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Pfizer Announces Results from XELJANZ® XR (tofacitinib) ORAL Shift Study, The First Phase 3b/4 Study to Evaluate Methotrexate Withdrawal with a JAK Inhibitor

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Results to be Presented During a Late-Breaking Oral Session at the Annual European Congress of Rheumatology (EULAR 2019)

Pfizer Inc. (NYSE:PFE) announced today positive results from ORAL Shift, a Phase 3b/4 study in adult patients with moderately to severely active rheumatoid arthritis (RA). Patients who achieved low disease activity (LDA) with XELJANZ® (tofacitinib) extended release (XR) 11 mg once daily (QD) plus methotrexate (MTX) after a 24-week open-label run-in period, were randomized to evaluate the efficacy and safety of XELJANZ XR 11 mg QD as monotherapy after MTX withdrawal compared with XELJANZ XR with continued MTX. The study demonstrated non-inferiority of MTX withdrawal with XELJANZ XR 11 mg QD compared to XELJANZ XR 11 mg QD plus MTX at week 48 as measured by the primary endpoint, the change in the Disease Activity Score (DAS28-4[ESR]) from randomization at week 24 to the end of the double-blind MTX withdrawal phase at week 48. The study results will be presented during a late-breaking oral session at the Annual European Congress of Rheumatology (EULAR 2019) in Madrid, Spain (15 June).

“The results of ORAL Shift provide important information on the use of XELJANZ XR as monotherapy after methotrexate withdrawal, which is significant as some people living with rheumatoid arthritis are unable or unwilling to use methotrexate,” said Stanley Cohen, MD, Metroplex Clinical Research Center, Dallas, TX. “From a clinical perspective, these results give physicians data to help inform the decision to take appropriate patients off methotrexate.”

Efficacy Results

For the primary efficacy analysis, patients who achieved Clinical Disease Activity Index (CDAI) low disease activity at week 24 were randomized into the MTX withdrawal phase resulting in least squares (LS) mean changes in DAS28-4(ESR) from weeks 24 to 48 of 0.33 and 0.03 in the XELJANZ XR monotherapy and XELJANZ XR plus MTX groups, respectively [LS mean difference = 0.3; 95% CI, 0.12-0.48; non-inferiority $p<0.0005$]. The primary analysis showed that XELJANZ XR 11 mg QD monotherapy was non-inferior to XELJANZ XR 11 mg QD with MTX at week 48.

“ORAL Shift exemplifies Pfizer’s commitment to ongoing JAK research with the goal of meeting the evolving needs of patients living with this chronic inflammatory condition,” said Michael Corbo, Chief Development Officer, Inflammation & Immunology, Pfizer Global Product Development. “We are extremely pleased with the findings from ORAL Shift, which to date is the only non-inferiority study to evaluate and demonstrate the efficacy of a JAK inhibitor after methotrexate withdrawal in adults with moderately to severely active RA who

achieved low disease activity after combination therapy.”

Safety Results

The safety findings in ORAL Shift include the most frequently reported adverse events (AEs) for each study group in the double-blind treatment period of nasopharyngitis, upper respiratory tract infection and bronchitis. Rates of AEs, serious AEs (SAEs) and discontinuations due to AEs were generally comparable between treatment arms. In the XELJANZ XR monotherapy group, there were 10 SAEs and 5 discontinuations due to AEs. In the XELJANZ XR plus MTX group, there were 5 SAEs and 5 discontinuations due to AEs. During the double-blind withdrawal phase of the study, AEs were reported in 40.5% of patients (n=107) in the XELJANZ XR monotherapy treatment group and 41.0% of patients (n=109) in the XELJANZ XR plus MTX treatment group. In addition, SAEs were reported in 3.8% of patients (n=10) in the XELJANZ XR monotherapy treatment group and 1.9% of patients (n=5) in the XELJANZ XR plus MTX treatment group. In the double-blind treatment period, there were two deaths reported in the XELJANZ XR plus MTX treatment group. The full Prescribing Information for XELJANZ/XELJANZ XR includes a BOXED WARNING for serious infection and malignancy.

About the Study

ORAL Shift was a 12-month randomized, double-blind, placebo-controlled, non-inferiority, methotrexate (MTX) withdrawal study in subjects with moderate to severe rheumatoid arthritis (RA) who were also inadequate responders to treatment with MTX alone. The study included 694 patients with moderate to severe RA. During the run-in phase, all patients received open-label XELJANZ XR 11 mg QD plus MTX using their previously stabilized MTX dose. At week 24, patients who achieved low disease activity (LDA) as assessed by CDAI (n=530) were randomized into the 24-week double-blind, placebo-controlled MTX withdrawal phase, for a total of 48 weeks. The primary efficacy endpoint was the difference between the two treatment groups in change in DAS28-4(ESR). Change was measured from the time of randomization, at Week 24, to the end of the double-blind MTX withdrawal phase at Week 48. In the double-blind phase, subjects were randomized in a 1:1 ratio to either continue on XELJANZ XR plus MTX (n=266) or to receive XELJANZ XR monotherapy plus blinded matching placebo for MTX (n=264).

About XELJANZ® (tofacitinib)

XELJANZ® (tofacitinib) is approved in the U.S. for adult patients in three indications: moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis (PsA) and moderately to severely active ulcerative colitis (UC). Globally, XELJANZ is approved in more than 130 countries for the treatment of moderately to severely active RA and has been prescribed to an estimated 205,000 patients.

As the developer of tofacitinib, Pfizer is committed to advancing the science of JAK inhibition and enhancing understanding of tofacitinib through robust clinical development programs in the treatment of immune-mediated inflammatory conditions.

INDICATIONS

Rheumatoid Arthritis

- XELJANZ/XELJANZ XR (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Psoriatic Arthritis

- XELJANZ/XELJANZ XR (tofacitinib) is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs).
- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ulcerative Colitis

- XELJANZ (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).
- Limitations of Use: Use of XELJANZ in combination with biologic therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with XELJANZ/XELJANZ XR are at increased 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 XELJANZ/XELJANZ XR until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Avoid use of XELJANZ/XELJANZ XR in patients with an active, serious infection, including localized infections, or with chronic or recurrent infection.

In the UC population, XELJANZ 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with XELJANZ 10 mg twice daily.

The risks and benefits of treatment with XELJANZ/XELJANZ XR should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection, or those who have lived or traveled in areas of endemic TB or mycoses. Viral reactivation including herpes virus and Hepatitis B reactivation have been reported. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infection.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy.

Malignancies (including solid cancers and lymphomas) were observed more often in patients treated with XELJANZ 10 mg twice daily dosing in the UC long-term extension study.

Other malignancies were observed in clinical studies and the post-marketing setting including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer. NMSCs have been reported in patients treated with XELJANZ. In the UC population, treatment with XELJANZ 10 mg twice daily was associated with greater risk of NMSC. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal perforations have been reported in XELJANZ clinical trials, although the role of JAK inhibition is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids. XELJANZ/XELJANZ XR should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs).

HYPERSENSITIVITY

Angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients receiving XELJANZ/XELJANZ XR some events were serious. If a serious hypersensitivity reaction occurs, promptly discontinue tofacitinib while evaluating the potential cause or causes of the reaction.

LABORATORY ABNORMALITIES

Lymphocyte Abnormalities: Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a count less than 500 cells/mm^3. In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3, treatment with XELJANZ/XELJANZ XR is not recommended. Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Monitor lymphocyte

counts at baseline and every 3 months thereafter.

Neutropenia: Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with an ANC less than 1000 cells/mm^3. For patients who develop a persistent ANC of 500-1000 cells/mm^3, interrupt XELJANZ/XELJANZ XR dosing until ANC is greater than or equal to 1000 cells/mm^3. In patients who develop an ANC less than 500 cells/mm^3, treatment with XELJANZ/XELJANZ XR is not recommended. Monitor neutrophil counts at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Anemia: Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a hemoglobin level less than 9 g/dL. Treatment with XELJANZ/XELJANZ XR should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment. Monitor hemoglobin at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Liver Enzyme Elevations: Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury.

Lipid Elevations: Treatment with XELJANZ was associated with dose-dependent increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. There were no clinically relevant changes in LDL/HDL cholesterol ratios. Manage patients with hyperlipidemia according to clinical guidelines. Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of XELJANZ/XELJANZ XR therapy.

VACCINATIONS

Avoid use of live vaccines concurrently with XELJANZ/XELJANZ XR. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ/XELJANZ XR therapy.

PATIENTS WITH GASTROINTESTINAL NARROWING

Caution should be used when administering XELJANZ XR to patients with pre-existing severe gastrointestinal narrowing. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable extended release formulation.

HEPATIC and RENAL IMPAIRMENT

Use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended.

For patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 5 mg twice daily, reduce to XELJANZ 5 mg once daily.

For UC patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 10 mg twice daily, reduce to XELJANZ 5 mg twice daily.

ADVERSE REACTIONS

The most common serious adverse reactions were serious infections. The most commonly reported adverse reactions during the first 3 months in controlled clinical trials in patients with rheumatoid arthritis (RA) with XELJANZ 5 mg twice daily and placebo, respectively, (occurring in greater than or equal to 2% of patients treated with XELJANZ with or without DMARDs) were upper respiratory tract infection, nasopharyngitis, diarrhea, headache, and hypertension. The safety profile observed in patients with active psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in RA patients.

Adverse reactions reported in ?5% of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and ? 1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials for ulcerative colitis were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

USE IN PREGNANCY

Available data with XELJANZ/XELJANZ XR use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy. In animal studies, tofacitinib at 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings. The relevance of these findings to women of childbearing potential is uncertain. Consider pregnancy planning and prevention for females of reproductive potential.

Please see full Prescribing Information, including BOXED WARNING for XELJANZ/XELJANZ XR available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=959.

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At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

DISCLOSURE NOTICE: The information contained in this release is as of June 12, 2019. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about XELJANZ (tofacitinib) and XELJANZ (tofacitinib) extended release (XR) that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; risks associated with interim data;

the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; uncertainties regarding the commercial success of XELJANZ and XELJANZ XR; uncertainties regarding the commercial impact of the results of the ORAL Shift trial; uncertainties regarding the commercial impact of actions by regulatory authorities based on analysis of clinical trial A3921133 or other data, which will depend, in part, on labeling determinations; whether and when any applications that may be pending or filed for any potential indications for XELJANZ or XELJANZ XR in any jurisdictions may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy, and, if approved, whether they will be commercially successful; decisions by regulatory authorities impacting labeling, safety, manufacturing processes and/or other matters that could affect the availability or commercial potential of XELJANZ and XELJANZ XR; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2018 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

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