Study Published in The Lancet Shows Benefit of Baricitinib 4 mg for the Treatment of Systemic Lupus Erythematosus (SLE)

July 19, 2018

INDIANAPOLIS, July 19, 2018 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) and Incyte Corporation (NASDAQ: INCY) announced today that results of a global systemic lupus erythematosus (SLE) Phase 2 study for baricitinib were published by *The Lancet*. The study, the first completed Phase 2 study of a JAK inhibitor in SLE, showed that a statistically significant proportion of patients treated with 4 mg of baricitinib achieved resolution of their SLE-related arthritis or rash compared to placebo at week 24, the primary endpoint for the trial.

"Despite existing treatments for SLE management, there is a significant need for innovation and alternative treatment options to help patients manage their disease," said Lotus Mallbris, M.D., vice president, immunology development, Lilly Bio-Medicines. "We are very happy to share these data suggesting baricitinib's impact on disease activity and symptoms that matter to patients, including joint pain, and look forward to further investigation of this important new compound in Phase 3 trials."

Lilly plans to initiate Phase 3 trials to evaluate the safety and efficacy of baricitinib for the treatment of SLE in the second half of 2018.

In the study, 314 patients were randomized 1:1:1 to receive placebo, baricitinib 2 mg or baricitinib 4 mg. Patients treated with 4 mg of baricitinib experienced improvements compared to placebo on several pre-specified secondary endpoints. Compared to placebo, a statistically significant greater proportion of patients treated with 4 mg of baricitinib experienced lower overall disease activity at week 24 as measured by the SLE Responder Index 4 (SRI-4). A statistically significant greater proportion of patients treated with 4 mg of baricitinib achieved a state of low disease activity, as measured by the Lupus Low Disease Activity State, and experienced improvements in pain from baseline, two exploratory endpoints of the study.

The percentage of patients stopping therapy through the 24-week treatment period was 21 percent in the placebo group, 18 percent in the 2-mg dosing group and 17 percent in the 4-mg dosing group. The most common treatment emergent adverse events (TEAEs) in the baricitinib groups were upper respiratory tract infections, including viral upper respiratory infections, and urinary tract infections. The frequency of serious adverse events (SAEs) was 5 percent for placebo, 10.5 percent in the 2-mg dosing group and 9.6 percent in the 4-mg dosing group; the most common SAEs were serious infections. One case of deep vein thrombosis was reported in the 4-mg dosing group. There were no deaths, malignancies, major adverse cardiovascular events, tuberculosis, or serious herpes zoster infections.

"Systemic lupus erythematosus is a chronic, multi-organ autoimmune disease characterized by periods of flare and remission and is associated with a variety of symptoms, including joint pain and swelling," said Daniel Wallace, M.D., lead author and Professor of Medicine and Associate Director of the Rheumatology Fellowship Program at Cedars-Sinai Medical Center. "Notably, these Phase 2 data showed improvements in pain associated with SLE, one of the more challenging symptoms for these patients, and I look forward to the investigation of baricitinib in Phase 3 trials for SLE."

The data were also presented at the Annual European Congress of Rheumatology (EULAR 2018).

About the Phase 2 Study Results

Over the 24-week treatment period, 67.3 percent of patients treated with 4 mg of baricitinib and standard of care achieved resolution of their SLE-related arthritis or rash compared to 53.3 percent for placebo ($p<0.05$).

The percentage of patients achieving a SRI-4 response at Week 24 was significantly greater for those treated with baricitinib 4-mg compared to placebo (64.4% for baricitinib 4-mg versus 47.6% for placebo, $p<0.05$).

No statistically significant differences were observed between the 2-mg and placebo groups across primary or secondary endpoints at Week 24.

About the Phase 2 Study Methodology

This study is a 24-week Phase 2, randomized, double-blind, placebo-controlled global trial evaluating the safety and efficacy of two doses of baricitinib administered orally (2 mg or 4 mg daily) compared with placebo in adult patients with SLE. To be eligible for the trials, patients must have:

- Received a diagnosis of SLE at least 24 weeks prior to screening
- A positive antinuclear antibody (ANA) and/or a positive anti-double-stranded deoxyribonucleic acid (dsDNA)
- A Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of four or greater
- Active arthritis and/or rash, as defined by the SLEDAI-2K

The primary endpoint was the proportion of patients achieving resolution of arthritis and/or rash, as defined by the SLEDAI-2K, over the 24-week double-blind treatment phase.

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.

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 antimicrobial 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 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic, multi-organ autoimmune disease that can cause widespread tissue and organ damage.[1] SLE is characterized by periods of flare and remission and is associated with a variety of symptoms, including extreme fatigue, unexplained fever, joint pain/swelling and butterfly rash.[1,2] Approximately 90 percent of all cases occur in women at a time when life and family demands are greatest.[3]

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.[4] 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.[5] 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.[5] OLUMIANT is approved in more than 40 countries.

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. P-LLY

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 potential treatment for patients with systemic lupus erythematosus and reflects Lilly and Incyte's current belief. However, as with any pharmaceutical products, there are substantial risks and uncertainties in the process of development and commercialization. Among other things, there can be no guarantee that future study results will be consistent with the results to date, that baricitinib will receive additional regulatory approvals, or be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly and Incyte's most recent Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly and Incyte undertakes no duty to update forward-looking statements to reflect events after the date of this release.

[1] Kyttaris VC. Systemic Lupus Erythematosus: From Genes to Organ Damage. Methods in molecular biology (Clifton, NJ). 2010;662:265-283. doi:10.1007/978-1-60761-800-3_13.

[2] Dubois EL, Tuffanelli DL. Clinical Manifestations of Systemic Lupus Erythematosus: Computer Analysis of 520 Cases. JAMA. 1964;190(2):104–111. doi:10.1001/jama.1964.03070150014003
[3] Lupus Foundation of America, Lupus facts and statistics, https://resources.lupus.org/entry/facts-and-statistics. Accessed on June 7, 2018.
[4] Olumiant [package insert]. Indianapolis, IN: Eli Lilly and Company; 2018.
[5] Walker JG and Smith MD. J Rheumatol. 2005;32;1650-1653.

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