [redacted] content release method.

Final Report Submission: 12/2013

7. Provide a protocol describing the conditions and criteria which will be applied for assessing the stability of any drug substance lot held for the maximum hold time allowed at each [redacted]

Final Report Submission: 12/2011

8. Provide information and summary data on the product specific dye-ingress container closure, integrity test method and provide an updated post-marketing stability protocol replacing the sterility test with CCIT.

Final Report Submission: 12/2012

9. Perform a study to support multiple freezing-thawing of drug substance (DS) that incorporates conditions reflective of the intended use (multiple freeze-thaws, including

shipping). Also, provide DS stability data confirming a cumulative stability limit of greater than 12 months at 2-8°C before and after multiple freeze-thaw cycles. In addition, provide stability data for drug product produced from DS that has undergone multiple freeze-thaw cycles.

Interim Report Submission: 12/2011
Final Report Submission: 12/2013

10. Develop characterization methodology for micron and submicron subvisible particulates using stressed and/or accelerated drug product samples to assess whether a correlation may exist between subvisible particulates in the micron and submicron ranges and propose an appropriate control strategy for drug product stored under the approved conditions.

    Final Report Submission: 12/2012

Sincerely,
June Germain, MS
Senior Regulatory Project Manager

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE:	March 25, 2011
TIME:	2:00 PM to 3:00 PM EST
APPLICATION:	BLA 125288
DRUG NAME:	belatacept
MEETING CHAIR:	Renata Albrecht, MD Division Director
MEETING RECORDER:	June Germain, MS Regulatory Project Manager

FDA ATTENDEES:

Renata Albrecht, MD	Division Director (DSPTP)
Ozlem Belen, MD	Deputy Director for Safety (DSPTP)
Joette Meyer, PharmD	Clinical Team Leader (DSPTP)
Patrick Archdeacon, MD	Medical Reviewer (DSPTP)
Phillip Colangelo, PhD	Clinical Pharmacology Team Leader (OCP/DCP 4)
L. Shenee Toombs, PharmD	Safety Evaluator (DMEPA)
Irene Chan, PharmD	Acting Team Leader (DMEPA)
June Germain, MS	Regulatory Health Project Manager (DSPTP)

EXTERNAL CONSTITUENT ATTENDEES:

Elyse Stock, MD	Vice President, Developmental Lead belatacept
Laura Bessen, MD	VP Medical Affairs US
Mary Christian, PharmD	Group Director, Global Regulatory Sciences
Alan Traettino, MS	Director, Regulatory Sciences US
Mary Beth Harler, MD	Executive Director, Global Clinical Research
Isolde Puschmann, PhD	Director, Global Regulatory Sciences
Christian Klem, PharmD	Global Scientific Communications
Sheila Gujrathi, MD	Vice President, Global Clinical Research

BACKGROUND:

On March 24, 2011 the Division requested a teleconference with BMS to discuss issues with the **DOSAGE AND ADMINISTRATION** section 2.1 and 2.2 of the package insert.

MEETING OBJECTIVES:

To notify BMS of the issues relating to the dosing of the drug product and the silicone free syringe supplied in the container.

DISCUSSION POINTS:

The Division stated that the content of section 2.2 was generally acceptable but they would be sending some updates on formatting and rearranging of text in the section. The Division noted that the major issue was with section 2.1 of the dosing section. The Division stated that the silicone free syringe used in the clinical trials had markings in units (b) (4) however BMS plans to market the product using a syringe with markings in units of 0.5 ml. The Division also noted that the (b) (4) (b) (4)

(b) (4). The Division noted that the concern was that the drug product could only be used with the silicone free syringe provided which does not support the dose as prescribed (b) (4). The Division referred BMS to the Orencia labeling for pediatric patients with JRA for an example of the dosing used in that package insert. The FDA also suggested asking the syringe manufacturer if it would be possible to make a syringe specifically to be used with Nulojix and to provide wording on the syringe sterile overwrap to the effect that it is to be used only with Nulojix. BMS agreed to provide a sample of the drug product with its packaging that includes the syringe, vial and container for review. BMS also agreed with the concerns shared by the FDA and agreed to continue internal discuss by looking at other antibiotics their specific labeling text in 2.1 and the appropriate volume and syringe used for Nulojix.

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE:	March 23, 2011
TIME:	10:00 AM to 11:00 AM EST
APPLICATION:	BLA 125288
DRUG NAME:	belatacept
MEETING CHAIR:	Ozlem Belen, MD Deputy Director for Safety
MEETING RECORDER:	June Germain, MS Regulatory Project Manager

FDA ATTENDEES:

Ozlem Belen, MD	Deputy Director for Safety (DSPTP)
Joette Meyer, PharmD	Clinical Team Leader (DSPTP)
Patrick Archdeacon, MD	Medical Reviewer (DSPTP)
Suzanne Robottom, PharmD	Team Leader (DRISK)
Amarilys Vega, MD	Deputy Director and Acting Team Leader (Depi)
Kate Heinrich, MA	Health Education Reviewer (DRISK)
Anahita Tavakoli, MA	Health Education Reviewer (DRISK)
June Germain, MS	Regulatory Health Project Manager (DSPTP)

EXTERNAL CONSTITUENT ATTENDEES:

Elyse Stock, MD	Development Lead for belatacept
Marybeth Harler, MD	Medical Lead for belatacept
Joseph Lamendola, VP	US Regulatory
Laura Bessen, MD, VP	US Medical, Immunoscience & Neuroscience
Pamela Turnbo, MD	Global Safety and PV
Mary Christian, PharmD	Global Regulatory
Alan Traettino, MS	US Regulatory

BACKGROUND:

On March 1, 2011 the Division sent via email a copy of the propose language for the REMS supporting documents. On March 18, 2011 BMS requested a teleconference to discuss their proposed revisions to the documents and clarify their proposed edits/revisions in the package insert.

MEETING OBJECTIVES:

To clarify the language added to the REMS documents and package insert.

DISCUSSION POINTS:

On the March 23, 2011 teleconference BMS provide clarified that the webinar would be prerecorded, scripted with voice over that walks the HCP through the slide deck which will be available (b) (4). BMS agreed to submit the script for the webinar, their plans on how it will promote the availability of the (b) (4) webinar and also provide a name for the US registry. The FDA questioned why BMS wanted to include the pre-infusion checklist in the carton and container. BMS noted that since most distributors will not ship tear pads it is the most reliable way to deliver the checklist in the carton and container

with a glow sticker indicated that it was included to help remind the HCP and pharmacy to discuss with the patient. BMS agreed to provide information in real time with manufactures of shipping the product. FDA agreed to provide comments on the package insert and the REMS supporting document within the coming week.

Wrap-Up meeting and Safety Discussion Minutes
Date: March 22, 2011
Time: 9:00 AM to 11:00 AM EST

BLA 125288
Nulojix (belatacept)
Indication: Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants

The original BLA was submitted on June 30, 2009, received July 1, 2009 (Standard review, CR issued May 1, 2010)

Resubmission of BLA:

August 16, 2010: Response to the proposed REMS deficiency
September 9, 2010: Response to the CMC product quality deficiency
September 24, 2010: Responses to the clinical, product quality microbiology, facility inspections, safety update, labeling, nonclinical study reports, clinic study reports, and medication guide deficiencies.
December 15, 2010: Response to facilities inspection readiness

1. Important Goal Dates

   Review Completion Goal Date according to GRMP: **March 23, 2011**

   Division Goal Date: **April 15, 2011**

   PDUFA Goal Date: **June 15, 2011**

2. Discipline Specific Reviews of Application

   a. CMC – Jack Ragheb indicated that his primary review was completed and that he would have additional labeling changes. He also stated that a teleconference was to take place with BMS on March 22, 2011 as 3 pm to discuss and clarify the PMCs related to the drug product stability study and the container closure integrity test.

      -Bo Chi indicated her review was finalized and in the eroom and no labeling changes. She also indicated that the inspection at the Manati Puerto Rico facility indicated that there may be a possible OAI issued but a final decision could be another week away at the closeout meeting.

   b. P/T – Janice Lansita indicated they would have additional labeling changes and her review was with her TL

   c. Micro-Aaron Ruhland indicated primary review sent to TL and on track for target date with additional labeling changes

   d. Clin Pharm/Biopharm – Gerlie indicated her review was complete and with TL with additional labeling change

e. Stats – Cheryl Dixon indicated her review was finalized and in eroom and no labeling change

f. Clinical- Patrick Archdeacon indicated review complete and with TL. He indicated there was still an issue with ummunogenicity and would be discussing with Pharmacology/Toxicology and Microbiology reviewers to finalized

g. REMS – Suzanne Robottom indicated REMS supporting documents sent to the sponsor, working on REMS document and Tcon with sponsor to discuss their proposal to include pre-infusion checklist in arton container

h. DMEPA- Shenee Toombs stated that DMEPA had some labeling changes for section 2.1 and 2.2 of the Dosage section

i. DDMAC-Sharon Mills indicated the her review was finalized

3. Discussion of Proposed Action To Be Taken – Renata Albrecht stated that in light of a possible OAI issued to the manufacturing facility the application would receive a CR action. She stated that the review timetable should be continued to be followed.
4. Labeling: The current labeling was reviewed section by section with input from each discipline's on their proposed changes.
5. Safety Discussion: Chris Jones and Kelly Cao was briefed on the safety concerns with PML and PTLD and that they would be handle through REMS and PMC/PMR

Authored: June Germain, MS
Regulatory Health Project Manager

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE:	March 22, 2011
TIME:	03:00 PM EST
APPLICATION:	BLA 125288
DRUG NAME:	belatacept
MEETING CHAIR:	Barry Cherney, PhD Deputy Director (DTP)
MEETING RECORDER:	June Germain, MS Regulatory Project Manager

FDA ATTENDEES:

Barry Cherney, PhD	Deputy Director (DTP)
Susan Kirshner, PhD	Associate Chief Laboratory of Immunology (DTP)
Jack Ragheb, MD	Product Quality Reviewer (DTP)
June Germain, MS	Regulatory Health Project Manager (DSPTP)

EXTERNAL CONSTITUENT ATTENDEES:

Denise Perniciaro, MS	Director CMC Regulatory
Meena Bakhshi, PhD	Manager, CMC Regulatory
Mark Rosolowsky, PhD	Vice President CMC Regulatory
Steven Klohr, PhD	Group Director, Research & Development
Madhav Kamat, PhD	Research Fellow, R&D
Teresa Feeser, PhD	Director, Quality Operations
Mary Christian, Pharm D	Global Regulatory
Alan Traettino, MS	US Regulatory

BACKGROUND:

On March 16, 2011 the Division sent via facsimile a copy of the propose language for the PMC and PMR. On March 18, 2011 BMS emailed a request for a teleconference to discuss and clarify PMC (b) (4) content, (b) (4) and (b) (4) on the container closure.

MEETING OBJECTIVES:

To clarify the CMC PMCs on (b) (4) content, stability and container closure. BMS seeks clarification on the rationale for the (b) (4) content, the design of the stability study and clarification on the design and timing on the container closure PMC

DISCUSSION POINTS:

On March 22, 2011 a teleconference was held with BMS. Regarding PMC (b) (4) BMS agreed to propose revise language of the study to be conducted and timeline. Regarding PMC (b) (4) BMS agreed to propose new wording on the specifics language of the study to be perform with new timelines for the protocol submission, study completion and final report, and to perform separate analysis if the batch data is outside of the limits. Regarding PMC (b) (4) BMS agreed to revise the language of the protocol to be conducted and agreed the June 30, 2010 final report submission date would be acceptable. BMS to agreed to submit PMC/PMR proposed language on March 24, 2011.

STN: BLA 125288
Belatacept
Bristol-Myers Squibb

May 18, 2011

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009 and received July 1, 2009. We also refer to your resubmission of the BLA dated December 15, 2010. Enclosed please find our comments on your submission dated March 15, 2011 that included a final draft protocol for Study IM103076, a draft informed consent form, a draft statistical analysis plan, draft non-formatted case report forms and an approach and timeline for transplant center engagement.

We reviewed the revised protocol for Study IM103076 including the draft statistical analysis plan (SAP) and have the following comments and clarifications:

(b) (4)



Sincerely,
June Germain, MS
Senior Regulatory Project Manager

STN: BLA 125288
Belatacept
Bristol-Myers Squibb
Information request

March 16, 2011

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009 and received July 1, 2009. We also refer to your resubmission of the BLA dated December 15, 2010. In order to facilitate the review of your submission we request that you submit the following information by March 24, 2011, if possible.

POST-MARKETING REQUIREMENTS (PMRs)

1. Conduct a study to quantify at the end of the (b) (4) Provide a worst case risk assessment for those (b) (4) including potential toxicity to humans, in your final report.

   Final Protocol Submission Date:
   Study Completion Date:
   Final Report Submission Date:

2. Conduct a prospective, observational study utilizing data from the United Network for Organ Sharing (UNOS) on the pattern of belatacept use in US adult kidney-only transplant recipients at transplant and one year post-transplant. Specifically, the study should assess the prevalence of belatacept use, characteristics of belatacept users, including Epstein-Bar Virus (EBV) and cytomegalovirus (CMV) serostatus. In addition, the study should collect information on adult kidney-only transplant recipients who switch to or from belatacept within one year post-transplant. (Protocol Number IM103074)

   Final Protocol Submission Date: April 2012
   Study Completion Date: April 2019
   Final Report Submission Date: April 2020

3. Conduct a prospective observational study utilizing data from the United Network for Organ Sharing (UNOS) on the incidence rates of post-transplant lymphoproliferative disorder (PTLD) in US adult kidney-only transplant recipients who are treated with belatacept compared to recipients treated with calcineurin inhibitor (CNI)-based regimens. Recipient characteristics will be collected, including EBV and CMV serostatus, location of the PTLD, and outcome (survival or mortality). Incidence rates of PTLD in belatacept-exposed patients will be quantified beginning when 500 belatacept-exposed patients have at least 1 year of follow-up. Relative risks of PTLD for belatacept compared to CNI-based regimens will be

estimated after 1,000 person years have been accumulated in transplant recipients initiated on belatacept at transplantation. (Protocol Number IM103075)

Final Protocol Submission Date: April 2012
Interim Analysis Report Date:

Note to BMS: Please include a proposed date for an interim analysis, for example 3 years after starting data collection.

Study Completion Date: April 2019
Final Report Submission Date: April 2020

4. Conduct a prospective registry of use of belatacept in US adult kidney-only recipients to estimate the incidence rates of PTLD, PTLD in the central nervous system (CNS PTLD), and progressive multifocal leukoencephalopathy (PML) (b) (4) (b) (4) All US adult kidney transplant centers dispensing belatacept will be asked to participate in the study (i.e., if a center does not respond or declines to participate, the reason(s) for nonparticipation will be identified and documented). Recipient characteristics will be collected, including EBV and CMV serostatus, location of the PTLD, and outcome (survival or mortality). (Protocol Number IM103076)

Final Protocol Submission Date: April 2012
Study Completion Date: April 2019
Final Report Submission Date: April 2020

POST-MARKETING COMMITMENTS (PMCs)

5. (b) (4)

6.

7. (b) (4)

Please propose any dates that has not been provided. You should consider giving yourself leeway for unexpected/unavoidable delays. Additionally, for dates that we have provided, you can propose alternate dates, if you feel it is warranted.

Let me know if you have any questions or if you are unable to meet the deadline for responding to this information request.

Thanks
June Germain, MS
Regulatory Health Project Manager

Germain, June

From: Germain, June
ent: Friday, March 11, 2011 2:05 PM
o: 'Christian, Mary'
Subject: Syringe package: BLA 125288/belatacept

Hi Mary,

DMEPA has asked that you submit a draft of the syringe label to the BLA, we will have comments on it and need an official submission.

June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

BLA 125288
Belatacept
Bristol-Myers Squibb
REMS Information request

March 1, 2011

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009 and received July 1, 2009. We also refer to your resubmission of the BLA dated August 16, 2010.

We have reviewed your August 16, 2010 submission which contains your proposed REMS and REMS supporting documents and we have the following comments/recommendations:

A. REMS

1. All approved REMS materials should include a footnote statement communicating that the material is part of a REMS. For example "This <<piece>> is part of the NULOJIX REMS."
2. We recommend including information on the Registry in the REMS materials to increase its visibility.
3. Revise all materials to ensure information is consistent with the final approved labeling.

B. Goals

1. Revise the goals of the REMS as follows:

The goals of the belatacept REMS are:

- To inform healthcare providers of the increased risk of PTLD, predominantly in the CNS, associated with belatacept
- To inform healthcare providers of the increased risk of CNS infections, including PML, associated with belatacept
- To inform patients of the serious risks associated with belatacept

C. Medication Guide

Comments on the Medication Guide will be provided under separate cover.

D. Communication Plan
DHCP Letter

1. The DHCP Letter will be disseminated with the Fact Sheet. Therefore, revisions to the DHCP letter are provided with this in mind.
2. See attached revised DHCP letter.

HCP Fact Sheet

1. See attached revised HCP Fact Sheet.

Infusion Letter

1. Clarify whether infusion centers/suites that are part of an outpatient transplant clinic will receive the infusion letter.
2. We recommend a copy of the Infusion Checklist accompany the Infusion Specialist Letter. Therefore, revisions to the letter are provided with this in mind.
3. See attached revised infusion letter.

Pre-Infusion Checklist

1. We do not recommend including the checklist as part of vial carton packaging. We recommend providing tear pads to transplant centers and infusion centers along with making an electronic version available on the belatacept REMS website. We agree that the checklist should be distributed when belatacept is ordered. Transplant centers and infusion centers should be able to order tear pads through various mechanisms (sales rep, phone, website, etc.)
2. The electronic version of the checklist should be in a format that allows it to be incorporated into exisitng electronic medical records/systems.
3. Ensure the language written to the patient in plain language is consistent with the Medication Guide.
4. See attached revised Checklist.

Journal Information Piece

1. You state that the journal information piece will be based on the Fact Sheet. We recommend that you condense the information for the journal information piece.
2. Submit the proposed journal information piece.

Website

1. Submit the proposed website for review.

Webinar

1. Clarify if the webinar will be a slide set accessible via the web or if you intend to augment the slides with voiceover, video, or other media/technology.
2. Clarify how you plan to use the proposed slides. For example, will these slides be presented as part of a slide presentation or only as a standalone presentation/webinar?
3. Revise the slide set based on the comments and revisions on the other materials and submit a revised proposed slide set.

E. Supporting Document

Revise the REMS Supporting Document to be consistent with all changes made to the REMS document.

F. Submission Instructions

1. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document. Provide responses to outstanding questions from the September 29, 2010 comments and this comment set.
2. Format Request:
   a. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.
   b. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.
   c. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document. However, changes must be noted using PDF mark-up tools.

ATTACHMENTS

- DHCP Letter
- HCP Fact Sheet
- Infusion specialist letter
- Pre-Infusion checklist

We request that you submit the following information by February 15, 2011, if possible. Please call me if you are unable to meet this deadline.

Sincerely,
June Germain, MS
Regulatory Health Project Manager

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

BLA 125288
Belatacept
Bristol-Myers Squibb
Information request

February 23, 2011

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009 and received July 1, 2009. We also refer to your amendment dated September 9, 2010. In order to facilitate the review of your submission we request that you submit the following information by March 4, 2011, if possible.

1. For the (b) (4) stability study presented in Table 1d.T01 and Table 1d.T02 of your September 9, 2010 amendment, please provide the DS lot #s and the temperature and hold times for each of the (b) (4)

2. Regarding the criteria applied to the data in Table 1d.T01 and Table 1d.T02, as there are (b) (4) Stability Assay/Tests specifications for the (b) (4) must be equivalent to or more stringent than those for DS release (e.g. oxidation). Please justify the specifications you have set or revise accordingly.

Please call me if you have any questions.

Thanks
June Germain, MS
Regulatory Health Project Manager

MEMORANDUM OF MEETING

Meeting Date:	February 1, 2011
Application Number:	BLA 125,288
Product Name:	belatacept
Indication:	Prophylaxis of organ rejection in adult patients receiving renal transplant
Sponsor:	Bristol-Myers Squibb
Meeting Chair:	Renata Albrecht, MD
Meeting Recorder:	June Germain, MS

FDA ATTENDEES:

Renata Albrecht, MD	Director, DSPTP
Patrick Archdeacon, MD	Medical Reviewer, DSPTP
Joette Meyer, PharmD	Clinical Team Leader, DSPTP
Suzanne Robottom, PharmD	Team Leader, OSE/DRISK
Ozlem Belen, MD	Safety Deputy Director, DSPTP
Hyun Son, PharmD	Safety Project Manager, DSPTP
Cheryl Dixon, Ph.D	Statistical Reviewer, OB/DBIV
LaRee Tracy, PhD	Statistical Team Leader for Safety, OB/DBVII
John Yap, PhD	Statistical Safety Reviewer, OB/DBVII
Elizabeth Maloney, MS DRPhD	Epidemiology Team Leader, OSE/DEPI
Andrew Mosholder, MD	Medical Officer, OSE/DEPI
June Germain, MS	Regulatory Project Manager, DSPTP

BMS ATTENDEES:

Mary Christian, PharmD	Group Director, Global Regulatory Sciences
Alan Traettino, MS	Director, Regulatory Sciences, US
Laura Bessen, MD	Vice President, Medical Affairs, US
Kalyan Ghosh, PhD	Executive Director, Global Biometric Sciences
Andres Gomez, PhD	Executive Director, Pharmacoepidemiology
Mary Beth Harler, MD	Executive Director, Global Clinical Research
Chen-Sheng Lin, PhD	Director, Global Biometric Sciences
Pamela Turnbo, MD	Associate Medical Director, Global Pharmacovigilance and Epidemiology
Elyse Stock, MD	Vice President, Developmental Lead belatacept

BACKGROUND:

On June 30, 2009 Bristol-Myers Squibb (BMS) submitted a biologics license application (BLA) for belatacept in electronic format following the electronic CTD structure. On May 1, 2010 a Complete Response letter was issued to the BLA.

On September 27, 2010 a face to face meeting was held with representative of BMS and the FDA to discuss post-marketing studies of belatacept. At that meeting BMS agreed to conduct a prospective registry study not based on UNOS data collection (refer to meeting minutes of that meeting).
On November 24, 2010, the applicant submitted a request for a meeting to discuss the proposal for a US registry study design. The Division granted the meeting on December 8, 2010 and BMS submitted a briefing package in support of the meeting discussion on December 20, 2010. On January 25, 2011 the Division sent preliminary responses to the question posted in the November 24, 2010 briefing document. On January 27, 2011 BMS submitted comments and clarification for questions 2, 5, 6, 7, 9 and 11 in response to the Division's preliminary comments. And on January 28, 2011 BMS submitted the statistical responses to question 6 along with the references cited therein. The face to face meeting was converted to a teleconference and was held on February 1, 2011.

MEETING OBJECTIVE:
The purpose of the meeting was to discuss BMS' proposed draft protocol IM103076 for the prospective (b) (4)' study (Postmarketing Registry Study).

For the purposes of these minutes, BMS' questions posted in the briefing document are in **bold** font, the FDA's preliminary comments are in *italics* and a summary of the meeting discussion is in regular font.

Question 1: Does the Agency concur with BMS overall objectives and study design for the conduct of the US registry?

FDA Response:

(b) (4)

We note that the primary objective of the study should be to estimate the incidence rates of PTLD, CNS PTLD, and PML in EBV seropositive adults undergoing kidney transplantation, as the proposed labeling contradicts its use in patients who are EBV seronegative or have unknown EBV serostatus. (b) (4)

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: January 25, 2011

To: Mary Christian, PharmD Director, Global Regulatory Strategy	**From:** June Germain, MS Regulatory Health Project Manager
Company: Bristol-Myers Squibb	Division of Special Pathogens and Transplant Products
Fax number: (609) 252-6000	**Fax number:** (301) 796-9881
Phone number: (609) 252-5281	**Phone number**(301) 796-4024

Subject: Preliminary responses briefing package questions submission dated December 20, 2010.

Total no. of pages including cover: 9

Comments:

Document to be mailed: **YES** ☑ **NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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BLA 125288
Belatacept
Bristol-Myers Squibb
Briefing Package Comments

Dear Dr. Christian,

The following are the Division's preliminary responses to the questions posted in your briefing package dated December 20, 2010 for belatacept for the prophylaxis of rejection in adult patients receiving renal transplants and the draft protocol IM103076 for the prospective (b) (4) study (Postmarketing Registry Study).

If these answers and comments to your questions are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting. You can also request that the face-to-face meeting be converted to a teleconference.

Please note that if there are any major changes to your development plan, or the purpose of the meeting, or new questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting to be held on January 26, 2011. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

For the purposes of this response, your questions are in **bold** font and our responses are in normal font.

Question 1: Does the Agency concur with BMS overall objectives and study design for the conduct of the US registry?

FDA Response:
The proposed overall study design is a prospective registry of belatacept users which will (b) (4)

We note that the primary objective of the study should be to estimate the incidence rates of PTLD, CNS PTLD, and PML in EBV seropositive adults undergoing kidney transplantation, as the proposed labeling contradicts its use in patients who are EBV seronegative or have unknown EBV serostatus (b) (4)

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

(b) (4)

[redacted]

Thanks
June Germain
Regulatory Health Project Manager

BLA 125288
Belatacept
Bristol-Myers Squibb
Information request

January 20, 2011

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009 and received July 1, 2009. We also refer to your resubmission of the BLA dated September 24, 2010.

In the September 24, 2010 submission which contains your revised belatacept PLR, we note that you included a paragraph describing the results seen in the EBV seropositive sub-population for both Study 1 and Study 2, as requested. However, you only discuss the rates of patient and graft survival. Please explain why you did not discuss overall efficacy failure, which includes BPAR, graft loss, death, and lost to follow-up

Please call me if you have any questions.

Thanks
June Germain, MS
Regulatory Health Project Manager

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
ER-DDMAC-RPM	June Germain, RPM, OAP/DSPTP Patrick Archdeacon, MD Medical reviewer, OAP/DSPTP

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
January 19, 2011		BLA 125288	(PLEASE CHECK OFF BELOW) PI, carton and container, medguide

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Belatacept	(b) (4)	Immunosuppressant	March 11, 2011

NAME OF FIRM:	
Bristol-Myers Squibb	PDUFA Date: April 16, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☒ CARTON/CONTAINER LABELING
☒ MEDICATION GUIDE
☐ STRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☒ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☒ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: Bristol Myers Squibb (BMS) submitted a Biologics Licensing Application (BLA 125,288) for belatacept on June 30, 2009 for use as an immunosuppressant for the prophylaxis of acute rejection in adult recipients of kidney transplants. The BLA received a CR letter on May 1, 2010. The final unit of the resubmission was sent on December 15, 2010 although the PDUFA date is June 16, 2011. The Division would like to take an action on April 16, 2011. Please assign a reviewer
\\cber-fs3\m\eCTD Submissions\STN125288\125288.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: February 16, 2011

Labeling Meetings: March 5, 2011

)-Up Meeting: March 19, 2011

SIGNATURE OF REQUESTER June Germain

Germain, June

From: Germain, June
ent: Friday, January 14, 2011 2:12 PM
To: 'Christian, Mary'
Subject: BLA 125288/belatacept/BMS

Hi Mary,

Can you send us word versions of the REMS documents Appendix B to F that you submitted in PDF versions on 8-16/10.

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office): Division of Biometrics 7, LaRee Tracy	FROM: Division of Special Pathogen and Transplant Products/Office of Antimicrobial Products June Germain PM and Patrick Archdeacon, MD Medical Reviewer 301-796-4024

DATE	IND NO.	STN NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 21, 2010		BLA 125288	BLA	December 13, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Belatacept		Immunosuppressant	January 19, 2010

NAME OF FIRM: Bristol-Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☒ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Bristol Myers Squibb (BMS) submitted a Biologics Licensing Application (BLA 125,288) for belatacept on June 30, 2009 for use as an immunosuppressant for the prophylaxis of acute rejection in adult recipients of kidney transplants. At the time of the original submission, the Sponsor proposed (b) (4) post-marketing studies to address outstanding concerns related to belatacept:

- IM103074 – Pattern of Use of Belatacept in US Transplant Recipients
- IM103075 – Belatacept and Risk of PLTD in US Renal Transplant Recipients
- IM103076 – (b) (4)

(b) (4)

(b) (4)

On May 1, 2010, FDA issued a Complete Response to the BLA submission detailing deficiencies in the original application. On September 27, 2010, FDA met with BMS to discuss potential designs of post-marketing studies. FDA also provided written comments regarding the four protocol synopses provided by BMS on September 24, 2010 and on November 12, 2010.

In this December 13, 2010 submission, BMS has provided a complete draft protocol for IM103075 (b) (4)

(b) (4)

Note to Stat Safety Team:
In the previous communications with BMS, FDA has stated that a dedicated belatacept registry which would collect data with regard to PTLD and PML for all adult kidney transplant patients in the US maintained on belatacept would provide a more reliable estimate of the incidence rate of PTLD and PML (b) (4)

(IM103076). On November 24, 2010, BMS requested a face-to-face meeting to further discuss a new proposal for the registry study. FDA has granted that meeting request; the meeting has been scheduled for January 26, 2011. BMS has stated that it intends to submit a meeting briefing package by December 26, 2010. DSPTP will forward the briefing package consult when it becomes available. Please assign reviewer to attend the meeting with the sponsor.

The submission is dated December 13, 2010 and received December 13, 2010.
Link to eCTD submission \\cbsap58\m\eCTD_Submissions\STN125288\125288.enx

SIGNATURE OF REQUESTER June Germain	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125288/0

ACKNOWLEDGE COMPLETE RESPONSE

December 21, 2010

Bristol Myers-Squibb
Attention: Mary Christian, PharmD
Group Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Christian:

We have received your December 15, 2010 resubmission to your biologics license application for belatacept on December 15, 2010.

This submission, in response to our May 1, 2010 complete response letter, notes your facilities are now ready for re-inspection.

We consider this submission a complete, class 2 response to our May 1, 2010 action letter. Therefore, the goal date for this application is June 15, 2011.

We also acknowledge receipt of the following submissions:

1. August 16, 2010- Response to the proposed REMS deficiency
2. September 9, 2010- Response to the CMC product quality deficiency
3. September 24, 2010- Responses to the clinical, product quality microbiology, facility inspections, safety update, labeling, nonclinical study reports, clinic study reports, and Medication Guide deficiencies

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact me at (301) 796-1600.

Sincerely,

_____/

June Germain, MS
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): Division of Epidemiology Attn: OSE, Karen Townsend, RPM			FROM: Division of Special Pathogen and Transplant Products/Office of Antimicrobial Products June Germain PM and Patrick Archdeacon, MD Medical Reviewer 301-796-4024	
DATE December 17, 2010	IND NO.	STN NO. BLA 125288	TYPE OF DOCUMENT BLA	DATE OF DOCUMENT December 13, 2010
NAME OF DRUG Belatacept	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG Immunosuppressant	DESIRED COMPLETION DATE January 19, 2010

NAME OF FIRM: Bristol-Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
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- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
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III. BIOPHARMACEUTICS

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- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

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- ☒ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
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- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Bristol Myers Squibb (BMS) submitted a Biologics Licensing Application (BLA 125,288) for belatacept on June 30, 2009 for use as an immunosuppressant for the prophylaxis of acute rejection in adult recipients of kidney transplants. At the time of the original submission, the Sponsor proposed (b) (4) post-marketing studies to address outstanding concerns related to belatacept:

- IM103074 – Pattern of Use of Belatacept in US Transplant Recipients
- IM103075 – Belatacept and Risk of PLTD in US Renal Transplant Recipients
- IM103076 – (b) (4)

(b) (4)

On May 1, 2010, FDA issued a Complete Response to the BLA submission detailing deficiencies in the original

application. On September 27, 2010, FDA met with BMS to discuss potential designs of post-marketing studies. FDA also provided written comments regarding the four protocol synopses provided by BMS on September 24, 2010 and on November 12, 2010.

... this December 13, 2010 submission, BMS has provided a complete draft protocol for IM103075. (b) (4)

(b) (4)

[redacted]

Note to DEPI:
In the previous communications with BMS, FDA has stated that a dedicated belatacept registry which would collect data with regard to PTLD and PML for all adult kidney transplant patients in the US maintained on belatacept would provide a more reliable estimate of the incidence rate of PTLD and PML (b) (4)

[redacted] (IM103076). On November 24, 2010, BMS requested a face-to-face meeting to further discuss a new proposal for the registry study. FDA has granted that meeting request; the meeting has been scheduled for January 26, 2011. BMS has stated that it intends to submit a meeting briefing package by December 26, 2010. DSPTP will forward the briefing package for DEPI's consult when it becomes available. Please assign reviewer to attend the meeting with the sponsor.

The submission is dated December 13, 2010 and received December 13, 2010.
Link to eCTD submission \\cbsap58\m\eCTD_Submissions\STN125288\125288.enx

!ATURE OF REQUESTER Germain	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125288

MEETING REQUEST GRANTED
December 8, 2010

Bristol-Myers Squibb
Attention: Mary Christian, Pharm.D
Group Director, Global Regulatory Sciences
PO Box 4000 Mailstop D32-08
Princeton, NJ 08543-4000

Dear Dr. Christian:

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

We also refer to your November 24, 2010, correspondence requesting a meeting to discuss your proposal for a US postmarketing registry. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: January 26, 2011
Time: 11:00 am to 12:00 PM EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20993

Probable CDER participants:

Renata Albrecht, M.D.	Division Director
Ozlem Belen, M.D.	Deputy Director for Safety
Joette Meyer, PharmD	Clinical Team Leader
Patrick Archdeacon, M.D.	Medical Reviewer
Suzanne Robottom, PharmD	Team Leader/DRISK
Hyun Son, PharmD	Safety Project Manager
June Germain, MS	Regulatory Health Project Manager

Please e-mail me any updates to your attendees at june.germain@fda.hhs.gov , at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA Building 22, provide the guards with either of the following numbers to request an escort to the conference room: June Germain, RPM at 301-796-4024 of Karin Klunk, Division secretary at 301-796-0743.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 9 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by December 27, 2010, we may cancel or reschedule the meeting.

Submit the 9 desk copies to the following address:

June Germain, MS
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6133
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

In preparation for the meeting, be aware of the following issues:

1. Only FDA owned equipment and computers can be used on FDA equipment. If you want to use your own laptop, you will have to bring your own projector. Sponsor supplied flash drives, thumb drives, or CDs are not allowed on FDA computers. If you want to use slides during our meeting, you must send me an e-mail with the slides, hand out paper copies of your slides, or use your own computer and projector.

2. Cameras are not allowed on the White Oak Campus. The guards will not allow cameras in the building and will not hold any cameras for you. Please leave cameras in another location during your visit.

If you have any questions, call me at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

June Germain, MS
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office): Division of Epidemiology
Mail: OSE, Karen Townsend, RPM

FROM: Division of Special Pathogen and Transplant Products/Office of Antimicrobial Products
June Germain PM and Patrick Archdeacon, MD Medical Reviewer 301-796-4024

DATE	IND NO.	STN NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 3, 2010		BLA 125288	BLA	November 30, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Belatacept		Immunosuppressant	

NAME OF FIRM: Bristol-Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
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- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☒ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The Division has received a meeting request for STN 125288, belatacept for the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.
The submission is dated November 30, 2010 and received November 30, 2010.
Link to eCTD submission \\cbsap58\m\eCTD_Submissions\STN125288\125288.enx
Based on comments received from DEpi and the Division on September 23, 2010 on the draft registry proposal, BMS would like to discuss their proposal for the US registry study.
Please assign a reviewer.
We anticipate the meeting will take place around January 26, 20111.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
.IATURE OF RECEIVER	SIGNATURE OF DELIVERER

Germain, June

From: Germain, June
Sent: Tuesday, November 23, 2010 1:05 PM
To: 'Christian, Mary'
Subject: RE: Belatacept BLA 125288 - Fax Dated Oct 1 2010- Request for information

Hi Mary,

I received your voicemail. Please provide the complete response including analysis datasets on Dec. 8 and then we can teleconference, if needed. Is it possible to provide a short email summary of your analysis findings now?

June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Tuesday, November 23, 2010 12:20 PM
To: Germain, June
Subject: Belatacept BLA 125288 - Fax Dated Oct 1 2010- Request for information

Hi June,

Related to my voice mail and the attached fax BLA Information Request, we are finalizing the analyses now and expect to have a reviewed draft response by Friday Dec 3. The complete response, including analysis datasets will be ready for submission by approximately Wed Dec 8. We are open to submitting to you the draft response (Dec 3) and having a discussion with your team the following week on the analyses/findings before finalizing the submission OR providing the complete response (Wed Dec 8) and having a teleconference with you sometime later, if you have additional questions.

The former would allow for us to discuss our findings and revise the response, potentially including additional analyses, after your input. The latter would allow for a more comprehensive review of our responses before the discussion. We defer to you on your preference.

Also, we have heard from the San Juan District Office regarding the Manati manufacturing site and they have granted us a meeting on December 14 at 9:30am. The Agenda for the meeting will be for BMS to present the completion of our Warning Letter remediation actions. We plan to ask the SJDO for their agreement that the remediation is acceptable and the site is inspection ready. I will communicate to you as soon as I know this answer and will plan to provide a submission to the BLA either Dec 14 or 15th acknowledging our inspection readiness to complete the Resubmission to the Complete Response so that the PDUFA clock may begin.

Best regards,
Mary

Bristol-Myers Squibb
Mary Christian, Pharm.D., MBA
Group Director
Global Regulatory Sciences

(609) 252-5281 Work
(908) 507-8167 Mobile
(609) 252-6000 Fax

PO Box 4000, Mailstop D32-08
Princeton, NJ 08543-4000
mary.christian@bms.com

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

BLA 125288

November 16, 2010

Bristol-Myers Squibb
Attention: Mary Christian, Pharm.D
Director, Global Regulatory Strategy
PO Box 4000 Mailstop D32-08
Princeton, NJ 08543-4000

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009, received July 1, 2009, submitted under section 351 of the Public Health Service Act for belatacept lyophilized powder, 250 mg.

We also refer to the face to face meeting held between representative of your firm and the FDA on September 27, 2010. The purpose of the meeting was to discuss the planned resubmission, planned postmarketing studies and REMS.

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, please do not hesitate to call June Germain, Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

/Renata Albrecht/
Renata Albrecht, MD
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING

Meeting Date:	September 27, 2010
Application Number:	BLA 125,288
Product Name:	belatacept
Indication:	Prophylaxis of organ rejection in adult patients receiving renal transplant
Sponsor:	Bristol-Myers Squibb
Meeting Chair:	Renata Albrecht, MD
Meeting Recorder:	June Germain, MS

FDA ATTENDEES:

Renata Albrecht, MD	Director, DSPTP
Patrick Archdeacon, MD	Medical Reviewer, DSPTP
Joette Meyer, PharmD	Clinical Team Leader, DSPTP
Suzanne Robottom, PharmD	Team Leader, DRISK
Ozlem Belen, MD	Safety Deputy Director, DSPTP
Hyun Son, PharmD	Safety Project Manager, DSPTP
Philip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader, OCP/DCP 4
Gerlie Gieser, PhD	Clinical Pharmacology Reviewer, OCP/DCP 4
Seong Jang, PhD	Clinical Pharmacology Reviewer, OCP/DCP 4
Shashi Amur, PhD	Pharmacometrics Reviewer OTS/OCP
Shukal Bala, PhD	Microbiology Team Leader, DSPTP
Aaron Ruhland, PhD	Microbiology Reviewer, DSPTP
Cheryl Dixon, Ph.D	Statistical Reviewer, OB/DBIV
LaRee Tracy, PhD	Statistical Team Leader for Safety,
Stephen Chang, PharmD	Drug Utilization Analyst, OSE/DEpi
Elizabeth Maloney, MS DRPhD	Epidemiology Team Leader, OSE/DEpi
Amarilys Vega, MD	Deputy Director and Acting Team Leader, OSE/DEpi
Andrew Mosholder, MD	Medical Officer, OSE/DEpi
Ergun Velidedeoglu, MD	Medical Reviewer, DSPTP
June Germain, MS	Regulatory Project Manager, DSPTP

BMS ATTENDEES:

Laura Bessen, MD	Vice President, Global Medical Affairs
Mary Christian, PharmD	Group Director, Global Regulatory Sciences
Jeffrey Gelb, MD	Vice President-Full Development Team Lead LEA29Y
Andres Gomez, PhD	Executive Director, Global Epidemiology
Mary Beth Harler, MD	Executive Director, Global Clinical Research
Sheila Gujrathi, MD	Vice President, Global Clinical Research

Chen-Sheng Lin, PhD	Director, Global Biometric Sciences
Isolde Puschmann, PhD	Director, Global Regulatory Sciences
Pamela Turnbo, MD	Associate Medical Director, Global Pharmacovigilance and Epidemiology
Anthony Waclawski, PhD	Vice President, Global Regulatory Sciences

BACKGROUND:
On June 30, 2009 Bristol-Myers Squibb (BMS) submitted a biologics license application (BLA) for belatacept in electronic format following the electronic CTD structure. On May 1, 2010 a Complete Response letter was issued to the BLA.

On May 18, 2010, the applicant submitted a request for a meeting to present and discuss the 36 month data from the two Phase 3 clinical trials IM103008 and IM103027. On August 13, 2010 the applicant submitted a briefing package in support of the meeting discussion, which included two questions, (1) regarding comments on the 36 month data for the Phase 3 studies and (2) comments on the planned resubmission, REMS and post-marketing studies. Question one was discussed during the September 1, 2010 a teleconference. On September 23, 2010 the Division sent preliminary responses to the second question posted in the August 13, 2010 briefing document in preparation for the September 27, 2010 meeting.

MEETING OBJECTIVE:
To discuss the planned resubmission, the proposed REMS and post-marketing studies for belatacept.

For the purposes of these minutes, question two from the August 13, 2010 submission from BMS is in **bold** font, the FDA's preliminary comments are in *italics* and a summary of the meeting discussion is in regular font.

Q2. Does the Agency have comments on the planned resubmission, REMS, planned postmarketing studies, label, or any other aspect of the remaining review of the BLA?

FDA Response:

1. Postmarketing Studies

The Division of Epidemiology in the Office of Surveillance and Epidemiology has reviewed three of your postmarketing pharmacoepidemiology studies, designated IM103074, IM103075, and IM103076. The Division of Epidemiology and the Division of Special Pathogen and Transplant Products have discussed the review internally and would like to provide you the following comments:

Study IM103074: This will be a descriptive study of the patterns of belatacept use after market launch, and as such, will provide a limited contribution to the risk assessment of the drug. However, we believe the study has value in monitoring prescriber compliance with the

Contraindication to not use the product in patients who are EBV negative or EBV unknown serology. We recommend that this postmarketing study be conducted.

Study IM103075: The objective of this study, to enumerate cases of PTLD occurring with belatacept, is highly relevant. However, the usefulness of the data will be compromised by the limitations of the UNOS/OPTN database. Specifically, the fact that some aspects of reporting PTLD in the UNOS/OPTN system are voluntary may lead to underascertainment. The study will also be limited by the inability of the UNOS/OPTN database to reliably capture switches between belatacept and calcineurin inhibitors (CNIs). Because of these deficiencies, we are not confident that this study would provide a valid estimate of the incidence of PTLD with belatacept use. However, we recognize that the proposed approach would provide estimates (albeit not entirely reliable estimates) of the incidence of PTLD both with belatacept and also with calcineurin inhibitor use, which would afford some measure of comparison to the existing standard of care. In addition, since the study leverages existing and available data from the UNOS/OPTN database, its conduct does not represent a significant burden. We therefore recommend that this postmarketing study be conducted.

Study IM103076: (b) (4)

(b) (4)

(b) (4). *We recommend that instead of this proposed postmarketing study you set up a patient registry of belatacept users with the goal of enrolling the vast majority of patients, confirmed by utilization data, from as close to the time of initial marketing as feasible. Further details are provided below.*
The principle outcomes to be assessed in a registry of belatacept patients would be PTLD (especially in the CNS) and PML. Such a registry would allow a reasonably rapid and accurate estimate of the absolute incidence of PTLD, CNS PTLD, and PML among transplant patients maintained on belatacept. Such a registry would not provide a similar estimate of the absolute incidences of PTLD, CNS PTLD, and PML among transplant patients maintained on a CNI-based regimen. Nonetheless, given existing data suggesting that CNS PTLD and PML are rare among transplant patients maintained on a CNI-based regimen, accurate absolute incidences of these events among belatacept patients would have significant informative value. We would like to discuss the strengths, limitations, and practicality of such an approach.
We invite you to develop a suitable statistical analysis plan for the data on PTLD and PML with belatacept use that would be obtained from such a registry. Because the registry will enroll only belatacept users, we realize it would not have an intrinsic comparison group. However, other comparisons could be planned, specifically: (1) compare the incidence of PML and PTLD among postmarketing users of belatacept to the incidences observed in the premarketing clinical trial data; (2) compare the incidence of PML and PTLD between users of belatacept from the

time of the initial transplant and belatacept users who were switched to belatacept after first receiving a CNI.

If, after a sufficient number of patients are enrolled and followed, the risk estimates for these outcomes have sufficient precision to be reassuring, discontinuation of the registry could then be considered. As part of the analysis plan, we invite you to propose such numerical criteria, which if met after a suitable length of time, would support discontinuation of this patient registry program.

(b) (4)

We look forward to discussing these comments with you further at the meeting on September 27, 2010.

Meeting Discussion:

After introductions, BMS provided an update on recently submitted documents, including the September 21, 2010 response to the Warning Letter to the Manati, PR manufacturing site, the September 24, 2010 submission of the final reviewable unit response to the Complete Response letter, the MedWatch Form regarding the patient who developed CNS infection (submitted September 24, 2010), and the September 27, 2010 submission of the September 1, 2010 teleconference minutes. BMS asked whether the Division could provide a response in 2 weeks on whether the review clock would start on the September 27, 2010 although the Manati site would not be ready to be inspected until after December 15, 2010. The Division deferred a response to the question until confirmation with all disciplines not present at the meeting.

BMS noted that there was a transcription error with the initial MedWatch report of a patient with possible progressive multifocal leukoencephalopathy (PML) after follow-up laboratory results revealed the patient was positive for BK virus and negative for JC virus. The Division noted that the MedWatch report did not provide clarification on the error in laboratory results. BMS agreed to provide clear documentation of circumstances leading to the transcription error and a clear description of the process undertaken to clarify the data relevant to this patient.

BMS stated that it was in general agreement with the FDA with regards to its written comments on the three proposed postmarketing studies: IM103074, IM103075, (b) (4). BMS indicated that they would submit protocols for IM103074 and IM103075.

The discussion shifted to the objectives of IM103076. FDA and BMS agreed that the focus of IM103076 should be to provide an estimate of the absolute risk of PTLD, CNS PTLD, and PML

in belatacept-treated patients. BMS noted that they project (b) (4) will use belatacept in the first year and (b) (4) will use it in the second year. (b) (4)

(b) (4)

The Division suggested that a simple safety registry design might provide estimates of the absolute risk of PTLD, CNS PTLD, and PML more quickly than the study proposed by BMS. While center participation in the registry would be mandatory (or due diligence documented), enrollment of individual patients would not be mandatory. The Division emphasized that patient participation in the US should exceed a target of 95% of treated adults with kidney transplants. The Division also noted that similar voluntary registries for products indicated for rheumatoid arthritis have been successful in meeting similar goals. Drug utilization data could be used to confirm that the registry had captured the vast majority of patients. The inclusion of patients receiving belatacept other than adults with kidney transplants was also discussed. The Division indicated that as much data as possible should be captured in the registry, but recognized certain limitations would arise. BMS noted interest in establishing the absolute rate of PTLD in the global patient population, including non-US patients. The Division emphasized that additional data may be useful, but the focus of the registry should be on US patients.

The discussion shifted to the overall objectives of the REMS. The Division noted that tuberculosis (TB) and serious infections are not currently envisioned as part of the REMS, but that additional internal discussions were needed before confirming that the REMS would be specific to PML and PTLD. BMS indicated that they intend to address the imbalance of TB events in the Highlights and the Warning and Precautions sections of the package insert. BMS agreed to continued discussions on the labeling.

2. Labeling:

FDA Response:

We have no further comments on the label at this time.

Meeting Discussion:

No further discussion.

ACTION ITEMS:

- FDA agreed to notify BMS within two weeks whether the September 27, 2010 submission of the final reviewable units of the resubmission of the BLA would start the review clock.
- BMS agreed to submit a protocol synopsis of the newly proposed registry study to replace IM103076. In addition, they agreed to submit protocols for the other (b) (4) postmarketing studies: IM103074, IM103075, (b) (4)
- FDA agreed to provide preliminary comments on the REMS documents submitted on August 16, 2010 by September 30, 2010
- BMS agreed to provide updated information on the MedWatch report on the laboratory result for the patient with the CNS infection

ADDENDUM TO ACTION ITEMS:

- On September 29, 2010, the Division issued preliminary comments on the REMS documents submitted on August 16, 2010.
- On October 8, 2010, the Division issued an acknowledgement letter noting that the September 24, 2010 submission was not a complete response to the May 1, 2010 complete response letter for BLA 125288
- On October 8, 2010, BMS submitted an updated MedWatch report with information on the patient with CNS infection

HANDOUTS:

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

BLA 125288
Belatacept
Bristol-Myers Squibb
comments and information request

November 12, 2010

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009 and received July 1, 2009. Upon further pharmacogenomic analysis of your submission we have the following comments and request for information:

> While CMV serostatus has not been clearly identified as a risk factor for the development of PTLD in a non-belatacept context, the observed rates of PTLD among EBV positive patients maintained on belatacept in IM103100, IM103008, and IM103027 were higher among those recipients who were CMV negative (4/205, 1.9%) than among those recipient who were CMV positive (2/509, 0.3%). Such an association is biologically plausible, as CMV disease has been established as a risk factor for the development of PTLD. We recommend that IM103075 should include a sub-analysis of PTLD rates according to recipient CMV status to evaluate further whether CMV serostatus at time of transplant may represent an independent risk of the development of PTLD among kidney transplant patients maintained on belatacept. In addition, should BMS conduct a prospective cohort safety study (whether as a PMR or on its own initiative) such as originally proposed for Study IM103076. We recommend that the data collection support a similar analysis for both the belatacept group and the calcineurin inhibitor group.

Please call me if you have any questions.

Thanks
June Germain, MS
Regulatory Health Project Manager

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125288/0

ACKNOWLEDGE INCOMPLETE RESPONSE

Bristol-Myers Squibb Company
Attention: Mary Christian, PhD
Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Christian:

We have received the following submissions to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for belatacept:

Date of Submission	Content of Submission
August 16, 2010	Response to the proposed REMS deficiency
September 9, 2010	Response to the CMC product quality deficiency
September 24, 2010	Responses to the clinical, product quality microbiology, facility inspections, safety update, labeling, nonclinical study reports, clinic study reports, and Medication Guide deficiencies

We have determined that these submissions do not completely respond to our May 1, 2010 Complete Response letter. We stopped the review clock when we issued our Complete Response letter and, because we have determined that these submissions do not constitute a complete response to our letter, we will not restart the clock until you have responded to the following deficiencies:

Facility Inspections

During recent pre-licensure inspections of the Bristol-Myers Squibb Company (BMS) facility in East Syracuse, NY by CDER inspectors, and of the BMS facility in Manati, Puerto Rico by an inspector from the SJN-District Office, deficiencies were conveyed to the BMS representatives at the facilities. Satisfactory resolution of the deficiencies is required before this application may be approved.

In your September 24, 2010 submission you state that the drug substance manufacturing site in East Syracuse, New York is now ready for inspection and that you anticipate the drug product manufacturing site in Manati, Puerto Rico will be ready for inspection after December 15, 2010. Please note that you must submit a letter stating that all manufacturing sites are ready for inspection before the review clock for your resubmission is started.

During the September 27, 2010 meeting with this Division, you asked if your response to our May 1, 2010 Complete Response letter would be a Class 1 or Class 2 resubmission, therefore, we refer you to the document, "Guidance for Industry: Classifying Resubmissions in Response to Action Letters." [1]

If you have any questions, please contact Ms. June Germain, Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

10-7-10

[Renata Albrecht, MD]
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079303.pdf

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

BLA 125288

October 1, 2010

Bristol-Myers Squibb
Attention: Mary Christian, Pharm.D
Director, Global Regulatory Strategy
PO Box 4000 Mailstop D32-08
Princeton, NJ 08543-4000

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009, received July 1, 2009, submitted under section 351 of the Public Health Service Act for belatacept lyophilized powder, 250 mg.

We also refer to the teleconference held between representative of your firm and the FDA on September 1, 2010. The purpose of the meeting was for BMS to present and discuss the 36 month data from the two Phase 3 pivotal clinical trials.

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, please do not hesitate to call June Germain, Regulatory Health Project Manager, at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Dr BELEN
for DR ALBRECHT
10.1.2010

Renata Albrecht, MD
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING

Meeting Date:	September 1, 2010
Meeting Location:	Teleconference
Application number:	BLA 125288
Product Name:	belatacept
Indication:	Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplant.
Sponsor:	Bristol-Myer Squibb
Meeting Chair:	Renata Albrecht, MD
Meeting Recorder:	June Germain, MS

FDA ATTENDEES:

Renata Albrecht, MD	Director, DSPTP
Patrick Archdeacon, MD	Medical Reviewer, DSPTP
Marc Cavaille-Coll, MD, PhD	Medical Reviewer, DSPTP
Suzanne Robottom, PharmD.	Team Leader, DRISK
Carolyn Yancey, MD	Senior Medical Officer, DRISK
Ozlem Belen, MD	Safety Deputy Director, DSPTP
Hyun Son, PharmD.	Safety Project Manager, DSPTP
Phillip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader, OCP/DCP 4
Gerlie Gieser, PhD	Clinical Pharmacology Reviewer, OCP/DCP 4
Seong Jang, PhD	Clinical Pharmacology Reviewer, OCP/DCP 4
Shashi Amur, PhD	Pharmacometrics Reviewer OTS/OCP
Jiang Lui, PhD	Pharmacometrics Reviewer OTS/OCP
Shukal Bala, PhD	Microbiology Team Leader, DSPTP
Aaron Ruhland, PhD	Microbiology Reviewer, DSPTP
Cheryl Dixon, Ph.D.	Statistical Reviewer, OB/DBIV
June Germain, MS	Regulatory Project Manager, DSPTP

BMS ATTENDEES:

Mary Christian, Pharm.D.	Group Director, Global Regulatory Sciences
Victoria Demby, PhD,	Coordinator, Global Regulatory Sciences
Pushkal Garg, M.D.	Executive Director, Global Clinical Research
Jeffrey Gelb, M.D.	Vice President-Full Development Team Lead
Mary Beth Harler	Executive Director, Global Clinical Research
Kalyan Ghosh, Ph.D.	Executive Director, Global Biometric Sciences
Sheila Gujrathi, M.D.	Vice President, Global Clinical Research
Mathias Hukkelhoven, Ph.D.,	Sr. Vice President, Global Regulatory Sciences, Pharmacovigilance & Epidemiology

Joseph Lamendola,	Vice President, Global Regulatory Sciences
Chen-Sheng Lin, Ph.D.	Director, Global Biometric Sciences
Daniel MacNeil, M.D.	Executive Director, Clinical Safety
Isolde Puschmann, Ph.D.	Director, Global Regulatory Sciences
Anthony Waclawski, Ph.D.	Vice President, Global Regulatory Sciences

BACKGROUND:
On June 30, 2009 Bristol-Myers Squibb (BMS) submitted a biologics license application (BLA) for belatacept (Nulojix®) in electronic format following the electronic CTD structure. On May 1, 2010 a Complete Response letter was issued to the BLA.

On July 12, 2010, the applicant submitted a request for a meeting to present and discuss the 36 month data from the two Phase 3 pivotal clinical trials. On August 13, 2010 the applicant submitted a briefing package in support of the meeting discussion.

MEETING OBJECTIVE:
To reach a common understanding on the 36 month data presented and any concerns about the maintenance of the benefit-risk of belatacept established by the data.

For the purposes of the minutes, BMS original question is in **bold** font and a summary of the meeting discussion is in regular font.

Question 1. Does the Agency have any comments or concerns, based on the 36 month data presented, about the maintenance of the benefit-risk of belatacept established by the data in the BLA 125,288?

Meeting Discussion:

BMS opened the meeting by presenting a summary overview of the 36 month data that included the safety and efficacy results. The Division noted that there were two primary reasons for requesting the results of the 36 month data:

1. To evaluate any new or augmented safety signals present
2. To evaluate whether any differences in cardiovascular outcomes emerged across treatment groups to support a position that the measured differences in CV risk factors at 12 months translates to meaningful clinical differences

The Division indicated that the preliminary data suggested no major changes in the safety signals or CV outcomes and the 36 month data is consistent with the 24 month data.

The Division noted however, that there is the difference in NODAT measured at 12 months did not appear to be preserved at 36 months. The Division asked BMS to comment on these data and how they intended to present them in the label. BMS stated that they were aware of those data. They proposed that the convergence of the NODAT incidences across treatment groups at 36

months might be attributable to data collection methods (differences across groups in terms of missing data, etc). BMS stated an intent to present information in the label based on what was observed at 1, 2, and 3 years and provide brief data on cyclosporine and belatacept regimens. The Division indicated its willingness to review new labeling reflecting NODAT data collected at time points out to 36 months.

The Division also noted that the 36 month data appeared to confirm previous safety signals regarding an association between belatacept and tuberculosis (TB). The Division asked BMS to comment on how they intended to present those data in the package insert. BMS noted that in the LI arm there were 2 additional cases from the 24 months to the 36 months but that they had not yet decided on how to best present those data in the package insert or how to reflect the information in the REMS materials. The Division noted that the Project manager would schedule a meeting at the end of September 2010 to discuss approaches to the REMS materials. The Division stated that the labeling should be updated to reflect the new data regarding the incidence of TB at the 36 month time point.

BMS provided a summary of an analysis of death and graft loss at 36 months across treatment groups. The analysis suggested that belatacept patients who experienced acute rejection may have worse outcomes than cyclosporine patients who experience acute rejection, but that cyclosporine patients who do not experience acute rejection may have worse outcomes than belatacept patients who do not experience acute rejection. The Division noted that the patterns observed by BMS could be viewed to support a conclusion that the rejection events which occurred in the belatacept patients were more severe than those which occurred in the cyclosporine patients. BMS indicated that pattern of worse outcomes among non-rejectors maintained on cyclosporine compared to belatacept could be interpreted as supporting a conclusion that cyclosporine was associated with worse toxicities including cardiovascular outcomes and nephrotoxicities.

The Division inquired whether anti-donor antibodies were measured in the study and available at 36 months. BMS stated that anti-donor antibody at 36 month occurs less frequently in the Study 008 belatacept regimen with LI at 5 versus 11% and in study 027 6 versus 15%. BMS stated that they plan to include in the study report detail narratives of the population data of anti donor antibody in the resubmission of the BLA.

BMS stated they received a warning letter from the Agency that their response to the deficiencies cited at Manati, PR manufacturing site was not acceptable. BMS stated they were in the process of replying to the warning letter but is still planning to follow the agreed upon schedule to submit the complete reviewable units of the BLA by the end of September. The Division note that representatives from the CMC group were not present on the teleconference to address this particular issue but agreed that BMS could continue with the planned resubmission of the BLA.

ACTION ITEMS:

- FDA and BMS agreed to schedule a Type B meeting around the end of September to discuss the REMS, (b) (4) and planned postmarketing studies

HANDOUTS:

34 Page(s) have been Withheld in full as b4 (CCI/TS) immediately following this page

BLA 125288
Belatacept
Bristol-Myers Squibb
Clinical Pharmacology comments and information request

October 1, 2010

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009 and received July 1, 2009. Upon further clinical pharmacology analysis of your submission we have the following comments and request for information regarding IgG levels and outcomes:

1. The following three tables summarize the findings of our analysis that explored the potential association between hypogammaglobulinemia at Month 6 and the therapeutic outcomes in belatacept Phase 3 trials. Only patients who had normal IgG titers (IgG $\geq$ 694 mg/dL) at baseline were included in the analysis. For brevity, the analysis findings with IgG levels at Month 12 are not included. The clinical events rates were derived using the analysis datasets in SN-006 (submitted 9/10/2009), except CNS events which were based on the analysis dataset in SN-029 (submitted 2/11/2010).

   Based on our findings, in belatacept LI- and belatacept MI- treated patients with IgG below the lower limit of normal (<LLN; <694 mg/dL) at Month 6 versus belatacept-treated patients with normal IgG titers (694-1618 mg/dL), there was a higher incidence of CNS-PTLD [2.1% (4/193) versus 0.3% (1/294)], PML[0.5% (1/193) versus 0% (0/294)], serious infections [43.5% (84/193) versus 32.3% (95/294)] and malignancies [9.8% (19/193) versus 2.7% (8/294)], acute rejections including high-grade acute rejections [20.7% (40/193) versus 10.2% (30/294)], lower mean measured or calculated GFR, and death [6.2% (12/193) versus 1.7% (5/294)]. In cyclosporine-treated patients with IgG <LLN at Month 6 versus cyclosporine-treated patients with normal IgG titers, there was a higher incidence of serious infections [45.8% (33/720 versus 36% (54/150)], malignancies [11.1% (8/72) versus 6.7% (10/150)], acute rejections [15.3% (11/720 versus 8% (12/150)], lower mean measured or calculated GFR, and death [4.2% (3/72) versus 3.3% (5/150)].

   The clinical implications of these findings with respect to use of belatacept, or use of other immunosuppressant drugs in general, are not known. However, these findings suggest that IgG titers may serve as a potentially useful biomarker of undesirable outcomes of the immunosuppressant drug regimen, including belatacept, in kidney transplant patients.

2. We also recommend that you perform further exploratory analyses to investigate the potential influence of concomitant treatment with immune globulin containing preparations (e.g., IVIG, thymoglobulin, cytogam) on the safety and efficacy of belatacept and cyclosporine, as well as on belatacept trough concentrations in the Phase 3 trials. Please submit the summary report and the supporting analysis datasets for our

review. Note that we are particularly interested in knowing whether the administration of the concomitant immune globulin treatment contributed to the resolution of acute rejection or of an adverse event (e.g., serious infection). Therefore, we request that you also include in the analysis dataset details such as the duration of concomitant therapy, and the date of event resolution relative to the start date of concomitant treatment.

Table 1. Effect of Reductions in IgG Titers at Month 6 on the Incidence of Serious Infections, CNS Events, and Malignancies Observed in Phase 3 trials (%, n/N)

	IgG Level at Month 6	Serious Infections	CNS Events[a]	Malignancies
Treatment Group				
Belatacept Less-Intensive (LI)	Normal Range (694 – 1618 mg/dL)	**30.49** (50/164)	**0.61** (1/164)	**1.83** (3/164)
	Below LLN (< 694 mg/dL)	**39.08** (34/87)	**2.30** (2/87)	**5.75** (5/87)
	Above ULN (> 1618 mg/dL)	-	-	-
Belatacept More-Intensive (MI)	Normal Range (694 – 1618 mg/dL)	**34.62** (45/130)	**2.31** (3/130)	**3.85** (5/130)
	Below LLN (< 694 mg/dL)	**47.17** (50/106)	**4.72** (5/106)	**13.21** (14/106)
	Above ULN (> 1618 mg/dL)	-	-	-
Belatacept Less-Intensive (LI) and More-Intensive (MI)	Normal Range (694 – 1618 mg/dL)	**32.31** (95/294)	**1.36** 4/294	**2.72** (8/294)
	Below LLN (< 694 mg/dL)	**43.52** (84/193)	**3.63** (7/193)	**9.84** (19/193)
	Above ULN (> 1618 mg/dL)	-	-	-
Cyclosporine	Normal Range (694 – 1618 mg/dL)	**36** (54/150)	**0** (0/150)	**6.67** (10/150)
	Below LLN (< 694 mg/dL)	**45.83** (33/72)	**0** (0/72)	**11.11** (8/72)
	Above ULN (> 1618 mg/dL)	**50** (1/2)	**0** (0/2)	-

[a] total of CNS infections, CNS-PTLD, PML, and other CNS infections
LLN: Lower Limit of Normal Range; ULN: Upper Limit of Normal Range

Table 2. Effect of Reductions in IgG Titers at Month 6 on the Incidence of Acute Rejections, Death, and Graft Loss Observed in Phase 3 trials (%, n/N)

	IgG Level at Month 6	Acute Rejections (AR)		Death	Graft Loss
Treatment Group					
		Total AR	High-grade AR[a]		
Belatacept Less-Intensive (LI)	Normal Range (694 – 1618 mg/dL)	**9.15** (15/164)	**2.44** (4/164)	**0.61** (1/164)	**3.05** (5/164)
	Below LLN (< 694 mg/dL)	**18.39** (16/87)	**3.45** (3/87)	**8.05** (7/87)	**1.15** (1/87)
	Above ULN (> 1618 mg/dL)	-	-	-	-
Belatacept More-Intensive (MI)	Normal Range (694 – 1618 mg/dL)	**11.54** (15/130)	**6.92** (9/130)	**3.08** (4/130)	**0.77** (1/130)
	Below LLN (< 694 mg/dL)	**22.64** (24/106)	**9.43** (10/106)	**4.72** (5/106)	**3.77** (4/106)
	Above ULN (> 1618 mg/dL)	-	-	-	-
Belatacept Less-Intensive (LI) and More-Intensive (MI)	Normal Range (694 – 1618 mg/dL)	**10.20** (30/294)	**4.42** (13/294)	**1.70** (5/294)	**2.04** (6/294)
	Below LLN (< 694 mg/dL)	**20.73** (40/193)	**6.74** (13/193)	**6.22** (12/193)	**2.59** (5/193)
	Above ULN (> 1618 mg/dL)	-	-	-	-
Cyclosporine	Normal Range (694 – 1618 mg/dL)	**8.00** (12/150)	**0.67** (1/150)	**3.33** (5/150)	**0.67** (1/150)
	Below LLN (< 694 mg/dL)	**15.28** (11/72)	**0** (0/72)	**4.17** (3/72)	**0** (0/72)
	Above ULN (> 1618 mg/dL)	**0** (0/2)	**0** (0/2)	**0** (0/2)	**50** (1/2)

[a]Acute Rejection Grade IIB and higher
LLN: Lower Limit of Normal Range; ULN: Upper Limit of Normal Range

Table 3. Effect of Reductions in IgG Titers at Month 6 on Renal Function Observed in Phase 3 trials [Mean ± SD (n) or % (n/N)]

	IgG Level at Month 6	Measured GFR (mGFR; (mL/min/1.73m^2) (Mean ± SD)	Calculated GFR (cGFR- MDRD; (mL/min/1.73m^2) (Mean ± SD)	Decrease in mGFR ≥ 10 mL/min from Month 3 to Month 12 (mGFR10; n,%)	Change in cGFR from Month 0 to Month 12[a] (mL/min/1.73m^2) (Mean ± SD)
Treatment Group					
Belatacept Less-Intensive (LI)	Normal Range (694 – 1618 mg/dL)	**61.3 ± 26.1** (n=163)	**64.2 ± 20.1** (n=156)	**26.99** (44/163)	**55.4 ± 20.7** (n=146)
	Below LLN (< 694 mg/dL)	**55.1 ± 27.8** (n=85)	**60.3 ± 16.7** (n=78)	**34.12** (29/85)	**50.8 ± 16.5** (n=69)
	Above ULN (> 1618 mg/dL)	-	-	-	-
Belatacept More-Intensive (MI)	Normal Range (694 – 1618 mg/dL)	**62.4 ± 28.6** (n=129)	**65.8 ± 21.3** (n=120)	**22.66** (29/128)	**56.6 ± 22.8** (n=109)
	Below LLN (< 694 mg/dL)	**55.0 ± 25.1** (n=103)	**56.5 ± 19.8** (n=102)	**27.18** (28/103)	**46.0 ± 20.6** (n=97)
	Above ULN (> 1618 mg/dL)	-	-	-	-
Belatacept Less-Intensive (LI) and More-Intensive (MI)	Normal Range (694 – 1618 mg/dL)	**61.8 ± 27.2** (n=292)	**64.9 ± 20.6** (n=276)	**25.09** (73/291)	**55.9 ± 21.6** (n=255)
	Below LLN (< 694 mg/dL)	**55.1 ± 26.3** (n=188)	**58.1 ± 18.6** (n=180)	**30.32** (57/188)	**48.0 ± 19.1** (n=166)
	Above ULN (> 1618 mg/dL)	-	-	-	-
Cyclosporine	Normal Range (694 – 1618 mg/dL)	**48.5 ± 17.6** (n=149)	**50.9 ± 17.3** (n=131)	**30.87** (46/149)	**41.9 ± 18.5** (n=123)
	Below LLN (< 694 mg/dL)	**49.9 ± 22.0** (n=70)	**52.1 ± 17.9** (n=57)	**34.29** (24/70)	**43.3 ±18.5** (n=51)
	Above ULN (> 1618 mg/dL)	**63** (n=1)	**57.4** (n=1)	**0** (0/1)	**47.6** (n=1)

[a] calculated as (cGFR at Month 12) – (cGFR at Month 0)
LLN: Lower Limit of Normal Range; ULN: Upper Limit of Normal Range

We look forward to discussing our analyses and findings with you at a future date. Please call to schedule a teleconference for this discussion.

Thanks
June Germain, MS
Regulatory Health Project Manager

BLA 125288
Belatacept
Bristol-Myers Squibb
REMS preliminary comments

September 29, 2010

Dear Dr. Christian,

We have reviewed the August 18, 2010 submission and have the following general comments. Be aware that we anticipate additional comments as your submission(s) undergoes further review. We request you receive the next set of comments before resubmitting the REMS and related materials.

1. REMS Document

The general elements of the Nulojix REMS outlined in the REMS Document are acceptable. However, considerable edits will need to be made to the REMS document including references to the Attachments (MG and CP materials). Please see the attached template for the REMS document and the REMS Supporting Document (SD).

The CP section needs to be expanded to include specific targeting and outreach efforts (identify audience, frequency of distribution).

(b) (4)



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



7. Attachments

a. REMS Document, Supporting Document Template and Victoza's Highlighted Information for Prescribers

Thanks
June Germain
Regulatory Health Project Manager

Appendix A: REMS Template

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

(b) (4)

[redacted]

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix B: supporting document



BLA 125288
Belatacept
Bristol-Myers Squibb

September 23, 2010

Dear Dr. Christian,

Please refer to your briefing document dated August 13, 2010, for a Type B meeting for belatacept for the prophylaxis of organ rejection in adult patients receiving renal transplants. We also refer you to the teleconference held on September 1, 2010, where we discussed question one posted in that document on the results of the 36 month data from the two Phase 3 pivotal clinical trials.

The following are the Division's preliminary responses to the second question posted in your briefing document, dated August 13, 2010, for a Type B meeting for belatacept for the prophylaxis of rejection in adult patients receiving renal transplants. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting or rescheduling as a teleconference.

Please note that if there are any major changes to your development plan, or the purpose of the meeting, or new questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting to be held on September 27, 2010. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

For the purpose of these comments your question will be in **bold** font and the FDA responses will be in normal format.

Q2. Does the Agency have comments on the planned resubmission, REMS, planned postmarketing studies, label, or any other aspect of the remaining review of the BLA?

FDA Response:

1. <u>Postmarketing Studies</u>

The Division of Epidemiology in the Office of Surveillance and Epidemiology has reviewed (b) (4) of your postmarketing pharmacoepidemiology studies, designated IM103074, IM103075, (b) (4) The Division of Epidemiology and the Division of Special Pathogen and Transplant Products have discussed the review internally and would like to provide you the following comments:

> Study IM103074: This will be a descriptive study of the patterns of belatacept use after market launch, and as such, will provide a limited contribution to the risk assessment of the drug. However, we believe the study has value in monitoring prescriber compliance with the Contraindication to not use the product in patients who are EBV negative or EBV unknown serology. We recommend that this postmarketing study be conducted.

Study IM103075: The objective of this study, to enumerate cases of PTLD occurring with belatacept, is highly relevant. However, the usefulness of the data will be compromised by the limitations of the UNOS/OPTN database. Specifically, the fact that some aspects of reporting PTLD in the UNOS/OPTN system are voluntary may lead to underascertainment. The study will also be limited by the inability of the UNOS/OPTN database to reliably capture switches between belatacept and calcineurin inhibitors (CNIs). Because of these deficiencies, we are not confident that this study would provide a valid estimate of the incidence of PTLD with belatacept use. However, we recognize that the proposed approach would provide estimates (albeit not entirely reliable estimates) of the incidence of PTLD both with belatacept and also with calcineurin inhibitor use, which would afford some measure of comparison to the existing standard of care. In addition, since the study leverages existing and available data from the UNOS/OPTN database, its conduct does not represent a significant burden. We therefore recommend that this postmarketing study be conducted.



The principle outcomes to be assessed in a registry of belatacept patients would be PTLD (especially in the CNS) and PML. Such a registry would allow a reasonably rapid and accurate estimate of the absolute incidence of PTLD, CNS PTLD, and PML among transplant patients maintained on belatacept. Such a registry would not provide a similar estimate of the absolute incidences of PTLD, CNS PTLD, and PML among transplant patients maintained on a CNI-based regimen. Nonetheless, given existing data suggesting that CNS PTLD and PML are rare among transplant patients maintained on a CNI-based regimen, accurate absolute incidences of these events among belatacept patients would have significant informative value. We would like to discuss the strengths, limitations, and practicality of such an approach.

We invite you to develop a suitable statistical analysis plan for the data on PTLD and PML with belatacept use that would be obtained from such a registry. Because the registry will enroll only belatacept users, we realize it would not have an intrinsic comparison group. However, other comparisons could be planned, specifically: (1) compare the incidence of

PML and PTLD among postmarketing users of belatacept to the incidences observed in the premarketing clinical trial data; (2) compare the incidence of PML and PTLD between users of belatacept from the time of the initial transplant and belatacept users who were switched to belatacept after first receiving a CNI.

If, after a sufficient number of patients are enrolled and followed, the risk estimates for these outcomes have sufficient precision to be reassuring, discontinuation of the registry could then be considered. As part of the analysis plan, we invite you to propose such numerical criteria, which if met after a suitable length of time, would support discontinuation of this patient registry program.

(b) (4)

We look forward to discussing these comments with you further at the meeting on September 27, 2010.

2. **Labeling:**
   We have no further comments on the label at this time.

Thanks
June Germain
Regulatory Health Project Manager

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): OSE/Division of Risk Management/Karen Townsend, RPM			FROM: June Germain, MS RPM, 301-796-4024 /Dr. Ozlem Belen, MD Deputy Director for Safety/Division of Special Pathogen and Transplant Products	
DATE: August 23, 2010	IND NO.	BLA No.: STN 125288	TYPE OF DOCUMENT: Proposed REMS amendment	DATE OF DOCUMENT: August 16, 2010
NAME OF DRUG: belatacept	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG: immunosuppressant	DESIRED COMPLETION DATE: "To be decided once complete BLA is resubmitted"

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The Division has received the proposed REMS amendment to the BLA resubmission for STN 125288, belatacept for the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. A CR letter was issued on May 1, 2010.

The submission is dated and received August 16, 2010. The elements of the proposed REMS include a Medication Guide and a communication plan. Please review the REMS proposal.

The submission can be found at:
\\cber-fs3\m\eCTD Submissions\STN125288\125288.enx

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125288

MEETING REQUEST GRANTED
August 3, 2010

Bristol-Myers Squibb
Attention: Mary Christian, Pharm.D
Director, Global Regulatory Strategy
PO Box 4000 Mailstop D32-08
Princeton, NJ 08543-4000

Dear Dr. Christian:

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

We also refer to your July 12, 2010, correspondence requesting a Pre-BLA meeting to present the 36 month data from the two Phase 3 pivotal clinical trials. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: September 1, 2010
Time: 10:00 am to 11:00 AM EST
Location: 10903 New Hampshire Avenue
White Oak Building 21, Conference Room: 1537
Silver Spring, Maryland 20993

Probable CDER participants:

Renata Albrecht, M.D.	Division Director
Ozlem Belen, M.D.	Deputy Director for Safety
Joette Meyer, PharmD.	Clinical Team Leader
Patrick Archdeacon, M.D.	Medical Reviewer
William Taylor, PhD.	Pharmacology/Toxicology Team Leader/CDTL
Suzanne Robottom, PharmD	Team Leader/DRISK
Carolyn Yancey, MD	Senior Medical Officer/DRISK
Cheryl Dixon, PhD	Statistical Reviewer
Karen Higgins, ScD	Statistical Team Leader
Seong Jang, PhD	Clinical Pharmacology Reviewer
Gerlie Gieser, PhD	Clinical Pharmacology Reviewer
Phillip Colangelo PharmD, PhD	Clinical Pharmacology Team Leader
June Germain, MS	Regulatory Health Project Manager

Please e-mail me any updates to your attendees at june.germain@fda.hhs.gov , at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA Building 22, provide the guards with either of the following numbers to request an escort to the conference room: June Germain, RPM at 301-796-4024 of Karin Klunk division secretary at 301-796-0743.

If you have any questions, call me at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

_____/
June Germain, MS
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM *(Name, Office/Division, and Phone Number of Requestor)*:
CDER Pediatric and Maternal Health Staff, Maternal Health Team: Tammie Brent Howard 301-796-1409	Ozlem Belen, MD Safety Deputy Director, OAP/D. Special Pathogen and Transplant Products and June Germain PM 301-796-4024

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 29, 2010		STN 125288	BLA	June 30, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
belatacept	(b) (4)	Immunosuppresant	August 27, 2010

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☒ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The Division has received the BLA submission for STN 125288, belatacept for the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. The submission is dated June 30, 2009 and received July 1, 2009. The BLA received a CR letter on May 1, 2010. A resubmission is expected in September 2010. (b) (4)

Link to original eCTD submission \\cbsap58\m\eCTD_Submissions\STN125288\125288.enx

(b) (4)

SIGNATURE OF REQUESTOR Lane Germain, MS Project Manager	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

BLA 125288

Bristol-Myers Squibb
Attention: Mary Christian, Pharm.D
Director, Global Regulatory Strategy
PO Box 4000 Mailstop D32-08
Princeton, NJ 08543-4000

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009, received July 1, 2009, submitted under section 351 of the Public Health Service Act for belatacept lyophilized powder, 250 mg.

We also refer to the end-of-review conference meeting held between representative of your firm and the FDA on June 11, 2010. The purpose of the meeting was to discuss the elements of the complete response letter and to ensure common understanding of deficiencies and the your expected responses.

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, please do not hesitate to call June Germain, Regulatory Health Project Manager, at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

/_____\
Renata Albrecht, MD
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING

Meeting Date:	June 11, 2010
Meeting Location:	FDA/CDER 10903 New Hampshire Ave Building 22, Room 1309 Silver Spring, MD 20993
Application number:	BLA 125288
Product Name:	belatacept
Indication:	Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplant.
Sponsor:	Bristol-Myer Squibb
Meeting Chair:	Renata Albrecht, MD
Meeting Recorder:	June Germain, MS

FDA ATTENDEES:

Renata Albrecht, MD	Director, DSPTP
Patrick Archdeacon, MD	Medical Officer, DSPTP
Joette Meyer, Pharm.D	Clinical Team Leader, DSPTP
Suzanne Robottom, PharmD.	Team Leader, DRISK
Carolyn Yancey, MD	Senior Medical Officer, DRISK
Ozlem Belen, MD	Safety Deputy Director, DSPTP
William Taylor, PhD	Pharmacology/Toxicology Team Leader/CDTL, DSPTP
Janice Lansita, PhD	Pharmacology/Toxicology Reviewer, DSPTP
Susan Kirshner, PhD	Associate Chief, Laboratory Immunology,DTP
Barry Cheney, PhD	Deputy Director, DTP
Jack Ragheb, MD	Product Quality Reviewer, DTP
Bo Chi, PhD.	Microbiologist, DMPQ
June Germain, MS	Regulatory Project Manager, DSPTP

BMS ATTENDEES:

Mary Christian, PharmD.	Director, Global Regulatory Sciences
Pushkal Garg, MD	Executive Director, Belatacept Medical Lead
Jeffrey Gelb, MD,	Vice President, Full Development Team Lead
Claudia Arana, PhD	Group Leader, Analytical Research & Development
Laura Bessen, MD,	Vice President Immunoscience
Kalyan Ghosh, PhD,	Executive Director, Global Biometrics Sciences
Margo Herron	Regulatory Affairs, Washington Liaison

Chen-Sheng Lin, PhD,	Director Global Biometric Sciences
Mary Beth Harler, MD	Executive Director, Belatacept Medical
Daniel MacNeil, MD	Executive Director, Clinical Safety
Anthony Waclawski, PhD	Vice President, Global Regulatory Sciences
Sheila Gujrathi, MD	Vice President, Global clinical Research
Michael Grace, PhD	Executive Director, Biologics Process and Product Development
Bernard Schilling, PhD	Group Leader, Manufacturing Sciences and Process Transfer
David Smolin, PhD	Vice President, Biologics Process and Product Development
Mark Rosolowsky, PhD	Executive Director, Global Regulatory Sciences, CMC

BACKGROUND:
On June 30, 2009 Bristol-Myers Squibb (BMS) submitted a biologics license application (BLA) for belatacept (Nulojix®) in electronic format following the electronic CTD structure. On May 1, 2010 a Complete Response letter was issued to the BLA.

On May 18, 2010, the applicant submitted a request for an end-of-review conference that included a meeting briefing package to discuss the deficiencies and expected responses. Preliminary comments on the questions posted in the briefing package were emailed to the sponsor on June 10, 2010.

For the purposes of the minutes, BMS original questions are in **bold** font, the FDA's preliminary responses to all the questions are in *italics*, and a summary of the meeting discussion is in regular font.

MEETING OBJECTIVE:
To reach a common understanding of the deficiencies and further steps needed by the applicant for resubmission of the BLA.

Meeting Discussion:
On June 10, 2010, BMS indicated that they would like to focus the meeting discussion on Clinical question 2; Safety update questions 1 and 2; CMC questions 1, 3 and 6; REMS question 2; Labeling question 1 and Other/Timelines question 2

Clinical
Question 1.
In the Complete Response (CR) re-submission, the 36 month data from the Phase 3 studies IM103008 and IM103027 will be provided in the form of full 36 month clinical study reports. The clinical study reports will be modeled after the 24 month clinical study reports submitted with the 90 day safety update report and will provide data on mortality, graft loss, GFR, PTLD and other serious adverse reactions.
Does FDA agree with this approach?

FDA Response:
Yes we agree.

Meeting Discussion:
No further discussion.

(b) (4)

[redacted]

Safety Update
Question 1.
The Safety Update report to be included in the CR re-submission is outlined in Attachment 2 and will include the elements described in the Complete Response letter. Does FDA agree with the approach outlined in Attachment 2?

FDA Response:

The outlined approach appears acceptable. We view biopsy proven acute rejection (BPAR) and GFR as important safety outcomes; it will be particularly important to include data regarding these outcomes in the 36 month clinical study report if not also included in the Safety Update Report.

Meeting Discussion:
BMS stated that data on acute rejections and GFR will be described in detail in the 36 month Clinical Study Reports the Division agreed with this plan.

Question 2.
As indicated in the Safety Update outline, narratives written for discontinuations from study treatment for AEs will be included in the Safety Update, as requested in the CR letter. Narratives will not be written for discontinuations for other reasons. For the 36 month clinical study reports, we will use this convention for inclusion of narratives.
Is this acceptable?

FDA Response:
We note your proposal to submit narratives for discontinuations from study treatment for AEs but not for other discontinuations. Previously you considered discontinuations due to efficacy failures separately from discontinuations due to AEs. As belatacept was associated with higher rates of efficacy failure in the initial submission, please also include narratives for discontinuations due to efficacy failure as well as AEs. Please also document the primary cause of discontinuation for all patients to the greatest degree possible.

Meeting Discussion:
BMS agreed to include narratives for all patients who discontinued study treatment regardless of cause for the discontinuation from the three studies 008, 027 and 100, as well as narratives for discontinuations due to AEs from the other studies. These narratives will include the primary reason for discontinuation. In addition, BMS stated they plan to summarize the 12 and 24 month data and provide incremental observations followed by cumulative rates through 36 months. The Division agreed to this plan.

Question 3.
As was done for the Safety Update Report provided in November 2009, datasets for the two phase 3 studies (IM103008 and IM103027) and the two phase 2 studies (IM103100 and IM103034) using the same conventions as were employed for the initial BLA submission will be provided in this response.
Is this acceptable?

FDA Response:
Yes, we agree.

Meeting Discussion:
No further discussion.

Question 4.
Case Report Forms (CRFs) will be provided for the five clinical phase 2 and 3 studies (IM103008, -027, -100, -047, -and 034) using the same conventions as were used in the initial BLA.
Is this acceptable?

FDA Response:
Yes we agree.

Meeting Discussion:
No further discussion.

CMC: Product Quality
Question 1.
Given when the (b) (4) **were produced (i.e. during the clinical manufacturing campaign) does the Agency still require the submission of additional drug substance trending data or is the characterization and release testing data presented in 3.2.S.3.1 and 3.2.S.4.4, respectively, sufficient to address the Agency's question?**

FDA Response:
(b) (4)

(b) (4)

Meeting Discussion:
BMS noted the following points:

(b) (4)

Question 2.
Does the Agency still require the submission of additional information with regard to the belatacept cell line stability or the control of passages?

FDA Response:
The information provided is sufficient. No additional information is needed at this time.

Meeting Discussion:
No further discussion.

Question 3.
Given that (b) (4) s will be used for belatacept (b) (4) production, and that BMS will provide detailed data and safety assessments on (b) (4) does the Agency require additional information such as clearance studies or DS/DP testing for (b) (4)?

FDA Response:
As the responsible entity you have experienced several biological product deviations that have involved the unintended introduction of (b) (4) *into DS,* (b) (4) *. In your response please provide information demonstrating the control of this parameter, now and in the future.* (b) (4) (b) (4) *We believe confirmatory testing of the bulk drug substance for* (b) (4) *will provide added assurance that the quality and stability of the material have not been impacted by* (b) (4) *and in conjunction with a strong equipment qualification and maintenance plan should diminish the need to perform* (b) (4) *clearance studies or* (b) (4) *testing as a release test.*
With regards to (b) (4) *as this question pertains to any potential impact on safety, the need for further studies/testing will be based upon review of the additional information you will provide, which should include a risk-based, worst case scenario analysis supporting your conclusion that the level of* (b) (4) *does not impact product quality or safety. As this question pertains to any potential impact on product quality, the need for further studies/testing will be assessed upon review of trended data of DS and DP stability indicating CQA from lots held in the* (b) (4) *Accelerated stability studies may be helpful in this regard.*

Meeting Discussion:
BMS agreed to perform confirmatory (b) (4) testing of 3 lots of belatacept drug substance (DS) and noted that DS was made from (b) (4). BMS agreed that (b) (4) BMS plan to submit equipment qualification and maintenance plans. BMS agreed to provide safety risk assessments from the original toxicology study reports and provide DS stability indicating CQA for (b) (4). BMS stated that they will perform (b) (4) Given the history of unintended introduction of (b) (4) during manufacturing the Division asked that BMS test 3 lots by the (b) (4). The Division noted that BMS also has the option to provide a worst case scenario for (b) (4) removal and specifically include the risk assessment data and supporting data that the (b) (4) BMS agreed.

Post-meeting note: BMS stated that recent technical issues have occurred at their media supplier which will likely result in a delivery delay, BMS plans to initiate the 2010 belatacept DS manufacturing campaign with available (b) (4) that has historically been used for belatacept manufacturing. When (b) (4) BMS plans to use this source for the remainder of the DS manufacturing campaign.

Question 4.
Does the Agency agree that based on 30 month -40°C stability data that IEF is not limiting to the 30 month proposed use dating?

FDA Response:
This is a review issue, but the claim would be strengthened by more quantitative and reliable data from a method such as Capillary Electrophoresis-IEF.

Meeting Discussion:
No further discussion.

Question 5.
Does the Agency agree that it is not necessary to assess (b) (4) as part of belatacept drug product stability?

FDA Response:
Yes we agree.

Meeting Discussion:
No further discussion.

Question 6.
Is the information contained in the BLA sufficient to support the administration of the product as recommended in the package insert (i.e. SWFI, NS and D5W as constitution fluids, NS and D5W as infusion fluids, IV bags, non-siliconized syringes and 0.2-1.2µm filters)?

FDA Response:
No, based on the information contained in BLA Section 3.2.P.2.6 and Tables 3.2.P.8.3.2.T45 to 3.2.P.8.3.2.T95 and 3.2.P.8.3.2.T72 to 3.2.P.8.3.2.T89 all conditions of constitution and dilution generate large numbers of visible particles and subvisible particulates. The studies to assess whether (b) (4) filters can effectively remove visible and subvisible particulates were not performed under conditions that suitably mimic the intended conditions of use, particularly with regards to infusion rate. We recommend that you provide data demonstrating the capacity of (b) (4) (b) (4) filters (b) (4) to remove visible and subvisible particulates under worst case conditions. Assessing samples that have been stressed to increase visible and subvisible particulate levels above those seen under routine conditions of use should be considered.

Meeting Discussion:
BMS stated they conducted a study where belatacept drug product samples were aged for at least 30 months were constituted, and infused at a rate of 300 mL/hour. Then the samples were evaluated for particulates before and after filtration. BMS noted that the results showed removal of particulates when using (b) (4) filters and they will submit the data including filter and containers types in response to the CR letter. BMS stated they do have visible and subvisible particulates data. BMS stated that it also had data for particles in th (b) (4) size rate by microscopic testing and HIAC testing.

Question 7.
Does the Agency agree that the described approach is reasonable to address the removal of particulates during product administration?

FDA Response:
The proposed approach appears to be reasonable. The use of an orthogonal approach such as micro flow imaging may help in this assessment.

Meeting Discussion:
No further discussion.

Question 8.
Additional real time stability data for belatacept drug substance (30 months) and drug product (24 months) are now available; BMS would like to update the BLA with this new information.
Does the Agency concur?

FDA Response:
We will accept the inclusion of additional real time stability data in the CR response.

Meeting Discussion:
No further discussion.

Question 9.
Facility changes were made at Syracuse in response to EMEA observations.
An amendment to the BLA was filed to capture these changes with the exception of modifications to the cell banking area because data on this area was not available at that time. BMS would like to update the BLA with the facility changes to the cell banking area.
Does the Agency concur?

FDA Response:
Yes, we concur.

Meeting Discussion:
No further discussion.

Facility Inspections:
Question 1.
Can the Agency provide an update on the status of the Establishment Inspections and subsequent review of BMS responses for the Syracuse, NY and Manati, Puerto Rico facilities?

FDA Response:
Your responses to the 483 observations issued during the BMS Syracuse and Manati facility inspections are currently under review. Additional information has been requested for the

Syracuse facility. The review of the response will continue once the requested information is provided.

Meeting Discussion:
BMS stated they would have the final responses for the Syracuse facility by the end of June. The Division stated that the response to the Manati facility is still under review.

Risk Evaluation and Mitigation Strategy (REMS):
Question 1.
Included in the Complete Response re-submission will be an updated proposed REMS document and REMS Supporting Document as requested to communicate risks of PTLD and PML. This submission will also include an updated Medication Guide and communication plan, and samples of proposed communication tools. A timetable for submission of assessments and the REMS assessment plan will be included. While the precise language for these documents will be subject to the final negotiated label language and REMS, does a REMS that includes a communication plan and the Medication Guide appropriately address the risks of belatacept?

FDA Response:
Yes, an approach consistent with the REMS outlined in the May 1, 2010 Complete Response letter appropriately addresses the risks of belatacept at this time. However, a complete review of the proposed REMS after the BLA is re-submitted will be necessary to determine whether it is acceptable, since additional information regarding risks and safe product use may emerge during the review of your BLA resubmission.

Meeting Discussion:
No further discussion.

Question 2.
In the Complete Response letter, FDA commented that the "...proposed REMS does not adequately communicate the risk of PTLD and PML".
Can FDA please clarify this comment with respect to the Communication Points for HCPs included in the February 17, 2010 submission, Seq. 0033 to the BLA (response to FDA comments of January 13), noting if these communication points are appropriate or suggest how they can be modified to adequately communicate risk?

FDA Response:
In follow-up to your responses to our questions and comments about the belatacept REMS proposal (submitted February 17, 2010; sequence 033), we have the following recommendations for the communication plan. We also remind you that all planned belatacept REMS materials identified in your REMS proposal must be submitted to the Agency for review.
1. Provide further specific details on your plan to engage and collaborate with the professional organizations in the REMS development and implementation. Based on the February 17, 2010 submission, the role of these organizations appears passive (receiving REMS materials). We encourage more active collaboration.

2. Clarify whether, as part of the REMS, you propose to include training tools under development with transplant organizations.
3. We encourage you to continue to consider the utility of broad reaching communications via information pieces published in major transplantation and nephrology publications. This type of communication can be recurring at regular intervals and succinct.
4. We note you propose "standing" communication such as the Nulojix website. Provide more specific details on frequency of dissemination of other materials, meeting participation, webinar offerings, etc.
5. Clarify how the proposed Healthcare Provider Fact Sheet distribution to healthcare providers (HCPs) and allied healthcare professionals differs from the proposed Dear Healthcare Provider letter (DHCP). Specify the purpose of these two pieces and the time intervals/frequency for dissemination. For example, every 6 months for three years from the date of product launch.
6. Clarify the specific plan for dissemination of the Infusion Specialist Letter and Infusion Specialist Checklist (submitted April 1, 2010; sequence 045) to HCPs at kidney transplant centers, nephrologists at community centers, and to infusion centers' staff.
7. Clarify the role and responsibilities of the BMS field medical science liaisons to support dissemination of the specific communication plan materials that communicate the risks and appropriate-use information for belatacept.

Meeting Discussion:

(b) (4)

The Division stated that it could not approve (b) (4) The Division noted that the final REMS language is dependent on the final negotiated labeling. The Division agreed to provide more detailed comments when the final wording is substantially complete for the package insert.

BMS noted that they were still in discussions with UNOS with regards to the use of the OPTN database as a functional belatacept registry. BMS stated that UNOS had provided some information regarding patterns of EBV serostatus determination across transplant centers: in summary, the data suggested that approximately three-quarters of centers ascertain EBV serostatus reliably while approximately one-quarter of centers rarely ascertain EBV serostatus. BMS reported that UNOS has determined, however, that it could not make available to BMS information regarding which centers followed which practice – though it could provide such information to HRSA and/or FDA. The Division stated that they have a general interest in safety

signals related to PTLD and have previously considered pursuing such information from the OPTN. The Division further noted that they have a general interest in determining the suitability of the OPTN data collection system for informing safety issues related to transplant drug regulation.

Question 3.

In our February 17, 2010 submission, we also proposed a number of elements of the [redacted] (b) (4)

FDA Response:

Please refer to FDA Response to the REMS Question #2 above. In addition please address how you plan to identify and target new prescribers.

Meeting Discussion:

No further discussion.

Labeling:

Question 1.

The CR response strategy was designed to provide the clinical data such that FDA can confirm, with more long term data, the benefit/ risk established with the 24 month data. We will provide those analyses that would be needed to support an updated label. We, therefore, propose to provide an updated label with 36 month data from the Phase 3 trials for efficacy, safety, and including proposed updates to other sections of the label in this response. Consistent with our proposed draft label submitted via email on March 22, 2010, we plan to focus Section 6, Adverse Reactions, on data from the 2 Phase 3 studies to align with the efficacy section.

Is this acceptable?

FDA Response:

Yes, we agree.

Meeting Discussion:

BMS stated that they plan to remove the [redacted] (b) (4) in the efficacy section and only focus on the LI vs CsA arms. The Division agreed. BMS agreed to include safety and efficacy in the clinical trials section. The Division also noted that they are working on additional sections of the package insert and will provide them to BMS for consideration to be included in the resubmission of the BLA.

Question 2.
We have completed qualitative market research of the previous medication guide and propose to include an updated medication guide, with language at a 7th grade health-literacy reading level in the CR submission.
Is this acceptable?

FDA Response:
Yes, we agree to a 7th grade health-literacy reading level overall.

Meeting Discussion:
No further discussion.

Does the Agency have other comments on the Medication Guide at this time?

FDA Response:
At this time we have no additional comments on the Medication Guide. Once the revisions to the package insert are substantially complete, we will consult on the Medication Guide with the Division of Risk Evaluation (DRISK) at the Office of Surveillance and Epidemiology (OSE) and will provide you further comments.

Meeting Discussion:
No further discussion.

Question 3.
Based on FDA's review of the initial or subsequent draft label submissions, does FDA have any additional comments to provide at this time that can guide us in revising the label for the CR submission?

FDA Response:
At this time we have no additional comments. However, we have been working on revisions to various sections of the package insert and will provide you a revised version in the next few weeks.

Meeting Discussion:
The Division stated that they are working on revisions to Sections 4, 5, 6, 7, 12, and 14 to the draft package insert and will send those back to BMS within the next few weeks. The Division also cautioned that the Safety Endpoints and Labeling Development (SEALD) group will only provide comments on a substantively complete labeling. Since, the other sections of the belatacept labeling are not complete from the Division's perspective, BMS should understand that the sections of the package insert that are forthcoming will not have been reviewed by SEALD and additional revisions may be suggested by SEALD at a later date.

Other/ Timelines:
Question 1.
We expect the elements of this re-submission to be available for submission between June and October 2010. For example, some aspects (REMS, Immunogenicity Assay) will be

available in June/ July, while some of the CMC responses and Clinical responses will be available in September/October to conduct additional studies (CMC) and compile the necessary information from the ongoing studies (Clinical).
Would FDA consider submission of the response elements as available in the form of "reviewable units" of information grouped by topic and/or availability, e.g. REMS, Immunogenicity Assay, Drug Substance, Drug Product, Microbiology, Clinical (by elements of IM103027, IM103008, Safety Update)?
If this is acceptable, BMS can provide a schedule of submissions for your endorsement before the first submission.

FDA Response:
We agree with a rolling response, provided that each reviewable unit is complete on itself, and you provide us with a timetable of the proposed submission, including dates that you expect the facilities to be ready for reinspection. Please note that the BLA review clock will not begin until all information is submitted and the facilities are ready for reinspection.

Meeting Discussion:
No further discussion.

Question 2.
We had provided updated versions of the postmarketing studies proposals as requested in the March 19, 2010, Seq. 0044 to the BLA. We are now planning these studies and your feedback will help to ensure we are preparing the adequate scope of work, especially for the cohort study. Based on available data, are the proposed prospective cohort study and other (UNOS-based) epidemiology studies sufficient to assess the postmarketing safety events and patterns of use (e.g. capture of potential use in serostatus EBV negative/unknown patients)?
Does the Agency have any specific feedback at this time to further inform these study designs?
Would the Agency accept draft protocols of the planned postmarketing epidemiology studies for review as they are available, in advance of an action?

FDA Response:
We have consulted the study proposals for the postmarketing studies to the Maternal Health Team (MHT) and the Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology (OSE). The DEPI consult is still pending. We hope to have a response by the end of July.

(b) (4)

[redacted]

Meeting Discussion:
BMS agreed to wait for feedback on the synopses undergoing review in DEPI before submitting the complete protocols to the Division.

(b) (4)

BMS also noted their plan is to assess the use of belatacept according to EBV status working with the UNOS-based registry. They also acknowledged potential hurdles. BMS worked with UNOS to understand the current rate of EBV serostatus testing of kidney transplant recipients and learned that 24% of patients were reported as either unknown or not done. BMS would like to work further with UNOS to try and understand the current rate of EBV serostatus testing at kidney transplant centers and proposes a disease education program targeting sites with high rates of missing data. However, UNOS is not permitted to disclose this information to BMS and under Health Insurance Portability and Accountability Act (HIPAA) privacy rules they are not able to provide patient level data to BMS. (b) (4)

(b) (4)

(b) (4) BMS requested any advice or assistance in working through these issues. The Division requested that BMS provide a written document summarizing their efforts and the hurdles encountered and would see what, if anything, else could be done to facilitate these interactions.

ACTION ITEMS:

- FDA and BMS agreed to a presubmission Type B meeting around the end of September to discuss the 36 month clinical trial data
- BMS agreed to submit a timeline for the rolling submission of reviewable units
- BMS agreed to submit actual disseminated plans and assessment of REMS
- FDA agreed to provide feedback on postmarketing studies synopses
- FDA agreed to provide BMS with draft Sections 4, 5, 6, 7, 12, and 14 of the package insert within the next few weeks, followed by the other sections at a later date, so that BMS can refer to these revisions in the resubmission

(b) (4)

- BMS agreed to submit a writing document outlining their plan and the hurdles they have encountered in collecting data on EBV serostatus from transplant centers.

HANDOUTS:

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

Germain, June

To: Germain, June
Subject: FW: Belatacept BLA (125288/0)

Importance: High

From: Clark-Stuart, Michelle
Sent: Thursday, March 11, 2010 1:29 PM
To: 'Bakhshi, Meena'
Subject: Belatacept BLA (125288/0)
Importance: High

Hello Meena,

I am in the process of finalizing my drug substance review memo and I have a few questions. Please let me know where the following information is in the submission;

(b) (4)

3) Where is the qualification data for the endotoxin assays for this process?

4) Please clarify the established (b) (4) for this process (in days) at 2-8 degrees C.

5) For Table 3.2.S.2.5.6.9.T02, clarify whether the bioburden and endotoxin parameters listed are (b) (4)

6) What is the endotoxin safety margin referred to in 3.2.S.4.1 , Specification?

7) Is the microbial aerosol challenge all that was done to assess the drug substance container/closure on the (b) (4)? Discuss the numbers and names of the microorganisms used for this study.

8) Please describe the (b) (4) mentioned the bioburden qualification report in Table 1.

Thank you kindly for a prompt reply. I am sorry if I missed them in the BLA.

Regards,

Michelle

Michelle Y. Clark-Stuart, MGA/MIS, MT (ASCP)
FDA/CDER/OC/DMPQ
Biotech. Manufacturing Team
CMC reviewer
White Oak Bldg. 51, Room #4222
10903 New Hampshire Avenue
Silver Spring, MD 20993

BLA 125288
Belatacept
Bristol-Myers Squibb
CMC Information Request

February 25, 2010

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009; we request that you submit the following CMC information by March 4, 2010, if possible.

Stability Studies

1. Please provide a table(s) that summarizes all the data for Appearance (particles) and Particulates (HIAC) in Section 3.2.P.8.3.2. If available, also include data for particulate matter that is (b) (4).
    a. Report all particulate data as particles/container and particles/mL.
    b. USP <788> Test 1. A reporting is used for solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of more than (b) (4). Justify its applicability to DP that has been diluted to 1 or 10 mg/mL for infusion.
    c. Provide a description and discussion of the studies showing that the (b) (4) filters adequately remove particulate matter during IV administration.

2. In process hold time studies are performed to address the stability of DS during manufacturing. The data provided in the BLA does not include critical quality attributes (CQA) known to be associated with belatacept stability, such as (b) (4) In addition, no potency assays where performed as part of these stability studies as described in USP <1049>. Please provide these data or justify their absence.

3. Please provide the location in the BLA submission of studies to assess extractables and leachables from in-process hold vessels/containers; if those items were not included in the BLA submission, please submit them as an amendment.

4. Please justify why the Moisture Content acceptance criteria for shelf life differ from those used for release testing.

Thanks
June Germain, MS
Regulatory Health Project Manager

Germain, June

From: Germain, June
Sent: Tuesday, February 23, 2010 3:20 PM
To: 'Christian, Mary'
Subject: RE: BLA 125288 - Request For Information- DSI Sponsor Request - Feb 22 2010

Hi Mary,

Those are the correct subject numbers, but the wrong site number as noted, it should have been Dr. Rostaing site 035 for protocol IM103027.

June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
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Center for Drug Evaluation and Research
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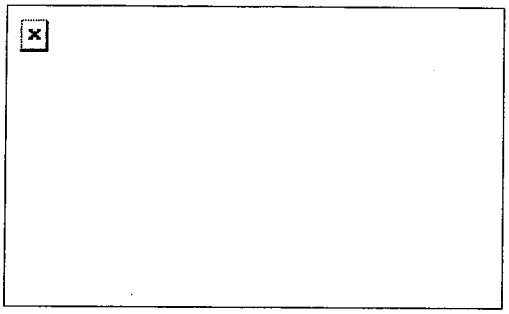
From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Monday, February 22, 2010 7:04 PM
To: Germain, June
Subject: BLA 125288 - Request For Information- DSI Sponsor Request - Feb 22 2010

Hi June,

For this request for information, please note that the Subjects listed for item 7 (10060 & 10136), Dr Rostaing's site #076 (IM103008) were actually Patient Numbers for Subjects at Dr Rostaing's site # 035 (IM103027). Can you please confirm that these are the patient numbers for which the response is requested?

Thank you.

Best regards,
Mary



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BLA 125288
Belatacept
Bristol-Myers Squibb
DSI Information Request

February 22, 2010

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009; we request that you submit the following information by February 25, 2010, if possible.

We have received and reviewed your written response dated December 8, 2009 to the Form FDA 483 issued at the conclusion of the sponsor monitor inspection at Bristol-Myers Squibb in Princeton, N.J. by Consumer Safety Investigator Dawn Wydner.

On page 4 of your letter in the table accompanying your response to Item 1.C. "Sponsor failed to ensure adequate measures were established to verify stability of the Investigational Product (Belatacept) was maintained once reconstituted this includes all eight (8) sites reviewed - sites 006 (Bresnahan), 0002 (Florman), 0010 (Vincente), 076 (Rostaing), 0116 (Mondragon), 0123 (Reyes), 0091 (Medina), and 0093 (Garcia)", you state that the information for 7 of 8 sites inspected, the date and time of study drug reconstitution is available in Pharmacy or other paper or electronic records.
Please provide from each of the seven sites listed below, where it is available, copies of the records which document the date and time of belatacept reconstitution for the following subject visits:

1. Bresnahan 006:	Subject 20050 Visit 60, Subject 20053 Visit 56,
2. Vincenti 010:	Subject 20028 Visit 4, Subject 20044 Visit 52
3. Mondragon 116:	Subject 20185 Visit 160, Subject 20450 Visit 36
4. Reyes 123:	Subject 20316 Visit 88, Subject 20732 Visit 96
5. Medina 091:	Subject 10070 Visit 96, Subject 10297 Visit 12,
6. Garcia 093:	Subject 10338 Visit 24, Subject 10359 Visit 48
7. Rostaing 076:	Subject 10060 Visit 60, Subject 10136 Visit 44

Thanks
June Germain, MS
Regulatory Health Project Manager

Germain, June

From: Christian, Mary [mary.christian@bms.com]
Sent: Monday, February 22, 2010 6:56 PM
To: Germain, June
Subject: RE: BLA 125288/belatacept/BMS/Clarification of adcg dataset

Thanks, June.

The LOCF data sets were based on BLA lock, therefore they have less observations than ADCG data sets submitted with the safety update.

Hope this helps. Let me know if you have any other questions.

Best regards,
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Monday, February 22, 2010 4:36 PM
To: Christian, Mary
Cc: Germain, June
Subject: BLA 125288/belatacept/BMS/Clarification of adcg dataset

Hi Mary,

In the adcg datasets submitted today for Study 008 there were 7772 total observations, whereas there were 8632 total observations in the adcg dataset submitted with the safety update. Why is the total number of observations in the new datasets less than the total number of observations in the datasets that were submitted with the safety update.

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

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Germain, June

From: Christian, Mary [mary.christian@bms.com]
Sent: Monday, February 22, 2010 9:16 AM
To: Germain, June
Subject: RE: BLA 125288/belatacept/BMS information request

Thanks. This is clear. I wasn't sure if there was another document you were referring to.

Working on the email now for Question 2. Question 1 will follow shortly.

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Monday, February 22, 2010 8:50 AM
To: Christian, Mary
Subject: RE: BLA 125288/belatacept/BMS information request

Hi Mary,

Question 2 refers to clarification of the Feb 11, 2010 submission seq# 0029 pg. 18 for figure 1 "Renal function at month 12 by rejection status" and pg. 27 for Protocol 008 and pg. 28 Protocol 027 " Summary of calculated GRF with Imputation at Month 12 by Acute rejection status within Year 1".

June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Sunday, February 21, 2010 1:00 PM
To: Germain, June
Subject: RE: BLA 125288/belatacept/BMS information request

Hi June,

Could you please clarify what Ques 2 refers to when noting Figure 1 and Tables on page 27 and 28? Are these

Germain, June

From: Christian, Mary [mary.christian@bms.com]
Sent: Monday, February 22, 2010 9:24 AM
To: Germain, June
Subject: BLA 125 288 Belatacept; Issues to be discussed on Wednesday Feb 24 telecon
Attachments: Mary Christian Pharm D MBA.vcf

Dear June,

Here are some of the areas we have been discussing and would like to review with you. This arise from a review of your briefing document and are presented for your review as we continue our preparation for the March 1 AC.

1. BPAR (AR) characterization: Detailed characterization of all reports of rejection has been a goal of the development program, with the objective of providing data to fully assess the clinical impact and importance in the overall b/r. We noted that FDA did not comment regarding the data that support this characterization or indicate that this is important when considering how to weigh them in the determination of efficacy. We believe this is a critical issue for discussion, and we are concerned that this aspect may not be fully considered. Such a discussion will not only assure these aspects are considered for belatacept, but also could benefit future development programs as well.

Considering the expected make-up of the Committee, would FDA consider (in the questions, preamble to the questions, or otherwise) ask the Committee to be mindful of the clinical impact of these rejection when considering how to weigh them in the determination of anti-rejection efficacy?

(b) (4)

(b) (4)

3. Potential influence of 027 study results on interpretation of PTLD data for the indicated patient population and comparison to reference databases: As noted in the FDA presentation of PTLD by study (table 28), all 3 cases of CNS PTLD for the LI regimen were observed in the 027 study. This ECD population is thought to be an older and sicker population with higher risks for adverse events. The MI regimen had 2 cases of CNS PTLD across all three studies. The only PTLD events on the LI regimen observed in the -008 study are the 2 cases of renal PTLD which were diagnosed as not being PTLD in the unplanned and post-hoc blinded pathology assessment. This raises the question of the risk of PTLD for LI, EBV positive patients in the SCD population. The comparison to the epidemiology databases may also be limited because our pooled trial population was 1/2 patients with ECD donors and the epidemiology databases are more representative of the 008 study population since only ~14% of the US population is thought to be ECD.

In response to a question about the difference in PTLD risk by study (ECD v SCD), we plan to make the points noted above. Has the FDA any comments about the potential differences in PTLD risk by study population and the comparison to other clinical trials and reference databases?

4. Characterization of prespecified endpoints as efficacy reported as safety endpoints: In our presentation, we followed the prespecified classification of the endpoints as discussed with FDA. FDA presents all the endpoints except rejection as safety endpoints. If we understand the FDA position correctly, FDA still considered these endpoints important and the differences between treatments clinically relevant. To avoid confusion, we plan to point out this difference in classification of these endpoints (safety v efficacy) in the introduction.

We ask if FDA would consider doing the same. We think it will be important to note that calling these endpoints safety endpoints this should not be interpreted as a signal to reduce the weight these endpoints have in the overall B/R.

5. Difference in Epi analyses and planned responses:
Based on the presentation of comparison of rate in the FDA background document, we think the explanation for the difference in the rates quoted from the reference databases may be a result of the data collection methodology. Our interpretation is that the differences are due to different patient populations based on induction therapy and the capture of PTLD cases from the UNOS database. FDA and SRTR used the UNOS follow-up form and BMS used the UNOS follow-up form and the UNOS malignancy form. BMS also included any PTLD cases listed as the cause of death or contributing cause of death on the follow-up form, it is unclear if FDA and SRTR included these as well.

We think the differences in reported reference rates will spark a question from the Committee regarding the origin of this difference and would like to discuss how to respond to this.

Best regards,
Mary

Bristol-Myers Squibb
Mary Christian, Pharm.D., MBA
Director, Global Regulatory Strategy
ImmunoScience
(609) 252-5281 Work
(908) 507-8167 Mobile
(609) 252-6000 Fax
PO Box 4000, Mailstop D32-08
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BLA 125288
Belatacept
Bristol-Myers Squibb
Clarification on Information Request

February 19, 2010

Dear Dr. Christian,

We acknowledge receipt of your February 11, 2010 submission that includes the analyses datasets and programming to support presentations of data in the Advisory Committee briefing document and planned slide presentation, and also the analysis data sets and programming for additional exploratory analyses. We are requesting clarification regarding this submission. Please respond by February 22, 2010, if possible.

1. You noted in the cover letter that the programming to support the presentation of data in the Advisory Committee briefing document and planned slide presentation and also the programming for additional exploratory analyses were included in the submission. However, we were unable to locate them. Please provide this programming for our review.

2. We acknowledge that the adcg.xpt was previously provided in sequence #0025 dated January 22, 2010. However, this dataset does not include imputation of last observation carried forward (locf) that is now being applied to the analyses presented in Figure 1 and Tables on page 27 and page 28. Please provide the analyses dataset which includes the imputed locf values for month 12. In addition, please clarify if the locf for those patients with a rejection is only a value that was collected after the rejection.

Thanks 2-19-10
June Germain, MS
Regulatory Health Project Manager

BLA 125288
Belatacept
Bristol-Myers Squibb
CMC Information Request

February 16, 2010

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009; we request that you submit the following CMC information by February 23, 2010, if possible.

1. Please provide a fuller description of the Belatacept Lot numbering System with a legend.

2. Please update all process parameters tables in Section S.2.4 of the BLA "Controls of Critical Steps and Intermediates" to include the values for set points, alert limits and action limits.

Thanks 2/16/10
June Germain, MS
Regulatory Health Project Manager

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): Peter Diak (OSE, DPV II) , Karen Grisend, RPM
Mail: OSE

FROM: June Germain, RPM and Dr. Ozlem Belen DDS
Division of Special Pathogen and Transplant Products

DATE	IND NO.	BLA No.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 2, 2010		125118		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Abatacept	(b) (4)	Immunosuppresant	February 23, 2010

NAME OF FIRM: Bristol Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☒ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: On July 1, 2009 The Division received the submission for BLA 125288 belatacept (Nulojix) seeking an indication for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. The PDUFA goal date is May 1, 2010, but the Advisory Committee is scheduled for March 1, 2010 (b) (4)

Although there was no evidence of autoimmunity in toxicology studies with belatacept in rats and monkey, nonclinical studies of a related product, abatacept, showed evidence of inflammation and autoimmunity in rats, one of three animal species tested. Abatacept differs from belatacept by two amino acid substitutions and, in rodents, has greater *in vitro* binding affinity and *in vivo* inhibition of a T-cell dependent antibody response than belatacept. In [illegible]ns, belatacept has greater potency than abatacept. Toxicology studies of abatacept are therefore considered to be relevant to the belatacept safety assessment.

The following are the terms we are interesting in searching, please use another treatment modality of your choice that is used in rheumatoid arthritis patients to provide comparison.

- Autoimmune thyroid disease
- Hashimoto's thyroiditis
- Graves' disease
- Hemolytic anemia
- Idiopathic thrombocytopenic purpura (ITP)
- Lupus (SLE)
- Insulin-dependent diabetes (type1)

Please contact June Germain or Dr. Ozlem Belen for any questions that may come up during the consult process. Thank you.

SIGNATURE OF REQUESTER June Germain 2/2/10	METHOD OF DELIVERY (Check one) ☑ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Germain, June

From: Christian, Mary [mary.christian@bms.com]
Sent: Wednesday, March 17, 2010 11:55 AM
To: Germain, June
Subject: RE: BLA 125288/belatacept/BMS/meeting attendees

Sure, That would be fine. I may see if Tony or Pushkal can join if you don't mind?

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Wednesday, March 17, 2010 11:39 AM
To: Christian, Mary
Subject: RE: BLA 125288/belatacept/BMS/meeting attendees

Can we (Joette and I) call you at 1 to discuss this?

June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Tuesday, March 16, 2010 6:21 PM
To: Germain, June
Subject: RE: BLA 125288/belatacept/BMS/meeting attendees

Sure.

Chen-Sheng Lin, PhD, Global Biostatistics
Sheila Gujrathi, MD, Therapeutic Area Head, Global Clinical Research
Pushkal Garg, MD, Medical Lead, Global Clinical Research
Anthony Waclawski, PhD, Regulatory
Jeff Gelb, MD Development Lead
Mary Christian, PharmD, Regulatory

I have a question re: the label edits from today. In section 6.1, you use the terms (b) (4). We have applied an algorithm to discern Adverse Reactions, as per labeling guidance, and do not provide (b) (4) here as a result. The algorithm is provided in the Clinical Overview and excerpted here (section 5.3.6.).

Should we provide the revisions, employing this algorithm to identify Adverse Reactions, with the new cut points (>10%, < 10% as you noted) and by studies (as you noted)? Also, do you think we'll have the section 14 (CLinical Studies) before next week?

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Thanks
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Tuesday, March 16, 2010 5:58 PM
To: Christian, Mary
Subject: BLA 125288/belatacept/BMS/meeting attendees

Hi Mary,

Can you verify the BMS attendees at the Sept. 18, 2009 teleconference where we discussed the standard review designation.

June

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BLA 125288
Belatacept
Bristol-Myers Squibb
Label Information Request

March 16, 2010

Dear Dr. Christian,

Please refer to your Biologics license application (BLA), dated June 30, 2009, received July 1, 2009.

We also refer to your submission dated February 18, 2010, containing a proposed package insert for belatacept. We are providing you with our preliminary revisions and comments to sections 4, 5 and 6 of the labeling to facilitate negotiations. Please consider this information a precursor to further labeling discussions and revisions, rather than a formal labeling request.

Please submit a response to the BLA by March 23, 2010, if possible.

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



Thanks
June Germain, MS
Regulatory Health Project Manager

Germain, June

From: Germain, June
Sent: Tuesday, March 16, 2010 9:17 AM
To: 'Christian, Mary'
Subject: RE: BLA 125288 -belatacept - fax re label
Attachments: BLA 125288 label March 16.doc

Hi Mary,

Enclosed please find the clean word version of these section of the label. These are our preliminary revisions and comments, since we are in the negotiation phase please feel free to either propose new language or accept our changes. We expect that you would look at all the changes.

June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Tuesday, March 16, 2010 9:00 AM
To: Germain, June
Cc: Christian, Mary
Subject: RE: BLA 125288 -belatacept - fax re label

As I look at the Fax more closely, I see there are many changes in the text too. If you have a word version, track changes or clean that you could email, we could do a compare doc and have a starting point to insert our responses to your label version. Is this consistent with what you would like by 3/23 or are you only expecting the text/data for the boxed comments and new sections?

Thanks,
Mary

From: Christian, Mary
Sent: Tuesday, March 16, 2010 8:47 AM
To: June Germain (june.germain@fda.hhs.gov)
Subject: BLA 125288 -belatacept - fax re label

Hi June,

I received the fax. Thank you very much.

Do you also have this in a word version? Not really needed if your comments are all in the inserted boxes, but if there is new label text included (or changes to proposed), it would be helpful.

Thanks!

Best regards,
Mary

Bristol-Myers Squibb
Mary Christian, Pharm.D., MBA
Director, Global Regulatory Strategy
ImmunoScience

(609) 252-5281 Work
(908) 507-8167 Mobile
(609) 252-6000 Fax

PO Box 4000, Mailstop D32-08
Princeton, NJ 08543-4000
mary.christian@bms.com

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Division of Biometrics 6, Yi Tsong Deputy Director and Jinglin Zhong Reviewer	Jack Ragheb, Chemistry Reviewer (OPS/OBP/DTP 301-435-4566 and June Germain project manager (DSPTP) 301-796-4024

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/2/2010		BLA 125288	supplement	February 11, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
belatacept	(b) (4)	Immunosuppression	March 14, 2010

NAME OF FIRM: Bristol-Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Bristol Myers Squibb filed a BLA application (STN 125288) on July 1, 2009 for belatacept for the indication of prophylaxis of acute rejection in kidney allograft recipients. This is an eCTD submission: \\cbsap58\m\eCTD_Submissions\STN125288\125288.enx. General Background: The biological drug belatacept utilizes 2 bioassays as a release specification. An in vitro binding assay (SPR) and an ex vivo cell based assay, the measure of which is inhibition of IL-2 production.

We asked the applicant to respond to two questions about the analytical procedures of belatcept.
The first question was "Please provide a full statistical package using the raw data from lots LEC07005, LEC07006, and LEC07007 that will permit independent assessment of the validity of the belatacept bioassay SAS program" Background to Question 1: During the Prior Approval Inspection of the BMS facility, I witnessed analysis of the IL-2 inhibition bioassay results. The analysis was performed on the operator's desktop computer. A proprietary four-parameter logistic fit is used to analyze the transformed data and a relative potency calculation is performed. The bioassay release spec is reported as a % of reference. The reference has a defined EC50. I observed that the relative potency of the QC test article was calculated to be 101% even though the QC test article EC50 (9.14) was only 46%

of the reference material. The sponsor attributed this to an outlier point in the QC article dilution series that disproportionately impacted the EC50. However, after dropping this point, the QC test article EC50 was still only 89% of the reference material while the calculated relative potency remained at 101%. I can provide the statistical reviewer copies of this analysis.

The second question was "The combined trend of the results for the B7 binding and cell-based bioassay methods from 50 belatacept lots used for setting the release specifications are presented in Figure 3.2.S.4.2.3.F01. You concluded that the trend data for B7 binding and the cellbased bioassay demonstrate good agreement between the two tests. However, our own correlation analyses, based on calculating a simple correlation coefficient (-0.0453) between 2 variables, indicates there is no relationship between B7 binding and IL-2 inhibition in these assays. We recognize that you do "not consider the release data appropriate for use with statistical correlation analyses." Please justify this position and describe the steps you will take to establish B7 binding and cell-based bioassay release specifications that show a good correlation with one another.

Background to Question 2: In Figure 3.2.S.4.2.3.F01 of their BLA submission, the sponsor claims that there is a good correlation between the two bioassays. However, based on calculating a simple correlation coefficient (-0.0453) between 2 variables, Cheryl Dixon statistical reviewer (OTS/OB/DBIV) found there is no relationship between B7 binding and IL-2 inhibition in these assays (data attached as separate excel file).

Please review the applicant's response to the analytical questions and provide your feedback. Their response was submitted electronically on February 11, 2010 eCTD sequence #0030 amendment 125288/0.28. \\cbsap58\m\eCTD_Submissions\STN125288\125288.enx. Please provide feedback on the applicant's response to both questions. An excel file is also attached pertaining to question 2.

Please call Jack Ragheb for further clarification if needed. Thanks.

SIGNATURE OF REQUESTOR Jack A. Ragheb M.D. Ph.D 3/3/10 3/3/10	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

BLA 125288
Belatacept
Bristol-Myers Squibb
CMC Information Request

January 29, 2010

Dear Dr. Christian,

In order to facilitate the review of your biologics license application, dated June 30, 2009, received July 1, 2009; we request that you submit the following CMC information by February 12, 2010, if possible.

Drug product

1. With regard to the dye ingress test (container closure integrity test), it is stated that the sample vials were exposed to (b) (4) Provide the limit of detection (leak volume and the corresponding leak size) of the dye ingress test. Indicate if the worst-case speeds and forces for the crimping machine were simulated in the container closure integrity study.

2. Formulated bulk solution is sterile (b) (4) Please submit a formal request with justification for an exemption from the 21 CFR 610.12 requirement for bulk sterility testing. Confirm that the sterility test samples for release are collected (b) (4)

3. Is the formulated bulk drug substance held after (b) (4)

4. An in-process bioburden test should be in place for all the formulated bulk (b) (4) steps to ensure adequate bioburden control of the bulk. Please establish a bioburden testing on all bulks (b) (4)

5. The in-process bioburden limits should be expressed as CFU/testing volume. Please update the in-process bioburden limits. The bioburden limit for the bulk (b) (4) is expected to be (b) (4)

6. With regard to (b) (4) validation, please provide information and summary data for the following:
(b) (4)



7. With regard to stopper sterilization, provide the population and D_{121} value of the biological indicators (BIs) used during the qualification runs. Clarify if BIs were directly inoculated on the stoppers. Did the qualification runs use the maximum load configuration? Explain why the minimum load configuration was not qualified.

8. Provide information and summary data for stopper washing validation. The information should include removal of endotoxin, particulates, and bioburden. Do the incoming stoppers have specifications on endotoxin, particulates, bioburden, and silicon, if applicable? If the information is in DMF, please provide the Letter of Authorization (LOA) to reference the DMF and provide the exact location of the information in the DMF.

9. With regard to vial (b) (4), please provide actual summary endotoxin data demonstrating three-log reduction during the qualification runs. The data should include endotoxin percent recoveries from the stoppers. In addition, provide temperature of vials exiting the cooling zone during the qualification runs.

10. Provide the following items for the (b) (4) for belatacept:
    - (b) (4) retention validation summary report
    - Summary data and the number of (b) (4)

11. With regard to (b) (4), provide:
    - A description of the simulation of (b) (4)
    - A summary of environmental monitoring data obtained during the (b) (4)
    - A list of routine and non-routine interventions performed.
    - The type of (b) (4) (b) (4)

12. With regard to the routine environmental monitoring (EM) program, provide the

frequency of monitoring for viable and nonviable particulates, surfaces, and personnel monitoring. Are yeasts, molds, and anaerobes monitored? Provide the alert and action limits and monitoring sites for personnel monitoring. Describe actions taken when EM limits are exceeded.

13. Provide information and summary shipping validation data for belatacept vial transportation. The shipping validation study should cover the worst-case handling (mechanical impact), and worst-case shipping temperature and duration.

14. The proposed drug product endotoxin specification is (b) (4) The endotoxin specification does not take into consideration the endotoxin from the infusion fluid (b) (4) Please (b) (4) the endotoxin specification to provide adequate safety margin (b) (4)

15. With regard to the comparability protocol for the (b) (4) batch size, clarify if any of the process parameters and hold times will change due to the increased batch size. Provide information to justify that the (b) (4) described in the BLA submission support the (b) (4) batch size filtration/filling process.

16. Provide information and summary data for the qualification of the sterility and endotoxin tests for belatacept drug product. In addition, provide information and summary data for the qualification of the bioburden test for belatacept formulated drug substance.

17. A container closure integrity test (CCI) is recommended for lots on stability in lieu of the sterility test. In addition, sterility/CCI and endotoxin tests should be performed annually and at expiry on the stability lots. Please update the stability program.

18. With regard to (b) (4) sterilization of the co-packaged (b) (4) syringe, provide,
    - Validation cycle parameters compare to the routine sterilization cycle
    - Procedures used to monitor and control routine production cycles to assure that performance is within validated limits
    - The maximum and minimum load configurations
    - Location within the pallet of syringes containing BIs, and the basis for choosing these locations for BI placement. Diagrams would be useful.
    - Describe the full and half cycles
    - Information of BIs for validation runs
    - Summary validation data and acceptance criteria
    - Auditing frequency of bioburden on the syringes and the most recent results for bioburden testing
    - levels of (b) (4) and (b) (4) residues and limits for validation runs

19. Clarify if the (b) (4) submitted for the co-packaged syringe has been cleared by FDA.

20. With regard to [redacted] validation runs, provide the acceptance criterion for F_0. In addition, provide the D_{121} value of BIs used. Provide summary data for three of the most recen[redacted] re-qualification runs for [redacted]

21. Your proposed labeling claims that the prepared belatacept infusion solution is stable at 2° to 8°C (36° to 46°F) [redacted] for 24 hours. Please submit microbiological studies in support of the 24-hour post-constitution storage time of the infusion solution at 2° to 8°C (36° to 46°F) [redacted] o [redacted]. 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 and further dilution. It is generally accepted that growth is evident when the population increases more than 0.5 Log10. The test should be run at the label's recommended storage conditions and be conducted for 2 times (48 hours) the label's recommended storage period and using the label-recommended fluids. 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-constitution storage period of the infusion solution is not more than 4 hours at 2° to 8°C or room temperature.

22. Please clarify if the non-viable particulate specifications for environmental monitoring provided in Table 3.2.A1.4.2.2.T01 is for particles/m^3 or particles/ft^3.

Please consider that a full response to our request may likely constitute a major amendment to the BLA. In order to expedite the review of your response, please provide a narrative response or written explanation to each question and additionally its location in the BLA, if applicable.

Thanks
June Germain, MS 1-29-10
Regulatory Health Project Manager

BLA 125288
Belatacept
Bristol-Myers Squibb
Clinical Information Request

January 27, 2010

Dear Dr. Christian,

In order to facilitate the review of your biologics license application, dated June 30, 2009, received July 1, 2009; we request that you submit the following information by noon on January 29, 2010, if possible.

1. We are unable to locate four narratives for patients who died in Studies IM103008 and IM103027 as shown below, please provide their location in the BLA or submit narratives for these patients:

   a. IM103008: 76-20171

   b. IM103027: 60-10260, 10-10275, 29-10427

Thanks
June Germain, MS 1/27/10
Regulatory Health Project Manager

BLA 125288
Belatacept
Bristol-Myers Squibb
CMC Information Request

January 27, 2010

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009; we request that you submit the following CMC information by February 11, 2010, if possible.

Occupancy of CD80/86 vs Bioactivity

Scientific Report 930028781

1. CD80, CD86, and HLA-DR are all expressed on human T cells as well as on dendritic cells (DC). Was CD3 or some other marker used to establish that the occupancy determinations were based on staining of DC and not T cells? Please re-evaluate your results in the context of these comments.
2. The CD28 dependence of IFN-g production in humans is time dependent and only indirectly related to CD28 signaling but directly related to IL-2 receptor signaling (McDyer et al J Immunol. 2002 Sep 1;169(5):2736-46). To obtain a more direct assessment of ligand occupancy and bioactivity, please report the IL-2 data from the study shown in Fig 3b of your scientific report.
3. These studies cannot distinguish whether CD86 is a more potent ligand than CD80 for CD28, or whether CD80 and CD86 are equally potent and both most be blocked to prevent signaling. To better understand the mechanism of action, please perform these studies in the presence of saturating amounts of anti-CD80 or anti-CD86 mAb to help distinguish between these two possibilities.

Analytical Procedures Section 3.2.S.4.2.3

1. Please provide a full statistical package using the raw data from lots LEC07005, LEC07006, and LEC07007 that will permit an independent assessment of the validity of the belatacept bioassay SAS program (BMS).
2. The combined trend of the results for the B7 binding and cell-based bioassay methods from 50 belatacept lots used for setting the release specifications are presented in Figure 3.2.S.4.2.3.F01. You concluded that the trend data for B7 binding and the cell-based bioassay demonstrate good agreement between the two tests. However, our own correlation analyses, based on calculating a simple correlation coefficient (-0.0453) between 2 variables, indicates there is no relationship between B7 binding and IL-2 inhibition in these assays. We recognize that you do "not consider the release data appropriate for use with statistical correlation analyses." Please justify this position and describe the steps you will take to establish B7 binding and cell-based bioassay release specifications that show a good correlation with one another (see Agency comments below regarding your forced degradation studies).

Forced Degradation Studies Section 3.2.S.7.1.1

1. Oxidation: The data presented in Table 3.2.S.7.1.1.T06 are insufficient to support the conclusions that have been drawn. It's the Agency's interpretation that the data is most consistent with a correlation between binding to CD86 and bioactivity rather than binding to CD80. Please provide the ka, kd, and Keq for CD80 & CD86 in these studies and revise or justify your conclusions accordingly.
2. UV exposure: Figure 3.2.S.7.1.1.F03 is presented to establish a correlation between binding to CD80 and bioactivity. However, CD80 and CD86 binding were affected similarly by UV, thus, with respect to any possible differential signaling via these ligands, these studies are not informative. Furthermore, the 1:1 correlation between CD80 binding and bioactivity in Figure 3.2.S.7.1.1.F03 is not consistent with the occupancy studies described in Scientific Report 930028781. In addition, the conclusion drawn from these UV studies is contrary to the conclusions suggested by the oxidation studies. Please provide the kd for CD80, CD86 and the Keq for CD86 in these studies and revise or justify your conclusions accordingly.

DS/DP Release Specifications

1. Develop and report quantitative IEF specifications analogous to those used for abatacept
2. Develop and validate a SPR assay using CD86. Report Keq and/or kd as these are the relevant characteristics.

IEF

1. Please quantitate the bands in the (b) (4) IEF.

(b) (4)

Stability Studies

1. Please identify the location within the BLA, providing table and figure numbers, the data that supports the 24 hour stability of the DP infusion at 1 and 10 mg/mL at room temperature and room light or refrigerated at 2° to 8°C (36°-46°F).
2. For all on-going stability studies of belatacept drug product lots currently in the long-term stability study program and as part of the monitoring of on-going production via the post-approval stability protocol, perform the described stability testing on constituted DP at least every 12 months.

Anti-LEA29Y Antibody ECL Assay

1. It doesn't appear that selectivity has been demonstrated for the ECL assay (e.g. hemolysis, uremia, lipemia, etc.). Please report these results.
2. Does the monkey anti-LEA29Y positive control Ab cross-react with CTLA4?
    a. If so, to what extent does it interfere with the immunoassays?
3. Is there soluble CTLA4 in the dialysis control serum samples or the transplant patient serum samples?
    a. If so, to what extent does it interfere with the immunoassays?
4. Do patient anti-LEA29Y Abs cross-react with CTLA4?

a. If so, to what extent does it interfere with the immunoassays?
b. If so, do such Abs have agonistic or antagonistic activity?

5. Do patient anti-LEA29Y Abs cross-react with CD28?
   a. If so, to what extent does it interfere with the immunoassays?
   b. If so, do such Abs have agonistic or antagonistic activity?
6. Using Ag specific Ab purified from patient samples, confirm the sensitivity of the assays.
7. Previously, the guidance in Mire-Sluis et al. (2004) was used to establish ELISA cut-off values that would result in a 5% false positive rate in the screening assay. Were the cut-off values for the ECL assay established with the same goal?
8. It would be most appropriate to determine the interfering concentration of belatacept at the assay's LLOQ (or at least at 200 ng/mL of anti-belatacept).
9. In different submissions, the sensitivity of the ECL assay has been variously reported as 6.3 or 12.5 ng/mL and the drug tolerance of the assay in the presence of 10 ug/mL of belatacept as 400 or <250 ng/mL of anti-belatacept antibodies. Please clarify.

Thanks
June Germain, MS 1/27/10
Regulatory Health Project Manager

BLA 125288
Belatacept
Bristol-Myers Squibb (BMS)
Comments and Advice

January 12, 2010

Dear Dr. Christian,

We refer to your submission dated December 18, 2009 containing a draft copy of your Advisory Committee Briefing Document and your January 6, 2010 submission containing a draft Advisory Committee Powerpoint presentation.

We note your request for general feedback regarding your draft briefing document and draft Advisory Committee presentation. Many of the questions posed in your request for feedback are rather broad in scope (e.g., "Does the presentation appropriately describe the important aspects of the BLA?"). Rather than attempt to provide comprehensive answers to those questions, the Division has several specific comments to offer. The specific comments reflect the areas of concern identified to date by the Division. You may infer that topics covered in the draft briefing document and Advisory Committee presentation not specifically addressed in these comments have not been identified as concerning to date.

(b) (4)

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



Thanks
June Germain, MS
Regulatory Health Project Manager

Germain, June

From: Kirshner, Susan L
Sent: Monday, January 04, 2010 11:21 AM
To: Clark-Stuart, Michelle
Cc: Germain, June
Subject: FW: BLA 125288/belatacept/BMS/information request - confirmation needed for CMC information
Attachments: BLA 125288 BLA information request 12-23-09 (5).pdf

June,
Could you please notify BMS that we confirm bullet point one. Bullet point two should be addressed by DMPQ.
Thanks.
Susan and Jack

From: Ragheb, Jack A
Sent: Sunday, January 03, 2010 10:28 PM
To: Kirshner, Susan L
Cc: Ragheb, Jack A
Subject: FW: BLA 125288/belatacept/BMS/information request - confirmation needed for CMC information

Hi Susan,

Happy New Year. Let's discuss after OBP reg mtg.

Tx, Jack

From: Bakhshi, Meena [mailto:Meena.Bakhshi@bms.com]
Sent: Tuesday, December 29, 2009 10:53 AM
To: Ragheb, Jack A
Cc: Germain, June; Christian, Mary
Subject: BLA 125288/belatacept/BMS/information request - confirmation needed for CMC information

Hi Jack,

I would like clarification on two issues with respect to the questions we received recently (Fax-Dec 23, 2009 attached).

- If BMS amends the BLA and removes the option to perform manufacturing of belatacept using (b) (4) this will obviate the need to respond to Questions 6 through 14. Please confirm
- Responses to other elements (questions 3, 4 and 5), if provided to the BLA by January 9, will not constitute a major amendment. Please confirm.

Regards,

Meena Bakhshi

Meena Bakhshi,
Global Regulatory Sciences,
CMC

Germain, June

From: Ragheb, Jack A
Sent: Monday, January 04, 2010 3:11 PM
To: 'Bakhshi, Meena'; Germain, June
Cc: Christian, Mary; Kirshner, Susan L; Ragheb, Jack A
Subject: RE: BLA 125288/belatacept/BMS/information request - confirmation needed for CMC information

Hi June,

Just wanted to confirm that you had rec'd the earlier e-mail from Susan and I confirming that if BMS amends the BLA to remove the option to perform manufacturing of belatacept using (b) (4) this will obviate the need to respond to Questions 6 through 14.

Questions 3, 4, and 5 originated from DMPQ and we would defer to them as to whether BMS's response would constitute a major amendment.

Best,

Jack

From: Bakhshi, Meena [mailto:Meena.Bakhshi@bms.com]
Sent: Tuesday, December 29, 2009 10:53 AM
To: Ragheb, Jack A
Cc: Germain, June; Christian, Mary
Subject: BLA 125288/belatacept/BMS/information request - confirmation needed for CMC information

Hi Jack,

I would like clarification on two issues with respect to the questions we received recently (Fax-Dec 23, 2009 attached).

- If BMS amends the BLA and removes the option to perform manufacturing of belatacept using (b) (4) this will obviate the need to respond to Questions 6 through 14. Please confirm
- Responses to other elements (questions 3, 4 and 5), if provided to the BLA by January 9, will not constitute a major amendment. Please confirm.

Regards,

Meena Bakhshi

Meena Bakhshi,
Global Regulatory Sciences,
CMC
Meena.Bakhshi@bms.com
609-818-3449

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BLA 125288
Belatacept
Bristol-Myers Squibb
Information Request

December 23, 2009

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009; we request that you submit the following information by January 9, 2010, if possible.

Clinical

1. You have cited data from several registries, including the Collaborative Transplant Study, to estimate incidence rate of PTLD among EBV+ recipients of kidney transplants receiving standard-of-care immunosuppression. (b) (4) (b) (4) . Also, we refer you to an October 27, 2009 publication in *Transplantation* authored by the Collaborative Transplant Study (Opelz et al, "Epidemiology of Pretransplant EBV and CMV Serostatus in Relation to Posttransplant Non-Hodgkin Lymphoma", *Transplantation* 2009; 88: 962-7). Figure 6 of that article suggests that the cumulative incidence of NHL among EBV+ recipients of kidney transplants approximates 300 per 100,000 patients at 3 years – which would equate to an incidence around 0.1 per 100 patient years. While we recognize that PTLD represents a broader diagnosis than NHL, we also recognize that this paper represents the best effort of the CTS group to study the epidemiology of PTLD. Please comment on this discrepancy.

Statistics

2. Please submit all statistical programming code and detailed methods from BMS for BLA 125288/Belatacept on the analysis of USRDS and UNOS data presented in the "Study IM103028 Epidemiology Report" and the corresponding Addendum items "Epidemiology Report Addendum 01" and "Epidemiology Report Addendum 02"

Drug Substance

3. Please submit your data for the qualification of the bioburden assay used for belatacept drug substance in your Bristol-Myers Squibb, Syracuse, NY site.

4. Please provide summary shipping validation data for shipment of the belatacept drug substance from Bristol-Myers Squibb, NY to the drug product manufacturing site in Manati, PR.

5. Please provide the data for the intermediate hold time studies you performed. You reference your small-scale and large scale hold time studies in 3.2.S.2.5.6.6; however, there is no data in this section.

Chemistry

(b) (4)

Furthermore, data presented in Section 3.2.S.2.6.3.1 of your BLA 125288, Development of the (b) (4) (belatacept, BMS-Syracuse), are either insufficient to establish comparability or do not support the comparability of currently approved (b) (4)

Please respond fully to the questions and comments below:

(b) (4)

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(b) (4)

Please consider that a full response to our request is likely to constitute a major amendment to the BLA. After review of the data requested above, the Agency will make a determination whether preclinical and/or clinical studies will be required to demonstrate comparability of DS produced by (b) (4) Alternatively, you may amend your BLA to remove the option to perform (b) (4), at this time.

Thanks 12/23/09
June Germain, MS
Regulatory Health Project Manager

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	November 20, 2009
TIME:	2:30 PM TO 3:00 PM EST
LOCATION:	Teleconference
APPLICATION:	STN 125288
DRUG NAME:	belatacept

MEETING CHAIR: Patrick Archdeacon, MD

MEETING RECORDER: June Germain, Project Manager

FDA ATTENDEES:

Patrick Archdeacon, MD	Medical Reviewer
June Germain, MS	Regulatory Health Project Manager

BMS ATTENDEES:

Mary Christian, PharmD	Regulatory Liaison
Jennifer Wood Ives	Epidemiology
Marylou Skovron	Epidemiology
Puskal Garg, MD	Medical Lead

BACKGROUND:

The Division requested a teleconference with Bristol-Myers Squibb (BMS) to discuss our information request of November 17, 2009 for datasets used to generate Study IM103028 Epidemiology Report title "Population-based observational study of post-transplant comorbidity in renal transplant recipients in the United States: An Analysis of the USRDS Database", and reanalyzes of the data to look at the subset of patients induced with IL-2 blockers and maintained on CNI, MMF, and CS.

DISCUSSION POINTS:

The Division stated that they wanted to understand if PTLD is comparable with EBV patients based on the title of the study population and whether this reflected UNOS data versus CMS data. The BMS stated that it was a combination of CMS and UNOS dataset. BMS indicated that it has a contract with a company called (b) (4) who owns the data. The Division noted that it was looking for the best possible ways of comparing the rate of PTLD patients with CS and with belatacept and considering different ways to look at this comparison. The Division suggested that BMS also do this comparison in parallel. BMS agreed. The Division recommended BMS work with the same datasets and provide this data to the Division. BMS indicated that they had gone back and analyze the impact of induction on PTLD

incidence rate by EBV status and would report PTLD risk for the total population. The Division indicated they were interesting in reviewing the data that BMS identified as subgroup of patients with IL-2 blockers and the years that were looked covered. BMS indicated that based on the information available there is a 2 year lag. BMS agreed to provide the study report on November 30, 2009.

In a follow-up phone call on November 24, 2009, the Division requested specification of the datasets, including exact name of the data files and SAS codes that (b) (4) used for the analyses. The Division indicated that it needed the estimated PTLD incidence rates in subgroups of patients defined by whether they were exposed to T-cell depleting agents, use with CNI and EBV serostatus. BMS stated they had already requested that (b) (4) provide them with the exact data files used in the analyses, however, that information would not be available for submission to the Division until the end of December 2009.

June Germain
Regulatory Health Project Manager

BLA 125288
Belatacept
Bristol-Myers Squibb
Information Request

November 17, 2009

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009; we request that you submit the following information by November 23, 2009, if possible.

1. For Study IM103028 Epidemiology report title "Population-based observational study of post-transplant comorbidity in renal transplant recipients in the United States: An Analysis of the USRDS Database", please submit the datasets used to generate this report. In addition, please re-analyze the data to look at the subset of patients induced with IL-2 blockers and maintained on CNI, MMF, and CS.

Thanks 11/17/09
June Germain, MS
Regulatory Health Project Manager

BLA 125288
Belatacept
Bristol-Myers Squibb
Information Request

November 5, 2009

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009; we request that you submit the following information by November 30, 2009, if possible.

1. The information for PTLD cases, based on the ADEBV dataset provided in amendment 7 to the BLA (dated: 9-18-2009), is summarized in Table 1. However, some information regarding the EBV serostatus for the donor or recipient, the test used or its performance characteristics were not available in the datasets (shaded cells). Please fill in the missing information in the table below.

2. Please provide information available on the EBV viral loads (baseline and at the time points tested, if any) for the EBV positive samples, including all the PTLD cases.

Table 1. Tests used to determine EBV status in the 15 patients who developed PTLD. (unk = unknown or not provided by applicant)

Clinical Trial - atient ID	Treatment Arm	Donor EBV status	Recipient EBV status	EBV test used	Assay Type	Manufacturer	Specificity	Sensitivity
03008 - 20019	CsA	+	-	VCA (P-18) IgG	ELISA	Trinity Biotech	100%	95%
03008 - 20060	Belatacept - LI	+	+	Captiva EBV VCA IgG	ELISA	Trinity Biotech	100%	IgG: 95.5%
03008 - 20256	Belatacept - LI	+	+	VCA IgM, EBNA IgG	ELISA	Zeus Scientific	89.9-97.5%, 98-100%	70.8-98.9% 90-97.3%
03008 - 20039	Belatacept - MI	+	-	VCA IgG	ELISA	Wampole Laboratories	98%	98%
03008 - 20734	Belatacept - MI	+	+	LIAISON EBV IgM, LIAISON VCA IgG, LIAISON EBNA IgG	ELISA	DiaSorin, Inc.	99.22% 96.19% 97.61%	97.83% 98.54% 98.84%
03008 - 20548	Belatacept - MI	-	-	VCA IgG, VCA IgM	ELISA	Demeditec Diagnostics	100% 97.4%	98% 97.2%
03027 - 10029	Belatacept - LI		-	EBNA-1 IgG	ELISA	Diamedix		
03027 - 10093	Belatacept - LI		+	ETI-VCA-IgG, ETI-EBV-IgM reverse, ETI-EA-IgG, ETI-EBNA-IgG	ELISA	DiaSorin, Inc.	97%, 86%, 95%,99%	98% 96% 95% 92%
03027 - 10593	Belatacept - LI	+	-	EBV-VCA (P-18) IgG	ELISA	Trinity Biotech	100%	95%
03027 - 10185	Belatacept - MI	+	+	LIAISON EBV IgM, LIAISON VCA IgG, LIAISON EBNA IgG	ELISA	DiaSorin, Inc.	99.22% 96.19% 97.61%	97.83% 98.54% 98.84%
03027 - 10447	Belatacept - MI		-					
03100 - 00025	CsA			EBNA-1 IgG	ELISA	Diamedix		
03100 - 00006	Belatacept - MI		-					
03100 - 00031	Belatacept - MI			EBNA-1 IgG	ELISA	Diamedix		
03100 - 00004	Belatacept - MI		-	VCA IgG, EBNA-1 IgG	ELISA	Medac Diagnostika	97.9%, 98%	96.3%, 100%

Thanks 11/5/09
June Germain, MS
Regulatory Health Project Manager

BLA 125288 **November 3, 2009**
Belatacept
Bristol-Myers Squibb
Clinical Pharmacology QT-IRT Information Request

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009; we request that you provide the following clarification for Study IM103027-Table 5.7.4C in the CSR -Summary of ECG parameters at specified time points, all randomized and transplanted subjects (ITT). Please provide your response by November 9, 2009.

> Please clarify the mean and maximum values for QTc, PR and QRS intervals in month 12 for the belatacept -LI group. They appear to be out of range.

Thanks
June Germain, MS
Regulatory Health Project Manager

Germain, June

From: Germain, June
Sent: Friday, October 30, 2009 12:25 PM
To: Thompson, Susan (CDER)
Subject: Inspection site contact info:FW: BLA 125288/belatacept/BMS - change in PI contact information
Attachments: Mary Christian Pharm D MBA.vcf; List for FDA (2).xls

Hi Susan,

Just wanted to update you with a new investigator for site IM103027-002 is now Dr. Zhang.

Thanks
June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Friday, October 30, 2009 12:19 PM
To: Germain, June
Subject: BLA 125288 - change in PI contact information

Hi June,

There was a change in PI at one of our clinical sites for which you previously requested contact information for the purpose of inspections. We will be submitting the updated 1572 to IND 9418 and I provide the updated contact information here and in the attached excel. The site is for IM103027-002, formerly PI Dr. Florman, now Dr Zhang.

Rubin Zhang, MD
Phone: 504-988-7867
Fax: 504-988-7510
Email: rubin.zhang@hcahealthcare.com

Best regards,
Mary

Bristol Myers Squibb
Mary Christian, Pharm.D., MBA
Director, Global Regulatory Strategy
ImmunoScience
(609) 252-5281 Work
(908) 507-8167 Mobile
(609) 252-6000 Fax
PO Box 4000, Mailstop D32-08
Princeton, NJ 08543-4000
mary.christian@bms.com

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Germain, June

From: Germain, June
Sent: Thursday, October 22, 2009 2:30 PM
To: 'Christian, Mary'
Subject: RE: BLA 125288-Belatacept-Non Clinical request for clarification

Yes, Thanks I'm aware of both and was on that call. And I will be drafting the letter and can email it to you.
June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Thursday, October 22, 2009 9:06 AM
To: Germain, June
Subject: RE: BLA 125288-Belatacept-Non Clinical request for clarification

Thanks, June!

Were you aware of the teleconference on Monday with the Liver DMC, BMS and FDA? I was not on the call, but understand we should expect a partial clinical hold letter from you, relating to the one arm of the trial for which enrollment was discontinued based on the DMC recommendation. When this letter is available, if you could email it to me or fax it, that would be ideal.

Also, FYI (thought I'm sure you're in the loop on this), there is a clinical site inspection ongoing (started yesterday) for belatacept BLA 125 288 at a site in California and 2 more are planned for sites in Brazil (Nov 30-Dec. 11).

Best regards,
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Thursday, October 22, 2009 8:12 AM
To: Christian, Mary; Milstein, Judit
Subject: RE: BLA 125288-Belatacept-Non Clinical request for clarification

Thanks Mary, I will be handling the BLA application again.

June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Wednesday, October 21, 2009 5:49 PM
To: Milstein, Judit; Germain, June
Subject: RE: BLA 125288-Belatacept-Non Clinical request for clarification

Hi Judit, June,

Attached find the response to your request for clarification from our nonclinical reviewers that was submitted today via the eGateway. The full response is in Module 1 behind the cover letter.

Any questions, please let me know.

Best regards,
Mary

From: Milstein, Judit [mailto:Judit.Milstein@fda.hhs.gov]
Sent: Thursday, October 08, 2009 9:39 AM
To: Christian, Mary; Germain, June
Subject: BLA 125288-Belatacept-Non Clinical request for clarification

<<AR-M620U_20091008_092522.pdf>>

Mary,
Find enclosed a request for clarification form our nonclinical reviewers, with regard to Study DS04029.

Thank you
Judit Milstein
Chief, Project Management Staff
DSPTP/OAP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6170
Silver Spring, MD 20993
Phone: 301-796-0763
Fax: 301-796-9881

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BLA 125288 **October 16, 2009**
Belatacept
Bristol-Myers Squibb
Clarification on Clinical Pharmacology Information Request

Dear Dr. Christian,

We acknowledge receipt of your August 31, 2009 response to our clinical pharmacology information request and the supporting analysis datasets. We are requesting clarification regarding specific analysis datasets in your submission. Please respond by October 30, 2009, if possible.

1. Regarding your response to Question D: pharmacodynamic (PD) biomarker datasets

   In the August 25, 2009 navigational meeting, we noted that the exploratory PD biomarker substudy was initiated during the long-term extension phase of Study IM103100 and so it appeared that the Variable "Day" in the analysis datasets represented the day relative to the start of the PD substudy. In the meeting, we requested that you include a Variable "NDAY" to provide the day relative to the transplant day. Please confirm that the Variable "Day" in the PD biomarker datasets submitted on August 31, 2009 indeed represents the day relative to transplant rather than relative to the start of the PD substudy, and that "TIMEPT = Day 1 pre-dose" is pre-transplant rather than prior to the start of the PD substudy.

2. Regarding your response to Question C: ADPK analysis dataset

   a. In the ADPL.xpt dataset, 0 of 145 belatacept-treated patients from Study IM103100 had acute rejection (AR). However, in the TREJ.xpt dataset included in the original BLA submission, there were subjects with BPAR, i.e., Belatacept MI (n=26), Belatacept LI (n=28), and Cyclosporine (n=14), and the total number of subjects in the dataset is 112. Please reconcile this apparent discrepancy and populate the "AR_event", "AR_grade", and "AR_DTP" columns of the ADPK dataset appropriately.

   b. Please provide the criteria used in assigning the "PTLD" status in this analysis dataset. We note that several subjects with "PTLD_DTP" << 364 days were not categorized as "PTLD=1".

Thanks
June Germain, MS
Regulatory Health Project Manager

BLA 125288
Belatacept
Bristol-Myers Squibb
Pharmacology/Toxicology Information Request

October 8, 2009

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009, we request that you provide the following clarification for the nonclinical study (b) (4) . We would appreciate your response by no later than October 22, 2009, if all possible.

(b) (4)

Thanks
Judit Milstein
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BLA 125288

OCT 0 6 2009

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

ATTENTION: Mary Christian, PharmD, MBA
Director, Global Regulatory Strategy

Dear Dr. Christian:

Please refer to your Biologics License Application (BLA) dated June 30, 2009, received July 1, 2009, submitted under section 351 of the Public Health Service Act, for Belatacept for Injection 250 mg/vial.

We also refer to your July 8, 2009, correspondence, received July 8, 2009, requesting review of your proposed proprietary name, Nulojix. We have completed our review of the proposed proprietary name, Nulojix and have concluded that it is acceptable.

The proposed proprietary name, Nulojix, will be re-reviewed 90 days prior to the approval of the BLA. 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 July 8, 2009, submission 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 Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, June Germain at 301-796-4024.

Sincerely,

Denise P. Toyer for

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

Jenkins, Darrell

From: Christian, Mary [mary.christian@bms.com]
Sent: Tuesday, October 06, 2009 6:32 PM
To: Jenkins, Darrell
Subject: RE: BLA125288
Attachments: Mary Christian Pharm D MBA.vcf

Thank you, Darrell. I have received the fax copy of the "proprietary name request, conditionally acceptable" letter.

Best regards,

Mary

Bristol Myers Squibb
Mary Christian, Pharm.D., MBA
Director, Global Regulatory Strategy
ImmunoScience
(609) 252-5281 Work
(908) 507-8167 Mobile
(609) 252-6000 Fax
PO Box 4000, Mailstop D32-08
Princeton, NJ 08543-4000
mary.christian@bms.com

From: Jenkins, Darrell [mailto:Darrell.Jenkins@fda.hhs.gov]
Sent: Tuesday, October 06, 2009 6:17 PM
To: Christian, Mary
Subject: BLA125288

Per our telephone conversation, please confirm that you are in receipt of the fax regarding your proprietary name request. Should you have any questions, please feel free to contact me at (301) 796-0558. Thanks. Darrell Jenkins.

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BL 125288
Belatacept
Bristol-Myers Squibb
Navigational Meeting Action items

September 29, 2009

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009, received July 1, 2009, submitted under section 351 of the Public Health Service Act, for belatacept, 250 mg, lyophilized powder.

We also refer to the meeting held between representative of your firm and the FDA on August 25, 2009. The purpose of the meeting was for Bristol-Myers Squibb (BMS) to show how to navigate through the eCTD submission of the BLA and demonstrate examples of analysis in the jReview program.

A copy of the meeting action items 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) 796-4024.

Thanks

9/29/09

/June Germain /
June Germain, MS
Regulatory Health Project Manager

Enclosure- Meeting Actions Items

MEMORANDUM OF MEETING

MEETING DATE:	August 25, 2009
TIME:	12:00 p.m.-1:30 p.m.
LOCATION:	FDA/CDER 10903 New Hampshire Ave Building 22, Room 1415 Silver Spring, MD 20993
APPLICATION:	BLA 125288
DRUG NAME:	Belatacept
TYPE OF MEETING:	Type C
MEETING CHAIR:	Joette Meyer, Pharm.D,
MEETING RECORDER:	June Germain, MS

FDA ATTENDEES: Division of Special Pathogen and Transplant Products (DSPTP)

Renata Albrecht, MD	Division Director
Eileen Navarro-Almario, MD	Acting Deputy Director
Joette Meyer, Pharm.D	Clinical Team Leader
Patrick Archdeacon, MD	Clinical Reviewer
Gerlie Gieser, PhD	Clinical Pharmacology Reviewer
Seong Jang, PhD	Clinical Pharmacology Reviewer
Shukal Bala, PhD	Microbiology Team Leader
Aaron Ruhland, PhD	Microbiology Reviewer
Simone Shurland, PhD	Microbiology Reviewer
William Taylor, PhD	Pharmacology/Toxicology Team Leader/CDTL
Ying Mu, PhD	Pharmacology/Toxicology Reviewer
Mina Hohlen	Regulatory Information Specialist
Patricia Hughes	OC/BMT Team Leader
Cheryl Dixon, Ph.D.	Statistical Reviewer
Eugenio Andraca-Carrera, PhD	Statistical Safety Reviewer
LaRee Tracy, PhD	Statistical Safety Team Leader
Michelle Clark-Stuart, PhD	OC/CMC Reviewer/Drug Substance Lead Inspector
June Germain, MS	Regulatory Health Project Manager

EXTERNAL CONSTITUENTS ATTENDEES: Bristol-Myers Squibb

Mary Christian, PharmD	Director, Global Regulatory Sciences
Meena Bakhshi, PhD	Manager Global Regulatory Sciences-CMC
Chen-Sheng Lin, PhD	Director, Global Biometric Sciences
Deborah Gilman	Dossier Management, eCTD
David Bocobo	Data Management
Pam Ferrer	I Review Team

BACKGROUND:
On June 30, 2009 Bristol-Myers Squibb submitted a biologics license application (BLA) in electronic format following the electronic CTD structure. A meeting was scheduled for August 25, 2009 to orient the Division on navigational issues of the BLA submission.

MEETING OBJECTIVES:

To navigate through the eCTD submission of the BLA and demonstrate examples of analysis in jReview.

MEETING DISCUSSION:

After introductions, Bristol Myers Squibb (BMS) began the meeting by going through the different modules of the BLA application and highlighting the specific location of information requested by the Division. BMS also demonstrated how to use the JReview program to analyze data from the BLA submission.

ACTION ITEMS:

1. **BMS will provide derived datasets to allow for replication of primary analyses, such as components of the primary endpoints by September 18, 2009.**

2. **BMS will provide a summary table to support the statement regarding the lack of association between malignancies and immunoglobulin levels in the package insert section 12.2 Pharmacodynamics.**

3. **BMS will submit local data on EBV central and local assay information by September 18, 2009.**

4. **BMS will submit any new cases of PTLD data to the IND and by email to the Division's project manager.**

5. **BMS will submit a statement describing the applicability of foreign data to the US population.**

6. **BMS will provide additional analysis datasets on immunogenicity, pharmacodynamic biomarkers, and exposure-response, as requested in a fax communication dated August 19, 2009. BMS will also provide a column for NDAY (nominal day from transplant) in the ATP and IDO analysis datasets.**

Post-meeting note: ***These analyses datasets were received by FDA on 31 August 2009.***

Thanks

9/29/09

/June Germain

June Germain, MS
Regulatory Health Project Manager

Germain, June

From: Germain, June
Sent: Tuesday, September 29, 2009 11:02 AM
To: Mu, Ying
Subject: FW: A list of P/T request dates on IND9418/BLA 125288/belatacept
Attachments: List of Reports Submitted to IND 9418.doc

Hi Ying,

The dates you requested.

Thanks
June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Tuesday, September 29, 2009 10:55 AM
To: Germain, June
Subject: RE: A list of P/T request dates on IND9418/BLA 125288/belatacept

Dear June,

Please see the attached list of studies and dates submitted to the IND 9418 that was requested. Note one study appeared twice and we were not sure if you meant to include a different study the second time. If so, just let me know and we can provide the information.

If you would like this formally submitted to the IND or BLA, please let me know.

Best regards,
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Monday, September 28, 2009 2:56 PM
To: Christian, Mary
Subject: A list of P/T request dates on IND9418/BLA 125288/belatacept

Hi Mary,
Enclosed please find a list of studies that we would like to have the dates they were submitted to the IND 9418.
June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

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BLA 125288
Belatacept
Bristol-Myers Squibb
Clinical Pharmacology Information Request

September 24, 2009

Dear Dr. Christian,

Please refer to your biologics license application (BLA), dated June 30, 2009, received July 1, 2009, submitted under section 351 of the Public Health Service Act, for belatacept, 250 mg, lyophilized powder.

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 include 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, postmarketing requirement requests, and Risk Evaluation and Mitigation Strategy (REMS) by March 16, 2010.

Thanks 9-24-09
June Germain, MS
Regulatory Health Project Manager

BLA 125288 **September 23, 2009**
Belatacept
Bristol-Myers Squibb
Clinical Pharmacology Information Request

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009; we request that you resubmit the following analysis datasets with the described modifications by September 30, 2009, if possible.

1. **ER_AR.xpt**
   It appears that the EPID column was truncated making it impossible to merge this dataset with the other datasets. Please check that the patient or subject ID numbers are complete.

2. **adhla.xpt and adat1.xpt**
   Please add the following columns to both analysis datasets:

   a. Overall Seroconversion Status (similar to the "OS" column of the adimmu.xpt analysis dataset, where 1=seropositive, 2=possible or indeterminate, 0=seronegative)
   b. Month (similar to the "Month" column of the adimmu.xpt dataset)

Thanks 9/23/09
June Germain, MS
Regulatory Health Project Manager

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	September 18, 2009
TIME:	12:00 PM TO 1:00 PM EST
LOCATION:	Teleconference
APPLICATION:	STN 125288
DRUG NAME:	belatacept
MEETING CHAIR:	Renata Albrecht
MEETING RECORDER:	June Germain, Project Manager

FDA ATTENDEES:

Renata Albrecht, MD	Director
Joette Meyer, PharmD	Acting Clinical Team Leader
Patrick Archdeacon, MD	Medical Reviewer
William Taylor, PhD	Pharmacology/Toxicology Team Leader/CDTL
June Germain, MS	Regulatory Health Project Manager

BMS ATTENDEES:

Mary Christian, PharmD,	Regulatory Liaison
Chen-Sheng Lin, PhD,	Global Biostatistics
Sheila Gujrathi, MD,	Therapeutic Area Head, Global Clinical Research
Pushkal Garg, MD,	Medical Lead, Global Clinical Research
Anthony Waclawski, PhD,	Regulatory
Jeff Gelb, MD	Development Lead

BACKGROUND:

Bristol-Myers Squibb (BMS) requested a teleconference for September 18, 2009 to discuss the standard review designation and other ways to best help the Division review the BLA application. BMS provided the following points for discussion during the meeting:

1. We would like to gain an understanding of FDA's thinking that led to the assignment of a Standard Review for the Belatacept BLA 125288.

2. Based upon a Standard Review, we propose to submit a safety update at approximately day 120. At this time, we can append the 2 year clinical study reports for IM103008 and IM103027 as well as 1 yr clinical study reports for IM103010 and IM103034. Is this acceptable?

3. In line with the GRMP and 21 CFR 314.102, would you find it useful to have a 90 Day Conference to share the progress of the application and advise BMS of any other potential issues not yet shared?

4. Is there any other guidance you can provide to us that would enable us to facilitate your review?

DISCUSSION POINTS:

(b) (4)

(b) (4) BMs acknowledge the Division's decision. The Division requested that BMS submit complete 2 year clinical study reports for Studies IM103008 and IM103027 as well as 1 year clinical study reports for Studies IM103010 and IM103034. BMS agreed to amendment the BLA application with this information. The Division stated that due to time constraints a 90-day conference to share the progress of the application could not be granted. However, the Division offered BMS an opportunity to have a face-to-face meeting mid January 2010 to provide feedback on BMS's advisory committee meeting presentation and background document. BMS agreed this suggestion. The Division indicated that they would request any additional information needed during the review process of the application.

June Germain
Regulatory Health Project Manager

Germain, June

From: Germain, June
Sent: Thursday, September 17, 2009 12:05 PM
To: 'Rosolowsky, Mark'
Cc: Christian, Mary
Subject: RE: Belatacept Teleconference

Hi Mark,

Sept. 22 9:30-10:30 am works for us. However I need to know the nature of this meeting so that I have all the right people present. We usually have an internal discussion prior to meetings in order to reach an agreement. At this point we may not be prepared to discuss or reach an agreement and the meeting may not be abundantly productive as you would like.

June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

From: Rosolowsky, Mark [mailto:mark.rosolowsky@bms.com]
Sent: Thursday, September 17, 2009 11:32 AM
To: Germain, June; Ragheb, Jack A; Hughes, Patricia; Kirshner, Susan L
Cc: Christian, Mary
Subject: Belatacept Teleconference

All,

Please find agenda and details below for Sept. 22 teleconference. Please confirm that this date/time still works for you.

Thanks.

Mark

Agenda

1. Introductions
2. Purpose of meeting
3. Discuss data and investigation
4. Discuss next steps

Dial In - 866-217-3840
Conference Code - 6587171
Leader PIN - Mark

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Wednesday, September 16, 2009 2:10 PM
To: Rosolowsky, Mark
Subject: RE: Bela

Hi Mark,

I am trying to set up the Tcon. the best day for us is Tues Sept. 22 at 9:30-10:30 am please send us an agenda and the dial in information.
June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

From: Rosolowsky, Mark [mailto:mark.rosolowsky@bms.com]
Sent: Wednesday, September 16, 2009 10:45 AM
To: Kirshner, Susan L
Cc: Germain, June; Ragheb, Jack A; Hughes, Patricia
Subject: Re: Bela

Tx.
I'm in seattle and won't return until Thurs PM. Would Fri work?

M

From: Kirshner, Susan L <Susan.Kirshner@fda.hhs.gov>
To: Rosolowsky, Mark
Cc: Germain, June <June.Germain@fda.hhs.gov>; Ragheb, Jack A <Jack.Ragheb@fda.hhs.gov>; Hughes, Patricia <Patricia.Hughes@fda.hhs.gov>
Sent: Wed Sep 16 10:21:34 2009
Subject: RE: Bela

Hi Mark,
Sorry for the delay. It has been a bad week. I am cc'ing June on this so she can set up the T con and the others so they have a heads up when this appears on their calendar. Thanks.
Susan

From: Rosolowsky, Mark [mailto:mark.rosolowsky@bms.com]
Sent: Monday, September 14, 2009 8:21 AM
To: Kirshner, Susan L
Subject: Bela

Susan,

Do you have sometime today(this morning is better for me) where we can discuss an emerging issue with you re: Belatacept? It would be useful if Jack and Patricia Hughes could also be available.

Thanks

Mark

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125288/0

September 11, 2009

Bristol-Myers Squibb
Attention: Mary Christian, Pharm.D
Director, Global Regulatory Strategy
PO Box 4000 Mailstop D32-08
Princeton, NJ 08543-4000

Dear Dr. Christian:

Please refer to your biologics license application (BLA), dated June 30, 2009, received July 1, 2009, submitted under section 351 of the Public Health Service Act, for belatacept. Also refer to our filing letter dated August 30, 2009.

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 include 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.

We plan to communicate the planned timelines for sending you initial proposed labeling comments, and, if necessary, any postmarketing commitment and postmarketing requirement requests, and Risk Evaluation and Mitigation Strategy (REMS) comments by September 25, 2009. If subsequent significant changes to these planned timelines occur, these will be conveyed to you.

While conducting our filing review we identified the following potential review issues and have the following requests:

1. Provide information and summary data for the rabbit pyrogen test for belatacept.

2. Provide information and summary data for the (b) (4) sterilization of the co-packaged (b) (4) syringe. Alternatively, a Letter of Authorization referencing the

relevant drug master file (DMF) file and the exact locations of the validation information and data in the DMF should be provided.

3. A rationale for the applicability of foreign data to the US population and US medical practice could not be located in the application. Provide the location of this justification in your electronic common technical document (eCTD) submission. If such a rationale was not provided, submit a justification that the foreign data from the clinical studies are applicable to the US population and US medical practice, as approximately 75% of the patients in the pivotal Phase 3 trials were non-US.

4. A coding dictionary used for mapping investigator verbatim terms to preferred terms could not be located in the eCTD. If such a dictionary was submitted, provide the location in your eCTD submission. If one was not provided, submit it as an amendment to the BLA.

5. We generated a random sample of 10% of the Phase 3 pivotal trial population and examined the case report forms (CRFs) for these patients. Some of the CRFs in the random sample corresponded to CRFs already included in your submission (i.e., deaths, SAEs, discontinuations). Submit the remaining CRFs from this 10% random sample for our review (see attached Appendix).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application, and as we conduct further review of the application, additional review issues or deficiencies may be identified.

We request that you submit the information requested in Items 1 through 5 above, as well as the information requested in facsimiles sent by the Division last month and listed in Items 6 through 9 below. All submissions should be submitted as amendments to the BLA.

6. Complete responses to all items requested in the Division's August 4, 2009 CMC facsimile request.

7. Complete responses to all items requested in the Division's August 17, 2009 information facsimile request.

8. Complete responses to all items requested in the Division's August 19, 2009 Clinical Pharmacology facsimile request.

9. Complete responses to all items requested in the Division's August 28, 2009 package insert facsimile request.

Please respond to all of the above requests for additional information by September 25, 2009. 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. Following a complete review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

If you have any questions, call June Germain, Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

R. A.

/Renata Albrecht, MD/
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Appendix

Appendix

IM103027-105-10177
IM103027-110-10190
IM103027-2-10007
IM103027-2-10258
IM103027-20-10208
IM103027-24-10548
IM103027-28-10265
IM103027-31-10287
IM103027-32-10149
IM103027-34-10082
IM103027-35-10145
IM103027-35-10551
IM103027-41-10161
IM103027-52-10544
IM103027-53-10111
IM103027-53-10490
IM103027-55-10134
IM103027-83-10095
IM103027-84-10063
IM103027-84-10234
IM103027-84-10367
IM103027-85-10162
IM103027-89-10381
IM103027-91-10044
IM103027-91-10070
IM103027-93-10131
IM103027-97-10357
IM103027-97-10455
IM103027-97-10473
IM103008-10-20028
IM103008-10-20233
IM103008-10-20525
IM103008-100-20517
IM103008-108-20388
IM103008-108-20724
IM103008-109-20187
IM103008-116-20387
IM103008-116-20448
IM103008-116-20450
IM103008-118-20487
IM103008-118-20714
IM103008-120-20420

IM103008-125-20320
IM103008-131-20671
IM103008-146-20490
IM103008-149-20530
IM103008-150-20482
IM103008-16-20080
IM103008-17-20395
IM103008-18-20544
IM103008-27-20061
IM103008-36-20300
IM103008-37-20701
IM103008-42-20306
IM103008-45-20008
IM103008-51-20360
IM103008-58-20349
IM103008-62-20077
IM103008-64-20225
IM103008-64-20695
IM103008-66-20244
IM103008-76-20057
IM103008-85-20680
IM103008-91-20021
IM103008-91-20117
IM103008-98-20049
IM103008-98-20232
IM103008-98-20444
IM103008-99-20461

Germain, June

From: Germain, June
Sent: Thursday, September 10, 2009 2:30 PM
To: Thompson, Susan (CDER)
Subject: FW: BLA 125288 Belatacept - response to request for datasets with decode/embedded variables and for replication of primary analyses

Hi Susan,

In response to your question on whether study related activity was performed at the office address please see Mary's response below.

June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Thursday, September 10, 2009 1:27 PM
To: Germain, June
Subject: RE: BLA 125288 Belatacept - response to request for datasets with decode/embedded variables and for replication of primary analyses

Thank you. Will do. Here is the dial in information and I will provide questions for the meeting discussion shortly.

Dial in number: 866-217-3840
Participant Code: 2525281

On the previous question regarding the request from the Division of Scientific Investigations (DSI, inspections) for clarification if any study related activities occurred at the clinical addresses identified in Appendix 1.5 as Office locations, such that they would be included in the inspection. I can confirm that the Office address is uniquely the Investigator office address (as would be in Box 1 of a 1572). For the study related activities, consistent with the Box 3 of the 1572, is reflected in the addresses identified as Patient Treatment Centers in the Appendices 1.5 of the clinical study reports.

Best regards,
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Thursday, September 10, 2009 1:17 PM
To: Christian, Mary
Subject: RE: BLA 125288 Belatacept - response to request for datasets with decode/embedded variables and for replication of primary analyses

Hi Mary,

I just heard back from Dr. Albrecht. We are available next Friday from 12-1 pm please provide specific questions, etc and anything they wish to share with us before the telecon. Let me know if that will work for you. Scheduling meeting times here is becoming harder and harder.

June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Thursday, September 10, 2009 1:03 PM
To: Germain, June
Subject: BLA 125288 Belatacept - response to request for datasets with decode/embedded variables and for replication of primary analyses

Dear June,

See attached the cover letter for the submission made today to the BLA via the eGateway. Let me know if you have any questions related to this submission.

Also, were you able to schedule a teleconference for Friday or Wednesday to discuss the review status decision, discussion of the safety update timing/content and other ways to best progress the application review?

Best regards,
Mary

Bristol-Myers Squibb
Mary Christian, Pharm.D., MBA
Director, Global Regulatory Strategy
ImmunoScience
(609) 252-5281 Work
(908) 507-8167 Mobile
(609) 252-6000 Fax
PO Box 4000, Mailstop D32-08
Princeton, NJ 08543-4000
mary.christian@bms.com

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125288/0

FILING COMMUNICATION (b) (4)

August 28, 2009

Bristol-Myers Squibb
Attention: Mary Christian, Pharm.D
Director, Global Regulatory Strategy
PO Box 4000 Mailstop D32-08
Princeton, NJ 08543-4000

Dear Dr. Christian:

This letter is in regard to your biologics license application (BLA), dated June 30, 2009, received July 1, 2009, submitted under section 351 of the Public Health Service Act, for belatacept, 250 mg, lyophilized powder.

We have completed an initial review of your application and have determined that it is sufficiently complete for filing; Therefore, this application is filed under 21 CFR 601.2(a). This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before September 13, 2009.

(b) (4)

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 has an orphan-drug designation for the prophylaxis of organ rejection in renal allograft recipients, you are exempt from this requirement.

Please also find enclosed a copy of CDER Quality Assessment form. The purpose of this assessment form is to record your experience with the review process during the review period

and capture key review process issues solely to facilitate discussion between you and the agency during the post-action feedback meeting.

If you have any questions, call June Germain, Regulatory Health Project Manager, at (301) 796-4024.

Sincerely,

R.A.

/Renata Albrecht, MD/
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: CDER Quality Assessment for NDA/BLA Submissions (version 051309)

Quality Assessment for NDA/BLA Submissions

Purpose: This assessment is intended to be used by both the applicant and members of CDER's review team. It is designed to guide them through the pertinent sections of an application and to assist in assessing the content of the NDA/BLA submission as well as the overall review process. It is to be used to record information solely to facilitate discussion of lessons learned at the post-action feedback meeting of both parties. It is to play no role in the FDA action taken on an application and is not to be used in dispute resolution. It will not be archived with the application by FDA.

When to Use: At this time, CDER will offer this assessment and the post-action feedback meeting for all NMEs and original BLAs; CDER may offer these for other applications and supplements. The Quality Assessment form should be distributed to each of the review team members, as well as to the applicant, at the pre-NDA/BLA meeting with an explanation of how it will be used. If a pre-NDA/BLA meeting is not held, this assessment should be provided to the applicant via email. Both the applicant and review team members are encouraged to periodically add information to their Quality Assessment form during the review process. This assessment should be used to guide post-action feedback meetings between the FDA and the application.

Instructions for Completing the Quality Assessment

FDA: This assessment is be filled out during the review cycle by individual reviewers as issues relating to the review and application arise. It should be completed by the end of the review and used during the post-action feedback meetings with the applicant. Reviewers should capture as much additional information as possible on the last page of the assessment.

Applicant: This assessment should be filled out both while preparing the submission and during the review cycle. You can use it to record your experience with the review process, including the steps preceding submission of the BLA/NDA.

The Post-Action Feedback Meeting: This assessment will be used in the post-action feedback meeting only as a guide for the discussion. The applicant and all CDER reviewers should bring their completed assessment and use it as a reference for issues that are pertinent to the discussion. Due to the sizable content of the assessment, it is not expected that every question be discussed. The meeting should focus on those items that provide lessons learned (i.e., things that worked well and things that did not) for future applications.

Collection and Archiving: This assessment is not to be collected and it is not to be archived. It is for the applicant and each CDER reviewer to retain and dispose of at their discretion.

Quality Assessment for NDA/BLA Submissions

__ Applicant Assessment Applicant: _____ NDA# _____ BLA# _____
__ FDA Assessment OND Division: _____ Action on Application: _____ (after ___ review cycles)
Number of amendments: _____ (including ____ major amendments)

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
Pre- and Peri-Submission Activities	A Target Product Profile (TPP) was used during drug development that improved the review process by aligning sponsor goals with proposed label claims during the IND process. http://www.fda.gov/cder/guidance/6910dft.htm	
	Special Protocol Assessments were utilized and benefited the application.	
	The pre-NDA/BLA meeting included discussion of all topics important for preparation of a complete, high quality application.	
	(If electronic submission) A pre-NDA/BLA application format discussion, held with FDA in advance of submission, facilitated development of a higher quality application.	
	The FDA indicated prior to submission that test results appeared to meet pre-specified endpoints and should be submitted for review.	
	An (optional) orientation session was held (within 21 days of submission) to permit applicant to familiarize reviewers with the content and navigation of the submission; this resulted in a more efficient FDA review.	
	Leading up to submission, interactions between FDA and the applicant throughout the drug development process were optimal for developing a high quality application.	
Overall Application Format and Content	The presentation and construction of the application followed the required format and was indexed appropriately.	
	(If electronic submission) The electronic submission loaded without difficulty.	

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	(If electronic submission) Proper eCTD lifecycle XML relationships were established in all submissions.	
	(If electronic submission) All hyperlinks in the application worked appropriately.	
	The application included: • Required forms appropriately completed • Information requested by FDA during pre-submission drug development **and** per applicable guidance and regulations	
	The application appropriately reflected previous advice and requests from FDA (e.g., regarding development program, study design and endpoints, GCP issues and analysis of results, CMC issues) or included reasonable justification for all deviations from FDA guidance or pre-submission advice.	
Summaries/ Overviews	The summaries highlighted the important issues.	
	The summaries accurately reflected supporting data, including appropriate links.	
Technical Sections	Datasets were complete and in a format to facilitate FDA analysis.	
	Appropriate analyses were performed by the applicant to evaluate efficacy, safety, and product quality, e.g., claims were based on pre-specified endpoints and analyses; any deviations justified; conformed to ICH and other guidelines.	
Site Inspections	Facilities were available for inspection upon application submission.	
	Facility inspections were completed in a timely manner.	
	Clinical site inspections were completed in a timely manner.	

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	All deviations from GCP were identified for each clinical site in the initial submission and impact of deviations were discussed in the application.	
Post-marketing Require-ments (PMR) and Commit-ments (PMC)	PMRs and PMCs, with timelines, conforming to ICH guidelines were included in the initial submission. Examples include PREA studies, confirmatory studies for accelerated approval, studies to evaluate previously identified safety issues.	
	If the need for PMRs or PMCs was identified by FDA during application review, discussion of postmarketing study proposals and timelines followed GRMP timelines.	
Risk Evaluation and Mitigation Strategy (REMS)	REMS, as discussed during pre-submission meeting, were included in the initial submission.	
	If a need for REMS was identified by FDA during application review, request for/discussion of REMS followed GRMP timelines.	
	FDA provided rationale for modifications to applicant's REMS.	
	Applicant followed FDA Guidance regarding content/organization of REMS.	
Labeling	Labeling contained annotations and/or hyperlinks to the location of supporting data in the application.	
	All references in proposed labeling were included in the submission.	
	Applicant followed FDA Guidance regarding content/ organization of labeling, including patient labeling or Medication Guide and carton/container labeling.	
	FDA provided rationale for substantive modifications to applicant's labeling and FDA proposed changes were consistent with Guidances/policy.	
	FDA and applicant followed GRMP timelines for labeling discussions.	

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	Applicant's submission of proprietary name review request followed FDA guidance (e.g., more than on proposed name). If submitted during the IND review, did this "add value" to proprietary name review? If not, why not?	
Communi-cation	FDA requests for information were clearly stated and reflected understanding of application contents.	
	The applicant responded to information requests raised during the review in a *timely* manner, including: • Information requests during first 60 days • Day-74 letter • Information requests after 60 days • Discipline Review letters	
	Applicant responded to issues raised during the review in a *complete* manner, i.e., no follow-up was required.	
	Did application contain information requested during IND review? Were there deficiencies communicated by FDA during the review (e.g., day 74, etc.) that should have been anticipated based on FDA comments prior to submission of the application?	
	Could issues raised by FDA during application review have been identified by FDA or applicant prior to submission?	
	How might communication or discussion of information requests been more efficient?	
	Significant deviations from the milestone timeline by FDA were communicated to the applicant.	

Additional comments from any disciplines or consultant reviewers:

Overall Assessment:

- Identify three critical factors that contributed to the application's outcome.
  1.
  2.
  3.
- In retrospect, would a refusal-to-file decision have better utilized resources and expedited time to approval?

- Provide any comments on how to improve the process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125288/0

INFORMATION REQUEST
August 28, 2009

Bristol-Myers Squibb
Attention: Mary Christian
Director, Global Regulatory Sciences
PO Box 4000
Princeton, NJ 08543-4000

Dear Dr. Christian:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act for belatacept.

We have reviewed your proposed labeling in structured product labeling (SPL) dated June 30, 2009, received July 1, 2009, and have identified the following issues:

HIGHLIGHTS:

- Please do not use the "TM" symbol after the drug name in the Highlights or the Table of Contents. Use the "TM" symbol only once in the content of label (full prescribing information).
- The **WARNINGS AND PRECAUTIONS** section should contain a concise summary of the most clinically significant safety concerns along with recommendations for patient monitoring to ensure safe use and measures that can be taken to prevent or mitigate harm.

FULL PRESCRIBING INFORMATION:

- The manufacture information should be located after the Patient Counseling Information section, at the end of labeling.
- In the **ADVERSE REACTIONS** section the presentation of adverse reactions information identified from clinical trials must be preceded by information necessary to interpret the adverse reactions (§ 201.57(c)(7)(i)). This information would ordinarily include a description of the overall clinical trial database from which adverse reaction data have been drawn, including a discussion of overall exposure (number of patients, dose, schedule, duration), demographics of the exposed population, designs of the trials in which exposure occurred (e.g., placebo-controlled, active-controlled), and any critical exclusions from the safety database.

Sample Database Description
The data described below reflect exposure to drug X in [n] patients, including [n] exposed for 6 months and [n] exposed for greater than one year. Drug X was studied primarily in placebo and active-controlled trials (n = __, and n = ___, respectively), and in long-term follow up studies. The population was [age range], [gender distribution], [race distribution] and had [diseases/conditions]. Most patients received doses [describe range, route of administration, frequency, duration, as appropriate].

Please also see the Guidance for Industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf)

We request that you submit revised labeling in response to the items enumerated above by September 28, 2009. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of your application is continuing.

Submit revised 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. We would also appreciate the submission of this information in word format.

If you have any questions, please contact me, at (301) 796-4024.

Sincerely,

/June Germain, MS/ 8-28-09
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Germain, June

From: Germain, June
Sent: Tuesday, August 25, 2009 10:41 AM
To: 'Christian, Mary'
Subject: RE: BLA 125288- Fax Dated August 19 -clarification please

Hi Mary,

These definitions are acceptable.

June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Tuesday, August 25, 2009 9:07 AM
To: Germain, June
Subject: BLA 125288- Fax Dated August 19 -clarification please

Dear June,

The biomarker group here has a question regarding the fax if August 19, item b, specifically related to the definition of "indeterminant". BMS proposes the following as definitions of "indeterminate" for the anti-donor HLA assay and the anti-AT1 receptor assay.

> For the anti-AT1 receptor assay, indeterminate is defined as any result with a borderline value. A borderline value is defined as a value less than the positive threshold of 2.0 units (the reactivity of a 1:800 dilution of a positive control serum sample) but greater than or equal to 1.50 units. Values below 1.50 units are defined as negative. For the anti-donor HLA antibody assay, indeterminate is defined as either a result with a borderline or weakly positive value (1000-1999 MFI) or a result which was positive (2000 MFI or higher) but no donor HLA information for that locus is available to determine donor specificity (e.g. donor HLA-C and/or

HLA-DQ are often not reported).

Are these definitions acceptable to the FDA?

Best regards,
Mary

Bristol-Myers Squibb
Mary Christian, Pharm.D., MBA
Director, Global Regulatory Strategy
ImmunoScience

(609) 252-5281 Work
(908) 507-8167 Mobile
(609) 252-6000 Fax

PO Box 4000, Mailstop D32-08
Princeton, NJ 08543-4000
mary.christian@bms.com

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Germain, June

From: Germain, June
Sent: Tuesday, August 25, 2009 10:33 AM
To: Gieser, Gerlie
Subject: FW: BLA 125288- Clin Pharm Fax Dated August 19 -clarification please/
Attachments: Mary Christian Pharm D MBA.vcf

Hi Gerlie,

BMS needs clarification on the definition of indeterminant from our request item b. See below.

Thanks
June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Tuesday, August 25, 2009 9:07 AM
To: Germain, June
Subject: BLA 125288- Fax Dated August 19 -clarification please

Dear June,

The biomarker group here has a question regarding the fax if August 19, item b, specifically related to the definition of "indeterminant". BMS proposes the following as definitions of "indeterminate" for the anti-donor HLA assay and the anti-AT1 receptor assay.

> For the anti-AT1 receptor assay, indeterminate is defined as any result with a borderline value. A borderline value is defined as a value less than the positive threshold of 2.0 units (the reactivity of a 1:800 dilution of a positive control serum sample) but greater than or equal to 1.50 units. Values below 1.50 units are defined as negative. For the anti-donor HLA antibody assay, indeterminate is defined as either a result with a borderline or weakly positive value (1000-1999 MFI) or a result which was positive (2000 MFI or higher) but no donor HLA information for that locus is available to determine donor specificity (e.g. donor HLA-C and/or HLA-DQ are often not reported).

Are these definitions acceptable to the FDA?

Best regards,
Mary

Bristol-Myers Squibb
Mary Christian, Pharm.D., MBA
Director, Global Regulatory Strategy
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Germain, June

From: Germain, June
Sent: Thursday, August 20, 2009 8:40 AM
To: 'Christian, Mary'
Subject: RE: BLA 125288/belatacept/BMS/Example of jReview analyses for the navigational meeting

Hi Mary,

I forgot to added that we also propose to set a criteria for a patient profile ahead of time so that during the meeting you could show an individual patient profile for a patient in one of the below examples of analyses. However, Dr. Archdeacon is on leave this week. We will not be able to create the profile until Monday. Is that too late?

Thanks
June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Wednesday, August 19, 2009 4:42 PM
To: Germain, June
Subject: RE: BLA 125288/belatacept/BMS/Example of jReview analyses for the navigational meeting

Thanks, June!

M

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Wednesday, August 19, 2009 4:17 PM
To: Christian, Mary
Subject: BLA 125288/belatacept/BMS/Example of jReview analyses for the navigational meeting

Hi Mary,

As discussed during the teleconference today, here are some examples of the analyses that can be demonstrated. Please feel free to choose which ones you would like to demonstrate at the navigational meeting.

1. Show patient and graft survival rate by treatment group using the ITT population in Study 1 (as shown in Line 1 of Table 6 on page 21 of the package insert). Of these results, show the subset of patients who received a kidney from a living related donor.

2. Show the decrease in measured GFR >= 10 mL/min from Month 3 to Month 12 in the ITT population in Study 1 (as shown in Line 6 in Table 6 on page 21 of the package insert).

3. Show the number of patients with an adverse event in either the LI or MI treatment groups using the pooled population from Studies 1 and 2.

4. Create a table for all patients showing whether or not they completed Study 1 and, if they

did not complete, the reason for discontinuation.

5. Create a table showing Patient ID, Sex, Treatment Arm, and Visit Number for patients with a measured GFR of < 60 mL/min in Study 1.

June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Interdisciplinary Review Team for QT Studies			FROM *(Name, Office/Division, and Phone Number of Requestor)*: June Germain, Regulatory Project Manager 301-796-4024/Gerlie Gieser Clinical Pharmacology Reviewer - Division of Special Pathogen and Transplant Products	
DATE 8/19/09	IND NO.	NDA NO.	TYPE OF DOCUMENT BLA submission 125288	DATE OF DOCUMENT June 30, 2009
NAME OF DRUG belatacept	PRIORITY CONSIDERATION Sept. 7, 2009		CLASSIFICATION OF DRUG Immunosuppressant	DESIRED COMPLETION DATE November 1, 2009

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The Division has received the BLA submission for STN 125288, belatacept for the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. The submission is dated June 30, 2009 and received July 1, 2009. The PDUFA goal date is May 1, 2010.

Please refer to your memorandum regarding belatacept(IND 9,418), dated 04 April 2008, where you commented: "Because belatacept is a large protein (b) (4) and is highly specific for its target, it is reasonable to perform similar QT evaluation as for monoclonal antibodies. For monoclonal antibodies, we have given the following recommendations to other review divisions:

1) Monoclonal antibodies do not need to be evaluated in a thorough clinical QT study because:

a) As large molecules, monoclonal antibodies cannot access the hERG pore via the intracellular side, which is the target site for most small-molecule QT-prolonging drugs; and

b) Monoclonal antibodies can have off-target cardiac effects but QT prolongation has not been observed.

2) We recommend that routine ECG monitoring in clinical studies should continue to be performed to capture any

important cardiovascular effects.
3) For nonclinical evaluation, we recommend that standard in vivo toxicology studies in dogs or monkeys with CV and ECG assessments incorporated into the design.
In this case, the sponsor has collected ECGs in phase 1 and 2 studies and plans to continue ECG monitoring in phase [illegible]tudies. In our opinion, this is a reasonable approach to capture any important cardiac effects of administering [illegible]elatacept.
No additional nonclinical studies are recommended."

Because belatacept is a large protein and is highly specific for its target, a thorough clinical QT study was not conducted. ECG monitoring was performed in clinical trials involving healthy subjects and *de novo* renal transplant patients. Although two belatacept-based (more-intensive and less-intensive) regimens were evaluated in Phase 2 and 3 trials, the sponsor is seeking approval for the less-intensive (LI) regimen of belatacept, when used with MMF, corticosteroids and an IL-2 receptor antagonist (basiliximab).

Key question for the CDER QT-IRT to address:
Based on nonclinical and clinical findings, the sponsor concluded that belatacept does not prolong the QT interval. In Phase 3 trials, the proportion of subjects with a prolonged QTc interval > 30 msec or > 60 msec compared with baseline and > 450 msec was similar across the 3 treatment groups (belatacept MI, belatacept LI, and cyclosporine). Do you agree with the sponsor's conclusion?

This is an eCTD submission. Select the link to access the .enx file:
<\\cbsap58\M\eCTD_Submissions\STN125288\125288.enx>

This is a [redacted] (b) (4) review with an Advisory Committee meeting on 01 March 2010. The PDUFA due date is 01 May 2010. Please review the ECG data listings and the analysis datasets and let us know by 07 September 2009 if there are any additional datasets or other information that you need from the sponsor.

SIGNATURE OF REQUESTOR [illegible] 8/19/09	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Germain, June

From: Christian, Mary [mary.christian@bms.com]
Sent: Wednesday, August 19, 2009 6:39 PM
To: Germain, June
Subject: RE: IND 9,418/belatacept/BMS/request for submission dates
Attachments: Copy of IND 9418 PharmTox study submission request.xls

Hi June,

See attached excel in which we reference the IND submission dates. Note that 3 of the reports were not previously submitted to the IND and one was only submitted to the abatacept IND. If there are any questions on this, or if you need a formal submission of this response to the BLA or these reports to the IND, just let me know.

Best regards,
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Tuesday, August 18, 2009 3:48 PM
To: Christian, Mary
Subject: IND 9,418/belatacept/BMS/request for submission dates

Hi Mary,

Enclosed you will find a list of studies that we need the dates of when they were submitted to the IND to help facilitate the BLA review.

June

<<IND 9418 PharmTox study submission request.xls>>

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

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List of Studies to Request Letter Date			IND 9418	(b) (4)	IND 9391 (aba)
Study No	TITLE	BMS Doc No			
930023829	Review of Historical In vitro Potency and Binding Data for BMS-224818 (LEA29Y) in Murine Cells and to Murine B7 Molecules		10/11/04 (0104)		
(b) (4)					
930008556	Review of historical LEA29Y in vivo study		10/11/04 (0104)		
930011015	Binding of Abatacept to Fc Receptors				4/18/06 (0379)
(b) (4)					
97607	Single-dose INTRAVENOUS Comparative Efficacy STUDY IN MONKEYS	DCN 910069206	10/19/00 (0000) x-ref to 8206		
930019020	Efficacy Comparison of Abatacept and Belatacept in Murine Primary Immune Response Model	DCN 930019020	11/28/07 (0325)		
str-103	Fc Receptor Binding and functional Activity - ABATACEPT	DCN 930016593	9/29/06 (0223)		
930023833	Development of a CD86 Receptor Competition Assay: A Method for Measuring CD86 receptor occupancy on monocytes in whole blood	DCN 930023833	11/28/07 (0325)		
DS00129	Single-dose IV Comparability Study in Cynomolgus Monkeys	DCN 930000262	11/20/01 (0026)		
DS03028	Single-dose IV Exploratory Comparative PK Study in Mice (MONKEYS ?)	DCN 930004678	5/10/04 (0094)- Section 6		
DS03019	Single-dose SC Exploratory Irritation Study in Rats	DCN 930004100	6/18/03 (0068) x-ref to 8206		
DS07122	Single-dose SC Local Tolerance Study in Rats	DCN 930023508			
(b) (4)					

Not submitted to IND

BL 125288
Belatacept
Bristol-Myers Squibb
Information Request

August 19, 2009

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009; we request that you submit the following analysis datasets in .xpt format by August 31, 2009, if possible. Alternatively, if any of these datasets was included in the BLA submission, please provide the exact location of the information, at the time of the navigational meeting with FDA on 25 August 2009.

a. Anti-belatacept antibody response and incidence of therapeutic endpoints
   Required Columns:
   -Unique Subject ID, Study Number, Treatment (MI or LI belatacept), age, gender, bodyweight, race, nominal days from transplant
   -confirmed binding with anti-belatacept antibody, NAB, cross-reactivity with abatacept (positive, negative, or indeterminate at pre- and post-transplant)
   -death, graft loss, AR and AR grade, acute infusional or peri-infusional AEs, (status and time-to-event)

b. Anti-donor HLA antibody response or anti-AT1-receptor antibody response and incidence of therapeutic endpoints
   Required Columns:
   -Unique Subject ID, Study Number, Treatment (MI or LI belatacept), age, gender, bodyweight, race, nominal days from transplant
   -Anti-donor HLA antibody, anti-AT1-receptor antibody (positive, negative, or indeterminate at pre- and post-transplant)
   -death, graft loss, AR and AR grade, acute infusional or peri-infusional AEs (status and time-to-event)

c. Additional ER_Cmin dataset
   Required Columns:
   -Unique Subject ID, Study Number, Treatment (MI or LI belatacept), age, gender, bodyweight, race, nominal days from transplant
   -Cmin
   -mGFR < 60 mL/min/1.73 m^2 at Month 12, decrease in mGFR ≥ 10 mL/min/1.73 m^2 at Months 3 to 12, death, graft loss, CAN (status, and if applicable, time-to-event)
   -new onset diabetes, hypertension, dyslipidemia, tuberculosis, herpes, BK virus, congestive heart failure (status, and if applicable, time-to-event)

d. Analysis datasets of ATP (pharmacodynamic biomarker)
*Format similar to that of the IDO datasets

Thanks

JG 8-19-09

/June Germain /
June Germain, MS
Regulatory Health Project Manager

BL 125288
Belatacept
Bristol-Myers Squibb
Information Request

August 17, 2009

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009 and received July 1, 2009, we request that you provide the following information:

Microbiology:

1. Please provide the following information as originally requested at the pre-BLA meeting held on May 20, 2009 (see minutes issued on July 1, 2009).
   - Specify the assay used for determining EBV status in the BLA submission. If the assay is FDA approved, then the product brochure should be included. If the assay is not FDA approved, please provide details of the method and the performance characteristics for the assay.
   - Details of the method used, including storage, shipping and handling of samples.
   - Specify whether testing was done at the site or a central laboratory.
   - Specify the time of testing.

2. It will be helpful for our review if the datasets are formatted as shown in the template (Table 1). If EBV titer results were quantified, then please include the results in the table as well.

Table 1. EBV testing and status data

Study ID	**Subject ID**	**Site ID**	**Laboratory name and location**	**EBV Screening Assay Used**	**Donor EBV Status (Day)***	**Recipient EBV Status (Day)***	**Developed PTLD (Day)***	**Developed CNS-PTLD (Day)***
IM103100	12345	City, State Country	Lab X, City, State, Country	Company X ELISA	Positive (Day -1)	Negative (Day -5)	Yes (Day 100)	No

*Day of observation or measurement relevant to transplantation

3. It is unclear if the EBV test was repeated post-transplant or at different time points for the allograft recipients. Please clarify and provide the results of these tests in the above table as suggested in comment #2 if they were performed.

CMC:

4. Please provide the location of the following items in your eCTD submission; if those items were not included in the BLA submission, please submit them as an amendment to the BLA.

    a. DS-justification/validation for elimination of certain DS release tests
    b. DS-justification of limits for in-process tests
    c. DS-validation of stability methods
    d. DS-no mention of mycoplasma testing
    e. DP-process validation used 2 pairs of consecutive lots (4 total) rather than 4 consecutive lots; please explain why
    f. DP-hold time validation

5. Please provide the raw data used to generate Figure 3.2.S.4.2.3.F01 in an Excel spreadsheet.

Clinical:

6. At the May 20, 2009 pre-BLA meeting, you stated that approximately 20 patients in the pivotal belatacept trials developed evidence of immunogenicity against belatacept during the course of the study. At that meeting, you also stated that those patients would be identifiable by patient identification number at the time of the BLA submission so that subgroup analysis could be performed. Please direct us to the section of the eCTD where those patients are identified. Alternatively, if those patients were not identified in the BLA submission, please provide the patient identification numbers of those patients.

Please submit all information no later than September 18, 2009.

Thanks

June Germain 8/14/09

/June Germain /
June Germain, MS
Regulatory Health Project Manager

Germain, June

From: Germain, June
Sent: Tuesday, August 18, 2009 9:54 AM
To: 'Christian, Mary'
Subject: RE: BLA 125288 Belatacept- follow up to telecon re CMC information Aug 14

Hi Mary,

In response to your questions below:

1. No
2. No
3. Yes, please demonstrate how to use the I review tool to analyze the belatacept data which has already been loaded by the FDA. (we call it jReview since it is web-based but should have the same functionality)
4. It has not been customized for FDA use.(we use version 9.0.9)

We note in a prior communication with you on 8/10/09 where we mentioned the datasets do not have embedded codes. we would like to have all the analysis datasets submitted together in the 4 weeks time frame you mentioned. We thought it would be useful for you to see the datasets as we see them and to give us a brief demonstration.
June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Saturday, August 15, 2009 10:30 AM
To: Germain, June
Subject: BLA 125288 Belatacept- follow up to telecon re CMC information Aug 14

Hi June,

As a follow up to Dr Archdeacon's question yesterday about manipulation of datasets, I have a couple of questions to clarify what is needed so that we can be sure the right people are with us on Aug 25.

- Do you have question(s) about loading the SAS datasets into the I Review tool?
- Would you like assistance in loading the datasets into I Review?
- Would you like us to demonstrate how to use the I Review tool?
- If these datasets are already in the I Review tool, what version of I Review do you use? Has it been customized for FDA use? (We use I Review as well, but yours may be different than ours, I understand).

Our goal is to be sure our time is used as efficiently as possible, while providing whatever your team needs to most easily review the application. Any specific direction you can provide on how we can help is be welcome.

Thanks!

Mary

Bristol-Myers Squibb
Mary Christian, Pharm.D., MBA
Director, Global Regulatory Strategy
ImmunoScience
(609) 252-5281 Work
(908) 507-8167 Mobile
(609) 252-6000 Fax
PO Box 4000, Mailstop D32-08
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DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*	FROM
Quantitative Safety and Pharmacoepidemiology Group (QSPG)	Patrick Archdeacon, DSPTP/OAP/CDER

[redacted]009	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
		BLA 125288		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Belatacept	Standard	Immunosuppresion	1/15/2010

NAME OF FIRM
Bristol Myers Squibb

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ PMANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(Spectfy below)*

BLA submission for NME

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER _____
☐ [redacted]IER _____	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE E.G. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below in comments)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Bristol Myers Squibb filed a BLA application (STN125288) on July 1, 2009 for belatacept for the indication of prophylaxis of acute rejection in kidney allograft recipients. This is an eCTD submission: <\\cbsap58\M\eCTD_Submissions\STN125288\125288.enx>

The aapplicant has suggested that belatacept will constitute a significant advance in transplantation medicine because it does not exhibit some of the significant toxicities associated with calcineurin inhibitors (the current cornerstone of most immunosuppressive regimens among patients receiving kidney transplants).

A critical component of the belatacept review will involve an evaluation of the incidence of post transplant lymphoproliferative disorder (PTLD). In the phase 2 and phase 3 trials, the incidence of PTLD was higher among belatacept treated patients than cyclosporine treated

[redacted]URE OF REQUESTER	METHOD OF DELIVERY *(Check One)*
	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERY

8/14/09

FORM FDA 3291 (7/83)

PSC Media Arts (301) 443-1090 EF

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	August 14, 2009
TIME:	10:00 AM TO 11:00 AM EST
LOCATION:	Teleconference
APPLICATION:	STN 125288
DRUG NAME:	belatacept

MEETING CHAIR: Jack Ragheb

MEETING RECORDER: June Germain, Project Manager

FDA ATTENDEES:

Patrick Archdeacon, MD	Medical Reviewer/DSPTP
Jack Ragheb, MD	Chemistry Reviewer
Susan Kirshner, PhD	Chemistry Team Leader
June Germain,MS	Regulatory Health Project Manager

BMS ATTENDEES:

Mary Christian	Regulatory Liaison
Mark Rosolowsky	Regulatory CMC
Meena Bakhshi	Regulatory CMC
Michael Grace	Bioanalytical Sciences
Jinshan Shen	Discovery Medicine/Clinical Pharmacology

BACKGROUND:

On August 4, 2009 the Division faxed a CMC information request to Bristol-Myers Squibb (BMS) to provide a table with side-by-side comparisons of the abatacept and belatacept products to include drug substance (DS) and drug product (DP) manufacturing equipment and validated analytical test methods, manufacturing processes (b) (4)

Tables should also include DS & DP in-process controls with their limits and acceptance criteria, DS & DP release tests and specifications, DS & DP stability testing and limits, product-related variants.

On August 7 2009, the applicant requested clarification since abatacept DS was no longer manufactured at the BMS Syracuse site, and inquired if it was possible to provide the requested comparisons between abatacept and belatacept DS processes based on the current marketed abatacept process, which occurs at (b) (4). BMS also asked to clarify whether the validated analytical test methods, mentioned in the fax meant the final release testing methods.

On August 10, 2009 the project manager sent an email clarifying this question. On August 14, 2009 a teleconference was held with BMS to provide further clarification on the Division's initial request.

DISCUSSION POINTS:

BMS inquired how this comparison would facilitate the Division's review of the belatacept BLA application submitted June 30, 2009 and how they should present the data since they are two molecules that are manufactured differently. The Division noted that the difference and similarities would be helpful in this review and overall to get a clear picture of the products. The Division indicated that although there was no specific review issue generated by the request, a table comparing the manufacturing processes would help in abatacept's post approval aspect its comparability in respect to belatacept. The Division stated that BMS should start by providing a high level description in table format and flow diagrams of the two products similarities and differences of the drug substance and drug product to include process testing and referencing the method numbers, manufacturing differences, immunoassay differences. BMS agreed to amendment the BLA application to include the needed information.

June Germain
Regulatory Health Project Manager

Germain, June

From: Germain, June
Sent: Friday, August 14, 2009 8:26 AM
To: Meyer, Joette M
Subject: FW: BLA 125288/belatacept/BMS/Site contact information needed
Attachments: List for FDA for inspection sites.xls

Hi Joette,

Here is the contact information for the sites. Let if all the sites were covered.
June

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Friday, August 14, 2009 8:18 AM
To: Germain, June
Subject: RE: BLA 125288/belatacept/BMS/Site contact information needed

Hi June,

See attached the requested contact information for these clinical investigators at the sites you provided for inspection. Would you like me to submit this to the BLA as well?

I would appreciate if you could let us know, when available, the approximate timing of these inspections.
Thanks.

Best regards,
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Thursday, August 13, 2009 10:52 AM
To: Christian, Mary
Subject: BLA 125288/belatacept/BMS/Site contact information needed

Hi Mary,

Enclosed is a listing of sites to be inspected for the application, we will need the contact information for the clinical investigators at each site, to include if possible the phone, fax and email. The inspectors will actually use this information to contact the site prior to the inspection.

June <<BLA 125288 site contact information.doc>>

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager

Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
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Germain, June

From: Germain, June
Sent: Thursday, August 13, 2009 4:40 PM
To: 'Christian, Mary'
Subject: RE: BLA 125288/belatacept/BMS/Site contact information needed

Yes we would still like the navigation meeting as planned.

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Thursday, August 13, 2009 4:09 PM
To: Germain, June
Subject: RE: BLA 125288/belatacept/BMS/Site contact information needed

Thanks. We can talk tomorrow during the CMC telecon, but does the team still want the Navigation meeting on Aug 25?

Best regards,
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Thursday, August 13, 2009 1:20 PM
To: Christian, Mary
Subject: RE: BLA 125288/belatacept/BMS/Site contact information needed

We now putting together the consult to DSI. Once everyone knows the review timing then it will be scheduled.

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Thursday, August 13, 2009 12:59 PM
To: Germain, June

Subject: RE: BLA 125288/belatacept/BMS/Site contact information needed

Any idea when the clinical site inspections will occur? Likely I'll be asked next. Thanks.

Best regards,
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Thursday, August 13, 2009 12:30 PM
To: Christian, Mary
Subject: RE: BLA 125288/belatacept/BMS/Site contact information needed

Sorry, Mary I won't have the official word on review timing until Monday. We are waiting on the Office Director's word, he is out of town.
June

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Thursday, August 13, 2009 12:27 PM
To: Germain, June
Subject: RE: BLA 125288/belatacept/BMS/Site contact information needed

Thanks, June. I'll get this information for you as soon as possible.

Any word from the meeting yesterday? Biggest question for at this time is around review timing. I'm back in the office tomorrow.

Best regards,
Mary

From: Germain, June [mailto:June.Germain@fda.hhs.gov]
Sent: Thursday, August 13, 2009 10:52 AM
To: Christian, Mary
Subject: BLA 125288/belatacept/BMS/Site contact information needed

Hi Mary,

Enclosed is a listing of sites to be inspected for the application, we will need the contact information for the clinical investigators at each site, to include if possible the phone, fax and email. The inspectors will actually use this information to contact the site prior to the inspection.

June <<BLA 125288 site contact information.doc>>

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
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Germain, June

From: Germain, June
Sent: Monday, August 10, 2009 4:12 PM
To: 'Christian, Mary'
Subject: RE: Belatacept BLA 125288- Clarification of Fax dates August 4, 2009 requesting CMC information

Hi Mary,

The answers are:

- Yes
- This was intended as a catch-all for validated methods performed on DS & DP, which would include but is not limited to final release testing methods. Besides in-process testing, and release testing, other methods would include e.g. immuno-assays for immunogenicity and PK

Please let me know if you need additional help.

Thanks

June Germain, MS, M.T. (ASCP)
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22 Room 6133
Silver Spring, MD 20993
Phone: 301 796-4024
Fax 301 796-9881

From: Christian, Mary [mailto:mary.christian@bms.com]
Sent: Friday, August 07, 2009 4:05 PM
To: Germain, June
Subject: Belatacept BLA 125288- Clarification of Fax dates August 4, 2009 requesting CMC information

Dear June,

Thank you for the request for belatacept BLA CMC information dated August 4, 2009. We wish to clarify 2 aspects of the request:

- As we proceed with preparing this information, the team would like to recognize that the (b) (4) (b) (4) As such, we propose to provide the requested comparisons between abatacept and belatacept DS processes based on the current marketed abatacept process, which occurs at (b) (4)

Is this acceptable?

- In referring to "validated analytical test methods", do you mean the final release testing methods?

We also welcome a brief teleconference at your convenience to confirm that we understand the request completely and to ensure we prepare a response that provides the information you are seeking.

Best regards,
Mary

Bristol-Myers Squibb
Mary Christian, Pharm.D., MBA
Director, Global Regulatory Strategy
ImmunoScience

(609) 252-5281 Work
(908) 507-8167 Mobile
(609) 252-6000 Fax

PO Box 4000, Mailstop D32-08
Princeton, NJ 08543-4000
mary.christian@bms.com

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 4, 2009

To: Mary Christian, Pharm.D, Director	**From:** June Germain, MS Regulatory Health Project Manager
Company: Bristol-Myers Squibb Company	Division of Special Pathogens and Transplant Products
Fax number: (609) 252-6000	**Fax number:** (301)796-9881
Phone number: (609) 252-5281	**Phone number:** (301) 796-0424

Subject: BLA CMC information request

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

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BL 125288
Belatacept
Bristol-Myers Squibb
Information Request

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009 and received July 1, 2009, we request that you provide the following information:

> Please provide tables with side-by-side CMC comparisons of the abatacept and belatacept. This should include, but is not limited to DS & DP manufacturing equipment and validated analytical test methods, manufacturing processes including (b) (4) [redacted] (b) (4). Tables should also include DS & DP in-process controls with their limits and acceptance criteria, DS & DP release tests and specifications, DS & DP stability testing and limits, product-related variants.

Thanks
June Germain, MS
Regulatory Health Project Manager

8/4/09

BLA 125288 **October 2, 2009**
Belatacept
Bristol-Myers Squibb
Clinical Pharmacology Information Request

Dear Dr. Christian,

In order to facilitate the review of your application, dated June 30, 2009, received July 1, 2009, we request that you submit the following datasets and codes by no later than October 16, 2009, if all possible.

1. PopPK analysis dataset, i.e., the final (clean) dataset that would allow us to run your NONMEM code directory

2. The SAS code and analysis dataset used in the risk factor analysis for developing PTLD and CNS PTLD

Thanks JM 10/2/09
Judit Milstein
Chief, Project Management Staff

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): OSE/Division of Risk Management/Darrell Jenkins, RPM			FROM: June Germain, MS RPM, 301-796-4024 /Dr. Ozlem Belen, MD Deputy Director for Safety/Division of Special Pathogen and Transplant Products	
DATE: July 30, 2009	IND NO.	BLA No.: STN 125288	TYPE OF DOCUMENT: REMS Proposal	DATE OF DOCUMENT: June 30, 2009
NAME OF DRUG: Belatacept	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG: immunosuppressant	DESIRED COMPLETION DATE: December 20, 2009

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The Division has received the BLA submission for STN 125288, belatacept for the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. The submission is dated June 30, 2009 and received July 1, 2009. The PDUFA goal date is May 1, 2010. A proposal for REMS was included in the submission. The elements of the proposed REMS include a Medication Guide and a communication plan. Please review the REMS proposal. An advisory committee meeting is plan for February 2010. The submission can be found at:
<\\cbsap58\M\eCTD_Submissions\STN125288\125288.enx>

SIGNATURE OF REQUESTER: June Germain 8/4/09	METHOD OF DELIVERY (Check one): ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 9418

Bristol-Myers Squibb Company
Attention: Mary Christian, Pharm.D.
Director, Global Regulatory Sciences
P. O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Christian:

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

We also refer to the meeting held between representatives of your firm and the FDA on May 20, 2009. The purpose of the meeting was to discuss the target indication for belatacept, present and discuss the proposed Risk Evaluation and Mitigation Strategy (REMS) and assure alignment regarding agreements previously reached with the FDA.

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, contact June Germain, Regulatory Health Project Manager, at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Eileen Navarro-Almario, MD
Acting Deputy Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	May 20, 2009
TIME:	11:00 a.m.-12:30 p.m.
LOCATION:	FDA/CDER 10903 New Hampshire Ave Building 22, Room 1415 Silver Spring, MD 20993
APPLICATION:	IND 9,418
DRUG NAME:	Belatacept
TYPE OF MEETING:	Pre-BLA
MEETING CHAIR:	Patrick Archdeacon, MD
MEETING RECORDER:	June Germain, MS

FDA ATTENDEES: Division of Special Pathogen and Transplant Products (DSPTP)

Renata Albrecht, MD	Division Director
Eileen Navarro-Almario, MD	Acting Deputy Director
Ozlem Belen, MD	Deputy Director for Safety
John Farley, MD	Deputy Director OAP
Dave Roeder, MS	ADRA, OAP
Hyun Son, Pharm.D	Acting Safety Project Manager
Joette Meyer, Pharm.D	Clinical Team Leader
Patrick Archdeacon, MD	Clinical Reviewer
Marc Cavaille Coll, MD, PhD	Clinical Team Leader
Ergun Velidedeoglu, MD	Clinical Reviewer
Susan Kirschner, PhD	Associate Chief, Laboratory of Immunology
Jack Ragheb, MD, PhD	Senior Regulatory Research Officer
Philip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader
Gerlie Gieser, PhD	Clinical Pharmacology Reviewer
Shashi Amur, PhD	Pharmacogenomics Reviewer
Yoriko Harigaya, PharmD	Clinical Pharmacology Reviewer
Karen Higgins, ScD	Statistical Team Leader
John Yap, PhD	Safety Statistical Reviewer
Shukal Bala, PhD	Microbiology Team Leader
Aaron Ruhland, PhD	Microbiology Reviewer
William Taylor, PhD	Pharmacology/Toxicology Team Leader
Ying Mu, PhD	Pharmacology/Toxicology Reviewer

Janice Lansita, PhD	Pharmacology/Toxicology Reviewer
June Germain, MS	Regulatory Health Project Manager
Judit Milstein	Chief Project Management Staff

EXTERNAL CONSTITUENT ATTENDEES:

Mary Christian, PharmD	Director, Global Regulatory Sciences
Pushkal Garg, MD	Executive Director, Belatacept Medical Lead
Jeffrey Gelb, MD	Vice President-Full Development Team Lead LEA29Y
Deborah Gilman	Associate Director, Global Dossier Management
Sheila Gujrathi, MD	Vice President, Global Clinical, Immunology
Helen Haggerty, PhD	Group Director, Immunotoxicology
Margo Herron	Director, Regulatory Affairs, Washington Liaison
Daniel MacNeil, MD	Executive Director, Clinical Safety
Tifani McGann, PhD	Group Director, Global Biometric Sciences
Jinshan Sen, PhD	Associate Director, Discovery Medicine and Clinical Pharmacology
MaryLou Skovron, PhD	Group Director, Epidemiology
Anthony Waclawski, PhD	Vice President, Global Regulatory Sciences
Dominic Labriold	Vice President, Biometric Science

BACKGROUND:
On March 12, 2009, Bristol-Myers Squibb (BMS) requested a pre-BLA meeting to discuss the target indication for belatacept an immunosuppressant for the prophylaxis of rejection in renal transplant recipients, present and discuss the proposed Risk Evaluation and Mitigation Strategy (REMS) and assure alignment regarding agreements previously reached with the FDA.

On April 15, 2009, BMS submitted a pre-meeting package, containing eight questions for discussion and background information needed to address the questions. On May 18, 2009, the Division sent preliminary comments to the questions posed in the meeting package.

MEETING OBJECTIVES:

To discuss the BLA submission of belatacept and ensure regulatory alignment.

DISCUSSION POINTS:
For the purpose of these minutes, the following format is used:

- BMS original questions are in normal font.
- FDA's responses sent per email to the sponsor on May 18, 2009, are in italics.
- The meeting discussion is in bold font.
- No further discussions were held on Questions 2, 4, and 7 as the sponsor was satisfied with the Division's written responses.
- Pertinent miscellaneous issues or items discussed during the meeting are recorded under "meeting addendum" section.

After introductions, Bristol-Myers Squibb (BMS) began the meeting with a brief overview of the belatacept program. BMS agreed to start the discussion with the first question and proceed through the remaining questions as outlined in the briefing package.

Q1. The Summary of Clinical Efficacy and Summary of Clinical Safety will be final early June, 2009. In addition to these analyses, does the Agency anticipate any additional information that may be useful during the review, or for presentation at the Advisory Committee meeting?

FDA Response:
Clinical

The following is a list of specific topics and requests for additional information that should be addressed in your BLA submission.

- *Post-Transplant Lymphoproliferative Disorder (PTLD): As communicated at the December 2008 meeting, additional information regarding the specifics of the PTLD cases identified in the phase 2 and 3 trials would be helpful. Of the cases with CNS involvement, describe what was the EBV status of the recipients and donor, what specific treatments were required to treat the PTLD cases and what were the outcomes.*

  Case Report Forms (CRFs) and detailed narratives of the cases of PTLD occurring in both the belatacept and comparator-treated groups should be provided as they may help elucidate whether these cases are similar or distinct from those typically seen in the transplant population (other than the apparent dissimilarity with regards to a preponderance of CNS involvement). Details regarding cell type, clonality, virological studies, and architectural background should also be included.

- *Tuberculosis (TB): Your current submission states that an imbalance in the incidence of TB in belatacept-treated patients has emerged. As above, please submit the CRFs and detailed narratives for all patients in both treatment groups who developed TB, including treatments required, outcomes, current prognoses, etc.*

- *Donor Specific Antibodies (DSAs): Your current submission indicates that a difference in the incidence of DSAs was noted favoring the belatacept arm. We look forward to hearing more details regarding this recent finding. We are especially interested in what methodology was employed to measure DSAs.*

- *Biopsy Data: We are also interested in whether data regarding antibody mediated rejection (based on biopsies) will be available in the BLA submission for review. Please be prepared to discuss how patient-level data regarding biopsies will be submitted in the BLA.*

- *Analysis of Rejection Episodes: Please include an analysis to show the time relationship between the occurrence of biopsy proven acute rejection episodes and infusion of Belatacept*

Meeting Discussion:

BMS provided information on the clinical data of patients with PTLD and agreed to provide a detailed narrative (including treatment and prognosis) for each patient and all relevant raw data collected during their investigations of the PTLD cases. However, BMS indicated that the work was ongoing and not all results may be available at the time of the BLA submission. BMS also discussed their findings on the trend towards more TB cases in patients treated with belatacept compared to control and agreed that patient-level details and narratives would be included in the BLA submission with regards to the TB cases, as well. In regards to donor-specific antibodies (DSAs), BMS agreed to provide further detail regarding the methodology used to measure DSAs and stated that the submitted data would allow the Agency to investigate whether a temporal relationship existed between episodes of acute rejection and infusions of belatacept (i.e., whether events tended to occur more often towards the end of a dose cycle).

Q3. Does the Agency have any comments on the planned evaluation to investigate the brain level of belatacept in monkeys (submitted 23-Mar-2009, SN 0426)?

FDA Response:
We are providing the following comments on Study DS09027 which investigates the brain concentrations of belatacept in monkeys. However, we note that the study has already commenced and that it may not be possible to modify the study design at this time.

1. *To control for any impact that other immunosuppressive agents may have on belatacept concentrations in the CNS, we recommend that belatacept be administered to the monkeys with the same combination of immunosuppressive medications that were used by the renal transplant patients in the ongoing Phase 3 trials.*

2. *It is known that certain other immunosuppressive drugs (e.g., mycophenolate) can increase the risk of lymphoproliferative disease and progressive multifocal leukoencephalopathy (PML). We recognize from the findings of the MPA/MPAG PK substudies of the ongoing Phase 3 trials that MPA concentrations could be significantly (~40%) higher when given with belatacept than with cyclosporine.*

   Thus, to rule out the possibility that the increased MPA concentration is a contributing factor to the alteration of CNS immunity (i.e., increased CNS-PTLD and PML risk) associated with belatacept, we recommend that you measure the MPA/MPAG concentrations in the blood, CSF and brain samples obtained from the monkeys that received immunosuppressive therapy with or without belatacept.

3. *We recognize that the ability of belatacept (a large fusion protein) to cross the blood-*

brain barrier (BBB) is yet to be proven. Since belatacept will likely be used with other 'small molecule' immunosuppressive agents (e.g., mycophenolate) that may or may not have the potential to cross the BBB, it is also important to characterize the potential effects of belatacept on the integrity of the BBB. According to your submission, Study DS09027 will also investigate the effect of belatacept on BBB transporters. However, we note that the study protocol that we received did not include the methodology for BBB transporters.

4. *We note that you plan to obtain blood samples for belatacept PK profiling starting on Day 22. Instead of at 3 minutes, we recommend that you obtain a PK sample at 30 minutes, the approximate Tmax of belatacept following a 30-minute infusion.*

5. *Finally, we note that the protocol does not provide much detail about the immunohistochemistry and immunofluorescent staining that will be performed, though it states that the "potential" for such staining exists. You also suggest that you may pursue staining of lymphocyte and endothelial surface cell markers, though you do not specify further. We recommend investigating binding of belatacept to the vascular endothelium which comprises the BBB, any detectable interactions with CNS cell types known to express ligands of belatacept (e.g., microglia), and any patterns of belatacept localization elucidated by immunohistochemistry analysis of various brain sections. We recognize that you may already intend to conduct such studies.*

We also have the following recommendation for an additional nonclinical study to investigate the effects of belatacept on the integrity of the BBB in humans.

An in vitro human BBB model exists, i.e., human brain microvascular cells (HBMEC). We encourage you to use this in vitro model to evaluate the effect of belatacept on BBB transporters (e.g., P-gp, MRP, BCRP) and BBB tight junctions. We also encourage you to use this model to explore the potential effect of belatacept on the ability of JC virus and Epstein-Barr virus to penetrate across and proliferate in the human brain.

Please consult the literature for more information about the application of HBMEC for these investigational purposes. Examples of these references are provided below. [1]

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[1] Quezada, et al. Effect of tacrolimus on activity and expression of P-glycoprotein and ATP-binding cassette transporter A5 (ABCA5) proteins in hematoencephalic barrier cells, *Biol Pharm Bull.* 2008 Oct;31(10):1911-6.

Warren et al. Comparative gene expression profiles of ABC transporters in brain microvessel endothelial cells and brain in five species including human, *Pharmacol Res.* 2009 Jun;59(6):404-13. Epub 2009 Feb 24.

Dhillon et al. Cocaine-mediated alteration in tight junction protein expression and modulation of CCL2/CCR2 axis across the blood-brain barrier: implications for HIV-dementia, *J Neuroimmune Pharmacol.* 2008 Mar;3(1):52-6. Epub 2007 Nov 29

Chapagain et al. Polyomavirus JC infects human brain microvascular endothelial cells independent of serotonin receptor 2A, *Virology.* 2007 Jul 20;364(1):55-63. Epub 2007 Mar 30.

Meeting Discussion:

BMS gave an overview of their ongoing investigation into the effect of belatacept in the CNS.
Regarding FDA Comment #3, BMS clarified that the investigation of BBB transporters is not a part of the ongoing monkey study. However, BMS indicated that the *in vitro* HBMEC model will be discussed with experts and the approach will be considered as they move forward.
Regarding FDA Comment #4, BMS clarified that belatacept will be administered to the monkeys as a slow IV bolus and so they consider 3 minutes as an appropriate timepoint for PK sampling.
BMS also indicated that the influence of MPA on belatacept-associated CNS PTLD will be investigated.
BMS asked the Division how the CNS-related investigations would affect the BLA submission and proposed to provide updates on their ongoing investigation into the CNS issues during the review cycle. The Division emphasized that it had an interest in the ongoing investigations, but stated the review of the BLA submission would be limited to the data submitted with the initial BLA application. The Division indicated that under current Good Review Management Practices (GRMPs) the NDA application needs to be complete at the time of initial submission. The Division noted, however, that the application would certainly be strengthened if the issues could be elucidated.

The Division also stated that BMS should decide whether the current data supports a positive risk-benefit analysis for belatacept and requested the submission of a complete application. BMS responded that they were convinced the data would support such an analysis and would not delay submission of the BLA.

Q5. Does the Division and the Office of Safety Evaluation (OSE) have any comments on the current proposal for the Risk Evaluation and Mitigation Strategy (REMS) or other aspects of the routine or enhanced plans for pharmacovigilance?

FDA Response:
You propose a REMS which includes a Medication Guide and a Communication Plan. This may be a reasonable approach since similar drugs of the transplant class are now required to have REMS. However, at this time we are unable to provide additional comments as we cannot state with certainty that the risks you have identified are the only risks associated with the use of belatacept. A risk assessment will be undertaken during the BLA review and at that time a determination will be made if further REMS elements are needed.

Meeting Discussion:

BMS asked whether any other elements, other than a Medication Guide and Communication Plan would be required as part of the REMS. The Division stated that the elements of the REMS proposed by BMS appear reasonable, but that the necessary elements may change during the BLA review to reflect the safety issues that may arise. The Division stated that, while it is true that the approval of the product cannot be made without the approval of the REMS program, a REMS program cannot be properly designed prior to the review process where the all risks are identified. The Division stated that in the course of the review process comments regarding the REMS program would be communicated early and continued communication would be needed.

The Division also emphasized that risks mitigation can be achieved through product labeling. However, REMS specifically refers to a required risk management plan that uses tools as specified in the Food and Drug Administration Amendments Act of 2007 (FDAAA) on risk evaluation and mitigation strategies beyond routine professional labeling (the package insert) necessary to ensure the benefits of the drug outweigh its risks. The elements of a REMS may potentially include a Medication Guide, patient package insert, communication plan, and elements to assure safe use.



Q6 Does the Agency have any additional comments on the content of the BLA, or additional information that may be useful during the review, or during preparation for the Advisory Committee meeting?

FDA Response:
To aid in the Clinical Pharmacology review of the BLA, please address the following:

Please provide not only the tables and graphs depicting the time course of the measured concentrations of belatacept, but also those of other immunosuppressive drugs that were either used in combination with belatacept MI, belatacept LI or the control treatment (e.g., cyclosporine, tacrolimus, sirolimus, MPA/MPAG).
This information and the supportive datasets could be included in and/or linked to the Exposure-Response analysis section of the BLA submission.

We also understand that you are including in the BLA submission a summary of the pharmacodynamic (Indoleamine 2,3 dioxygenase (IDO) and the ATP (Immuknow®) assay

results but only for the IM103100-LTE PK Substudy. Please include in your BLA submission an integrated study report based on the findings of all pertinent clinical trials regarding these two pharmacodynamic (PD) biomarkers and other planned exploratory biomarkers, i.e., CD86 receptor occupancy, T-cell allo-reactivity (cytokine proliferation/production), phenotypic characterization of circulating leukocyte subsets by flow cytometry, and HLA anti-donor antibodies. This integrated report should also include a discussion of the findings of exploratory PK-PD, PD-efficacy and PD-safety analyses.

To aid in the Immunopharmacology/Microbiology review of the BLA, please provide the following:

1. *In addition to the integrated summary of pharmacodynamic biomarkers stated above, it would be helpful to include in the study reports detailed information which includes the methods used for immunological PD measurements and results such as patient level data and summary tables.*

2. *Please specify the assay used for determining EBV status. If the assay is FDA approved then the product brochure should be included. If the assay is not FDA approved, please provide details of the method and the performance characteristics for the assay. Also, please specify the laboratory where testing was done.*

Meeting Discussion:

BMS provided a summary of the PK and concentration data to be included in the BLA submission. Regarding the effect of MPA/MPAG exposure on response, BMS stated that they will also include a literature abstract as supportive information.

BMS presented a table summarizing the data regarding specific biomarkers that were investigated, the clinical trial(s) that included the particular biomarker and the proposed location of the information in the BLA submission. The Division inquired about the status of other biomarkers indicated in the study protocols that were reviewed, but that were not included in the sponsor's summary table. BMS indicated that for some of these biomarkers, technical difficulties were likely encountered during collection and processing. BMS will send the Division follow-up information regarding the biomarkers.

BMS stated that they will provide detailed reports of laboratory methods used (product brochures where applicable) and cell types including the methods used for determining EBV status. BMS indicated that the samples were banked before the patients underwent transplantation. The Division asked for clarification on whether the EBV results were obtained from the study site laboratories or the central laboratory and whether the EBV assay used was the same across different study sites. BMS stated that for some study sites the samples were sent to a central laboratory, whereas for other sites testing was done at an on-site laboratory. BMS agreed to obtain information from the sites regarding the assays used and provide the information to the Division, and indicated it may not be available at the time of BLA submission. The Division also requested BMS provide all the details of the methods used, including storage, shipping, and handling of samples; as well as specifics on

the laboratories where testing was done. The Division also stated that this requested information regarding the use of different EBV assays and the laboratories where testing was done, should also be clearly specified in the datasets.

Q8 Does the Agency have any additional guidance or recommendations for supportive activities that should be planned or data that should be provided by the Applicant during the review period to support the review process?

FDA Response:
Chemistry:
Please ensure that issues raised during the CMC pre-BLA meeting held on July 8, 2008 are adequately addressed. In addition, please address the high prevalence of neutralizing antibodies that were observed in the immunogenicity studies and include this as part of the REMS or long-term safety studies.

Meeting Discussion:

BMS discussed the immunogenicity assessment program. The sponsor indicated that a few patients in the Phase 2 and 3 trials developed detectable antibodies against belatacept. They expressed a belief that the low incidence of antibody formation was related to the continued exposure to immunosuppresion in the context of a transplant patient. The Division expressed some concern that the development of neutralizing antibodies could become a more significant issue if physicians were to attempt to decrease immunosuppression at some point (e.g., withdraw steroids after several months post-transplantation). BMS indicated that there was not enough data to evaluate these concerns at the current time, but they would continue to assess such issues and to collect data over time. The Division also asked whether the outcomes of the approximately 20 patients who had developed detectable antibodies were known. BMS stated that it would be possible to identify those specific patients in the BLA submission and to perform additional subgroup analyses of their outcomes.

Additional FDA Comments:

(b) (4)



(b) (4)

[redacted]

2. *Please find also enclosed a document titled "General Clinical Comments Regarding BLA/NDA Applications" which has been provided to BLA applicants by other review divisions in CDER. Reference to the document may provide you with useful information regarding the expectations of the Division regarding the content of the belatacept BLA. Please let us know if your pending submission deviates significantly from the suggestions in this document.*

Meeting Discussion:

The Division acknowledged that the document titled "General Clinical Comments Regarding BLA/NDA Applications" was meant to provide general guidance and was not specific to the belatacept BLA submission.

BMS stated that the BLA submission would not be in CDISC format. The Division indicated that they would like to use iReview for examining the datasets, but would have to verify whether or not iReview could be used with non-CDISC data. BMS stated that the belatacept datasets should be compatible with iReview and that the program does not require CDISC data.

The Division requested that BMS submit a complete listing of the manufacturing and testing sites, a preliminary manufacturing schedule, and a list of potential dates for FDA inspection of the manufacturing facilities prior to the BLA submission. The sponsor agreed to provide the requested information.

The Division also requested that BMS submit a list of clinical investigators who participated in the belatacept trials in order to aid in the recruitment of potential Advisory Committee members. The sponsor agreed to provide the requested information.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 9418	BRISTOL MYERS SQUIBB	Belatacept [LEA29Y (BMS-224818) (human, recombinant, CHO cells, Bristol-Myers Squibb) to CD80 and CD86]

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

/s/

EILEEN E NAVARRO ALMARIO
07/01/2009

IND 9,418/SN 0424
Belatacept
Bristol-Myers Squibb
CMC meeting minutes clarification

Dear Ms Bakhshi,

Please refer to pre- BLA teleconference held on July 28, 2008. We also refer to your submission dated March 20, 2009, containing a request for clarification on the contents of the discussion of Question 1, as described on the minutes issued by the Division on February 5, 2009.

We agree with your clarification and note that the discussion on Question 1, should read:

"BMS stated that they would provide the requested information in the BLA submission. BMS specified that belatacept DS will be characterized in the BLA. With regard to the cell-based bioassay, BMS stated that the belatacept bioassay was 2-3 fold better than abatacept due in part to the completely roboticized plate loading. BMS will provide additional information regarding the bioassay in the BLA. BMS stated that they are seeing correlations between the (b) (4) results and the bioassay results for belatacept in forced degradation and stability data set. This data will be provided in the BLA submission.

The Division inquired about being able to distinguish abatacept and belatacept in the (b) (4) method. BMS replied that there is no distinction in the (b) (4) assay and will have to look into the data further and present the findings in the BLA. BMS clarified regarding the identity testing, that there will be a release test using tryptic peptide mapping that is capable of distinguishing between belatacept and abatacept and that they will use the CE method as the primary ID test. FDA requested BMS to provide trend data for release lots showing separation time between abatacept and belatacept. FDA also requested that BMS provide a SOP specifying steps that the technician would follow if separation between abatacept and belatacept could not be achieved. The SOP will be included in the BLA."

Please, give me a call if you need further assistance.

Thanks
June Germain, MS
Regulatory Health Project Manager

Linked Applications	Sponsor Name	Drug Name / Subject
IND 9418	BRISTOL MYERS SQUIBB	Belatacept [LEA29Y (BMS-224818) (human, recombinant, CHO cells, Bristol-Myers Squibb) to CD80 and CD86]

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

/s/

JUNE GERMAIN
04/09/2009

BLA 125288
Belatacept
Bristol-Myers Squibb
Clarification on Information Request

January 5, 2009

Dear Dr. Christian,

We acknowledge receipt of your December 14, 2009 response to our information request on datasets for IM103028 and an additional analysis of the USRDS data. We are requesting clarification of this submission. Please respond by January 15, 2010, if possible.

Statistics

1. Please clarify the time frames (i.e. 1995-2006 or 2000-2006) covered in supplemental tables (i.e. Tables S.2b, c and S.2d (USRDS 3-Year (or 18-month) Incidence Rates by Exposure to TCD Induction, CNI-based Maintenance Regimen and EBV Serostatus of Recipient) in Appendix B of IM103028 Addendum 3 (dated 12/12/2009).

Thanks
June Germain, MS
Regulatory Health Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 9418

Bristol-Myers Squibb Company
Attention: Mary Christian, Pharm.D., MBA
Director, Global Regulatory Sciences
P. O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Christian:

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

We also refer to the meeting held between representatives of your firm and the FDA on December 15 2008. The purpose of the meeting was to discuss the 1 year preliminary analysis of the belatacept phase 3 studies.

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, contact Hyun J. Son, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Eileen Navarro-Almario, M.D.
Acting Deputy Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	December 15, 2008
TIME:	1:00 p.m.-2:30 p.m.
LOCATION:	Food and Drug Administration 10903 New Hampshire Ave. BLDG 22, Room 1419 Silver Spring, MD 20993
APPLICATION:	IND 9418
DRUG NAME:	Belatacept
TYPE OF MEETING:	Type B Meeting
MEETING CHAIR:	Marc Cavaille-Coll, MD, MPH
MEETING RECORDER:	Hyun Son, Pharm.D.

FDA ATTENDEES: Division of Special Pathogen and Transplant Products (DSPTP)

Renata Albrecht, MD	Division Director
David Roeder, MS	Associate Director of Regulatory Affairs, OAP
Eileen Navarro-Almario, MD	Acting Division Deputy Director
Marc Cavaille Coll, MD, PhD	Medical Team Leader
Arturo Hernandez, MD	Medical Reviewer
Patrick Archdeacon, MD	Medical Reviewer
Ergun Velidedeoglu, MD	Medical Reviewer
Philip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader
Gerlie Gieser, PhD	Clinical Pharmacology Reviewer
Shukal Bala, PhD	Microbiology Team Leader
Aaron Ruhland, PhD	Microbiology Reviewer
Karen Higgins, ScD	Statistics Team Leader
Cheryl Dixon, PhD	Statistics Reviewer
June Germain, MS	Regulatory Project Manager
Hyun Son, PharmD	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Mary Christian, PharmD	Director, Global Regulatory Sciences
Brian Daniels, MD	Sr. Vice President, Global Development
Greg DiRusso, MD	Director, Global Clinical Research
Pushkal Garg, MD	Executive Director, Belatacept Medical Lead
Jeffrey Gelb, MD	Vice President, Global Development
Sheila Gujrathi, MD	Vice President, Global Clinical, Immunology
Dominic Labriola, PhD	Vice President, Global Biometrics Sciences
Chen Sheng Lin, PhD	Director, Global Biostatistics
Daniel MacNeil, MD	Executive Director, Global Clinical Safety

Tifani McCann, PhD	Group Director, Global Biostatistics
Jinshan Shen, PhD	Assoc. Director, Clinical Pharmacology
Dolca Thomas, MD	Assoc. Director, Global Clinical Research
Robert Townsend, PhD	Assoc. Director, Immunology Biomarkers, Discovery Medicine
Anthony Waclawski, PhD	Vice President, Global Regulatory Sciences

BACKGROUND:

Belatacept is a protein being developed by Bristol-Myers Squibb (BMS) as an immunosuppressant for the prophylaxis of rejection in renal transplant recipients. The sponsor requested a type B meeting to discuss the 1 year preliminary analysis of the belatacept phase 3 studies. Briefing package was submitted on November 11, 2008. Preliminary comments on the questions posted in the briefing package were e-mailed to the sponsor on December 11, 2008. BMS provided additional slides that were presented during the meeting (attached). For the purposes of the minutes, BMS questions are **bolded**, FDA preliminary comments are in normal text, and the discussions are *italicized.*

DISCUSSION

Question 1: Belatacept demonstrated favorable effects on renal function and structure in both study populations. Based upon the results of large epidemiologic studies, this is expected to result in a positive impact on long-term subject and graft survival (see Section 4.1, Clinical Importance of the Observed Renal Benefit).

Have we characterized this benefit in a balanced way, recognizing the clinical importance of the positive effects on renal function and structure, while respecting the limitations of extrapolating the observational data, and do you have any suggestions for further evaluation?

FDA: You documented a difference in GFR at 12 months between patients treated with belatacept and patients treated with CsA (~ 14 mL/min/1.73m*2 for SCD kidney recipients and ~5-7mL/min/1.73m*2 for ECD kidney recipients, as noted on p.44 of the submitted Briefing Document). You suggest that avoidance of calcineurin inhibitor toxicity and associated chronic allograft nephropathy (CAN) may be responsible for this observed difference. However, you note the difference in GFR between the two treatment groups was detectable essentially immediately after transplantation and subsequently preserved for the length of the study (see Figure 4.1A on p.47 of the Briefing Document). One wonders whether the differences in measured GFR reflect differences in histopathology or in renal physiology between the treatment groups (or some combination of both). You did detect a trend towards decreased prevalence of CAN at 12 months between treatment arms (30.3% for Belatacept MI, 33.5% for Belatacept LI, and 41.2% for CsA) in favor of Belatacept but this would not explain the differences in GFR detected far earlier.

A difference in renal blood flow causing a decrease in GFR secondary to afferent renal artery vasoconstriction (as could result from CsA exposure) may explain the difference in GFR detected at the start of the study. This possibility could have been assessed by measuring PAH clearance in the two arms. Such a measure would have been admittedly difficult to introduce into large studies and is obviously not feasible to perform retrospectively. Afferent renal artery vasoconstriction secondary to CsA effect, however, remains a likely explanation of the difference in mean GFR detected between the treatment arms in the first weeks after transplantation. Theoretically, one might exclude the possibility that the difference detected at month 12 still derives from this reversible physiologic effect by crossing-over CsA patients to a Belatacept regimen: if afferent renal vasoconstriction remains the cause of the decreased GFR (as opposed to CAN), the GFR of the crossed-over patients should increase after the CsA is held. It is not clear, however, that such a cross-over experiment is either necessary or ethical given the risk of changing immunosuppressive regimens in stable transplant patients.

You also noted that the use of blood pressure medicines differed across the treatment arms (the CsA arm demonstrated more HTN and required treatment with a greater number of agents). Differential use of ACE inhibitors in the CsA arm could represent a less likely explanation for the early difference noted between the two randomized arm – ACE inhibitors limit vasoconstriction of efferent renal arteries, thereby causing a physiologic decrease in GFR. A comparison of the use of ACE inhibitors across treatment arms would help exclude this explanation. This is probably feasible to perform retrospectively with inspection of medication records. Similarly, excluding differential use of other medications affecting renal physiology (NSAIDS, diuretics) would strengthen the interpretability of the differences in GFR between the two groups.

One might speculate that the difference in GFR noted in the immediate post-transplant period reflected reversible physiologic differences, but that the difference noted 12 months after transplantation reflected structural differences within the kidney parenchyma. The above discussion, however, may elucidate the Agency's concerns about preferentially considering the primary endpoint of GFR preservation over the co-primary endpoint of acute rejection (in which both Belatacept regimens in the SCD study were statistically inferior to CsA, though the assessment of non-inferiority with a margin of 20% was met for the LI regimen).

Regarding the GFR data collection rates reported in Tables 3.2.3 and 3.3.3, please provide this information by treatment arm and also by treatment arm and rejection status.

Discussion: *BMS stated that upon review of the medications that may confound the assessment of renal function (ACEIs, ARBs, NSAIDs), there was no difference in use across the treatment arms in Study IM10300, however further evaluation and analysis along with longer follow-up data will be presented in the BLA. BMS pointed out that the CAN differences (Tablet 4.1.A, slide 5) may be due to the avoidance of the calcineurin inhibitors. FDA indicated that further analyses to elucidate the causes and durability of the renal function improvements would be helpful to the review. FDA also indicated that it would be helpful to review the GFR data in*

comparison to CsA treated subjects with high versus low trough levels of CsA. FDA indicated that additional information on CAN (e.g., further characterization of the biopsies, grading and trends) in the BLA would be helpful.

Question 2: The frequency of AR was increased in belatacept-treated subjects as compared with CsA-treated subjects, particularly in SCD study. Our preliminary assessment supports the conclusion that these rejections have limited impact on renal function and subject and graft survival at 1 year. The accumulating long-term experience will add additional assurance that the long-term outcomes are not detrimental to subject outcomes. The data and our assessment are discussed further in Section 4.2.

Considering the totality of AR data, including the frequency, severity and impact on renal function and outcomes, what is your impression of the clinical relevance of these data, and do you have any suggestions for further evaluation?

FDA: Clinical Pharmacology

Regarding your plan to understand the mechanism involved in the increased incidence of acute rejection, particularly Banff IIb in belatacept more-intensive (MI) regimen versus less-intensive (LI) regimen, we recommend that you consider exposure-response and immunogenicity analyses as two approaches to potentially explain this apparent inverse dose-response relationship.

Clinical

Figure 4.2.2 (on p.53) of the Briefing Document depicts the apparently mild impact of the episodes AR on mean month 12 GFR in the pivotal studies. It is noted that the impact of AR on GFR seems somewhat greater in Study IM103027 (where the difference in reported AR rates between Belatacept and CsA was negligible) than in Study IM103008 (where rates differed but GFR appeared largely unaffected).

Concerns remain, however, about the nature of the AR episodes and the subsequent treatments that these patients received. Eighty-one of the 150 Belatacept patients who developed acute rejection were taken off study drug. The Briefing Document implies that the majority of them were treated subsequently with tacrolimus based regimens (p.52). The Briefing Document further indicates that significant differences existed between the Belatacept arms and the CsA arms in terms of acute rejection episodes requiring treatment, acute rejection episodes resistant to corticosteroid treatment, and acute rejection episodes requiring initial lymphocyte-depleting treatments (see Table 2, Appendix 3, p.86 and Table 2, Appendix 4, p. 91).

One wonders about the implication of the approach to treatment of rejection on Belatacept in the trials:

1. Does it suggest that patients who reject on Belatacept will require salvage treatment with CNI-based regimens?
2. Does it explain the differences detected in terms of PTLD episodes or the occurrence of the PML event (i.e., because these patients required intensive

rescue with lymphocyte depleting agents, they were more likely to experience adverse events associated with over-immunosuppression)?

3. Did periods of over-immunosuppression during regimen changes (i.e., where patients may have been administered tacrolimus while Belatacept remained in their system) explain the differences detected in terms of PTLD incidence or the occurrence of the PML event?

More data regarding which patients were switched to tacrolimus and which patients remained on Belatacept (e.g., biopsy reports, creatinine elevations, exposure to specific lymphocyte depleting agents, etc.) may help inform these issues further. Detailed information describing how the regimen changes (replacing Belatacept with tacrolimus) were executed would similarly help the review process. Detailed data regarding outcomes for patients receiving lymphocyte-depleting agents (e.g., rituximab, thymoglobulin) could also help evaluate whether differences in AR management may have contributed to the incidents of PTLD and/or PML.

We note further that the rejection episodes are grouped by Banff Grades from IA – III (Tables 3.2.5B, p.25 and 3.3.5B, p.36 of the Briefing Document). These appear to correspond to the grades given to classes of cellular rejection in the Banff 97 criteria. No information is given regarding the incidence of antibody mediated rejection (a separate component of the Banff 97 criteria). Please provide results for incidences of AMR or clarify that there were no episodes of AMR in the any of the treatment arms of either pivotal study.

Discussion: *Looking at the exposure response of belatacept, BMS noted that the trough concentrations in subjects with and without AR were generally similar. This will be further explored in the population exposure-response analyses in the BLA. Immunogenicity response rate in phase 3 was low (3% for IM103008 and 5% for IM103027). For subjects with an immunogenicity response, AR rate was generally similar to that for patients without an immunogenicity response. These data will be included in the BLA.*

Among the belatacept subjects with AR, the 12 month GFR outcome was reasonable and death/graft loss was not impacted by the incidence of AR. With high grade rejection (IIb/III), there were no cases of graft loss (death censored).

In regard to the treatability of episode (CNI rescue), BMS stated that about 50% of subjects stayed on therapy after the AR (slide 8). At 12 month, the mean GFR of the subjects after AR was similar regardless of continuation or discontinuation of the study drug.

BMS explained that with regard to antibody mediated rejection (AMR), there were low rates in study IM103027 (3-5% donor specific antibodies in belatacept treated subjects and 7-8% in CsA subjects, using the Banff definition of AMR). Among the patients with AR, none had developed donor-specific antibodies.

FDA inquired about the availability of C4d positivity data. BMS stated that there is very little data on C4d positivity and that only some local data is available which showed very few C4d positive results. (b) (4) [redacted]

Questions 3: PTLD was more frequently observed in belatacept – versus CsA-treated subjects and the number of cases of CNS PTLD is a concern. We have presented our characterization of the risk of PTLD, including the analysis of the Phase 3 data and what is known form the literature and epidemiology in Section 4.3. No increased risk of PTLD was observed among EBV positive recipients, and all reported cases of PTLD have occurred within the first 18 months post-transplant.

Is our approach to the characterization of the risk of PTLD appropriate at this stage, and are there any other analyses or aspects that should be investigated?

FDA: Clinical Pharmacology

1. Since over-immunosuppression could contribute to the development of PTLD, we recommend that you include PTLD in your planned belatacept exposure-safety analysis.
2. Regarding your plan to understand the mechanism underlying the apparent increased risk of CNS-PTLD with belatacept, we recommend that you consider exploring the contribution of viral and/or host genetic factors. Specifically, we recommend that you conduct exploratory pharmacogenetic analysis on the biological samples that have been collected/banked to potentially identify genetic subgroups of EBV-seronegative transplant recipients at particular risk for belatacept-associated PTLD.
3. If applicable, we recommend that you consider the same analytical approaches above for belatacept-associated progressive multifocal leukoencephalopathy (PML).

Clinical

The question itself contains two statements that require examination:

A. "No increased risk of PTLD was observed among EBV positive recipients"
B. "all reported cases of PTLD have occurred within the first 18 months post-transplant".

In Table 4.3.2B, you show that the rate of PTLD among EBV+ recipients in the Belatacept experience is similar to the incidence as reported by USRDS. This alone, however, may not suffice to show that there is no increased risk among the EBV+ population. Note that a comparison to the incidence as reported by CTS would be less favorable to Belatacept. We further note that 5 EBV+ patients in the Belatacept treatment arms developed PTLD compared to none in the CsA treatment arms. We recognize that follow-up data beyond 18 months exists for more than 600 patients. Fewer patients, however, have follow-up data considerably beyond 21 months. In addition, the trials were remarkable for the high rate of CNS PTLD. Past experience with PTLD suggests that

CNS PTLD is usually a relatively late event. We agree that the risk is greater for the EBV- recipient population and we recognize that, to date, all reported cases of PTLD have occurred within the first 18 months post-transplant. We have not yet concluded, however, that any increased PTLD risk is confined to EBV- patients or that the risk is limited to the first 18 months.

Review of the Briefing Document suggests that the patients who received Belatacept were not generally over-suppressed. The treatment arms demonstrated rather similar profiles of systemic infections (looking at both overall infections and infections specific to the transplant population such as CMV, BK, HSV, and TB – see Table 3.2.6B, p.29; Table 3.3.6B, p.41). The concerning signals, such as they were, related specifically to viral-related adverse events in the CNS: 8 cases of CNS PTLD and 1 case of PML (compared 0 cases of CNS PTLD and 0 cases of PML in the CsA arm). As you note, the degree of CNS involvement in the Belatacept-associated PTLD is disproportionate to historical averages (62% vs 11-13%). The incidence of non-CNS PTLD cases associated with Belatacept, however, were comparable to that seen in the CsA control arm (2 for MI Belatacept, 3 for LI Belatacept, and 2 for CsA).

While it is difficult to interpret the significance of a single incident of PML, some context is provided by literature which suggests an incidence of PML on standard MMF-containing immunosuppressive regimens of 14.4 cases per 100,000 patient-years (Transplantation 86(10): 1474-8, Nov 27, 2008). This single episode of PML in the Belatacept trials would translate to an incidence approaching 100 cases per 100,000 patient-years. These two signals may represent the earliest clinical data to suggest that Belatacept may have a particular impact on CNS immunity. The Agency would like to know whether you have entertained a similar concern. Certainly an alternate explanation of the unusually high rate of CNS PTLD may emerge and the case of PML may prove isolated. It would seem prudent, however, to have a heightened alertness for other signals that might support this explanation. Such signals would include (but not be limited to) cases of encephalitis (HSV, CMV, or other), viral meningitis, and additional cases of CNS PTLD and/or PML.

One alternate explanation could relate to the greater requirement for use of lymphocyte depleting agents to treat rejection episodes in the Belatacept arm. It is noted from Table 4.3.2A of the Briefing Document that use of "T Cell Depleting Agents" corresponded to a HR of 5.32 for PTLD incidence and 6.79 for CNS PTLD incidence among the Belatacept patients. It would be informative to have greater information about precisely what "T cell depleting agent" each patient who developed PTLD received. It would also be important to know whether these patients received treatment with rituximab (a B cell depleting agent). Such an alternative explanation, however, would still not account for the unusual predominance of CNS PTLD.

Beyond the history of exposure to lymphocyte depleting agents, additional information regarding the PTLD cases identified in the phase 2 and 3 trials would be helpful. Full reports (including the EBV status of the recipients and donors) of the 13 cases of Belatacept-related PTLD may help elucidate whether these cases are similar or distinct

from those typically seen in the transplant population. If available, biopsy details regarding cell type, clonality, virological studies, and architectural background would be helpful. One would hypothesize that these will prove to be EBV-driven B cell lymphomas, but it is important to exclude other possibilities (e.g., that these events are actually EBV-negative PTLDs or T cell PTLDs). A review of the interventions performed in response to the diagnoses (e.g., changes to IS regimens, treatment with rituximab or other agents) and the subsequent outcomes achieved may also help inform plans for future courses of action.

Discussion: *The analysis of BMS indicated that the trough belatacept concentrations in subjects with and without PTLD were similar. BMS stated that because of the limited number of PTLD cases, an exploratory graphical POPPK analysis will be performed. The same exposure-response analysis will be done for PML.*

FDA recommended that theMMF doses and the MPA levels be mapped out in the BLA submission. BMS responded that the status of the MPA PK substudy was underway and will be included in the BLA. The preliminary data showed that an overall MPA exposure was about 37% higher in the belatacept treated subjects than the CsA treated subjects.

FDA recommended that BMS compare the belatacept rates to PTLD rates in the USRDS. BMS described the review of their data for other CNS infections and neoplasms and found few primary CNS infections and no primary CNS malignancies (slide 14 and 15). The few CNS infections were primarily cryptococcal meningitis, predominantly in subjects receiving the MI regimen. BMS presented their hypothesis for PTLD and the incidence of CNS lymphomas (slides 17 and 18). FDA mentioned about the Pgp efflux of CsA from the CNS (blood brain barrier; BBB) and questioned whether belatacept crosses the BBB. BMS stated that currently there are no data to support the ability of belatacept to cross the BBB. FDA suggested that a discussion of this topic should be included in the BLA submission.

BMS gave additional details of PTLD and stated that the investigator's brochure will have detailed outlines of the cases of PTLD (histopathology, treatment by each individual). FDA inquired if PK data for belatacept concentrations was available. BMS stated that blood samples were not taken at these time points, however they would be able to extrapolate the data. BMS also stated that they would provide additional information of when subjects developed PTLD with respect to the discontinuation of belatacept and addition of other agents.

<u>Questions 4:</u> Identified risk factors (particularly EBV status) can support risk minimization approaches to PTLD. In the transplant field, risk communication and monitoring of risk minimization may be facilitated by the relatively small transplant community and a focused network of health care providers. While still being developed, we have explained our current thinking regarding risk minimization approaches for PTLD in Section 4.3.4.

Does the FDA agree that the appropriate measures to minimize this risk are being considered?

FDA: In Section 4.3.4 of the Briefing Document, you state that you will exclude EBV negative recipients, recommend use of CMV prophylaxis, and provide information to transplant physicians regarding the populations at heightened risk of PTLD development.

These seem reasonable first steps. The association between CMV disease and PTLD is uncertain: some studies have made this link, but several others have failed to confirm this association. Efforts to demonstrate that ganciclovir may prevent PTLD through a direct effect on the EBV virus have so far failed to show benefit. Use of CMV prophylaxis, however, is standard-of-care and its pre-emptive use represents a reasonable course of action. Excluding the EBV naïve population should address the risk of PTLD with some degree of efficacy, though the Agency notes again that 5 Belatacept-associated PTLD cases were reported within the EBV+ population while no CsA-associated PTLD cases were reported within the EBV+ population.

Additional measures that could further address the risk would include monitoring EBV viral loads and EBV-specific cytotoxic T lymphocyte responses. Some degree of uncertainty exists regarding the sensitivity and specificity of these risk markers. While PTLD patients clearly have higher EBV viral loads than non-PTLD transplant recipients, it is not clear what level represents a threshold predictive for PTLD. Further, no consensus exists regarding whether EBV-DNA load is best measured in plasma, PBMCs, or whole blood. Similarly, while diminished EBV-specific CTL responses may correlate with a higher risk of PTLD, no clear thresholds have been established.

These are questions that will require further (but prompt) thought and discussion. Given that approximately 75 EBV- recipients of kidney transplantations are currently receiving Belatacept, institution of an approach to viral load monitoring is critical. We note from the general correspondence received from Dr. Mary Christian on November 26, 2008 that the you plan to

1. provide an Investigator's Brochure update to communicate the PTLD data,
2. require that all patients be re-consented with a revised Informed Consent form,
3. institute potential additional monitoring for patients who are currently enrolled.

We look forward to discussing the progress made in these areas at our December 15, 2008 meeting.

Discussion: *BMS described the ongoing and planned actions related to risk management (see slides 24 and 25). The FDA inquired about what actions would be taken after an EBV (-) subject seroconverts. BMS will collect data and address these issues in their action plan. FDA asked if the investigator's brochure (IB) mentions PML and BMS reassured the Agency that information regarding PML is included in the IB.*

Question 5: The key data from the SCD study and the ECD study are provided in Section 3. The accumulating longer-term data is discussed in Section 4, where the key issues are addressed.

What are your initial impressions of the Phase 3 data and the issues identified?

FDA: Please see answers 1-4. These are the main issues identified.

Additionally, given the results with the acute rejection endpoint, how will the efficacy of Belatacept be concluded based on the results from these studies (i.e., how do we know that the increase in rejection and the increase in GFR is not merely due to the removal of CSA)? As with all non-inferiority studies, you will need to discuss how the efficacy of Belatacept can be determined based on the results the pivotal non-inferiority studies. We recommend that this information be included as part of the study report. We recommend that you address the following three pieces of information, as outlined in ICH-E9 and in more detail in ICH-E10, to explain "why the drugs should be considered effective in the study" as stated in 21 CFR 314.126.

1. Evidence of the historical sensitivity to drug effects. This would include a data-driven estimate of the smallest effect size (as specified in ICH -E10) that the control would have over what would have been expected from a placebo arm in this study, if one were included. Note that in this study, a placebo arm would consist of the test regimen without Belatacept.
2. An explanation for why the chosen magnitude of the loss of effectiveness would be clinically acceptable.
3. An evaluation of the constancy of the effect of the control in the current trial, e.g. patient populations, definitions of endpoints, timing of endpoints etc. as they were used in the previous trials that were used to determine the effect size (point 1 above) and how they relate to the current trials under review.

Discussion: *The FDA requested that BMS justify the efficacy of belatacept given the non-inferiority design, specifically justify the selected NI margins for AR. BMS agreed. FDA stated that BMS can submit the justification for review prior to the submission of the BLA. FDA agreed that the justification for the non-inferiority margin can be included in the Clinical Efficacy Summary instead of the study reports.*

Question 6: We plan to prepare a BLA for submission in Jun-2009 (see Section 5, Regulatory Filing Plan Strategy). This application is primarily driven by our desire to include accumulated long-term data. (b) (4)

(b) (4)

Does the FDA agree with our filing plan?

FDA: This is best discussed at our December 15, 2008 meeting.

Discussion: *BMS stated that their plan for June 2009 BLA submission is to allow for additional accumulation of data beyond the one year primary endpoints with median 2 year exposure. FDA stated that the following information should be included in the BLA submission:*

a) *Other safety signals (for example, FDA noted that the median onset of PML is approximately 37 months)*
b) *The CsA trough concentrations seem to be high at month 12. Follow-up with 24 month data for CsA levels*
c) *Additional data on risk of PTLD in EBV (+) patients*

Additional discussion

FDA stated that the Office of Surveillance and Epidemiology would be present at the Pre-BLA meeting and would review the draft risk management plan. FDA requested that BMS submit a written summary of the status of the (b) (4).

ACTION ITEMS

1. FDA will provide additional comments on the interpretation of the extrapolation of GFR benefit.
2. BMS will provide a response to FDA clinical pharmacology comments regarding exploration of the contribution of viral and/or host genetic factors with respect to PTLD and PML.
3. BMS will investigate the brain level of belatacept (BBB).
4. BMS will provide justification of the non-inferiority margin before the BLA submission and upon receipt, FDA will review the justification.
5. BMS will provide a written summary of the (b) (4) status.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 9418	BRISTOL MYERS SQUIBB	Belatacept [LEA29Y (BMS-224818) (human, recombinant, CHO cells, Bristol-Myers Squibb) to CD80 and CD86]

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/s/

EILEEN E NAVARRO ALMARIO
03/11/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 9418

Bristol-Myers Squibb Company
Attention: Meena R. Bakhshi, Ph.D.
Manager, Global Regulatory Sciences-CMC
P. O. Box 5400
Princeton, NJ 08543-5400

Dear Dr. Bakhshi:

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

We also refer to the teleconference meeting held between representatives of your firm and the FDA on July 28, 2008. The purpose of the meeting was to discuss and obtain concurrence on the content and format of the CMC section of the 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, contact Hyun J. Son, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Marc Cavaille-Coll, MD, PhD
Medical Team Leader
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	July 28, 2008
TIME:	12:30 p.m.-2:00 p.m.
LOCATION:	Teleconference
APPLICATION:	IND 9418
DRUG NAME:	Belatacept
TYPE OF MEETING:	Pre-BLA CMC
MEETING CHAIR:	Steven Gitterman, MD, PhD
MEETING RECORDER:	Hyun Son, Pharm.D.

FDA ATTENDEES: Division of Special Pathogen and Transplant Products (DSPTP)

Renata Albrecht, MD	Division Director
Steven Gitterman, MD, PhD	Division Deputy Director
Marc Cavaille Coll, MD, PhD	Clinical Team Leader
Arturo Hernandez, MD	Clinical Reviewer
Patrick Archdeacon, MD	Clinical Reviewer
Ergun Velidedeoglu, MD	Clinical Reviewer
Susan Kirschner	Acting Associate Chief, Laboratory of Immunology
Jack Ragheb, MD,PhD	Senior Regulatory Research Officer
Michelle Clark-Stuart	Office of Compliance
Philip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader
Gerlie Gieser, PhD	Clinical Pharmacology Reviewer
Shukal Bala, PhD	Microbiology Team Leader
Aaron Ruhland, PhD	Microbiology Reviewer
William Taylor, PhD	Pharm/Tox Team Leader
Rama Dwivedi, PhD	Pharm/Tox Reviewer
June Germain, MS	Regulatory Project Manager
Sherry Spriggs, MPH	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Mary Christian, PharmD	Director, Global Regulatory Sciences
Helen Haggerty, PhD	Director, Immunotoxicology
Jeffrey Gelb, MD	Vice President-Full Development Team Lead LEA29Y
Meena Bakhshi, PhD	Manager, Global Regulatory Sciences-CMC
Claudia Arana, Ph. D.	Group Leader, Stability
Michael Grace, Ph.D.	Director, Protein Therapeutics Development/Bioanalytical Sciences
Madhav Kamat, Ph.D., R.Ph	Sr. Principal Scientist, Biopharmaceutics
Denise Perniciaro	Director, Global Regulatory Sciences-CMC
Mark Rosolowsky, Ph.D	Ex. Director, Global Regulatory Sciences-CMC
Joyce Whitehead, Ph. D	Group Leader, Manufacturing Support

BACKGROUND:
Belatacept is a protein being developed by Bristol-Myers Squibb (BMS) as an immunosuppressant for the prophylaxis of rejection in renal transplant recipients. The sponsor requested a pre-BLA CMC meeting to discuss and reach agreement on the format and content of the CMC section for the future BLA submission. Briefing package was submitted on June 27, 2008. Preliminary comments on the questions posted in the briefing package were e-mailed to the sponsor on July 22, 2008. For the purpose of the minutes, BMS questions are in normal text, Agency's preliminary comments are in **bold** text, and the discussions are in *italicized* text.

DISCUSSION

Question 1

Does the Agency agree with the proposed portfolio of tests for belatacept drug substance and drug product to support the BLA submission? (Refer to section 7)

FDA: The tests proposed for belatacept DS and DP are essentially those described in the BLA and PMC for abatacept. A number of questions arose during the abatacept BLA and PMC reviews which remain unresolved and these issues should be addressed with regards to belatacept in the BLA submission and include the following points:



(b) (4)

Discussion
BMS stated that they would provide the requested information in the BLA submission. BMS specified that belatacept DS will be characterized in the BLA. With regard to the cell-based bioassay, BMS stated that the belatacept bioassay was 2-3 fold better than abatacept due in part to the completely roboticized plate loading. BMS will provide additional information regarding the bioassay in the BLA. BMS stated that they are seeing correlations between the (b) (4) *results and the bioassay results for belatacept in forced degradation and stability data set. This data will be provided in the BLA submission.*

The Division inquired about being able to distinguish abatacept and belatacept in the (b) (4) *method. BMS replied that there is no distinction in the* (b) (4) *assay and will have to look into the data further and present the findings in the BLA. BMS clarified regarding the identity testing, that there will be a release test with tryptophan to distinguish between belatacept and abatacept and that they will use the CE method as the primary ID test. FDA requested BMS to provide trend data for release lots showing separations time between abatacept and belatacept. FDA also requested that BMS provide a SOP specifying steps that the technician would follow if separation between abatacept and belatacept could not be achieved. The SOP will be included in the BLA.*

FDA stated that the proposed DS/DP portfolio of tests in the package appears acceptable in support of the BLA submission except as indicated in Question 1 above.

Question 2

a) Does the Agency have any comments regarding the overall stability plan for belatacept drug substance and drug product to support the BLA submission?

FDA: Although the proposed plan appears acceptable, we will not be able to make a definitive conclusion until we review the information in its totality. Your stability program should monitor potential degradants as identified in your characterization of the product subjected to various stress conditions. A measure of large protein aggregates (1um - < 50 um) should be included in the stability program for drug product. The proposed expiry dating for the drug substance should reflect the current amount of real time stability data available to support the proposed commercial storage conditions. (b) (4) .

Discussion

BMS agreed with the Agency's recommendations and clarified that BMS' intent is to support storage of the drug substance for a cumulative length of time of (b) (4)

BMS requested clarification in regard to the Agency's request for a measure of large protein aggregates for drug product. The Agency clarified that we are interested in the contribution of subvisible particles in the range of 1-10 microns. The Agency further explained that new assessment criteria are being applied, beyond the current USP for particulate matter due to the potential impact on product quality. FDA requested that BMS monitor the formation of particulate matter in the range from 1-10 microns in long term stability studies (for characterization and comparability), which could be obtainable with the use of current instrumentation.

Question 3

A comparability protocol with pre-specified acceptance criteria to support implementation of an optimized drug substance manufacturing process will be included in the BLA. The comparability plan is described in the meeting background document. Does the Agency have any comments? (Refer to section 9)

FDA: The agency recommends that the (b) (4) **drug substance manufacturing process and related matters be addressed separately from the original BLA submission as the proposed changes to the** (b) (4) **that are not discernable by physico-chemical tests. Thus, in addition to a robust physico-chemical comparison, a comparative pharmacokinetic analysis should be performed. In this situation, a comparability protocol provides little benefit since agency approval of the proposed change prior to marketing the post change product would still be required.**

Discussion
BMS acknowledged FDA's comments and requested clarification as to why the Agency believes physico-chemical comparison would not be sufficient to demonstrate comparability. FDA indicated that with previous experiences, the types of changes result in changes to the molecule that would require a PK study. Comparability protocol would not be appropriate and without seeing the data, it cannot be determined that a PK study would not be needed. The agency strongly recommended that the (b) (4) *drug substance manufacturing process and related matters be addressed separately from the original BLA submission.*

Question 4

A comparability protocol with pre-specified acceptance criteria, to support implementation of a (b) (4) will be included in the BLA. The comparability plan is described in the meeting background document. Does the Agency have any comments? (Refer to section 10)

FDA: As the addition of a (b) (4) , the agency recommends this submission be bundled with the change in drug substance manufacturing (see response to Ques. 3 above) to avoid any potential delay in completion of the original review.

Discussion
BMS stated that the (b) (4) for belatacept is an independent change and not linked to the (b) (4) drug substance manufacturing process. Therefore, BMS proposes to include the comparability protocol for the (b) (4) in the BLA. The FDA agreed that including a comparability protocol for drug product in the belatacept BLA would be appropriate. FDA also requested that BMS conduct stability studies on drug product material incorporating this change.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 9418	BRISTOL MYERS SQUIBB	Belatacept [LEA29Y (BMS-224818) (human, recombinant, CHO cells, Bristol-Myers Squibb) to CD80 and CD86]

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

/s/

MARC W CAVAILLE COLL
02/05/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 9418

Bristol-Myers Squibb Company
Attention: Mary Christian, PharmD, MBA
Director, Global Regulatory Sciences
P. O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Christian:

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

We also refer to the meeting held between representatives of your firm and the FDA on April 7, 2008. The purpose of the meeting was to discuss and obtain concurrence on the content and format of a planned 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 Judit Milstein at (301) 796-0763.

Sincerely,

{See appended electronic signature page}

Steven Gitterman, MD, PhD
Deputy Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	April 7, 2008
TIME:	12:00 a.m.-1:00 p.m.
LOCATION:	Teleconference
APPLICATION:	IND 9418
DRUG NAME:	Belatacept
TYPE OF MEETING:	Pre-BLA

MEETING CHAIR: Steven Gitterman, MD, PhD

MEETING RECORDER: Judit Milstein

FDA ATTENDEES: Division of Special Pathogen and Transplant Products (DSPTP)
Steven Gitterman, MD, PhD, Division Deputy Director
Marc Cavaille Coll, MD, PhD, Clinical Team Leader
Karen Higgins, ScD, Statistics Team Leader
Cheryl Dixon, PhD, Statistics Reviewer
Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader
Gerlie Gieser, PhD, Clinical Pharmacology Reviewer
Shukal Bala, PhD, Microbiology Team Leader
Aaron Ruhland, PhD, Microbiology Reviewer
Susan Kirschner, PhD, Product Quality Team Leader
Judit Milstein, Chief Project Management Staff

EXTERNAL CONSTITUENT ATTENDEES:
Mary Christian, PharmD, Director, Global Regulatory Sciences
Pushkal Garg, MD, Executive Director, Belatacept Medical Lead
Deborah Gilman, Associate Director, Global Document and Dossier Management
Suzette Girgis, MS, PhD, Associate Director, Discovery Medicine and Clinical Pharmacology
Helen Haggerty, PhD, Director, Immunotoxicology
Margo Herron, Director, Regulatory Affairs, Washington Liaison Office
Jeffrey Gelb, MD, Vice President-Full Development Team Lead LEA29Y
Chen-Sheng Lin, PhD, Director, Global Biometric Sciences
Tifani McCann, PhD, Group Director, Global Biometrics Sciences, Immunology
Amit Roy, PhD, Associate Director, Strategic Modeling and Simulation

BACKGROUND:
Belatacept is a protein being developed as an immunosuppressant for the prophylaxis of rejection in renal transplant recipients. The sponsor requested this pre-BLA meeting to discuss and reach agreement on the format and content for the future BLA submission.
Briefing package was submitted on February 29, 2008.
Preliminary comments on the questions posted in the briefing package were e-mailed to the sponsor on April 4, 2008. An addendum to question #3 was sent to the sponsor on April 28, 2008.

For the purposes of these minutes, questions posted by the sponsor in their briefing package are in **bolded** font, preliminary comments are in *italics*, and discussions during the meeting are in normal font.

Question 1: Is the proposed format and overall content of the BLA described in this briefing book acceptable to the FDA?

Preliminary Responses: Yes, with regard to the PK datasets. Refer also to our responses to your Clinical Pharmacology Questions.

Discussion: No additional comments

Question 2: Would the FDA find provision of the data sets in eCTD format acceptable, as BMS is proposing, or is the CDISC format preferred/essential for review?

Preliminary Responses: Datasets submitted in accordance with the guidance provided in Study Data Specifications *are acceptable. CDISC/SDTM is not a requirement at this time. To ensure a successful review of the BLA, it is recommended that sham analysis datasets for the primary and major secondary efficacy analyses be submitted for review closer to the BLA submission.*

Discussion: The Division would like the sponsor to submit the analysis datasets for the primary and secondary endpoints for efficacy, and the primary safety analyses before the filing of the BLA. The datasets can consist of dummy data. .

Question 3: Does the FDA agree that these nonclinical studies are sufficient to support the filing and review of the BLA?

Preliminary Responses: The preclinical studies pertaining to activity listed in Table 4.1 of the briefing package appear to be appropriate for filing the BLA. Please ensure that the study reports include details of the experimental design and results for our review.

Discussion: No additional Comments.
Note: The Division issued an addendum to the preliminary comments on April 28, 2008.

Question 4: Does the FDA have any comments on the PPK analysis plan previously submitted?

Preliminary Comments:

a. *Regarding the Population PK analysis plan, we recommend that you explore, in addition to age, gender, race, body weight, albumin, and GFR, the effect of concomitant medications (e.g., sirolimus, azathioprine) and concomitant diseases (e.g., diabetes) on the clearance of belatacept.*

Discussion: The sponsor will include the additional covariates to the extent that the available data allows.

Preliminary Comments:

b. *We note that you have fully characterized the PK of belatacept in stable renal transplant patients receiving maintenance belatacept doses of 5 mg/kg. It is also important to understand fully the PK of belatacept 10 mg/kg during the early post-transplant period because it is at this critical stage that acute rejection is more common, and also since the belatacept less-intensive (LI) regimen being evaluated in pivotal Phase 3 trials was modified to add an extra dose of 10 mg/kg dose on Day 5. We also note that Study IM103047 will explore PK/PD and exposure-response*

relationships, evaluate the effect of proteinuria on the urinary excretion of belatacept, assess immunogenicity, and monitor belatacept trough concentrations in renal transplant patients. Furthermore, the findings of this PK/PD study could assist in establishing the mechanism of action of belatacept in preventing renal transplant rejection. Therefore, we expect you to provide at the time of the BLA submission, information on the full PK characterization of belatacept 10 mg/kg, as well as the other findings of Study IM103047 that are available at that time.

Discussion: The sponsor clarified that the full PK characterization of the 10 mg/kg dose will be performed during the Population PK analysis. The sponsor also indicated that 4-months PK data obtained from Study IM 103047 will be included in the original BLA submission.
With regard to a question from the Division on the use of pharmacodynamic biomarkers, the sponsor indicated that data on the CD86 receptor occupancy will be included in the original BLA submission.

The Division concurred with both proposals.

Question 5: Does the FDA agree that the clinical pharmacology studies listed herein are sufficient to support the filing and review of the BLA?

Preliminary Comments: Please refer to our responses to the Clinical Pharmacology questions.

Discussion: No additional comments

Question 6: Does the FDA agree with this approach to characterizing MPA levels in a belatacept-based vs. a CsA-based regimen?

Preliminary Comments:

a. *At this time we have no comments regarding the design of the planned substudy that will compare the MPA and MPAG concentrations between the belatacept-based and the CsA-based regimens. We expect the findings of this PK substudy to be included in the BLA submission.*

b. *While we understand that the goal of the substudy is to determine whether MPA levels differ between belatacept- and CsA-based regimens, we believe that determination of MPA concentrations are important towards the interpretation of the efficacy and safety of the belatacept + MMF regimen versus the CsA + MMF regimen in the ongoing Phase 3 studies. Thus, we recommend that, if possible, MPA concentrations be also determined in those patients who experience acute rejection or serious adverse events, as close as possible to the time of either of these events , and that these data be included in the BLA submission.*

Discussion: The sponsor clarified that the majority of patients are approaching or reached the 1 year point in time, and that some of these patients who experienced acute rejection or serious adverse events episodes have dropped out during the earlier part of the study; however the sponsor indicated their willingness to collect this data on MPA assessments in ongoing and future studies. The sponsor indicated that available data will be included in the BLA submission; additional data will be provided during the review period. The Division clarified that the BLA will not be considered officially filed until all the data are submitted to the FDA. The sponsor stated that they will bring back such information to their constituents and will see if adjustments could be made to expedite MPA data collection.

Question 7: Does the FDA agree with this proposal to not conduct formal drug-drug interaction studies with belatacept for the BLA?

Preliminary Comments: No additional formal drug-drug interaction studies are required. See also our responses to Clinical Pharmacology Questions 4 and 11.

Discussion: No additional comments.

Question 8: Does the FDA have any comments with respect to this approach to the exposure-response analysis?

Preliminary Comments: We will consider the findings of your Exposure-Response analysis when we review the proposed belatacept dosing regimen for the prevention of renal transplant rejection. Therefore, we recommend that you include the findings of your Exposure-Response analysis in the BLA submission.

Discussion: The sponsor proposed to include the data and preliminary analysis on Exposure-Response (ER) data at the time of the BLA submission, and a more comprehensive analysis with the 120 day safety update submission. The Division indicated that based on current guidelines, a BLA has to be complete at the time of initial submission and that these analyses are needed at the time of the filing, as it is very difficult to determine how important is this information in the context of the overall results of the studies. The Division indicated that the application would be reviewable without the comprehensive ER analyses, however the review clock might be extended if this information is provided at a later time and its review is relevant to the application.

Question 9: Does the FDA agree with the proposed data cutoffs for the BLA?

Preliminary response: Yes

Discussion: No additional comments

Question 10: Does the FDA agree with the planned evaluation and comparison of key efficacy data across the Phase 3 studies?

Preliminary comments: We agree with the proposed analysis plan to evaluate CAN. However; any positive findings that correlate with a better GFR will require full and individual evaluation of each phase 3 study to determine its relevance for labeling.

Discussion: The Division indicated that good compliance with biopsies will be key to interpreting these data, and expects that minimizing CAN (chronic allograft nephropathy) would result in better GFR (glomerular filtration rate); However, the interpretation of the clinical significance of these findings will be a review issue.
The sponsor indicated that their efforts to collect biopsy information is going well and that they have a collection rate approaching 80 %.

Question 11: Does the FDA have any comment regarding the proposed subgroup analyses of efficacy data?

Preliminary Comments: In addition to the covariates you propose to evaluate, we recommend that you explore the effects of concomitant medications (e.g., sirolimus, azathioprine) and concomitant diseases (e.g., active diabetes) on the clinical efficacy and safety of belatacept.

Discussion: The Division concurred with the sponsor's proposal to conduct exploratory analysis on theses covariates.

Question 12: Does the FDA have any comment on the planned analyses and presentation of the efficacy data collected beyond Year 1?

Preliminary comments: No clinical comments

Discussion: No additional comments

Question 13: Does the FDA have any comment on the approach to the analysis and presentation of these cardiovascular and metabolic endpoints in the BLA?

Preliminary comment: No clinical comments

Discussion: No additional comments

Question 14: Does the FDA agree on the planned primary safety analyses?

Preliminary Comment: Yes

Discussion: No additional comments

Question 15: Does the FDA have any comment regarding the proposed subgroup analyses of safety data?

Preliminary Comments: We are in general agreement with the proposed subgroup analyses of safety data. We recommend that the ECD (study IM 103027) analyses include the specific data on each donor that determined the ECD status (i.e. age, year with h/o hypertension, final SCr etc.) as well as any biopsy data available.

Discussion: The Division indicated that the sponsor's plan to look at ECD (Expanded Criteria Donors) status of the donor, including baseline biopsy and fibrosis information, is acceptable.

Question 16: Does the FDA have any comment on the proposed pooling of safety data in the BLA?

Preliminary comment: In addition to the proposed pooling of safety data analyses, the agency also expect the individual safety analyses in each phase 3 study.

Discussion: No additional comments

Question 17: Does the FDA have any comment on the presentation of safety data collected after the 1-year time points?

Preliminary comment: No clinical comments

Discussion: No additional comments

Question 18: Does the FDA have any comment on the planned assessment and presentation of immunogenicity data in the BLA?

Preliminary comments: You intend to provide immunogenicity data from samples obtained during belatacept treatment and up to 8 weeks after termination of belatacept treatment. Please provide data from samples obtained at later time points after the termination of treatment if such data are available. The FDA is concerned that development of antibody responses may arise after 8 weeks due to the long half life of belatacept.

Discussion: The sponsor clarified that belatacept half life is approximately 8 days, and that an 8-week period represents 7 half lives. Therefore, they do not expect the development of antibody responses as the product would have washed out by then. The sponsor also clarified that based on the time course of belatacept Cmin concentrations in renal transplant patients (Study IM103100), the time to steady state was actually 8 weeks and 12 weeks for the LI and the MI regimens, respectively. The Division accepted the sponsor's clarification

Question 19: Does the FDA have any comment on the safety data from ongoing Phase 1 and 2 studies to be provided in the BLA?

Preliminary comment: No clinical comments

Discussion: No additional comments

Question 20: Does the FDA agree with the proposed plan for inclusion of subject narratives in the BLA?

Preliminary comments: FDA expects the CRF for all the reported SAE and all patient discontinuations.

Discussion: The Division indicated that they would like to see in the original submission at least the CRFs for all deaths, graft loses, serious AEs (drug and not drug related), and premature discontinuation of study medication. The sponsor expressed their concern on this request, as 70-80% of the patients would experience an AE that falls in these categories.
As this issue still needs concurrence, it was agreed that the sponsor will submit to the Division their proposal for which CRFs and narratives for selected AEs will be submitted, for both belatacept and comparator arms, and agreement on this issue will be reached after the meeting. The sponsor also agreed to propose a timeframe for potential requests on specific CRFs the Division might request during the review of the BLA.

Question 21: Does the FDA agree that the completed and ongoing evaluations outlined above are sufficient to characterize the effects of belatacept on the QT interval?

Preliminary comments: Comments on the effects of belatacept on the QT interval are being evaluated by the QT Interdisciplinary Review Team (QTIRT). We will provide responses to this question at a later date.

Discussion: The Division indicated that the QTIRT review on the effects of belatacept on QT interval was complete and that no further studies are needed.

Question 22: Does the FDA have any comment on the plans to provide a safety update during the review period?

Preliminary comments: No clinical comments

Discussion: No additional comments

Question 23: Does the FDA have any comments that would inform the planning of the Risk Evaluation and Mitigation Strategy assessment?

Preliminary comment: The final determination for the need of a Risk Evaluation and Mitigation Strategy plan would depend on the review of the data.

Discussion: No additional comments.

Linked Applications	Sponsor Name	Drug Name
IND 9418	BRISTOL MYERS SQUIBB	Belatacept [LEA29Y (BMS-224818) (human, recombinant, CHO cells, Bristol-Myers Squibb) to CD80 and CD86]

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

/s/

STEVEN R GITTERMAN
06/02/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

February 20, 2008

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Attention: Mary Christian, Pharm.D., M.B.A.
Director, Global Regulatory Sciences

Re: Designation request # 07-2539

Dear Dr. Christian:

Reference is made to your request for orphan-drug designation submitted November 19, 2007, of belatacept for "prophylaxis of organ rejection in renal allograft recipients." Please also refer to our letter of November 21, 2007.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan-drug designation of belatacept is granted for *prophylaxis of organ rejection in renal allograft recipients.* Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you need further assistance in the clinical development of your drug, please feel free to contact Jeffrey Fritsch, R.Ph., at (301) 827-0989. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

Timothy R. Coté, M.D., M.P.H.
Director, Office of Orphan Products Development

cc:

HF-35/OP File # 07-2539
HF-35/Chron
HF-35/EMcNeilly
jb 2/15/08
DESIGNATION GRANTED

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our Reference: BB-IND 9418

Bristol-Myers Squibb
Attention: Benjamin R. Johnson, Ph.D.
Associate Director, Global Regulatory Strategy
P.O Box 4000
Rt. 206 and Provinceline Road
Princeton, NJ 08543 - 4000

SEP 22 2005

Dear Dr. Johnson:

Please refer to your **Investigational New Drug Application (IND)** for "Belatacept [LEA29Y (BMS-224818) (human, recombinant, CHO cells, Bristol-Myers Squibb) to CD80 and CD86]," and to your August 5, 2005, **Request For Special Protocol Assessment**, received August 8, 2005. The protocol (#IM103008) is entitled "Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT)."

We have completed our review of your submission and, based on the information submitted, we have the following responses to your questions:

Questions:

The pivotal Phase 3 studies are designed to test the following hypotheses:

(1) non-inferiority in patient and graft survival at 12 months
(2) superiority in preservation of renal function at 12 months and
(3) non-inferiority in acute rejection at 12 months

The renal function endpoint is defined as a glomerular filtration rat of< 60 mL/min at Month 12 and/or a decrease of > 10 mL/min in GFR from T 3 to 12, measured using isothalamate clearance. At the End-of-Phase 2 meeting FDA requested that calculated estimates of GFR based on the MDRD/Levey formula be provided as secondary endpoints. Both Phase 3 protocols include these calculated me as key secondary endpoints.

1. *Does the FDA agree that the co-primary renal function endpoint as defined in section 3.1.3 of the protocol is an appropriate and medically relevant endpoint for this pivotal Phase 3 study?*

   FDA Response: The protocol specifies that success on the first primary endpoint of subject and graft survival by 12 months is a prerequisite for conducting further evaluation of other endpoints.

We agree that the co-primary renal function endpoint is appropriate and medically relevant to the proposed study. We acknowledge that in the submitted accompanying addendum you state that both non-inferiority in death and graft loss and superiority in renal function are necessary for the study to support approval.

As discussed at the End-of-Phase 2 meeting, BMS expects data on measured GFR will not be available for all patients at all time points specified in the protocol. The approach to imputation of missing data is provided in Section 4.2.2 of the protocol.

2. *Does the FDA agree with BMS's strategy for imputation to address any missing measured GFR data?*

   FDA Response: The proposed imputation plan for the missing data is acceptable. Results on sensitivity analyses will also be important to assess the robustness of the study result.

Chronic therapy with cyclosporine (C5A) is associated with hypertension, diabetes, and hyperlipidemia. Based on the experiences of the Phase 2 study (1103100), BMS anticipates that CsA-treated patients will be treated more aggressively with concomitant therapy aimed at controlling these conditions. As discussed at the End-of-Phase 2 meeting, BMS intends to document differences in the use of concomitant therapies required to treat these co-morbidities, and describe these differences in product labeling. The relevant prespecified analyses are outlined in Section 4.2.2 of the protocol.

3. *Does the FDA agree that the methods to assess differences in concomitant therapy for hypertension, lipids, and diabetes mellitus are appropriate, and if positive, would be sufficient to support product labeling?*

   FDA Response: Yes, the Agency agrees that the methods proposed to assess the differences in concomitant therapy for hypertension, hyperlipidemia, and diabetes mellitus are appropriate. If the result is positive and demonstrates a meaningful difference, it may support description in the product labeling. The exact wording in the product label would be a review issue and would depend on the results.

4. *Is this approach for evaluating CAN acceptable to the FDA?*

   FDA Response: The Agency acknowledges the difficulty in obtaining protocol-mandated renal biopsies but thinks it is very important to obtain as complete a data set as possible. The proposed intent-to-treat analysis along with a secondary analysis of pre-selected sites striving for complete data collection represents an acceptable approach.

As response to the CHMP Scientific Advice, BMS is specifying biopsy prove as a third co-primary endpoint in the Study IM103008. This endpoint will be tested for non inferiority with a 20% margin. BMS has also defined an approach to the supportive analyses of acute rejection; especially to pre-define those analyses considered important for securing a positive benefit/risk assessment should all study endpoints be met with numerically more acute rejections with belatacept. In particular, an analysis by treatment group of acute rejections associated with residual effects on renal function will be conducted. This proposed analysis is based upon the observation that rejection episodes do not impact graft survival.

5. *Does FDA agree that the proposed analyses of biopsy proven acute rejection are appropriate to assess the clinical implications of acute rejection in the context of the overall benefit risk assessment?*

   FDA Response: A 20% non-inferiority margin for acute rejection has the potential to show a positive result for a product with a somewhat higher rate of acute rejection than control. The proposed analyses of the residual effects of acute rejection on renal function represent an appropriate approach to assessing the clinical implications of acute rejection episodes. We also acknowledge your accompanying addendum, which states that considering the relatively wide margin for non-inferiority, the acute rejection endpoint would not support a comparative labeling claim with respect to cyclosporine.

Regarding the design, endpoints, and planned analysis of Protocol IM103008

6. *Will this protocol provide the FDA with the data required to make an assessment of the use of belatacept for the prophylaxis of organ rejection in renal transplant recipients?*

   FDA Response: The protocol will provide the data required to make an assessment of the use of belatacept for the prophylaxis of organ rejection in renal transplant recipients.

7. *If the protocol meets its primary objectives, and demonstrates non-inferiority in death and graft loss along with superior preservation of renal function compared to CsA while excluding a 20% margin of non inferiority for acute rejection, does the FDA agree that a clinically meaningful benefit of belatacept in the prophylaxis of organ rejection in renal transplant recipients would be documented?*

   FDA Response: The FDA agrees that, in principle, if the study meets its objectives and demonstrates non inferiority in death and graft loss, superior preservation of renal function compared to CsA while excluding a 20% margin of non inferiority for acute rejection that the study would demonstrate a clinically meaningful benefit. However, the other results of the study would be scrutinized for whether they support the primary endpoints. In addition, to support approval the clinical benefits would need to outweigh any safety concerns observed.

We have determined that the design and planned analysis of your study does adequately address the objectives necessary to support a regulatory submission. This special protocol assessment can be modified to improve the study, if you submit a revised special protocol assessment and, FDA agrees in writing to the modification. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.
Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.
Effective August 29, 2005, the new address for all submissions to this application is:

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

If you have any questions, please contact the Regulatory Project Manager, Diana Willard, at (301) 796-0833.

Sincerely yours,

Kay Schneider for

Wendy Aaronson, M.S.
Acting Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our Reference: BB-IND 9418

OCT 19 2004

Bristol-Myers Squibb Company
Attention: Benjamin Johnson, PhD
Associate Director, Global Regulatory Strategy
Immunology, Inflammation, Pulmonary Products
Pharmaceutical Research Institute
P.O. Box 4000
Rt. 206 and Provinceline Road
Princeton, NJ 08543

Dear Dr. Johnson:

Please refer to your **Investigational New Drug Application (IND)** for "LEA29Y (BMS-224818)(human, recombinant, CHO cells, Bristol-Myers Squibb) to CD80 and CD86," and to the meeting held on September 21, 2004, between representatives of your firm and this agency. As requested in your letter of July 28, 2004, a copy of our memorandum of that meeting is attached for your information.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

Cristi Stark, MS
Regulatory Project Manager
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Summary

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

Memorandum

Date: OCT 19 2004

From: *Cristi Stark, DRMP, ODEVI, HFM-589*

To: IND 9418

Subject: Type B Meeting Summary

Meeting or Teleconference Date: September 21, 2004 **Time:** 11:00am-12:30pm

Location: WOC2, Conference Room G

Meeting Requestor/Sponsor: Bristol-Myers Squibb

Product: LEA29Y (BMS-224818) (human, recombinant, CHO cells, Bristol-Myers Squibb) to CD80 and CD86

Proposed Use: Treatment of solid organ renal transplant

Type of meeting: End of Phase 2

Meeting Purpose: To review the Phase 2 data from Study IM103100 and to reach consensus on BMS's plans for moving the development of LEA29Y forward in renal transplant.

Sponsor questions and FDA response:

1. ***For the pivotal registration trials, would the FDA accept co-primary endpoints of non-inferiority in death/graft loss at 12 months and superiority in renal function (measured by clearance of a true renal filtration marker such as iohexol) at 12 months to support registration of LEA29Y in renal transplantation?***

   Yes, if you are able to demonstrate that LEA29Y (as a part of a quadruple-drug regimen) is non-inferior to CsA with respect to patient death and/or graft loss at 12 months and that LEA29Y (as a part of a quadruple-drug regimen) is superior to CsA in preserving renal function at 12 months, the Agency would accept both co-primary endpoints in support of registration of LEA29Y in renal transplantation. However, you expect to have a large amount of missing data for iohexol-determined GFR and will impute the missing data using

the Levey formula for GFR. It is important to note that to assess superiority with respect to renal function it will be necessary to determine the impact of missing data and to demonstrate the clinical significance of the differences.

BMS responded that it is their intention to get as complete a dataset as possible.

The Agency would also recommend the following additions to the study to better evaluate the efficacy of LEA29Y in renal transplantation:

a. The addition of a secondary endpoint evaluating the GFR calculated by the Levey method at Months 3 and 12. This endpoint should have very minimal missing data and should give a reasonable idea of GFR in all subjects completing the study. Ideally, this secondary endpoint should be supportive of the primary endpoint analysis of renal function.

b. You should commit to following subjects for the primary endpoints of non-inferiority in patient death/graft loss and renal function at 24 and 36 months (You could file for the BLA after the 12-month timepoint data is available; however, the point is to plan your study upfront.).

2. ***BMS will propose margins for the non-inferiority testing of death and graft loss of 10% for the absolute difference between treatment groups. Is this margin acceptable?***

The proposed non-inferiority testing of death and graft loss of 10% for the absolute difference between treatment groups is acceptable as a prospective selection, and for use in setting sample size.

Given the difficulty of determining an accurate treatment effect size for CsA, and consequently uncertainty in the choice of a non-inferiority margin of 10%, the Agency notes that if the 95% CI of the difference is within a 5% margin that this would demonstrate strong support of the non-inferiority of LEA29Y compared to CsA; however, if the 95% CI of the difference is outside the 5% range but still within the 10% margin then establishing efficacy would be based on an assessment of the totality of the data.

3. ***The pivotal Phase 3 studies will be powered to detect a benefit in renal function at 12 months as a co-primary endpoint. The rationale, justification, and definition for this endpoint are described in Sections 8.2.3 and 8.2.4. Is the definition of this endpoint acceptable to the FDA?***

Yes, given the correlation between post-transplantation renal function and long-term renal outcome the proposed endpoint appears to be adequate. The Agency stresses however that every attempt should be made to limit the amount of missing data as large amounts of

missing data could compromise interpretation of the trial and may affect the ability of the Agency to draw conclusions as to the superiority of LEA29Y. Moreover, the Agency considers the surrogate marker of improved GFR at 1 year as being indicative of a possible long-term clinical benefit; however, although renal function at 1 year has been associated with long-term graft survival with currently used immunosuppressive therapies, the correlation has not been established with LEA29Y. Therefore, these data cannot be presumed to predict long-term graft survival with only the 1 year time point. Consequently, the Agency is asking you to commit to following the proposed co-primary endpoints to 24 and 36 months. Also, as noted in the answer to question #1, we request the addition of a secondary endpoint evaluating the GFR calculated by the Levey method at Months 3 and 12. This endpoint should support the primary endpoint, have minimal missing data, and should give a reasonable idea of GFR in all subjects completing the study.

BMS agreed.

4. *The pivotal Phase 3 studies will be randomized, controlled trials, blinded for LEA29Y doses, with blinded central biopsy assessment. However, for practical and medical reasons, blinding the drug regimen (CsA or LEA29Y) will not be feasible (due to both CsA monitoring needs and clinical decisions to be made based on this information). The endpoints will be assessed at 1 year based on an intent-to-treat (ITT) analysis. This analysis may include patients switched to a calcineurin regimen (or other rescue immunosuppressant regimens). Are these general principles acceptable for the purpose of pivotal registration studies?*

In general the Agency recognizes the difficulty of blinding drug regimen regarding CsA versus LEA29Y and consequently the study design proposed is acceptable. Given that the study is unblinded, it is particularly important that there is good compliance with all assessments, that subjects receive similar well-formulated management (e.g., standard of care CsA dosing/trough values), that clear rules are applied to all treatment arms when biopsies are warranted, and that subjects receive similar treatment for allograft rejection in all arms. Poor compliance would be a major problem in interpreting the results in this open-label trial design, especially if compliance was different across treatment arms.

BMS stated that it is their intention to conduct the trial in this manner; however, they recognize that there may be larger differences in the treatment of acute rejection.

5. *Chronic allograft nephropathy (CAN) is characterized by standardized histopathological findings on renal biopsy. Data from the completed Phase 2 study suggest that treatment with LEA29Y, rather than CsA, may result in a lower incidence of CAN. The pivotal Phase 3 study will designate CAN as a key secondary endpoint supporting the expected benefit on renal function. Explicit histological determinants of CAN will be described in*

the protocol. The incidence and severity of CAN will be assessed on post-baseline biopsies within 1 year (by blinded assessors).

a. ***Assuming that the study is positive on the co-primary endpoints; would the FDA accept a demonstration of a benefit in the key secondary endpoint of CAN for product labeling?***

Yes, given the seriousness of CAN in post-transplantation graft survival a robust positive finding would be an important benefit of LEA29Y and likely could be included in product labeling. Again, the Agency stresses that every attempt should be made to limit the amount of missing data as large amounts of missing data could compromise interpretation of the trial on this endpoint and may affect the ability of the Agency to draw conclusions as to the superiority of LEA29Y depending on the results and amount of missing data. Poor compliance with protocol biopsies would be a problem given the open-label study design. How do you propose to account for missing data?

BMS suggested the option of designating centers to deal with the compliance issues.

FDA added that in order to make a labeling claim, BMS must have good compliance in pre-specified centers.

Additionally, subjects may need to be followed longer than 1 year to ascertain whether LEA29Y reduces the frequency of CAN or rather only delays the onset of CAN. Consequently, the limitation of the 12 month data would need to be addressed in any labeling of LEA29Y. The Agency suggests that you perform exploratory analyses of the subjects with missing data to determine if there are factors that indicate inaccuracies in the point estimates or could bias the comparisons between study arms. For example if elevated S_{Cr} is strongly correlated with CAN and patients with elevated S_{Cr} are more common in the group with missing data this would suggest that the incidence of CAN might be underestimated by using the patients with available biopsies.

b. ***Given the difficulty in obtaining protocol-mandated renal biopsies in all subjects (particularly CsA subjects), it is expected that per-protocol biopsies would be obtained in approximately two-thirds of all subjects. BMS will seek FDA comment regarding this approach to the analysis of these data.***

The Agency recognizes the difficulty in obtaining protocol-mandated renal biopsies but thinks it is very important to obtain as complete a dataset as possible. Achieving only two-thirds of all subjects could prove problematic. What approaches could be considered to account for missing biopsies? One suggestion would be to pre-specify an analysis of protocol biopsies for those centers that are committed to a high rate of compliance.

BMS agreed.

6. ***The FDA had previously indicated that the endpoint of biopsy proven acute rejection was important, but should not be the primary endpoint in a pivotal Phase 3 study comparing LEA29Y to CsA. Given the substantial uncertainty regarding the clinical significance of subclinical rejection detected on routine biopsy, the Phase 3 program will define acute rejection as a clinico-pathological event requiring clinical evidence and biopsy confirmation. The definition of acute rejection is provided in Sections 8.3.2. Does the FDA find this definition acceptable?***

   The proposed definition of acute rejection would be acceptable with modification given the uncertain correlation between biopsy proven acute rejection (BPAR) in the absence of clinical signs or symptoms; however, this does not dismiss the potential importance of subclinical BPAR and given the uncertain correlation to CAN, the results would be relevant to assessing the clinical efficacy. The proposed definition should be modified to specify that subjects who receive treatment for rejection (e.g., corticosteroids or lymphocyte-depleting antibodies) based on a renal biopsy that demonstrated subclinical rejection should be considered as having had an acute rejection event.

   BMS stated that they considered this but had a concern around the difference in clinical practice and how the cases are handled. They do plan to capture the subclinical data and all information around it.

7. ***The diagnosis of acute rejection, as defined above, will require clinical evidence and biopsy confirmation. Other incidental histological observations typically classified as subclinical rejections will be noted, but because the clinical significance of these finding is not firmly established, they will not be considered a key measure of anti-rejection efficacy. Based on Phase 2 data, we also anticipate at least a modest ascertainment bias of subclinical rejections between the LEA29Y treatment groups and the CsA treatment group. This ascertainment bias will likely increase the relative incidence of subclinical rejection in the LEA29Y treatment groups. The proposed analyses of acute rejection and subclinical rejection are outlined in Section 8.7.2. Does the FDA find the proposed analyses of acute rejection and subclinical rejections acceptable?***

   Yes, the proposed analyses are acceptable. However, you should specify if you are testing superiority or non-inferiority, or just providing descriptive statistics.

   BMS stated they will provide descriptive statistics as there is no single descriptor to define this.

8. ***BMS also plans standardized blood pressure measurement, measurement of blood lipids, and the incidence of post-transplant diabetes mellitus (PTDM) as important secondary endpoints. Section 8 describes the proposed endpoints and analysis. BMS considers these additional potential benefits of LEA29Y in avoiding CNI toxicity to be clinically relevant, and would like to include them in product labeling. Does the FDA have any concerns with this approach?***

The selected endpoints may not be sufficient for clinical interpretation. You should first define the criteria that will be used for the diagnosis of hypertension, hyperlipidemia, and PTDM. For example, in the past the Agency has accepted the definition of PTDM as requiring insulin therapy to achieve glucose homeostasis for at least 30 days in a patient without previous history of diabetes mellitus. The Agency recommends analyzing the proportion of subjects requiring the initiation, or increase, of an antihypertensive, lipid-lowering, or antihyperglycemic medication(s) for treating hypertension, hyperlipidemia, and PTDM, respectively, based on accepted treatment guidelines. Analyses of the trial should include analysis of the values that triggered therapy for the aforementioned disorders. Please be aware that it may be difficult to assess differences between treatment arms due to the open-label design of the trial.

BMS agreed.

FDA added that PTDM will be the clearest endpoint to make a claim from as the other endpoints will be more difficult to determine differences.

(b) (4)

(b) (4)

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

[redacted] (b) (4)

12. ***At the August 20, 2000 pre-Investigational New Drug (IND) application meeting, the FDA indicated that a safety database of about 600 patients for 12 months is recommended to support the safety assessment of LEA29Y in renal transplantation. The proposed Phase 3 development program is designed to provide data to exceed this recommendation. Does the FDA have any further comments or recommendations about the scope of the Phase 3 safety database?***

The proposed safety plan is acceptable and the Agency also recommends an independent DSMB be established for each trial to monitor safety of LEA29Y.

13. ***This briefing package summarizes the toxicology data available for LEA29Y and the*** [redacted] (b) (4) ***In a prior discussion with FDA, the Agency agreed that BMS may use the*** [redacted] (b) (4) ***to support the LEA29Y clinical program. Does the FDA have any further comments or suggestions about the toxicology package?***

No, the Agency does not agree to use the [redacted] (b) (4) to support the LEA29Y clinical program. Specifically, BMS should conduct the reproductive and developmental toxicity studies to support its phase 3 clinical program. LEA29Y has two amino acid substitutions (L104E and A29Y) at the B7-binding region of CTLA4Ig. The substitutions significantly change the binding activity and biological property of LEA29Y [redacted] (b) (4)

14. ***This briefing package summarizes the clinical pharmacology studies planned for LEA29Y (see Section 11). Does the FDA agree that the proposed plan is adequate for the registration of LEA29Y in the target indication?***

Yes, the proposed plan is adequate.

(b) (4)

16. ***Does the FDA have any other comments about the Phase 3 development plan?***

All subjects should be randomized by site.

BMS is planning to randomize by site.

Issues Requiring Further Discussion:

BMS will follow up with FDA regarding the rationale for using (b) (4) to support the LEA29Y clinical program.

Action Items:

BMS plans on submitting a Fast Track Designation request as well as an SPA request (the SPA will be on one of the two studies).

Page 10, LEA29Y End of Phase 2 – September 21, 2004

FDA Attendees: Marc Cavaille-Coll, MD, PhD, OSPIDP/ODEIV
Wen-Yi Gao, PhD, DTBOP/ODEVI
Arturo Hernandez, MD, OSPIDP/ODEIV
Keith Hull, MD, DTBIMP/ODEVI
Iftekhar Mahmood, PhD, DTBIMP/ODEVI
Satish Misra, PhD, BTSS/OB
Jeffrey Siegel, MD, DTBIMP/ODEVI
Cristi Stark, MS, DRMP/ODEVI

Sponsor Attendees: Scott Batty, MD, Medical Director, Global Medical Affairs, Immunology
Fred Fiedorek, MD, Vice President, Global Clinical Research
Helen Haggerty, PhD, Associate Director, Toxicology
Margo Herron, Director, Regulatory Relations and Policy
Suzette Girgis, PhD, Associate Director, Clinical Discovery
Rusty Johnson, PhD, Associate Director, Global Regulatory Sciences
Nancy Krieger, MD, Director, Global Clinical Research
Elliott Levy, MD, Vice President, Global Clinical Research
Kannan Natarajan, PhD, Director, Clinical Biostatistics
James Rusnak, MD, PhD, Director, Global Clinical Research
Anthony Waclawski, PhD, Executive Director, Global Regulatory Sciences

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 125288	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Nulojix Established/Proper Name: belatacept Dosage Form: For injection, for intravenous use		Applicant: Bristol-Myers Squibb Agent for Applicant (if applicable):
RPM: June Germain		Division: Transplant and Ophthalmology 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)):

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

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 June 15, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR May 1, 2011
❖ 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):

☐ 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
❖ 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 FDA information Advisory

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

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

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

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

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

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

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

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

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *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]	6-16-11
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) AP June 15, 2011, CR May 1, 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.	June 1, 2011
• Original applicant-proposed labeling	September 24, 2010
• 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.	June 1, 2011
• Original applicant-proposed labeling	June 30, 2009, September 24, 2010
• Example of class labeling, if applicable	N/A
❖ 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	June 1, 2011, June 30, 2009
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	Acceptability February 28, 2011
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM August 28, 2009 ☒ DMEPA March 23, 2011 ☒ DRISK March 2, 2011 ☒ DDMAC March 10, 2011 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review 8-28-09, memo of filing meeting 8-27-09 ☐ Not a (b)(2) ☐ 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 drug designation • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	Orphan drug designation ☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	May 27, 2011 May 18, 2011

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

	May 13, 2011 April 22, 2011 March 16, 2011 March 1, 2011, February 23, 2011 January 25, 2011 January 20, 2011, December 21, 2010 December 8, 2010 November 12, 2010 October 7, 2010 October 1, 2010 September 29, 2010 September 23, 2010 August 3, 2010, March 16, 2010, February 25, 2010, February 22, 2010, February 19, 2010, January 29, 2010, January 27, 2010 (2), January 12, 2010, January 5, 2009, December 23, 2009, November 17, 2009, November 5, 2009, November 3, 2010, October 16, 2009, October 8, 2009, October 2, 2009, September 24, 2009, September 23, 2009, September 11, 2009, August 28, 2009,(2), August 19, 2009, August 17, 2009, August 4, 2009, February 8, 2008September 22, 2005 Emails: June 1, 2011, March 11, 2011, January 26, 2011, January 14, 2011, November 23, 2010, MArch 16, 2010, MArch 11, 2010, February 23, 2010, February 22, 2010, January 4, 2010, October 22, 2009, September 29, 2009, September 17, 2009, September 10, 2009, August 25, 2009(2), August 20, 2009, August 18, 2009, August 19, 2009, august 14, 2009, August 13, 2009, August 10, 2009
❖ Internal memoranda, telecons, etc.	Wrap-up meeting 3-22-11, March 25, 2011 CMC Tcon 3-22, 2011, REMS Tcon 3-23-11, Syringe and dosing Tcon 3-25-11, November 20, 2009, September 18, 2009, August 14, 2009
❖ 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 June 3, 2010
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg May 20, 2009, Dec.15, 2008, April 7, 2008

• EOP2 meeting *(indicate date of mtg)*	☐ No mtg September 21, 2004
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	CMC Pre-BLA July 28, 2008, February 1, 2011, September 27, 2010, September 1, 2010, July 23, 2010, August 25, 2009, May 20, 2009
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	March 1, 2010
• 48-hour alert or minutes, if available *(do not include transcript)*	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None June 15, 2011, May 1, 2010
Division Director Summary Review *(indicate date for each review)*	☐ None June 15, 2011, May 1, 2010
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 5-31-11, April 30, 2010
PMR/PMC Development Templates *(indicate total number)*	☐ None 10
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	None
• Clinical review(s) *(indicate date for each review)*	March 25, 2011, April 30, 2010, September 9, 2009,
• 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)*	In clinical review dated April 30, 2010 page 32
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None February 18, 2010
❖ 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)*	June 1, 2011 May 1, 2010 ☐ None June 8, 2011, April 30, 2010
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested March 9, 2010, DSI letters June 24, 2010, June 21, 2010, April 23, 2010, March 5, 2010 (3), February 26, 2010, January 11, 2010

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

Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None March 24, 2011, June 3, 2011
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None March 23, 2011, March 26, 2010
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None March 11, 2011, Feb 10, 2011, March 23, 2010, August 10, 2009
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
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None March 24, 2011, ~~August 12, 2009~~ March 24, 2010, August 12, 2009, November 23, 2009
❖ 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 April 22, 2010
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None March 28, 2011 May 1, 10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None May 6, 2011, April 30, 2010
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None May 2, 2011, April 29, 2010, August 11, 2009, August 12, 2009
❖ 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 March 7, 2011 March 22, 2010, March 23, 2010, August 19, 2009
❖ 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)*	Bo Chi CMC microbiology review page 11 and Susan Kirshner CMC TL review dated 5-6-11 page 4
☐ 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: June 2, 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 DRA.