OLUMIANT® Long-Term Safety Profile Established Up to 9.3 Years in Integrated Analysis of More Than 3,700 Patients with Rheumatoid Arthritis

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INDIANAPOLIS, Nov. 9, 2021 /PRNewswire/ -- OLUMIANT® (baricitinib) maintained a consistent safety profile in a long-term, integrated safety analysis of patients with rheumatoid arthritis (RA) who received OLUMIANT for 14,744 patient years of exposure, in line with previously published findings. Eli Lilly and Company (NYSE: LLY) and Incyte (NASDAQ: INCY) will present these results, along with real-world safety results from 3,445 patients with RA in Japan, at ACR Convergence 2021, the American College of Rheumatology's virtual annual meeting taking place November 3-9, 2021. Detailed and additional results from the long-term, integrated safety study for OLUMIANT were recently published in the *Annals of the Rheumatic Diseases*.

"Rheumatoid arthritis is a chronic inflammatory disease that requires long-term treatment to manage symptoms, including joint pain, swelling and tenderness, and if left uncontrolled, can be associated with significant morbidity complications," said Professor Peter C. Taylor, M.D., Ph.D., Professor of Musculoskeletal Sciences at the University of Oxford, and lead author of this analysis. "As one of the longest safety trials for a JAK inhibitor in this disease, these data can help healthcare providers and people living with rheumatoid arthritis in better understanding OLUMIANT when considering treatment options that can be used for prolonged periods of time."

OLUMIANT RA Safety Profile Remains Consistent Up to 9.3 Years

A pooled analysis across nine randomized studies and one long-term extension study evaluated the safety of OLUMIANT 4-mg and OLUMIANT 2-mg over time in 3,770 patients with RA, who were exposed to treatment for a total of 14,744 patient years of exposure. Participants had a median exposure of 4.6 years and a maximum exposure of 9.3 years.

Among those treated with OLUMIANT, the overall incidence rate of adverse events per 100 patient years of exposure was 22.6, and the incidence rate of serious adverse events was 7.4. Incidence rates remained stable over time across the 14,744 patient years of exposure. The incidence rate of serious infections was 2.58 per 100 patient years of exposure.

Adverse events of special interest included venous thromboembolic events (pulmonary embolism, incidence rate=0.26; deep vein thrombosis, incidence rate=0.35; deep vein thrombosis and/or pulmonary embolism, incidence rate=0.49) and major adverse cardiovascular events (incidence rate=0.51) within the range of incidence rates described in epidemiological studies in the general RA population. Incidence rates of safety events of special interest among those treated with OLUMIANT remained stable through exposures up to 9.3 years and were generally similar between the OLUMIANT 2-mg and 4-mg groups. In a subgroup of patients over 50 years old who had at least one cardiovascular risk factor (current smoker, hypertension, high-density lipoprotein cholesterol <40 mg/dL, diabetes, or arteriosclerotic cardiovascular disease), the incidence rate of major adverse cardiovascular events (MACE) was 0.77 per 100 patient years of exposure vs. 0.51 in the total study population.

In this study, age-adjusted incidence rates for malignancy (incidence rate=0.92) and mortality (incidence rate=0.6) for patients treated with OLUMIANT appear similar to the general U.S. population.

For methodology, see the full abstract on the ACR website.

Real-World Evidence Study Reinforces OLUMIANT 4-mg and 2-mg Safety Profile at 24-Weeks

A post-marketing surveillance study of 3,445 patients with RA in Japan evaluated the safety of OLUMIANT 4-mg and OLUMIANT 2-mg in clinical practice and no new safety signals were identified. Of the population, 54% were 65 years or older, and 65% started with an initial dose of OLUMIANT 4-mg/day. Three out of four patients in the study (74%) continued treatment for 24 weeks, and the majority of patients maintained a consistent dosage.

Overall, 26% of patients (n=887) reported an adverse event and 4% of patients (n=122) reported a serious adverse event, with six deaths, none of which were related to deep vein thrombosis or pulmonary embolisms. Priority survey events included herpes zoster (3%, n=100), liver dysfunction (3%, n=100), serious infection (1.5%, n=51), anemia (1%, n=41), hyperlipidemia (1%, n=40), malignancy (0.3%, n=11), interstitial pneumonia (0.2%, n=8), MACE (0.1%, n=5) and venous thromboembolism (0.1%, n=3).

For methodology, see the full abstract on the ACR website.

"OLUMIANT has one of the largest and longest sets of available safety data in the JAK inhibitor class, spanning 19,000 total patient years of exposure, including almost 15,000 patient years in RA, over a period of over nine years across the clinical development program," said Lotus Mallbris, M.D., Ph.D., vice president of global immunology development and U.S. and global medical affairs at Lilly. "We are pleased to present this extensive set of data at ACR, which illustrate OLUMIANT's long-term safety profile in rheumatoid arthritis. When taken in totality with previously published, well-established efficacy data, these new insights further characterize the benefit/risk profile of OLUMIANT and support better informed treatment decisions by HCPs and patients affected by this painful disease."

About OLUMIANT®

OLUMIANT, a once-daily, oral JAK inhibitor was discovered by Incyte and licensed to Lilly. It is approved in the U.S. and more than 75 countries as a treatment for adults with moderate to severe rheumatoid arthritis and is approved in more than 50 countries, including the European Union and Japan, for the treatment of adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy. Marketing authorization for the treatment of hospitalized patients with COVID-19 has been granted for OLUMIANT in multiple countries. The U.S. FDA-approved labeling for

OLUMIANT includes a Boxed Warning for Serious Infections, Malignancy, and Thrombosis. See the full Prescribing Information here. Baricitinib is also being investigated in alopecia areata (AA), juvenile idiopathic arthritis (JIA) and systematic lupus erythematosus (SLE).

In December 2009, Lilly and Incyte announced an exclusive worldwide license and collaboration agreement for the development and commercialization of baricitinib and certain follow-on compounds for patients with inflammatory and autoimmune diseases.

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: Not recommended for use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

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. If positive, start treatment for latent infection 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 localized 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 of ALT ≥5x upper limit of normal (ULN) and increases of AST ≥10x ULN were observed 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.

HYPERSENSITIVITY: Reactions such as angioedema, urticaria, and rash that may reflect drug sensitivity have been observed in patients receiving Olumiant, including serious reactions. If a serious hypersensitivity reaction occurs, promptly discontinue Olumiant while evaluating the potential causes of the reaction.

ADVERSE REACTIONS

Most common adverse reactions include: upper respiratory tract infections (16.3%, 11.7%), nausea (2.7%, 1.6%), herpes simplex (0.8%, 0.7%), and herpes zoster (1.0%, 0.4%) for Olumiant 2 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 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 Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease characterized by inflammation and progressive destruction of joints.[1,2] More than 23 million people worldwide suffer from RA.[3] Approximately three times as many women as men have the disease.[5] Patients and physicians indicate there remains an important opportunity to improve patient care. Current treatment of RA includes the use of non-steroidal anti-inflammatory drugs, oral disease-modifying anti-rheumatic drugs such as methotrexate, and injectable biological response modifiers that target selected mediators implicated in the pathogenesis of RA.[4]

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 health care leader that unites caring with discovery to create medicines that 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 lilly.com and lilly.com/newsroom.

About Incyte

Incyte is a Wilmington, Delaware-based, global biopharmaceutical company focused on finding solutions for serious unmet medical needs through the discovery, development and commercialization of proprietary therapeutics. For additional information on Incyte, please visit Incyte.com and follow @Incyte.

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Lilly Forward-Looking Statement

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 as a possible treatment for other conditions and reflects Lilly's and Incyte's current beliefs and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug research, development, and commercialization. Among other things, there can be no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with the results to date, and 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.

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4. Hunter TM, et al. Rheumatol Int. 2017;37:1551–1557.

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