

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125288Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

PMR Description: 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 will assess the prevalence of belatacept use and the characteristics of belatacept users, as related to the risk of PTLD, including Epstein-BarrVirus (EBV) and cytomegalovirus (CMV) serostatus. In addition, the study will collect information on adult kidney-only transplant recipients who switch to or from belatacept within one year post-transplant. (Protocol Number IM103074)

PMR Schedule Milestones:	Final Protocol Submission:	04/2012
	Study/Trial Completion:	04/2019
	Final Report Submission:	04/2020
	Other:	NA

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

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

Clinical trial experience leading up to approval suggests increased incidence of rates of post-transplant lymphoproliferative disorder PTLD, particularly PTLD in the central nervous system (CNS PTLD). Therefore, it is necessary to define the profile of Belatacept users post-approval, particularly Epstein-Bar Virus (EBV) and cytomegalovirus (CMV) serostatus as these variables are considered risk factors for PTLD post-transplant. United Network for Organ Sharing (UNOS) already collects data among kidney transplant recipients.

Boxed Warning/Contraindication states not to use belatacept in transplant recipients who are EBV seronegative or with unknown serostatus, therefore this study will evaluate how well prescribers are following the approved PI. Additionally, belatacept was studied in de novo patients during registrational trials; this observational study will also identify switch use (i.e. patients converted to belatacept after initial transplant period) and its implications.

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

Increased incidence of rate of post-transplant lymphoproliferative disorder PTLN, PTLN in the central nervous system (CNS PTLN) has been identified during registrational trials for belatacept especially in EBV seronegative patients. Therefore, it is important to define the profile of belatacept users post-approval, particularly Epstein-Bar Virus (EBV) and cytomegalovirus (CMV) serostatus as these variables are considered risk factors for PTLN post-transplant. In addition, defining EBV serostatus will provide information about compliance among the prescribers since belatacept is contraindicated and carries a boxed warning in patients whose EBV serostatus is either unknown or negative.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

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

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)

Agreed upon:

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

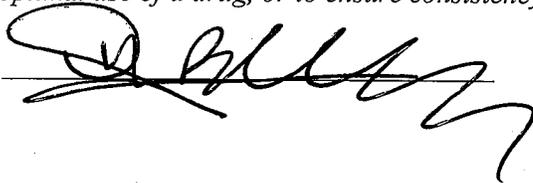
5. Is the PMR/PMC clear, feasible, and appropriate?

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

PMR/PMC Development Coordinator:

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

Ozlem Belen, MD, MPH
(signature line for BLAs)



6/1/2011

PMR/PMC Development Template

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

PMR Description: 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 PTLT, and outcome (survival or mortality). Incidence rates of PTLT in belatacept-exposed patients will be quantified beginning when 500 belatacept-exposed patients have at least 1 year of follow-up. Relative risks of PTLT 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)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/2012</u>
	Study/Trial Completion:	<u>04/2019</u>
	Final Report Submission:	<u>04/2020</u>
	Other: <u>Interim Analysis Report Date:</u>	<u>06/2014</u>

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

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

Clinical trial experience leading up to approval suggests increased incidence of rates of post-transplant lymphoproliferative disorder PTLT, particularly PTLT in the central nervous system (CNS PTLT). United Network for Organ Sharing (UNOS) already collects data relating to EBV and CMV serostatus, location of the PTLT, and survival outcome among kidney transplant recipients. This observational study will enhance our knowledge of the risk factors, better define this serious risk and its outcome among kidney transplant recipients exposed to belatacept.

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

Clinical trial experience leading up to approval suggests increased incidence of rates of post-transplant lymphoproliferative disorder PTLD, particularly PTLD in the central nervous system (CNS PTLD) and progressive multifocal leukoencephalopathy (PML).

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met in March 2010 (during previous review cycle) to discuss biologics license application (BLA) 125,288 for belatacept. Although several members agreed that safety was demonstrated, the majority of the Committee felt concern regarding the increased risk of PTLD with CNS involvement and PML. A registry was recommended to more precisely estimate the incidence of PTLD, and PML.

This registry is meant to collect near complete post marketing data on renal transplant patients exposed to belatacept to better define the incidence of PTLD and associated risk factors such as EBV and CMV serostatus as well as PML in a prospective manner.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

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

This will be a prospective registry of belatacept use in US adult kidney-only transplant recipients to determine the incidence rates of post-transplant lymphoproliferative disorder PTLN, PTLN in the central nervous system (CNS PTLN), and progressive multifocal leukoencephalopathy (PML) in US adult EBV seropositive kidney transplant recipients treated with belatacept in clinical practice. 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, timing of initiation of belatacept in relation to the transplant, location of the PTLN, and outcome (survival or mortality).

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

 Other

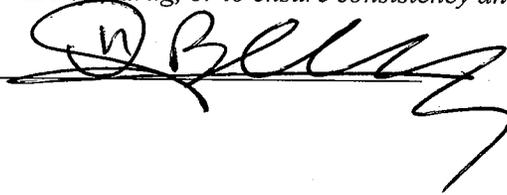
5. Is the PMR/PMC clear, feasible, and appropriate?

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

PMR/PMC Development Coordinator:

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

Ozlem Belen, MD, MPH
(signature line for BLAs)



6/1/2011

PMR/PMC Development Template

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

PMR Description: Conduct a prospective registry of Belatacept use in US adult kidney-only transplant recipients to determine the incidence rates of post-transplant lymphoproliferative disorder PTLD, PTLD in the central nervous system (CNS PTLD), and progressive multifocal leukoencephalopathy (PML) in US adult EBV seropositive kidney transplant recipients treated with belatacept in clinical practice. 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, timing of initiation of belatacept in relation to the transplant, location of the PTLD, and outcome (survival or mortality). (Protocol Number IM103076)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	04/2012
	Study/Trial Completion:	04/2019
	Final Report Submission:	04/2020
	Other:	NA

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

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

Clinical trial experience leading up to approval suggests increased incidence of rates of post-transplant lymphoproliferative disorder PTLD, particularly PTLD in the central nervous system (CNS PTLD) and progressive multifocal leukoencephalopathy (PML).

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). This registry is meant to collect near complete post marketing data on renal transplant patients exposed to belatacept to better define the incidence of PML and PTLD and associated risk factors for PTLD such as EBV and CMV serostatus in a prospective manner.

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

Increased incidence of rates of post-transplant lymphoproliferative disorder PTLN, PTLN in the central nervous system (CNS PTLN) has been identified during registrational trials for belatacept especially in EBV seronegative patients. Therefore, it is important to define the profile of belatacept users post-approval, particularly Epstein-Bar Virus (EBV) and cytomegalovirus (CMV) serostatus as these variables are considered risk factors for PTLN post-transplant. In addition, information regarding the nature of PTLN (location) and its outcome (survival or mortality) will be collected in order to better define this serious risk as opposed patients exposed to CNI-based regimens. Incidence rates of PTLN will be quantified among belatacept- vs. CNI-exposed renal transplant recipients.

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

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

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

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 PTLT, and outcome (survival or mortality). Incidence rates of PTLT in belatacept-exposed patients will be quantified beginning when 500 belatacept-exposed patients have at least 1 year of follow-up. Relative risks of PTLT 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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

-
- Other
-

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

Ozlem Belen, MD, MPH
(signature line for BLAs)



6/14/2011

PMR/PMC Development Template

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

PMR/PMC Description: Conduct a trend analysis of (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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	n.a.
	Study/Trial Completion:	n.a.
	Final Report Submission:	12/2013
	Other:	n.a.

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

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

Recent data indicates there may be emerging change in the trend of this product quality attribute (b) (4). A change in the (b) (4) has the potential to impact pharmacokinetics.

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

(b) (4)

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Laboratory based investigation of drug substance and risk to product quality.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)



6/11/2011

PMR/PMC Development Template

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

PMR/PMC Description: Conduct a trend analysis for (b) (4) content using an extended characterization (b) (4) 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 (b) (4) content release method.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>n.a.</u>
	Study/Trial Completion:	<u>n.a.</u>
	Final Report Submission:	<u>12/2013</u>
	Other:	<u>n.a.</u>

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

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

(b) (4)

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

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Laboratory based investigation of drug substance and risk to product quality.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)



6/11/2011

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Laboratory based investigation of drug substance and risk to product quality based on existing clinical experience.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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


(signature line for BLAs)

6/11/2014

PMR/PMC Development Template

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

PMR Description: 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

PMR Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	09/2012
	Other:	NA

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

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

BMS needs to conduct laboratory studies to develop a dye ingress test to replace the sterility test on the stability program. This is appropriate as a PMC because the test will provide an improved assessment of the maintenance of sterility of lots on stability.

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

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.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

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 by September 30, 2012.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

Ozlem Belen, MD, MPH
(signature line for BLAs)

 6.3.2011

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Laboratory based investigation of drug substance and risk assessment based on the study data and accepted ^{(b) (4)} exposure levels.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)



6/1/2011

PMR/PMC Development Template

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

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>n.a.</u>
	Study/Trial Completion:	<u>n.a.</u>
	Final Report Submission:	<u>12/2013</u>
	Other: <u>Interim Report Submission Date</u>	<u>12/2011</u>

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

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

The sponsor has purposed (b) (4) freeze-thaw cycles for DS and intends to (b) (4) DS, but has only provided DS data to support (b) (4). Freeze-thawing is a condition that is can cause changes in product quality and thus poses at least a theoretical risk to this DS. The length of the study needed to support the proposed storage conditions precludes performing the study preapproval.

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

While this drug has shown to be stable when frozen, freeze-thawing and agitation during shipping are conditions that are generally associated with changes in protein structure and function and thus pose at least a theoretical risk to this specific DS. The goal of this study is to demonstrate the stability of the DS under the proposed storage conditions and of DP produced from DS subjected to these storage conditions.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Laboratory based investigation of drug substance quality.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)



6/11/2011

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

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Laboratory based investigation of drug product.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
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 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Laboratory study of product quality.
-

Agreed upon:

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

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- Are the objectives clear from the description of the PMR/PMC?
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PMR/PMC Development Coordinator:

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(signature line for BLAs)



6/1/204

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Pre-Decisional Agency Information

Date: March 10, 2011

To: June Germain, Regulatory Project Manager
Division of Special Pathogen and Transplant Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications *Christine Corser 3/10/11*

Michelle Safarik, PA-C, Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications *Michelle Safarik 3/10/11*

Sam Skariah, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications *Sam Skariah 03/10/11*

Subject: BLA #125288
Nulojix (belatacept)

As requested in your consult dated January 19, 2011, DDMAC has reviewed the draft labeling for Nulojix (belatacept).

DDMAC's PI and PPI comments are based on the substantially complete version of the labeling titled, "BLA 125288 latest PI_12-8-10.doc" which was sent via email from June Germain on February 24, 2011.

DDMAC's comments are provided in the attached, clean version of the labeling.

If you have any questions about DDMAC's comments on the PI, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov. If you have any questions about our comments on the Patient Labeling, please contact Michelle Safarik at 6-0616 or at Michelle.Safarik@fda.hhs.gov.

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



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 3, 2010

To: Renata Albrecht, M.D., Director
**Division of Special of Special Pathogens and
Transplant Products**

Through: Claudia Karwoski, Pharm D, Director
Division of Risk Management (DRISK)

Sharon R. Mills, BSN, RN, CCRP *Sharon R. Mills 5/3/2010*
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: John Hubbard, MPAS, PA-C
Patient Labeling Reviewer
Division of Risk Management

Subject: Memo to File re: Review of Patient Labeling (Medication
Guide)

Drug Name(s): TRADENAME (belatacept) Lyophilized Powder for
Intravenous Infusion

Application Type/Number: BLA 125288

Applicant/sponsor: Bristol-Myers Squibb Company

OSE RCM #: 2009-1396

The Division of Special and Transplant Products (DSPTP) requested that the Division of Risk Management review proposed labeling for an original Biologic License Application, BLA 125288, submitted by Bristol-Myers Squibb Company for TRADENAME (belatacept) Lyophilized Powder for Intravenous Infusion on June 30, 2009.

DSPTP does not plan to address labeling during this review cycle; therefore, we will defer our review of Medication Guide until such time as the review division plans to address labeling. Please send us a new consult at that time. This memo serves to close-out the consult request for TRADENAME (belatacept).

Please let us know if you have any questions.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

PATIENT LABELING REVIEW

Date: March 2, 2011

To: Renata Albrecht, M.D., Director
**Division of Special Pathogen and Transplant Products
(DSPTP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK) *LaShawn Griffiths 3/2/11*

Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management *Barbara Fuller 3/2/11*

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Risk Management *Sharon R. Mills 3/2/11*

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): NULOJIX (belatacept)

Dosage Form and Route: For Injection

Application Type/Number: BLA 125288

Applicant: Bristol-Myers Squibb

OSE RCM #: 2009-1396

1 INTRODUCTION

This review is written in response to a request by the Division of Special Pathogen and Transplant Products (DSPTP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for NULOJIX (belatacept) for injection. On December 15, 2010, the Applicant submitted a complete class 2 response to the Agency's Complete Response letter dated May 1, 2010. This was a rolling re-submission. The Applicant seeks approval of their Biologics License Application (BLA) 125288 for NULOJIX (belatacept) for injection. NULOJIX is indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant. NULOJIX is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.

The proposed REMS is being reviewed by DRISK and will be provided to DSPTP under separate cover.

2 MATERIAL REVIEWED

- Draft NULOJIX (belatacept) for injection Medication Guide (MG) received on September 24, 2010.
- Draft NULOJIX (belatacept) for injection prescribing information (PI) received on September 24, 2010, revised by the Review Division throughout the current review cycle and received by DRISK on February 24, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG

Please let us know if you have any questions.

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

Cc List:

Division of Special Pathogen and Transplant Products

Renata Albrecht

Ozlem Belen

Joette Meyer

June Germain

Office of Surveillance and Epidemiology

Claudia Karwoski

Mary Willy

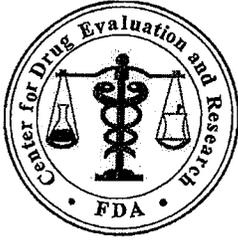
Mary Dempsey

LaShawn Griffiths

Barbara Fuller

Sharon Mills

Brantley Dorch



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: 9-2-2010

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Subject: Proposed postmarketing observational studies of belatacept

Drug Name(s): Belatacept

Application Type/Number: BLA 125288

Applicant/sponsor: Bristol-Myers Squibb (BMS)

OSE RCM #: 2010-721

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EXECUTIVE SUMMARY

- A. If approved, belatacept is predicted to be associated with significant drug-related mortality and morbidity in the postmarketing environment

Of chief concern are post-transplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy (PML), both of which carry high case fatality rates. Number needed to harm calculations yield an estimate of one excess case of PTLT among every 145 patients given belatacept for two years, above and beyond the number of cases attributable to cyclosporine treatment. With respect to PML, two cases of PML observed in belatacept clinical trials represent a risk of 1 in 542 patients exposed, higher than the risk of PML with natalizumab (1 in 2000 patients treated for any duration). Neither does it compare favorably to the estimate of 1 PML case per 7000 patients per year given mycophenolate mofetil.

However, the most recent data from three-year follow-up in the pivotal kidney transplant trials indicate a survival advantage for belatacept over cyclosporine, with a statistically significant effect size and a number needed to treat for mortality versus cyclosporine of 26. This provides reassurance that the clinical benefits of belatacept outweigh these specific drug-related risks.

- B. Because of belatacept's significant risks, quantification of PTLT and PML occurring with belatacept will be essential to its risk-benefit assessment
- C. The applicant's proposed observational studies will have some, but limited, utility in the risk assessment for belatacept

Study IM103074:

(b) (4)

(b) (4)

Study IM103075: The objective of this prospective observational study, to be conducted entirely within the UNOS database, will be to enumerate cases of PTLT occurring with belatacept compared to calcineurin inhibitors (CNIs). However, the usefulness of the data will be severely compromised by the limitations of the UNOS database. The inability to reliably capture switches between belatacept and CNI will necessitate an intent-to-treat analytic approach, but this will result in misclassification of exposure and bias the study towards the null.

Study IM103076:

(b) (4)

(b) (4)

- D. Given the weaknesses of the sponsor's proposed studies, a close-to-universal patient registry of belatacept users would be required to quantify the safety concerns regarding belatacept-related morbidity and mortality

Because the risk estimates from the relatively small sample of subjects in clinical trials are inherently unstable, an accurate quantification of these risks in the postmarketing environment will be vital to the continued risk-benefit assessment for the product. A non-mandatory registry that managed to enroll and follow-up 90% or 95% of belatacept users postmarketing should be adequate, however, for risk-quantification purposes. Drug utilization data could be used to assess the degree of success in enrolling belatacept users in the patient registry.

In addition to quantifying the risks of PTLD and PML with belatacept, a patient registry that included all (or almost all) belatacept users, both those started on belatacept at the time of transplantation and those switched to belatacept at a later time, might help address the issue of whether the risk for PTLD is greater when belatacept is initiated at the time of transplantation. A registry would have the added benefit of assessing how well the contraindication against use in EBV negative or missing serostatus patients is being honored.

Importantly, the most recent data suggests that belatacept offers an overall survival advantage, judging from the three year follow-up data from the pivotal kidney transplant trials. Given those data, it would be important not to delay marketing of the product inordinately while the mechanism for a registry is being developed; accordingly, while FDA will need to review and approve the protocol for the registry, the protocol would not necessarily need to be approved prior to marketing, but could be finalized soon after market launch, in order not to delay the availability of the product.

1 BACKGROUND/HISTORY

A. Belatacept

Belatacept is a recombinant DNA protein product, a fusion protein of CTLA-4 and immunoglobulin G1. It is related to abatacept, a product marketed for rheumatoid arthritis. Belatacept produces immunosuppression by inhibiting CD28:CD80/CD86 interactions which are key costimulatory signals for T cell activation. The belatacept BLA is under review for the proposed indication of preventing acute rejection in renal transplant recipients. It is intended as a substitute for calcineurin inhibitors (CNIs) such as cyclosporine or tacrolimus, and is to be used with mycophenolate mofetil, steroids, and an interleukin 2 receptor antagonist.

Belatacept clinical development program

The following table summarizes the key clinical trials in the belatacept clinical development program that are most relevant to the safety profile assessment for the drug. Note that two dosage regimens have been studied, a less intensive (LI) and a more intensive (MI) regimen. Only the LI is proposed for approval; this involves injections of 10 mg/kg on days 1, 5, 14, 28, month 2 and month 3, followed by 5 mg/kg monthly.

Table. Belatacept Clinical Development Program

Study	Design	Sample	Treatment groups
IM103008	Randomized, partially blind, active controlled, 3 yr	Renal transplant, from living donors or standard criteria deceased donors (n=666)	Belatacept LI (n=226), Belatacept MI (n=219), Cyclosporine (n=221)
IM103027	Randomized, partially blind, active controlled, 3 yr	Renal transplant, extended donor criteria (i.e., lower quality donor kidney) (n=543)	Belatacept LI (n=175), Belatacept MI (n=184), Cyclosporine (n=184)
IM103100	Randomized, partially blind, active controlled, 1 yr	Renal transplant (n=218)	Belatacept LI (n=71), Belatacept MI (n=74), Cyclosporine (n=73)
IM103045		Liver transplant (n=250)	Belatacept (n=146), Control (n=100)

LI = less intensive dosing regimen, MI = more intensive

For the Phase 3 trials in kidney transplant recipients, the following shows the total numbers of patients having 2 years of follow-up data. Roughly 75% of patients in each of the three treatment groups had exposure to study medication of 12 months or longer.

Belatacept MI	n=477	
Belatacept LI	n=472	[Belatacept total n=949]
Cyclosporine	n=476	

B. Safety signals relevant to this consult

In the following section, I will briefly summarize the safety signals that emerged from the belatacept clinical development program and which are relevant to the plans for postmarketing safety studies.

1. Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder (PTLD) is a relatively common type of malignancy which appears after transplant, and is associated with a high mortality (up to 50%); most cases involve B-cells, and Epstein Barr virus (EBV) is a prominent risk factor.¹ In the belatacept trials, a higher number of PTLD cases occurred with belatacept than with cyclosporine, and the frequency was considerably higher among EBV seronegative subjects.

¹ Parker A, Bowles K, Bradley JA, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients - BCSH and BTS Guidelines. Br J Haematol 2010, 149: 675-692.

Table. Frequency of PTLD 24-months post-renal transplant, Phase 3 trials, pooled data

Treatment group	Total Cases of PTLD/n (%)	EBV + Cases of PTLD/n (%)	EBV - Cases of PTLD/n (%)	EBV status unknown Cases of PTLD/n (%)
Belatacept LI	6/472 (1.3)	4/401 (1.0)	2/51 (2.9)	0/20 (0)
Belatacept MI	8/477 (1.7)	2/404 (0.5)	5/45 (11.1)	1/28 (3.6)
Total Belatacept	14/949 (1.5)	6/805 (0.7)	7/96 (7.3)	1/48 (2.0)
Cyclosporine	2/478 (0.4)	0/399 (0)	1/79 (1.2)	1/22 (4.5)

The incidence of PTLD in belatacept-treated EBV+ subjects in this dataset (all regimens) was 3.5 per 1000 person-years after 2 years of follow-up. There have also been two cases of PTLD with belatacept, and none with controls, in the liver transplant trial. For comparison, Bristol-Myers Squibb (BMS) reports that in their analysis of United Network for Organ Sharing (UNOS) data from 2000-2006, the incidence of PTLD in EBV+ adult kidney transplant patients with CNI treatment was 1.1 per 1000 person-years during the first two years post transplant.²

In addition to negative EBV serostatus, negative cytomegalovirus (CMV) serostatus may also be a risk factor for PTLD with belatacept treatment, since CMV- patients were over-represented among the 6 EBV+ patients who developed PTLD with belatacept (comprising 4 out of the 6).

Of relevance regarding this risk assessment is the observation that in prior randomized controlled trial data submitted to FDA with renal transplant subjects, there were no cases of PTLD reported among a combined 534 cyclosporine-treated patients.

A particular feature of the PTLD observed with belatacept treatment is the preponderance of cases involving the CNS. In a case series of 1094 non-Hodgkins lymphoma cases presenting in renal transplant patients, 12% involved the CNS.³ However, of the 14 PTLD cases in belatacept-treated renal transplant patients, 9 involved the CNS.

From the incidence derived from pooled clinical trial data in the belatacept renal transplant studies, for all regimens of belatacept treatment in EBV+ patients, the number needed to harm (NNH) versus cyclosporine to yield one additional case of PTLD after two years of treatment is estimated at 145 (95% c.i. -532, 64). Although the confidence interval for this NNH crosses zero and thus includes the possibility of a small protective effect, a subsequent analysis pooling cyclosporine control groups from belatacept trials and other renal transplant trials yielded a 2-year NNH of similar magnitude (161), with confidence limits that in this case excluded a protective effect (69-698).⁴ The NNH would be considerably smaller in EBV- patients.

² BMS Draft protocol for study IM103075ST, 17-Mar-2010

³ Opetz G, Dohler, B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Amer J of Transplantation* 2003; 4:222-230.

⁴ FDA Briefing Package, Cardiovascular and Renal Drugs Advisory Committee Meeting, March 1, 2010

Because of the much higher incidence of PML in patients who are EBV negative, the applicant's proposed labeling for belatacept would contraindicate its use in "transplant recipients who are EBV seronegative or with unknown serostatus."

2. Progressive multifocal leukoencephalopathy (PML)

One fatal case of PML occurred in a renal transplant patient who had received the belatacept MI regimen. A second case of PML occurred in a subject who received belatacept in the liver transplant study. Thus, as shown in the table below, there have been 2 cases of PML among the 1085 transplant patients who received belatacept in Phase 3 trials (representing a risk of 1 in 542 patients exposed). While only two cases cannot provide a precise estimate of the true incidence, these two cases are likely to represent an association between PML and belatacept treatment. In contrast, the incidence of PML was estimated at 14 per 100,000 per year (or roughly 1 in 7000 patients per year) in a retrospective study of kidney transplant patients receiving mycophenolate mofetil.⁵ Indeed, a survey by Dr. Carolyn Yancey of DRISK did not disclose any examples of approved drugs or biologic products with cases of PML observed in premarketing clinical trials. For comparison, natalizumab, which because of its risk of PML is marketed via a restricted distribution system for its indications in multiple sclerosis and Crohn's disease, has been associated with 0.5 cases of PML per thousand patients treated (i.e., 1 case per 2000 patients treated for any duration, with a rate of 1 case per 1000 patients receiving 30 or more infusions).⁶

Table. PML cases in belatacept clinical trials

Treatment group	Cases of PML/n
Belatacept LI	0/472
Belatacept MI	1/477
Cyclosporine	0/478
Belatacept/liver transplant subjects	1/146

3. Serious infections

The clinical safety review of the belatacept BLA revealed an imbalance in opportunistic CNS infections among belatacept treated subjects, as shown in the table below. These infections with belatacept included CNS herpes zoster, cryptococcal meningitis, cerebral aspergillosis, West Nile virus, and PML; there was one case of cryptococcal meningitis with cyclosporine. Seven of the 8 cases were with the MI dosing regimen. In addition, cases of tuberculosis (TB), mainly in extrapulmonary sites, were more frequent with belatacept treatment than with cyclosporine, including one case with the LI regimen that was fatal.

⁵ Nef RT, Hurst FP, Falta EM, et al. Progressive Multifocal Leukoencephalopathy and Use of Mycophenolate Mofetil after Kidney Transplantation. *Transplantation* 2008, 86:1476-8.

⁶ FDA Drug Safety Communication: Risk of Progressive Multifocal Leukoencephalopathy (PML) with the use of Tysabri (natalizumab). Available at:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm199872.htm#_Ref252346653

Table. Serious infections in the belatacept clinical development program

Treatment group	N	Cases of CNS infections	Cases of TB
Belatacept LI	472	1	3
Belatacept MI	477	7	4
Cyclosporine	478	1	1

4. 36-month follow-up data from the pivotal kidney transplant trials

On August 13, 2010⁷ the sponsor submitted a summary of safety and efficacy data from the 36 month time point in pivotal trials 3008 and 3027. These new data provide important perspectives on the long term safety of belatacept. The following table summarizes selected safety outcomes in data pooled from the two studies. (It should be borne in mind that the data presented below do not account for patients lost to follow-up; a separate enumeration of patients lost to follow-up was not provided in the August 13, 2010 submission.)

Table. Selected safety outcomes in 36 month data pooled from belatacept clinical trials 3027 and 3008

Treatment group	N	Cases of TB	Cases of PTLD*	Cases of PML	Deaths from any cause
Belatacept LI	401	6	5	0	25
Belatacept MI	403	6	5	1	31
Cyclosporine	405	1	1	0	41

*Subgrouping by EBV serostatus not provided. No new PTLD cases between months 24 and 36; 1 case each with belatacept LI and cyclosporine after month 36

At 36 months, the data yield an estimated relative risk for TB versus cyclosporine of 6, regardless of dose, and for PTLD versus cyclosporine of 5, regardless of dose. Pooling belatacept LI and MI data yields the following Numbers Needed to Harm (NNH) versus cyclosporine (with the differences approaching nominal statistical significance at the 5% level):

NNH for TB = 80 (p=0.07, Fisher's exact, Stata software)

NNH for PTLD =100 (p=0.11, Fisher's exact, Stata software)

However, for deaths from all causes (combining deaths involving acute rejection with deaths not involving acute rejection), the 36 month data indicate lower mortality with belatacept compared to cyclosporine. Most of the deaths did not involve acute rejection. The estimates for Number Needed to Treat (NNT) to prevent one death after 36 months with belatacept versus cyclosporine are indicated below. (Calculations are with Stata software, chi-squared test.)

RR for mortality, LI versus cyclosporine	0.62
95% c.i.	0.38-0.99
p-value	0.04
NNT	26
RR for mortality, LI+MI versus cyclosporine	0.69
95% c.i.	0.47 – 1.01
p-value	0.06
NNT	32

⁷ BMS background document for Type B meeting, August 13, 2010

These results displayed above represent a simple combinations of data from two studies. It can be argued that a more appropriate statistical technique is to calculate a combined risk ratio using the Mantel-Haenszel method;⁸ for the LI group versus cyclosporine in the two trials, this method yields a risk ratio of 0.62 (95% confidence limits 0.39-1.00), which is quite similar to the risk ratio from the pooled data.

C. Regulatory background

1. Advisory committee meeting

The Cardiovascular and Renal Drugs Advisory Committee considered the belatacept BLA at a meeting March 1, 2010. The Committee voted 13 to 5 in favor of approval. According to the minutes,⁹ the majority of the Committee expressed concerns regarding the signals for CNS PTLD and PML. Their recommendations included a “tight registry” to monitor PTLD, in addition to a REMS, and observational studies. Additional long-term safety data was also viewed as desirable.

2. Complete Response letter

On May 1, 2010, FDA issued a Complete Response letter for the belatacept BLA. To address clinical deficiencies, the applicant was asked to provide 3 year follow-up data on their clinical trial subjects, particularly with respect to “mortality, graft loss, GFR, PTLD and other serious adverse reactions.” The applicant was also asked to address the question of whether the apparent advantage for belatacept over cyclosporine with respect to renal function can be properly attributed to belatacept’s efficacy, and not the well-known nephrotoxicity of cyclosporine.

D. United Network for Organ Sharing (UNOS)

The United Network for Organ Sharing (UNOS) is the contractor for the Organ Procurement and Transplantation Network, established pursuant to the National Organ Transplant Act of 1984. Collecting and maintaining data on organ transplant candidates, recipients, and donors is one of the functions of UNOS, and it currently is thought to capture virtually 100% of solid organ transplants performed in the U.S. Note that roughly 18,000 kidney transplants are performed in the U.S. annually; in 2007 the number was 17,513.¹⁰ Institutions belonging to UNOS are mandated to report data to the network electronically. The sponsor’s analysis estimated that the cumulative loss to follow-up among UNOS adult kidney transplant recipients is \leq 5.5% at 2 years.

The following is a listing of the data collection timepoints and forms for the UNOS system.¹¹ There are separate data forms for pediatric and adult patients, and for each

⁸ Epi Info software, CDC.

⁹ Summary Minutes, Meeting of the Cardiovascular and Renal Drugs Advisory Committee, March 1, 2010

¹⁰ U.S. Renal Data System, USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2009. Available at <http://www.usrds.org/reference.htm>

¹¹ See www.unos.org/data/about/collection.asp#dcf

organ type (relevant to this review, there are specific forms for kidney transplant). The forms have some fields which are required for completion, and some which are optional. Belatacept is not a choice currently on the lists of immunosuppressive medications.

1. Transplant candidate registration: This data collection occurs when a patient is placed on the waiting list for a transplant.
2. Transplant Recipient Registration: This form is completed after a transplant has been performed, either at hospital discharge or 6 weeks post-transplant (whichever is earliest). Typically data are abstracted from the medical charts, and are required to be submitted to UNOS within 60 days. Post-transplant immunosuppressive information is a required field for completion of the form. EBV serostatus is also a required field. According to the applicant's analysis of UNOS data, from 1-1-2008 through 8-31-2009, roughly 17% of forms had EBV serostatus checked as not done, and 7% as unknown; the applicant is exploring the possibility of obtaining EBV serostatus data on such patients retrospectively from medical records.¹²
3. Transplant Recipient Follow-Up: This form is completed six months post-transplant, and thereafter on the anniversary of the transplant. One required field relevant to this review is "Post-transplant malignancy." This required field is limited to a choice of yes, no, or unknown; according to the applicant's analysis, roughly 7% of forms in 2008 had this field as missing or unknown. Relevant to PTLD, an optional subfield can be checked to describe the malignancy as "De Novo Lymphoproliferative disease and Lymphoma." However, completion of the fields for "Immunosuppressive information" (including specifying immunosuppressive medications) is optional. There is no field on the form in which to record a diagnosis of PML, unless it was the cause of death. Similarly, there is no field to record a diagnosis of tuberculosis, except as a cause of death.
4. A Post-transplant Malignancy form is required if such a malignancy has occurred, and there are separate versions for children and adults. A section of the Post-transplant Malignancy form is reserved for a description of PTLD. According to UNOS data obtained by the sponsor, from 2-2-2007 to 4-3-2009 roughly 48% of PTLD records included location of the PTLD.¹³

E. Reason for this consult

DEPI was asked to review synopses of the following three postmarketing studies proposed by the applicant. (b) (4)

1. IM103074: Pattern of Use of Belatacept in Renal Transplant Recipients
2. IM103075: Belatacept and Risk of PTLD in US Renal Transplant Recipients

¹² Bristol-Myers Squibb letter dated 3-19-2010.

¹³ Bristol-Myers Squibb letter dated 3-19-2010.

2 REVIEW METHODS AND MATERIALS

The following materials were used to prepare this consult response.

- Briefing materials, slides and minutes from the Anti-Infective Drugs Advisory Committee Meeting, March 1, 2010
- Draft clinical BLA review (Patrick Archdeacon, M.D., medical officer)
- Applicant's draft labeling submitted with original BLA
- Applicant's synopses of proposed postmarketing observational studies (versions forwarded with the OSE consult)
- Supplemental information in applicant's March 19, 2010 letter
- Consult from DRISK dated April 30, 2010 (Dr. Carolyn Yancey, Scientific Lead)
- United Network for Organ Sharing data collection website (<http://www.unos.org/data/about/collection.asp#dcf>)

3 RESULTS OF REVIEW

3.1 STUDY IM103074: PATTERN OF USE OF BELATACEPT IN RENAL TRANSPLANT RECIPIENTS

3.1.1 Proposed Objectives

3.1.1.1 Proposed Objective

(b) (4)

3.1.1.2 DEPI Comments on Proposed Objectives

These objectives may be of academic interest, or of interest to the applicant with respect to how the drug is being marketed, but are not likely to contribute to either the risk assessment or risk management for the compound.

3.1.2 Proposed Design

3.1.2.1 Proposed Design

The study will gather descriptive statistics prospectively on kidney transplant recipients from the UNOS data system. No separate data collection is being proposed, and so all data will be collected according to the variables available in the UNOS data system. Data for the primary analysis will be limited to that collected within one year of transplantation.

3.1.2.2 DEPI Comments on Proposed Design

The data to be analyzed will be derived entirely from the UNOS data system. A weakness of the UNOS data for the purpose of this study is that reporting immunosuppressive medications is voluntary after the initial entry for the transplant recipient in UNOS.

3.1.3 Informed Consent

3.1.3.1 Proposed Informed Consent (if any)

(b) (4)

3.1.3.2 DEPI Comments on Proposed Informed Consent (if any)

This study would require appropriate Institutional Review Board (IRB) approval, especially with respect to confidentiality of patient information.

3.1.4 Data Source(s)

3.1.4.1 Data Source(s)

The data source, as noted, is the UNOS data system, designated as UNetsm.

3.1.4.2 DEPI Comments on Proposed/Actual Data Sources

The limitations of this data source have been noted above (Background/History section D), chiefly, the voluntary nature of reporting of immunosuppressant therapy following the transplant procedure.

3.1.5 Study Time Period(s)

3.1.5.1 Study Time Period(s)

(b) (4)

3.1.5.2 DEPI Comments on Proposed/Actual Study Time Period(s)

No specific comments, the proposed time frame seems appropriate.

3.1.6 Population

3.1.6.1 Population

The population will encompass all patients in the UNOS system, with specific analyses of patients who received kidney transplants or received belatacept, (b) (4) after the approval of belatacept.

3.1.6.2 DEPI Comments on Proposed/Actual Population

In theory, this should include all patients who received kidney transplants in the U.S. since enrollment in the UNOS system is essentially universal.

3.1.7 Exposure

3.1.7.1 Exposure

(b) (4)

3.1.7.2 DEPI Comments on Proposed Exposure

One important weakness of the UNOS data for the purpose of this study is that data on immunosuppressive medications is mandatory for reporting only at the time of the receipt of the transplant. On follow-up, reporting of immunosuppressive medications is optional. Accordingly, there is likely to be missing or incorrect data on use of belatacept at times subsequent to the initial receipt of the transplant. On this point, the sponsor's study proposal states that (b) (4).

(b) (4) but I was able to confirm from primary sources only that it is mandatory at the time of transplantation.

3.1.8 Disease Outcome of Interest

3.1.8.1 Disease Outcome of Interest

(b) (4)

3.1.8.2 DEPI Comments on Proposed/Actual Disease Outcome of Interest

None.

3.1.9 Sample Size

3.1.9.1 Sample Size

The sample size is not specified per se, since the sample will consist of all UNOS kidney transplant recipients during the study period.

3.1.9.2 DEPI Comments on Proposed/Actual Sample Size

None.

3.1.10 Analyses

3.1.10.1 Analyses

(b) (4)

3.1.10.2 DEPI Comments on Proposed Analyses

From a regulatory standpoint, analysis of data on EBV status of belatacept users could be informative, since it would illustrate the extent to which the anticipated contraindication in EBV negative/unknown patients is being respected. The informative value will be mitigated somewhat by the fact that roughly one-quarter of patients in the UNOS database have EBV serostatus recorded as either not done or unknown; however, use of belatacept in any of those patients would be considered contraindicated under the proposed labeling. BMS is exploring whether follow-up can be performed on such patients.

3.2 STUDY IM10375 ST: BELATACEPT AND RISK OF PTLD IN US RENAL TRANSPLANT RECIPIENTS

3.2.1 Proposed Objectives

3.2.1.1 Proposed Objective

(b) (4)

3.2.1.2 DEPI Comments on Proposed Objectives

The proposed primary objectives are important and highly relevant to the post-marketing risk assessment for belatacept. The same may be said for the secondary objectives also. Regarding the comparisons by calendar year, it is not clear to me that significant temporal trends in the incidence of PTLD would be expected, but certainly such a finding if present would be of potential interest.

3.2.2 Proposed Design

3.2.2.1 Proposed Design

This will be a prospective observational cohort study. All study data will be obtained from the UNOS system, and there will be no additional data collection for this study. Please see the forgoing discussion for a description of the UNOS database (Background/History section D). (b) (4)

3.2.2.2 DEPI Comments on Proposed Design

A prospective observational design with an endpoint determined by a minimum exposure to belatacept is reasonable.

3.2.3 Informed Consent

3.2.3.1 Proposed Informed Consent

(b) (4)

3.2.3.2 DEPI Comments on Proposed Informed Consent

The study will need to be approved by the appropriate IRB(s). Protecting the privacy of individual patient information will be essential for ethical conduct of this study.

3.2.4 Data Source

3.2.4.1 Data Source

The only source of data for this study will be the UNOS database.

3.2.4.2 DEPI Comments on Proposed Data Source

The principal limitations of this data source have been discussed above. After the initial registration of the transplant recipient, recording immunosuppressive therapy is optional. With respect to studying the clinical characteristics of PTLD, the applicant's assessment of UNOS data revealed a missing anatomical location in roughly half (52%) of the PTLD cases. As a preponderance of CNS PTLD with belatacept is one of the hypotheses to be evaluated, such an amount of missing data would be undesirable.

3.2.5 Study Time Period

3.2.5.1 Study Time Period

(b) (4)

3.2.5.2 DEPI Comments on Proposed Study Time Period

For a prospective study of this nature, continuing observation until a target number of exposures is reached is a reasonable approach, but it remains to be seen how quickly this target could be reached, since this number of patients represents approximately one-third of the annual number of renal transplants nationally.

3.2.6 Population

3.2.6.1 Population

The study population will be adult kidney (only) transplant recipients started on belatacept. A total of (b) (4) belatacept patients will be accrued from the UNOS database, and UNOS patients starting CNI treatment during the enrollment period for belatacept users will comprise the comparison group.

3.2.6.2 DEPI Comments on Proposed/Actual Population

The study population is relevant for the purposes of this study.

3.2.7 Exposure

3.2.7.1 Exposure

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill.

3.2.7.2 DEPI Comments on Proposed Exposure

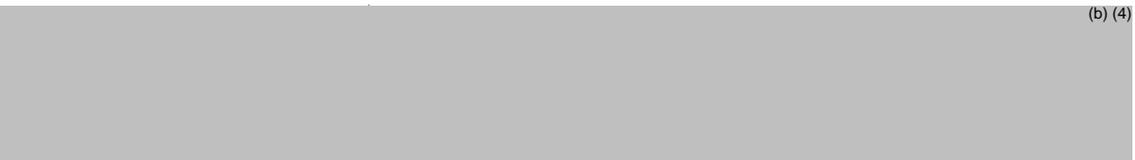
(b) (4)

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3.2.8 Disease Outcome of Interest

3.2.8.1 Disease Outcome of Interest

(b) (4)

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3.2.8.2 DEPI Comments on Proposed Disease Outcome of Interest

(b) (4)

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3.2.9 Sample Size

3.2.9.1 Sample Size

(b) (4)

3.2.9.2 DEPI Comments on Proposed/Actual Sample Size

If the sponsor's power calculations are accurate the study would have power to exclude a relative risk of (b) (4) but this fails to account for other design features that will bias the study towards the null, chiefly the misclassification of exposure, as discussed in section 3.17 above.

The size of the CNI comparison group is not prespecified, but is likely to be larger than the belatacept group, although BMS did not specify their assumption about that for the power calculation. Given the novelty of belatacept as a treatment, an assumption that CNI-treated patients will outnumber belatacept-treated patients is reasonable.

3.2.10 Analyses and/or Study Results

3.2.10.1 Analyses and/or Study Results

(b) (4)

3.2.10.2 DEPI Comments on Proposed Analyses

(b) (4)

3.3 STUDY IM103076: [REDACTED] (b) (4)

3.3.1 Proposed Objectives/Actual Objectives

3.3.1.1 Proposed Objective

[REDACTED] (b) (4)

3.3.1.2 DEPI Comments on Proposed Objectives

The proposed objectives are relevant to the risk-benefit assessment for belatacept in kidney transplantation.

3.3.2 Proposed Design

3.3.2.1 Proposed Design

[REDACTED] (b) (4)

3.3.2.2 DEPI Comments on Proposed Design

[REDACTED] (b) (4)

[REDACTED] This study will not be relying on the UNOS database, and should therefore allow more complete data collection regarding exposure to belatacept and clinical outcomes.

3.3.3 Informed Consent

3.3.3.1 Proposed Informed Consent

[REDACTED] (b) (4)

3.3.3.2 DEPI Comments on Proposed Informed Consent

Relevant IRB approval will be required for this study.

3.3.4 Data Source(s)

3.3.4.1 Data Source(s)

[Redacted] (b) (4)

3.3.4.2 DEPI Comments on Proposed Data Sources

This study should have a much greater likelihood of obtaining complete, detailed clinical data than the observational studies using only the UNOS database. It was not clear how missing data will be handled, however; [Redacted] (b) (4)

[Redacted] (b) (4)

3.3.5 Study Time Period(s)

3.3.5.1 Study Time Period

[Redacted] (b) (4)

3.3.5.2 DEPI Comments on Proposed Study Time Period

The study will obviously take many years to yield data; [Redacted] (b) (4)

[Redacted] (b) (4)

3.3.6 Population

3.3.6.1 Population

[Redacted] (b) (4)

3.3.6.2 DEPI Comments on Proposed Population

If off-label pediatric use is anticipated or is found to occur, including such patients should be considered.

3.3.7 Exposure

3.3.7.1 Exposure

[Redacted] (b) (4)

3.3.7.2 DEPI Comments on Proposed Exposure

If BMS intends to adopt an intent-to-treat analytic approach with respect to exposure, all of the aforementioned drawbacks in study IM103075 will apply here also.

3.3.8 Disease Outcome of Interest

3.3.8.1 Disease Outcome of Interest

[Redacted] (b) (4)

3.3.8.2 DEPI Comments on Proposed Disease Outcome of Interest

The outcomes are relevant to the risk-benefit assessment of belatacept in this population. Randomized controlled trial data should be viewed as more informative than observational data for efficacy-related outcomes such as acute rejection and GFR.

3.3.9 Sample Size

3.3.9.1 Sample Size

[Redacted] (b) (4)

3.3.9.2 DEPI Comments on Proposed Sample Size

The issue of misclassification of exposure if an intent-to-treat analytic approach is adopted was not addressed. This would weaken the power of the study, unless for some reason exposure to immunosuppressants after the initial transplant hospitalization bears no relationship to the probability of the study outcomes. An as-treated analysis would seem to be more appropriate from the standpoint of biological plausibility, but switching might reduce the observed person-time exposure in the belatacept group.

3.3.10 Analyses

3.3.10.1 Analyses

(b) (4)

3.3.10.2 DEPI Comments on Proposed Analyses

(b) (4)

4 SUMMARY AND RECOMMENDATIONS

- A. If approved, belatacept is predicted to be associated with significant drug-related mortality and morbidity in the postmarketing environment

Based on the clinical trial experience with belatacept, it should be anticipated that its use will be associated with considerable drug-related morbidity, and even mortality, in the post-marketing environment. Of chief concern are PTLD and PML. With respect to PTLD, this is a recognized sequela from organ transplantation, but the risk with belatacept appears to be greater than with cyclosporine. While this risk can be reduced by limiting recipients to those with EBV+ serostatus, even with this precaution, estimates of the number needed to harm (NNH) versus cyclosporine suggest that on the order of one excess case of PTLD will occur among every 145 patients given belatacept for two years, above and beyond the number of cases attributable to cyclosporine treatment. As PTLD carries a high case fatality rate, drug-related mortality from PTLD with belatacept will not be insignificant.

With respect to PML, including liver transplantation patients, there have been two cases of PML in belatacept clinical trials, representing a risk of 1 in 542 patients exposed. This does not compare favorably to the estimate in one study of 1 PML case per 7000 patients per year with mycophenolate mofetil, or to the risk of 1 in 2000 patients treated with natalizumab (for any duration). While an incidence estimate from only two cases is unstable, it seems quite possible that the incidence of PML with belatacept will exceed that for natalizumab. As PML is similarly associated with a high case-fatality rate, this adverse event too is predicted to be a source of belatacept-related morbidity and mortality.

Other safety issues of concern with belatacept treatment, for which the risk is not as well quantified, include CNS infections and tuberculosis.

- B. Because of belatacept's significant risks, quantification of PTLD and PML occurring with belatacept will be essential to its risk-benefit assessment

To the extent that there are offsetting advantages to belatacept (such as less nephrotoxicity and less hypertension) that warrant its clinical use, accurate quantification of its risks (particularly for PTLD and PML) is crucial to the weighing of its benefits against these clinical risks.

In fact, noteworthy support for the hypothesis that there are offsetting advantages to belatacept outweighing the risks of PTLD and PML is provided by the 36 month mortality follow-up data from the two pivotal kidney transplant studies. For the LI regimen, the imbalance in mortality favoring belatacept over cyclosporine resulted in a number needed to treat estimate of 26 after 3 years.

- C. The applicant's proposed observational studies will have limited utility in the risk assessment for belatacept

Study IM103074: This descriptive study of the patterns of belatacept use after market launch will have limited regulatory value and will contribute little to the risk assessment of the drug. Of potential usefulness is the assessment of EBV status in patients administered belatacept; this would provide a way to assess how well the proposed contraindication in EBV- patients is being honored. However, EBV serostatus is expected to be missing in UNOS for up to one quarter of patients; such patients should not receive belatacept according to the proposed labeling. Parenthetically, the fact that serostatus is not recorded in UNOS for so many patients does not instill confidence in the ability to preclude use of belatacept in EBV- patients by contraindicating it.

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 severely compromised by the limitations of the UNOS database. Specifically, the fact that some aspects of reporting PTLD in the UNOS system are voluntary may lead to underascertainment; more importantly, the necessity of an intent-to-treat analytic approach, due to the inability to reliably capture switches between belatacept and CNI regimens after the initial transplantation registration, will bias the study towards the null.

Study IM103076:

(b) (4)

(b) (4)

- D. Given the weaknesses of the sponsor's proposed studies, a close-to-universal patient registry for all belatacept users would be required to quantify the safety concerns regarding belatacept-related morbidity and mortality.

The most expedient way to quantify belatacept-related morbidity and mortality, particularly for PTLD and PML, would be to institute a universal patient registry of belatacept users. Such a registry has been used successfully to quantify the risk of PML with natalizumab, for example, and it should be recalled that the expected incidence rate of PML with belatacept

may well exceed that of natalizumab. While it could be argued that the UNOS data system is close to a universal registry of transplant recipients in the U.S., the problem is that there are too many gaps in the data collected by UNOS for the data to be relied upon in a risk assessment for an immunosuppressant treatment. In addition, a registry that included all or nearly all belatacept users, both those started on belatacept at the time of transplantation and those switched to belatacept at a later time, might help address the important question of whether the risk for PTLD is greater when belatacept is initiated at the time of transplantation. None of the proposed studies are capable of addressing this issue because exposures would be defined by the initial immunosuppressant treatment.

An additional advantage of a registry would be that it would provide data on how well the contraindication with EBV negative or missing serostatus is being respected. While UNOS may provide some of these data, that would cover mainly patients receiving belatacept from the time of initial transplant.

FDA may not have the regulatory authority to require a mandatory patient registry for the purpose of risk assessment rather than risk mitigation; a discussion of this is beyond the scope of this consult. However, a mandatory registry would not be necessary from a pharmacovigilance and pharmacoepidemiology standpoint, if a voluntary patient registry involving the vast majority of belatacept users could be implemented. Because the risk estimates from the relatively small sample of subjects in clinical trials are inherently unstable, an accurate quantification of these risks in the postmarketing environment will be vital to the continued risk-benefit assessment for the product. A non-mandatory registry that managed to enroll and follow-up 90% or 95% of belatacept users postmarketing should be adequate, however, for risk-quantification purposes. Drug utilization data could be used to assess the degree of success in enrolling belatacept users in the patient registry.

That said, the most recent data suggests that belatacept offers an overall survival advantage, from the three year follow-up data from the pivotal kidney transplant trials. Given those data, it is important not to delay marketing of the product inordinately while the mechanism for a registry is being developed; accordingly, while FDA will need to review and approve the protocol for the registry, the protocol would not necessarily need to be approved prior to marketing, but could be finalized soon after market launch.

5 PROPOSED COMMENTS/RECOMMENDATIONS TO BE COMMUNICATED TO THE SPONSOR

DEpi proposes the following comments which could be communicated to BMS regarding their postmarketing safety studies.

We have evaluated your three postmarketing pharmacoepidemiology studies, designated IM103074, IM103075, and IM103076, and would like to provide the following observations.

We concur with your assessment, as stated in your August 13, 2010 submission of the three year follow-up data from the pivotal kidney transplant trials, that the principle safety concerns with belatacept remain the incidence of PTLD (particularly with CNS involvement) and PML. Both of these conditions carry substantial morbidity and mortality, and an accurate quantification of the risk of these events with belatacept will be paramount in the postmarketing environment, particularly since the risk estimates from the clinical trial data are based on small numbers and are therefore somewhat unstable. Indeed, this was discussed at the March 1, 2010 Advisory Committee meeting, and as stated in the minutes, "Members expressed that a tight registry should be maintained to monitor the risks involved with the

drug.” That said, we do note that the data on all-cause mortality in your August 13, 2010 submission indicate an overall survival advantage after three years for belatacept compared to cyclosporine, suggesting that there were offsetting benefits with belatacept in the trials despite the apparent risks of PTLD and PML. Accordingly, we view it as a responsibility to monitor these risks post-marketing to ensure that they are not greater than expected. With these issues in mind, we provide the following specific comments on your proposed postmarketing studies.

Study IM103074:

(b) (4)

(b) (4)

However, FDA would have no objection to your conducting this study. Of potential usefulness is the assessment of EBV status in patients administered belatacept; this would provide a way to assess how well the proposed contraindication in EBV- patients is being honored. Based on your assessment of the UNOS database, EBV serostatus may be missing in up to one fourth of patients; however, none of those patients should receive belatacept, according to the proposed labeling.

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 severely compromised by the limitations of the UNOS database. Specifically, the fact that some aspects of reporting PTLD in the UNOS system are voluntary may lead to underascertainment; more importantly, the necessity of an intent-to-treat analytic approach, due to the inability to reliably capture switches between belatacept and CNI regimens after the initial transplantation registration, could bias the study towards the null. Because of these deficiencies, we are not confident that this study would provide a valid estimate of the incidence of PTLD with belatacept use. Accordingly, we do not recommend using this study to estimate the incidence of PTLD in users of belatacept.

Study IM103076:

(b) (4)

(b) (4)

In short, although your proposed postmarketing studies would have some utility if you can successfully address the issues mentioned above, we find that none of your proposed studies would provide a “tight registry” (to use the words of the Advisory Committee) for monitoring belatacept-associated morbidity and mortality from PTLD and PML. Accordingly, we feel a patient registry of belatacept users would be a more beneficial strategy for this purpose. This would not need to be a universal registry involving a restricted distribution system, with enrollment a prerequisite for receiving the drug, nor would it necessarily have to be rolled out prior to marketing. However, it should have the goal of enrolling the vast majority of belatacept users (albeit on a voluntary basis), from as close to the time of initial marketing as feasible. The principle outcomes to be assessed would be PTLD (especially with a CNS location) and PML.

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 to historical controls such as literature observational studies; and (3) 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 the voluntary registry program.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 23, 2011

Application Type/Numbers: BLA 125288

To: Renata Albrecht, MD, Director
Division of Special Pathogens and Transplant Products

Through: Irene Z. Chan, PharmD, BCPS, Acting Team Leader *3/23/11*
Carol Holquist, RPh, Director *Carol Holquist 3/23/11*
Division of Medication Error Prevention and Analysis (DMEPA)

From: L. Shenece' Toombs, PharmD, Safety Evaluator *HT 3/23/2011*
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Nulojix (Belatacept) for Injection
250 mg per vial

Applicant/sponsor: Bristol-Myers Squibb

OSE RCMI#: 2010-2585

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3.1	COMMENTS TO THE DIVISION.....	4
3.2	COMMENTS TO THE APPLICANT	7

1 INTRODUCTION

This review evaluates the proposed labels and labeling for Nulojix from a medication error perspective.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA)¹, principals of human factors, and lessons learned from postmarketing experience in our evaluation of labels and labeling of drug products. This review evaluates the labels and labeling submitted on April 15, 2010 (see Appendices A through B) and the substantially complete revised insert labeling forwarded from the Division on February 24, 2011 (no image).

3 RESULTS AND DISCUSSION

The following section describes the findings and analysis of the labels and labeling.

3.1 PRODUCT DESIGN

On March 8, 2011, a joint meeting between DMEPA, CMC, and DSPTP was held to inform DSPTP of concerns related to the silicone-free dosing syringe packaged with Nulojix. (b) (4)

(b) (4) Additionally, DMEPA was concerned that the deficient dosing syringe would lead to more medication errors if pharmacists, not capable of measuring accurate volumes with the proposed silicone-free syringe, use an alternate syringe from the pharmacy inventory. The chance of an alternate syringe being silicone-free is unlikely.

After discussion with the Division, (b) (4) (b) (4) include language for prescribers to round final calculated doses to the nearest 12.5 mg. This will allow for measurable reconstituted volumes with the dosing syringe proposed by the Applicant.

3.2 LABELS AND LABELING

Our review of the labels and labeling identified the following deficiencies:

- Use of inappropriate established name presentation and route of administration statement
- Use of error-prone symbol
- Inadequate prominence of the route of administration statement
- Lot number and expiration date not included

We provide recommendations to address these deficiencies in Section 4.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the container labels and carton labeling identified areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 5.1 Comments to the Division. We request the recommendations for the container labels and carton labeling in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact OSE Project Manager, Karen Townsend, at 301-796-5413.

4.1 COMMENTS TO THE DIVISION

A. Dosage and Administration Sections of Full Prescribing Information

- 1) *Per discussion with DSPTP, we recommend modifying section 2.1 of the insert labeling as follows:*

Due to an increased risk of post transplant lymphoproliferative disease (PTLD) predominantly involving the CNS, progressive multifocal leukoencephalopathy (PML), and serious CNS infections, administration of higher than the recommended doses or more frequent dosing of NULOJIX is not recommended [see *Warnings and Precautions* (5.1, 5.4, 5.6) and *Adverse Reactions* (6.1)].

NULOJIX is for intravenous infusion only.

Patients do not require premedication prior to administration of NULOJIX.

The total infusion dose of NULOJIX should be based on the actual body weight of the patient at the time of transplantation, and should not be modified during the course of therapy, unless there is a change in body weight of greater than 10%.

(b) (4)

- 2) As currently presented, section 2.2 is difficult to follow and can be presented in a more logical sequence. Additionally we note a discrepancy between the storage instructions on the carton labeling and in this section. We recommend consistency in these instructions. Therefore we propose revising section 2.2 as follows:

Nulojix is for intravenous infusion only.

*Caution: Nulojix must be reconstituted/prepared using the **SILICONE-FREE DISPOSABLE SYRINGE** provided with each vial.*

If the **SILICONE-FREE DISPOSABLE SYRINGE** is dropped or becomes contaminated, use a new **SILICONE-FREE DISPOSABLE SYRINGE** from inventory. For information on obtaining additional **SILICONE-FREE DISPOSABLE SYRINGES**, contact Bristol-Myers Squibb at 1-888-NULOJIX.

Preparation for Administration

- 1) Reconstitute the vial(s) of Nulojix with 10.5 mL of a suitable diluent using the **SILICONE-FREE DISPOSABLE SYRINGE** provided with each vial and an 18- to 21- gauge needle. (Suitable diluents include: sterile water for injection (SWFI), 0.9% sodium chloride (NS), or 5% dextrose in water (D5W))

Note: If the NULOJIX powder is accidentally reconstituted using a different syringe than the one provided, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.

- 2) Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of diluent (10.5 mL of SWFI, NS, or D5W) to the glass wall of the vial.
- 3) To minimize foam formation, rotate the vial and invert with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. Do not shake.
- 4) The reconstituted solution contains a concentration of 25 mg/mL and should be clear to slightly opalescent and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.
- 5) Prior to intravenous administration, the reconstituted NULOJIX solution must be further diluted with a suitable infusion fluid (NS or D5W). NULOJIX reconstituted with:
- SWFI should be further diluted with either NS or D5W
 - NS should be further diluted with NS
 - D5W should be further diluted with D5W
- 6) From the appropriate size infusion container, withdraw a volume of infusion fluid that is equal to the volume of the reconstituted NULOJIX solution required to

provide the dose. With the same **SILICONE-FREE DISPOSABLE SYRINGE** used for reconstitution, withdraw the required amount of belatacept solution from the vial, inject it into the infusion container, and gently rotate the infusion container to ensure mixing.

The final belatacept concentration should range from 2 to 10 mg/mL. Typically, an infusion volume of 100 mL will be appropriate for most patients and doses, but total infusion volumes ranging from 50 mL to 250 mL may be used. Any unused solution remaining in the vials must be discarded.

- 7) Prior to administration, the NULOJIX infusion should be inspected visually for particulate matter and discoloration. Discard the infusion if any particulate matter or discoloration is observed
- 8) The entire NULOJIX infusion should be administered over a period of 30 minutes and must be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (with a pore size of 0.2-1.2 µm)
 - The NULOJIX infusion must be completed within 24 hours of reconstitution of the NULOJIX lyophilized powder. If not used immediately, the reconstituted vials and infusion solution may be stored under refrigeration conditions: 2°-8°C (36°-46°F) and protected from light for up to 24 hours (a maximum of 4 hours of the total 24 hours can be at room temperature, 20°-25°C (68°-77°F), and room light)
 - Infuse Nulojix in a separate line from other concomitantly infused agents. NULOJIX should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of NULOJIX with other agents

B. Storage (16.1)

This section should include storage conditions for the unreconstituted product during its shelf life. Delete the second paragraph, (b) (4)

C. Syringe Pouch Labeling

On March 11, 2011, DMEPA received a sample silicone-free syringe submitted by Bristol-Myers Squibb that they intend to market with Nulojix. We reviewed Orenzia post-marketing reports, another product which requires the use of a silicone-free syringe for preparation and identified reports of the use of inappropriate syringes when reconstituting the product. cursory review of the syringe and syringe pouch labeling identified the following deficiencies:

- **Pouch Labeling Deficiencies**
 - Confusing presentation of the total milliliter volume measurable by the syringe [because it currently states (b) (4)]
 - Lack of prominence of the “silicone oil free” statement
 - Lack of statement on the pouch labeling which clearly conveys that the pharmacist/preparer must use the enclosed syringe when preparing Nuojix
 - Overcrowding of pouch labelin; (b) (4); which are not useful to the US (English speaking) population.

- **Syringe Deficiencies**

- Volumetric designation, “mL” appears next to the (b) (4) line rather than next to the number 12.

Additionally, since this syringe will be co-packaged with Nulojix, the Applicant should submit the proposed pouch labeling with syringe to the BLA for review prior to approval.

4.2 COMMENTS TO THE APPLICANT

A. General Comments (Container Label and Carton Labeling)

1. Revise the presentation of the proprietary and established name, strength and route of administration statement is a follows:

Nulojix
(Belatacept) for Injection
250 mg per vial
For Intravenous Use

2. As described in comment A.1. above, revise the strength presentation, (b) (4) to read “250 mg per vial”. The (b) (4) Abbreviations, Symbols, and Dose Designations² which states they should never be used when communicating medical information. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed to not allow such designations to appear in the approved labeling of products. In addition, increase the prominence of the statement.
3. Modify the statement instructing pharmacist/preparers to use the silicone free syringe located on the container label and carton labeling to read, “Only use the included silicone-free syringe included in this package for reconstitution”.
4. Per 21 CFR 208.24, modify the medication guide statement, “Medication Guide Included in Package” to include how the medication guide is provided. For example, the statement could read “Pharmacist: Dispense the enclosed Medication Guide to each patient”.

B. Container Label

1. Relocate the statement, “Discard unused portion” to immediately follow the statement, “Single-Use Vial”.
2. Per 21 CFR 201.55, modify the statement, “See package insert for dosage...information” to read, “Usual Dosage: See complete prescribing information.”
3. As currently presented the principal display panel looks crowded. Minimize the company name and address so as to not overcrowd the principal display panel.

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, accessed 15APR2009.

C. Carton Labeling

1. Revise the statement (b) (4) located on the back panel to read "Single-Use Vial, Discard Unused Portion."
2. Revise the usual dosage statement to read, "Usual Dosage: See complete prescribing information." In addition, delete the statement, (b) (4) because this statement provides partial dosage and administration information.
3. Remove the statement, (b) (4)
4. A placeholder for the lot number and expiration date is not indicated on the proposed carton labeling, include the lot number and expiration date.

Appendix A : Container Label



(b) (4)

Appendix E- Carton Labeling

(b) (4)



MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: March 9, 2010

TO: June Germain, M.S Regulatory Project Manager
Patrick Archdeacon, M.D., Medical Officer
Division of Special Pathogen and Transplant Products

FROM: Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: BLA # 125288

APPLICANT: Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, N.J. 08543-4000

DRUG: Nulojix (belatacept)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants

CONSULTATION REQUEST DATE: August 14, 2009

DIVISION ACTION GOAL DATE: May 1, 2010

PDUFA DATE: May 1, 2010

I. **BACKGROUND:** Maintenance of a functioning renal transplant mandates lifelong immunosuppressive therapy to prevent immune destruction of the graft. Current immunosuppressive regimens yield 1 year survival rates of 89% for cadaveric and 94% for living donor grafts, and 5 year survival rates for cadaveric and living related donor renal transplants of 66% and 79%, respectively. The most common causes of long-term subject and graft loss are cardiovascular disease and chronic allograft nephropathy (CAN), respectively. The principal therapies currently available for renal transplantation are the calcineurin inhibitors (CNIs), cyclosporine (CsA) and tacrolimus; however, these contribute to long-term allograft loss and subject death, since they are inherently nephrotoxic. In addition, they cause or exacerbate cardiovascular risks, including hypertension, hypercholesterolemia, and diabetes mellitus. At present, there are no other approved agents that can replace CNIs as maintenance therapy after renal transplant. One agent, sirolimus, has been approved for use in a CNI-sparing regimen. However, CNIs must still be used with sirolimus for at least 3 months post-transplantation, and it is approved only for subjects at low to moderate risk of graft loss.

Belatacept is a member of a new class of immunosuppressive therapy for renal transplantation. It is a fusion protein that binds to the B7 molecules on the surface of antigen-presenting cells (APCs) inhibiting requisite co-stimulation for T cell activation. Belatacept differs from existing immunosuppressants in the restricted distribution of its molecular target and the specificity of its effect. In preclinical studies, the major safety concern identified relates to the potential for an increased incidence of virally-induced tumors in the presence of long-term immunomodulation.

The current BLA is submitted in support of belatacept in the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. Belatacept is used in combination with an interleukin-2 (IL-2) receptor antagonist (basiliximab), a mycophenolic acid (MPA), and corticosteroids. The two pivotal studies for this application include a more intensive belatacept regimen (MI: 10 mg/kg on Days 1 and 5, then every 2 weeks through Month 3 then every 4 weeks through 6 months; after 6 months, 5 mg/kg of belatacept every 4 weeks until completion of the trial at 36 months) and a less intensive (LI; belatacept 10 mg/kg on Days 1 and 5, and then every 2 weeks through Month 1, and then every 4 weeks through Month 3; after 3 months, 5 mg/kg every 4 weeks until completion of the trial at 36 months). Belatacept is administered intravenously. Subjects in the cyclosporine (CsA) arm were administered cyclosporine twice daily to achieve a trough serum target of 150 – 300 ng/mL the first month and 100 – 250 ng/mL thereafter. Subjects in the CsA treatment group who experienced impaired renal allograft function with anticipated delayed graft function were eligible to receive a polyclonal antilymphocyte preparation until therapy with CSA could be initiated. In such cases, the second dose of basiliximab (IL-2 receptor antagonist) was withheld.

Brief summaries of the two pivotal studies to be inspected are given below.

Study IM 103008: Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunosuppression Trial (BENEFIT)

This multicenter Phase 3 randomized, partially-blinded, active-controlled, parallel-group, multicenter clinical trial was conducted at 104 sites (34 in the U.S. and 70 at foreign sites). The trial was initiated in January, 2006 and concluded in June, 2007.

This study enrolled adults > 18 years of age who were the recipient of a living donor or deceased donor kidney transplant with an anticipated cold ischemia time (CIT) of < 24 hours. Eligible patients were randomized in equal numbers to receive belatacept in a more intensive regimen (MI), a less intensive regimen (LI), or CsA. Blinding between the LI and MI groups was preserved with the use of placebo infusions in the LI treatment group at Weeks 6 and 10. All subjects also received a background immunosuppressive regimen consisting of basiliximab induction therapy and corticosteroid immunosuppressive therapy. See the protocol page 107 - 115 for the Schedule of Study Procedures and Events.

The co-primary endpoints were:

- Subject and graft survival at Month 12. If the lower bound of the CI (belatacept-CsA) was > -10%, then the corresponding belatacept regimen was considered non-inferior to CsA.
- Composite endpoint of measured GFR: Proportion of subjects with a measured GFR < 60 mL/min/1.73 m² at Month 12 or a decrease in measured GFR \geq 10 mL/min/1.73 m² from Month 3 to Month 12.
- Acute rejection. If the upper bound of the CI (belatacept - CsA) was <20%, then the corresponding belatacept regimen was considered non-inferior to CsA.

The key secondary endpoints were:

- Measured GFR at Month 12
- Prevalence of CAN at Month 12

Safety endpoints included the frequency of adverse events (AEs), serious adverse events, and discontinuations due to AEs, as well as results for electrocardiograms, vital signs, and clinical laboratory tests.

Brief Summary of Results

A total of 666 subjects were randomized and transplanted; 660 were randomized, transplanted, and treated. A total of 133 subjects discontinued treatment during the first 12 months after transplantation: 46 (21%) in the belatacept MI group, 45 (20%) in the belatacept LI group, and 42 (20%) in the CsA group. The most common reasons for treatment discontinuation during the first 12 months were lack of efficacy (MI, 12%; LI, 11%; CsA, 5%) and AEs (MI 4%, LI 5%, CsA 9%). Subject and graft survival in the belatacept MI and LI groups at Month 12 was comparable to that for CsA, meeting the pre-specified 10% non-inferiority margin. Both belatacept regimens resulted in improvement over CsA in renal function at Month 12 as assessed by measured GFR and calculated GFR. The proportion of subjects with acute rejection at Month 12 was higher in the belatacept MI (21.9%) and LI (17.3%) groups compared with the CsA (7.2%) group; however acute rejection did not have a clinically meaningful impact on subject and graft survival, renal structure, or function in the belatacept groups.

The safety profile was comparable among the three treatment groups, as was the proportion of subjects with serious infections. Malignant neoplasms occurred in 9, 4, and 2 subjects in the belatacept MI, LI, and CsA groups, respectively. Four cases of post-transplant

lymphoproliferative disorder occurred: 1 in the belatacept MI, 2 in belatacept LI, and 1 in the CsA group. There were no serious autoimmune events in belatacept-treated subjects.

Study IM103027: Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial – EXTended Criteria Donors (BENEFIT-EXT)

This multicenter Phase 3 randomized, partially-blinded, active-controlled, parallel-group, multicenter clinical trial was conducted at 79 sites (28 in the U.S. and 51 at foreign sites). The trial was initiated in March, 2005 and concluded in May, 2008.

This study enrolled adults > 18 years of age who were the first-time recipient of a deceased donor kidney transplant. The donor and/or donor kidney was required to meet at least 1 of the following extended criteria for organ donation:

- Donor age \geq 60 years
- Donor age 50 – 59 years and 1 of the following: cerebrovascular accident (CVA) + hypertension + SCr > 1.5 mg/dL or CVA + hypertension or CVA + SCr > 1.5 mg/dL or hypertension + SCr > 1.5 mg/dL
- Anticipated CIT > 24 hours (subjects should not be randomized if actual CIT is < 20 hours)
- Donor with cardiac death (non-heart beating donor)

Eligible patients were randomized in equal numbers to receive belatacept in a more intensive regimen (MI), a less intensive regimen (LI), or CsA. Blinding between the LI and MI groups was preserved with the use of placebo infusions in the LI treatment group at Weeks 6 and 10.

All subjects also received a background immunosuppressive regimen consisting of basiliximab induction therapy and mycophenolate mofetil and corticosteroid immunosuppressive therapy. See the protocol page 106 - 114 for the Schedule of Study Procedures and Events.

The co-primary endpoints were:

- Subject and graft survival at Month 12. If the lower bound of the CI (belatacept-CsA) was > -10%, then the corresponding belatacept regimen was considered non-inferior to CsA.
- Composite endpoint of measured GFR: Proportion of subjects with a measured GFR < 60 mL/min/1.73 m² at Month 12 or a decrease in measured GFR \geq 10 mL/min/1.73 m² from Month 3 to Month 12.

The key secondary endpoints were:

- Measured GFR at Month 12
- Prevalence of CAN at Month 12

Safety endpoints included the frequency of adverse events (AEs), serious adverse events, and discontinuations due to AEs, as well as results for electrocardiograms, vital signs, and clinical laboratory tests.

Brief Summary of Results

A total of 543 subjects were randomized and transplanted; 536 were randomized, transplanted, and treated. A total of 149 subjects discontinued treatment during the first 12 months after transplantation: 50 (27%) in the belatacept MI group, 45 (26%) in the belatacept LI group, and 54 (30%) in the CsA group. The most common reasons for treatment discontinuation during the first 12 months were AEs (MI, 12%; LI, 16%; CsA, 17%) and lack of efficacy (MI 9%, LI

9%, CsA 8%). A smaller proportion of belatacept-treated subjects had diabetes as the cause of end stage renal disease (14% and 11% in the MI and LI groups, respectively) compared with the CsA group (20%). The mean duration of exposure to belatacept or CsA up to Month 12 was comparable in all treatment groups. Subject and graft survival in the belatacept MI and LI groups at Month 12 was comparable to that for CsA, meeting the pre-specified 10% non-inferiority margin. The MI belatacept regimen was significantly better than CsA in renal function at Month 12 as assessed by measured GFR and calculated GFR; the results for the LI regimen were favorable for the composite endpoint but not statistically significant. Both belatacept regimens resulted in improvement in renal function at Month 12 as assessed by measured GFR and calculated GFR. Both belatacept MI and LI met the 20% protocol-specified margin for non-inferiority for acute rejection; however the proportion of subjects with acute rejection at Month 12 was higher in the belatacept MI (17.4%) and LI (17.7%) groups compared with the CsA group (14.1%). The prevalence of CAN at Month 12 was 45%, 46%, and 52% in the belatacept MI, LI, and CsA groups, respectively.

The safety profile was comparable among the three treatment groups, as was the proportion of subjects with serious infections. Malignant neoplasms occurred in 6 (3%), 5 (3%), and 9 (5%) subjects in the belatacept MI, LI, and CsA groups, respectively. Three cases of post-transplant lymphoproliferative disorder occurred in belatacept-treated subjects: 1 in the belatacept MI and 2 in belatacept LI group. There was one serious autoimmune event (Guillain-Barre syndrome) in a belatacept-treated subject.

Rationale for Site Selection

Belatacept is a new molecular entity; the NDA was submitted for the indication of prophylaxis of organ rejection. The two pivotal trials submitted in support of the belatacept NDA (IM103008 and IM103027) were conducted at Sites 105 and 79, respectively. In Study IM103008, 74% of the subjects were from 71 non-U.S. sites. Sites in Mexico (6) and sites in France (7) enrolled approximately 13% of the total subjects each. In Study IM103027, 77% of the subjects were from 53 non-U.S. sites. Nine sites in France enrolled 18% of the total and 6 sites in Brazil enrolled about 15% of the total subjects.

No major concerns regarding data integrity have emerged from the NDA review thus far. The requested inspection sites represent the largest foreign sites for each of the two pivotal studies. In Study IM103027, it is notable that Site 0091 (Pestana) may have some impact on the conclusions for the endpoint of composite renal function; removing this site from the analysis leads to a significant difference compared to CsA for both of the belatacept arms, whereas overall, the comparison of the belatacept LI arm to CsA was not significant.

II. RESULTS (by Site):

Name of CI or Sponsor Location	Protocol #: and # of Subjects:	Inspection Dates	Interim Classification	Final Classification
Lionel Rostaing, MD/PhD Hopital de Rangueil C H U De Toulouse (Office) Chu De Toulouse Hopital Rangueil Nephrologie- Hemodialyse-Transplantation 1 Avenue Du Pr Jean Pouihes Toulouse Cedex 31054 France	IM103008 Site 076 41 subjects IM 103027 Site 0035 24 subjects	12/07/09 – 12/18/09	Pending	Pending
Guillermo Mondragon-Ramirez, M.D. Instituto Mexicano De Transplantes, SC (Office and Patient Treatment) Av. Alta Tension 580-2 Colonia Cantarranas Cuernavaca, Morelos 62448 Mexico	IM103008 Site 0116 24 subjects	12/14/09 – 12/17/09	NAI	NAI
Rafael Reyes-Acevedo, MD Centenario Hospital Miguel Hidalgo (Office) Galeana Sur 465, Col. Obraje Aguascalientes, Aguascalientes 20230 Mexico	IM103008 Site 0123 25 subjects	12/7/09 – 12/11/09	NAI	NAI
Jose Medina Osmar Pestana, MD Hospital Do Rim E Hipertensao Rua Borges Lagoa 960	IM103027 Site 0091 36 subjects	11/30/09 – 12/4/09	NAI	NAI

Name of CI or Sponsor Location	Protocol #: and # of Subjects:	Inspection Dates	Interim Classification	Final Classification
Vila Clementino Sao Paulo 04028-002 Brazil				
Valter Duro Garcia, PhD Hosp. Dom Vicente Scherer (Office) Avenue Independencia, 155 6° Andar Porto Alegre, Rio Grands Do Sul 90020-090 Brazil	IM103027 Site 0093; 21 subjects	12/7/09 – 12/11/09	NAI	NAI
Flavio Vincenti, MD University of California San Francisco Medical Center Transplant Service 505 Parnassus Avenue, Room 884M San Francisco, CA 94143-0780	IM103008 Site 0010 25 subjects IM103027 Site 010 7 subjects	10/21/09 – 11/04/09	VAI	Pending
Barbara Bresnahan, MD Froedtert Memorial Hospital 9200 Wisconsin Ave. FMCLB 216 Milwaukee, WI 53226	IM103008 Site 006 15 subjects	11/12/09 – 12/3/09	VAI	VAI
Sander Scott Florman, MD (Replaced by Rubin Zhang, MD) Tulane University Hospital and Clinic 1415 Tulane Avenue TW-35 New Orleans, LA 70112	IM103027 Site 0002 26 subjects	12/2/09 – 12/8/09	NAI	NAI
Bristol-Myers Squibb 10 Waterview Blvd., 3 rd Floor Parsippany, NJ 07054	IM103008 IM103027	11/09/09 – 11/25/09	VAI	Pending

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

1. **Lionel P. Rostaing, M.D., Ph.D.**
Chef de Service de Nephrologie-Hemodialyse-Transplantation d'Organes
1 avenue du Pr. Jean Poulhes
Chu de Toulouse Hospital Rangueil
Tourlouse Cedex 9 31054 France
 - a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 41 subjects enrolled in Protocol IM 103008 and 24 subjects enrolled in Protocol IM 103027 at this site. The

observations noted are based on discussions with the FDA field investigator, the Form FDA 483, and Dr. Rostaing's written response to the Form FDA 483 dated January 6, 2010. There were no limitations to the inspection.

- b. **General observations/commentary:** Several deviations from FDA regulations were noted and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan in violation of 21 CFR 312.60, did not maintain adequate drug dispensation records with respect to dates, quantity, and use by subject in violation of 21 CFR 312.62(a), and did not obtain informed consent in accordance with 21 CFR Part 50 from each subject prior to conducting study related tests.

Protocol Violations [21 CFR 312.60]

1. In Protocol IM 103008, Subject 20075 received a kidney from a living donor greater than 60 years of age in violation of the protocol exclusion criterion that living donors be less than 60 years of age.
2. In Protocol 103027, Subject 10055 received a cadaver kidney from a donor between age 50 and 59 years of age, with no extended criteria (CVA + HTN + elevated serum creatinine or CVA + HTN or CVA + elevated serum creatinine or HTN+ elevated serum creatinine) in violation of the inclusion criterion that these extended criteria be present for this donor age.
3. In Protocol 103008, Subject 20057 had the following protocol deviations:
 - a. Pregnancy test results were not documented from Week 4 to Week 52 and from Week 64 to Week 76.

Medical Officer's Comment: Dr. Rostaing's written response states that source documents are available for 13 of the 20 pregnancy test results and that all 20 were performed. Examination of the attachments to Dr. Rostaing's letter confirmed that 13 pregnancy test results for this subject were available. There was no documentation of the remaining seven pregnancy test results.

- b. The source document could not be located for the Day 1 infusion time.
- c. The subject's weight was not documented for Week 40 and 44.

Medical Officer's Comment: Dr. Rostaing's written response acknowledges the missing weights, but note that the medical notes contain weights which indicate that belatacept dosing did not require dose adjustment for weight during Weeks 40 to 44.

4. In Protocol IM 103008, Subject 20112 had the following protocol deviations:
 - a. No baseline biopsy records were located.

Medical Officer's Comment: Dr. Rostaing notes in his written response that the subject was on PLAVIX during the transplant, a contraindication to renal biopsy before clamp removal.
 - b. There is no baseline mammogram documented.
 - c. There is no documentation of administration of Basiliximab on Day 5.

Medical Officer's Comment: Dr. Rostaing provides a copy of this administration record in the attachments to his written response.
5. In Protocol IM 103027, Subject 10060 had the following protocol deviations:

- a. No baseline or Week 52 biopsy was documented.
Medical Officer's Comment: According to Dr. Rostaing's written response, the subject was receiving anticoagulation, a contraindication to renal biopsy.
 - b. No documentation of antiviral prophylaxis for 10 days post-transplantation
Medical Officer's Comment: According to Dr. Rostaing's written response, the subject did not receive prophylaxis for CMV since both donor and recipient were seronegative.
 - c. No source documents were located for belatacept infusions on Day 1, Day 5, and Week 2.
Medical Officer's Comment: Dr. Rostaing in his written response provides copies of source documents of all of these infusions in the attachments.
6. In Protocol IM 103008, Subject 20004 had the following protocol violations:
- a. No baseline biopsy records were located.
Medical Officer's Comment: According to Dr. Rostaing's written response, the decision to not perform a baseline biopsy was made by the operating surgeon based on his intraoperative findings, and this information was recorded on the CRF. A copy of the CRF documenting the surgeon's decision is included in the attachments.
 - b. No documentation exists for the administration of methylprednisolone or an oral corticosteroid on Day 4, as required by the protocol.
Medical Officer's Comment: Dr. Rostaing includes a copy of the source document demonstrating prednisolone administration on Day 4 in the attachments.
7. In Protocol IM 103027, Subject 10055 had a weight of 59 kg on Day 1 and a weight of 52 kg at the Week 52 visit, representing a 10% decrease in weight. The inspector states that no belatacept dose adjustment was performed as required by the protocol at the next visit, Week 56.
Medical Officer's Comment: Dr. Rostaing's written response states that the belatacept dose was adjusted at Week 56 based on the subject's weight at Week 52, as required by the protocol. Examination of the attachments confirms Dr. Rostaing's observations.
8. In Protocol IM 103027, there is no documentation that Subject 10185 received either methylprednisolone or an oral corticosteroid as required by the protocol on Day 4.
9. For Protocols IM 103027 and IM 103088, no tracking documentation for the refrigerated storage exists for belatacept 100 mg or 250 mg vials received from the sponsor.
10. Both protocols state that belatacept infusions should be administered using a 0.2 μ filter. Filters supplied with the first shipments of drug were utilized, without documentation of where subsequent filters were obtained.
Medical Officer's Comment: Dr. Rostaing's written response states that all subjects received belatacept infusions utilizing 0.2 μ filters, and that he will add a statement to this effect to the study file.
11. In Protocol IM 103027, Subject 10156 had the following protocol deviations:
- a. No baseline biopsy is documented.
Medical Officer's Comment: Dr. Rostaing's written response states that a biopsy was not performed due to a renal hematoma, and states that this is documented on the CRF. Examination of a copy of the CRF which is included in the attachments

confirms Dr. Rostaing's observation.

- b. The medication listing source document for the Day 1 infusion is dated 4/30/06, while the infusion time source document is dated 4/29/09.
- c. There is no documentation of the protocol specified basiliximab on Day 1.

Medical Officer's Comment: Dr. Rostaing included in the attachments a copy of the source document showing that this dose of basiliximab was administered.

Inadequate Drug Disposition Records [21 CFR 312.62(a)]

For Protocol IM 103027 the "Master Clinical Supplies Inventory" record for belatacept 100 mg vials had no batch number documented on any of the pages. The inventory contained doses dispensed, but failed to document subject number, date dispensed, and number of vials dispensed.

Medical Officer's Comment: In discussions with the inspector, she was not aware of another source where the batch number of belatacept given to an individual subject could be determined. However, review of the IVRS records from Dr. Rostaing's site which were submitted as exhibits from the Bristol-Myer Squibb inspection (detailed below) demonstrates that the patient number, date dispensed, vial number(s) dispensed, and number of vials dispensed is recorded on this source document. Therefore, it appears that confirmation of the identity of the 100 mg belatacept vial number dispensed for a given subject can be confirmed.

Informed Consent [21 CFR Part 50]

1. For Protocol IM 103008, 15 of the 41 Informed Consent documents reviewed did not contain contact address and telephone number by which a subject could obtain information on the study.
2. For Protocol IM 103027, 9 of the 27 Informed Consent documents reviewed did not contain contact address and telephone number by which a subject could obtain information on the study.

- c. **Assessment of data integrity:** There were numerous protocol violations cited by the inspector at this site, in addition to drug dispensation and informed consent violations. Based on a review of Dr. Rostaing's written response and attachments dated January 6, 2010, it appears that the majority of the protocol violations could not be supported. The remaining protocol violations are minor in nature and should not impact study outcome. The Informed Consent violations do not appear to significantly impact subject safety. The Master Clinical Supplies Inventory for belatacept 100 mg doses did not have batch numbers, subject numbers, date dispensed, and number of vials dispensed documented although doses dispensed were recorded. However, the IVRS log records patient number, date and time of assignment, number of vials assigned, and vial number(s) assigned, thus allowing for determination of this information for each subject. At present, the data derived from this site appear acceptable for use in support of the NDA. If conclusions change upon receipt of the EIR, the review division will be notified expeditiously.

2. **Guillermo Mondragon-Ramirez, M.D.**
Instituto Mexicano de Transplantes, SC
Av. Alta Tension 580-2

**Colonia Cantarranas
Cuernavaca, Morelos 62448**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 28 subjects screened and 24 subjects were enrolled. There were 20 records reviewed comprehensively by the inspector; 100% of Informed Consent documents were reviewed. The observations noted are based on the EIR. There were no limitations to the inspection.
- b. **General observations/commentary:** The belatacept reconstitution and infusion times were not recorded prior to 2007 at this site; however, clinic source documents were available to determine reconstitution times. In 2007, the site started to record the exact preparation time for the infusion and the administration of the test article in study records, so that the protocol-specified requirement for infusion within 24 hours of reconstitution is documented. Clinical monitoring was adequate. No significant issues concerning the clinical investigator site were identified during the inspection, and a Form FDA 483 was not issued.
- c. **Assessment of data integrity:** Based on the EIR for this site, data derived from this site appear acceptable for use in support of the NDA.
3. **Rafael Reyes-Acevedo, M.D.
Centenario Miguel Hidalgo de Aguascalientes, SC
C. Galeana Sur 465 Col. Obraje
C.P., Aguascalientes 20230
Mexico**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 27 subjects screened and 25 subjects were enrolled; 2 subjects discontinued due to death and one subject discontinued due to an adverse event. There were 19 records reviewed comprehensively by the inspector; 100% of Informed Consent documents were reviewed. The observations noted are based on the EIR. There were no limitations to the inspection.
- b. **General observations/commentary:** This clinical site generated a worksheet in 2008 to capture the belatacept reconstitution and infusion times. For all study subjects, belatacept was administered less than 24 hours after reconstitution, as required by the protocol. Clinical monitoring by (b) (4) was adequate, and BMS Quality Assurance monitors visited the site on a regular basis. Although monitor queries were sometimes not addressed within 5 days, the latest response observed was 10 days. No significant issues concerning the clinical investigator site were identified during the inspection, and a Form FDA 483 was not issued.

- c. **Assessment of data integrity:** Based on the EIR for this site, data derived from this site appear acceptable for use in support of the NDA.

4. Jose Medina Osmar Pestana, M.D.

**Hospital Do Rim E Hipertensao
Rua Borges Lagoa 960
Vila Clementino
Sao Paulo 04028-002
Brazil**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 44 subjects screened, 37 subjects were enrolled, and 36 received study drug; 2 subjects died and 1 was discontinued. The observations noted are based on the EIR. A comprehensive audit of seven enrolled subject records was conducted, and 100% of the Informed Consent documents were reviewed. There were no limitations to the inspection.
- b. **General observations/commentary:** The inspection of this site did not reveal regulatory violations. A Form FDA 483 was not issued. The following inspectional findings are reported at the request of the review division. All episodes of acute rejection, graft loss, and death were accurately recorded. Creatinine clearance was collected as specified in the protocol and recorded accurately in the CRF. The EBV serostatus and Banff scores were accurately reported in the CRF. There were no unreported cases of progressive multifocal leukoencephalopathy or post-transplant lymphoproliferative disorder. Concomitant medications were accurately recorded.
- c. **Assessment of data integrity:** Based on the EIR for this site, data derived from this site appear acceptable for use in support of the NDA.

5. Valter Duro Garcia Ph.D.

**Avenue Independencia, 155 6°
Andar
Porto Alegre, RioGrands Do Sul
90020-090
Brazil**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 25 subjects screened and 21 subjects were enrolled; 2 subjects died and 3 were discontinued. The observations noted are based on the EIR. A comprehensive audit of 17 enrolled subjects' records was conducted, and 100% of the Informed Consent documents were reviewed. There were no limitations to the inspection.

- b. **General observations/commentary:** The inspection of this site did not reveal regulatory violations. A Form FDA 483 was not issued. The following inspectional findings are reported at the request of the review division. All episodes of acute rejection, graft loss, and death were accurately recorded. Creatinine clearance was collected as specified in the protocol and recorded accurately in the CRF. The EBV serostatus and Banff scores were accurately reported in the CRF. There were no unreported cases of progressive multifocal leukoencephalopathy or post-transplant lymphoproliferative disorder. Concomitant medications were accurately recorded.
- c. **Assessment of data integrity:** Based on the EIR for this site, data derived from this site appear acceptable for use in support of the NDA.

6. **Flavio Vincenti, M.D.**
University of California San Francisco Medical Center
Transplant Service
505 Parnassus Avenue
Room 884M
San Francisco, CA 94143-0780

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. For Protocol IM 103008 there were 27 subjects screened, 25 subjects enrolled, and 12 subjects completed the study; all 27 subject records were reviewed by the inspector. For Protocol IM 103027, there were 9 subjects screened, 7 subjects enrolled, and 7 subjects completed the study; 9 subject records were reviewed. The observations noted are based on the EIR, preliminary communications with the FDA field investigator, and a written response from Dr. Vincenti dated November 9, 2009. There were no limitations to the inspection.
- b. **General observations/commentary:** Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60, did not promptly report to the sponsor a serious adverse event (SAE), in violation of 21 CFR 312.64, and did not obtain informed consent in accordance with 21 CFR Part 50 from each subject prior to conducting study related tests.

Protocol Violation [21 CFR 312.60]

Subjects 20051, 20181, and 20254 were enrolled in Protocol IM 103008 in violation of the exclusion criteria for donors with extended criteria, specifically enrolling subjects who received kidneys from donors age \geq 60 years of age. The subjects were allowed to continue in the study.

Delay in Serious Adverse Event Reporting [21 CFR 312.64]

Subject 20254 enrolled in Protocol IM 103008 died suddenly in hospice on

(b) (6) The subject's wife notified the study coordinator at Dr. Vincenti's site of the death on 2/19/09. The EIR states that the SAE form was completed and faxed on 4/29/09 to the sponsor, in violation of the protocol requirement that SAEs be reported to the sponsor immediately. However, in Dr. Vincenti's written response, he states that the form was transmitted to the sponsor on 2/21/09. At the sponsor's request, corrections were made on this form to reflect new information from the death certificate, so the original date was crossed out, initialed, and replaced with 4/28/09. A copy of this form is included with his written response.

Medical Officer's Comment: The SAE appears to have been reported (b) (6) after the site became aware of the subject's death, rather than several months later, as described in the EIR. However, the death should have been reported "immediately", rather than (b) (6)s later. The necessity for alterations made to the original SAE report form (rather than filing updates or amended forms) is unclear, although there does not appear to be any fraudulent intent.

Informed Consent Violations [21 CFR Part 50]

Subjects 20264 and 203118 enrolled in Protocol IM 103008 did not sign the most recent version of the Informed Consent document. The most recent version of the Informed Consent document dated 8/3/09 and approved by the IRB on 9/7/09 were not signed by these two subjects who were active in the study protocol as outpatients at the time of the inspection. In Dr. Vincenti's written response of November 9, 2009, he notes that the subjects had been informed of the changes in the Informed Consent document and the intent was to have them sign the document at their upcoming visits on 11/13/09 and 11/17/09.

- c. **Assessment of data integrity:** Although there were protocol, serious adverse event reporting, and informed consent violations reported at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

7. Barbara Bresnahan, M.D.
Froedtert Memorial Hospital
9200 Wisconsin Ave.
FMCLB 216
Milwaukee, WI 53226

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 16 subjects screened and 16 subjects were randomized, although one subject was dropped at the time of surgery because study drug was not administered. There were five records reviewed comprehensively by the inspector, and two additional records were skimmed; 100% of the informed consent documents were reviewed. The observations noted are based on the EIR and preliminary communications with the FDA field investigator. There were no limitations to the inspection.

- b. **General observations/commentary:** Deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60.

Protocol Violations [21 CFR 312.60]

Subject 20102 received only the second of two scheduled doses of basiliximab and Subject 20243 received the first dose of basiliximab two days late. These protocol deviations were not reported to the sponsor.

- c. **Assessment of data integrity:** Although there were protocol violations reported at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

**8. Sander Scott Florman, M.D.
Rubin Zhang, M.D.
Tulane University Hospital and Clinic
1415 Tulane Avenue TW-35
New Orleans, LA 70112**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. The EIR states that Dr. Zhang took over the responsibilities of the Principal Investigator for the study on 9/21/09. Dr. Sander Florman was the Principal Investigator for the study from 3/9/05 until 9/20/09; he subsequently moved out of state for employment reasons. There were 27 subjects screened and 27 subjects were enrolled. There were nine records reviewed comprehensively by the inspector and 100% of the Informed Consent documents were reviewed. The observations noted are based on the EIR. There were no limitations to the inspection.
- b. **General observations/commentary:** The inspection of Dr. Zhang's site did not reveal regulatory violations. A Form FDA 483 was not issued.
- c. **Assessment of data integrity:** Based on the EIR for this site, data derived from this site appear acceptable for use in support of the NDA.

**9. Bristol-Myers Squibb
Route 206 & Province Line (PO Box 4000)
Princeton, NJ 08543**

- a. **What was inspected:** The FDA inspector reviewed Bristol-Myers Squibb procedures and records for Protocols IM 103008 and IM 103027. The inspection began on November 9, 2009 and was concluded on November 25, 2009. Inspectional coverage was given to the eight clinical investigators identified by DSI for clinical site inspection. The inspection focused on evaluation of the adequacy of monitoring and corrective actions taken by the

sponsor/CRO, deviations related to key safety and efficacy endpoints, test article accountability, adverse events evaluation and reporting, delegation of responsibilities, contractual agreements, and general site monitoring practices. The observations noted are based on the EIR including the Form FDA 483 and Bristol-Myer Squibb's written response dated December 8, 2009.

- b. **General observations/commentary:** Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these observations. The investigation documented that the investigator did not provide investigators with the information needed to conduct the study properly, did not ensure proper monitoring of the study, and did not ensure the study was conducted in accordance with the protocol and/or investigational plan in violation of 21 CFR 312.50 and failed to ensure compliance of study conduct through clinical site monitoring in violation of 21 CFR 312.56.

Failure to provide investigators with necessary information, failure to ensure proper monitoring of an investigational study, and failure to ensure that the study was conducted in accordance with the protocol [21 CFR 312.50]

1. For 3 out of 8 clinical sites reviewed the Sponsor and CRO failed to ensure that all deviations and ongoing issues of non-compliance noted during site monitoring visits were resolved in a timely manner. Examples include delay in central lab result interpretations, delayed SAE notifications, and belatacept infusions not being done per protocol at Dr. Rostaing's site; acute rejection biopsies not being forwarded to the Central Path Lab at Dr. Mondragon's site; and failure to provide the subject's weight for drug dosing at Dr. Reyes' site.

Medical Officer's Comment: At the sites of Dr. Mondragon and Reyes, all of the issues identified as problematic during monitoring were ultimately resolved, although not in a timely fashion (five months to more than one year). At Dr. Rostaing's site, most of the action items of noncompliance were also ultimately resolved. There are four items for which no resolution date is recorded; however, the items no longer appear on subsequent monitoring sheets as outstanding. These items for which no resolution is documented are: confirmation of biopsies for Subjects 20003 and 20004, a discrepancy between source data regarding treatment of acute rejection, incomplete operative reports of transplantation for Subjects 20605 and 20734, and RNA sampling taken without consent in Subjects 20023, 20075, and 20110.

2. For 3 out of 8 clinical sites reviewed, the sponsor and CRO failed to ensure that subinvestigators who performed study specific procedures on subjects were provided with the training that they needed to conduct the investigation properly. At Dr. Florman's site, 3 sub-investigators had no documentation of training and 2 sub-investigators had training 6 and 10 months after signing the 1572. There were five sub-investigators with no documented training at Dr. Rostaing's site and two at Dr. Mondragon's site.

Medical Officer's Comment: It is not clear from the EIR or the sponsor's written response whether those sub-investigators with no documentation of training did not actually complete the training or if documentation of completed training was absent.

3. The sponsor failed to ensure adequate measures were established to verify stability of the investigational product (belatacept) once reconstituted. This includes all eight clinical sites reviewed. The protocol specifies that the belatacept study drug must be administered within 24 hours (stored at 2 – 8°C) or 6 hours (at room temperature) after reconstitution to 25 mg/mL. The inspector noted that the IVRS records did not allow documentation of the time of reconstitution; the IVRS records contain only the time that the pharmacist called for the belatacept vials. At the inspector's request, the sponsor provided the Master Clinical Supplies Inventory log; however, this document also did not contain the time of drug reconstitution. Since the sponsor has thus far provided stability data for 1 and 24 hours as part of the NDA submission (per Dr. Ragheb, chemist in DSPTP), administration of belatacept 24 hours or more after reconstitution may result in administration of a lower dose (possibly with degradants) than anticipated. During the inspection, the sponsor's representative stated that the pharmacist would place a sticker on the bag indicating the expiration date based on the time of reconstitution. However, the bag would then be disposed of after completion of the intravenous infusion. The numbers of subjects with study drug doses apparently administered after the 24 hour expiration period (based on the source documents) are given below, together with the range of doses missed.

- a. Vincenti – 13 subjects; 1 – 28 doses per subject
- b. Bresnahan – 9 subjects; 1 – 13 doses per subject
- c. Florman/Zhang – 13 subjects; 2 - 18 doses per subject
- d. Rostaing – 15 subjects; 1 – 16 doses per subject
- e. Mondragon – 2 subjects; 1 dose each
- f. Reyes – 5 subjects; 1 dose each
- g. Medina – 20 subjects; 1 – 10 doses
- h. Garcia – 12 subjects; 1 – 6 doses

Medical Officer's Comment: *Inability to document the time of study drug reconstitution for each subject together with infusion times which are apparently more than 24 hours after the IVRS dispensation time would make it difficult to be assured that the anticipated belatacept dose was actually administered to the subject, since drug degradation may have occurred. In the sponsor's written response dated December 8, 2009, the sponsor states that local pharmacy practice at 7 of the 8 sites inspected would allow determination of the time of reconstitution based on Pharmacy dept records at the sites. DSI requested that the sponsor provide this documentation for the 7 sites where it is available for a sampling of 2 subjects per site where it appears (from the records submitted by the inspector) that the intravenous infusion was administered more than 24 hours after reconstitution. The sponsor provided a written response to this request on February 25, 2010 which included the requested records for 6 of the 7 sites (site records from 1 site are still pending). Review of the provided information demonstrated that records exist at the clinical sites to demonstrate that infusions were administered to subjects within 24 hours of reconstitution. The single exception in this sample of 12 subjects is Subject 20316 at Dr. Reyes site, in whom reconstitution occurred on 8/26/08 (no time given) and intravenous infusion was initiated on 8/27/08 at 9:20 am. Based on this small sample of randomly chosen subjects, it appears likely that most intravenous infusions occurred within 24 hours after reconstitution. If documentation of the time interval between reconstitution and intravenous infusion is critical for all*

records, the review division may wish to consider requesting further records from the sponsor for verification of additional reconstitution times. It should be noted that the failure to include space for recording reconstitution time on the source documents was a significant sponsor oversight in a product with undocumented stability more than 24 hours of reconstitution.

4. Study monitors failed to ensure that the study was monitored in accordance with study specific procedures, monitoring plans, and specific requirements for home infusions. Specifically,
- a. At Dr. Vincente's site, the study monitor did not observe that Subjects 20051 and 20181 received kidneys from donors who were more than 60 years of age, in violation of the protocol.
 - b. For a home infusion visit at the site of Dr. Florman/Zhang, the monitor did not observe that there was no documentation of infusion start and stop times for dosing Week 72, Subject 10006.
 - c. For a home infusion visit at the site of Dr. Florman/Zhang, the inspector noted that post-infusion vital signs were not always taken 30 minutes after completion of the infusion, and instead were taken at infusion completion or 10-20 minutes after infusion completion.

Medical Officer's Comment: The sponsor in the written response of December 9, 2009 notes that the timing of post-infusion vital signs is not specified in the protocol, although the Home Infusion Guidance specifies 30 minute post-infusion vital signs.

5. The sponsor failed to ensure that monitoring reports were submitted as per the Study Specific Procedures and Plan. The monitoring plan states that the "Clinical Site Monitoring Report" would be submitted within five days after completion of the site visit. Monitoring reports submitted outside this timeframe occurred at sites 006 (Bresnahan), 0116 (Mondragon), and 0123 (Reyes). The inspector noted the following monitoring reports submitted later than one month after conducting the site visit:
- a. Bresnahan: 8 of the 41 monitoring reports were submitted more than 1 month after conducting the site visit, ranging from 1 ½ months to 2 years 8 months.
 - b. Mondragon: 12 of the 39 monitoring reports were submitted more than 1 month after conducting the site visit, ranging from 3 to 6 months.
 - c. Reyes: 20 of the 36 monitoring reports were submitted more than 1 month after conducting the site visit, ranging from 2 to 6 months.

Failure to ensure compliance of study conduct through clinical site monitoring [21 CFR 312.56]

The sponsor failed to ensure compliance of study conduct through clinical site monitoring when sites 0123 (Reyes), 0116 (Mondragon), and 076 (Rostaing) were continually found to inadequately conduct the studies in accordance with the signed statement of the investigator and the investigational plan. (See also

Item 1.a. above).

Medical Officer's Comment: As previously discussed in Item 1.a. above, compliance with study conduct was problematic at the sites of Dr. Reyes, Mondragon, and Rostaing. The inspector documents that most issues were ultimately resolved by detection during monitoring with attempts at resolution by follow-up letters and teleconferences, as well as continued monitoring. The sponsor agrees that the problematic items were not always resolved in a timely fashion. These issues do not appear to impact data integrity.

- c. **Assessment of data integrity:** A major issue of concern with respect to data integrity identified during the inspection of Bristol-Myers Squibb was the inability to document time of reconstitution prior to intravenous administration in a product with stability data only out to 24 hours. The sponsor's written response states that at most sites, other site records allow precise determination of time of belatacept reconstitution to ensure that intravenous administration actually occurred less than 24 hours after reconstitution. Sample documents from each site inspected (with the exception of Drs. Vincenti Florman/Zhang) confirm the sponsor's claim that reconstitution date and time can be verified in 11 of the 12 examples requested. Although this is a small sample, it appears that in most cases, verification of time of reconstitution and infusion is available at the study sites.

Another issue of concern is the ability of the sponsor to ensure compliance with study procedures and requirements, in particular at Dr. Rostaing's site. Study monitoring appears to have been effective at detecting issues requiring resolution, but achievement of resolution of these issues was not always documented. The issues identified as unresolved do not appear to affect data integrity.

The sponsor has demonstrated that reconstitution occurred less than 24 hours prior to intravenous infusion in most of the instances requested by DSI. Since this issue has been satisfactorily resolved, the data collected and maintained at the sponsor's site, as it pertains to the eight clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348.810 appear consistent with that submitted to the agency as part of and in support of BLA125288 and are considered reliable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, inspection of the sites of Drs. Mondragon-Ramirez, Reyes-Acevedo, Pestana, Garcia, Vincenti, Bresnahan, and Florman/Zhang revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspections documented minor regulatory violations at the sites of Drs. Vincenti, Bresnahan, and Florman/Zhang regarding protocol, adverse event reporting, and informed consent violations. In general, the studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

There were numerous protocol violations cited by the inspector at Dr. Rostaing's site, in addition to drug dispensation and informed consent violations. From review of Dr. Rostaing's

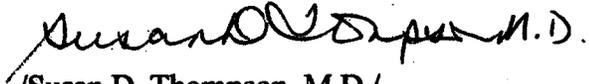
written response and attachments dated January 6, 2010, it appears that the majority of the protocol violations were cited in error. The Informed Consent violations do not appear to significantly impact subject safety. The belatacept Master Clinical Supplies Inventory for belatacept 100 mg did not have batch numbers documented and doses dispensed were recorded; the subject number, date dispensed, and number of vials dispensed were not recorded. However, the IVRS records contained information for vial numbers, subject numbers, date, and number of vials dispensed. Although failure to complete the Master Clinical Supplies Inventory is a regulatory violation, drug accountability appears acceptable at Dr. Rostaing's site.

An issue of concern with respect to data integrity which resulted from the inspection of Bristol Myers Squibb was the inability to document time of belatacept reconstitution prior to intravenous administration in a product with stability data submitted to the FDA only out to 24 hours. Study records obtained during the inspection contained time of dispensation in the IVRS log and belatacept infusion start and stop date and times are contained in the infusion log. However, neither document contained entries for time and date of belatacept reconstitution. The sponsor's written response stated that at most sites, other site records (e.g., Pharmacy records) would allow precise determination of time of belatacept reconstitution. Sample documents from each site inspected (with the exception of Dr. Florman/Zhang; the sponsor has yet to provide Dr. Vincente's records) to document the sponsor's claim that reconstitution date and time can be verified were requested and provided in a written submission of February 25, 2010. Sample documents from each site inspected (with the exception of Drs. Vincenti Florman/Zhang) document the sponsor's claim that reconstitution date and time can be verified in 11 of the 12 examples requested. Although this is a small sample, it appears that in most cases, verification of time of reconstitution and infusion is available at the study sites.

Another issue raised during the inspection of Bristol-Myer Squibb is the ability of the sponsor to ensure compliance with study procedures and requirements, in particular at Dr. Rostaing's site. Study monitoring appears to have been effective at detecting issues requiring resolution, but achievement of resolution of these issues was not always documented. Additionally, resolution was not always accomplished in a timely manner. The issues identified as unresolved do not appear to affect data integrity.

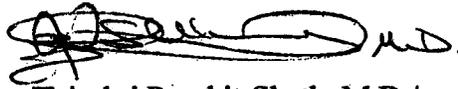
In conclusion, the sponsor has demonstrated that belatacept reconstitution occurred less than 24 hours prior to intravenous infusion in the majority of the examples requested. Therefore, the data collected and maintained at the sponsor's site and the eight clinical sites audited appear consistent with that submitted to the agency as part of and in support of BLA125288 and may be used to support the NDA.

Follow-Up Actions: The observations for Drs. Rostaing are based on preliminary communications with the FDA Field investigators and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.



/Susan D. Thompson, M.D./
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Good Clinical Practice Branch II
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CONCURRENCE:



/Tejashri Purohit-Sheth, M.D./
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Memorandum

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: November 23, 2009

From: Suchitra Balakrishnan, M.D., Ph.D.
Christine Garnett, Pharm. D. *Christine Garnett*

Through: Norman Stockbridge, M.D., Ph.D. *Norman Stockbridge*
Division Director
Division of Cardiovascular and Renal Products /CDER

To: June Germain
Regulatory Project Manager
Division of Special Pathogens and Transplant Products

Subject: QT-IRT Consult to BLA 125288

This memo responds to your consult to us dated Aug 21 2009, regarding QT assessment for belatacept sponsored by Bristol-Myers Squibb (BMS). The QT-IRT received and reviewed the following materials:

- Your consult
- Summary of Clinical safety (eCTD 2.7.4) dated September 21, 2009
- CSRs for IM103027 and IM 103008 Previous review by the QT-IRT for belatacept dated April 4, 2008 under BBIND 1418

Question from Review Division

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 ms or > 60 ms compared with baseline and > 450 ms was similar across the 3 treatment groups (belatacept MI, belatacept LI, and cyclosporine). Do you agree with the sponsor's conclusion?

QT-IRT Comments for DSPTP

Based on review of the ECG data and narratives for AEs associated with QT prolongation, i.e. sudden death, cardiac arrest, significant ventricular arrhythmias, in clinical trials IM103008 and IM 103027, it seems reasonable to conclude that there are no large effects on the QT interval due to belatacept based on the following:

- The number of subjects with an absolute QTcB over 500 ms or with a 60 ms change from baseline was similar across the cyclosporine and belatacept treatment arms.
- SAEs related to QT prolongation occurred in all treatment arms. On review of the narratives it seems reasonable to conclude that they were related to underlying comorbidities (HTN, DM, CAD) and complications (hypotension, sepsis, pulmonary embolism, renal vein thrombosis, acute MI etc.) expected in this population of renal transplant recipients. There were no reports of QT prolongation associated with these events.

BACKGROUND

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. Because belatacept is a fusion protein with molecular weight of approximately 90,619 Da and is highly specific for its target, a thorough clinical QT study was not conducted. Routine safety ECG monitoring was performed in clinical trials involving healthy subjects and *de novo* renal transplant patients. Although two belatacept-based [more-intensive (MI) and less-intensive(LI)] 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).

Non-Clinical Experience

In vivo assessments of the cardiovascular safety pharmacology of belatacept following intravenous (i.v.) administration in monkeys have included a single-dose study at doses up to 90 mg/kg, and 1-month (every 2 days) and 6-month (once weekly) intermittent-dose toxicity studies at doses up to 50 mg/kg. Non-clinical evaluations have suggested no evidence of cardiovascular or hemodynamic abnormalities.

Reviewer's Comment: This information was reviewed by the QT-IRT in our previous review dated April 4, 2008 under BB IND 1418.

Clinical Experience

Source: Summary of Clinical Safety eCTD 2.7.4

In the clinical development program, 1436 subjects were treated with belatacept, of whom 949 were treated in 3 core *de novo* renal transplant studies. The median exposure was approximately 2 years, with approximately 70 subjects treated for > 5 years, permitting an adequate assessment of safety.

Overall, the total number of deaths from the 3 core studies up to database lock was lower in the belatacept LI [19 (4.0%)] group than in the belatacept MI [29 (6.1%)] and cyclosporine [36 (7.6%)] groups. There was no predominant cause of death among study subjects in any treatment group.

Table 1: Adverse Events in at Least 2 Subjects Leading to the Outcome of Death Up to Database Lock (Pooled Core Studies)

System Organ Class (4) Preferred Term (4)	Belatacept - MI N = 477	Belatacept - LI N = 472	Cyclosporine N = 476	Total N = 1425
TOTAL SUBJECTS WITH AN EVENT	28 (5.9)	17 (3.6)	35 (7.4)	80 (5.6)
INFECTIONS AND INFESTATIONS	12 (2.5)	7 (1.5)	12 (2.5)	31 (2.2)
PNEUMONIA	3 (0.6)	9 (1.9)	4 (0.8)	7 (0.5)
SEPSIS	1 (0.2)	2 (0.4)	1 (0.2)	4 (0.3)
SEPTIC SHOCK	1 (0.2)	1 (0.2)	4 (0.8)	6 (0.4)
POLYMA VIRUS-ASSOCIATED NEPHROPATHY	0	2 (0.4)	0	2 (0.1)
CARDIAC DISORDERS	7 (1.5)	2 (0.4)	11 (2.3)	20 (1.4)
CARDIAC ARREST	3 (0.6)	0	5 (1.1)	8 (0.6)
MYOCARDIAL INFARCTION	0	2 (0.4)	2 (0.4)	4 (0.3)
CARDIO-RESPIRATORY ARREST	1 (0.2)	0	2 (0.4)	3 (0.2)
RESPIRATORY, THORACIC AND MEDGASTRINAL DISORDERS	3 (0.6)	3 (0.6)	7 (1.5)	13 (0.9)
ACUTE RESPIRATORY FAILURE	0	1 (0.2)	2 (0.4)	3 (0.2)
PULMONARY EMBOLISM	0	0	2 (0.4)	2 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE REACTIONS	6 (1.2)	2 (0.4)	2 (0.4)	10 (0.7)
SUDEN DEATH	4 (0.8)	1 (0.2)	0	5 (0.4)
MULTI-ORGAN FAILURE	2 (0.4)	0	1 (0.2)	3 (0.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL. CYSTS AND POLYPS)	2 (0.4)	3 (0.6)	3 (0.6)	8 (0.6)
GASTROINTESTINAL DISORDERS	2 (0.4)	2 (0.4)	3 (0.6)	7 (0.5)

System Organ Class (4) Preferred Term (4)	Belatacept - MI N = 477	Belatacept - LI N = 472	Cyclosporine N = 476	Total N = 1425
TRAUMA, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.2)	0	4 (0.8)	5 (0.4)
COMPLICATIONS OF TRANSPLANTED KIDNEY	1 (0.2)	0	2 (0.4)	3 (0.2)
NEURALS SYSTEM DISORDERS	2 (0.4)	1 (0.2)	2 (0.4)	5 (0.4)
CEREBROVASCULAR ACCIDENT	2 (0.4)	0	2 (0.4)	4 (0.3)
VASCULAR DISORDERS	0	0	3 (0.6)	3 (0.2)
PSYCHIATRIC DISORDERS	0	0	2 (0.4)	2 (0.1)

Source: ISG Appendix 5.15.8

Source table 2.1.2A Summary of Clinical Safety

In the two Phase 3 studies (IM103008 and IM103027), assessments were based upon local non-standardized evaluations of ECGs. Overall, belatacept had no effect on prolongation of the QTc interval. The proportion of subjects with a prolonged QTc interval > 30 ms or > 60 ms compared with baseline and > 450 ms was similar across the 3 treatment groups.

Narrative Reviews for cases of cardiac arrest, cardiopulmonary arrest and sudden death-IM103008

Belatacept MI group

- IM103008-46-20330, a 77 yr old male with history of ischemic heart disease and ESRD due to hypertension died on Day 12 post receiving a renal transplant from cardiac arrest secondary to hypovolemic shock. The subject received the last dose of study medication on day 5.
- IM103008-46-20650, a 74 year old male with HTN and ESRD experienced cardiac arrest on day 76 post renal transplant secondary to sepsis from a complicated UTI. The last dose of belatacept was on Day 75.
- IM103008-118-20353, a 72 yr old male with ESRD due to polycystic kidneys developed cardiopulmonary arrest on Day 206 post-transplant due to adenocarcinoma of the lung.
- IM103008-84-20669, a 41 yr old male with ESRD from indeterminate cause died on Day 160 post-renal transplant due to a sudden death at home. The cause of death was reported

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to be cardiovascular and secondary factors included chronic renal failure, diabetes mellitus and systemic arterial hypertension. The last dose of study drug was on day 141

- IM103008-159-20686 a 53 yr old male with ESRD secondary to type II DM died at home on Day 191 post transplant (reported as sudden death. The cause of death was confirmed as due to pulmonary aspergillosis.

Belatacept LI arm

- IM103008-46-20592, a 61 yr old female with history of ESRD due to polycystic kidney disease and atrial fibrillation died on Day 25 post renal transplant due to cardiac arrest secondary to sepsis from acinetobacter infection. She last received belatacept on Day 5. On day 5 post transplant she experienced cardiac arrest due to PEA from which she was successfully resuscitated.
- IM103008-123-20230 a 19-year-old female with ESRD of unknown cause died on Day 17 post-renal transplant due to bleeding from a coagulation disorder reported as sudden death.

Cyclosporine arm

- IM103008-89-20350 a 50 yr old male with ESRD due to HTN, died on day 4 post renal transplant from cardiac arrest secondary to myocardial ischemia. The last dose of study drug was on day 2.
- IM103008-118-20353, a 20 yr old male with ESRD due to hypoplastic kidney died on day 37 post-renal transplant due to cardiac arrest secondary to pneumonia/respiratory insufficiency.

IM103027

Belatacept MI arm

- IM103027-22-10496, a 70 yr old female with ESRD secondary to type 2 DM died on day 3 post-transplant due to cardiac arrest secondary to hyperkalemia, hypotension and hemorrhage.
- IM103027-93-10027, a 65 yr old male with ESRD secondary to HTN died on day 181 post-transplant due to a cardiac arrest secondary to an acute MI.
- IM103027-53-10399, a 63 yr old female with ESRD secondary to Type II DM developed acute pulmonary edema on Day 17 post transplant and died of cardio-respiratory arrest. She also experienced post-operative iliac vein thrombosis and graft loss.
- IM103027-58-10390, a 68 yr old female with ESRD due to Type 1 DM died on Day 331 post-transplant suddenly. The cause of death was reported as ischemic heart disease but no autopsy was performed. The subject last received study drug on Day 317.
- IM103027-85-10249, a 50 yr old male with ESRD secondary to Type 1 DM, died suddenly at home on day 98 post-transplant immediately after experiencing chest pain. The cause of death was reported as myocardial infarction but no autopsy was performed.

Cyclosporine arm

- IM103027-57-10086, a 64 yr old male with ESRD secondary to Type II DM developed cardiac arrest on Day 49 post-transplant secondary to a PE. Life support was discontinued on Day 55.
- IM103027-2-10002 a 56 year old male with ESRD secondary to Type II DM died on day 196 post-transplant while driving to the hospital when he veered off the road and collapsed. The cause of death was reported as "sudden cardiac standstill and acute renal failure".

Reviewer's Comments: It appears reasonable to conclude that all these cases were due to underlying co-morbidities (HTN, DM, CAD) and complications (hypotension, sepsis, pulmonary embolism, renal vein thrombosis, acute MI etc.) expected in this population of renal transplant recipients. There were no reports of QT prolongation associated with these events. Compared to cyclosporine, there were more AEs of acute pulmonary edema and CHF with the belatacept groups. There are no reports of TdP or other significant ventricular arrhythmias with temporal association to belatacept administration.

ECG RESULTS IN INDIVIDUAL STUDIES

IM 103008 (BENEFIT)

This was a Phase 3, randomized, active-controlled, parallel-group study of the efficacy of 2 partially-blinded belatacept regimens vs. cyclosporine (CsA) as part of a quadruple therapy with mycophenolate mofetil (MMF), corticosteroids, and basiliximab in subjects receiving a renal transplant from a living donor or a deceased donor with anticipated cold ischemic time (CIT) < 24 hours. Subjects were randomized 1:1:1 to treatment with either belatacept (more intensive [MI] or less intensive [LI] regimen) or CsA. Blinding between the LI and MI groups was preserved with the use of placebo infusions in the LI treatment group at Weeks 6 and 10.

12 lead ECGs were obtained at baseline prior to transplant, prior to administration study drug for belatacept subjects at week 12 and at week 52. Subjects were not excluded from the study based on any ECG criteria. Bazett's correction for QT interval was used.

Absolute QTcB values over 500 ms at baseline, 3 months and 12 months were noted in all three treatment and appeared comparable. Increases in QTc interval that were > 60 ms compared with baseline were observed in 4%, 5%, and 2% of subjects in the belatacept MI, belatacept LI, and CsA groups, respectively, at Month 3, and in 5%, 7%, and 4% of subjects in the respective groups at Month 12 (see table 2).

There appeared to be no clinically relevant effects on the PR and QRS intervals (see Table 2 and Table 3).

Table 2: Categorical QTc analyses and Summary of mean ECG parameters at Specified time points -IM103008

Protocol: IM103008

Table 3.7.4A
Proportion of Subjects with Absolute QTc Interval Prolongation at Specified Time Points All Randomized and Transplanted Subjects (ITT)

Page 1 of 1

Visit	Category	Number (%) of Subjects		
		Belatacept - M1 N=219	Belatacept - I1 N=226	Cyclosporine N=221
BASELINE	QTc INTERVAL >450 msec	63/ 214 (29.4)	55/ 220 (25.0)	47/ 208 (22.6)
	QTc INTERVAL >480 msec	23/ 214 (10.7)	11/ 220 (5.0)	16/ 208 (7.7)
	QTc INTERVAL >500 msec	14/ 214 (6.5)	4/ 220 (1.8)	10/ 208 (4.8)
MONTH 3	QTc INTERVAL >450 msec	24/ 196 (12.2)	14/ 195 (7.2)	12/ 191 (6.3)
	QTc INTERVAL >480 msec	7/ 196 (3.6)	5/ 195 (2.6)	2/ 191 (1.0)
	QTc INTERVAL >500 msec	3/ 196 (1.5)	3/ 195 (1.5)	0/ 191 (0.0)
MONTH 12	QTc INTERVAL >450 msec	16/ 187 (8.6)	17/ 185 (9.2)	16/ 183 (8.8)
	QTc INTERVAL >480 msec	4/ 187 (2.1)	2/ 185 (1.1)	5/ 183 (2.7)
	QTc INTERVAL >500 msec	3/ 187 (1.6)	0/ 185 (0.0)	3/ 183 (1.6)

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Table 3.7.4B
Proportion of Subjects with Increase in QTc Interval from Baseline at Specified Time Points All Randomized and Transplanted Subjects (ITT)

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Visit	Category	Number (%) of Subjects		
		Belatacept - M1 N=219	Belatacept - I1 N=226	Cyclosporine N=221
BASELINE	QTc INTERVAL INCREASES FROM BASELINE >20 msec	0/ 214 (0.0)	0/ 220 (0.0)	0/ 208 (0.0)
	QTc INTERVAL INCREASES FROM BASELINE >60 msec	0/ 214 (0.0)	0/ 220 (0.0)	0/ 208 (0.0)
MONTH 3	QTc INTERVAL INCREASES FROM BASELINE >20 msec	13/ 196 (6.6)	22/ 195 (11.3)	12/ 191 (6.3)
	QTc INTERVAL INCREASES FROM BASELINE >60 msec	7/ 196 (3.6)	18/ 195 (9.2)	4/ 191 (2.1)
MONTH 12	QTc INTERVAL INCREASES FROM BASELINE >20 msec	24/ 187 (12.8)	27/ 185 (14.6)	21/ 183 (11.5)
	QTc INTERVAL INCREASES FROM BASELINE >60 msec	8/ 187 (4.3)	12/ 185 (6.5)	7/ 183 (3.8)

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Table 3.7.4C
Summary of ECG Parameters at Specified Time Points All Randomized and Transplanted Subjects (ITT)

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ECG Parameter	Month	Number (%) of Subjects			
		Belatacept - M1 N=219	Belatacept - I1 N=226	Cyclosporine N=221	
QTc (msec)	BASELINE	N	212	217	207
		MEAN (SD)	410.4 (59.4)	408.6 (60.9)	417.1 (61.5)
		MEAN	418.0	419.0	414.0
		MIN - MAX	208.0 - 554.0	70.0 - 620.0	136.0 - 534.0
	MONTH 3	N	196	195	191
		MEAN (SD)	396.3 (44.4)	393.1 (44.3)	390.8 (40.5)
		MEAN	403.0	400.0	397.0
		MIN - MAX	280.0 - 489.0	200.0 - 491.0	241.0 - 487.0
	MONTH 12	N	187	185	183
		MEAN (SD)	396.5 (44.6)	392.7 (46.4)	393.2 (46.7)
		MEAN	403.0	400.0	393.0
		MIN - MAX	285.0 - 502.0	216.0 - 508.0	160.0 - 573.0
Q1 - Q3	376.0 - 424.0	378.0 - 416.0	370.0 - 420.0		

Summary of ECG Parameters at Specified Time Points
All Randomized and Transplanted Subjects (ITT)

ECG Parameter	Month		Number (%) of Subjects		
			Belatacept - MI N=219	Belatacept - LI N=226	Cyclosporine N=221
PR INTERVAL (msec)	BASELINE	N	215	221	207
		MEAN (SD)	162.5 (29.1)	160.8 (25.8)	158.4 (29.3)
		MEDIAN	160.0	160.0	160.0
		MIN - MAX	40.0 - 262.0	30.0 - 240.0	45.0 - 260.0
	Q1 - Q3	146.0 - 160.0	146.0 - 160.0	146.0 - 160.0	
	MONTH 3	N	196	198	186
		MEAN (SD)	164.7 (53.9)	159.9 (26.3)	156.0 (28.5)
		MEDIAN	160.0	160.0	156.5
		MIN - MAX	30.0 - 769.0	34.0 - 294.0	30.0 - 240.0
	Q1 - Q3	140.0 - 180.0	143.0 - 174.0	138.0 - 170.0	
	MONTH 12	N	187	183	180
		MEAN (SD)	165.1 (32.9)	164.0 (26.0)	159.2 (28.1)
MEDIAN		160.0	160.0	156.0	
MIN - MAX		43.0 - 216.0	78.0 - 240.0	45.0 - 260.0	
Q1 - Q3	144.0 - 182.0	146.0 - 164.0	140.0 - 176.0		

Summary of ECG Parameters at Specified Time Points
All Randomized and Transplanted Subjects (ITT)

ECG Parameter	Month		Number (%) of Subjects		
			Belatacept - MI N=219	Belatacept - LI N=226	Cyclosporine N=221
QRS INTERVAL (msec)	BASELINE	N	215	221	212
		MEAN (SD)	89.9 (45.0)	84.9 (17.3)	86.7 (20.2)
		MEDIAN	84.0	84.0	86.0
		MIN - MAX	27.0 - 580.0	17.0 - 162.0	12.0 - 220.0
	Q1 - Q3	30.0 - 86.0	30.0 - 52.0	30.0 - 58.0	
	MONTH 3	N	196	196	192
		MEAN (SD)	80.1 (22.7)	87.5 (19.0)	85.1 (20.3)
		MEDIAN	80.0	86.0	88.0
		MIN - MAX	5.0 - 200.0	20.0 - 160.0	5.0 - 160.0
	Q1 - Q3	30.0 - 97.5	30.0 - 58.0	30.0 - 58.0	
	MONTH 12	N	187	185	183
		MEAN (SD)	80.4 (27.6)	85.7 (20.2)	80.2 (25.4)
MEDIAN		80.0	85.0	88.0	
MIN - MAX		10.0 - 244.0	14.0 - 192.0	24.0 - 232.0	
Q1 - Q3	30.0 - 100.0	35.0 - 101.0	30.0 - 58.0		

Source: CSR for IM103008

IM103027 (BENEFIT-EXT)

This was a Phase 3, randomized, active-controlled, parallel-group study of the efficacy of 2 partially-blinded belatacept regimens vs. CsA as part of a quadruple therapy with mycophenolate mofetil (MMF), corticosteroids, and basiliximab in subjects who are recipients of a renal transplant from an 'extended criteria' donor. The randomization and treatment schemes were similar to IM103008.

In the initial submission maximum values for QRS, PR and QT intervals at month 12 for the belatacept-LI regimen were out of range although the median values were comparable to baseline. Clarification from the sponsor was requested. BMS concurred that there are several out of range ECG values, specifically for subject IM103027-2-10006 and IM103027-74-10552. The sponsor submitted a revised analysis excluding the two subjects (see Table 3).

Again, absolute QTcB values over 500 ms at baseline, 3 months and 12 months were noted in all three treatment and appeared similar. Increases in QTc interval that were > 60 ms compared with baseline were observed in 4%, 5%, and 2% of subjects in the belatacept MI, belatacept LI, and CsA groups, respectively, at Month 3, and in 5%, 7%, and 4% of subjects in the respective groups at Month 12.

Table 3: Categorical QTc analyses and Summary of mean ECG parameters at Specified time points IM103027

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**Summary of ECG Parameters at Specified Time Points
All Randomized and Transplanted Subjects (ITT)**

ECG Parameter	Month	N	Number (%) of Subjects		
			Belatacept - MI N=184	Belatacept - LI N=175	Cyclosporine N=184
QTc BASETIT (MSEC)	BASELINE	N	172	159	176
		MEAN (SD)	428.3 (50.2)	435.0 (58.1)	422.5 (76.9)
		MEDIAN	428.2	430.9	427.8
	MONTH 3	N	141	140	134
		MEAN (SD)	412.5 (39.8)	418.4 (64.8)	405.5 (49.3)
		MEDIAN	410.5	409.7	404.9
	MONTH 12	N	130	126	126
		MEAN (SD)	407.1 (54.8)	405.0 (34.6)	405.4 (34.1)
		MEDIAN	408.2	405.8	410.1
MIN - MAX	36.1 - 679.8	208.9 - 484.5	312.1 - 495.6		
Q1 - Q3	386.7 - 431.0	387.7 - 429.5	389.8 - 431.6		

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**Proportion of Subjects with Absolute QTc Interval Prolongation at Specified Time Points
All Randomized and Transplanted Subjects (ITT)**

Visit	Category	Number (%) of Subjects		
		Belatacept - MI N=184	Belatacept - LI N=175	Cyclosporine N=184
BASELINE	QTc INTERVAL >450 MSEC	54/ 172 (31.4)	52/ 159 (32.7)	48/ 176 (27.3)
	QTc INTERVAL >480 MSEC	16/ 172 (9.3)	20/ 159 (12.6)	14/ 176 (8.0)
	QTc INTERVAL >500 MSEC	7/ 172 (4.1)	7/ 159 (4.4)	5/ 176 (2.8)
MONTH 3	QTc INTERVAL >450 MSEC	17/ 141 (12.1)	22/ 140 (15.7)	17/ 134 (12.7)
	QTc INTERVAL >480 MSEC	6/ 141 (4.3)	9/ 140 (6.4)	4/ 134 (3.0)
	QTc INTERVAL >500 MSEC	6/ 141 (4.3)	6/ 140 (4.3)	3/ 134 (2.2)
MONTH 12	QTc INTERVAL >450 MSEC	12/ 130 (9.2)	9/ 126 (7.1)	12/ 126 (9.5)
	QTc INTERVAL >480 MSEC	5/ 130 (3.8)	1/ 126 (0.8)	2/ 126 (1.6)
	QTc INTERVAL >500 MSEC	3/ 130 (2.3)	0/ 126 (0.0)	0/ 126 (0.0)

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**Proportion of Subjects with Increase in QTc Interval from Baseline at Specified Time Points
All Randomized and Transplanted Subjects (ITT)**

Visit	Category	Number (%) of Subjects		
		Belatacept - MI N=184	Belatacept - LI N=175	Cyclosporine N=184
BASELINE	QTc INTERVAL INCREASES FROM BASELINE >30 MSEC	0/ 172 (0.0)	0/ 159 (0.0)	0/ 176 (0.0)
	QTc INTERVAL INCREASES FROM BASELINE >60 MSEC	0/ 172 (0.0)	0/ 159 (0.0)	0/ 176 (0.0)
MONTH 3	QTc INTERVAL INCREASES FROM BASELINE >30 MSEC	19/ 141 (13.5)	19/ 140 (13.6)	17/ 134 (12.7)
	QTc INTERVAL INCREASES FROM BASELINE >60 MSEC	8/ 141 (5.7)	12/ 140 (8.6)	10/ 134 (7.5)
MONTH 12	QTc INTERVAL INCREASES FROM BASELINE >30 MSEC	17/ 130 (13.1)	14/ 126 (11.1)	14/ 126 (11.1)
	QTc INTERVAL INCREASES FROM BASELINE >60 MSEC	7/ 130 (5.4)	3/ 126 (2.4)	11/ 126 (8.7)

ECG Parameter	Month		Number (%) of Subjects		
			Belatacept - M1 N=184	Belatacept - L1 N=175	Cyclosporine N=184
PR INTERVAL (MSEC)	BASELINE	N	189	159	174
		MEAN (SD)	162.6 (32.5)	167.9 (38.9)	162.7 (49.2)
		MEDIAN	160.0	160.0	160.0
		MIN - MAX	0.0 - 240.0	0.0 - 300.0	0.0 - 566.0
		Q1 - Q3	144.0 - 180.0	142.0 - 184.0	142.0 - 180.0
MONTH 3	N	N	139	139	123
		MEAN (SD)	166.1 (37.5)	169.1 (36.8)	162.6 (37.7)
		MEDIAN	160.0	160.0	160.0
		MIN - MAX	0.0 - 370.0	0.0 - 368.0	0.0 - 350.0
		Q1 - Q3	146.0 - 184.0	142.0 - 182.0	144.0 - 176.0
MONTH 12	N	N	128	124	125
		MEAN (SD)	165.1 (34.4)	169.9 (36.5)	177.2 (41.1)
		MEDIAN	161.0	160.0	160.0
		MIN - MAX	0.0 - 250.0	0.0 - 320.0	0.0 - 940.0
		Q1 - Q3	152.0 - 182.0	150.0 - 190.0	152.0 - 166.0

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ECG Parameter	Month		Number (%) of Subjects		
			Belatacept - M1 N=184	Belatacept - L1 N=175	Cyclosporine N=184
QTc INTERVAL (MSEC)	BASELINE	N	173	160	176
		MEAN (SD)	117.6 (14.4)	121.7 (17.2)	108.6 (10.7)
		MEDIAN	80.0	80.0	80.0
		MIN - MAX	32.0 - 260.0	0.0 - 300.0	12.0 - 360.0
		Q1 - Q3	80.0 - 100.0	80.0 - 100.0	80.0 - 100.0
MONTH 3	N	N	140	140	124
		MEAN (SD)	100.9 (34.5)	94.9 (31.3)	115.5 (12.2)
		MEDIAN	80.0	87.5	80.0
		MIN - MAX	40.0 - 320.0	35.0 - 330.0	40.0 - 320.0
		Q1 - Q3	80.0 - 100.0	80.0 - 100.0	80.0 - 100.0
MONTH 12	N	N	121	126	126
		MEAN (SD)	98.5 (30.6)	111.9 (11.8)	106.2 (10.3)
		MEDIAN	80.0	80.0	80.0
		MIN - MAX	40.0 - 360.0	40.0 - 380.0	40.0 - 320.0
		Q1 - Q3	80.0 - 100.0	80.0 - 100.0	80.0 - 100.0

Reviewer's Comments: One subject had QT prolongation reported as an AE but no actions were taken. One subject had Long QT syndrome and cardiac arrest listed under medical history. Further information is unavailable.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

APPENDIX

Clinical Pharmacology

The following table describes the clinical pharmacology characteristics of belatacept.

Therapeutic dose	Include maximum proposed clinical dosing regimen. More Intensive (MI) regimen [maximum proposed clinical dosing regimen]: 10 mg/kg IV belatacept infusion on Days 1, 5, 15, 29, 43, 57, 85, 113, 141, 169. Then 5mg/kg IV belatacept infusion once every 4 weeks in the maintenance phase. Less Intensive (LI) regimen: 10 mg/kg IV belatacept infusion on Days 1, 5, 15, 29, 57, 85. Then 5 mg/kg IV belatacept infusion once every 4 weeks in the maintenance phase. Infusion time for MI or LI = 0.5 h
Maximum tolerated dose	Include if studied or NOAEL dose In monkeys: Single dose >90 mg/kg Repeat dosing for 1 month Q2D > 50 mg/kg Repeat dosing for 6 months QW > 50 mg/kg
Principal adverse events	Include most common adverse events; dose limiting adverse events Two dose regimens (MI and LI) of belatacept were studied in a completed Phase 2 study in renal transplant recipients in which

	<p>belatacept was given in combination with other drugs. The maximum single dose in both regimens was 10 mg/kg. The most common AEs (occurring in 20-30% of subjects) were: peripheral edema, pyrexia, nausea, diarrhea, UTI, incision-site complications, post-procedural pain, hypophosphatemia, insomnia, and hypertension. There were no dose limiting adverse events detected; however, ongoing exposure may be associated with infection and malignancy based upon its immunosuppressive activity.</p> <p>Footnote a: this LI regimen is as described above with the exception of no dose on Day 5.</p> <p>IM103-001 study in healthy subjects (single doses of 0.1-20 mg/kg IV belatacept infusion): the most common adverse events were headache and flu-like symptoms. Incidence of headache in the belatacept treated subjects was 23% compared to 10% in the placebo group. The incidence of flu-like symptoms in the belatacept treated subjects was 16.7% compared to 10% in the placebo group.</p>	
Maximum dose tested	Single Dose	Specify dose 20 mg/kg IV belatacept infusion in healthy subjects (infusion time = 1 hr)
	Multiple Dose	Specify dosing interval and duration 10 mg/kg IV belatacept infusion on Days 1, 5, 15, 29, 43, 57, 85, 113, 141, 169 in renal transplant patients (infusion time = 0.5 hr)
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC 20mg /kg IV single infusion : Geometric Mean (%CV) Cmax: 466 (10%) µg /ml Geometric Mean (%CV) AUC(INF): 41380 (4%) µg.h/ml
	Multiple Dose	Mean (%CV) Cmax and AUC MI on Day 85: Geometric Mean (%CV) Cmax: 251.2 (19.9%) µg/ml Geometric Mean (%CV) AUC(0-6h): 1230.4 (18.2%) µg.h/ml
Range of linear PK	Specify dosing regimen 1-20 mg/kg single doses of belatacept IV infusion 5-10 mg/kg multiple doses of belatacept IV infusion	
Accumulation at steady state	Mean (%CV); specify dosing regimen MI regimen: Geometric Mean (%CV): 1.19 (18%) on Day 85 LI regimen: Geometric Mean (%CV): 1(25 %) on Day 85	
Metabolites	Include listing of all metabolites and activity Not applicable	
Absorption	Absolute/Relative Bioavailability	Mean (%CV) Not applicable (this is an IV infusion, bioavailability is 100%)
	Tmax	• Median (range) for parent

		Median(range): 0.5 (0.5-2) h • Median (range) for metabolites Not applicable
Distribution	Vd/F or Vd	Mean (%CV) Arithmetic Mean Vd (SD): 0.12 (0.03) L/kg
	% bound	Mean (%CV) Not studied as belatacept is a protein.
Elimination	Route	• Primary route; percent dose eliminated Belatacept is believed to be hepatically eliminated through receptor mediated endocytosis followed by catabolism. No ADME study was conducted. • Other routes
	Terminal t _{1/2}	• Mean (%CV) for parent Arithmetic Mean (SD): ~ 8 (2) days • Mean (%CV) for metabolites Not applicable
	CL/F or CL	Mean (%CV) Arithmetic Mean CL (SD): 0.51 (0.14) ml/h/kg
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC Effect of age on belatacept pharmacokinetics will be investigated in the population PK analysis
	Sex	Specify mean changes in C _{max} and AUC Effect of sex on belatacept pharmacokinetics will be investigated in the population PK analysis
	Race	Specify mean changes in C _{max} and AUC Effect of race on belatacept pharmacokinetics will be investigated in the population PK analysis
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC Renal impairment effect (in terms of glomerular filtration rate) on belatacept pharmacokinetics will be investigated in the population PK analysis Hepatic impairment is not studied; however pharmacokinetic data is being collected from an ongoing liver transplant study to assess the pharmacokinetics of belatacept in this population.

Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC. Belatacept is a fusion protein that is not metabolized by the Cytochrome P450 (CYP 450) enzymes, and is not expected to have any effect on the CYP 450 enzymes, in terms of inhibition or induction. In addition, any change in the CYP 450 enzymes, as a result of administration of concomitant medications with belatacept is not expected to have any effect on belatacept metabolism and elimination. Therefore, belatacept should not have the potential to be involved in drug-drug interactions.
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat) Not applicable (belatacept is given as an IV infusion)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in C _{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose. There are no potential factors that may affect belatacept absorption (since it is given intravenously) and /or elimination, which may result in higher exposure than expected. In addition, belatacept is given as an IV infusion in a controlled manner, hence, there should not be a potential for overdosing.	

From QT-IRT Review for BB IND 1418

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information	
NDA # BLA# 125288	NDA Supplement #:S- Efficacy Supplement Type SE-
Proprietary Name: Nulojix Established/Proper Name: belatacept Dosage Form: lyophilized powder Strengths: 250 mg/vial	
Applicant: Bristol-Myers Squibb Agent for Applicant (if applicable):	
Date of Application: 06-30-09 Date of Receipt: 07-1-09 Date clock started after UN: N/A	
PDUFA Goal Date: 5-1-2010	Action Goal Date (if different):
Filing Date: 8-30-09 Date of Filing Meeting: 8-12-09	
Chemical Classification: (1,2,3 etc.) (original NDAs only)	
Proposed Indication(s): prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR

601.42)	
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 9418	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aiplist.html	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
If yes, explain:	
If yes, has OC/DMPQ been notified of the submission?	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status	<input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
Comments:	
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? <i>(NDAs/NDA efficacy supplements only)</i></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES # years requested: <input type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use <i>(NDAs only)</i>:</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? *Check the Electronic Orange Book at: <http://www.fda.gov/cder/ob/default.htm>*

YES
 NO

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL).

Comments:

All paper (except for COL)
 All electronic
 Mixed (paper/electronic)

CTD
 Non-CTD
 Mixed (CTD/non-CTD)

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

If electronic submission:
paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?

Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.

Comments:

YES
 NO

If electronic submission, does it follow the eCTD guidance?
(<http://www.fda.gov/cder/guidance/7087rev.pdf>)

YES
 NO

If not, explain (e.g., waiver granted):

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p>PREA</p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable (orphan drug)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/> YES <input type="checkbox"/> NO
<i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	
Comments:	
Prescription Labeling	
Check all types of labeling submitted.	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Comments:	
Is electronic Content of Labeling submitted in SPL format?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<i>If no, request in 74-day letter.</i>	
Comments:	
Package insert (PI) submitted in PLR format?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request?	<input type="checkbox"/> YES <input type="checkbox"/> NO
<i>If no, request in 74-day letter.</i>	
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

OTC Labeling	
Check all types of labeling submitted. Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
Is electronic content of labeling submitted? <i>If no, request in 74-day letter.</i> Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting.</i> Comments:	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i> Comments:	<input checked="" type="checkbox"/> YES Date(s): May 20, 2009 <input type="checkbox"/> NO
Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i> Comments:	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

 8-28-09

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 12, 2009

NDA/BLA #: 125288

PROPRIETARY/ESTABLISHED NAMES: Nulojix

APPLICANT: Bristol-Myers Squibb

BACKGROUND: Belatacept is a second generation cytotoxic T-lymphocyte antigen 4 immunoglobulin fusion protein. It is a new molecular entity in transplant immunosuppression. Belatacept is intended for the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplant. This product has been granted orphan drug designation on February 20, 2008.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	June Germain, MS	Y
	CPMS/TL:	Judith Milstein	Y
Division Director	Renata Albrecht, MD		Y
Cross-Discipline Team Leader (CDTL)	William Taylor, PhD		Y
Clinical	Reviewer:	Patrick Archdeacon, MD	Y
	TL:	Joette Meyer, PharmD	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE, DRISK	Reviewer:	Tselaine Jones-Smith, Mary Dempsey	Y
	TL:	Darrell Jenkins	N
Clinical Microbiology (for antimicrobial products)	Reviewer:	Aaron Ruhland, PhD	Y
	TL:	Shukal Bala	Y

Clinical Pharmacology	Reviewer:	Gerlie Gieser, PhD, Shashi Amur	Y
	TL:	Phillip Colangelo, PhD, PharmD	Y
Biostatistics	Reviewer:	Cheryl Dixon, PhD	Y
	TL:	Karen Higgins, ScD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ying Mu, PhD and Janice Lansita, PhD	Y
	TL:	William Taylor, PhD	Y
Statistics, S	Reviewer:	Eugenio Andraca-Carrera, Antonio Paredes	Y Y
	TL:	John Yap	N
Product Quality (CMC)	Reviewers:	Jack Ragheb, MD, Edward Max, Norihisa Sakamoto, Joao Pedras-Vasconcelaos, Barbara Rallahan	Y
	TL:	Susan Kirshner, PhD	Y
Facility (for BLAs/BLA supplements)	Reviewer:	Bo Chi, PhD, Laura Dillon	Y
	TL:	Patricia Hughes,	Y
Microbiology, sterility (for NDAs/NDA efficacy supplements)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:	Susan Thompson	N
Pharmacometrics	Reviewer:	Jiang Liu	Y
	TL:	Pravin Jadhav	Y

OTHER ATTENDEES: John Farley, OAP, Dave Roeder, OAP, Ergun Velidedeoglu, MD, Neera Patel, Student

505(b)(2) filing issues?	<input checked="" type="checkbox"/> Not Applicable
If yes, list issues:	<input type="checkbox"/> YES
	<input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable</p>
<p>CLINICAL</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical study site(s) inspections(s) needed?</p> <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>• Advisory Committee Meeting needed?</p> <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p><input checked="" type="checkbox"/> YES Date if known: March 1, 2009 <input type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p>
<p>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIostatistics Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: Biologics are handled by OC/BMT</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Sterile product? <p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
FACILITY (BLAs only)	<input type="checkbox"/> Not Applicable

Comments:	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
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REGULATORY PROJECT MANAGEMENT

Signatory Authority: Edward Cox, MD

GRMP Timeline Milestones: May 1, 2010

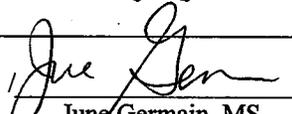
Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review

ACTIONS/ITEMS

<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74


 June Germain, MS
 Regulatory Health Project Manager


 Judit Milstein, Chief Project Management Staff

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Special Pathogen and Transplant Products

Application Number: BL STN 125288

Name of Drug: belatacept

Applicant: Bristol-Myers Squibb

Material Reviewed:

Submission Date(s): June 30, 2009

Receipt Date(s): July 1, 2009

Submission Date of Structure Product Labeling (SPL): June 30, 2009

Type of Labeling Reviewed: SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to Bristol-Myers Squibb. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57 and 610), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in belatacept proposed labeling.

HIGHLIGHTS:

- [REDACTED] (b) (4)
[REDACTED]. Use the "TM" symbol only once in the content of label (full prescribing information).
- Under the **DOSAGE FORMS AND STRENGTHS** include lyophilized powder.
- Under **USE IN SPECIFIC POPULATIONS** remove colon from "Pregnancy Registry available."
- 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.

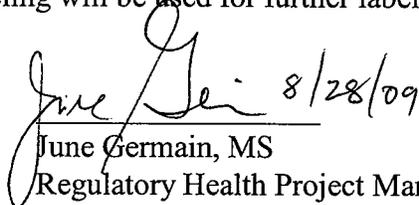
Sample Database Description

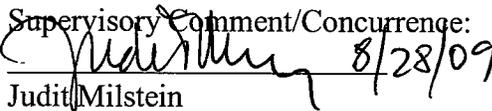
The data described below reflect exposure to drug X in [n] patients, including [n] exposed for 6 months and [n] exposed for greater than one year. Drug X was studied primarily in placebo and active-controlled trials (n = __, and n = __, respectively), and in long-term follow up studies. The population 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>)

Recommendations

Bristol-Myers Squibb should address the identified deficiencies/issues and re-submit labeling by September 28, 2009. This updated version of labeling will be used for further labeling discussions.


June Germain, MS
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Judith Milstein
Chief, Project Management Staff

Drafted: JG/7-17-09

Revised/Initialed:

Finalized:

Filename: CSO Labeling Review Template (updated 1-16-07).doc

DSI CONSULT: Request for Clinical Inspections

Date: 8/14/2009

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Patrick Archdeacon, MD, Division of Special Pathogen and Transplant Products (DSPTP)

Joette Meyer, PharmD, Clinical Team Leader, DSPTP

From: June Germain, MS, Regulatory Health Project Manager/Division of Special Pathogen and Transplant Products *JG 8/17/09*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: BLA-belatacept/STN-125288

Applicant/ Applicant contact information (to include phone/email):

Mary Christian, Pharm.D.

Director, Global Regulatory Strategy

(609) 252-5281, mary.christian@bms.com

Drug Proprietary Name: Nulojix

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. Nulojix has been used in combination with an interleukin-2 (IL-2) receptor antagonist, a mycophenolic acid (MPA), and corticosteroids.

Submission Date: 7/1/2009

Action Goal Date: 5/1/2010

Inspection Summary Goal Date: 3/1/2010

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

The primary efficacy and safety data in support of belatacept comes from three similarly designed studies in *de novo* renal transplant recipients: a Phase 2 study (IM103100) and two Phase 3 studies (IM103008 and IM103027).

These studies compared two dose regimens of belatacept (more intensive [MI] and less intensive [LI]) versus cyclosporine when administered in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids in recipients of living donor and standard criteria deceased donor organs (Study 1; IM103008) or extended criteria donor organs (Study 2; IM103027).

Study 1 and Study 2 were three years in length and the primary endpoints were pre-specified to be assessed at 1 year. The co-primary efficacy endpoints were:

1. the composite of patient and graft survival at 12 months, and
2. the composite of renal impairment as assessed by measured glomerular filtration rate (GFR) $< 60 \text{ mL/min/1.73m}^2$ at Month 12 or a decrease in measured GFR $\geq 10 \text{ mL/min/1.73m}^2$ from Month 3 to Month 12, as measured by the cold-iothalamate method.

Study 1 included the additional co-primary endpoint of the incidence of acute rejection (AR) at 12 months. Incidence of AR was a secondary endpoint in Study 2.

A copy of the draft package insert is also included.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects*	Indication
<p>Site 076 Lionel Rostaing, MD/PhD Hopital de Rangueil C H U De Toulouse (Office) Chu De Toulouse Hopital Rangueil Nephrologie- Hemodialyse-Transplantation 1 Avenue Du Pr Jean Poulhes Toulouse Cedex 31054 France Telephone: +33 5 61 32 25 84 Fax: +33 5 61 32 28 64 Email: ROSTAING.L@CHU-TOULOUSE.FR</p>	<p>IM103008</p>	<p>41</p>	<p>Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.</p>

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects*	Indication
<p>Site 0116</p> <p>Mondragon-Ramirez, Guillermo MD Instituto Mexicano De Transplantes, SC (Office) Av. Alta Tension 580-2 Colonia Cantarranas Cuernavaca, Morelos 62448 Mexico</p> <p>Instituto Mexicano De Transplantes, SC (Patient Treatment) Av. Alta Tension 580-2 Colonia Cantarranas Cuernavaca, Morelos 62448 Mexico</p> <p>Technologica Medica (Patient Treatment) Technologica Medica Av. Plande Ayala 210 Col. Amatitlan Cuernavaca, Morelos 62410 Mexico Telephone: +(52 777)318-3362 or 318- 2789 or 312-6669 or 169-8465 Fax: +(52 777) 312-6479 Email: imt@imtsc.com.mx</p>	<p>IM103008</p>	<p>24</p>	<p>Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.</p>

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects*	Indication
<p>Site 0010 Flavio Vincenti, MD University of California San Francisco Medical Center Kidney Transplant Service 505 Parnassus Avenue, Room 884M San Francisco, CA 94143-0780 USA Telephone: 415-476-4496 Fax: 415-353-1579 Email: vincentif@surgery.ucsf.edu</p>	<p>IM103008</p>	<p>25</p>	<p>Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.</p>
<p>Site 006 Barbara Bresnahan, MD Froedtert Memorial Hospital 9200 W. Wisconsin Ave FMCLB 216 Milwaukee, WI 53226 USA Telephone: 414-805-1892 Fax: 414-805-9059 Email: BBRESNAH@MCW.EDU</p>	<p>IM103008</p>	<p>15</p>	<p>Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.</p>

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects*	Indication
<p>Site 0123 Reyes-Acevedo, Rafael MD Centenario Hospital Miguel Hidalgo (Office) Galeana Sur 465, Col. Obraje Aguascalientes, Aguascalientes 20230 Mexico</p> <p>Hospital Miguel Hidalgo De Aguascalientes (Patient Treatment) C. Galeana Sur 465 Col Obraje C.P., Aguascalientes 20230 Mexico Telephone: 52 449 91 28 748 Fax: 52 449 91 28 749 Email: NA</p>	<p>IM103008</p>	<p>25</p>	<p>Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.</p>

* number randomized and transplanted per site

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects *	Indication
<p>Site 0091 Jose Medina Osmar Pestana, MD Hospital Do Rim E Hipertensao Rua Borges Lagoa 960 Vila Clementino Sao Paolo Sao Paolo 04028-002 Brazil Telephone: 55 11 5087-8056 Fax: 55 11 5087-8145 Email: MEDINA@HRIM.COM.BR</p>	<p>IM103027</p>	<p>36</p>	<p>Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.</p>
<p>Site 0035 Lionel Rostaing, MD/PhD Hopital de Rangueil C H U De Toulouse (Office) Chu De Toulouse Hopital Rangueil Nephrologie-Hemodialyse- Transplantation 1 Avenue Du Pr Jean Poulhes Toulouse Cedex 31054 France Telephone: +33 5 61 32 25 84 Fax: +33 5 61 32 28 64 Email: ROSTAING.L@CHU-TOULOUSE.FR</p>	<p>IM103027</p>	<p>24</p>	<p>Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.</p>
<p>Site 0002 Sander Scott Florman, MD Tulane University Hospital and Clinic 1415 Tulane Avenue TW-35 New Orleans, LA 70112 USA Telephone: 504-988-7867 Fax: 504-988-7510 Email: sflorman@tulane.edu</p>	<p>IM103027</p>	<p>26</p>	<p>Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.</p>

<p>Site 0093 Garcia, Valter Duro PhD Hosp. Dom Vicente Scherer (Office) Avenue Independencia, 155 6º Andar Porto Alegre, Rio Grande Do Sul 90020-090 Brazil</p> <p>Hosp. Dom Vicente Scherer (Patient Treatment) Rua Prof. Annes Dias, 285 Porto Alegre/Rs, Rio Grande Do Sul 90020-090 Brazil</p> <p>Hosp. Dom Vicente Scherer (Patient Treatment) Avenue Independencia, 155 6a Andar-Auxiliadora Porto Alegre/Rs, Rio Grande Do Sul 90035-074 Brazil Telephone: 55 51 3214 8459 Fax: 55 51 3225 3998 Email: VDUROGARCIA@TERRA.COM.BR</p>	<p>IM103027</p>	<p>21</p>	<p>Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.</p>
<p>Site 010 Flavio Vincenti, MD University of California San Francisco Medical Center Kidney Transplant Service 505 Parnassus Avenue, Room 884M San Francisco, CA 94143-0780 USA Telephone: 415-476-4496 Fax: 415-353-1579 Email: vincentif@surgery.ucsf.edu</p>	<p>IM103027</p>	<p>7</p>	<p>Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.</p>

* number randomized and transplanted per site

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

A DSI consult is requested because belatacept is a new molecular entity for the prophylaxis of organ rejection. No major concerns regarding the integrity of the data have emerged at this time. The BLA studies were performed under IND. The two pivotal trials (IM103008 and IM103027) had 105 and 79 sites, respectively, and no site enrolled more than 41 patients (6% of the total enrolled in IM103008). The median number of subjects enrolled and/or randomized and transplanted in both studies was 6 subjects per site which (or about 2 subjects per treatment arm). The majority of the sites enrolled 10 or fewer subjects. In Study IM103008, 26% of the subjects were from 34 US sites the rest were from non-US sites. Of the non-US sites, sites in Mexico (6) and sites in France (7) enrolled about 13% of the total subjects each. In Study IM103027, 23% of the subjects were from 26 US sites the rest were from non-US sites. Of the non-US sites, 9 sites in France enrolled 18% of the total and 6 sites in Brazil enrolled about 15% of the total subjects.

In Study IM103027, site 0091 may have had a slight impact on the conclusions for the endpoint of composite renal function: removing this site from the analysis leads to a significant difference compared to CsA for both of the belatacept arms (overall the comparison of the belatacept LI arm to CsA was not significant).

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include at least one foreign site in the DSI inspections to verify the quality of conduct of the study).

This would be the first approval of this new drug and much of the experience has been at foreign sites: approximately 75% of the study subjects across the two Phase 3 trials were enrolled at foreign sites.

Five or More Inspection Sites (delete this if it does not apply):

We have requested these potential sites for inspection (international and/or domestic) because of the following reasons:

Of the 105 and 79 sites used in IM103008 and IM103027, respectively, the sites proposed in the above tables represent the largest foreign and domestic sites for each pivotal study. Of note, Site 0076 in study IM103008 and Site 0035 in study IM103027 (France) are both the same investigator. Also, Site 0010 in both studies is the same investigator (US). The countries of Mexico and Brazil, also had two top enrolling sites each: Sites 0116 and 0123 in study IM103008 are in Mexico; Sites 0091 and 0093 in study IM103027 are in Brazil. Because this would be the first approval of this new drug and much of the experience has been at foreign sites, inspection of some foreign sites would be reasonable.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Adverse Events: Did the sites capture adverse events related to immunosuppression accurately? We are especially interested in unreported cases of infections (e.g., tuberculosis, viral, and fungal) and/or malignancies. Other AEs of interest include new-onset diabetes mellitus, hypertension, and dyslipidemia which were reported at lower rates in the belatacept arms than in the comparator arms.

In the database one patient developed progressive multifocal leukoencephalopathy (PML) and 13 developed post-transplant lymphoproliferative disorder (PTLD) in the belatacept arms. It would be extremely critical if any additional unreported cases were identified.

Concomitant medications: We would like to confirm that all medications related to immunosuppression were recorded accurately, particularly those given at and around the time of transplant. Please confirm that patients received only the medications specified on the CRFs at those times. Unrecorded use of thymoglobulin or alemtuzumab (Campath®) would be of particular interest. We would also like to confirm that treatments related to episodes of acute rejection were accurately recorded. Unrecorded use of thymoglobulin or rituximab (Rituxan®) at such times would be of particular interest.

Efficacy failure: Were there any undocumented cases of BPAR at any of the sites? Graft loss? Death?

Laboratory parameters: Was CLcr collected appropriately (as specified in the protocol) and recorded accurately in the CRF? Was information on EBV serostatus recorded accurately in the CRF?

Histopathology: Was the Banff score reported on biopsies accurately recorded in the CFR?

Should you require any additional information, please contact June Germain, Regulatory Project Manager, at 301-796-4024 or Patrick Archdeacon, Medical Officer, at 301-796-3952.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

*****Things to consider in decision to submit request for DSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*

We are still evaluating the data, but it would appear unlikely that even site(s) with particularly high efficacy could drive the results given the large number of study sites.

- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*

We are still evaluating the data, but because none of the sites represents a substantial fraction of the overall population, it would appear unlikely that even the larger sites could drive the results.

- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*

To be determined.

- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*

Not at this time.

- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*

We are still evaluating the studies. We do not suspect trial misconduct at this time.

- *Is this a new molecular entity or original biological product?*

Yes

- *Is the data gathered solely from foreign sites?*

No

- *Were the NDA studies conducted under an IND?*

Yes

JY
8/17/09