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Pfizer Shares Co-Primary Endpoint Results from Post-Marketing Required Safety Study of XELJANZ® (tofacitinib) in Subjects with Rheumatoid Arthritis (RA)

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NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) announced today co-primary endpoint results from a recently completed post-marketing required safety study, ORAL Surveillance (A3921133; NCT02092467). The primary objective of this study was to evaluate the safety of tofacitinib at two doses (5 mg twice daily and 10 mg twice daily) versus a TNF inhibitor (TNFi) in subjects with rheumatoid arthritis (RA) who were 50 years of age or older and had at least one additional cardiovascular (CV) risk factor.

The co-primary endpoints of this study were non-inferiority of tofacitinib compared to TNFi in regard to major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer (NMSC)). Results showed that for these co-primary endpoints, the prespecified non-inferiority criteria were not met for the primary comparison of the combined tofacitinib doses to TNFi. Based on the prespecified secondary comparisons, there was no evidence of a difference in the primary endpoints between the two tofacitinib treatment groups.

The study included 4,362 subjects who received study treatments. The primary analyses included 135 subjects with MACE and 164 subjects with malignancies (excluding NMSC). For tofacitinib, the most frequently reported MACE was myocardial infarction and the most frequently reported malignancy (excluding NMSC) was lung cancer. In those subjects with a higher prevalence of known risk factors for MACE and malignancy (e.g., older age, smoking), a higher occurrence of events was seen across all treatment groups.

Adjudicated MACE*

	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID****	**Tofacitinib Doses Combined**	**TNFi**
Total number of subjects	1455	1456	2911	1451
Number of subjects with first event within the risk period*** (%)	47 (3.23)	51 (3.50)	98 (3.37)	37 (2.55)
Person-years	5166.32	4871.96	10038.28	5045.27
IR (95% CI) (number of subjects with event/100 person-years)	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.98 (0.79, 1.19)	0.73 (0.52, 1.01)
HR (95% CI) for tofacitinib vs TNFi	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)****	

BID=twice daily; CI=confidence interval; HR=hazard ratio; IR=incidence rate; MACE=major adverse cardiovascular event; TNFi=Tumor Necrosis Factor inhibitor.
(*) Based on Cox proportional hazard model
(**)The 10 mg BID treatment group includes patients that were switched from 10 mg BID to 5 mg BID as a result of a study modification in February 2019.
(***) The risk period was from start of therapy up to 60 days past last dose.
(****) The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNFi since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8, ie, 1.94 >1.8.

Adjudicated Malignancies Excluding NMSC*

	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID****	**Tofacitinib Doses Combined**	**TNFi**
Total number of subjects	1455	1456	2911	1451
Number of subjects with first event within the risk period*** (%)	62 (4.26)	60 (4.12)	122 (4.19)	42 (2.89)
Person-years	5491.48	5311.71	10803.19	5482.30
IR (95% CI) (number of subjects with event/100 person-years)	1.13 (0.87, 1.45)	1.13 (0.86, 1.45)	1.13 (0.94, 1.35)	0.77 (0.55, 1.04)
HR (95% CI) for tofacitinib vs TNFi	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)****	

BID=twice daily; CI=confidence interval; HR=hazard ratio; IR=incidence rate; NMSC=non-melanoma skin cancer; TNFi=Tumor Necrosis Factor inhibitor.
(*) Based on Cox proportional hazard model
(**)The 10 mg BID treatment group includes patients that were switched from 10 mg BID to 5 mg BID as a result of a study modification in February 2019.
(***) The risk period included all available follow-up regardless of treatment exposure.
(****) The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNFi since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8, ie, 2.09 >1.8.

“Providing information on the safe and effective use of our medicines is imperative,” said Tamas Koncz, M.D., Ph.D., Chief Medical Officer, Inflammation and Immunology, Pfizer. “We believe that extensive additional analyses of these study data, and communicating them as soon as possible, will further clarify the benefit and risk profile of tofacitinib to help inform medical decision making and patient care.”

Full study results, beyond the co-primary endpoints (including, but not limited to, secondary endpoints such as pulmonary embolism and mortality as well as efficacy data), are not yet available. Pfizer is working with the U.S. Food and Drug Administration (FDA) and other regulatory agencies to review the full results and analyses as they become available.

About the Study

In contrast to previous tofacitinib studies, ORAL Surveillance was specifically designed to assess the risk of CV events and malignancies, and therefore subjects were required to be 50 years of age or older and have at least one additional CV risk factor at screening. All subjects in this study were also required to be treated with background methotrexate to be eligible for enrollment.

About XELJANZ® (tofacitinib)

XELJANZ® (tofacitinib) isapproved in the U.S. in four indications: adults with moderately to severely active rheumatoid arthritis (RA) after methotrexate failure, adults with active psoriatic arthritis (PsA) after disease modifying antirheumatic drug (DMARD) failure, adults with moderately to severely active ulcerative colitis (UC) after tumor necrosis factor inhibitor (TNFi) failure, and patients 2 years of age or older with active polyarticular course juvenile idiopathic arthritis (pcJIA). XELJANZ has been studied in more than 50 clinical trials worldwide and prescribed to over 208,000 adult patients (the majority of whom were RA patients) worldwide in the last eight years.[1,2,3]

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.
- 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 is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or who are intolerant to TNF blockers.
- Limitations of Use: Use of XELJANZ in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Polyarticular Course Juvenile Idiopathic Arthritis

- XELJANZ/XELJANZ Oral Solution is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older.
- Limitations of Use: Use of XELJANZ/XELJANZ Oral Solution in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with XELJANZ* 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 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 use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ 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 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 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, 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.

MORTALITY

Rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular (CV) risk factor treated with XELJANZ 10 mg twice a day had a higher rate of all-cause mortality, including sudden CV death, compared to those treated with XELJANZ 5 mg given twice daily or TNF blockers in a large, ongoing, postmarketing safety study. XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily is not recommended for the treatment of RA or PsA. For UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

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 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 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.

THROMBOSIS

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. RA patients who were 50 years of age and older with at least one CV risk factor treated with XELJANZ 10 mg twice daily compared to XELJANZ 5 mg twice daily or TNF blockers in a large, ongoing postmarketing safety study had an observed increase in incidence of these events. Many of these events were serious and some resulted in death. Avoid XELJANZ in patients at risk. Discontinue XELJANZ and promptly evaluate patients with symptoms of thrombosis. For patients with UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response. XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily is not recommended for the treatment of RA or PsA. In a long-term extension study in UC, four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one death in a patient with advanced 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 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 and 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 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 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 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 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 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 treatment in patients with a hemoglobin level less than 9 g/dL. Treatment with XELJANZ 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 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 therapy.

VACCINATIONS

Avoid use of live vaccines concurrently with XELJANZ. 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 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 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 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 PsA 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 UC 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 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.

* Unless otherwise stated, “XELJANZ” in the Important Safety Information refers to XELJANZ, XELJANZ XR, and XELJANZ Oral Solution.

Please see full Prescribing Information, including BOXED WARNING available at: www.xeljanzpi.com.

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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, including innovative medicines and vaccines. 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 January 27, 2021. 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) 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, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical 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; 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; uncertainties regarding the commercial impact of or the results of clinical trial A3921133 or any potential actions by regulatory authorities based on analysis of clinical trial A3921133 or other data, which will depend, in part, on labeling determinations; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of XELJANZ and XELJANZ XR; uncertainties regarding the impact of COVID-19 on our business, operations and financial results; 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, 2019 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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[1] Pfizer Data on File. XELJANZ Worldwide Registration Status.
[2] ClinicalTrials.gov. Tofacitinib RA Studies. Accessed June 25, 2020.
[3] Pfizer. Data on File. Tofa Counts. April 2019

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