



# Phase 3 OCTAVE Studies of Oral Tofacitinib in Ulcerative Colitis Results Published in The New England Journal of Medicine

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Data Demonstrated Tofacitinib was Effective as Both Induction and Maintenance Therapy in the Treatment of Moderate to Severe Ulcerative Colitis

**“This robust data set provides evidence that tofacitinib, if approved, could be an important new oral treatment option with the potential to help patients with moderate to severe active ulcerative colitis achieve and maintain remission.”**

Pfizer Inc. (NYSE:PFE) announced today that detailed results from the Phase 3 Oral Clinical Trials for tofacitinib in ulcerative colitis (OCTAVE) clinical program were published in The New England Journal of Medicine (NEJM).

Data from all three pivotal Phase 3 studies – OCTAVE Induction 1, OCTAVE Induction 2 and OCTAVE Sustain – met their respective primary endpoints, demonstrating that tofacitinib citrate was more effective than placebo in inducing and maintaining remission in patients with moderate to severe ulcerative colitis (UC).<sup>1a,1b</sup> Remission was defined as a Mayo score\* of 2 points or lower, with no individual subscore exceeding 1 point, and a rectal bleeding subscore of 0.<sup>1c</sup>

“The publication of results from the full Phase 3 OCTAVE clinical program is a significant milestone,” said William J. Sandborn, MD, Chief, Division of Gastroenterology, Professor of Medicine at the University of California San Diego School of Medicine and study investigator. “This robust data set provides evidence that tofacitinib, if approved, could be an important new oral treatment option with the potential to help patients with

moderate to severe active ulcerative colitis achieve and maintain remission.”

\_\_\_\_\_ \*Mayo score is a measurement index comprised of four categories (stool frequency, rectal bleeding, findings on endoscopy, physician global assessment) that are each rated from 0 (normal) to 3 (most severe) for a total score that ranges from 0-12.

#### OCTAVE Induction 1 & 2

OCTAVE Induction 1 and OCTAVE Induction 2 each evaluated induction of remission by oral tofacitinib 10 mg twice-daily (BID) compared to placebo in adult patients with moderate to severe UC.<sup>1d</sup> The studies enrolled 598 and 541 patients, respectively.<sup>1d</sup> Eligible patients were randomly assigned to receive eight weeks of therapy with oral tofacitinib 10 mg BID (476 and 429 patients, respectively) or placebo (122 and 112 patients, respectively).<sup>1e,1f</sup>

In OCTAVE Induction 1, a statistically significant and greater proportion of patients receiving tofacitinib 10 mg BID (18.5%) were in remission at Week 8, compared to 8.2% receiving placebo ( $p=0.007$ ).<sup>1g</sup> Similar results were observed in OCTAVE Induction 2, with 16.6% of patients receiving tofacitinib 10 mg BID achieving remission at Week 8, compared to 3.6% receiving placebo ( $p<0.001$ ).<sup>1h</sup>

In addition, across each study, a statistically significant and greater proportion of patients receiving tofacitinib 10 mg BID achieved the key secondary endpoint of mucosal healing at Week 8, including 31.3% of patients compared to 15.6% receiving placebo in OCTAVE Induction 1, and 28.4% of patients compared to 11.6% receiving placebo in OCTAVE Induction 2 ( $p<0.001$  across both studies).<sup>1i,1j</sup>

#### OCTAVE Sustain

The OCTAVE Sustain study evaluated the efficacy of tofacitinib as maintenance therapy compared to placebo in adult patients with moderate to severe UC.<sup>1k</sup> It included patients who had completed one of the OCTAVE Induction studies and had achieved at least clinical response ( $\geq 3$  points reduction and  $\geq 30\%$  decrease from baseline Mayo score plus a decrease in rectal bleeding subscore of  $\geq 1$  or absolute rectal bleeding subscore  $\leq 1$ ).<sup>1l</sup> A total of 593 participants were randomized to receive maintenance treatment with tofacitinib 5 mg BID (198 patients), tofacitinib 10 mg BID (197 patients) or placebo (198 patients) for 52 weeks.<sup>1m</sup>

In OCTAVE Sustain, 34.3% and 40.6% of patients achieved remission at Week 52 with tofacitinib 5 mg BID and tofacitinib 10 mg BID, respectively, compared to 11.1% taking placebo ( $p<0.001$ ).<sup>1n</sup> In addition, both doses of tofacitinib met the key secondary

endpoints of the study, mucosal healing and sustained steroid-free remission among baseline remitters.<sup>1o</sup> Across tofacitinib 5 mg BID, tofacitinib 10 mg BID and placebo arms, mucosal healing was achieved by 37.4%, 45.7% and 13.1% of patients ( $p < 0.001$ ), respectively, and sustained steroid-free remission was achieved by 35.4%, 47.3% and 5.1% ( $p < 0.001$ ), respectively.<sup>1o</sup>

“Ulcerative colitis is a debilitating disease that affects all aspects of patients’ lives. We are pleased to share the results of this promising clinical trial of tofacitinib as part of our efforts to improve the lives of patients through our research with Janus kinase inhibitors,” said Michael Corbo, PhD, Chief Development Officer, Inflammation & Immunology, Global Product Development, Pfizer, Inc. “If approved for this indication, tofacitinib could potentially be an important new oral treatment option for people living with UC.”

During the OCTAVE Induction studies, overall infection and serious infection rates were higher with tofacitinib than placebo.<sup>1p</sup> In OCTAVE Induction 1, 23.3% and 1.3% of patients receiving tofacitinib 10 mg BID had infections and serious infections, respectively, compared to 15.6% and 0 receiving placebo.<sup>1p</sup> In OCTAVE Induction 2, 18.2% and 0.2% of patients receiving tofacitinib 10 mg BID had infections and serious infections, respectively, compared to 15.2% and 0 receiving placebo.<sup>1p</sup>

During OCTAVE Sustain, serious infection rates were similar across treatment groups (1.0%, 0.5% and 1.0% across tofacitinib 5 mg BID, 10 mg BID and placebo groups, respectively).<sup>1q</sup> Overall infection rates were higher with tofacitinib than placebo (35.9%, 39.8% and 24.2% across tofacitinib 5 mg BID, 10 mg BID and placebo groups, respectively). Cases of herpes zoster were more frequently observed with tofacitinib 10 mg BID compared to other treatment groups (1.5%, 5.1% and 0.5% across tofacitinib 5 mg BID, 10 mg BID and placebo groups, respectively).<sup>1q</sup>

Across all studies, five tofacitinib-treated patients had adjudicated non-melanoma skin cancer, five had adjudicated cardiovascular events and there were increases in lipids with tofacitinib.<sup>1r,1s,1t,1u</sup> There were two cases of malignancy in the control groups limited to one case of non-melanoma skin cancer and one case of invasive ductal breast carcinoma during OCTAVE Sustain.<sup>1t</sup>

The manuscript of full study results, which indicate that tofacitinib citrate was more effective than placebo in inducing and maintaining remission in patients with moderate to severe active UC, is available at <http://www.nejm.org/doi/full/10.1056/NEJMoa1606910>.

About Ulcerative Colitis

UC is a chronic, often debilitating inflammatory bowel disease that affects millions of people worldwide.<sup>2,3</sup> While the exact cause of UC is unknown, it is believed that UC is the result of complex interactions between multiple factors that include genetic predisposition and an exaggerated immune response to a microbial trigger.<sup>4</sup> It can cause chronic diarrhea with blood and mucus, abdominal pain and cramping, fever and weight loss.<sup>5</sup> UC can have a significant effect on work, family and social activities.<sup>6</sup> In up to one-third of patients with UC, treatment is not completely successful or complications may arise.<sup>7</sup> Under these circumstances, surgery to remove the colon (colectomy) may be considered.<sup>7</sup>

#### About XELJANZ® (tofacitinib citrate)

XELJANZ® (tofacitinib citrate) is a prescription medicine called a Janus kinase (JAK) inhibitor. XELJANZ is approved in more than 80 countries around the world for the treatment of moderately to severely active rheumatoid arthritis (RA). XELJANZ is being investigated for the treatment of moderate to severe UC and is not currently approved for this indication.

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

#### XELJANZ/XELJANZ XR U.S. Label Information

XELJANZ (tofacitinib citrate)/XELJANZ XR (tofacitinib citrate) extended-release is a prescription medicine called a Janus kinase (JAK) inhibitor. XELJANZ/XELJANZ XR is used to treat adults with moderately to severely active rheumatoid arthritis in which methotrexate did not work well. XELJANZ/XELJANZ XR may be used as a single agent or in combination with methotrexate (MTX) or other non-biologic disease-modifying antirheumatic drugs (DMARDs). Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants, such as azathioprine and cyclosporine, is not recommended.

It is not known if XELJANZ/XELJANZ XR is safe and effective in people with hepatitis B or C. XELJANZ/XELJANZ XR is not for people with severe liver problems. It is not known if XELJANZ/XELJANZ XR is safe and effective in children.

#### Important Safety Information

XELJANZ/XELJANZ XR can lower the ability of the immune system to fight infections. Some people can have serious infections while taking XELJANZ/XELJANZ XR, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections. Healthcare providers should test patients for TB before starting XELJANZ/XELJANZ XR, and monitor them closely for signs and symptoms of TB and other infections during treatment. People should not start taking XELJANZ/XELJANZ XR if they have any kind of infection unless their healthcare provider tells them it is okay. People may be at a higher risk of developing shingles.

XELJANZ/XELJANZ XR may increase the risk of certain cancers by changing the way the immune system works. Lymphoma and other cancers, including skin cancers, can happen in patients taking XELJANZ/XELJANZ XR. The risks and benefits of treatment should be considered prior to initiating XELJANZ/XELJANZ XR in patients with chronic or recurrent infection; who have been exposed to tuberculosis; 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.

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), was observed in clinical studies with XELJANZ.

Use of live vaccines should be avoided concurrently with XELJANZ/XELJANZ XR. Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ/XELJANZ XR therapy. Some people who have taken XELJANZ with certain other medicines to prevent kidney transplant rejection have had a problem with certain white blood cells growing out of control (Epstein Barr virus-associated post-transplant lymphoproliferative disorder). Some people taking XELJANZ/XELJANZ XR can get tears in their stomach or intestines. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate. 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 who have a narrowing within their digestive tract. Patients should tell their healthcare provider right away if they have fever and stomach-area pain that does not go away or a change in bowel habits.

XELJANZ/XELJANZ XR can cause changes in certain lab test results including low blood cell counts, increases in certain liver tests, and increases in cholesterol levels. Healthcare providers should do blood tests before starting patients on XELJANZ/XELJANZ XR and while they are taking XELJANZ/XELJANZ XR, to check for these side effects. Normal cholesterol levels are important to good heart health. Healthcare providers may stop

XELJANZ/XELJANZ XR treatment because of changes in blood cell counts or liver test results. Use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended.

Patients should tell their healthcare providers if they plan to become pregnant or are pregnant. It is not known if XELJANZ/XELJANZ XR will harm an unborn baby. To monitor the outcomes of pregnant women exposed to XELJANZ/XELJANZ XR, a registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Patients should tell their healthcare providers if they plan to breastfeed or are breastfeeding. Patients and their healthcare provider should decide if they will take XELJANZ/XELJANZ XR or breastfeed. They should not do both. In carriers of the hepatitis B or C virus (viruses that affect the liver), the virus may become active while using XELJANZ/XELJANZ XR. Healthcare providers may do blood tests before and during treatment with XELJANZ/XELJANZ XR. Common side effects include upper respiratory tract infections (common cold, sinus infections), headache, diarrhea, and nasal congestion, sore throat, and runny nose (nasopharyngitis). Please click the direct link to the full prescribing information for XELJANZ/XELJANZ XR, including boxed warning and Medication Guide: <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](http://www.pfizer.com). In addition, to learn more, please visit us on [www.pfizer.com](http://www.pfizer.com) and follow us on Twitter at @Pfizer and @PfizerNews, LinkedIn, YouTube and like us on Facebook at [Facebook.com/Pfizer](https://www.facebook.com/Pfizer)

DISCLOSURE NOTICE: The information contained in this release is as of May 3, 2017. 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 a potential new indication for XELJANZ for the treatment of adult patients with moderate to severe active UC (the “potential indication”), including its potential benefits, 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 trial commencement and completion dates and regulatory submission dates, as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; uncertainties regarding the commercial success of XELJANZ and XELJANZ XR; whether and when any applications for the potential indication may be filed with regulatory authorities in any jurisdictions; whether and when regulatory authorities in any jurisdictions may approve such applications and/or any other applications that are pending or may be filed for XELJANZ or XELJANZ XR, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of XELJANZ and XELJANZ XR, including the potential indication; 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, 2016 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](http://www.sec.gov) and [www.pfizer.com](http://www.pfizer.com).

\_\_\_\_\_ 1 W.J. Sandborn, C. Su, B.E. Sands, et al. Tofacitinib Induction and Maintenance Therapy for Ulcerative Colitis. *The New England Journal of Medicine*. 2017. 376;18:1723-1736. a) Page 1723/ Abstract/ Results/ Lines 1-3 b) Page 1723/ Abstract/ Results/ Lines 3-6 c) Page 1725/ Methods/ End Points/ Lines 1-4 d) Page 1723/ Abstract/ Methods/ Lines 1-6 e) Page 1725/ Methods/ Randomization and Treatments/ Lines 1-4 f) Page 1726/ Results/ Patient Characteristics/ Lines 1-10 g) Page 1726/ Results/ Efficacy/ Primary End Point/ Lines 1-5 h) Page 1728/ Results/ Efficacy/ Primary End Point/ Lines 1-6 i) Page 1728/ Results/ Efficacy/ Secondary End Points/ Lines 1-5 j) Page 1730/ Table 2/ Row 3 k) Page 1723/ Abstract/ Methods/ Lines 6-9 l) Page 1724/ Methods/ Patients/ Lines 36-40 m)

Page 1726/ Results/ Patient Characteristics/ Lines 11-15 n) Page 1728/ Results/ Efficacy/ Primary End Point/ Lines 13-20 o) Page 1728/ Results/ Efficacy/ Secondary End Points/ Lines 10-22 p) Page 1732/ Results/ Safety/ Lines 15-29 q) Page 1732/ Results/ Safety/ Lines 19-41 r) Page 1732/ Results/ Safety/ Lines 66-88 s) Page 1732/ Results/ Safety/ Lines 91-92 t) Page 1732/ Results/ Safety/ Lines 100-105 u) Page 1734/ Results/ Safety/ Lines 1-5 2 E. Loftus. Clinical Epidemiology of Inflammatory Bowel Disease: Incidence, Prevalence, and Environmental Influences. *Gastroenterology*. 2004;126:1504-1517. 3 M.D. Kappelman, et al. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. *Dig Dis Sci*. 2013;58:519-525. 4 R.B. Sartor. Mechanisms of Disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nature Clinical Practice Gastroenterology & Hepatology*. 2006;3:390-407. 5 Crohn's & Colitis Foundation. Updated IBD Factbook. 2014. <http://www.crohnscolitisfoundation.org/assets/pdfs/updatedibdfactbook.pdf>. Accessed 3 May 2017. 6 E. Louis, A. Roughly, R. Thakkar, et al. Impact of ulcerative colitis on patient quality of life in a real-world clinical setting. Presented at ECCO Congress 2013, Vienna, Austria. P180. <https://www.ecco-ibd.eu/index.php/publications/congress-abstracts/abstracts-2013/item/p180-impact-of-ulcerative-colitis-on-patient-quality-of-life-in-a-real-world-clinical-setting.html>. 7 J. Landy, A.L. Hart. Commentary: short-term efficacy of tacrolimus in steroid-refractory ulcerative colitis. *Alimentary Pharmacology Therapeutics*. 2013 Feb. <http://www.ncbi.nlm.nih.gov/pubmed/23336680>. Accessed 3 May 2017.

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