DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125288/30

SUPPLEMENT APPROVAL

Bristol-Myers Squibb
Attention: Ashley Pereira, Pharm.D
Director, Global Regulatory Sciences, U.S. Liaison
PO Box 4000
Princeton, NJ 08543

Dear Dr. Pereira;

Please refer to your Supplemental Biologics License Application (sBLA), dated and received December 5, 2012, submitted under section 351(a) of the Public Health Service Act for Nulojix (belatacept).

We acknowledge receipt of your amendments dated February 19 and 27, March 1 and 28, 2013.

This "Prior Approval" supplemental biologics application proposes revisions to the **HIGHLIGHTS, DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS** and **CLINICAL STUDIES** sections.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text which is identical to the labeling text submitted on March 28, 2013.

LABELING REVISIONS

The revisions to the package insert are as follow (additions are noted with double underline and deletions with ~~strikethrough~~):

In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, the following revisions have been made:

1. **----------RECENT MAJOR CHANGES----------**
   Dosage and Administration, Dosage in Adult Kidney Transplant Recipients (2.1) April/2013
   Warnings and Precautions, Acute Rejection and Graft Loss with Corticosteroid Minimization (5.7) April/2013

2. **----------WARNINGS AND PRECAUTIONS ----------**

- Acute Rejection and Graft Loss with Corticosteroid Minimization: corticosteroid utilization should be consistent with the NULOJIX clinical trial experience. (2.1, 5.7, 14.1)

In the **TABLE OF CONTENTS,** a new subsection **5.7 Acute Rejection and Graft Loss with Corticosteroid Minimization** has been added to the **WARNINGS AND PRECAUTIONS** section, and the subsection on **Immunization**s has been renumbered from **5.7** to **5.8**.

In the **FULL PRESCRIBING INFORMATION** section, the following revisions have been made:

3. In **2 Dosage and Administration/2.1 Dosage in Adult Kidney Transplant Recipients** a new first paragraph has been added as follows:

   NULOJIX should be administered in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids. In clinical trials the median (25^{th}-75^{th} percentile) corticosteroid doses were tapered to approximately 15 mg (10-20 mg) per day by the first 6 weeks and remained at approximately 10 mg (5-10 mg) per day for the first 6 months post-transplant. Corticosteroid utilization should be consistent with the NULOJIX clinical trial experience [see *Warnings and Precautions (5.7)* and *Clinical Studies (14.1)*].

4. In **5 WARNINGS AND PRECAUTIONS,** a new subsection has been added and the **Immunization** subsection has been renumbered from **5.7** to **5.8**

   5.7 Acute Rejection and Graft Loss with Corticosteroid Minimization

   In postmarketing experience, use of NULOJIX in conjunction with basiliximab induction, MMF, and corticosteroid minimization to 5 mg per day between Day 3 and Week 6 post-transplant was associated with an increased rate and grade of acute rejection, particularly Grade III rejection. These Grade III rejections occurred in patients with 4 to 6 HLA mismatches. Graft loss was a consequence of Grade III rejection in some patients.

   Corticosteroid utilization should be consistent with the NULOJIX clinical trial experience [see Dosage and Administration (2.1) and Clinical Studies (14.1)].

   ~~5.7~~ 5.8 **Immunization**

5. In **14 CLINICAL STUDIES/14.1 Prevention of Organ Rejection in Kidney Transplant Recipients,** a new subsection titled **Treatment Regimen** has been created and the additional information on the treatment used has been added as follows:

The efficacy and safety of NULOJIX in *de novo* kidney transplantation were assessed in two open-label, randomized, multicenter, active-controlled trials (Study 1 and Study 2). These trials evaluated two dose regimens of NULOJIX, the recommended dosage regimen [see *Dosage and Administration (2.1)*] and a regimen with higher cumulative doses and more frequent dosing than the recommended dosage regimen, compared to a cyclosporine control regimen. All treatment groups also received basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids.

Treatment Regimen

The NULOJIX recommended regimen consisted of a 10 mg per kg dose administered on Day 1 (the day of transplantation, prior to implantation), Day 5 (approximately 96 hours after the Day 1 dose), end of Weeks 2 and 4; then every 4 weeks through Week 12 after transplantation. Starting at Week 16 after transplantation, NULOJIX was administered at the maintenance dose of 5 mg per kg every 4 weeks (plus or minus 3 days). NULOJIX was administered as an intravenous infusion over 30 minutes [see *Dosage and Administration (2.1)*].

Basiliximab 20 mg was administered intravenously on the day of transplantation and 4 days later.

The initial dose of MMF was 1 gram twice daily and was adjusted, as needed based on clinical signs of adverse events or efficacy failure.

The protocol specified dosing of corticosteroids in Studies 1 and 2 at Day 1 was methylprednisolone (as sodium succinate) 500 mg IV on arrival in the operating room, Day 2, methylprednisolone 250 mg IV, and Day 3, prednisone 100 mg orally. Actual median corticosteroid doses used with the NULOJIX recommended regimen from Week 1 through Month 6 are summarized in the table below (Table 6).

Table 6: Actual Corticosteroid* Dosing in Studies 1 and 2

Day of Dosing	Median (Q1–Q3) Daily Dose[†,‡]	
	Study 1	Study 2
Week 1	31.7 mg (26.7-50 mg)	30 mg (26.7-50 mg)
Week 2	25 mg (20-30 mg)	25 mg (20-30 mg)
Week 4	20 mg (15-20 mg)	20 mg (15-22.5 mg)
Week 6	15 mg (10-20 mg)	16.7 mg (12.5-20 mg)
Month 6	10 mg (5-10 mg)	10 mg (5-12.5 mg)

* Corticosteroid = prednisone or prednisolone.

† The protocols allowed for flexibility in determining corticosteroid dose and rapidity of taper after Day 15. It is not possible to distinguish corticosteroid doses used to treat acute rejection versus doses used in a maintenance regimen.

‡ Q1 and Q3 are the 25th and 75th percentiles of daily corticosteroid doses, respectively.

Study 1 enrolled recipients of living donor and standard criteria deceased donor organs and Study 2 enrolled recipients of extended criteria donor organs. Standard criteria donor organs were defined as organs from a deceased donor with anticipated cold ischemia time of <24 hours and not meeting the definition of extended criteria donor organs. Extended criteria donors were defined as deceased donors with at least one of the following: (1) donor age ≥60 years; (2) donor age ≥50 years and other donor comorbidities (≥2 of the following: stroke, hypertension, serum creatinine >1.5 mg/dL); (3) donation of organ after cardiac death; or (4) anticipated cold ischemia time of the organ of ≥24 hours. ~~Both studies~~ Study 1 excluded recipients undergoing a first transplant whose current Panel Reactive Antibodies (PRA) were ≥50% and recipients undergoing a retransplantation whose current PRA were ≥30%; Study 2 excluded recipients with a current (PRA) ≥30%. Both studies excluded recipients with HIV, hepatitis C, or evidence of current hepatitis B infection; recipients with active tuberculosis; and recipients in whom intravenous access was difficult to obtain.

Efficacy data are presented for the NULOJIX recommended regimen and cyclosporine regimen in Studies 1 and 2.

The NULOJIX regimen with higher cumulative doses and more frequent dosing of belatacept was associated with more efficacy failures. Higher doses and/or more frequent dosing of NULOJIX are not recommended [see *Dosage and Administration (2.1)*, *Warnings and Precautions (5.1)*, and *Adverse Reactions (6.1)*].

6. In **14 CLINICAL STUDIES/14.1 Study 1: Recipients of Living Donor and Standard Criteria Deceased Donor Kidneys,** the first paragraph has been modified as follows:

In Study 1, 666 patients were enrolled, randomized, and transplanted: 226 to the NULOJIX recommended regimen, 219 to the NULOJIX regimen with higher cumulative doses and more frequent dosing than recommended, and 221 to cyclosporine control regimen. The median age was 45 years; 58% of organs were from living donors; 3% were re-transplanted; 69% of the study population was male; 61% of patients were white, 8% were black/African-American, 31% were categorized as of other races; 16% had PRA ≥10%; 41% had 4 to 6 HLA mismatches; and 27% had diabetes prior to transplant. The incidence of delayed graft function was similar in all treatment arms (14% to 18%).

7. In **14 CLINICAL STUDIES/Study 2: Recipients of Extended Criteria Donor Kidneys,** the first paragraph has been modified as follows:

In Study 2, 543 patients were enrolled, randomized, and transplanted: 175 to the NULOJIX recommended regimen, 184 to the NULOJIX regimen with higher cumulative

doses and more frequent dosing than recommended, and 184 to the cyclosporine control regimen. The median age was 58 years; 67% of the study population was male; 75% of patients were white, 13% were black/African-American, 12% were categorized as of other races; 3% had PRA ≥10%; 53% had 4 to 6 HLA mismatches; and 29% had diabetes prior to transplantation. The incidence of delayed graft function was similar in all treatment arms (47% to 49%).

8. Throughout this section, the tables numbering has been updated to take into account the addition of Table 6 (minor editorial changes).

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE: Content of Labeling

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

/s/

RENATA ALBRECHT
04/08/2013