Updates on OLUMIANT® (baricitinib) Phase 3 lupus program and FDA review for atopic dermatitis

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INDIANAPOLIS, Jan. 28, 2022 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) and Incyte (NASDAQ:INCY) today announced updates on the Phase 3 development program for OLUMIANT® (baricitinib) in adults with active systemic lupus erythematosus (also referred to as SLE and lupus) and the status of the U.S. atopic dermatitis supplemental new drug application (sNDA).

Lupus program update

Based on top-line efficacy results from two pivotal Phase 3 trials (SLE-BRAVE-I and II), Lilly has decided to discontinue the Phase 3 development program for OLUMIANT in lupus.

In SLE-BRAVE-I, the baricitinib 4-mg oral dose met the primary endpoint, demonstrating a statistically significant reduction in disease activity as measured by the proportion of adults with active lupus who achieved an SRI-4 response (a composite measurement of overall disease activity) at Week 52 compared to placebo. The SLE-BRAVE-II study, which also studied adults with active lupus, did not meet the primary endpoint of SRI-4 response. Key secondary endpoints were not met in either study. Safety findings from both lupus studies were consistent with previously published OLUMIANT data and did not impact our decision to discontinue the program. Lilly intends to analyze the totality of our lupus data to help inform our understanding of the disease and advance the science and intends to publish findings at a later date.

Lilly is working with investigators to appropriately conclude the Phase 3 SLE long-term extension trial, SLE-BRAVE-X, which was designed to evaluate the long-term safety and efficacy of OLUMIANT over three years in adults who completed SLE-BRAVE-I or II.

Atopic dermatitis regulatory update

Lilly is in ongoing discussion with the U.S. Food and Drug Administration (FDA) regarding the status of the sNDA for OLUMIANT for the treatment of adults with moderate-to-severe atopic dermatitis. At this point, the company does not have alignment with the FDA on the indicated population. Given the Agency's position, there is a possibility that this could lead to a Complete Response Letter (CRL). The efficacy and safety profile of OLUMIANT was evaluated in eight atopic dermatitis clinical trials (six double-blind, randomized, placebo-controlled studies and two long-term extension studies) inclusive of patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The safety profile in these trials was consistent with previously published OLUMIANT data.

OLUMIANT was the first JAK inhibitor approved to treat moderate-to-severe patients with atopic dermatitis who have an inadequate response to topical treatments in the European Union and Japan.

"On behalf of all of us at Lilly, we thank the participants, trial sites and clinical investigators for their essential contributions to the OLUMIANT atopic dermatitis and lupus programs. We are disappointed for the millions of people who suffer from these complex and hard-to-treat autoimmune diseases and are in need of more treatment options, and we remain committed to pursuing treatment advances in immunology that can make life better for people around the world," said Lotus Mallbris, M.D., Ph.D., vice president of global immunology development and medical affairs at Lilly. "These decisions do not affect Lilly's other research efforts for OLUMIANT or its approved indications. We are confident in OLUMIANT for approved indications in the U.S. and globally as OLUMIANT has one of the largest and longest sets of available safety data in the JAK inhibitor class, including nine years across the clinical development program."

"This year, we are eager to provide OLUMIANT to more patients in therapeutic areas where there is significant unmet medical need," Mallbris said. "We look forward to potential regulatory approvals for OLUMIANT in 2022, including COVID-19 for certain hospitalized patients in the U.S. and severe alopecia areata in the U.S., European Union and Japan, where OLUMIANT has the potential to be a first-in-disease treatment."

More than 325,000 people worldwide have been treated with OLUMIANT to date across approved indications. On January 13, 2022, the World Health Organization (WHO) released new guidelines on treatments for COVID-19, strongly recommending the use of baricitinib in combination with corticosteroids for severely or critically ill patients. To read Lilly's statement about the WHO COVID-19 guidelines update, click here. Baricitinib is approved or authorized for emergency use for treatment of certain hospitalized patients with COVID-19 in 14 countries. To date, more than 740,000 patients globally are estimated to have been treated with baricitinib for COVID-19. In the U.S., baricitinib is authorized by the FDA for emergency use in hospitalized adults and pediatric patients two years of age or older requiring supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The FDA has granted priority review for the sNDA for baricitinib for the treatment of certain hospitalized patients with COVID-19, with an anticipated regulatory action in Q2 2022.

Authorized Use Under the EUA and Important Safety Information for baricitinib (in the United States) for COVID-19

Baricitinib is authorized for use under an Emergency Use Authorization (EUA) for treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

Baricitinib has not been approved for the treatment of COVID-19, but has been authorized for emergency use by the FDA. Baricitinib is authorized under an EUA only for the duration of the declaration that circumstances exist justifying the authorization of the EUA of baricitinib under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

For more information about the authorized use of baricitinib in COVID-19 and mandatory requirements of the EUA, please see the FDA Letter of Authorization, Fact Sheet for Healthcare Providers and Fact Sheet for Patients, Parents and Caregivers (English) (Spanish).

Important Safety Information about baricitinib for COVID-19

The following provides essential safety information on the unapproved use of baricitinib under the Emergency Use Authorization.

Warnings

Serious Infections: There is limited information regarding use of baricitinib in patients with COVID-19 and concomitant active serious infections.

Serious infections have occurred in patients receiving baricitinib. Avoid the use of baricitinib with known active tuberculosis. Consider if the potential benefits outweigh the potential risks of baricitinib treatment in patients with active serious infections other than COVID-19 or chronic/recurrent infections.

Thrombosis: In hospitalized patients with COVID-19, prophylaxis for venous thromboembolism is recommended unless contraindicated. If clinical features of deep vein thrombosis or pulmonary embolism occur, patients should be evaluated promptly and treated appropriately.

Abnormal Laboratory Values: There is limited information regarding use of baricitinib in patients with COVID-19 and any of the following clinical findings: absolute neutrophil count (ANC) <1000 cells/mm^3, absolute lymphocyte count (ALC) <200 cells/mm^3, and hemoglobin <8g/dL.

Evaluate estimated glomerular filtration rate (eGFR), liver enzymes, and complete blood count at baseline and thereafter according to local patient management practice. Monitor closely when treating patients with abnormal baseline and post-baseline laboratory values. Follow dose adjustments as recommended in the Fact Sheet for Healthcare Providers for patients with abnormal renal, hematological and hepatic laboratory values. Manage patients according to routine clinical guidelines.

Vaccinations: Avoid use of live vaccines with baricitinib.

Hypersensitivity: If a serious hypersensitivity occurs, discontinue baricitinib while evaluating the potential causes of the reaction.

See **Warnings and Precautions** in the FDA-approved full Prescribing Information and Medication Guide for additional information on risks associated with longer-term treatment with baricitinib.

Serious Side Effects

Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed in COVID-19 patients treated with baricitinib and are known adverse drug reactions of baricitinib.

Adverse Reactions

In the COVID-19 clinical trials, adverse drug reactions in the safety population occurring in ≥ 1% of patients treated with baricitinib were alanine aminotransferase (ALT) ≥3 x upper limit of normal (ULN) (18.0%), aspartate aminotransferase (AST) ≥3 x ULN (11.5%), thrombocytosis >600,000 cells/mm^3 (8.2%), creatine phosphokinase (CPK) >5 x ULN (3.7%), neutropenia <1000 cells/mm^3 (2.2%), deep vein thrombosis (1.5%), pulmonary embolism (1.4%), and urinary tract infection (1.3%).

Use in Specific Populations

Pregnancy: Baricitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Renal Impairment: There are limited data for baricitinib in patients with severe renal impairment. Baricitinib is not recommended for patients who are on dialysis, have end-stage renal disease, or have acute kidney injury.

Hepatic Impairment: Baricitinib has not been studied in patients with severe hepatic impairment. Baricitinib should only be used in patients with severe hepatic impairment if the potential benefit outweighs the potential risk.

Please see Fact Sheet for Healthcare Providers and Fact Sheet for Patients, Parents and Caregivers (English) or Fact Sheet for Patients, Parents and Caregivers (Spanish).

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About SLE-BRAVE-I and II Studies

SLE-BRAVE-I and II were global, double-blind, multicenter studies evaluating the efficacy and safety of baricitinib 2-mg and 4-mg oral once-daily compared to placebo in adults with active lupus. The predefined primary endpoint for the studies was the proportion of participants achieving an SRI-4 response at Week 52. The SRI-4 response is a composite clinical endpoint used in lupus trials to measure response to treatment based on decrease in overall disease activity. More than 1,500 adults with active lupus were enrolled across studies, with all patients in the baricitinib and placebo treatment groups receiving standard of care background therapy.

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. To date, more than 325,000 patients have been treated with OLUMIANT worldwide across approved indications. 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, Mortality, Malignancy, Major Adverse Cardiovascular Events, and Thrombosis. See the full Prescribing Information here. OLUMIANT is also being investigated in alopecia areata (AA) and juvenile idiopathic arthritis (JIA).

In December 2009, Lilly and Incyte announced an exclusive worldwide license and collaboration agreement for the development and commercialization of OLUMIANT 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) blockers. 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, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, 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.

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 use of 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.

Consider anti-TB therapy prior to initiation of 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.

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.

MORTALITY
In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Olumiant.

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with Olumiant. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer [NMSC]) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers and an additional increased risk of overall malignancies were observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Olumiant, particularly in patients with a known malignancy (other than successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

NMSCs have been reported in patients treated with Olumiant. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

MAJOR ADVERSE CARDIOVASCULAR EVENTS
In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction [MI], and stroke) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue Olumiant in patients that have experienced a myocardial infarction or stroke.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Olumiant, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Inform patients about the symptoms of serious cardiovascular events and the steps to take if they occur.

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. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid Olumiant in patients at risk. Discontinue Olumiant and promptly evaluate patients with symptoms of thrombosis.

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.

PREGNANCY AND LACTATION
Limited data on Olumiant use in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage. Advise women not to breastfeed during treatment with Olumiant.

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

Please click to access full Prescribing Information, including Boxed Warning about Serious Infections, Mortality, Malignancy, Major Adverse Cardiovascular Events, and Thrombosis, and Medication Guide.

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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 other approved indications and potential treatment for patients with systematic lupus erythematosus and 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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