Lilly and Incyte Announce Positive Top-Line Results from the North American (BREEZE-AD5) Phase 3 Study of Oral Selective JAK Inhibitor Baricitinib in Patients with Moderate to Severe Atopic Dermatitis

January 30, 2020

- Study met the primary endpoint of at least 75% improvement of skin inflammation and key secondary endpoints

- Safety profile was consistent with the known safety findings of baricitinib in atopic dermatitis

- Results from this study conducted in North America continue to support a U.S. submission

INDIANAPOLIS, Jan. 30, 2020 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) and Incyte (NASDAQ: INCY) announced today that baricitinib met the primary endpoint in BREEZE-AD5, an investigational Phase 3, randomized, placebo-controlled study evaluating the safety and efficacy of baricitinib for the treatment of adult patients with moderate to severe atopic dermatitis (AD). The primary endpoint was defined by the proportion of patients achieving at least a 75% or greater change from baseline in their Eczema Area and Severity Index (EASI) at Week 16.

"Today's results, together with the previously reported positive top-line results from our Phase 3 trials, reinforce our commitment to pursue the first oral JAK inhibitor treatment in the U.S. for individuals living with the chronic and often relapsing skin condition that is AD," said Lotus Mallbris, M.D., Ph.D., vice president of immunology development at Lilly.

BREEZE-AD5 is a multicenter, double-blind, randomized, placebo-controlled study designed for and conducted in North America, evaluating the efficacy and safety of the 1-mg and 2-mg doses of baricitinib monotherapy for the treatment of adult patients with moderate to severe AD. In this study, the 2-mg dose of baricitinib met the primary endpoint as defined by the proportion of participants achieving EASI75 at Week 16, and key secondary endpoints including another measure of skin inflammation defined by clear or almost clear skin and at least 2 points improvement on the validated Investigator's Global Assessment for AD (vIGA 0 or 1 at Week 16), and reduced itch severity.

	Placebo (n=147)	Baricitinib 1-mg (n=147)	Baricitinib 2-mg (n=146)
EASI75 at Week 16, n (%)	12 (8.2)	19 (12.9) ‡	43 (29.5)***
vIGA[a] of 0 or 1 at Week 16, n (%)	8 (5.4)	19 (12.9)*	35 (24.0)***
4-point improvement in Itch NRS at Week 16, n (%)	7 (5.7)	21 (15.9)*	33 (25.2)***

‡ P n.s. * P ≤ 0.05, and *** P≤0.001 for baricitinib compared to placebo by analysis unadjusted for multiplicity. Non-responder imputation upon rescue with Topical corticosteroid (TCS).

[a]vIGA = validated Investigator's Global Assessment.

The safety profile in BREEZE-AD5 was consistent with the known safety findings of baricitinib in AD. The most common treatment-emergent adverse events (TEAEs) included upper respiratory tract infections, nasopharyngitis, and diarrhea. No venous thromboembolic events (VTEs) or deaths were reported in the trial.

"The results show the potential that baricitinib could offer as an additional treatment option to patients where there are otherwise limited choices," said Eric Simpson, MD, MCR, Professor of Dermatology and Director of Clinical Research at Oregon Health & Science University in Portland, and global Principal Investigator for the BREEZE-AD5 clinical development program.

Lilly recently submitted baricitinib for regulatory review in Europe as a treatment for patients with moderate to severe AD and plans to submit for approval in the U.S. and Japan in 2020. The full results from the BREEZE-AD5 study will be disclosed at future scientific venues and in peer-reviewed journals.

Baricitinib is approved for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) in more than 60 countries, including the U.S., member states of the EU and Japan, and is marketed as OLUMIANT®.

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 BREEZE-AD5
BREEZE-AD5, a multicenter, double-blind, randomized, placebo-controlled, Phase 3 study in adult patients with moderate to severe atopic dermatitis (AD). BREEZE-AD5, designed for and conducted in North America, evaluated the efficacy and safety of the 1-mg and 2-mg doses of baricitinib monotherapy for the treatment of adult patients with moderate to severe AD. The primary endpoint was defined by the proportion of participants achieving Eczema Area and Severity Index 75 (EASI75) at Week 16. BREEZE-AD5 completes the read out from the BREEZE development program, following the recent topline results from BREEZE-AD4. BREEZE-AD1, -AD2 and -AD7 results were disclosed in 2019.

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.[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 60 countries.

About Atopic Dermatitis
Atopic dermatitis (AD), or atopic eczema, is a chronic, relapsing skin disease characterized by intense itching, dry skin and inflammation that can be present on any part of the body.[3] AD is a heterogeneous disease both clinically and biologically, but may be characterized by chronic baseline symptoms of itch, redness and skin damage that are often punctuated with episodic, sometimes unpredictable, flares or exacerbations.[4,5] AD affects approximately 1-3% of adults worldwide.[6]

Moderate to severe AD is characterized by intense itching, resulting in visibly damaged skin.[7] Like other chronic inflammatory diseases, AD is immune-mediated and involves a complex interplay of immune cells and inflammatory cytokines.[8]

About Lilly in Dermatology
By following the science through unchartered territory, we continue Lilly's legacy of delivering innovative medicines that address unmet needs and have significant impacts on people's lives around the world. Skin-related diseases are more than skin deep. We understand the devastating impact this can have on people's lives. At Lilly, we are relentlessly pursuing a robust dermatology pipeline to provide innovative, patient-centered solutions so patients with skin-related diseases can aspire to live life without limitations.

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

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

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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 moderate- to severe atopic dermatitis, 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 Prescribing Information, 2019.

[2] Walker JG and Smith MD. J Rheumatol. 2005;32;1650-1653.

[3] Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. The Journal of Allergy and Clinical Immunology. 2006;118: 226-32.

[4] Thijs JL, Strickland I, Bruijnzeel-Koomen C, et. al. Moving toward endotypes in atopic dermatitis: identification of patient clusters based on serum biomarker analysis. The Journal of Allergy and Clinical Immunology. 2017.

[5] Langan SM, Thomas KS, Williams HC. What is meant by "flare" in atopic dermatitis? A systematic review and proposal. Arch Dermatol. 2006;142:1190-1196.

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