FDA Approves NULOJIX® (belatacept)

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For Prophylaxis of Organ Rejection in Adult Patients Receiving a Kidney Transplant in Combination with Basiliximab Induction, Mycophenolate Mofetil, and Corticosteroids

- Offers Comparable Overall Efficacy versus Cyclosporine
- Clinical Trials Evaluated Renal Function Through 3 years versus Cyclosporine
- NULOJIX is a New Mechanism (Selective T-cell Costimulation Blocker) for Prevention of Rejection in Adult Kidney Transplant Patients
- Risk Evaluation and Mitigation Strategy and Patient Registry Developed with FDA

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) announced that the U.S. Food and Drug Administration (FDA) approved NULOJIX, the first selective T-cell costimulation blocker indicated for the prophylaxis of organ rejection in adult patients receiving a kidney transplant, in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids. NULOJIX should only be used in patients who are EBV seropositive. Use of NULOJIX for prophylaxis of organ rejection in transplanted organs other than kidney has not been established. NULOJIX will be available as 250 mg lyophilized powder. The efficacy and safety of NULOJIX in adult de novo kidney transplant patients was studied in two 3-year, phase 3, open-label, randomized, multicenter, active-controlled studies (BENEFIT and BENEFIT-EXT).

“The approval of NULOJIX exemplifies our company’s commitment to innovate in the areas of serious disease and biologics drug development,” said Lamberto Andreotti, Chief Executive Officer, Bristol-Myers Squibb.

NULOJIX is associated with an increased risk for post-transplant lymphoproliferative disorder (PTLD), predominantly in the central nervous system (CNS). NULOJIX is contraindicated in patients who are Epstein-Barr Virus (EBV) seronegative or with unknown EBV serostatus because the risk of PTLD is particularly increased in patients who are EBV seronegative. NULOJIX is to be used only in patients who are EBV seropositive. Immunosuppression may result in increased susceptibility to infection and development of malignancies. Patients should be monitored for new or worsening neurological, cognitive, or behavioral signs and symptoms. Higher than recommended doses or more frequent dosing of NULOJIX and concomitant immunosuppressives is not recommended. NULOJIX should be prescribed only by physicians experienced in immunosuppressive therapy and management of kidney transplant patients. Use in liver transplant patients is not recommended due to an increased risk of graft loss and death. Please see the Important Safety Information section of this press release for additional risk information, including Boxed WARNINGS.

The BENEFIT study enrolled recipients of Standard Criteria Deceased (SCD) and living donor kidneys. The BENEFIT-EXT study enrolled recipients of Extended Criteria Donor (ECD) kidneys and is the largest study conducted to date in patients receiving ECD kidneys. In the two studies, the recommended dose of NULOJIX (belatacept) was studied in 401 patients compared to 405 patients in cyclosporine, each in combination with basiliximab induction, MMF, and corticosteroids. Both studies excluded recipients undergoing first transplant with current panel reactive antibodies (PRA) ≥50% and recipients undergoing retransplantation with current PRA ≥30%; with HIV, hepatitis C, or evidence of current hepatitis B infection; with active tuberculosis; and in whom intravenous access was difficult to obtain. Through 3 years, both studies evaluated measures of efficacy (patient/graft survival and Efficacy Failure) and renal function. For additional study design information, please see the section, “Additional Information about NULOJIX in 2 Large Phase 3 Studies...”

NULOJIX Demonstrated Comparable Overall Efficacy and Superior and Sustained Renal Function Through 3 Years versus Cyclosporine in Clinical Trials

In both studies, overall efficacy (patient/graft survival and Efficacy Failure) was comparable between
NULOJIX and cyclosporine, and NULOJIX demonstrated superior renal function at 1 year which was sustained through 3 years compared to cyclosporine. At 1 year in the BENEFIT study, mean calculated Glomerular Filtration Rate (cGFR), based on Modification of Diet in Renal Disease (MDRD) formula, was 65.4 mL/min/1.73m² for NULOJIX-treated patients (n=200) compared to 50.1 mL/min/1.73m² for cyclosporine-treated patients (n=199), a difference of 15.3 mL/min/1.73m² [97.3% CI = (10.3, 20.3)]. At 3 years, mean cGFR was 65.8 mL/min/1.73m² for NULOJIX-treated patients (n=190) compared to 44.4 mL/min/1.73m² for cyclosporine-treated patients (n=171), a difference of 21.4 mL/min/1.73m² [97.3% CI = (15.4, 27.4)]. By 1 year in the BENEFIT-EXT study, mean cGFR was 44.5 mL/min/1.73m² for NULOJIX-treated patients (n=158) compared to 36.5 mL/min/1.73m² for cyclosporine-treated patients (n=159), a difference of 8.0 mL/min/1.73m² [97.3% CI = (2.5, 13.4)]. At 3 years, mean cGFR was 42.2 mL/min/1.73m² for NULOJIX-treated patients (n=154) compared to 31.5 mL/min/1.73m² for cyclosporine-treated patients (n=143), a difference of 10.7 mL/min/1.73m² [97.3% CI = (4.3, 17.2)].

In the BENEFIT study, patient and graft survival between NULOJIX-treated patients (N=226) and cyclosporine-treated patients (N=221) were comparable at both 1 year (96.5% vs. 93.2%; difference = 3.2%; 97.3% CI [-1.5, 8.4]) and 3 years (91.2% vs. 86.9%; difference = 4.3%; 97.3% CI [-2.2, 10.8]). Efficacy Failure (a composite of Biopsy-Proven Acute Rejection [BPAR], Graft Loss, Death, and Lost to Follow-up) was experienced by 21.7% of patients on NULOJIX, compared to 16.7% of patients treated with cyclosporine by 1 year (difference = 4.9%; 97.3% CI [-3.3, 13.2]) and by 25.7% of patients on NULOJIX, compared to 25.8% of patients treated with cyclosporine by 3 years (difference = -0.1%; 97.3% CI [-9.3, 9.0]). The rate of BPAR, defined as histologically confirmed acute rejection by a central pathologist on a biopsy done for any reason, whether or not accompanied by clinical signs of rejection, was higher in patients treated with NULOJIX compared to cyclosporine-treated patients (19.9% vs. 10.4% at 1 year and 22.1% vs. 14.0% at 3 years, respectively). In NULOJIX (belatacept)-treated patients, most BPAR episodes (70.0%) occurred by Month 3 and 84.0% occurred by Month 6.

In the BENEFIT-EXT study (recipients of ECD organs), patient and graft survival between NULOJIX-treated patients (N=175) and cyclosporine-treated patients (N=184) were comparable at both 1 year (88.6% vs. 85.3%; difference = 3.2%; 97.3% CI [-4.8, 11.3]) and 3 years (81.7% vs. 77.7%; difference = 4.0%; 97.3% CI [-5.4, 13.4]) were comparable. Efficacy Failure was experienced by 29.1% of patients on NULOJIX, compared to 28.3% of patients treated with cyclosporine by 1 year (difference = 0.9%; 97.3% CI [-9.7, 11.5]) and by 36.0% of patients on NULOJIX, compared to 37.0% of patients treated with cyclosporine by 3 years (difference = -1.0%; 97.3% CI [-12.1, 10.3]). The rate of BPAR at 1 and 3 years was similar in patients treated with NULOJIX and cyclosporine (21.1% vs. 18.5% at year 1 and 24.0% vs. 22.8% at year 3, respectively). In NULOJIX-treated patients, most BPAR episodes (62.0%) occurred by Month 3, and 76.0% experienced BPAR by Month 6.

The most serious adverse reactions reported with NULOJIX are PTLD, predominantly CNS PTLD, and other malignancies, as well as serious infections, including JC virus-associated PML (often a rapidly progressive and fatal opportunistic infection) and polyoma virus nephropathy. Due to increased risks, including PTLD and PML, higher than recommended doses or more frequent dosing of NULOJIX is not recommended.

In these two clinical trials, the most commonly reported adverse reactions occurring in ≥20% of 401 patients treated with the recommended dose and frequency of NULOJIX were anemia (45.0%), diarrhea (39.0%), urinary tract infection (37.0%), peripheral edema (34.0%), constipation (33.0%), hypertension (32.0%), pyrexia (28.0%), graft dysfunction (25.0%), cough (24.0%), nausea (24.0%), vomiting (22.0%), headache (21.0%), hypokalemia (21.0%), hyperkalemia (20.0%), and leukopenia (20.0%).

“The NULOJIX approval is another example of the company’s growing expertise in targeted biologics, an important part of our research and development strategy,” said Elliott Sigal, M.D., Ph.D., Executive Vice President, Chief Scientific Officer, and President, R&D, Bristol-Myers Squibb. “As a first-in-class agent for kidney transplant, NULOJIX is the result of Bristol-Myers Squibb’s leadership in the use of selective T-cell costimulation blockade as a basis for novel therapies.”

“Selective T-cell costimulation blockade represents a new mechanism for the prevention of rejection in adult kidney transplant patients.” said Flavio Vincenti, M.D., Professor of Clinical Medicine, University of California, San Francisco, Division of Nephrology. “As NULOJIX is administered as an intravenous infusion, this may help increase awareness of patient non-compliance with this therapy.”

Bristol-Myers Squibb is committed to providing HCPs and patients support through MY NULOJIX NETWORK™, a single point of contact to assist with access to NULOJIX. This program will begin in July 2011 when the product becomes commercially available.

NULOJIX (belatacept) REMS Program

Patients treated with NULOJIX are at an increased risk for developing PTLD, predominantly involving the CNS. Progressive multifocal leukoencephalopathy (PML) has also been reported in
patients receiving NULOJIX at higher than recommended doses as part of an immunosuppressant regimen. Bristol-Myers Squibb has collaborated with the FDA to develop a Risk Evaluation and Mitigation Strategy (REMS) to help ensure that the benefits of NULOJIX outweigh the risks of PTLD and PML, both of which can be fatal. The risk mitigation strategy consists of a communication plan to potential prescribers and supportive HCPs and a medication guide for patients. The goals of the REMS are 1) to inform HCPs of the increased risk of PTLD, predominantly in the CNS, associated with NULOJIX, 2) to inform HCPs of the increased risk of PML, a CNS infection, associated with NULOJIX, and 3) to inform patients of the serious risks associated with NULOJIX. More information and downloadable safety education materials will be available at www.NULOJIX.com/rem.png.

ENLiST (Evaluating NULOJIX Long-term Safety in Transplant) Patient Registry

Bristol-Myers Squibb established the ENLiST Registry to further evaluate the safety profile of NULOJIX. The primary objective of ENLiST is to determine the incidence of PTLD, CNS PTLD, and PML in US adult EBV seropositive kidney transplant recipients treated with NULOJIX. ENLiST is intended to enroll all adult kidney transplant patients who are treated with NULOJIX.

Data collection will include the patients’ EBV and cytomegalovirus (CMV) serostatus as well as when NULOJIX was initiated relative to time of transplant. Patients who are EBV seropositive and CMV seronegative may be at increased risk of PTLD. Since CMV seronegative patients are at increased risk for CMV disease (a known risk factor for PTLD), the clinical significance of CMV serology for PTLD remains to be determined; however, these findings should be considered when prescribing NULOJIX.

Bristol-Myers Squibb encourages centers to participate in the ENLiST Registry. For more information on how to enroll in ENLiST and answers to other questions regarding the registry please call 1-800-321-1335. More information about the protocol will be available on www.clinicaltrials.gov in July.

Additional Information about NULOJIX (belatacept) in 2 Large Phase 3 Studies in Adult Kidney Transplant Patients

The efficacy and safety of NULOJIX in adult de novo kidney transplant patients were evaluated in 2 open-label, randomized, multicenter, active-controlled studies (BENEFIT and BENEFIT-EXT).

NULOJIX is administered as an intravenous infusion over 30 minutes. The NULOJIX recommended dosing is initially 10 mg/kg administered on Day 1 (the day of transplantation, prior to implantation), on Day 5 (approximately 96 hours after the Day 1 dose), and at the end of Weeks 2, 4, 8, and 12 after transplantation. Starting at the end of Week 16 after transplantation, NULOJIX was administered at the maintenance dose of 5 mg/kg every 4 weeks (plus or minus 3 days). NULOJIX (belatacept) dosing is based on actual body weight at the time of transplant unless there is more than a 10% change.

NULOJIX was studied at the recommended dose and frequency in a total of 401 adult patients in the 2 studies compared to a cyclosporine control regimen in a total of 405 adult patients, each in combination with basiliximab induction, MMF, and corticosteroids. These 2 trials also included a total of 403 adult patients treated with a NULOJIX regimen of higher cumulative dose and more frequent dosing than recommended. Administration of higher than the recommended doses or more frequent dosing of NULOJIX is not recommended due to an increased risk of PTLD predominantly involving the CNS, PML, serious CNS infections, and more efficacy failures.

The BENEFIT study enrolled recipients of SCD and living donor kidneys. SCD kidneys were defined as organs from a deceased donor with anticipated cold ischemia time (CIT) of <24 hours and not meeting the definition of ECD organs. CIT refers to the time the organ is cooled after organ procurement until implantation at the time of transplant.

The BENEFIT-EXT study enrolled patients who received ECD kidneys. In this study, ECD kidneys were defined as deceased donors with at least 1 of the following: (1) donor age ≥ 60 years; (2) donor age ≥50 years and other donor comorbidities (defined as 2 or more of the following: stroke, hypertension, serum creatinine > 1.5 mg/dL); (3) donation of organ after cardiac death; or (4) anticipated CIT of the organ of ≥ 24 hours.

Both studies excluded recipients undergoing a first transplant whose current panel reactive antibodies (PRA) were ≥50% and recipients undergoing a retransplantation whose current PRA were ≥50%; 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.

Studies Demonstrate that Patients Treated with NULOJIX (belatacept) Had Comparable Patient and Graft Survival to Cyclosporine-Treated Patients

In the BENEFIT study, patient and graft survival between NULOJIX-treated patients (N=226) and cyclosporine-treated patients (N=221) were comparable at both 1 year (96.5% vs. 93.2%; difference =
3.2%; 97.3% CI [-1.5, 8.4]) and 3 years (91.2% vs. 86.9%; difference= 4.3%; 97.3% CI [-2.2, 10.8]). In the BENEFIT-EXT study, patient and graft survival between NULOJIX-treated patients (N=175) and cyclosporine-treated patients (N=184) at both 1 year (88.6% vs. 85.3%; difference= 3.2%; 97.3% CI [-4.8, 11.3]) and 3 years (81.7% vs. 77.7%; difference= 4.0%; 97.3% CI [-5.4, 13.4]) were comparable.

Studies Demonstrate that Patients Treated with NULOJIX (belatacept) Had Comparable Efficacy Failure to Cyclosporine-Treated Patients

In BENEFIT, Efficacy Failure was experienced by 21.7% of patients on NULOJIX (N=226), compared to 16.7% of patients treated with cyclosporine (N=221) by 1 year (difference= 4.9%; 97.3% CI [-3.3, 13.2]) and by 25.7% of patients on NULOJIX, compared to 25.8% of patients treated with cyclosporine by 3 years (difference= -0.1%; 97.3% CI [-9.3, 9.0]). The rate of BPAR was higher in patients treated with NULOJIX compared to cyclosporine-treated patients (19.9% vs. 10.4% at 1 year and 22.1% vs. 14.0% at 3 years, respectively). In NULOJIX-treated patients, most BPAR episodes (70.0%) occurred by Month 3 and 84.0% occurred by Month 6. By 3 years, recurrent BPAR occurred with similar frequency across treatment groups (<3%). Patients treated with NULOJIX experienced episodes of BPAR classified as Banff grade IIb or higher (6.0% [14/226] at 1 year and 7.0% [15/226] at 3 years) more frequently compared to patients treated with the cyclosporine regimen (2.0% [4/221] at 1 year and 2.0% [5/221] at 3 years). T-cell depleting therapy was used more frequently to treat episodes of BPAR in NULOJIX-treated patients (10%; 23/226) compared to cyclosporine-treated patients (2%; 5/221). By three years, 22% (11/50) of NULOJIX-treated patients with a history of BPAR experienced graft loss and/or death compared to 10% (3/31) of cyclosporine-treated patients with a history of BPAR. Graft loss occurred in 2.2% and 4.0% of NULOJIX-treated patients at years 1 and 3, and 3.6% and 4.5% of cyclosporine-treated patients at years 1 and 3, respectively. Death occurred in 1.8% and 4.4% of NULOJIX-treated patients and in 3.2% and 6.8% of cyclosporine-treated patients at years 1 and 3, respectively. Lost to Follow-up occurred in 0.0% and 0.9% of NULOJIX (belatacept)-treated patients at years 1 and 3, and 0.5% and 2.3% of cyclosporine-treated patients at years 1 and 3, respectively.

In BENEFIT-EXT, Efficacy Failure was experienced by 29.1% of patients on NULOJIX (N=175), compared to 28.3% of patients treated with cyclosporine (N=184) by 1 year (difference= 0.9%; 97.3% CI [-9.7, 11.3]) and by 36.0% of patients on NULOJIX, compared to 37.0% of patients treated with cyclosporine by 3 years (difference= -1.0%; 97.3% CI [-12.1, 10.3]). The rate of BPAR at 1 and 3 years was similar in patients treated with NULOJIX (belatacept) and cyclosporine (21.1% vs. 18.5% at year 1 and 24.0% vs. 22.8% at year 3, respectively). In NULOJIX-treated patients, most BPAR episodes (62.0%) occurred by Month 3, and 76.0% experienced BPAR by Month 6. By 3 years, recurrent BPAR occurred with similar frequency across treatment groups (<3%). A similar proportion of patients in the NULOJIX group experienced BPAR classified as Banff grade IIb or higher (5.0% [9/175] by 1 year and 6.0% [10/175] at 3 years) compared to patients treated with the cyclosporine regimen (4.0% [7/184] by 1 year and 5.0% [9/184] at 3 years). T-cell depleting therapy was used with similar frequency to treat any episode of BPAR in NULOJIX-treated patients (5% or 9/175) compared to cyclosporine-treated patients (4% or 7/184). By three years, 24% (10/42) of NULOJIX-treated patients with a history of BPAR experienced graft loss and/or death compared to 31% (13/42) of cyclosporine-treated patients with a history of BPAR. Graft loss occurred in 9.1% and 12.0% of NULOJIX-treated patients at years 1 and 3, respectively, and 10.9% and 12.5% of cyclosporine-treated patients at years 1 and 3, respectively. Death occurred in 2.9% and 8.6% of NULOJIX (belatacept)-treated patients and in 4.3% and 9.2% of cyclosporine-treated patients at years 1 and 3, respectively. Lost to Follow-up occurred in 0.0% and 0.6% of NULOJIX-treated patients at years 1 and 3, and 1.1% and 2.7% of cyclosporine-treated patients at years 1 and 3, respectively.

Importance of Managing Patients and Monitoring for PTLD and PML

Only physicians experienced in immunosuppressive therapy and management of kidney transplant patients should prescribe NULOJIX. Patients should be managed in facilities with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient. Physicians should consider PTLD and PML in the differential diagnosis in patients reporting new or worsening neurological, cognitive, or behavioral signs and symptoms.

Clinical Trials Demonstrated Higher Kidney Function with NULOJIX as Early as the First Month after Transplant

In both studies (BENEFIT and BENEFIT-EXT), mean cGFR was significantly higher in patients treated with NULOJIX compared to patients treated with cyclosporine through 3 years. The differences in mean cGFR were apparent in the first month after transplant and were sustained through 3 years. In the BENEFIT study, the change of mean cGFR between 3 and 36 months demonstrated an increase of 0.8 mL/min/yr (95% CI [-0.2, 1.8]) for NULOJIX-treated patients and a decrease of 2.2 mL/min/yr (95% CI [-3.2, -1.2]) for cyclosporine-treated patients. In the BENEFIT-EXT study, the change of mean cGFR between 3 and 36 months demonstrated a decrease of 0.8 mL/min/yr (95% CI [-1.9, 0.3]) for NULOJIX-treated patients and a decrease of 2.0 mL/min/yr (95% CI [-3.1, -0.8]) for cyclosporine-treated patients.
NULOJIX (belatacept) Effects on Chronic Allograft Nephropathy (CAN)

Fewer patients treated with the NULOJIX regimen experienced CAN compared to patients treated with the cyclosporine regimen at 1 year; however, the clinical significance of these findings is unknown. In the BENEFIT study, the prevalence of CAN at 1 year, as defined by the Banff ’97 classification system, was 24.0% (54/226) in patients treated with NULOJIX and 32.0% (71/219) in patients treated with cyclosporine. In the BENEFIT-EXT study, the prevalence of CAN at 1 year was 46.0% (80/174) in patients treated with NULOJIX and 52.0% (95/184) in patients treated with cyclosporine. CAN was not evaluated after the first year following transplantation.

NULOJIX (belatacept) Effects on Donor Specific Antibodies (DSA)

NULOJIX-treated patients had a lower prevalence of DSA compared to cyclosporine-treated patients at 3 years. In the BENEFIT study, the overall prevalence of DSA was 5.0% in NULOJIX-treated patients and 11.0% in cyclosporine-treated patients, up to 36 months post-transplant. In the BENEFIT-EXT study, the overall prevalence of DSA was 6.0% in NULOJIX-treated patients and 15.0% in cyclosporine-treated patients, up to 36 months post-transplant.

In the BENEFIT study, the rate of BPAR was higher in patients treated with NULOJIX compared to cyclosporine-treated patients (19.9% vs. 10.4% at 1 year and 22.1% vs. 14.0% at 3 years, respectively). By three years, 22% (11/50) of NULOJIX-treated patients with a history of BPAR experienced graft loss and/or death compared to 10% (3/31) of cyclosporine-treated patients with a history of BPAR.

In the BENEFIT-EXT study, the rate of BPAR at 1 and 3 years was similar in patients treated with NULOJIX (belatacept) and cyclosporine (21.1% vs. 18.5% at year 1 and 24.0% vs. 22.8% at year 3, respectively). By three years, 24% (10/42) of NULOJIX-treated patients with a history of BPAR experienced graft loss and/or death compared to 31% (13/42) of cyclosporine-treated patients with a history of BPAR.

Some Additional NULOJIX Adverse Reactions in the Clinical Studies

The most serious adverse reactions with NULOJIX are 1) PTLD, predominantly in the CNS, and other malignancies and 2) serious infections, including PML and polyoma virus-associated nephropathy. Patients receiving immunosuppressants, including NULOJIX, are at increased risk of developing bacterial, viral (eg, CMV and herpes), fungal, and protozoal infections, including opportunistic infections and tuberculosis. Some infections were fatal. NULOJIX, as with other immunosuppressants, was associated with an increased risk of developing malignancies (in addition to PTLD), including non melanoma skin cancer.

The proportion of patients who discontinued treatment due to adverse reactions was 13% for NULOJIX and 19% for cyclosporine through three years of treatment. The most common adverse reactions leading to discontinuation in NULOJIX-treated patients were cytomegalovirus infection (1.5%) and complications of transplanted kidney (1.5%).

Infusion-related reactions within one hour of NULOJIX infusion (5% of patients) were similar to the placebo rate. No serious events were reported through Year 3. The most frequent reactions were hypotension and hypertension.

At Month 1 after transplantation in the BENEFIT and BENEFIT-EXT studies, the frequency of 2+ proteinuria on urine dipstick in patients treated with the NULOJIX recommended regimen was 33% (130/390) and 28% (107/384) in patients treated with the cyclosporine control regimen. The frequency of 2+ proteinuria was similar between the two treatment groups between one and three years after transplantation (<10% in both studies). The clinical significance of this increase in early proteinuria is unknown.

For NULOJIX (belatacept)-treated patients who developed antibodies to belatacept, there was no association with altered clearance.

NULOJIX Effects on Cardiovascular and Metabolic Measurements in Clinical Trials

At 1 year after transplantation, systolic/diastolic blood pressures were 8/3 mmHg lower in patients treated with NULOJIX compared to cyclosporine. At 3 years after transplantation, systolic/diastolic blood pressures were 6/3 mmHg lower in NULOJIX-treated patients compared to cyclosporine. By Year 3, one or more antihypertensive medications were used in 85% of NULOJIX-treated patients and 92% of cyclosporine-treated patients. Hypertension was reported as an adverse reaction in 32.0% of NULOJIX-treated patients and 37.0% of cyclosporine-treated patients.

Triglycerides were lower in NULOJIX-treated patients (N=401) compared to cyclosporine-treated patients (N=405) at both 1 year (151 mg/dL versus 195 mg/dL) and 3 years (141 mg/dL and 180 mg/dL); the clinical significance is unknown.

The incidence of New Onset Diabetes After Transplant (NODAT) was defined as use of an antidiabetic
agent for ≥30 days or ≥2 fasting plasma glucose values ≥126 mg/dL (7.0 mmol/L) post-transplantation. Of the patients treated with NULOJIX, 5.0% (14/304) developed NODAT by the end of year 1 compared to 10.0% (27/280) of patients on cyclosporine. By the end of year 3, the cumulative incidence of NODAT was 8.0% (24/304) in patients treated with the NULOJIX regimen and 10.0% (29/280) in patients treated with the cyclosporine regimen.

**NULOJIX is the First Costimulation Blocker for Maintenance Immunosuppression in Kidney Transplantation**

NULOJIX, a soluble fusion protein, is a selective T-cell costimulation blocker that binds to CD80 and CD86 on antigen-presenting cells. As a result, NULOJIX blocks CD28 mediated costimulation of T cells. In vitro, belatacept inhibits T lymphocyte proliferation and the production of the cytokines interleukin-2, interferon-γ, interleukin-4, and TNF-α. Activated T cells are the predominant mediators of immunologic rejection.

**MY NULOJIX NETWORK**

Bristol-Myers Squibb is committed to providing HCPs and patients with support for NULOJIX through MY NULOJIX NETWORK™. MY NULOJIX NETWORK offers a single point of contact to assist with locating potential infusion providers and providing reimbursement support services. In addition, the program will aim to provide updates to HCPs on whether or not patients who have enrolled have received their NULOJIX therapy.

**NULOJIX (belatacept) INDICATION AND IMPORTANT SAFETY INFORMATION**

**INDICATION**

- NULOJIX (in combination with basiliximab induction, mycophenolate mofetil [MMF], and corticosteroids) is indicated for prophylaxis of organ rejection in adults receiving a kidney transplant.
- Use NULOJIX only in patients who are EBV seropositive.
- Use of NULOJIX for prophylaxis of organ rejection in transplanted organs other than kidney has not been established.

**IMPORTANT SAFETY INFORMATION**

Post-Transplant Lymphoproliferative Disorder (PTLD)

- NULOJIX patients are at increased risk for developing PTLD, predominantly involving the central nervous system (CNS).
- Recipients without immunity to Epstein-Barr virus (EBV seronegative) are at particularly increased risk; therefore, NULOJIX is contraindicated in transplant recipients who are EBV seronegative or unknown serostatus.
- Monitor for new or worsening neurological, cognitive, or behavioral signs and symptoms.
- As the total burden of immunosuppression is a risk factor for PTLD, higher than recommended doses or more frequent dosing of NULOJIX or concomitant immunosuppressive agents are not recommended.
- Other known risk factors for PTLD include cytomegalovirus (CMV) infection and T-cell-depleting therapy.
  - CMV prophylaxis is recommended for at least 3 months after transplantation.
  - Use T-cell-depleting therapy to treat acute rejection cautiously.
- Patients who are EBV seropositive and CMV seronegative may be at increased risk of PTLD
  - Since CMV seronegative patients are at increased risk for CMV disease (a known risk factor for PTLD), the clinical significance of CMV serology for PTLD remains to be determined; however, these findings should be considered when prescribing NULOJIX.

**Management of Immunosuppression**

- Only physicians experienced in immunosuppressive therapy and management of kidney transplant patients should prescribe NULOJIX.
  - Patients should be managed in facilities with adequate laboratory and supportive medical resources.
  - The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

**Progressive Multifocal Leukoencephalopathy (PML)**

- NULOJIX (belatacept) patients are at increased risk for PML, often a rapidly progressive and fatal opportunistic infection
  - In clinical trials, two cases were reported in patients receiving NULOJIX at higher cumulative doses and more frequently than the recommended regimen, along with MMF and corticosteroids; one occurred in a kidney transplant recipient and one occurred in a liver transplant recipient
As PML has been associated with high levels of immunosuppression, higher than recommended doses or more frequent dosing of NULOJIX and concomitant immunosuppressive agents, including MMF, are not recommended.

- Monitor for new or worsening neurological, cognitive, or behavioral signs and symptoms
  - PML is usually diagnosed by brain imaging, cerebrospinal fluid testing for JC viral DNA by polymerase chain reaction, and/or brain biopsy.
  - Consultation with a specialist should be considered.
  - If PML is diagnosed, consider reduction or withdrawal of immunosuppression, weighing risk to the graft.

Other Malignancies and Serious Infections

- Increased susceptibility to infection and possible development of malignancies may result from immunosuppression.
- Patients should avoid prolonged exposure to ultraviolet light and sunlight.
- Patients receiving immunosuppressants, including NULOJIX, are at increased risk for bacterial, viral, fungal, and protozoal infections, including opportunistic infections and tuberculosis. Some infections were fatal.
  - Polyoma virus-associated nephropathy can lead to deteriorating renal function and graft loss; consider reduction in immunosuppression, weighing risk to the graft.
  - Tuberculosis was more frequently observed in patients receiving NULOJIX. Evaluate for tuberculosis and initiate treatment for latent infection prior to NULOJIX use.
  - CMV and *Pneumocystis jiroveci* prophylaxis is recommended after transplantation.

Liver Transplant: use in liver transplant patients is not recommended due to increased risk of graft loss and death in a clinical trial with more frequent administration of NULOJIX than studied in kidney transplant, along with MMF and corticosteroids.

Immunizations: avoid use of live vaccines during NULOJIX treatment.

Pregnancy Category C: based on animal data, NULOJIX (belatacept) may cause fetal harm. NULOJIX should not be used in pregnancy unless potential benefit to the mother outweighs potential risk to the fetus. To monitor maternal-fetal outcomes of pregnant women who have received NULOJIX, or whose partners have received NULOJIX, healthcare providers are strongly encouraged to register pregnant patients in the National Transplant Pregnancy Registry (NTPR) by calling 1-877-955-6877.

Nursing Mothers: discontinue NULOJIX or nursing, considering importance of NULOJIX to the mother.

Most Common Adverse Reactions (≥20%): anemia (45%), diarrhea (39%), urinary tract infection (37%), peripheral edema (34%), constipation (33%), hypertension (32%), pyrexia (28%), graft dysfunction (25%), cough (24%), nausea (24%), vomiting (22%), headache (21%), hypokalemia (21%), hyperkalemia (20%), and leukopenia (20%).

Please see accompanying Full Prescribing Information, including Boxed WARNINGS, or visit [www.NULOJIX.com](http://www.NULOJIX.com) or [www.bms.com](http://www.bms.com).

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company committed to discovering, developing and delivering innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit [www.bms.com](http://www.bms.com), or follow us on Twitter at [http://twitter.com/bmsnews](http://twitter.com/bmsnews).

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding product development. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that belatacept will become a commercially successful product. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb’s business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2010, in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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