Long-Term, 7-Year Study of Nulojix® (belatacept) Regimen Demonstrates Statistically Significant Relative Risk Reduction of Death or Graft Loss over Cyclosporine Regimen in Kidney Transplant

Release Date:
Wednesday, May 6, 2015 10:00 am EDT

Terms:
Dateline City:
PRINCETON, N.J.

- New BENEFIT study 7-year follow-up data show Nulojix regimen demonstrated a statistically significant 43% relative risk reduction of death or graft loss at 7 years, with survival benefit of 52% observed as early as 5 years post-transplant
- 7-year BENEFIT results demonstrated statistically significant and sustained difference in renal function of Nulojix- versus cyclosporine-treated patients
- In the long-term follow-up (years 3-7) of BENEFIT participants, the safety profile of Nulojix was similar to cyclosporine

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced results from a 7-year, long-term follow-up from a prospective, randomized Phase III trial (BENEFIT) in kidney transplant patients, which demonstrated a statistically significant 43% relative risk reduction of death or graft loss (transplant failure) in patients receiving the Nulojix (belatacept) FDA-approved dosing regimen over those receiving a cyclosporine regimen (hazard ratio=0.57, p=0.0286). Data also showed that there was a statistically significant survival benefit of 52% relative risk reduction of death or graft loss at 5 years post-transplant (hazard ratio=0.477, p=0.0045). In the long-term follow-up (years 3-7) on BENEFIT participants, the safety profile of the Nulojix regimen was similar to the cyclosporine regimen. Nulojix is the first selective T-cell costimulation blocker indicated in combination with basiliximab induction, mycophenolate mofetil (MMF) and corticosteroids for the prophylaxis of organ rejection in adult Epstein-Barr Virus (EBV) seropositive patients receiving a kidney transplant. The 7-year BENEFIT results were presented in the plenary session at the 2015 American Transplant Congress (ATC) in Philadelphia.

The BENEFIT trial is a 36-month clinical study with long-term follow-up through 84 months, with primary endpoints of composite patient and graft survival by 12 months, rate of acute rejection by 12 months, and composite measured glomerular filtration rate (GFR, a measure of renal function) <60 at month 12 or a decrease in measured GFR from month 3 to month 12. Secondary endpoints were measured at 36 months.

In the BENEFIT 7-year study follow-up, the rates of serious adverse events were similar across treatment groups (69% among patients receiving the Nulojix regimen and 76% among patients receiving the cyclosporine regimen). The incidence rates (calculated as per 100-person years) were also similar among both groups for fungal infections (6.7 and 7.6, respectively), viral infections (14.2 and 15.7, respectively) and malignancies (1.7 and 2.6, respectively). Post-transplant lymphoproliferative disease (PTLD) occurred in 2 patients in the Nulojix regimen group and 2 patients in the cyclosporine regimen group. Both PTLD cases in the group treated with the Nulojix regimen occurred before month 12.

"Advances in kidney transplant care have led to impressive improvements in short-term survival; conversely, long-term allograft survival has not appreciably improved. It is therefore very encouraging to see a therapeutic intervention associated with a long-term survival advantage," said Flavio Vincenti, M.D., Professor of Clinical Medicine, University of California, San Francisco, Division of Nephrology. "It is heartening for treating physicians and their patients to see a survival benefit as early as 5 years that continues out to 7 years post-transplant."

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 III, open-label, randomized, multicenter, active-controlled studies.

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 progressive multifocal leukoencephalopathy (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. Nulojix is only indicated in EBV seropositive patients.

In addition to the graft survival benefit, 7-year results demonstrate a statistically significant difference in renal function of patients receiving the Nulojix regimen versus those receiving the cyclosporine regimen (p=0.0286). At month 84, mean calculated GFR (cGFR) was 78 ml/min/1.73m² for the Nulojix regimen group and 51 ml/min/1.73m² for the cyclosporine regimen group. Rates and grades of acute rejection were higher in the Nulojix regimen group than in the cyclosporine regimen group, particularly in the first treatment year. By year 3, acute rejection was observed in 17.7% (39/226) of patients receiving the Nulojix regimen and 9.7% (19/221) of patients receiving the cyclosporine regimen. Between year 3 and year 7, there was one additional event of acute rejection in the Nulojix regimen group and two additional events of acute rejection in the cyclosporine regimen group. The Nulojix regimen demonstrated lower rates of de novo DSA formation at 7 years compared to cyclosporine (3.1% versus 11.6%).

“The 7-year BENEFIT results mark a significant research milestone for Nulojix and represent our commitment to this patient population,” said Douglas Manion, M.D., Head of Specialty Development, Bristol-Myers Squibb. “Bristol-Myers Squibb recognizes the importance of continuing to advance immunosuppressive therapeutic options.”

About BENEFIT: Study Design

The Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) is an open-label, randomized, comparative, multicenter study that enrolled 666 renal transplant recipients of standard criteria deceased donor (SCD) and living donor kidneys in 3 cohorts. SCD kidneys were defined as organs from deceased donors with an anticipated cold ischemia time (CIT) of less than 24 hours and not meeting the definition of extended criteria donor (ECD) organs. CIT refers to the time the organ is cooled after organ procurement until implantation at the time of transplant.

In the study, Nulojix was compared with cyclosporine; 1 cohort received a less intensive dose of Nulojix (n=226) and 1 received cyclosporine (n=221). All patients also received basiliximab induction, MMF and corticosteroids. The trial excluded recipients undergoing first transplant with current panel reactive antibodies (PRA, a measure of pre-existing antibodies that may negatively impact the kidney transplant) ≥50% and recipients undergoing retransplantation with current PRA ≥30%; patients with HIV, hepatitis C or evidence of current hepatitis B infection, active tuberculosis, and those in whom intravenous access was difficult to obtain. At 3 years, BENEFIT results demonstrated improvement in renal function in kidney transplant recipients treated with Nulojix compared to cyclosporine.

About Nulojix

Nulojix is the first selective T-cell costimulation blocker approved by the U.S. Food and Drug Administration, indicated for the prophylaxis of organ rejection in adult patients 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 of Nulojix for prophylaxis of organ rejection in transplanted organs other than kidney has not been established.

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

NULOJIX INDICATION

- NULOJIX® (belatacept) 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® (belatacept), 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.

Acute Rejection and Graft Loss with Corticosteroid Minimization

- In NULOJIX postmarketing experience, corticosteroid minimization to 5 mg/day between Day 3 and Week 6 post-transplant was associated with an increased rate and grade of acute rejection, particularly Grade III.
  - These Grade III rejections occurred in patients with 4-6 human leukocyte antigen (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.
  - Median (25th-75th percentile) corticosteroid doses were tapered to about 15 mg (10-20 mg)/day by the first 6 weeks and remained at about 10 mg (5-10 mg)/day for the first 6 months post-transplant.

Immunizations

- Avoid use of live vaccines during NULOJIX® (belatacept) 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%).

Click here for Full Prescribing Information, Including Boxed WARNINGS.

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, please visit http://www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

**Bristol-Myers Squibb Forward Looking Statement**

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. 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. 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, 2014, 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.

**Language:**
English

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**Ticker Slug:**
Ticker: BMY
Exchange: NYSE

**Source URL:** https://news.bms.com/press-release/long-term-7-year-study-nulojix-belatacept-regimen-demonstrates-statistically-significant