Lilly Begins a Phase 3 Clinical Trial with Baricitinib for Hospitalized COVID-19 Patients

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- Study Will Further Understanding of Baricitinib's Potential as a COVID-19 Treatment

- Data Will Complement Ongoing NIAID Trial and Investigator-Initiated Trials

INDIANAPOLIS, June 15, 2020 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today that the first patient has been enrolled in a Phase 3 randomized, double-blind, placebo–controlled study to evaluate the efficacy and safety of baricitinib, an oral JAK1/JAK2 inhibitor licensed from Incyte, in hospitalized adults with COVID-19. Baricitinib, marketed as OLUMIANT®, is approved in 70 countries as a treatment for adults with moderately to severely active rheumatoid arthritis (RA).

Lilly expects to enroll 400 patients in the trial, with data expected in the next few months. The study will be conducted in the U.S., Europe and Latin America and includes patients hospitalized with SARS-CoV-2 infection who have at least one elevated marker of inflammation but do not require invasive mechanical ventilation at study entry.

In COVID-19 infection, increased disease severity can be associated with a hyperinflammatory state. It is hypothesized that through JAK1 and JAK2 inhibition, baricitinib may reduce the cytokine storm associated with the complications of this infection. In addition, baricitinib may have a role in inhibiting the host cell proteins that assist in viral reproduction, reducing the ability of infected cells to make more virus. A manuscript detailing this mechanism of action of baricitinib in COVID-19 has been accepted for publication by *EMBO Molecular Medicine*.

The primary endpoint for Lilly's study is the proportion of patients who die or require non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation by Day 28 in patients treated with 4 mg of baricitinib daily (with background therapy) compared to placebo (with background therapy). Patients will receive baricitinib or placebo for up to 14 days or until discharge from the hospital. Key secondary outcomes of this study include the proportion of patients with clinical improvement at different time points, time to recovery, duration of hospitalization, number of ventilator-free days and mortality over a 28-day period.

"Lilly is committed to fighting this global pandemic, and this includes testing whether existing medicines including baricitinib could help treat the complications of COVID-19 in patients," said Patrik Jonsson, Lilly senior vice president and president of Lilly Bio-Medicines. "This randomized controlled study is an important step in our understanding of baricitinib as a potential COVID-19 treatment."

"While the approach to addressing COVID-19 continues to evolve, we're pleased to partner with Lilly in this trial to assess baricitinib's potential in the fight against COVID-19 and look forward to learning more about its impact on patients," said Patrick Milligan, M.D., of Community Health Network in Indianapolis, U.S., one of the first sites participating in the study.

"Following upon the success of remdesivir to treat moderate to severe COVID-19, hospitalized patients are still in need of novel approaches to reduce mortality," said Vincent C. Marconi, M.D., professor of medicine and global health at Emory University School of Medicine and Emory's Rollins School of Public Health. "Several ongoing studies with baricitinib will provide necessary data about this treatment that may combine antiviral activity with suppression of cytokine storm."

The data from Lilly's trial will complement data from the study of baricitinib with remdesivir in the second phase of the Adaptive COVID-19 Treatment Trial (ACTT-2) run by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). This study – which enrolled its first patient last month – assesses the efficacy and safety of the combination of a 4-mg daily dose of baricitinib plus remdesivir, compared to remdesivir.

Lilly is also supporting select ongoing multisite and single-site investigator-initiated trials in Europe and North America for hospitalized patients with COVID-19 infections. These studies by academic and government institutions will provide information on hundreds of additional patients treated with baricitinib and either placebo or active comparators.

Should research efforts for baricitinib in COVID-19 prove successful, Lilly will continue to create adequate supply to support both appropriate clinical and investigational use.

Studying baricitinib in controlled trials is important in order to better characterize its potential benefits and understand the safety of its use as a COVID-19 treatment. The U.S. prescribing information for the approved use of baricitinib for RA includes boxed warnings regarding the use of baricitinib, including warnings about risk for developing blood clots and serious infections.

About Lilly's COVID-19 Efforts

Lilly is bringing the full force of its scientific and medical expertise to attack COVID-19 around the world. We are fighting the pandemic with everything we can: discovering potential medicines to treat and prevent COVID-19, maintaining a reliable supply of our medicines, and supporting patients and communities in times of need. Lilly is studying multiple approaches to treat COVID-19, including potential antibodies designed specifically to attack the virus and existing Lilly medicines to understand their potential in treating complications of COVID-19.

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 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 approved in the U.S. 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, and approved outside of the U.S. for patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs.[i] 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.[ii] 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.[i]

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.

About Eli Lilly and Company
Lilly is a global healthcare 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 www.lilly.com and newsroom.lilly.com/social-channels. P-LLY

This press release also 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 potential treatment for patients with COVID-19, and about the supply of OLUMIANT, and reflects Lilly'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 continue to be commercially successful, that OLUMIANT will prove to be an effective treatment for COVID-19, or that we can provide an adequate supply of OLUMIANT in all circumstances. For further discussion of these and other risks and uncertainties, see Lilly'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 undertakes no duty to update forward-looking statements to reflect events after the date of this release.

[i] Olumiant Prescribing Information, 2019.
[ii] Walker JG and Smith MD. J Rheumatol. 2005;32;1650-1653.

Refer to: Kristen Basu; basu_kristen_porter@lilly.com; +1-317-447-2199 (media)
Kevin Hern; hern_kevin_r@lilly.com; +1-317-277-1838 (investors)

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