ACR 2018: Lilly Shares Updated Safety Analysis of OLUMIANT® (baricitinib) in Patients with Moderately-to-Severely Active Rheumatoid Arthritis

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- Integrated safety analysis reflects long-term results from 3,492 treated patients for 7,860 patient-years of exposure -

- Updated analysis of cardiovascular safety data for OLUMIANT will also be presented -

INDIANAPOLIS, Oct. 21, 2018 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) and Incyte Corporation (NASDAQ: INCY) announced today findings from an updated integrated safety analysis of OLUMIANT® (baricitinib) based on an ongoing long-term extension (LTE) study of rheumatoid arthritis (RA) patients treated up to six years. The analysis provides further support for the characterization of OLUMIANT's safety profile, and was shared as an oral presentation today at the American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (ARHP) Annual Meeting in Chicago, Illinois. OLUMIANT is indicated in the U.S. for the treatment of adults with moderately-to-severely active RA who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

"Overall, the data show that OLUMIANT maintained its recorded safety profile," said Terence Rooney, M.D., senior medical director, Lilly Bio-Medicines. "This integrated analysis reflects Lilly's commitment to patient safety and our goal to ensure that the benefits and risks of our medicines are well-understood by the healthcare community."

This long-term safety evaluation of OLUMIANT included all patients with active RA exposed to the medicine during eight randomized trials (including four Phase 3, three Phase 2 and one Phase 1b studies) and one LTE study (with data cut-off at April 1, 2017). Dose responses were evaluated based on the four Phase 2/3 trials in which patients were randomized to receive the 2-mg or 4-mg dose of baricitinib, including data from the LTE (the 4-mg dose of baricitinib is not approved for use in the U.S.). Incidence rates (IR) were calculated per 100 patient-years (PY).

In total, 3,492 patients received OLUMIANT for 7,860 patient-years of exposure (PYE). More than three-quarters of these patients were treated for at least one year, and half were treated for at least two and a half years. Key findings from the analysis include:

- Overall, adverse event (AE) IRs per 100 PYE were consistent with prior analyses, and did not show evidence of increase with longer-term treatment.
- The malignancy (excluding non-melanoma skin cancer) IR was 0.8.
- The major adverse cardiovascular event (MACE) IR was 0.5.
- The serious infection IR was 3.0.
- The IR for venous thromboembolism (VTE), which combined events of deep venous thrombosis (DVT) and pulmonary embolism (PE), was 0.5.
- Fewer than 1.0 percent of patients discontinued treatment with OLUMIANT due to abnormal lab results. The permanent discontinuation IR due to AEs was 5.4.

Follow up investigations will continue to assess OLUMIANT's long-term safety profile, including malignancies, VTE and MACE.

"Integrated data analyses can provide important insights for healthcare providers who are considering treatment options for their patients," said Kevin Winthrop, MD, MPH, Professor of Infectious Diseases, Public Health and Preventive Medicine, and Ophthalmology at Oregon Health and Science University. "The results of OLUMIANT's latest integrated safety analysis, now with up to six years of patient follow-up, show a similar safety profile to what has been previously reported."

Later in the meeting, Lilly will share an updated analysis of cardiovascular safety data from patients with moderately-to-severely active RA treated with OLUMIANT for up to six years.

Indication and Usage for OLUMIANT (baricitinib) tablets (in the United States) for RA patients

OLUMIANT® (baricitinib) 2 mg is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. Limitation of Use: Use of OLUMIANT in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION FOR OLUMIANT (baricitinib) tablets

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

***SERIOUS INFECTIONS*: Patients treated with Olumiant are at risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt Olumiant until the infection is controlled. Reported infections include:**

- **Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease. Test patients for latent TB before initiating Olumiant and during therapy. Treatment for latent infection should be considered prior to Olumiant use.**

- **Invasive fungal infections, including candidiasis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Carefully consider the risks and benefits of Olumiant prior to initiating therapy in patients with chronic or recurrent infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with Olumiant including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

***MALIGNANCIES*: Lymphoma and other malignancies have been observed in patients treated with Olumiant.**

***THROMBOSIS*: Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), has been observed at an increased incidence in patients treated with Olumiant compared to placebo. In addition, there were cases of arterial thrombosis. Many of these adverse events were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated.**

WARNINGS AND PRECAUTIONS

SERIOUS INFECTIONS: The most common serious infections reported with Olumiant included pneumonia, herpes zoster, and urinary tract infection. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, esophageal candidiasis, pneumocystosis, acute histoplasmosis, cryptococcosis, cytomegalovirus, and BK virus were reported with Olumiant. Some patients have presented with disseminated rather than local disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids. Avoid Olumiant in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating Olumiant in patients:

- with chronic or recurrent infection
- who have been exposed to TB
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for infections during and after Olumiant treatment. Interrupt Olumiant if a patient develops a serious infection, an opportunistic infection, or sepsis. Do not resume Olumiant until the infection is controlled.

Tuberculosis – Before initiating Olumiant evaluate and test patients for latent or active infection and treat patients with latent TB with standard antimycobacterial therapy. Olumiant should not be given to patients with active TB. Consider anti-TB therapy prior to initiating Olumiant in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection. Monitor patients for TB during Olumiant treatment.

Viral Reactivation – Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies with Olumiant. If a patient develops herpes zoster, interrupt Olumiant treatment until the episode resolves.

The impact of Olumiant on chronic viral hepatitis reactivation is unknown. Screen for viral hepatitis in accordance with clinical guidelines before initiating Olumiant.

MALIGNANCY AND LYMPHOPROLIFERATIVE DISORDERS: Malignancies were observed in Olumiant clinical studies. Consider the risks and benefits of Olumiant prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing Olumiant in patients who develop a malignancy. NMSCs were reported in patients treated with Olumiant. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

THROMBOSIS: Thrombosis, including DVT and PE, has been observed at an increased incidence in Olumiant-treated patients compared to placebo. In addition, arterial thrombosis events in the extremities have been reported in clinical studies with Olumiant. Many of these adverse events were serious and some resulted in death. There was no clear relationship between platelet count elevations and thrombotic events. Use Olumiant with caution in patients who may be at increased risk of thrombosis. If clinical features of DVT/PE or arterial thrombosis occur, evaluate patients promptly and treat appropriately.

GASTROINTESTINAL PERFORATIONS: Gastrointestinal perforations have been reported in Olumiant clinical studies, although the role of JAK inhibition in these events is not known. Use Olumiant with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Promptly evaluate patients who present with new onset abdominal symptoms for early identification of gastrointestinal perforation.

LABORATORY ABNORMALITIES:

Neutropenia – Olumiant treatment was associated with an increased incidence of neutropenia (absolute neutrophil count [ANC] <1000 cells/mm^3) compared to placebo. Avoid initiation or interrupt Olumiant treatment in patients with an ANC <1000 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management.

Lymphopenia – Absolute lymphocyte count (ALC) <500 cells/mm^3 were reported in Olumiant clinical trials. Lymphocyte counts less than the lower limit of normal were associated with infection in patients treated with Olumiant, but not placebo. Avoid initiation or interrupt Olumiant treatment in patients with an ALC <500 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management.

Anemia – Decreases in hemoglobin levels to <8 g/dL were reported in Olumiant clinical trials. Avoid initiation or interrupt Olumiant treatment in patients with hemoglobin <8 g/dL. Evaluate at baseline and thereafter according to routine patient management.

Liver Enzyme Elevations – Olumiant treatment was associated with increased incidence of liver enzyme elevation compared to placebo. Increases to ≥5x and ≥10x upper limit of normal were observed for both ALT and AST in patients in Olumiant clinical trials.

Evaluate at baseline and thereafter according to routine patient management. Promptly investigate the cause of liver enzyme elevation to identify potential cases of drug-induced liver injury. If increases in ALT or AST are observed and drug-induced liver injury is suspected, interrupt Olumiant until this diagnosis is excluded.

Lipid Elevations – Treatment with Olumiant was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Assess lipid parameters approximately 12 weeks following Olumiant initiation. Manage patients according to clinical guidelines for the management of hyperlipidemia.

VACCINATIONS: Avoid use of live vaccines with Olumiant. Update immunizations in agreement with current immunization guidelines prior to initiating Olumiant therapy.

ADVERSE REACTIONS
Adverse reactions (≥1%) include: upper respiratory tract infections (16.3%, 14.7%, 11.7%), nausea (2.7%, 2.8%, 1.6%), herpes simplex (0.8%, 1.8%, 0.7%), and herpes zoster (1.0%, 1.4%, 0.4%) for Olumiant 2 mg, baricitinib 4 mg, and placebo, respectively.

USE IN SPECIFIC POPULATIONS

PREGNANCY AND LACTATION: No information is available to support the use of Olumiant in pregnancy or lactation. Advise women not to breastfeed during treatment with Olumiant.

HEPATIC AND RENAL IMPAIRMENT: Olumiant is not recommended in patients with severe hepatic impairment or in patients with moderate or severe renal impairment.

Please click to access full Prescribing Information, including Boxed Warning about Serious infections, Malignancies, and Thrombosis, and Medication Guide.

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About OLUMIANT
OLUMIANT is a once-daily, oral JAK inhibitor for the treatment of adults with moderately-to-severely active rheumatoid arthritis who have had an inadequate response to one or more TNF inhibitor therapies.[1] There are four known JAK enzymes: JAK1, JAK2, JAK3 and TYK2. JAK-dependent cytokines have been implicated in the pathogenesis of a number of inflammatory and autoimmune diseases.[2] OLUMIANT has greater inhibitory potency at JAK1, JAK2 and TYK2 relative to JAK3; however, the relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.[1] OLUMIANT is approved in more than 50 countries.

About Rheumatoid Arthritis
Rheumatoid arthritis is a systemic autoimmune disease characterized by inflammation and progressive destruction of joints.[3,4] Approximately three times as many women as men have the disease.[5] Current treatment of RA includes the use of non-steroidal anti-inflammatory drugs, oral conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) — such as methotrexate, the current standard of care, and injectable, biological disease-modifying antirheumatic drugs (bDMARDs) that target selected mediators implicated in the pathogenesis of RA.[5] Despite current treatment options, many patients do not reach their therapeutic goals.[6,7] There remains an important need to provide additional treatment options to improve overall patient care.

About Lilly in Immunology
Lilly is bringing our heritage of championing groundbreaking, novel science to immunology and is driven to change what's possible for people living with autoimmune diseases. There are still significant unmet needs, as well as personal and societal costs, for people living with a variety of autoimmune diseases and our goal is to minimize the burden of disease. Lilly is investing in leading-edge clinical approaches across its immunology portfolio in hopes of transforming the autoimmune disease treatment experience. We've built a deep pipeline and are focused on advancing cutting edge science to find new treatments that offer meaningful improvements to support the people and the communities we serve.

About Eli Lilly and Company
Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at www.lilly.com and newsroom.lilly.com/social-channels.

About Incyte
Incyte Corporation is a Wilmington, Delaware-based biopharmaceutical company focused on the discovery, development and commercialization of proprietary therapeutics. For additional information on Incyte, please visit the company's website at www.incyte.com.

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This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about OLUMIANT (baricitinib) as a treatment for patients with rheumatoid arthritis and reflects Lilly's and Incyte's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. Among other things, there can be no guarantee that OLUMIANT will receive additional regulatory approvals or be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's and Incyte's most recent respective Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly and Incyte undertake no duty to update forward-looking statements to reflect events after the date of this release.

[1] Olumiant [package insert].Indianapolis, IN: Eli Lilly and Company; 2018.
[2] Walker JG and Smith MD. J Rheumatol. 2005;32;1650-1653.
[3] Hand Clinics, Advances in the Medical Treatment of Rheumatoid Arthritis, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3135413

/pdf/nihms305780.pdf. Accessed April 23, 2018.

[4] Curtis JR and Singh JA. Clin Ther. 2011;33(6):679-707.

[5] Hunter TM, et al. *Rheumatol Int*. 2017;37:1551–1557.

[6] Smolen JS, Aletaha D, McInnes IB. *Lancet*. 2016;388:2023-2038.

[7] Sustained Rheumatoid Arthritis Remission is Uncommon in Clinical Practice, Arthritis Research & Therapy, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3446437/. Accessed April 23, 2018.

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