Bristol-Myers Squibb Presents New 4-Year Data from the Long-Term Extensions of the BENEFIT and BENEFIT-EXT Clinical Trials of NULOJIX® (belatacept)

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- Renal function results comparable to the benefits observed for NULOJIX at three year analysis
- Safety profile of NULOJIX consistent over the 4th year compared with results at year 3, with no new safety signals identified

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced new 4-year results from the long-term extensions (LTE) of the BENEFIT and BENEFIT-EXT clinical trials of NULOJIX® (belatacept), the first selective T-cell costimulation blocker indicated for the prophylaxis of organ rejection in adult Epstein-Barr Virus (EBV) seropositive patients receiving a kidney transplant, in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids. Results showed that the safety profile of NULOJIX through year 4 was consistent compared with results at year 3 with no new safety signals being identified, and that the renal function benefit versus cyclosporine was maintained through 4 years in patients enrolled in the LTE from both the BENEFIT and BENEFIT-EXT trials. The new data were presented in oral sessions at the 2012 American Transplant Congress (ATC) in Boston.

“These findings show the NULOJIX safety and tolerability profile in adult kidney transplant recipients at 4 years was consistent with what we have observed previously and renal function sustained over time,” said Brian Daniels, M.D., senior vice president, Global Development and Medical Affairs, Bristol-Myers Squibb. “The results of these studies broaden our understanding of NULOJIX and will help physicians in the transplant community make informed decisions about treatment options.”

NULOJIX was approved by the U.S. Food and Drug Administration (FDA) in June 2011 for the prophylaxis of organ rejection in adult EBV seropositive patients receiving a kidney transplant (not for transplanted organs other than the kidney), in combination with basiliximab induction, MMF, and corticosteroids. FDA approval was based on data from BENEFIT and BENEFIT-EXT -- two 3-year, phase 3, open-label, randomized, multicenter, active-controlled studies.

The most serious adverse reactions reported with NULOJIX are post-transplant lymphoproliferative disorder (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® (belatacept) is not recommended.

4-Year Results of BENEFIT Long-Term Extension

A total of 457 of 471 patients who completed 3 years of treatment entered the long-term extension of the BENEFIT trial. Twenty-five patients discontinued the long-term extension between years 3 and 4 (n = 6 on more intensive regimen of NULOJIX; n = 6 on less intensive regimen of NULOJIX; n = 13 cyclosporine-treated patients); 4 patients died during year 4 (n = 1 MI; n = 3 cyclosporine-treated patients); and 1 patient experienced graft loss (n = 1 cyclosporine-treated patient). Two patients experienced an acute rejection episode (n = 1 MI; n = 1 cyclosporine-treated patient).

At 4 years, the mean calculated Glomerular Filtration Rate (a measure of renal function) was 73.8 ± 19.6 (MI), 75.1 ± 17.0 (LI), and 50.0 ± 18.7 (cyclosporine-treated patients) mL/min/1.73 m2.

The incidence rate of serious infections from initial randomization through year 4 was 10.3 (MI), 10.4 (LI), and 15.7 (cyclosporine-treated patients) events per 100 patient years of exposure, and the incidence rate of overall malignancies was 2.3 (MI), 1.4 (LI) and 3.0 (cyclosporine-treated patients) events per 100 patient years of exposure. No new cases of PTLD were observed between years 3 and 4, and no new safety signals were identified between years 3 and 4.

The NULOJIX MI regimen is not recommended for patients taking NULOJIX as it may result in higher incidence of serious—sometimes fatal—adverse reactions, including serious infections, overall malignancies and death.

4-Year Results of BENEFIT-EXT Long-Term Extension

A total of 304 of 323 patients who completed 3 years of treatment entered the long-term extension of the BENEFIT-EXT
Post-Transplant Lymphoproliferative Disorder (PTLD)

**IMPORTANT SAFETY INFORMATION**

**INDICATION**

interleukin-4, In vitro, belatacept inhibits T lymphocyte proliferation and the production of the cytokines interleukin-2, interferon-g, and TNF-a. Activated T cells are the predominant mediators of immunologic rejection.

**Use of NULOJIX for prophylaxis of organ rejection in transplanted organs other than kidney has not been established**

**INDICATION**

- **NULOJIX**® (belatacept) (in combination with basiliximab induction, mycophenolate mofetil [MMF], and corticosteroids) is indicated for prophylaxis of organ rejection in adults receiving a kidney transplant, in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. NULOJIX should only be used in patients who are EBV seropositive.
- Use **NULOJIX** only in patients who are Epstein-Barr virus (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 EBV (ie, 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® (belatacept)
  - 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 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® (belatacept). 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 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, also available on www.bms.com.

NULOJIX is available as 250 mg lyophilized powder for injection, for intravenous use. NULOJIX is a trademark of Bristol-Myers Squibb Company.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit www.bms.com, or follow us on Twitter at http://twitter.com/bmsnews.

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