CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203214Orig1s018

Trade Name:	XELJANZ
Generic or Proper Name:	tofacitinib
Sponsor:	PF Prism C.V. c/o Pfizer, Inc.
Approval Date:	May 30, 2018
Indication:	XELJANZ/XELJANZ XR is a Janus kinase (JAK) inhibitor. • Rheumatoid Arthritis: XELJANZ/XELJANZ XR 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). • Psoriatic Arthritis: XELJANZ/XELJANZ XR 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). • Ulcerative Colitis: XELJANZ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s018

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203214/S-018

SUPPLEMENT APPROVAL

PF PRISM C.V.
C/o Pfizer, Inc.
Attention: Louis M. Ferrara
Director, Worldwide Regulatory Strategy
445 Eastern Point Road
Groton, CT 06340

Dear Mr. Ferrara:

Please refer to your supplemental New Drug Application (sNDA) dated May 4, 2017, received May 4, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for XELJANZ (tofacitinib), 5 mg and 10 mg tablets.

We acknowledge receipt of your major amendment dated September 28, 2017, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication

Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your May 10, 2018, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages less than 2 years because necessary studies are impossible or highly impracticable. This is because there is a low incidence of the disease in this age group. In addition, difficulties exist in differentiating the subtypes of inflammatory bowel disease in infants and very young children.

We are deferring submission of your pediatric studies for ages 2 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

3400-1 A one-year, multi-center, randomized, controlled trial to evaluate the safety, efficacy and pharmacokinetics of XELJANZ (tofacitinib) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

The timetable you submitted on May 29, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2018
Final Protocol Submission:	10/2018
Study/Trial Completion:	04/2022
Final Report Submission:	09/2022

3400-2 A multi-center open-label extension study to evaluate the long-term safety of XELJANZ (tofacitinib) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in PMR 3400-1.

The timetable you submitted on May 29, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2018
Final Protocol Submission:	10/2018
Study/Trial Completion:	03/2024
Final Report Submission:	08/2024

Submit the protocol(s) to your IND 111294, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious

risk of malignancies associated with the long-term use of XELJANZ (tofacitinib) in the treatment of adults with moderate to severe ulcerative colitis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk. Therefore, based on appropriate scientific data, you are required to conduct the following:

3400-3 A long-term, observational study to assess the long-term safety of tofacitinib 5mg BID or 10mg BID versus other therapies used in the treatment of adults with moderately to severely active ulcerative colitis. The study's primary outcome is malignancy. Secondary outcomes of interest include, but are not limited to, opportunistic infections, thromboembolic events, and hepatic injury. Specify concise case definitions, and provide outcome validation for both primary and secondary outcomes. Describe and justify choice of appropriate comparator population(s) and estimated background rates relative to tofacitinib-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate, with a pre-specified statistical analysis method. For the tofacitinib-exposed and comparator(s), the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure adequate number of patients with at least 18 months of tofacitinib exposure at the end of the study. Follow for period of at least 7 years.

The timetable you submitted on May 29, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2018
Final Protocol Submission:	01/2019
Study Completion:	01/2026
Interim Report:	01/2023
Final Report Submission:	06/2026

Submit the protocol(s) to your IND 111294, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3400-4 A double-blind, randomized, controlled clinical trial to assess the relative efficacy of XELJANZ (tofacitinib) 5mg BID versus 10mg BID for maintaining remission in patients with moderate to severe ulcerative colitis who are in stable remission for at least 6 months on XELJANZ (tofacitinib) 10mg BID therapy.

The timetable you submitted on May 29, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2018
Final Protocol Submission:	12/2018
Study/Trial Completion:	01/2024
Final Report Submission:	07/2024

3400-5 A controlled clinical trial to assess both the clinical and immunological responses to Shingrix vaccination in adult patients with moderately to severely active ulcerative colitis treated with XELJANZ (tofacitinib).

The timetable you submitted on May 29, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	03/2019
Study/Trial Completion:	05/2022
Final Report Submission:	11/2022

Submit clinical protocols to your IND 111294 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Kelly Richards, Senior Regulatory Health Project Manager, at (240) 402-4276.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, MD, M.M.Sc.
Associate Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA J LEE
05/30/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s018

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XELJANZ/XELJANZ XR safely and effectively. See full prescribing information for XELJANZ.

XELJANZ® (tofacitinib) tablets, for oral use
XELJANZ® XR (tofacitinib) extended-release tablets, for oral use
Initial U.S. Approval: 2012

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ. (5.1)**
- **If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled. (5.1)**
- **Prior to starting XELJANZ/XELJANZ XR, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ/XELJANZ XR. (5.1)**
- **Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)**
- **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. (5.2)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	05/2018
Dosage and Administration (2)	05/2018
Warnings and Precautions (5.1)	05/2018
Warnings and Precautions (5.2, 5.3)	12/2017
Warnings and Precautions (5.5)	08/2017

---------- INDICATIONS AND USAGE----------
XELJANZ/XELJANZ XR is a Janus kinase (JAK) inhibitor.

- Rheumatoid Arthritis: XELJANZ/XELJANZ XR 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 potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)
- Psoriatic Arthritis: XELJANZ/XELJANZ XR 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 potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)
- Ulcerative Colitis: XELJANZ 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 biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)

----------DOSAGE AND ADMINISTRATION----------
Administration Instructions

- Do not initiate XELJANZ/XELJANZ XR if absolute lymphocyte count <500 cells/mm^3, an absolute neutrophil count (ANC) <1000 cells/mm^3 or hemoglobin <9 g/dL. (2.1)

Recommended Dosage
Rheumatoid Arthritis

- XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily. (2.2)
- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is XELJANZ 5 mg once daily. (2, 8.7, 8.8)

Psoriatic Arthritis (in combination with nonbiologic DMARDs)

- XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily. (2.2)
- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is XELJANZ 5 mg once daily. (2, 8.7, 8.8)

Ulcerative Colitis

- XELJANZ 10 mg twice daily for at least 8 weeks; then 5 or 10 mg twice daily. Discontinue after 16 weeks of 10 mg twice daily, if adequate therapeutic benefit is not achieved. Use the lowest effective dose to maintain response. (2.3)
- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment: half the total daily dosage recommended for patients with normal renal and hepatic function. (2, 8.7, 8.8)

Dosage Adjustment

- See the full prescribing information for dosage adjustments by indication for patients receiving CYP2C19 and/or CYP3A4 inhibitors; in patients with moderate or severe renal impairment or moderate hepatic impairment; and patients with lymphopenia, neutropenia, or anemia. (2.2, 2.3)
- Use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended in any patient population. (2.2, 2.3, 8.8)

---------- DOSAGE FORMS AND STRENGTHS ----------
XELJANZ Tablets: 5 mg, 10 mg tofacitinib (3)
XELJANZ XR Tablets: 11 mg tofacitinib (3)

---------- CONTRAINDICATIONS ----------
None (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Serious Infections: Avoid use of XELJANZ/XELJANZ XR during an active serious infection, including localized infections. (5.1)
- Gastrointestinal Perforations: Use with caution in patients that may be at increased risk. (5.3)
- Laboratory Monitoring: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.4)
- Immunizations: Live vaccines: Avoid use with XELJANZ/XELJANZ XR. (5.5)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions are:

- Rheumatoid and Psoriatic Arthritis: Reported during the first 3 months in rheumatoid arthritis controlled clinical trials and occurring in ≥2% of patients treated with XELJANZ monotherapy or in combination with DMARDs: upper respiratory tract infection, nasopharyngitis, diarrhea, and headache. (6.1)
- Ulcerative Colitis: 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: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS----------
See full prescribing information for clinically relevant drug interactions. (2, 7)

---------- USE IN SPECIFIC POPULATIONS ----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS
Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*. 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 risks and benefits of treatment with XELJANZ/XELJANZ XR should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

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 *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

Rheumatoid Arthritis
XELJANZ/XELJANZ XR 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 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).

- 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Do not initiate XELJANZ/XELJANZ XR in patients with an absolute lymphocyte count less than 500 cells/mm^3, an absolute neutrophil count (ANC) less than 1000 cells/mm^3 or who have hemoglobin levels less than 9 g/dL.
- Dose interruption is recommended for management of lymphopenia, neutropenia, and anemia *[see Warnings and Precautions (5.4), Adverse Reactions (6.1)]*.
- Interrupt use of XELJANZ/XELJANZ XR if a patient develops a serious infection until the infection is controlled *[see Warnings and Precautions (5.1)]*.
- Take XELJANZ/XELJANZ XR with or without food *[see Clinical Pharmacology (12.3)]*.
- Swallow XELJANZ XR tablets whole and intact. Do not crush, split, or chew.

2.2 Recommended Dosage in Rheumatoid Arthritis and Psoriatic Arthritis

Table 1 displays the recommended adult daily dosage of XELJANZ and XELJANZ XR and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, in patients with moderate or severe renal impairment or moderate hepatic impairment, with lymphopenia, neutropenia, or anemia.

Table 1: Recommended Dosage of XELJANZ and XELJANZ XR in Patients with Rheumatoid Arthritis[1] and Psoriatic Arthritis[2]

	XELJANZ	XELJANZ XR
Adult patients	5 mg twice daily	11 mg once daily
Patients receiving: • Strong CYP3A4 inhibitors (e.g., ketoconazole), or • a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole) *[see Drug Interactions (7)]*	5 mg once daily	Switch to XELJANZ 5 mg once daily
Patients with: • moderate or severe renal impairment *[see Use in Specific Populations (8.7)]* • moderate hepatic impairment *[see Use in Specific Populations (8.8)]**	5 mg once daily	Switch to XELJANZ 5 mg once daily
Patients with lymphocyte count less than 500 cells/mm^3, confirmed by repeat testing	Discontinue dosing.	
Patients with ANC 500 to 1000 cells/mm^3	Interrupt dosing. When ANC is greater than 1000, resume 5 mg twice daily.	Interrupt dosing. When ANC is greater than 1000, resume 11 mg once daily.
Patients with ANC less than 500 cells/mm^3	Discontinue dosing.	
Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL	Interrupt dosing until hemoglobin values have normalized.	

[1] XELJANZ/XELJANZ XR may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis.

[2] XELJANZ/XELJANZ XR is used in combination with nonbiologic disease modifying antirheumatic drugs (DMARDs) in psoriatic arthritis. The efficacy of XELJANZ/XELJANZ XR as a monotherapy has not been studied in psoriatic arthritis.

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

Switching from XELJANZ Tablets to XELJANZ XR Tablets

Patients treated with XELJANZ 5 mg twice daily may be switched to XELJANZ XR 11 mg once daily the day following the last dose of XELJANZ 5 mg.

2.3 Recommended Dosage in Ulcerative Colitis

Table 2 displays the recommended adult daily dosage of XELJANZ and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, with moderate or severe renal impairment or moderate hepatic impairment, with lymphopenia, neutropenia or anemia.

Table 2: Recommended Dosage of XELJANZ in Patients with UC

Ulcerative Colitis	XELJANZ
Adult patients	10 mg twice daily for at least 8 weeks; followed by 5 or 10 mg twice daily, depending on therapeutic response *[see Clinical Studies (14.3)]*. Use the lowest effective dose to maintain response *[see Warnings and Precautions (5.1, 5.2, 5.4)]*. Discontinue XELJANZ after 16 weeks of treatment with 10 mg twice daily, if adequate therapeutic benefit is not achieved.
Patients receiving: • Strong CYP3A4 inhibitors (e.g., ketoconazole), or • a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole) *[see Drug Interactions (7)]*	If taking 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, reduce to 5 mg once daily.
Patients with: • moderate or severe renal impairment *[see Use in Specific Populations (8.7)]* • moderate hepatic impairment *[see Use in Specific Populations (8.8)]**	If taking 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, reduce to 5 mg once daily.
Patients with lymphocyte count less than 500 cells/mm^3, confirmed by repeat testing	Discontinue dosing.
Patients with ANC 500 to 1000 cells/mm^3	If taking 10 mg twice daily, reduce to 5 mg twice daily. When ANC is greater than 1000, increase to 10 mg twice daily based on clinical response. If taking 5 mg twice daily, interrupt dosing. When ANC is greater than 1000, resume 5 mg twice daily.
Patients with ANC less than 500 cells/mm^3	Discontinue dosing.
Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL	Interrupt dosing until hemoglobin values have normalized.

*Use in patients with severe hepatic impairment is not recommended.

3 DOSAGE FORMS AND STRENGTHS

XELJANZ Tablets:

- 5 mg tofacitinib: White, round, immediate-release film-coated tablets, debossed with "Pfizer" on one side, and "JKI 5" on the other side.

- 10 mg tofacitinib: Blue, round, immediate-release film-coated tablets, debossed with "Pfizer" on one side, and "JKI 10" on the other side.

XELJANZ XR Tablets:

- 11 mg tofacitinib: Pink, oval, extended-release film-coated tablets with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infection, and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids.

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

Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

Avoid use of XELJANZ/XELJANZ XR in patients with an active, serious infection, including localized infections. 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.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR. XELJANZ/XELJANZ XR should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ/XELJANZ XR should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

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 infections.

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. Discontinuation and monitoring criteria for lymphopenia are recommended *[see Dosage and Administration (2.2, 2.3)]*.

Tuberculosis

Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of XELJANZ/XELJANZ XR.

Anti-tuberculosis therapy should also be considered prior to administration of XELJANZ/XELJANZ XR in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering XELJANZ/XELJANZ XR.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with XELJANZ. The impact of XELJANZ/XELJANZ XR on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ/XELJANZ XR. The risk of herpes zoster is increased in patients treated with XELJANZ/XELJANZ XR and appears to be higher in patients treated with XELJANZ in Japan and Korea.

5.2 Malignancy and Lymphoproliferative Disorders

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 were observed in clinical studies of XELJANZ *[see Adverse Reactions (6.1)]*.

In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving XELJANZ with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with XELJANZ.

During the 2 PsA controlled clinical studies there were 3 malignancies (excluding NMSC) in 474 patients receiving XELJANZ plus nonbiologic DMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus nonbiologic DMARD group (3 months exposure) and 0 malignancies in 106 patients in the adalimumab plus nonbiologic DMARD group (12 months exposure). No lymphomas were reported. Malignancies have also been observed in the long-term extension study in psoriatic arthritis patients treated with XELJANZ.

During the UC controlled clinical studies (8-week induction and 52-week maintenance studies), which included 1220 patients, 0 cases of solid cancer or lymphoma were observed in XELJANZ-treated patients. In the long-term extension study, malignancies (including solid cancers and lymphomas) were observed more often in patients treated with XELJANZ 10 mg twice daily.

In Phase 2B, controlled dose-ranging trials in *de-novo* renal transplant patients, all of whom received induction therapy with basiliximab, high-dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine.

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.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. In the UC population, treatment with XELJANZ 10 mg twice daily was associated with greater risk of NMSC.

5.3 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical studies with XELJANZ, although the role of JAK inhibition in these events 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). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation *[see Adverse Reactions (6.1)]*.

5.4 Laboratory Abnormalities

Lymphocyte Abnormalities
Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean absolute lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections.

Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a low lymphocyte count (i.e., 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.

Monitor lymphocyte counts at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts *[see Dosage and Administration (2.2, 2.3)]*.

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 a low neutrophil count (i.e., ANC less than 1000 cells/mm^3). For patients who develop a persistent ANC of 500 to 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. For recommended modifications based on ANC results *[see Dosage and Administration (2.2, 2.3)]*.

Anemia
Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a low hemoglobin level (i.e., 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. For recommended modifications based on hemoglobin results *[see Dosage and Administration (2)]*.

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.

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. If

drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded.

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. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of XELJANZ/XELJANZ XR therapy.

Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

5.5 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.

A patient experienced dissemination of the vaccine strain of varicella zoster virus, 16 days after vaccination with live attenuated (Zostavax) virus vaccine and 2 days after treatment start with tofacitinib 5 mg twice daily. The patient was varicella virus naïve, as evidenced by no previous history of varicella infection and no anti-varicella antibodies at baseline. Tofacitinib was discontinued and the patient recovered after treatment with standard doses of antiviral medication.

Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ/XELJANZ XR therapy.

5.6 Risk of Gastrointestinal Obstruction with a Non-Deformable Extended-Release Formulation such as XELJANZ XR
As with any other non-deformable material, caution should be used when administering XELJANZ XR to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). 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.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Malignancy and Lymphoproliferative Disorders *[see Warnings and Precautions (5.2)]*
- Gastrointestinal Perforations *[see Warnings and Precautions (5.3)]*
- Laboratory Abnormalities *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Rheumatoid Arthritis

The clinical studies described in the following sections were conducted using XELJANZ. Although other doses of XELJANZ have been studied, the recommended dose of XELJANZ is 5 mg twice daily.

The recommended dose for XELJANZ XR is 11 mg once daily.

The following data includes two Phase 2 and five Phase 3 double-blind, controlled, multicenter trials. In these trials, patients were randomized to doses of XELJANZ 5 mg twice daily (292 patients) and 10 mg twice daily (306 patients) monotherapy, XELJANZ 5 mg twice daily (1044 patients) and 10 mg twice daily (1043 patients) in combination with DMARDs (including methotrexate) and placebo (809 patients). All seven protocols included provisions for patients taking placebo to receive treatment with XELJANZ at Month 3 or Month 6 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Therefore, some analyses that follow include patients who changed treatment by design or by patient response from placebo to XELJANZ in both the placebo and XELJANZ group of a given interval. Comparisons between placebo and XELJANZ were based on the first 3 months of exposure, and comparisons between XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily were based on the first 12 months of exposure.

The long-term safety population includes all patients who participated in a double-blind, controlled trial (including earlier development phase studies) and then participated in one of two long-term safety studies. The design of the long-term safety studies allowed for modification of XELJANZ doses according to clinical judgment. This limits the interpretation of the long-term safety data with respect to dose.

The most common serious adverse reactions were serious infections *[see Warnings and Precautions (5.1)]*.

The proportion of patients who discontinued treatment due to any adverse reaction during the 0 to 3 months exposure in the double-blind, placebo-controlled trials was 4% for patients taking XELJANZ and 3% for placebo-treated patients.

Overall Infections
In the seven controlled trials, during the 0 to 3 months exposure, the overall frequency of infections was 20% and 22% in the 5 mg twice daily and 10 mg twice daily groups, respectively, and 18% in the placebo group.

The most commonly reported infections with XELJANZ were upper respiratory tract infections, nasopharyngitis, and urinary tract infections (4%, 3%, and 2% of patients, respectively).

Serious Infections
In the seven controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.5 events per 100 patient-years) who received placebo and 11 patients (1.7 events per 100 patient-years) who received XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 1.1 (-0.4, 2.5) events per 100 patient-years for the combined 5 mg twice daily and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, serious infections were reported in 34 patients (2.7 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 33 patients (2.7 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was -0.1 (-1.3, 1.2) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The most common serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infection *[see Warnings and Precautions (5.1)]*.

Tuberculosis
In the seven controlled trials, during the 0 to 3 months exposure, tuberculosis was not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven controlled trials, during the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg twice daily of XELJANZ and 6 patients (0.5 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.5 (0.1, 0.9) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

Cases of disseminated tuberculosis were also reported. The median XELJANZ exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days) *[see Warnings and Precautions (5.1)]*.

Opportunistic Infections (excluding tuberculosis)
In the seven controlled trials, during the 0 to 3 months exposure, opportunistic infections were not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven controlled trials, during the 0 to 12 months exposure, opportunistic infections were reported in 4 patients (0.3 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 4 patients (0.3 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0 (-0.5, 0.5) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The median XELJANZ exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days) *[see Warnings and Precautions (5.1)]*.

Malignancy
In the seven controlled trials, during the 0 to 3 months exposure, malignancies excluding NMSC were reported in 0 patients who received placebo and 2 patients (0.3 events per 100 patient-years) who received either XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 0.3 (-0.1, 0.7) events per 100 patient-years for the combined 5 mg and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, malignancies excluding NMSC were reported in 5 patients (0.4 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 7 patients (0.6 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.2 (-0.4, 0.7) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ. One of these malignancies was a case of lymphoma that occurred during the 0 to 12 month period in a patient treated with XELJANZ 10 mg twice daily.

The most common types of malignancy, including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma, and malignant melanoma *[see Warnings and Precautions (5.2)]*.

Laboratory Abnormalities

Lymphopenia
In the controlled clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm^3 occurred in 0.04% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

Confirmed lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections *[see Warnings and Precautions (5.4)]*.

Neutropenia
In the controlled clinical trials, confirmed decreases in ANC below 1000 cells/mm^3 occurred in 0.07% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

There were no confirmed decreases in ANC below 500 cells/mm^3 observed in any treatment group.

There was no clear relationship between neutropenia and the occurrence of serious infections.

In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical trials *[see Warnings and Precautions (5.4)]*.

Liver Enzyme Elevations
Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were observed in patients treated with XELJANZ. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of XELJANZ, or reduction in XELJANZ dose, resulted in decrease or normalization of liver enzymes.

In the controlled monotherapy trials (0-3 months), no differences in the incidence of ALT or AST elevations were observed between the placebo, and XELJANZ 5 mg, and 10 mg twice daily groups.

In the controlled background DMARD trials (0-3 months), ALT elevations greater than 3x ULN were observed in 1.0%, 1.3% and 1.2% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. In these trials, AST elevations greater than 3x ULN were observed in 0.6%, 0.5% and 0.4% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively.

One case of drug-induced liver injury was reported in a patient treated with XELJANZ 10 mg twice daily for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT greater than 3x ULN and bilirubin elevations greater than 2x ULN, which required hospitalizations and a liver biopsy.

Lipid Elevations
In the controlled clinical trials, dose-related elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were observed at one month of exposure and remained stable thereafter. Changes in lipid parameters during the first 3 months of exposure in the controlled clinical trials are summarized below:

- Mean LDL cholesterol increased by 15% in the XELJANZ 5 mg twice daily arm and 19% in the XELJANZ 10 mg twice daily arm.
- Mean HDL cholesterol increased by 10% in the XELJANZ 5 mg twice daily arm and 12% in the XELJANZ 10 mg twice daily arm.
- Mean LDL/HDL ratios were essentially unchanged in XELJANZ-treated patients.

In a controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy.

In the long-term safety population, elevations in lipid parameters remained consistent with what was seen in the controlled clinical trials.

Serum Creatinine Elevations
In the controlled clinical trials, dose-related elevations in serum creatinine were observed with XELJANZ treatment. The mean increase in serum creatinine was <0.1 mg/dL in the 12-month pooled safety analysis; however with increasing duration of exposure in the long-term extensions, up to 2% of patients were discontinued from XELJANZ treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

Other Adverse Reactions
Adverse reactions occurring in 2% or more of patients on 5 mg twice daily or 10 mg twice daily XELJANZ and at least 1% greater than that observed in patients on placebo with or without DMARD are summarized in Table 3.

Table 3: Common Adverse Reactions* in Clinical Trials of XELJANZ for the Treatment of Rheumatoid Arthritis With or Without Concomitant DMARDs (0-3 Months)

Preferred Term	XELJANZ 5 mg Twice Daily N = 1336 (%)	XELJANZ 10 mg Twice Daily** N = 1349 (%)	Placebo N = 809 (%)
Upper respiratory tract infection	4	4	3
Nasopharyngitis	4	3	3
Diarrhea	4	3	2
Headache	4	3	2
Hypertension	2	2	1

N reflects randomized and treated patients from the seven clinical trials.
* reported in ≥2% of patients treated with either dose of XELJANZ and ≥1% greater than that reported for placebo.
** the recommended dose of XELJANZ for the treatment of rheumatoid arthritis is 5 mg twice daily *[see Dosage and Administration (2)]*.

Other adverse reactions occurring in controlled and open-label extension studies included:

Blood and lymphatic system disorders: Anemia
Infections and infestations: Diverticulitis
Metabolism and nutrition disorders: Dehydration
Psychiatric disorders: Insomnia
Nervous system disorders: Paresthesia
Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion, interstitial lung disease (cases were limited to patients with rheumatoid arthritis and some were fatal)
Gastrointestinal disorders: Abdominal pain, dyspepsia, vomiting, gastritis, nausea

Hepatobiliary disorders: Hepatic steatosis
Skin and subcutaneous tissue disorders: Rash, erythema, pruritus
Musculoskeletal, connective tissue and bone disorders: Musculoskeletal pain, arthralgia, tendonitis, joint swelling
Neoplasms benign, malignant and unspecified (including cysts and polyps): Non-melanoma skin cancers
General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema

Clinical Experience in Methotrexate-Naïve Patients
Study RA-VI was an active-controlled clinical trial in methotrexate-naïve patients *[see Clinical Studies (14)]*. The safety experience in these patients was consistent with Studies RA-I through V.

Psoriatic Arthritis
XELJANZ 5 mg twice daily and 10 mg twice daily were studied in 2 double-blind Phase 3 clinical trials in patients with active psoriatic arthritis (PsA).

Study PsA-I (NCT01877668) had a duration of 12 months and enrolled patients who had an inadequate response to a nonbiologic DMARD and who were naïve to treatment with a TNF blocker. Study PsA-I included a 3-month placebo-controlled period and also included adalimumab 40 mg subcutaneously once every 2 weeks for 12 months.

Study PsA-II (NCT01882439) had a duration of 6 months and enrolled patients who had an inadequate response to at least one approved TNF blocker. This clinical trial included a 3-month placebo controlled period.

In these combined Phase 3 clinical trials, 238 patients were randomized and treated with XELJANZ 5 mg twice daily and 236 patients were randomized and treated with XELJANZ 10 mg twice daily. All patients in the clinical trials were required to receive treatment with a stable dose of a nonbiologic DMARD [the majority (79%) received methotrexate]. The study population randomized and treated with XELJANZ (474 patients) included 45 (9.5%) patients aged 65 years or older and 66 (13.9%) patients with diabetes at baseline.

The safety profile observed in patients with active psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in rheumatoid arthritis patients.

Ulcerative Colitis
XELJANZ has been studied in patients with moderately to severely active UC in 4 randomized, double-blind, placebo-controlled trials (UC-I, UC-II, UC-III, and dose-ranging UC-V) and an open-label long-term extension study (UC-IV) *[see Clinical Studies (14.3)]*.

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 were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

Induction Trials (Study UC-I, UC-II, and UC-V):
Common adverse reactions reported in ≥2% of patients treated with XELJANZ 10 mg twice daily and ≥1% greater than that reported in patients receiving placebo in the 3 induction trials were: headache, nasopharyngitis, elevated cholesterol levels, acne, increased blood creatine phosphokinase, and pyrexia.

Maintenance Trial (Study UC-III)
Common adverse reactions reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported in patients receiving placebo are shown in Table 4.

Table 4: Common Adverse Reactions* in -UC Patients during the Maintenance Trial (Study UC-III)

	XELJANZ 5 mg Twice Daily	**XELJANZ 10 mg Twice Daily**	**Placebo**
Preferred Term	**N = 198 (%)**	**N = 196 (%)**	**N = 198 (%)**
Nasopharyngitis	10	14	6
Elevated cholesterol levels**	5	9	1
Headache	9	3	6
Upper respiratory tract infection	7	6	4
Increased blood creatine phosphokinase	3	7	2
Rash	3	6	4
Diarrhea	2	5	3
Herpes zoster	1	5	1
Gastroenteritis	3	4	3
Anemia	4	2	2
Nausea	1	4	3

* reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported for placebo.
** includes hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased.

In the long-term extension study, malignancies (including solid cancers, lymphomas and NMSC) were observed more often in patients treated with XELJANZ 10 mg twice daily *[see Warnings and Precautions (5.2)]*. Four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one fatality in a patient with advanced cancer.

Dose-dependent adverse reactions seen in patients treated with XELJANZ 10 mg twice daily, in comparison to 5 mg twice daily, include the following: herpes zoster infections, serious infections, and NMSC *[see Warnings and Precautions (5.1, 5.2)]*.

7 DRUG INTERACTIONS

Table 5 includes drugs with clinically important drug interactions when administered concomitantly with XELJANZ/XELJANZ XR and instructions for preventing or managing them.

Table 5: Clinical Relevant Interactions Affecting XELJANZ and XELJANZ XR When Coadministered with Other Drugs

Strong CP3A4 Inhibitors (e.g., ketoconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ/XELJANZ XR is recommended *[see Dosage and Administration (2), Clinical Pharmacology, Figure 3 (12.3)]*
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ/XELJANZ XR is recommended *[see Dosage and Administration (2), Clinical Pharmacology, Figure 3 (12.3)]*
Strong CYP3A4 Inducers (e.g., rifampin)	
Clinical Impact	Decreased exposure to tofacitinib and may result in loss of or reduced clinical response
Intervention	Coadministration with XELJANZ/XELJANZ XR is not recommended *[see Clinical Pharmacology, Figure 3 (12.3)]*
Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)	
Clinical Impact	Risk of added immunosuppression; coadministration with biologic DMARDs or potent immunosuppressants has not been studied in patients with rheumatoid arthritis, psoriatic arthritis, or UC.
Intervention	Coadministration with XELJANZ/XELJANZ XR is not recommended *[see Indications and Usage (1), Clinical Pharmacology, Figure 3 (12.3)]*

8 USE IN SPECIFIC POPULATIONS

All information provided in this section is applicable to XELJANZ and XELJANZ XR as they contain the same active ingredient (tofacitinib).

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to XELJANZ/XELJANZ XR during pregnancy. Patients should be encouraged to enroll in the XELJANZ/XELJANZ XR pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call the toll free number 1-877-311-8972.

Risk Summary

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 *(see Clinical Considerations)*. In animal reproduction studies, fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73-times and 6.3-times the maximum

recommended dose of 10 mg twice daily, respectively. Further, in a peri and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73-times the recommended dose of 5 mg twice daily and approximately 36 times the maximum recommended dose of 10 mg twice daily, respectively *(see Data)*.

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriages are 2 to 4% and 15 to 20% of clinically recognized pregnancies, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk
Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data
In a rat embryofetal developmental study, in which pregnant rats received tofacitinib during organogenesis, tofacitinib was teratogenic at exposure levels approximately 146 times the recommended dose of 5 mg twice daily, and approximately 73 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 100 mg/kg/day in rats). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively; and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). In addition, there was an increase in post-implantation loss, consisting of early and late resorptions, resulting in a reduced number of viable fetuses. Mean fetal body weight was reduced. No developmental toxicity was observed in rats at exposure levels approximately 58 times the recommended dose of 5 mg twice daily, and approximately 29 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in pregnant rats).

In a rabbit embryofetal developmental study in which pregnant rabbits received tofacitinib during the period of organogenesis, tofacitinib was teratogenic at exposure levels approximately 13 times the recommended dose of 5 mg twice daily, and approximately 6.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3 times the recommended dose of 5 mg

twice daily, and approximately 1.5 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in pregnant rabbits).

In a peri- and postnatal development study in pregnant rats that received tofacitinib from gestation day 6 through day 20 of lactation, there were reductions in live litter size, postnatal survival, and pup body weights at exposure levels approximately 73 times the recommended dose of 5 mg twice daily, and approximately 36 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 50 mg/kg/day in rats). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in rats).

8.2 Lactation

Risk Summary

There are no data on the presence of tofacitinib in human milk, the effects on a breastfed infant, or the effects on milk production. Tofacitinib is present in the milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adults treated with XELJANZ/XELJANZ XR, such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 18 hours after the last dose of XELJANZ or 36 hours after the last dose of XELJANZ XR (approximately 6 elimination half-lives).

Data

Following administration of tofacitinib to lactating rats, concentrations of tofacitinib in milk over time paralleled those in serum, and were approximately 2 times higher in milk relative to maternal serum at all time points measured.

8.3 Females and Males of Reproductive Potential

Contraception

Females

In an animal reproduction study, tofacitinib at AUC multiples of 13 times the recommended dose of 5 mg twice daily and 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings *[see Use in Specific Populations (8.1)]*. However, there is uncertainty as to how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential.

Infertility

Females
Based on findings in rats, treatment with XELJANZ/XELJANZ XR may result in reduced fertility in females of reproductive potential. It is not known if this effect is reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use
The safety and effectiveness of XELJANZ/XELJANZ XR in pediatric patients have not been established.

8.5 Geriatric Use
Of the 3315 patients who enrolled in rheumatoid arthritis Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among XELJANZ-treated subjects 65 years of age and older was higher than among those under the age of 65.

Of the 1156 XELJANZ-treated patients in the UC program, a total of 77 patients (7%) were 65 years of age or older. The number of patients aged 65 years and older was not sufficient to determine whether they responded differently from younger patients.

As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly *[see Warnings and Precautions (5.1)]*.

8.6 Use in Diabetics
As there is a higher incidence of infection in diabetic population in general, caution should be used when treating patients with diabetes.

8.7 Renal Impairment

Moderate and Severe Impairment
XELJANZ-treated patients with moderate or severe renal impairment had greater tofacitinib blood concentrations than XELJANZ-treated patients with normal renal function. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate or severe renal impairment.

- Rheumatoid arthritis and psoriatic arthritis patients with moderate or severe renal impairment receiving XELJANZ XR should switch to XELJANZ and adjust the dosage *[see Dosage and Administration (2.2)]*.

Mild impairment
No dosage adjustment is required in patients with mild renal impairment.

8.8 Hepatic Impairment

Severe Impairment
XELJANZ/XELJANZ XR has not been studied in patients with severe hepatic impairment; therefore, use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended.

Moderate Impairment
XELJANZ-treated patients with moderate hepatic impairment had greater tofacitinib blood concentration than XELJANZ-treated patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Higher blood concentrations may increase the risk of some adverse reactions. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate hepatic impairment *[see Dosage and Administration (2.2, 2.3)]*.

- Rheumatoid arthritis and psoriatic arthritis patients receiving XELJANZ XR should switch to XELJANZ and adjust the dosage *[see Dosage and Administration (2.2)]*.

Mild Impairment
No dosage adjustment of XELJANZ/XELJANZ XR is required in patients with mild hepatic impairment.

Hepatitis B or C Serology
The safety and efficacy of XELJANZ/XELJANZ XR have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

10 OVERDOSAGE

There is no specific antidote for overdose with XELJANZ/XELJANZ XR. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions.

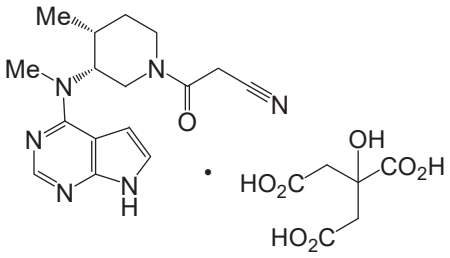
11 DESCRIPTION

XELJANZ/XELJANZ XR are formulated with the citrate salt of tofacitinib, a JAK inhibitor.

Tofacitinib citrate is a white to off-white powder with the following chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

The solubility of tofacitinib citrate in water is 2.9 mg/mL.

Tofacitinib citrate has a molecular weight of 504.5 Daltons (or 312.4 Daltons as the tofacitinib free base) and a molecular formula of $C_{16}H_{20}N_6O \cdot C_6H_8O_7$. The chemical structure of tofacitinib citrate is:



XELJANZ is supplied for oral administration as a 5 mg white round, immediate-release film-coated tablet. Each tablet of XELJANZ contains 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) and the following inactive ingredients: croscarmellose sodium, HPMC 2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

XELJANZ is supplied for oral administration as a 10 mg blue round, immediate-release film-coated tablet. Each 10 mg tablet of XELJANZ contains 10 mg tofacitinib (equivalent to 16 mg of tofacitinib citrate) and the following inactive ingredients: croscarmellose sodium, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/Indigo Carmine Aluminum Lake, HPMC 2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

XELJANZ XR is supplied for oral administration as a 11 mg pink, oval, extended-release film-coated tablet with a drilled hole at one end of the tablet band. Each 11 mg tablet of XELJANZ XR contains 11 mg tofacitinib (equivalent to 17.77 mg tofacitinib citrate) and the following inactive ingredients: cellulose acetate, copovidone, hydroxyethyl cellulose, hydroxypropylcellulose, HPMC 2910/Hypromellose, magnesium stearate, red iron oxide, sorbitol, titanium dioxide and triacetin. Printing ink contains, ammonium hydroxide, ferrosoferric oxide/black iron oxide, propylene glycol, and shellac glaze.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). Tofacitinib inhibited the *in vitro* activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC_{50} of 406, 56, and 1377 nM,

respectively. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known.

12.2 Pharmacodynamics

Treatment with XELJANZ was associated with dose-dependent reductions of circulating CD16/56+ natural killer cells, with estimated maximum reductions occurring at approximately 8-10 weeks after initiation of therapy. These changes generally resolved within 2-6 weeks after discontinuation of treatment. Treatment with XELJANZ was associated with dose-dependent increases in B cell counts. Changes in circulating T-lymphocyte counts and T-lymphocyte subsets (CD3+, CD4+ and CD8+) were small and inconsistent. The clinical significance of these changes is unknown.

Total serum IgG, IgM, and IgA levels after 6-month dosing in patients with rheumatoid arthritis were lower than placebo; however, changes were small and not dose-dependent.

After treatment with XELJANZ in patients with rheumatoid arthritis, rapid decreases in serum C-reactive protein (CRP) were observed and maintained throughout dosing. Changes in CRP observed with XELJANZ treatment do not reverse fully within 2 weeks after discontinuation, indicating a longer duration of pharmacodynamic activity compared to the pharmacokinetic half-life.

Similar changes in T cells, B cells, and serum CRP have been observed in patients with active psoriatic arthritis although reversibility was not assessed. Total serum immunoglobulins were not assessed in patients with active psoriatic arthritis.

12.3 Pharmacokinetics

XELJANZ

Following oral administration of XELJANZ, peak plasma concentrations are reached within 0.5-1 hour, elimination half-life is about 3 hours and a dose-proportional increase in systemic exposure was observed in the therapeutic dose range. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after twice daily administration.

XELJANZ XR

Following oral administration of XELJANZ XR, peak plasma concentrations are reached at 4 hours and half-life is about 6 hours. Steady state concentrations are achieved within 48 hours with negligible accumulation after once daily administration. AUC and C_{max} of tofacitinib for XELJANZ XR 11 mg administered once daily are equivalent to those of XELJANZ 5 mg administered twice daily.

Absorption

XELJANZ

The absolute oral bioavailability of XELJANZ is 74%. Coadministration of XELJANZ with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. In clinical trials, XELJANZ was administered without regard to meals *[see Dosage and Administration (2.1)]*.

XELJANZ XR
Coadministration of XELJANZ XR with a high-fat meal resulted in no changes in AUC while C_{max} was increased by 27% and T_{max} was extended by approximately 1 hour.

Distribution
After intravenous administration, the volume of distribution is 87 L. The protein binding of tofacitinib is approximately 40%. Tofacitinib binds predominantly to albumin and does not appear to bind to α1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

Metabolism and Excretion
Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged tofacitinib, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of tofacitinib is attributed to the parent molecule.

Pharmacokinetics in Patient Populations
Population pharmacokinetic analyses indicated that pharmacokinetic characteristics were similar between patients with rheumatoid arthritis, psoriatic arthritis, and UC. The coefficient of variation (%) in AUC of tofacitinib were generally similar across different disease patients, ranging from 22% to 34% (Table 6).

Table 6. XELJANZ Exposure in Patient Populations at 5 mg Twice Daily and 10 mg Twice Daily Doses

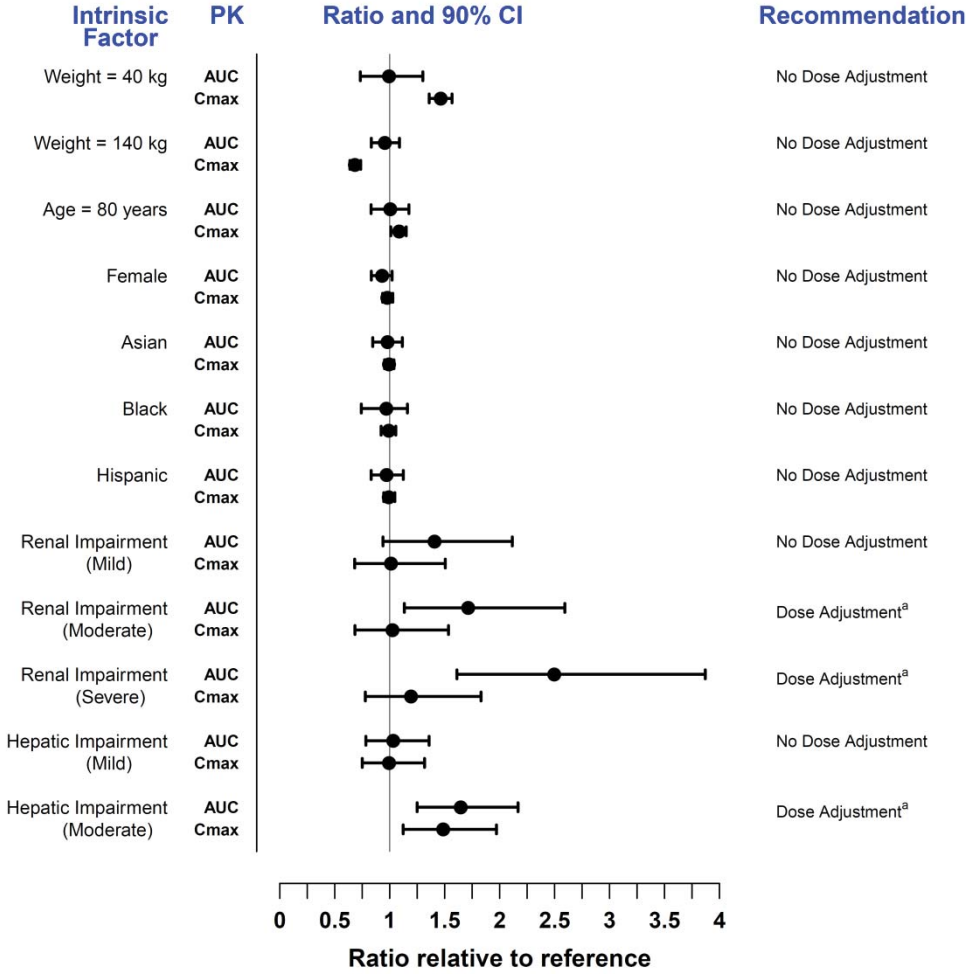
Pharmacokinetic Parameters[a] Geometric Mean (CV%)	**XELJANZ 5 mg Twice Daily**			**XELJANZ 10 mg Twice Daily**
	Rheumatoid Arthritis	**Psoriatic Arthritis**	**Ulcerative Colitis**	**Ulcerative Colitis**
$AUC_{0\text{-}24,ss}$ (ng·h/mL)	504 (22.0%)	419 (34.1%)	423 (22.6%)	807 (24.6%)

Abbreviations: $AUC_{0\text{-}24,ss}$=area under the plasma concentration-time curve over 24 hours at steady state; CV=coefficient of variation.
[a] Pharmacokinetic parameters estimated based on population pharmacokinetic analysis.

Specific Populations
Covariate evaluation as part of population PK analyses in patient populations indicated no clinically relevant change in tofacitinib exposure, after accounting for differences in renal function (i.e., creatinine clearance) between patients, based on age, weight, gender and race (Figure 1). An approximately linear relationship between body weight and volume of distribution was observed, resulting in higher peak (C_{max}) and lower trough (C_{min}) concentrations in lighter patients. However, this difference is not considered to be clinically relevant.

The effect of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics of tofacitinib is shown in Figure 1.

Figure 1: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics



Note: Reference values for weight, age, gender, and race comparisons are 70 kg, 55 years, male, and white, respectively; reference groups for renal and hepatic impairment data are subjects with normal renal and hepatic function.

[a] *[see Dosage and Administration (2.2, 2.3)]* for dosage adjustment in RA, PsA, and UC patients.

Drug Interaction Studies

Potential for XELJANZ/XELJANZ XR to Influence the PK of Other Drugs

In vitro studies indicate that tofacitinib does not significantly inhibit or induce the activity of the major human drug-metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations corresponding to the steady state C_{max} of a 10 mg twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the pharmacokinetics of midazolam, a highly sensitive CYP3A4 substrate, when coadministered with XELJANZ.

In vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug-metabolizing uridine 5'-diphospho-glucuronosyltransferases (UGTs) [UGT1A1,

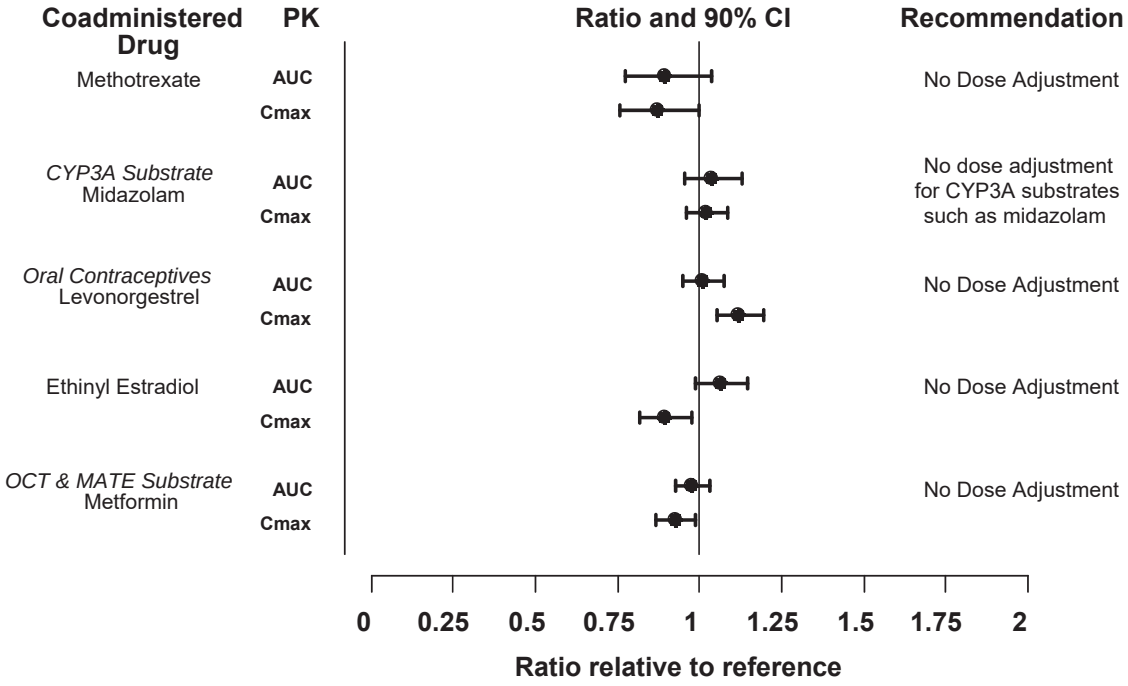
UGT1A4, UGT1A6, UGT1A9, and UGT2B7] at concentrations exceeding 250 times the steady state C_{max} of a 10 mg twice daily dose.

In rheumatoid arthritis patients, the oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalize CYP enzyme activity in rheumatoid arthritis patients. Therefore, coadministration with XELJANZ/XELJANZ XR is not expected to result in clinically relevant increases in the metabolism of CYP substrates in rheumatoid arthritis patients.

In vitro data indicate that the potential for tofacitinib to inhibit transporters such as P-glycoprotein, organic anionic or cationic transporters at therapeutic concentrations is low.

Dosing recommendations for coadministered drugs following administration with XELJANZ/XELJANZ XR are shown in Figure 2.

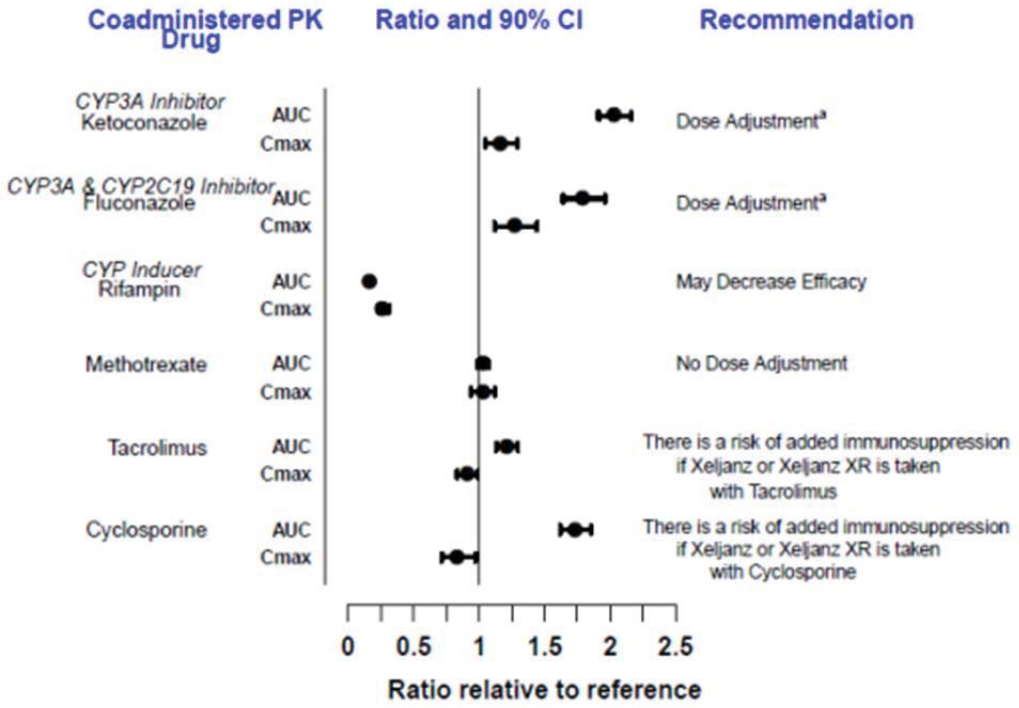
Figure 2: Impact of Tofacitinib on the Pharmacokinetics of Other Drugs



Note: Reference group is administration of concomitant medication alone; OCT = Organic Cationic Transporter; MATE = Multidrug and Toxic Compound Extrusion

Potential for Other Drugs to Influence the Pharmacokinetics of Tofacitinib
Since tofacitinib is metabolized by CYP3A4, interaction with drugs that inhibit or induce CYP3A4 is likely. Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to substantially alter the pharmacokinetics of tofacitinib (see Figure 3).

Figure 3: Impact of Other Drugs on the Pharmacokinetics of Tofacitinib



Note: Reference group is administration of tofacitinib alone.
[a] *[see Dosage and Administration (2.2, 2.3), Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 39-week toxicology study in monkeys, tofacitinib at exposure levels approximately 6 times the recommended dose of 5 mg twice daily, and approximately 3 times the 10 mg twice daily dose (on an AUC basis at oral doses of 5 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1 times the recommended dose of 5 mg twice daily, and approximately 0.5 times the 10 mg twice daily dose (on an AUC basis at oral doses of 1 mg/kg twice daily).

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib, at exposure levels approximately 34 times the recommended dose of 5 mg twice daily, and approximately 17 times the 10 mg twice daily dose (on an AUC basis at oral doses of 200 mg/kg/day) was not carcinogenic in mice.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hibernomas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 30 mg/kg/day (approximately 42 times the exposure levels at the recommended dose of 5 mg twice daily, and approximately 21 times the 10 mg twice daily dose on an AUC basis). The relevance of benign Leydig cell tumors to human risk is not known.

Tofacitinib was not mutagenic in the bacterial reverse mutation assay. It was positive for clastogenicity in the *in vitro* chromosome aberration assay with human lymphocytes in the presence of metabolic enzymes, but negative in the absence of metabolic enzymes. Tofacitinib was negative in the *in vivo* rat micronucleus assay and in the *in vitro* CHO-HGPRT assay and the *in vivo* rat hepatocyte unscheduled DNA synthesis assay.

In rats, tofacitinib at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the 10 mg twice daily dose (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the recommended dose of 5 mg twice daily, and approximately 0.5 times the 10 mg twice daily dose (on an AUC basis at oral doses of 1 mg/kg/day). Tofacitinib exposure levels at approximately 133 times the recommended dose of 5 mg twice daily, and approximately 67 times the 10 mg twice daily dose (on an AUC basis at oral doses of 100 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The XELJANZ clinical development program included two dose-ranging trials and five confirmatory trials. Although other doses have been studied, the recommended dose of XELJANZ is 5 mg twice daily.

Dose-Ranging Trials

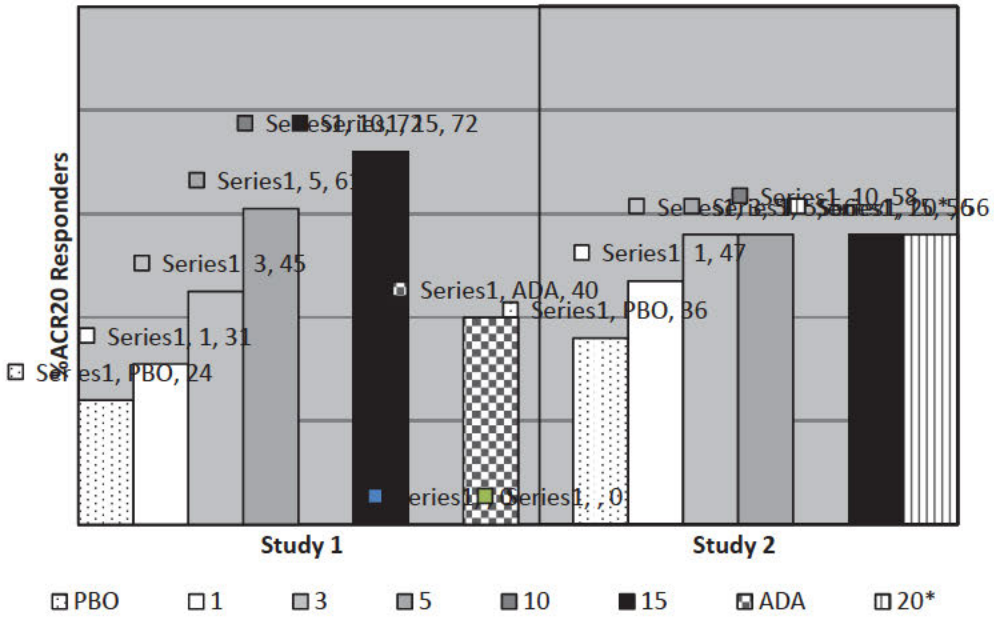
Dose selection for XELJANZ was based on two pivotal dose-ranging trials.

Dose-Ranging Study 1 was a 6-month monotherapy trial in 384 patients with active rheumatoid arthritis who had an inadequate response to a DMARD. Patients who previously received adalimumab therapy were excluded. Patients were randomized to 1 of 7 monotherapy treatments: XELJANZ 1, 3, 5, 10 or 15 mg twice daily, adalimumab 40 mg subcutaneously every other week for 10 weeks followed by XELJANZ 5 mg twice daily for 3 months, or placebo.

Dose-Ranging Study 2 was a 6-month trial in which 507 patients with active rheumatoid arthritis who had an inadequate response to MTX alone received one of 6 dose regimens of XELJANZ (20 mg once daily; 1, 3, 5, 10 or 15 mg twice daily), or placebo added to background MTX.

The results of XELJANZ-treated patients achieving ACR20 responses in Studies 1 and 2 are shown in Figure 4. Although a dose-response relationship was observed in Study 1, the proportion of patients with an ACR20 response did not clearly differ between the 10 mg and 15 mg doses. In Study 2, a smaller proportion of patients achieved an ACR20 response in the placebo and XELJANZ 1 mg groups compared to patients treated with the other XELJANZ doses. However, there was no difference in the proportion of responders among patients treated with XELJANZ 3, 5, 10, 15 mg twice daily or 20 mg once daily doses.

Figure 4: Proportion of Patients with ACR20 Response at Month 3 in Dose-Ranging Studies 1 and 2



* XELJANZ twice daily dosing in mg, except for 20 mg which is once daily dosing in mg.
PBO is placebo; ADA is adalimumab 40 mg subcutaneous injection every other week.

Study 1 was a dose-ranging monotherapy trial not designed to provide comparative effectiveness data and should not be interpreted as evidence of superiority to adalimumab.

Confirmatory Trials

Study RA-I (NCT00814307) was a 6-month monotherapy trial in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic or biologic) received XELJANZ 5 or 10 mg twice daily or placebo. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of XELJANZ 5 or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in Health Assessment Questionnaire – Disability Index (HAQ-DI), and rates of Disease Activity Score DAS28-4(ESR) less than 2.6.

Study RA-II (NCT00856544) was a 12-month trial in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a nonbiologic DMARD received XELJANZ 5 or 10 mg twice daily or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). At the Month 3 visit, nonresponding patients were advanced in a blinded fashion to a second predetermined treatment of XELJANZ 5 or 10 mg twice daily. At the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3, and rates of DAS28-4(ESR) less than 2.6 at Month 6.

Study RA-III (NCT00853385) was a 12-month trial in 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX. Patients received XELJANZ 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

Study RA-IV (NCT00847613) was a 2-year trial with a planned analysis at 1 year in which 797 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received XELJANZ 5 or 10 mg twice daily or placebo added to background MTX. Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

Study RA-V (NCT00960440) was a 6-month trial in which 399 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to at least one approved TNF blocking biologic agent received XELJANZ 5 or 10 mg twice daily or placebo added to background MTX. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of XELJANZ 5 or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, HAQ-DI, and DAS28-4(ESR) less than 2.6.

Study RA-VI (NCT01039688) was a 2-year monotherapy trial with a planned analysis at 1 year in which 952 MTX-naïve patients with moderate to severe active rheumatoid arthritis received XELJANZ 5 or 10 mg twice daily or MTX dose-titrated over 8 weeks to 20 mg weekly. The primary endpoints were mean change from baseline in van der Heijde-modified Total Sharp Score (mTSS) at Month 6 and the proportion of patients who achieved an ACR70 response at Month 6.

Clinical Response

The percentages of XELJANZ-treated patients achieving ACR20, ACR50, and ACR70 responses in Studies RA-I, IV, and V are shown in Table 7. Similar results were observed with Studies RA-II and III. In trials RA-I through V, patients treated with either 5 or 10 mg twice daily XELJANZ had higher ACR20, ACR50, and ACR70 response rates versus placebo, with or without background DMARD treatment, at Month 3 and Month 6. Higher ACR20 response rates were observed within 2 weeks compared to placebo. In the 12-month trials, ACR response rates in XELJANZ-treated patients were consistent at 6 and 12 months.

Table 7: Proportion of Patients with an ACR Response

	Percent of Patients								
	Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders[c]			MTX Inadequate Responders[d]			TNF Blocker Inadequate Responders[e]		
	Study I			Study IV			Study V		
N[a]	PBO	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg Twice Daily[f]	PBO + MTX	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX[f]	PBO + MTX	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX[f]
	122	243	245	160	321	316	132	133	134
ACR20									
Month 3	26%	59%	65%	27%	55%	67%	24%	41%	48%
Month 6	NA[b]	69%	70%	25%	50%	62%	NA	51%	54%
ACR50									
Month 3	12%	31%	36%	8%	29%	37%	8%	26%	28%
Month 6	NA	42%	46%	9%	32%	44%	NA	37%	30%
ACR70									
Month 3	6%	15%	20%	3%	11%	17%	2%	14%	10%
Month 6	NA	22%	29%	1%	14%	23%	NA	16%	16%

[a] N is number of randomized and treated patients.
[b] NA Not applicable, as data for placebo treatment is not available beyond 3 months in Studies I and V due to placebo advancement.
[c] Inadequate response to at least one DMARD (biologic or nonbiologic) due to lack of efficacy or toxicity.
[d] Inadequate response to MTX defined as the presence of sufficient residual disease activity to meet the entry criteria.
[e] Inadequate response to a least one TNF blocker due to lack of efficacy and/or intolerance.
[f] The recommended dose of XELJANZ is 5 mg twice daily.

In Study RA-IV, a greater proportion of patients treated with XELJANZ 5 mg or 10 mg twice daily plus MTX achieved a low level of disease activity as measured by a DAS28-4(ESR) less than 2.6 at 6 months compared to those treated with MTX alone (Table 8).

Table 8: Proportion of Patients with DAS28-4(ESR) Less Than 2.6 with Number of Residual Active Joints

	Study IV		
DAS28-4(ESR) Less Than 2.6	**Placebo + MTX**	**XELJANZ 5 mg Twice Daily + MTX**	**XELJANZ 10 mg Twice Daily + MTX***
	160	**321**	**316**
Proportion of responders at Month 6 (n)	1% (2)	6% (19)	13% (42)
Of responders, proportion with 0 active joints (n)	50% (1)	42% (8)	36% (15)
Of responders, proportion with 1 active joint (n)	0	5% (1)	17% (7)

	Study IV		
DAS28-4(ESR) Less Than 2.6	**Placebo + MTX** **160**	**XELJANZ 5 mg Twice Daily + MTX** **321**	**XELJANZ 10 mg Twice Daily + MTX*** **316**
Of responders, proportion with 2 active joints (n)	0	32% (6)	7% (3)
Of responders, proportion with 3 or more active joints (n)	50% (1)	21% (4)	40% (17)

*The recommended dose of XELJANZ is 5 mg twice daily.

The results of the components of the ACR response criteria for Study RA-IV are shown in Table 9. Similar results were observed for XELJANZ in Studies RA-I, II, III, V, and VI.

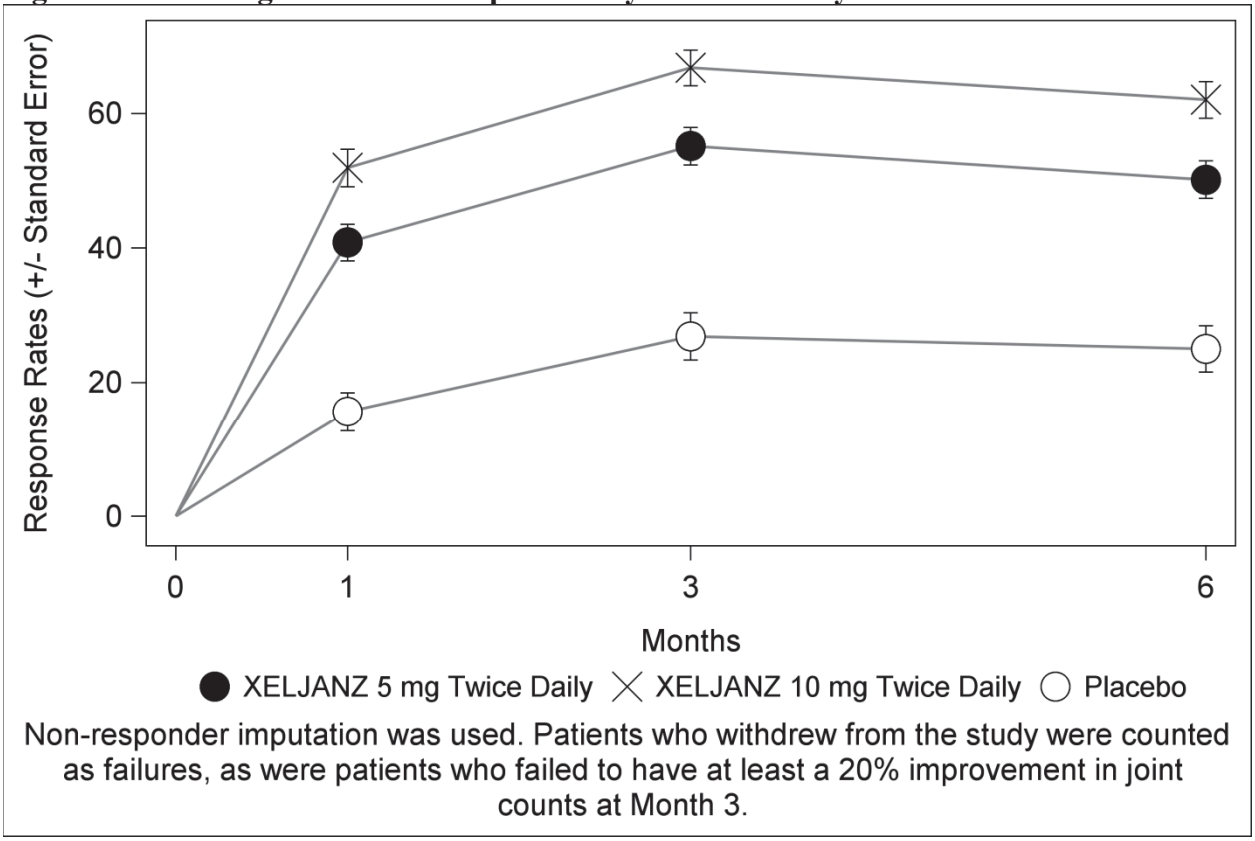
Table 9: Components of ACR Response at Month 3

	Study IV					
	XELJANZ 5 mg Twice Daily + MTX **N=321**		**XELJANZ 10 mg[d] Twice Daily + MTX** **N=316**		**Placebo + MTX** **N=160**	
Component (mean) [a]	Baseline	Month 3[a]	Baseline	Month 3[a]	Baseline	Month 3[a]
Number of tender joints (0-68)	24 (14)	13 (14)	23 (15)	10 (12)	23 (13)	18 (14)
Number of swollen joints (0-66)	14 (8)	6 (8)	14 (8)	6 (7)	14 (9)	10 (9)
Pain[b]	58 (23)	34 (23)	58 (24)	29 (22)	55 (24)	47 (24)
Patient global assessment[b]	58 (24)	35 (23)	57 (23)	29 (20)	54 (23)	47 (24)
Disability index (HAQ-DI)[c]	1.41 (0.68)	0.99 (0.65)	1.40 (0.66)	0.84 (0.64)	1.32 (0.67)	1.19 (0.68)
Physician global assessment[b]	59 (16)	30 (19)	58 (17)	24 (17)	56 (18)	43 (22)
CRP (mg/L)	15.3 (19.0)	7.1 (19.1)	17.1 (26.9)	4.4 (8.6)	13.7 (14.9)	14.6 (18.7)

[a] Data shown is mean (Standard Deviation) at Month 3.
[b] Visual analog scale: 0 = best, 100 = worst.
[c] Health Assessment Questionnaire Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[d] The recommended dose of XELJANZ is 5 mg twice daily.

The percent of ACR20 responders by visit for Study RA-IV is shown in Figure 5. Similar responses were observed for XELJANZ in Studies RA-I, II, III, V, and VI.

Figure 5: Percentage of ACR20 Responders by Visit for Study RA-IV



Radiographic Response

Two studies were conducted to evaluate the effect of XELJANZ on structural joint damage. In Study RA-IV and Study RA-VI, progression of structural joint damage was assessed radiographically and expressed as change from baseline in mTSS and its components, the erosion score and joint space narrowing score, at Months 6 and 12. The proportion of patients with no radiographic progression (mTSS change less than or equal to 0) was also assessed.

In Study RA-IV, XELJANZ 10 mg twice daily plus background MTX reduced the progression of structural damage compared to placebo plus MTX at Month 6. When given at a dose of 5 mg twice daily, XELJANZ exhibited similar effects on mean progression of structural damage (not statistically significant). These results are shown in Table 10. Analyses of erosion and joint space narrowing scores were consistent with the overall results.

In the placebo plus MTX group, 74% of patients experienced no radiographic progression at Month 6 compared to 84% and 79% of patients treated with XELJANZ plus MTX 5 or 10 mg twice daily.

In Study RA-VI, XELJANZ monotherapy inhibited the progression of structural damage compared to MTX at Months 6 and 12 as shown in Table 10. Analyses of erosion and joint space narrowing scores were consistent with the overall results.

In the MTX group, 55% of patients experienced no radiographic progression at Month 6 compared to 73% and 77% of patients treated with XELJANZ 5 or 10 mg twice daily.

Table 10: Radiographic Changes at Months 6 and 12

	Study IV				
	Placebo N=139 Mean (SD)[a]	**XELJANZ 5 mg Twice Daily N=277 Mean (SD) [a]**	**XELJANZ 5 mg Twice Daily Mean Difference from Placebo[b] (CI)**	**XELJANZ 10 mg Twice Daily[d] N=290 Mean (SD) [a]**	**XELJANZ 10 mg Twice Daily Mean Difference from Placebo[b] (CI)**
mTSS[c]					
Baseline	33 (42)	31 (48)	-	37 (54)	-
Month 6	0.5 (2.0)	0.1 (1.7)	-0.3 (-0.7, 0.0)	0.1 (2.0)	-0.4 (-0.8, 0.0)
	Study VI				
	MTX N=166 Mean (SD)[a]	**XELJANZ 5 mg Twice Daily N=346 Mean (SD) [a]**	**XELJANZ 5 mg Twice Daily Mean Difference from MTX[b] (CI)**	**XELJANZ 10 mg Twice Daily[d] N=369 Mean (SD) [a]**	**XELJANZ 10 mg Twice Daily Mean Difference from MTX[b] (CI)**
mTSS[c]					
Baseline	17 (29)	20 (40)	-	19 (39)	-
Month 6	0.8 (2.7)	0.2 (2.3)	-0.7 (-1.0, -0.3)	0.0 (1.2)	-0.8 (-1.2, -0.4)
Month 12	1.3 (3.7)	0.4 (3.0)	-0.9 (-1.4, -0.4)	0.0 (1.5)	-1.3 (-1.8, -0.8)

[a] SD = Standard Deviation
[b] Difference between least squares means XELJANZ minus placebo or MTX (95% CI = 95% confidence interval)
[c] Month 6 and Month 12 data are mean change from baseline.
[d] The recommended dose of XELJANZ is 5 mg twice daily.

Physical Function Response

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 and 10 mg twice daily demonstrated greater improvement from baseline in physical functioning compared to placebo at Month 3.

The mean (95% CI) difference from placebo in HAQ-DI improvement from baseline at Month 3 in Study RA-III was -0.22 (-0.35, -0.10) in patients receiving 5 mg XELJANZ twice daily and -0.32 (-0.44, -0.19) in patients receiving 10 mg XELJANZ twice daily. Similar results were obtained in Studies RA-I, II, IV and V. In the 12-month trials, HAQ-DI results in XELJANZ-treated patients were consistent at 6 and 12 months.

Other Health-Related Outcomes

General health status was assessed by the Short Form health survey (SF-36). In Studies RA-I, IV, and V, patients receiving XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily demonstrated greater improvement from baseline compared to placebo in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 at Month 3.

14.2 Psoriatic Arthritis

The XELJANZ clinical development program to assess efficacy and safety included 2 multicenter, randomized, double-blind, placebo-controlled confirmatory trials in 816 patients 18 years of age and older (PsA-I and PsA-II). Although other doses have been studied, the recommended dose of XELJANZ is 5 mg twice daily. All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender/painful joints and at least 3 swollen joints, and active plaque psoriasis. Patients randomized and treated across the 2 clinical trials represented different psoriatic arthritis subtypes at screening, including <5 joints or asymmetric involvement (21%), ≥5 joints involved (90%), distal interphalangeal (DIP) joint involvement (61%), arthritis mutilans (8%), and spondylitis (19%). Patients in these clinical trials had a diagnosis of psoriatic arthritis for a mean (SD) of 7.7 (7.2) years. At baseline, 80% and 53% of patients had enthesitis and dactylitis, respectively. At baseline, all patients were required to receive treatment with a stable dose of a nonbiologic DMARD (79% received methotrexate, 13% received sulfasalazine, 7% received leflunomide, 1% received other nonbiologic DMARDs). In both clinical trials, the primary endpoints were the ACR20 response and the change from baseline in HAQ-DI at Month 3.

Study PsA-I was a 12-month clinical trial in 422 patients who had an inadequate response to a nonbiologic DMARD (67% and 33% were inadequate responders to 1 nonbiologic DMARD and ≥2 nonbiologic DMARDs, respectively) and who were naïve to treatment with a TNF blocker. Patients were randomized in a 2:2:2:1:1 ratio to receive XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, adalimumab 40 mg subcutaneously once every 2 weeks, placebo to XELJANZ 5 mg twice daily treatment sequence, or placebo to XELJANZ 10 mg twice daily treatment sequence, respectively; study drug was added to background nonbiologic DMARD treatment. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a predetermined XELJANZ dose of 5 mg or 10 mg twice daily. Study PsA-I was not designed to demonstrate noninferiority or superiority to adalimumab.

Study PsA-II was a 6-month clinical trial in 394 patients who had an inadequate response to at least 1 approved TNF blocker (66%, 19%, and 15% were inadequate responders to 1 TNF blocker, 2 TNF blockers and ≥3 TNF blockers, respectively). Patients were randomized in a 2:2:1:1 ratio to receive XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, placebo to XELJANZ 5 mg twice daily treatment sequence, or placebo to XELJANZ 10 mg twice daily treatment sequence, respectively; study drug was added to background nonbiologic DMARD treatment. At the Month 3 visit, placebo patients were advanced in a blinded fashion to a predetermined XELJANZ dose of 5 mg or 10 mg twice daily as in Study PsA-I.

Clinical Response

At Month 3, patients treated with either XELJANZ 5 mg or 10 mg twice daily had higher ($p \leq 0.05$) response rates versus placebo for ACR20, ACR50, and ACR70 in Study PsA-I and for ACR20 and ACR50 in Study PsA-II; ACR70 response rates were also higher for both XELJANZ 5 mg or 10 mg twice daily versus placebo in Study PsA-II, although the differences versus placebo were not statistically significant ($p > 0.05$) (Tables 11 and 12).

Table 11: Proportion of Patients with an ACR Response in Study PsA-I* [Nonbiologic DMARD Inadequate Responders (TNF Blocker-Naïve)]

Treatment Group	Placebo	XELJANZ 5 mg Twice Daily		XELJANZ 10 mg[b] Twice Daily	
N[a]	105	107		104	
	Response Rate	Response Rate	Difference (%) 95% CI from Placebo	Response Rate	Difference (%) 95% CI from Placebo
Month 3					
ACR20	33%	50%	17.1 (4.1, 30.2)	61%	27.2 (14.2, 40.3)
ACR50	10%	28%	18.5 (8.3, 28.7)	40%	30.9 (19.9, 41.8)
ACR70	5%	17%	12.1 (3.9, 20.2)	14%	9.7 (1.8, 17.6)

Subjects with missing data were treated as non-responders.
* Subjects received one concomitant nonbiologic DMARD.
[a] N is number of randomized and treated patients.
[b] The recommended dose of XELJANZ is 5 mg twice daily.

Table 12: Proportion of Patients with an ACR Response in Study PsA-II* (TNF Blocker Inadequate Responders)

Treatment Group	Placebo	XELJANZ 5 mg Twice Daily		XELJANZ 10 mg[b] Twice Daily	
N[a]	131	131		132	
	Response Rate	Response Rate	Difference (%) 95% CI from Placebo	Response Rate	Difference (%) 95% CI from Placebo
Month 3					
ACR20	24%	50%	26.0 (14.7, 37.2)	47%	23.3 (12.1, 34.5)
ACR50	15%	30%	15.3 (5.4, 25.2)	28%	13.5 (3.8, 23.3)
ACR70	10%	17%	6.9 (-1.3, 15.1)	14%	4.5 (-3.4, 12.4)

Subjects with missing data were treated as non-responders.
* Subjects received one concomitant nonbiologic DMARD.
[a] N is number of randomized and treated patients.
[b] The recommended dose of XELJANZ is 5 mg twice daily.

Improvements from baseline in the ACR response criteria components for both studies are shown in Table 13.

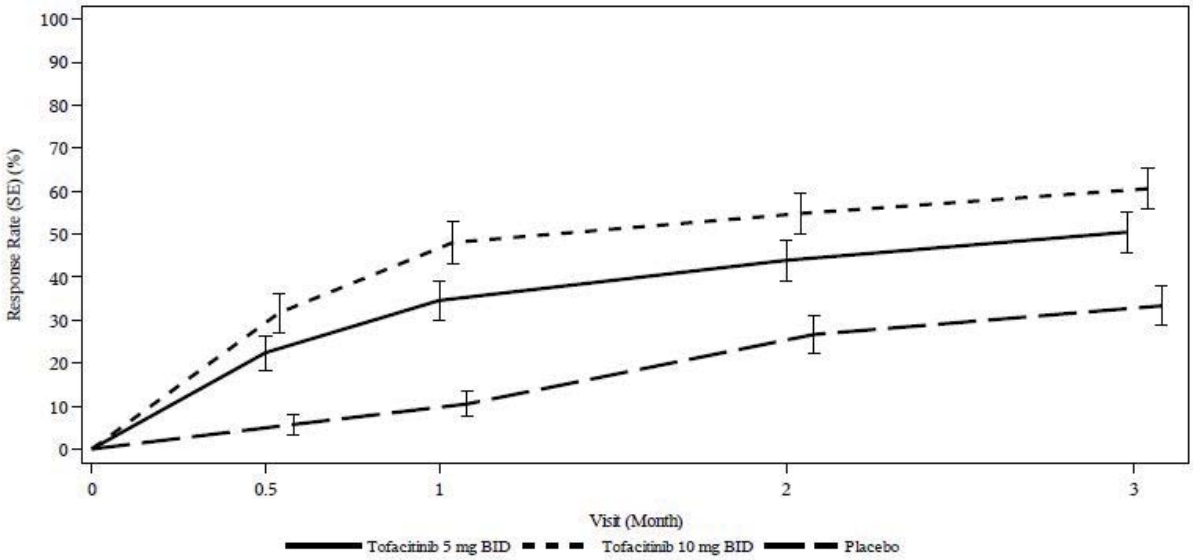
Table 13: Components of ACR Response at Baseline and Month 3 in Studies PsA-I and PsA-II

	Nonbiologic DMARD Inadequate Responders (TNF Blocker-Naïve)			TNF Blocker Inadequate Responders		
	Study PsA-I*			Study PsA-II*		
Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg[d] Twice Daily	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg[d] Twice Daily
N at Baseline	105	107	104	131	131	132
ACR Component[a]						
Number of tender/painful joints (0-68)						
Baseline	20.6	20.5	20.3	19.8	20.5	25.5
Month 3	14.6	12.2	9.9	15.1	11.5	14.5
Number of swollen joints (0-66)						
Baseline	11.5	12.9	11.7	10.5	12.1	12.8
Month 3	7.1	6.3	4.3	7.7	4.8	6.1
Patient assessment of arthritis pain[b]						
Baseline	53.2	55.7	54.4	54.9	56.4	59.5
Month 3	44.7	34.7	28.5	48.0	36.1	38.1
Patient global assessment of arthritis[b]						
Baseline	53.9	54.7	53.6	55.8	57.4	58.5
Month 3	44.4	35.5	29.8	49.2	36.9	38.8
HAQ-DI[c]						
Baseline	1.11	1.16	1.08	1.25	1.26	1.37
Month 3	0.95	0.81	0.71	1.09	0.88	1.03
Physician's Global Assessment of Arthritis[b]						
Baseline	53.8	54.6	55.2	53.7	53.5	55.8
Month 3	35.4	29.5	23.6	36.4	27.0	25.6
CRP (mg/L)						
Baseline	10.4	10.5	8.1	12.1	13.8	15.0
Month 3	8.6	4.0	2.7	11.4	7.7	7.3

* Subjects received one concomitant nonbiologic DMARD.
[a] Data shown are mean value at baseline and at Month 3.
[b] Visual analog scale (VAS): 0 = best, 100 = worst.
[c] HAQ-DI = Health Assessment Questionnaire – Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[d] The recommended dose of XELJANZ is 5 mg twice daily.

The percentage of ACR20 responders by visit for Study PsA-I is shown in Figure 6. Similar responses were observed in Study PsA-II. In both studies, improvement in ACR20 response on XELJANZ was observed at the first visit after baseline (Week 2).

Figure 6: Percentage of ACR20 Responders by Visit Through Month 3 in Study PsA-I*



BID=twice daily; SE=standard error.
Subjects with missing data were treated as non-responders.
* Subjects received one concomitant nonbiologic DMARD.
The recommended dose of XELJANZ is 5 mg twice daily.

In patients with active psoriatic arthritis evidence of benefit in enthesitis and dactylitis was observed with XELJANZ treatment.

Physical Function

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg or 10 mg twice daily demonstrated significantly greater improvement ($p \leq 0.05$) from baseline in physical functioning compared to placebo at Month 3 (Table 14).

Table 14: Change from Baseline in HAQ-DI in Studies PsA-I and PsA-II

	Least Squares Mean Change from Baseline In HAQ-DI at Month 3					
	Nonbiologic DMARD Inadequate Responders[b] (TNF Blocker-Naïve)			TNF Blocker Inadequate Responders[c]		
	Study PsA-I[*]			Study PsA-II[*]		
Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg[d] Twice Daily	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg[d] Twice Daily
N[a]	104	107	104	131	129	132
LSM Change from Baseline	-0.18	-0.35	-0.40	-0.14	-0.39	-0.35
Difference from Placebo (95% CI)	-	-0.17 (-0.29, -0.05)	-0.22 (-0.34, -0.10)	-	-0.25 (-0.38, -0.13)	-0.22 (-0.34, -0.09)

* Subjects received one concomitant nonbiologic DMARD.
[a] N is the total number of subjects in the statistical analysis.
[b] Inadequate response to at least one nonbiologic DMARD due to lack of efficacy and/or intolerability.
[c] Inadequate response to at least one TNF blocker due to lack of efficacy and/or intolerability.
[d] The recommended dose of XELJANZ is 5 mg twice daily.

In Study PsA-I, the HAQ-DI responder rate (response defined as having improvement from baseline of ≥0.35) at Month 3 was 53% in patients receiving XELJANZ 5 mg twice daily, 55% in patients receiving XELJANZ 10 mg twice daily, and 31% in patients receiving placebo. Similar responses were observed in Study PsA-II.

Other Health-Related Outcomes

General health status was assessed by the Short Form health survey (SF-36). In Studies PsA-I and PsA-II, patients receiving XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily had greater improvement from baseline compared to placebo in Physical Component Summary (PCS) score, but not in Mental Component Summary (MCS) score at Month 3. Patients receiving XELJANZ 5 mg twice daily reported consistently greater improvement relative to placebo in the domains of Physical Functioning, Bodily Pain, Vitality, and Social Functioning, but not in Role Physical, General Health, Role Emotional, or Mental Health.

Radiographic Response

Treatment effect on inhibition of radiographic progression in psoriatic arthritis could not be established from the results of Study PsA-I.

14.3 Ulcerative Colitis

Induction Trials (Study UC-I [NCT01465763] and Study UC-II [NCT01458951])

In two identical induction trials (UC-I and UC-II), 1139 patients were randomized (598 and 541 patients, respectively) to XELJANZ 10 mg twice daily or placebo with a 4:1 treatment allocation ratio. These trials included adult patients with moderately to severely active UC (total Mayo score of 6 to 12, with an endoscopy subscore of at least 2, and rectal bleeding subscore of at least 1) and who had failed or were intolerant to at least 1 of the following treatments: oral or intravenous corticosteroids, azathioprine, 6-MP or TNF blocker.

The disease activity was assessed by Mayo scoring index (0 to 12) which consists of four subscores (0 to 3 for each subscore): stool frequency, rectal bleeding, findings on endoscopy, and physician global assessment. An endoscopy subscore of 2 was defined by marked erythema, absent vascular pattern, any friability, and erosions; an endoscopy subscore of 3 was defined by spontaneous bleeding and ulceration.

Patients were permitted to use stable doses of oral aminosalicylates and corticosteroids (prednisone daily dose up to 25 mg equivalent). Concomitant immunosuppressants (oral immunomodulators or biologic therapies) were not permitted for UC patients during these studies.

A total of 52%, 73% and 72% of patients had previously failed or were intolerant to TNF blockers (51% in Study UC-1 and 52% in Study UC-II), corticosteroids (75% in Study UC-I and 71% in Study UC-II), and/or immunosuppressants (74% in Study UC-I and 70% in Study UC-II), respectively.

Oral corticosteroids were received as concomitant treatment for UC by 47% of patients (45% in Study UC-I and 48% in Study UC-II) and 71% were receiving concomitant aminosalicylates as treatment for UC (71% in Study UC-I, and 72% in Study UC-II). The baseline clinical characteristics were generally similar between the XELJANZ treated patients and patients receiving placebo.

The primary endpoint of Study UC-I and Study UC-II was the proportion of patients in remission at Week 8, and the key secondary endpoint was the proportion of patients with improvement of endoscopic appearance of the mucosa at Week 8.

The efficacy results of Study UC-I and Study UC-II based on the centrally read endoscopy results are shown in Table 15.

Table 15: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 8 (Induction Study UC-I and Study UC-II, Central Endoscopy Read)

Study UC-I			
Endpoint	**Placebo**	**XELJANZ 10 mg Twice Daily**	**Treatment Difference versus Placebo (95% CI)**
Remission at Week 8[a]			
Total Population	N=122 8%	N=476 18%	10%* (4.3, 16.3)
With Prior TNF Blocker Failure[b]	N=64 2%	N=243 11%	
Without Prior TNF Blocker Failure[3]	N=58 16%	N=233 26%	

Improvement of endoscopic appearance of the mucosa at Week 8[4]			
Total Population	N=122 16%	N=476 31%	16%** (8.1, 23.4)
With Prior TNF Blocker Failure[b]	N=64 6%	N=243 23%	
Without Prior TNF Blocker Failure[c]	N=58 26%	N=233 40%	
Study UC-II			
Endpoint	**Placebo**	**XELJANZ 10 mg Twice Daily**	**Treatment Difference (95% CI)**
Remission at Week 8[a]			
Total Population	N=112 4%	N=429 17%	13%** (8.1, 17.9)
With Prior TNF Blocker Failure[b]	N=60 0%	N=222 12%	
Without Prior TNF Blocker Failure[c]	N=52 8%	N=207 22%	
Improvement of endoscopic appearance of the mucosa at Week 8[d]			
Total Population	N=112 12%	N-429 28%	17%** (9.5, 24.1)
With Prior TNF Blocker Failure[b]	N=60 7%	N=222 22%	
Without Prior TNF Blocker Failure[c]	N=52 17%	N=207 36%	

* p-value <0.01, ** p-value <0.001.
CI = Confidence interval; N = number of patients in the analysis set; TNF = tumor necrosis factor
[a] Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.
[b] Prior TNF blocker failure was defined in this program as inadequate response, loss of response, or intolerance to TNF blocker therapy.
[c] Patients in this group had failed one or more conventional therapies (corticosteroid, azathioprine, 6-mercaptopurine) but did not have history of prior failure of TNF blocker therapy.
[d] Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).

Clinical Response at Week 8

Clinical response was defined as a decrease from baseline in Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the subscore for rectal bleeding of ≥1 point or absolute subscore for rectal bleeding of 0 or 1.

Clinical response was observed in 60% of patients treated with XELJANZ 10 mg twice daily compared to 33% of placebo patients in Study UC-I and 55% compared to 29% in Study UC-II.

Normalization of the Endoscopic Appearance of the Mucosa at Week 8
Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0 and was observed in 7% of patients treated with XELJANZ 10 mg twice daily compared to 2% of placebo patients in both Studies UC-I and UC-II.

Rectal Bleeding and Stool Frequency
Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in patients treated with XELJANZ.

Maintenance Trial (Study UC-III [NCT01458574])
A total of 593 patients who completed the induction trials (UC-I or UC-II) and achieved clinical response were re-randomized with 1:1:1 treatment allocation ratio to XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, or placebo for 52 weeks in Study UC-III. As in the induction trials, patients were permitted to use stable doses of oral aminosalicylates; however, corticosteroid tapering was required upon entrance into this study for patients who were receiving corticosteroids at baseline. Concomitant immunosuppressants (oral immunomodulators or biologic therapies) were not permitted.

At baseline of Study UC-III:

- 179 (30%) patients were in remission
- 289 (49%) patients were receiving oral corticosteroids
- 265 (45%), 445 (75%), and 413 (70%) patients had previously failed or were intolerant to TNF blocker therapy, corticosteroids, and immunosuppressants, respectively.

The primary endpoint was the proportion of patients in remission at Week 52. There were 2 key secondary endpoints: the proportion of patients with improvement of endoscopic appearance at Week 52, and the proportion of patients with sustained corticosteroid-free remission at both Week 24 and Week 52 among patients in remission at baseline of Study UC-III.

The efficacy results of Study UC-III based on the centrally read endoscopy results are summarized in Table 16.

Table 16: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints in Maintenance Study UC-III (Central Endoscopy Read)

				Treatment Difference versus Placebo (95% CI)	
Endpoint	**Placebo**	**XELJANZ 5 mg Twice Daily**	**XELJANZ 10 mg Twice Daily**	**XELJANZ 5 mg Twice Daily**	**XELJANZ 10 mg Twice Daily**
Remission at Week 52[a]					
Total Population	N=198 11%	N=198 34%	N=197 41%	23%* (15.3, 31.2)	30%* (21.4, 37.6)
With Prior TNF Blocker Failure[b]	N=89 11%	N=83 24%	N=93 37%		
Without Prior TNF Blocker Failure[c]	N=109 11%	N=115 42%	N=104 44%		
Improvement of endoscopic appearance of the mucosa at Week 52[d]					
Total Population	N=198 13%	N=198 37%	N=197 46%	24%* (16.0, 32.5)	33%* (24.2, 41.0)
With Prior TNF Blocker Failure[b]	N=89 12%	N=83 30%	N=93 40%		
Without Prior TNF Blocker Failure[c]	N=109 14%	N=115 43%	N=104 51%		
Sustained corticosteroid-free remission at both Week 24 and Week 52 among patients in remission at baseline[e]					
Total Population	N=59 5%	N=65 35%	N=55 47%	30%* (17.4, 43.2)	42%* (27.9, 56.5)
With Prior TNF Blocker Failure[b]	N=21 5%	N=18 22%	N=18 39%		
Without Prior TNF Blocker Failure[c]	N=38 5%	N=47 40%	N=37 51%		

* p-value <0.0001.
CI = Confidence interval; N = number of patients in the analysis set; TNF = tumor necrosis factor.
[a] Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.
[b] Prior TNF blocker failure was defined in this program as inadequate response, loss of response, or intolerance to TNF blocker therapy.
[c] Patients in this group had failed one or more conventional therapies (corticosteroid, azathioprine, 6-mercaptopurine) but did not have history of prior failure of TNF blocker therapy.
[d] Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).
[e] Sustained corticosteroid-free remission was defined as being in remission and not taking corticosteroids for at least 4 weeks prior to the visit at both Week 24 and Week 52.

Maintenance of Clinical Response

Maintenance of clinical response was defined as the proportion of patients who met the definition of clinical response (defined as a decrease from the induction study (UC-I, UC-II)

baseline Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the rectal bleeding subscore of ≥1 point or rectal bleeding subscore of 0 or 1) at both Baseline and Week 52 of Study UC-III.

Maintenance of clinical response was observed in 52% in the XELJANZ 5 mg twice daily group and 62% in the XELJANZ 10 mg twice daily group compared to 20% of placebo patients.

Maintenance of Remission (Among Patients in Remission at Baseline)
In the 179 patients who were in remission at baseline of Study UC-III (N = 59 for placebo, N = 65 for XELJANZ 5 mg twice daily, N = 55 for XELJANZ 10 mg twice daily), 46% in the XELJANZ 5 mg twice daily group and 56% in the XELJANZ 10 mg twice daily group maintained remission at Week 52 compared to 10% of placebo patients.

Normalization of the Endoscopic Appearance of the Mucosa
Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0 and was observed at Week 52 in 15% of patients in the XELJANZ 5 mg twice daily group and 17% of patients in the XELJANZ 10 mg twice daily group compared to 4% of placebo patients.

Open-label Extension Study (Study UC-IV [NCT01470612])
In Study UC-IV, 914 patients were treated of which 156 received 5 mg twice daily and 758 received 10 mg twice daily.

Of the 905 patients who were assigned to XELJANZ 10 mg twice daily in the 8-week induction studies (Study UC-I or Study UC-II), 322 patients completed the induction studies but did not achieve clinical response. Of these 322 patients, 291 continued to receive XELJANZ 10 mg twice daily (unblinded) and had available data after an additional 8 weeks in Study UC-IV. After 8 additional weeks (a total of 16 weeks treatment), 149 patients achieved clinical response, and 25 patients achieved remission (based on central endoscopy read). Among those 144 patients who achieved clinical response by 16 weeks and had available data at Week 52, 65 patients achieved remission (based on local endoscopy read) after continued treatment with XELJANZ 10 mg twice daily for 52 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

	Bottle Size (number of tablets)	**NDC Number**
XELJANZ **5 mg tofacitinib tablets** White, round, immediate-release film-coated tablets, debossed with “Pfizer” on one side, and “JKI 5” on the other side	28	NDC 0069-1001-03
	60	NDC 0069-1001-01
	180	NDC 0069-1001-02

	Bottle Size (number of tablets)	NDC Number
XELJANZ **10 mg tofacitinib tablets** Blue, round, immediate-release film-coated tablets, debossed with "Pfizer" on one side, and "JKI 10" on the other side	28	NDC 0069-1002-03
	60	NDC 0069-1002-01
	180	NDC 0069-1002-02
XELJANZ XR **11 mg tofacitinib tablets** Pink, oval, extended-release tablet with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet	14	NDC 0069-0501-14
	30	NDC 0069-0501-30

Store XELJANZ/XELJANZ XR at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature].

XELJANZ/XELJANZ XR
Do not repackage.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Serious Infections

Inform patients that XELJANZ/XELJANZ XR may lower the ability of their immune system to fight infections. Advise patients not to start taking XELJANZ/XELJANZ XR if they have an active infection. Instruct patients to contact their healthcare provider immediately during treatment if symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment *[see Warnings and Precautions (5.1)]*.

Advise patients that the risk of herpes zoster, some cases of which can be serious, is increased in patients treated with XELJANZ *[see Warnings and Precautions (5.1)]*.

Malignancies and Lymphoproliferative Disorders

Inform patients that XELJANZ/XELJANZ XR may increase their risk of certain cancers, and that lymphoma and other cancers have been observed in patients taking XELJANZ. Instruct patients to inform their healthcare provider if they have ever had any type of cancer *[see Warnings and Precautions (5.2)]*.

Important Information on Laboratory Abnormalities
Inform patients that XELJANZ/XELJANZ XR may affect certain lab test results, and that blood tests are required before and during XELJANZ/XELJANZ XR treatment *[see Warnings and Precautions (5.4)]*.

Pregnancy
Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy. Inform patients that Pfizer has a registry for pregnant women who have taken XELJANZ/XELJANZ XR during pregnancy. Advise patients to contact the registry at 1-877-311-8972 to enroll *[see Use in Specific Populations (8.1)]*.

Lactation
Advise women not to breastfeed during treatment with XELJANZ/XELJANZ XR and for at least 18 hours after the last dose of XELJANZ or 36 hours after the last dose of XELJANZ XR *[see Use in Specific Populations (8.2)]*.

Infertility
Advise females of reproductive potential that XELJANZ/XELJANZ XR may impair fertility *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]* It is not known if this effect is reversible.

Residual Tablet Shell
Patients receiving XELJANZ XR may notice an inert tablet shell passing in the stool or via colostomy. Patients should be informed that the active medication has already been absorbed by the time the patient sees the inert tablet shell.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

LAB-0445-13.0

Medication Guide

XELJANZ (ZEL' JANS')
(tofacitinib)
tablets, for oral use

XELJANZ XR (ZEL' JANS' EKS-AHR)
(tofacitinib)
extended-release tablets, for oral use

What is the most important information I should know about XELJANZ/XELJANZ XR?
XELJANZ/XELJANZ XR may cause serious side effects including:

1. Serious infections. XELJANZ/XELJANZ XR is a medicine that affects your immune system. XELJANZ/XELJANZ XR can lower the ability of your 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.

- Your healthcare provider should test you for TB before starting XELJANZ/XELJANZ XR and during treatment.
- Your healthcare provider should monitor you closely for signs and symptoms of TB infection during treatment with XELJANZ/XELJANZ XR.

You should not start taking XELJANZ/XELJANZ XR if you have any kind of infection unless your healthcare provider tells you it is okay. You may be at a higher risk of developing shingles (herpes zoster).

People taking the higher dose (10 mg twice daily) of XELJANZ have a higher risk of serious infections and shingles.

Before starting XELJANZ/XELJANZ XR, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweating, or chills
  - cough
  - blood in phlegm
  - warm, red, or painful skin or sores on your body
  - burning when you urinate or urinating more often than normal
  - muscle aches
  - shortness of breath
  - weight loss
  - diarrhea or stomach pain
  - feeling very tired
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, chronic lung disease, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use XELJANZ/XELJANZ XR. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B or C.

After starting XELJANZ/XELJANZ XR, call your healthcare provider right away if you have any symptoms of an infection. XELJANZ/XELJANZ XR can make you more likely to get infections or make worse any infection that you have.

2. Cancer and immune system problems. XELJANZ/XELJANZ XR may increase your risk of certain cancers by changing the way your immune system works.

- Lymphoma and other cancers including skin cancers can happen in patients taking XELJANZ/XELJANZ XR. People taking the higher dose (10 mg twice daily) of XELJANZ have a higher risk of skin cancers. Tell your healthcare provider if you have ever had any type of cancer.
- 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).

3. Tears (perforation) in the stomach or intestines.

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large

intestine) or ulcers in your stomach or intestines. 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.
Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

4. **Changes in certain laboratory test results.** Your healthcare provider should do blood tests before you start receiving XELJANZ/XELJANZ XR and while you take XELJANZ/XELJANZ XR to check for the following side effects:
   - **changes in lymphocyte counts.** Lymphocytes are white blood cells that help the body fight off infections.
   - **low neutrophil counts**. Neutrophils are white blood cells that help the body fight off infections.
   - **low red blood cell count**. This may mean that you have anemia, which may make you feel weak and tired.

Your healthcare provider should routinely check certain liver tests.
You should not receive XELJANZ/XELJANZ XR if your lymphocyte count, neutrophil count, or red blood cell count is too low or your liver tests are too high.
Your healthcare provider may stop your XELJANZ/XELJANZ XR treatment for a period of time if needed because of changes in these blood test results.
You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving XELJANZ/XELJANZ XR, and as needed after that. Normal cholesterol levels are important to good heart health.
See "What are the possible side effects of XELJANZ/XELJANZ XR?" for more information about side effects.

What is XELJANZ/XELJANZ XR?
XELJANZ/XELJANZ XR 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 whom methotrexate did not work well.
XELJANZ/XELJANZ XR is used to treat adults with active psoriatic arthritis in which methotrexate or other similar medicines called nonbiologic disease-modifying antirheumatic drugs (DMARDs) did not work well.
XELJANZ is used to treat adults with moderately to severely active ulcerative colitis.
It is not known if XELJANZ/XELJANZ XR is safe and effective in people with Hepatitis B or C.
XELJANZ/XELJANZ XR is not recommended for people with severe liver problems.
It is not known if XELJANZ/XELJANZ XR is safe and effective in children.

What should I tell my healthcare provider before taking XELJANZ/XELJANZ XR?
Before taking XELJANZ/XELJANZ XR, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection. See "What is the most important information I should know about XELJANZ/XELJANZ XR?"
- have liver problems
- have kidney problems
- have any stomach area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines
- have had a reaction to tofacitinib or any of the ingredients in XELJANZ/XELJANZ XR
- have recently received or are scheduled to receive a vaccine. People who take XELJANZ/XELJANZ XR should not receive live vaccines. People taking XELJANZ/XELJANZ XR can receive non-live vaccines.
- plan to become pregnant or are pregnant. XELJANZ/XELJANZ XR may affect the ability of females to get pregnant. It is not known if this will change after stopping XELJANZ/XELJANZ XR. It is not known if XELJANZ/XELJANZ XR will harm an unborn baby.
  - **Pregnancy Registry:** Pfizer has a registry for pregnant women who take XELJANZ/XELJANZ XR. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking XELJANZ/XELJANZ XR, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.

- plan to breastfeed or are breastfeeding. You and your healthcare provider should decide if you will take XELJANZ/XELJANZ XR or breastfeed. You should not do both. After you stop your treatment with XELJANZ/XELJANZ XR do not start breastfeeding again until:
    - 18 hours after your last dose of XELJANZ or
    - 36 hours after your last dose of XELJANZ XR

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XELJANZ/XELJANZ XR and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- any other medicines to treat your rheumatoid arthritis, psoriatic arthritis, or ulcerative colitis. You should not take tocilizumab (Actemra®), etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), rituximab (Rituxan®), abatacept (Orencia®), anakinra (Kineret®), certolizumab (Cimzia®), golimumab (Simponi®), ustekinumab (Stelara®),secukinumab (Cosentyx®), vedolizumab (Entyvio®), azathioprine, cyclosporine, or other immunosuppressive drugs while you are taking XELJANZ or XELJANZ XR. Taking XELJANZ or XELJANZ XR with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XELJANZ/XELJANZ XR? Take XELJANZ/XELJANZ XR exactly as your healthcare provider tells you to take it.

- Take XELJANZ 2 times a day with or without food.
- Take XELJANZ XR 1 time a day with or without food for rheumatoid or psoriatic arthritis. **Do not take XELJANZ XR for ulcerative colitis.**
- Swallow XELJANZ XR tablets whole and intact. Do not crush, split, or chew.
- When you take XELJANZ XR, you may see something in your stool that looks like a tablet. This is the empty shell from the tablet after the medicine has been absorbed by your body.
- If you take too much XELJANZ/XELJANZ XR, call your healthcare provider or go to the nearest hospital emergency room right away.
- For the treatment of psoriatic arthritis, take XELJANZ/XELJANZ XR in combination with methotrexate, sulfasalazine or leflunomide as instructed by your healthcare provider.

What are possible side effects of XELJANZ/XELJANZ XR?

XELJANZ/XELJANZ XR may cause serious side effects, including:

- See “What is the most important information I should know about XELJANZ/XELJANZ XR?”
- **Hepatitis B or C activation infection** in people who carry the virus in their blood. If you are a carrier of the hepatitis B or C virus (viruses that affect the liver), the virus may become active while you use XELJANZ/XELJANZ XR. Your healthcare provider may do blood tests before you start treatment with XELJANZ/XELJANZ XR and while you are using XELJANZ/XELJANZ XR. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B or C infection:
    - feel very tired
    - little or no appetite
    - clay-colored bowel movements
    - chills
    - muscle aches
    - skin rash
    - skin or eyes look yellow
    - vomiting
    - fevers
    - stomach discomfort
    - dark urine

Common side effects of XELJANZ/XELJANZ XR in rheumatoid arthritis patients and psoriatic arthritis patients include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- diarrhea
- nasal congestion, sore throat, and runny nose (nasopharyngitis)
- high blood pressure (hypertension)

Common side effects of XELJANZ in ulcerative colitis patients include:

- nasal congestion, sore throat, and runny nose (nasopharyngitis)
- increased cholesterol levels
- headache
- upper respiratory tract infections (common cold, sinus infections)
- increased muscle enzyme levels
- rash
- diarrhea
- shingles (herpes zoster)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of XELJANZ/XELJANZ XR. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Pfizer at 1-800-438-1985.

How should I store XELJANZ/XELJANZ XR?

- Store XELJANZ/XELJANZ XR at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away medicine that is out of date or no longer needed.

Keep XELJANZ/XELJANZ XR and all medicines out of the reach of children.

General information about the safe and effective use of XELJANZ/XELJANZ XR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XELJANZ/XELJANZ XR for a condition for which it was not prescribed. Do not give XELJANZ/XELJANZ XR to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about XELJANZ/XELJANZ XR. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about XELJANZ/XELJANZ XR that is written for health professionals.

What are the ingredients in XELJANZ 5 mg?

Active ingredient: tofacitinib citrate

Inactive ingredients: croscarmellose sodium, HPMC 2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

What are the ingredients in XELJANZ 10 mg?

Active ingredient: tofacitinib citrate

Inactive ingredients: croscarmellose sodium, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/Indigo Carmine Aluminum Lake, HPMC 2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

What are the ingredients in XELJANZ XR?

Active ingredient: tofacitinib citrate

Inactive ingredients: cellulose acetate, copovidone, hydroxyethyl cellulose, hydroxypropyl cellulose, HPMC 2910/Hypromellose, magnesium stearate, red iron oxide, sorbitol, titanium dioxide, and triacetin. Printing ink contains ammonium hydroxide, ferrosoferric oxide/black iron, propylene glycol, and shellac glaze.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s018

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental New Drug Application (sNDA)
Application Number(s)	203214, supplement 18
Priority or Standard	Standard
Submit Date(s)	May 4, 2017
Received Date(s)	May 4, 2017
PDUFA Goal Date	June 4, 2018 (extended goal date due to major amendment)
Division/Office	Gastroenterology and Inborn Errors/ODE III
Review Completion Date	May 29, 2018
Established Name	Tofacitinib
(Proposed) Trade Name	XELJANZ
Pharmacologic Class	Janus associated kinase inhibitor
Code Name	CP-690,550
Applicant	PF PRISM C.V. C/o Pfizer, Inc.
Formulation(s)	Tablet
Dosing Regimen	XELJANZ 10 mg twice daily for at least 8 weeks; then 5 or 10 mg twice daily
Applicant Proposed Indication(s)/Population(s)	XELJANZ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis with an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine (6-MP) or TNF inhibitor therapy (b) (4) (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with moderately to severely active ulcerative colitis (UC)

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COA= Clinical Outcome Assessment
DEPI= Division of Epidemiology
DMEPA= Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatrics and Maternal Health
OB= Office of Biostatistics
OCP= Office of Clinical Pharmacology
OPDP= Office of Prescription Drug Promotion
OPQ= Office of Pharmaceutical Quality
OSE= Office of Surveillance and Epidemiology
OSI= Office of Scientific Investigations

Glossary

AC	Advisory Committee
AEs	Adverse Events
AESIs	Adverse Events of Special Interest
BLA	Biologics License Application
BID	Twice (two times) a Day
CFR	Code of Federal Regulations
CI	Confidence Interval
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EIM	Extraintestinal Manifestation
FAS	Full Analysis Set
FDA	Food and Drug Administration
GIDAC	Gastrointestinal Drugs Advisory Committee
IBD	Inflammatory Bowel Disease
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NME	New Molecular Entity
NRI	Non-responder Imputation
PD	Predominant Dose
PK	Pharmacokinetics
PMR	Postmarketing Requirement
PPAS	per Protocol Analysis Set
PREA	Pediatric Research Equity Act
QD	Once Daily
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
sNDA	Supplemental New Drug Application
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

1. Executive Summary

1.1 Product Introduction

XELJANZ (tofacitinib) is an orally administered small molecule which inhibits Janus associated kinases (JAK). JAKs are intracellular enzymes (tyrosine kinases) that transmit signals arising from cytokine or growth factor receptor interactions on the cellular membrane to influence the cellular processes of hematopoiesis and immune cell function. Modulation of JAK signaling pathways is thought to affect multiple cytokine pathways involved in inflammatory bowel disease (IBD).

Tofacitinib was approved (November 6, 2012) at a dosage of 5 mg BID for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had inadequate response or intolerance to methotrexate, and for adults with active psoriatic arthritis (December 14, 2017) who have had inadequate response or intolerance to methotrexate or other disease modifying antirheumatic drugs. For the treatment of ulcerative colitis (UC), the supplemental new drug application (sNDA) proposes tofacitinib dosage of 10 mg BID for the first 8 weeks (for "induction of remission") followed by 5 mg BID for long-term ("maintenance") use. In patients with refractory disease, including those with a history of prior TNF blocker failure, the Applicant proposes a dosage of 10 mg BID for both "induction" and "maintenance" therapy, which may be used continuously.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of this sNDA, to expand the indications of tofacitinib to include "treatment of adults with moderately to severely active ulcerative colitis (UC)." This sNDA included data from two phase 3 placebo-controlled induction trials (Studies 1094 and 1095) and a single phase 3 placebo-controlled maintenance trial (Study 1096). The primary endpoint was the proportion of patients achieving remission. Remission is a clinically important measure of how patients feel and function, and was determined by the Mayo score, which has been used in the past to support drug approvals for the treatment of UC. In the tofacitinib phase 3 trials, remission was defined by a total Mayo score of 2 or less, with no individual subscore greater than 1, and a rectal bleeding subscore of 0. Results from the induction trials indicated that tofacitinib 10 mg BID resulted in a greater proportion of patients in remission at week 8, as compared to placebo (18% vs 8% in Study 1094; and 17% vs 4% in Study 1095).

Results from the maintenance trial (Study 1096) indicated that treatment with both 10 mg BID and 5 mg BID dosages were superior to placebo in achieving remission at week 52 (41%, 34%, and 11% for 10 mg BID, 5 mg BID, and placebo, respectively).

The Applicant also assessed other clinically relevant secondary endpoints, including: 1) the improvement in the appearance of the intestinal mucosa on endoscopy; and 2) sustained corticosteroid-free remission (in Study 1096). The results of these key secondary endpoints were supportive of the primary endpoint results. Both doses of tofacitinib in the maintenance study were superior to placebo in achieving sustained corticosteroid-free remission (47%, 35%, and 5% for 10 mg BID, 5 mg BID, and placebo, respectively), and improvement in the endoscopic appearance of the mucosa at week 52 of treatment (46%, 37%, and 13% for 10 mg BID, 5 mg BID, and placebo, respectively). The Applicant has demonstrated that tofacitinib is effective for the treatment of moderately to severely active UC, and has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126 to support approval.

Benefit-Risk Summary and Assessment

Tofacitinib represents a novel mechanism of action and mode of administration in the treatment of moderately to severely active UC. The benefits of treatment are evident in the results of three phase 3 clinical trials conducted in support of this application. In two identical, placebo-controlled induction trials, tofacitinib 10 mg BID for 8 weeks was superior to placebo in inducing remission. In a single, 52-week, randomized, double-blind, placebo-controlled maintenance trial, both 5 mg BID and 10 mg BID were superior to placebo in achieving remission at week 52, sustained corticosteroid-free remission (remission at week 24 and week 52 in those in remission at week 8) and improvement in the endoscopic appearance of the mucosa.

The risks associated with tofacitinib treatment in UC patients are generally comparable to those associated with other potent immunosuppressant medications and biologic agents currently used to treat this condition. These risks are communicated in a pre-existing boxed warning, which notes serious and opportunistic infections (including tuberculosis), and the increased risk of malignancy (including lymphoma). The common adverse events associated with tofacitinib treatment included elevated cholesterol levels, headache, herpes zoster (HZ) infection, increased blood levels of creatinine phosphokinase, nasopharyngitis, rash, and upper respiratory tract infection. Serious adverse events (SAEs) occurred infrequently in the induction trials, and occurred more frequently in the placebo-treated patients (6%) compared to those treated with tofacitinib (4%). The most commonly occurring Serious Adverse Events (SAEs) were related to the gastrointestinal (GI) system organ class (SOC). Within the maintenance trial, SAEs occurred with similar frequency in patients treated with placebo (7%), tofacitinib 10 mg BID (6%), and tofacitinib 5 mg BID (5%). The most common AE leading to discontinuation was “worsening UC”.

The overall tofacitinib UC program design led to an imbalance of patient exposure between the 10 mg BID dose and the 5 mg BID dose long-term, which created uncertainties regarding the adequacy of the data to determine the relative safety of the long-term use of 10 mg BID dose compared with 5 mg BID dose. However, based on available data, a dose-dependent increased risk was noted for HZ (shingles), serious infections, non-melanoma skin cancer, and elevations in blood cholesterol levels. Due to the long latency of the development of malignancies, in general, and the relatively small number of patients who were exposed predominantly to the 5 mg BID dosage long-term, it is not possible to

accurately quantify the risks of developing malignancies (excluding non-melanoma skin cancer) and determine whether such risk is attributed to the higher tofacitinib dose.

Despite these uncertainties, the overall benefit-risk profile of tofacitinib is generally acceptable and supports approval of this agent to provide a new and novel mechanism of action and mode of administration for the treatment of patients with moderately to severely active UC. Post-marketing surveillance and additional studies will be conducted to further assess some of these uncertainties, but should not preclude approval based on the available evidence.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• UC is an idiopathic, inflammatory condition that primarily affects the colon. It is a chronic and progressive disease, that when untreated, will result in serious morbidity (i.e., chronic diarrhea, rectal bleeding, weight loss, and extra-intestinal manifestations of disease), which may necessitate surgery and carries potential mortality risk. UC patients have increased lifelong risk of colon cancer, which increases with long duration of active disease.	UC is a serious, chronic disease that requires effective, long-term therapy to manage.
Current Treatment Options	• There are a number of approved pharmacological agents across multiple drug classes. This section focuses on those appropriate for management of the more severely affected patients (not those with mild disease). • Patients with moderate to severe disease may be managed with conventional therapies (corticosteroids, azathioprine, 6-mercaptopurine) or biologic agents (TNF blockers, anti-integrin agents).	Tofacitinib would provide a new treatment option, with a novel mechanism of action, and oral route of administration, for patients with moderately to severely active UC. There is a need for new and novel therapies, as a significant proportion of patients remain

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Conventional orally administered immunomodulators (azathioprine, 6-mercaptopurine) are commonly used in clinical practice, but are used off-label for this indication. These agents take an average of 12 weeks to take effect, often necessitating combination therapy with systemic corticosteroids in the initial phase of treatment, an approach which increases the risk of infection and other serious complications. • All the approved biologic therapies for UC are administered parenterally. This requires training on self-administration of subcutaneous injection, or travel to an infusion center or hospital regularly for scheduled infusions. • Loss of response to biologic agents is common (for example, in patients treated with TNF blockers, 30-40% will lose initial response within 1 year[1]). • Adverse reactions associated with both conventional and biologic therapies are significant, and include risks of severe and opportunistic infections, and malignancies. • Biologic agents are associated with the risk of immunogenicity, which may over time result in loss of efficacy and/or hypersensitivity reactions (which can be severe and include anaphylaxis).	symptomatic with active disease despite therapy with the approved agents.

[1] D'Haens, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: When to Start, When to Stop, Which Drug to Choose, and How to Predict Response? American Journal of Gastroenterology. 106, 199-212 (2011). https://www.nature.com/articles/ajg2010392

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Treatment effects for biologic therapies are modest, leaving a significant proportion of patients inadequately treated despite trials of the best available therapies.	
Benefit	• Tofacitinib 10 mg BID for 8 weeks was demonstrated to be superior to placebo in inducing remission (treatment difference from placebo of 10% and 13% in Studies 1094 and 1095). • Both tofacitinib 10 mg BID and 5 mg BID were demonstrated to be superior to placebo in achieving remission by week 52 of treatment in Study 1096 (treatment difference from placebo of 30% and 23%, respectively). • Both tofacitinib 10 mg and 5 mg BID proved to be effective in maintaining a durable steroid-free remission over time in Study 1096 (treatment difference from placebo for sustained corticosteroid-free remission, defined as being in remission at week 24 and week 52 of treatment among patients in remission at week 8, was 42% and 30% for 10 mg BID and 5 mg BID, respectively). • Tofacitinib 10 mg BID induction resulted in improvement in the endoscopic appearance of the mucosa at week 8 (treatment difference from placebo was 16% and 17% in Study 1094 and 1095). • Tofacitinib 10 mg BID or 5 mg BID treatment in Study 1096 resulted in improvement of the endoscopic appearance of the mucosa (treatment difference from placebo of 33% and 24%, respectively) at week 52.	The application contains substantial evidence of the effectiveness of tofacitinib in the treatment of moderately to severely active UC. Efficacy was demonstrated on primary and key secondary endpoints. Results of analyses of additional secondary/exploratory endpoints were consistent with the primary efficacy results, and provided additional useful information to providers/patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The safety profile of tofacitinib is informed by experience in other inflammatory conditions, including rheumatoid arthritis (for which there are 6 years post-marketing experience) as well as psoriatic arthritis (recently approved). • The risks identified in the UC program are generally similar to those already included in the label for the other approved indications. • Risks are generally comparable to the risks associated with other biologics used for this condition, including risks of serious infection, opportunistic infection, and increased risk of malignancies. • Common adverse events which occurred in the UC program included elevated cholesterol levels, headache, HZ infection, increased blood levels of creatine phosphokinase, nasopharyngitis, rash, diarrhea, and upper respiratory tract infection. • A focus of this review was potential dose-dependent risks that may be associated with the higher 10 mg BID dose, when used long-term, in comparison to the lower 5 mg BID long-term dose. • Dose-dependent risks were identified for certain laboratory parameters (elevation of lipid levels), as well as for HZ (shingles) infections, serious infections, and non-melanoma skin cancers (NMSC). • Rare cases of thromboembolic events occurred in the UC program. There is a concern that increased rates of thromboembolic events may be associated broadly with the JAK inhibitor class of drugs. This is being further assessed through pre and post marketing surveillance by sponsors	Overall, the adverse reactions seen in the UC development program were consistent with what is known about the safety of tofacitinib from its use in other indications. The adverse reaction profile generally appears comparable to that of other biologics used to treat moderate to severe UC. In general, patients and providers have been willing to accept these risks, due to the morbidity of active UC disease, as well as the risks of long-term untreated UC or inadequately treated disease (including a greatly increased risk of colon cancer). While there is uncertainty regarding the magnitude of the risks for AEs that have long latency periods (i.e., malignancies), and the potential dose-dependent increased risk of these events, the available data suggest that the safety of tofacitinib is comparable to other approved advanced therapies for UC, and the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and Food and Drug Administration (FDA), across multiple development programs. • The size of safety database, relatively short duration of follow-up, and design of the program (most patients predominantly received 10 mg BID long-term, while few patients predominantly received 5 mg BID long-term) have created uncertainties regarding the long-term safety profile of tofacitinib. In particular, it is not possible at the time of this action, to accurately quantify the degree of increased risk of malignancy that may be associated with the long-term treatment with the 5 mg BID or 10 mg BID dose.	efficacy data suggest that the benefit/risk profile remains favorable to support approval.
Risk Management	• The Applicant has proposed a comprehensive risk management program, which includes the following components: ○ One-time letter to GI providers to inform dosing recommendations and risks associated with treatment ○ Package labeling for the 10 mg bottles will clearly state that 10 mg is for UC only. ○ Outreach to prescribers will emphasize use of tofacitinib consistent with approved indications and reinforce that 10 mg is for UC only. (b) (4) [redacted]	From data available at the time of sNDA submission, the safety profile of tofacitinib appears to be comparable to other biologic agents approved for UC treatment, and similar to the experience with tofacitinib in other indications. Uncertainties described above will be further elucidated in the context of the comprehensive risk management program that includes the post marketing studies described in this section.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4) ▪ Required safety, efficacy and phamacokinetics (PK) studies in pediatric patients 2 to 17 years of age with UC	The Agency believes that the available data support the approval of tofacitinib for treatment of moderately to severely active UC. A formal REMS program was not deemed necessary.

2. Therapeutic Context

2.1 Analysis of Condition

Ulcerative colitis (UC), an IBD, is a chronic, idiopathic, intermittently relapsing disease of the colonic mucosa. The disease typically commences in the rectum and may extend proximally in an uninterrupted pattern into the colon, involving the entire colon (pancolitis), the left colon, or may manifest as isolated rectosigmoid disease. The disease may present at any age. The peak incidence occurs in the most productive years of a patient's life, with the typical age of onset between the ages of 15 and 30.[2] UC may affect as many as 907,000 Americans.[3] The annual incidence rates (IRs) of UC in the United States range from 1.55 to 15.0 cases per 100,000 person-years (PYs), and the prevalence ranges from 117 to 238 cases per 100,000 persons.[4,5]

While the pathogenesis of UC is not completely understood, it involves the complex interaction of genetic predisposition, epithelial barrier defects, dysregulated host immune responses, and environmental factors.[6] Abnormal leukocyte trafficking to the GI mucosa is believed to be an important component leading to colonic inflammation. The clinical course tends to wax and wane with periods of remission interspersed with periods of active disease. Symptoms can vary depending on the severity of inflammation and extent of disease; patients with UC most commonly present with bloody diarrhea, rectal bleeding, tenesmus, urgency, abdominal pain, and passage of mucus. Disease of moderate to severe activity may be associated with systemic symptoms, including, fatigue, fever, anorexia, nausea, weight loss, and dehydration. Patients

[2] Loftus EV. Inflammatory Bowel Disease, 2007; 13(3):254-261.
[3] Crohn's and Colitis Foundation. What is ulcerative colitis [Internet]. Available from: http://www.ccfa.org/what-are-crohns-and-colitis/what-is-ulcerative-colitis/02 March 2017.
[4] Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. Inflamm Bowel Dis 2007; 13(3):254-61.
[5] Kappelman MD, Moore KR, Allen JK, Cook SF. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. Dig Dis Sci 2013;58 (2):519-25.
[6] Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. Lancet 2016:1-15.

may also experience symptoms from anemia and hypoalbuminemia, including dyspnea and peripheral edema.

The clinical burden of UC is not limited to the colon. UC is associated with many extraintestinal manifestations (EIMs), which have been reported to affect a wide variety of organ systems, most commonly joints, skin, eyes, kidneys, and hepatobiliary tract.[7] Renal manifestations of IBD may include nephrolithiasis, amyloidoisis, tubulointerstitial nephritis, and glomerulonephritis.[8] Other EIMs may include ocular lesions, skin lesions, arthritis, and primary sclerosing cholangitis. Up to 47% of patients with IBD have at least one EIM, and up to one-quarter of those IBD patients with EIMs suffer from more than one EIM. While some EIMs such as erythema nodosum and episcleritis occur concurrently with flares of UC, others, including pyoderma gangrenosum, uveitis, and primary sclerosing cholangitis, may occur and progress independent of the bowel inflammation. The former (those that occur with flares) typically improve with treatment of the bowel inflammation, while the latter do not respond to such therapy (medically or surgically). Given the commonness and diversity of these disorders, EIMs represent a considerable source of morbidity and overall UC disease burden.

UC is a serious progressive disease that can be life-threatening.[9] There is evidence that the disease extends proximally over time and may also be complicated by structural and functional damage beyond the mucosal layer, leading to giant pseudopolyposis, bridging fibrosis, dysmotility, anorectal incontinence, and possibly impaired gut permeability. Severe colitis can result in ischemic colitis requiring surgical colectomy, which is associated with significant morbidity, including recurrent pouchitis in up to 25% of patients, fecal incontinence, and female infertility.

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[7] Vavricka SR, Schoepfer A, Scharl M, et al. Extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2015; 21(8):1982-92.

[8] Oikonomou K, Kapsoritakis A, Eleftheriadis T, Stefanidis I, Potamianos S. Renal manifestations and complications of inflammatory bowel disease. Inflammatory bowel diseases 2011;17 (4):1034-45.

[9] Torres J, Billioud V, Sachar DB, et al. Ulcerative colitis as a progressive disease: the forgotten evidence. Inflamm Bowel Dis 2012; 18:1356-63.

This disease also carries with it an increased risk of colorectal cancer, partially due to chronic inflammation in patients with long-standing UC.[10] The goals of UC treatment are to induce and maintain remission of clinical symptoms and mucosal inflammation in order to improve quality of life, decrease hospitalizations, and reduce the risk of surgery and colon cancer.[11] With poorly controlled disease, the rate of developing colorectal cancer increases with time. Ten years after diagnosis, the cumulative probability of developing colorectal cancer is 2% and increases to 18% after 30 years. Overall, the risk of a patient with UC developing colorectal cancer is up to 23-fold higher compared with the general population.[12]

2.2 Analysis of Current Treatment Options

The goals of UC treatment include reducing signs and symptoms, reducing long-term corticosteroid use, achieving mucosal healing, reducing colon cancer risk, and improving patient quality of life. For the treatment of mild to moderate UC, oral aminosalicylates, topical 5-aminosalicylic acid (5-ASA), such as mesalamine suppository and enemas, or topical steroids may be used.[13] Topical medications are first-line treatment for distal colitis in those who are willing to use rectal therapy. Oral corticosteroids, such as budesonide or oral prednisone, may be required in patients who are refractory to topical therapies or who are systemically ill and require more rapid treatment. Mesalamines and budesonide are FDA-approved treatments for mild to moderate UC. Immunomodulators, such as azathioprine and 6-mercaptopurine, can be considered for patients unresponsive to or dependent on oral corticosteroids and for those experiencing disease relapse on aminosalicylates, but these are used off-label.

The currently approved systemic therapies for the treatment of moderate to severe UC are summarized in **Table 1** below.

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[10] Velayos FS, Loftus EV, Jr., Jess T, Harmsen WS, Bida J, Zinsmeister AR, et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: A case control study. Gastroenterology 2006;130 (7):1941-9.
[11] Hoentjen F, et al., Curr Gastroenterol Rep 2011;13:475-485.
[12] Triantafillidis JK, Nasioulas G, Kosmidis PA. Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies. Anticancer Res 2009;29 (7):2727-37.
[13] Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010;105 (3):501-23.

Table 1: Currently Approved Treatments for Moderately to Severely Active UC

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
Tumor Necrosis Factor Blocker (TNF blocker)				
Infliximab[14] (Remicade®) BLA 103772 Infliximab Biosimilars: Inflectra® (Infliximab-DYYB) BLA 124544 Ixifi® (Infliximab-QBTX) BLA 761072 Renflexis® (Infliximab-ABDA) BLA 761054	Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use	Intravenous (IV) 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	69% and 62% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved clinical response at week 8 39% and 32% of patients taking infliximab 5 mg/kg and 10 mg/kg, respectively, achieved clinical remission at week 8 35% and 34% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved clinical remission at week 54 62% and 59% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved mucosal healing[15] at week 8	Boxed Warning Serious infections (including tuberculosis, bacterial sepsis, invasive fungal infections [such as histoplasmosis], and opportunistic infections), malignancies (including lymphoma, hepatosplenic T-Cell lymphoma [HSTCL], melanoma), hepatitis B virus reactivation, hepatotoxicity, hypersensitivity (serious infusion reactions including anaphylaxis or serum sickness-like reactions), cytopenias, demyelinating disease, heart failure, lupus-like syndrome. Most common adverse reactions: infections (e.g., upper respiratory,

[14] Remicade Prescribing Information. 2 October 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103772s5373lbl.pdf

[15] Mucosal healing was defined as a Mayo score of 0 or 1 on endoscopy.

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
			45% and 47% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved mucosal healing at week 54	sinusitis, pharyngitis), infusion-related reactions, headache, and abdominal pain.
Adalimumab[16] (Humira®) BLA 125057 Adalimumab Biosimilars: Amjevita® (Adalimumab-ATTO) BLA 761024 Cyltezo® (Adalimumab-ADBM) BLA 761058	Inducing and sustaining clinical remission in adult patients with moderately to severely active UC who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6 mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have	SQ • Initial dose (Day 1): 160 mg • Second dose two weeks later (Day 15): 80 mg • Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.	Study I: 18.5% of patients receiving adalimumab 160/80 mg achieved clinical remission at week 8 Study II: 16.5% of patients receiving adalimumab 160/80 mg achieved clinical remission at week 8. 8.5% of patients receiving adalimumab 160/80 mg achieved sustained clinical remission (clinical remission at both weeks 8 and 52).	Boxed Warning Serious infections including tuberculosis [TB], bacterial sepsis, invasive fungal infections, and opportunistic infections, malignancies (including lymphoma, HSTCL, leukemia, NMSC), anaphylaxis or serious allergic reactions, hepatitis B virus reactivation, demyelinating disease, cytopenias/pancytopenia, heart failure, lupus-like syndrome. Most common adverse reactions: infections (upper respiratory, sinusitis), injection site reactions, headache and rash.

[16] Humira Prescribing Information. 28 April 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125057s402lbl.pdf

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
	lost response to or were intolerant to TNF blocker.			
Golimumab[17] (Simponi®) BLA 125289	Indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: 1. inducing and maintaining clinical response 2. improving endoscopic	SQ 200 mg initially administered by subcutaneous injection at week 0, followed by 100 mg at week 2 and then 100 mg every 4 weeks	Study I: 51% of patients receiving golimumab 200/100 mg achieved clinical response at week 6 18% of patients achieved clinical remission at week 6 42% of patients achieved improvement in endoscopic appearance of the mucosa at week 6 Study II: 50% of patients receiving golimumab 100 mg achieved clinical response through week 54 28% of patients achieved clinical remission at both week 30 and week 54	Boxed Warning Serious infections including TB, invasive fungal infections, hepatitis B reactivation, malignancies (including lymphoma, melanoma, and Merkel cell carcinoma), congestive heart failure, demyelinating disorders, hematologic cytopenias, Lupus-like syndrome, hypersensitivity reactions. Most common adverse reactions: upper respiratory tract infection, nasopharyngitis, and injection site reactions.

[17] Golimumab Prescribing Information. 22 Jun 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125289s133lbl.pdf

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
	appearance of the mucosa during induction 3. inducing clinical remission 4. achieving and sustaining clinical remission in induction responders			
Anti-integrin Agent				
Vedolizumab[18] (Entyvio®) BLA 125476	Adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were	IV 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter	Study I: 47% of patients achieved clinical response at week 6 17% of patients achieved clinical remission at week 6 Study II: 42% of patients achieved clinical remission at week 52 57% of patients achieved clinical response at both weeks 6 and 52 52% of patients achieved improvement of endoscopic appearance of the mucosa at week 52	Serious infections including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, cytomegaloviral colitis. Most common adverse reactions: nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection.

[18] Vedolizumab Prescribing Information. 20 May 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125476s000lbl.pdf

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
	intolerant to, or demonstrated dependence on corticosteroids			

Source: Reviewer's table, created from data in current Prescribing Information for the relevant products.

Therapeutic proteins by nature have a risk of immunogenicity associated with their use; thus, there remains a significant need for additional choices for safe, tolerable and efficacious therapies for moderate to severe UC.

3. Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Tofacitinib has been studied across multiple inflammatory conditions. The summary below includes regulatory history from other approved indications.

Rheumatoid Arthritis (RA)

Tofacitinib was approved at the 5 mg BID immediate release (IR) tablets dosage on November 6, 2012, under NDA 203214 for the treatment of adult patients with active moderate to severe rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate (MTX). Tofacitinib may be used as monotherapy or in combination with MTX or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs) for patients with RA. The extended release (XR) tablet, dosage of 11 mg once daily (QD), was approved on February 23, 2016, under NDA 208246. (b) (4)

(b) (4)

(b) (4)

At the time of approval, an FDA Risk Mitigation Strategy (REMS) was required to mitigate serious risks, including serious infection and malignancy. This REMS included a boxed warning, medication guide, and a communication plan with a health provider letter to rheumatologists and rheumatology health care providers, infectious disease specialists, family practitioners, general practitioners, internal medicine specialist, emergency medicine specialists and

pharmacists. On February 8, 2016, the communication plan of the REMs was removed after its goals were deemed fulfilled based on the Applicant's three-year assessment.

In addition, under the Food, Drug, and Cosmetics Act (FDCA) Section 505(o), (b) (4)

(b) (4)

Plaque Psoriasis (PsO)

(b) (4)

(b) (4)

(b) (4)

Psoriatic Arthritis (PsA)

On February 22, 2017, sNDA (203214/017) was submitted for the treatment of psoriatic arthritis (PsA) to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). Both tofacitinib 5 mg BID and 10 mg BID dosages were evaluated in Phase 3 studies for PsA. The Applicant proposed only 5 mg BID dosing, given that the safety and efficacy of both dose levels was comparable. The supplemental application was approved on December 14, 2017. The extended release tablet of 11 mg QD dosage and administration was also approved at that time.

An Arthritis Advisory Committee meeting was held on August 3, 2017, to discuss the safety and efficacy of the tofacitinib PsA program. Overall, the Committee agreed that the results of the studies demonstrate the efficacy of tofacitinib in adult patients with active PsA with respect to signs and symptoms and physical function; however, the data did not provide substantial evidence to support that tofacitinib has an effect on radiographic progression in this patient population. The Committee agreed that the results of the studies demonstrate the safety of tofacitinib for the treatment of adult patients with active PsA. The safety profile and risks associated with the 5 mg BID dose regimen within the PsA population were thought to be similar to ones noted in the original RA population. The Committee members added that the risk for herpes zoster (HZ) infection with this drug product was clear and that a more aggressive risk mitigation strategy should be implemented to prevent infection given the availability of a vaccine.

Ulcerative Colitis (UC)

On May 4, 2017, the Applicant submitted an efficacy supplement to propose an additional indication for tofacitinib under NDA 203214 S-018 to treat adult patients with moderately to severely active UC who have demonstrated an inadequate response, loss of response or

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[20] Dr. Kendall Marcus, M.D., DDDP Director Review for of tofacitinib application for the treatment of Severe plaque psoriasis. 11 October, 2015.

[21] FDA Briefing Document, Arthritis Advisory Committee Meeting, August 3, 2017. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM569317.pdf

intolerance to corticosteroids, azathioprine, 6-mercaptopurine (6-MP) or TNF inhibitor therapy (subject of this review).

While S-018 was under review, on August 22, 2017, DPARP approved supplements S-014 and S-016 to NDA 203214 and S-001 and S-002 to NDA 208246, which included revisions to update the labeling for Xeljanz (NDA 203214) and Xeljanz XR (NDA 208246) to the Pregnancy and Lactation Labeling Rule format.

3.2 Summary of Pre-submission/ Submission Regulatory Activity

The Applicant met with the Division of Gastroenterology and Inborn Errors Products (DGIEP) during the course of the UC development program. Key recommendations and points of discussion are summarized below.

A pre-IND meeting was held on April 7, 2011, to discuss plans for an Investigational New Drug submission to support the development of tofacitinib for the treatment of UC. Key points are summarized as follows:

- The FDA stated that the duration of the proposed phase 3 trials, i.e., 8 weeks for induction and 52 weeks for maintenance, appeared reasonable.
- FDA acknowledged and agreed with the Applicant's plan to evaluate remission as the primary endpoint of the phase 3 maintenance trial. FDA suggested that the Applicant also consider incorporating a maintenance of response endpoint. However, FDA stated, "In order to demonstrate maintenance of response or remission, patients must meet the definitions of clinical response or remission, respectively, at the time of enrollment into the maintenance study."
- FDA stated that an endpoint of "clinical remission" should include a rectal bleeding score of 0 and no friability on endoscopy. Endoscopy results of "erythema" and "decreased vascular pattern" as part of a remission endpoint would be acceptable if friability is absent.
- FDA stated that its current recommendations for defining "clinical response" were a decrease in Mayo score from baseline ≥ 3 AND a 30% decrease in Mayo score, along with either a decrease in rectal bleeding score ≥ 1 OR an absolute rectal bleeding score of ≤ 1.

On April 13, 2011, a letter was issued to the Applicant in follow up to the April 7, 2011 meeting to clarify the FDA's position on Mayo scoring. The letter stated:

- "…we want to clarify our recommendation that remission include the absence of friability on endoscopy in addition to the absence of rectal bleeding. We note that during the teleconference you suggested a plan to require an overall endoscopy subscore of 0 to define remission. This would be acceptable to the Division; however, we would also accept endoscopy results of 'erythema' and 'decreased vascular pattern' as part of a remission endpoint if friability is absent."

An EOP2 meeting was held on June 14, 2011. Key points are summarized as follows:

- FDA stated that the proposed induction doses for phase 3 appeared reasonable, and the lack of phase 2 data beyond 8 weeks made it difficult to conclude that the doses for phase 3 maintenance trial were optimum doses.
- The standard Mayo score was acceptable as the basis for the primary endpoint.
- FDA recommended rectal bleeding subscore of 0 as a component of the definition of the primary endpoint.
- The proposed definition of "mucosal healing" based on an endoscopic subscore of 0 or 1 was acceptable; however, FDA raised concerns regarding including friability in an endoscopic remission definition.
- The FDA recommended use of centrally read endoscopy for efficacy analyses, and that the central read be used for the primary analyses.
- The FDA recommended the primary analyses be based on the Intention-to-Treat (ITT) population defined as all randomized patients. For the maintenance study, the analysis population should include all randomized patients.
- A "maintenance of remission" labeling claim would require assessment of remission after 52 weeks of maintenance treatment among only patients in remission at entry into the maintenance trial, as opposed to the proposed assessment of remission after 52 weeks of maintenance treatment among patients with clinical response or in remission at entry into the maintenance study. Stratified randomization based on induction clinical response versus remission was recommended for the maintenance trial.
- Regarding "corticosteroid-free remission," FDA stated the protocol will need to describe the corticosteroid taper regimen and how adherence to the taper will be documented. The timing and duration of complete corticosteroid elimination must be clearly documented, including how the timing relates to assessment of clinical remission.
- FDA stated that an "overall mucosal healing responder" definition should take into account colonoscopy findings at weeks 8 and 52, and that a "more robust definition of

mucosal healing would be that patients who entered the maintenance trial with mucosal healing and also had mucosal healing at week 52".

A Type C Guidance meeting occurred on June 23, 2014 (written responses only). The key feedback provided to the Applicant was as follows:

- sNDA submission should include data from both the induction and maintenance studies to inform dosing beyond the induction phase.
- It would be acceptable to include safety data from the RA, PsO, and Crohn's disease (CD) programs in the sNDA submission to provide additional safety information on tofacitinib. However, these data cannot provide direct support of safety in UC.
- FDA reminded the Applicant that gross endoscopic evaluation of mucosa using the Mayo endoscopic subscore would not be sufficient to support a labeling claim of "mucosal healing." However, these data may support a labeling claim that describes improvement in endoscopic appearance of the mucosa.

A Type C Guidance meeting with FDA occurred on May 11, 2016 (written responses only). The Applicant requested input on the statistical analysis plans (SAPs) for the phase 3 trials. FDA provided the following comments:

- FDA reiterated that the primary endpoint of clinical remission that includes a Mayo endoscopic score of 0 or 1 should not include friability.
- FDA stated that a "mucosal healing" claim would not be supported by assessment limited to visual appearance of the mucosa; "therefore, any claims related to findings on endoscopy would be limited to the endoscopic appearance of mucosa (e.g., improving endoscopic appearance of mucosa)."
- FDA did not consider the partial Mayo score (excluding endoscopic subscore) an appropriate endpoint to assess time to onset of action for the purposes of informing product labeling.
- For the maintenance trial, the FDA noted that the Applicant planned to randomize all induction responders and stated that to support a "maintenance of remission" labeling claim, the primary analysis should be based on the population that includes only the remitters who received study drug during induction.
- FDA recommended a number of exploratory analyses, including:
    - Analysis of the primary endpoint excluding the Physician Global Assessment subscore (Modified Mayo Score).

- Analysis of the primary endpoint using a revised remission definition: endoscopy subscore of 0 or 1, where a score of 1 does not include "friability", stool frequency subscore of 0, rectal bleeding subscore of 0.
- Analysis of the primary endpoint using the average versus worst of the most recent consecutive 3-day period for stool frequency and rectal bleeding subscores.

A follow-up advice letter was sent after review of the revised SAP (dated June 27, 2016) which again reiterated:

- To support a maintenance of remission or sustained remission claim, the primary analysis should be based on the population that includes only the remitters who received the study drug during the induction study. FDA requested that the Applicant revise the SAP accordingly.

Two pre-sNDA meetings with the FDA were held on November 1, 2016; the key points of discussion were the following:

- A priority review decision and the need for an Advisory Committee (AC) meeting will be decided based upon review of the data.
- The FDA noted the limitations of using uncontrolled open-label data to support duration of induction dosing. Despite these limitations, the FDA suggested that the Applicant submit the data for review.
- The FDA accepted the approach to defining the TNF blocker-failure population. Inclusion of detailed TNF blocker-failure subgroup data is not likely, but wording could be considered for inclusion in the indications and usage section.
- The size of the safety database was generally acceptable.
- For risk mitigation, the Applicant proposed to send a letter to gastroenterologists regarding the risk of serious infections and malignancy within 60 days of potential application approval.

A major amendment to the application was received on September 28, 2017. Accordingly, the goal date for the supplement was extended by 3 months, resulting in an extended user fee goal date of June 4, 2018.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

Inspections for this sNDA were conducted at four clinical investigation sites, and at the contract research organization (CRO) (b) (4), which was responsible for the central reading of the colonoscopy video to determine the endoscopy subscore of the Mayo Score. All the clinical investigator sites and the Contract Research Organization received a final classification of no action indicated (NAI). See **Table 2** below.

Table 2: Clinical Inspection Results by Study Site and CRO

	Name and Type of Inspected Entity / Address	Site #/ Protocol # / # of Subjects	Inspection Dates	Final Classification
1	CI: Prof. Dr. Harald Vogelsang AKH Wien, Universitaetsklinik fuer Innere Medizin III, Klinische Abteilung fuer Gastroenterologie und Hepatologie Waehringer Guertel 18-20 Vienna, 1090 Austria	Site # 1011 A3921094/ 29 Subjects A3921096/ 13 Subjects	October 9 to 13, 2017	NAI
2	CI: Dr. Severine A.R.A. Vermeire UZ Leuven (University Hospital Leuven) Campus, Gasthuisberg Department of Gastroenterology Herestraat 49, Leuven, 3000 Belgium	Site # 1017 A3921094/ 50 Subjects A3921096/ 23 Subjects	October 16 to 23, 2017	NAI
3	CI: Prof. Hyo Jong Kim Kyung Hee University Hospital 23 Kyungheedae-ro Dongdaemun-gu Seoul, 130-872 Republic of Korea	Site # 1124 A3921095/ 28 Subjects A3921096/ 13 Subjects	October 23 to 26, 2017	NAI

	Name and Type of Inspected Entity / Address	Site #/ Protocol # / # of Subjects	Inspection Dates	Final Classification
4	CI: Prof. Dr. Geert R.A.M. D'Haens Academic Medical Centre (AMC), Inflammatory Bowel Disease Centre, Department of Gastroenterology Meibergdreef 9, Amsterdam, 1105AZ Netherlands	Site # 1135 A3921095/ 28 Subjects A3921096/ 10 Subjects	October 20 to 27, 2017	NAI
5	(b) (4)			

Source: Table adapted from the OSI review by Susan Leibenhaut, MD, dated December 29, 2017; NAI letters by OSI CDR LaKisha Williams, USPHS (drafted by analyst Joseph Peacock) dated March 30, 2018, April 13, 2018, and April 26, 2018; NAI = No deviation from regulations.

The OSI reviewer states that the data generated by these studies are acceptable in support of the application. Refer to the review by Susan Leibenhaut, MD, dated December 29, 2017, for additional information.

4.2 Product Quality

At the time of the original NDA submission for the treatment of RA, Chemistry, Manufacturing, and Controls information for both the 5 mg and 10 mg tablets were submitted and reviewed. Refer to the review by Craig Bertha, PhD, dated June 26, 2012. In this supplement, no changes to the currently approved presentations, manufacturing, or controls were proposed in this submission. No novel excipients are present and all excipients conform to National Formulary (NF) or United States Pharmacopeia (USP) compendia Standards. There are no impurities of concern.

The Chemistry, Manufacturing, and Controls team recommends approval of this supplement, and no new PMR or Postmarketing Commitments were recommended. Refer to the review by Hossein Khorshidi, PhD, dated March 4, 2018.

4.3 Clinical Microbiology

Not applicable.

4.4 Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this supplement. Please refer to the initial nonclinical review by Lawrence Leshing, PhD, dated July 3, 2012, for details of the nonclinical data that were reviewed at the time of initial approval.

5. Clinical Pharmacology

5.1 Executive Summary

In this supplemental NDA for Xeljanz® (tofacitinib citrate), the Applicant seeks approval of oral immediate release tablets of tofacitinib 5 and 10 mg for induction and maintenance of remission for adult patients with moderately to severely active UC with an inadequate response, loss of response, or intolerance to corticosteroids, azathioprine (AZA), 6-mercaptopurine (6-MP), or tumor necrosis factor inhibitor (TNFi) therapy. Tofacitinib is an inhibitor of Janus kinase (JAK) family of kinases. The proposed dosage regimen is 10 mg twice daily (BID) for 8 weeks for induction of remission and 5 mg twice daily for maintenance of remission. The Applicant also proposes the extended treatment for 16 weeks at 10 mg for induction of remission in patients who do not achieve adequate therapeutic benefit by week 8, and 10 mg dose for maintenance of remission for TNF-α refractory patients.

In support of the newly proposed indication in this submission, the Applicant conducted one phase 2 placebo-controlled dose-ranging induction study evaluating 0.5 mg, 3 mg, 10 mg, 15 mg BID dose levels, two placebo-controlled phase 3 induction studies evaluating 10 mg BID dosing during 8-week treatment, one placebo-controlled phase 3 maintenance study evaluating 5 mg and 10 mg BID dosing during 52 weeks of treatment, and one open-labeled long-term safety extension study evaluating 5 mg and 10 mg BID dosing. Sparse PK blood samples were collected during the phase 2 and phase 3 trials for population PK analysis to characterize the PK in the UC patient population, and to identify intrinsic and extrinsic patient-specific factors that may impact the PK of tofacitinib and exposure-response analysis for both efficacy and safety.

The key review questions focus on the appropriateness of the Applicant's recommended dose of 10 mg BID for induction of remission and 10 mg BID for maintenance of remission in patients who failed prior TNF blocker therapy by evaluating dose/exposure-response analysis for both efficacy and safety and characterization of PK in UC population via population PK analysis.

An Office of Clinical Pharmacology (OCP) briefing was held on January 31, 2018, and the Gastrointestinal Drugs Advisory Committee (GIDAC) meeting was held on March 8, 2018, to discuss this sNDA.

5.1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this efficacy sNDA 203214/018. This sNDA is acceptable from a clinical pharmacology perspective.

The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Induction of remission: Two placebo-controlled phase 3 induction studies evaluating 10 mg BID dosing during 8-week treatment provided the primary evidence of effectiveness. Dose-response and exposure-response analyses for efficacy based on data from phase 2 dose-ranging trial and phase 3 trials provide supportive evidence for effectiveness. Maintenance of remission: One placebo-controlled phase 3 maintenance study evaluating 5 mg and 10 mg BID dosing during 52 weeks of treatment provided the primary evidence for maintenance of UC remission.
General dosing instructions	Induction of remission: 10 mg BID for 8 weeks Maintenance of remission: 5 mg BID
Dosing in patient subgroups (intrinsic and extrinsic factors)	• For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg BID can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg BID for maintenance. Discontinue therapy in patients who do not achieve adequate therapeutic benefit by week 16. • Consider 10 mg BID dosing for maintenance of UC remission in patients who had inadequate response, loss of response, or intolerance to TNF blocker therapy.

	• Reduce the dose to 5 mg twice daily when original recommended dose is 10 mg twice daily, and reduce the dose to 5 mg QD when original recommended dose is 5 mg twice daily in following cases: o in patients with moderate or severe renal impairment or o in patients with moderate hepatic impairment or o when tofacitinib is coadministrated with potent inhibitor of CYP3A4 or o when tofacitinib is coadministrated with one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 in UC patients
Labeling	We have recommended to consolidate the PK information and covariate analysis results in patients with Rheumatoid Arthritis, Psoriatic Arthritis and Ulcerative Colitis as there was no major difference in these analysis results between these different disease populations. We recommend the inclusion of PK parameters following 10 mg BID in UC patients. Please see **Section 11** of this review.
Bridge Between the To Be Marketed (TBM) and Clinical Trial Formulations	In addition to the currently marketed 5 mg tablet, the Applicant proposes a 10 mg tablet. In the phase 3 trials, only 5 mg tablet which is different from the marketed 5 mg tablet was studied, and 10 mg tablet was not studied. The relative BA study has established the bridge between phase 3 tablet (10 mg administered as 2 X 5 mg tablet) and commercial tablets (1 X 10 mg tablet). Furthermore, the commercial 5 mg and 10 mg strengths are considered similar from the biopharmaceutics perspective.
Other (specify)	Currently for both Rheumatoid Arthritis and Psoriatic Arthritis, the recommended dose is either XELJANZ 5 mg twice daily or XELJANZ XR 11 mg QD. However, for UC patients, approval for XELJANZ XR 11 mg QD is not being sought in this submission in place for XELJANZ 5 mg twice daily.

	The Applicant is considering plans to submit an sNDA for both the 11 and 22 mg QD XR formulations in the future, and plan to request a pre-sNDA meeting once their plans are finalized.

5.1.2 Post-Marketing Requirements and Commitments

No clinical pharmacology post-marketing studies are recommended.

5.2 Summary of Clinical Pharmacology Assessment

5.2.1 Pharmacology and Clinical Pharmacokinetics

Pharmacology

Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function.

New clinical pharmacology information submitted to this sNDA includes the PK characterization of tofacitinib in UC patients based on population PK analysis and exposure-response analysis for safety and efficacy in UC patients. The approved label includes clinical pharmacology information that were submitted and reviewed in support of previous submissions. The clinical pharmacology findings from the original submission are briefly summarized in **Section 5.3** of this review. For further details, please see Clinical Pharmacology Review for the original NDA 203214 submission by Dr. Lokesh Jain in DARRTS dated June 25, 2012. This section summarizes clinical pharmacology trials conducted to support the UC indication.

PK in patients with moderately to severely active UC

Based on the population PK analysis, tofacitinib apparent clearance (CL/F) was 26.3 L/h and the steady-state AUC_{24} after 5 mg BID dose was 423 ng•h/mL in UC patients. Tofacitinib CL/F in UC patients (26.3 L/h) was comparable to that of patients with PSO (26.7L/h) and PsA (20.4L/h), and 45% higher than that of patients with RA (18.4L/h). Tofacitinib exposure in UC patients (423 ng•h/mL), as measured by the steady-state AUC_{0-24} after 5 mg BID, was comparable with that of patients with PsO (404 ng•h/mL) and PsA (419 ng•h/mL), and about 20% lower than in

patients with RA (504 ng•h/mL)[22]. Mean $AUC_{0-24,ss}$ after 10 mg BID in UC patients was also similar to that in PsO and PSA patients.

Across these patient populations, systemic exposures are higher compared to healthy volunteers (geometric means of steady-state AUC_{0-24} in healthy volunteers is 311 ng•hr/mL). This may be related to the inflammation burden in the disease populations vs healthy patients as a consequence of down-regulation of CYP450s by inflammation stimuli.

Covariate analysis in patients with UC showed that there was no clinically relevant effect of age, body weight, sex, and race on the exposure of tofacitinib. This is consistent with the result of covariate analysis in PsA and RA patient populations as reflected in the current XELJANZ label.

5.2.2 General Dosing and Therapeutic Individualization

5.2.2.1 General Dosing

Induction

The Applicant proposed 10 mg BID for 8 weeks for induction of remission. The proposed regimen is supported by efficacy from two phase 3 induction trials that have evaluated tofacitinib at the proposed dose of 10 mg BID daily versus placebo in UC patients.

Maintenance

The Applicant proposed 5 mg BID dosing for maintenance of remission of UC. The proposed dose is supported by one phase 3 maintenance trial where the Applicant evaluated both 5 mg BID and 10 mg BID dosing versus placebo over 52 weeks of treatment.

5.2.2.2 Therapeutic Individualization

Per the label, dosage reduction by half is recommended in the following cases:

- in patients with moderate or severe renal impairment or
- in patients with moderate hepatic impairment or
- when tofacitinib is coadministrated with potent inhibitor of CYP3A4 or
- when tofacitinib is coadministrated with one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 in UC patients

[22] 2.7.2.3.3 Summary of Clinical Pharmacology

For 5 mg BID dosing, dose reduction to 5 mg QD is recommended, and it is also appropriate for UC patients who meet the above criteria. For 10 mg twice daily dosing, which is not previously approved for other indications, dose reduction to 5 mg twice daily is recommended. Use of tofacitinib in patients with severe hepatic impairment is not recommended.

TNF-α refractory patients

The Applicant proposes to consider 10 mg BID dosing for maintenance of UC remission in patients who had failed prior TNF inhibition therapy. In subgroup analysis of phase 3 maintenance study data, patients with prior TNF-α inhibitor failure, the observed treatment difference compared to placebo was greater for XELJANZ 10 mg (25.3%) compared to XELJANZ 5 mg (12.9%) for the primary endpoint of remission at week 52. The E-R analysis by prior TNF response status also showed that 10 mg dose gave numerically higher probability of achieving remission compared to 5 mg dose at week 52 in TNF blocker non-responders. This topic was discussed at the AC meeting extensively. Based on this subgroup analysis, the Applicant's proposal to keep patients with prior history of TNF blocker failure on 10 mg BID long-term is reasonable from the efficacy standpoint. In addition, the clinical reviewers concluded that "refractory disease" status may not be defined solely by prior failure of TNF blocker. As a result, the final dosing recommendation will state that after induction either the 5 mg BID or 10 mg BID maintenance dose may be used, based on clinical response to treatment, and that the lowest effective dose to maintain response should be selected for each patient. Refer to **Section 7** below for the risk-benefit assessment associated with the long-term use of tofacitinib.

5.2.2.3 Outstanding Issues

While we acknowledge some patients, such as those with inadequate response in induction treatment or patients who are TNF non-responders, may benefit from maintenance treatment with 10 mg BID dose, there is remaining uncertainty about the safety of long-term use of 10 mg BID dose for UC treatment. (b) (4) (b) (4) (b) (4). In the RA program, only the 5 mg BID dose was approved. In UC, the safety database for 10 mg BID dose was relatively limited, compared to other programs such as PSO. The small sample size, together with other limitations discussed in the clinical safety assessment (**Section 7**), makes the detection of rare adverse events such as malignancy difficult. Additional safety data for 10 mg dose is then warranted.

Refer also to the clinical safety assessment and risk-benefit assessment provided in **Sections 1** and **7**. The potential benefits of 10 mg BID long-term dosing for some patients were felt to outweigh the known and potential increased risks over 5 mg BID. The uncertainty regarding long-term safety of 10 mg BID in UC patients will be further assessed (b) (4)

(b) (4)

(b) (4)

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5.3 Comprehensive Clinical Pharmacology Review

5.3.1 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology

Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function.

Clinical Pharmacokinetics

Provided below is a high-level summary of the clinical pharmacology findings reflected in the current XELJANZ label. Please also refer to the original NDA clinical pharmacology review by Dr. Lokesh Jain, dated June 25, 2012, in DARRTS for further detail.

Table 3: Summary of Tofacitinib Absorption, Distribution, Metabolism, and Excretion

Absorption	• Following oral administration, peak plasma concentrations are reached within 0.5-1 hour and systemic exposure of tofacitinib increases in an approximately dose proportional manner in healthy subjects in dose range of (b) (4) mg. • Steady state concentrations are achieved within 24-48 hours with negligible accumulation. • The absolute bioavailability is 74% after oral administration.
Distribution	• Approximately 40% of circulating tofacitinib is bound to plasma proteins.
Metabolism	• The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. The pharmacologic activity of tofacitinib is attributed to the parent molecule.

Elimination	• The apparent terminal half-life ($t_{1/2}$) of tofacitinib is approximately 3 hours. • Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. • In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged tofacitinib, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity.

PK in UC patients: Population PK analysis was conducted with sparse PK samples collected in the phase 2 and phase 3 studies in UC patients using the nonlinear mixed-effects modeling approach with Non Linear Mixed Effects Modeling (NONMEM). A total of 1096 patients with 6230 plasma concentrations were included in the analysis. The population PK of tofacitinib in patients with moderately to severely active UC was described by a one-compartment disposition model with first order absorption with an absorption lag time.

Based on the population PK analysis, tofacitinib apparent clearance (CL/F) in UC patients (26.3 L/h) was similar to that of PSO (26.7L/h) and PsA patients (20.4L/h), 45% higher than in RA patients (18.4L/h), and 25% lower than that of healthy subjects (34.9L/h). Tofacitinib exposure in UC patients (423 ng•h/mL), as measured by the steady-state AUC_{0-24} after 5 mg BID, was comparable with that of patients with PsO (404 ng•h/mL) and PsA (419 ng•h/mL), and about 20% lower than in patients with RA (504 ng•h/mL). Mean $AUC_{0-24,ss}$ after 10 mg BID in UC patients was also similar to that in PsO and PSA patients. Inter-subject variability (percent coefficient of variation (%CV)) in AUC_{24} was generally similar across UC, PSO, PsA, and RA patients.

Table 4: PK Parameter of Tofacitinib in Various Patient Populations

PK Parameters [a] Geometric Mean (CV%)	10 mg BID			5 mg BID			
	UC[1]	PSO[2]	PsA[3]	UC[1]	PSO[2]	PsA[3]	RA[4]
C_{max} (ng/mL)	90.75 (19.5 %)	83.3 (24.7%)	88.9 (28.6%)	46.9 (19.4%)	41.03 (24.9%)	42.43 (31.6%)	51.98 (17.2%)
$AUC_{0-24,ss}$ (ng·h/mL)	807 (24.6 %)	810.9 (23.5%)	872.5 (33.3%)	423 (22.6%)	404 (22.5%)	419 (34.1%)	504 (22.0%)
CL/F (L/h)	26.3	26.7	20.4	26.3	26.7	20.4	18.4

a: PK parameters estimated based on population PK analysis; PSO= Plaque psoriasis; PSA= psoriatic arthritis

RA=Rheumatoid Arthritis; UC=Ulcerative Colitis

Source: reviewer's table based on information obtained from the following sources:

1 Population PK reports in UC patients, Study report PMAR-EQDD-A392i-sNDA-513

2 Population PK report in PSO patients, study report PMAR-EQDD-A392g-DP3-112

3 Population PK reports in PsA patients, Study report PMAR-EQDD-A392j-sNDA-601

4 Population PK reports in RA patients, Study report PMAR-00178

5.3.2 Clinical Pharmacology Questions

In support of UC indication in this sNDA submission, the Applicant has conducted the following 5 studies, which included PK evaluation as described below:

1. An 8-week phase 2 dose-ranging induction study (A3921063) evaluating 0.5 mg, 3 mg, 10 mg, 15 mg BID dose vs placebo BID. This study had PK evaluation and biomarker CRP and fecal calprotectin.
2. Two 8-week phase 3 induction studies (A3921094 and A3921095) of identical design with tofacitinib 10 mg (2 x 5 mg tablet) BID or placebo. These two studies had PK evaluation.
3. A 52-week phase 3 maintenance study (A3921096) with tofacitinib 5 mg, 10 mg (2 x 5 mg tablet), and placebo BID. This study had PK evaluation.
4. An ongoing open-label long-term extension (LTE) study (A3921139) with tofacitinib 5 mg BID and tofacitinib 10 mg BID.

5.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Efficacy of tofacitinib on the induction of remission was supported by two randomized, placebo-controlled phase 3 trials which evaluated 10 mg BID dose in comparison to placebo. In the two phase 3 induction of remission studies, a significantly greater proportion of patients treated with XELJANZ 10 mg twice daily achieved remission at week 8 compared to placebo (18.5% XELJANZ 10 mg versus 8.2% in placebo in study 1 and 16.6% in XELJANZ 10 mg versus 3.6% in placebo in study 2).

Dose(exposure)-dependent increase in the clinical remission rate observed in the phase 2 trial, which evaluated doses between 0.5 mg to 15 mg BID, provided supportive evidence of effectiveness of tofacitinib 10 mg in clinical remission. Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point.

The efficacy of tofacitinib on the maintenance of remission was supported by a single phase 3 clinical trial evaluating 5 mg and 10 mg BID doses in comparison to placebo. In phase 3 maintenance trial, tofacitinib treatment resulted in a significantly greater proportion of patients in remission at week 52 compared to placebo (34.3% for 5 mg and 46.06% for 10 mg versus 11.1% for placebo).

The remission rate for 10 mg was numerically higher than that of 5 mg in a subgroup of patients with prior TNF-α non-responders, and the exposure-response analysis showed consistent trend. E-R relationship in remission rate during maintenance trial provides supportive evidence of effectiveness. For the risk-benefit assessment for 10 mg dose in TNF-α non-responders, refer to the additional discussion of this subgroup in the efficacy and safety sections below.

5.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dose of 10 mg BID dosing for induction of UC remission and proposed 5 mg BID dosing for the maintenance of UC remission for the general patients with moderate to severe UC are acceptable. In addition, the Applicant proposes 10 mg BID maintenance dose for patients with inadequate response to induction treatment or patients who are TNF non-responders. The Applicant's proposal for 10 mg BID maintenance dose is supported by a numerically higher remission rate in patients who are TNF non-responders. The review team is recommending approval of both 5 mg and 10 mg BID doses for long-term treatment, as

clinically indicated. Because the long-term safety data for 10 mg in UC patients is considered limited, post-marketing studies will be conducted to better assess the safety profile of 10 mg BID. Please refer also to **Section 5.2.2.3**, and the clinical review team's risk benefit assessment.

Induction

The selection of the 10 mg BID dose for phase 3 induction trials (A3921094 and A3921095) was based on the dose-response relationship for efficacy from a dose-ranging phase 2 induction study (A3921063). This dose-ranging phase 2 study was a randomized, double-blind, placebo-controlled, parallel group, multicenter study conducted to evaluate the efficacy of tofacitinib in inducing a clinical response in 192 subjects with moderate to severe UC. UC patients were randomized to 0.5 mg, 3 mg, 10 mg and 15 mg of tofacitinib twice daily (BID) or placebo BID (2:2:2:3:3 ratio, respectively) with 8 weeks of treatment. Please note that tofacitinib 5 mg BID dose was not evaluated in this phase 2 dose-ranging study.

The primary clinical efficacy endpoint was the proportion of clinical responders at week 8. Clinical response was defined as a decrease from baseline in Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1. This was the secondary endpoint in two phase 3 induction studies.

The secondary endpoint of this phase 2 study was clinical remission at week 8. Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. In the study 1063, an endoscopy subscore of 1 could include friability (in contrast to the more stringent definition used in phase 3 to define remission) and a rectal bleeding subscore of 0 or 1 could be consistent with clinical remission. Regardless, clinical remission in this phase 2 trial was more similar to the primary endpoint used in the phase 3 studies (remission at Week 8), compared to clinical response. Remission in phase 3 studies was defined by a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0. Therefore, the secondary endpoint of clinical remission at week 8 is more relevant for selection of dose for phase 3 trials.

Table 5: Clinical Response and Clinical Remission at Week 8 in Dose-Ranging Phase 2 Induction Trial (Study 1063)

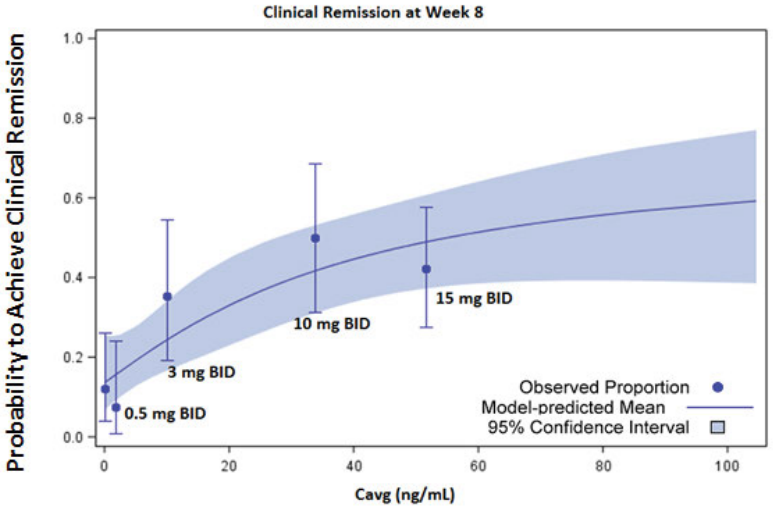
Treatment Dose	Placebo (N=40)	0.5 mg (N= 27)	3 mg (N=31)	10 mg (N=30)	15 mg (N=45)
Clinical Response (Primary Endpoint)	47.5%	29.6%	51.6%	63.6%	80%
Clinical Remission (Secondary Endpoint)	12.2%	7.4%	35.5%	50%	42.2%

Source: Study A3921063 Clinical Study Report (CSR), Table 17 (page 78) and Table 19 (page 82)

There was a dose-dependent increase in both clinical response rate (the primary endpoint) and clinical remission rate (the secondary endpoint) in this dose-ranging phase 2 study (Table 5). For clinical remission, the effect appears to plateau at 10 mg dose where 10 mg and 15 mg doses had similar clinical remission rates and 15 mg dose did not add any additional benefit compared to 10 mg dose. There was no clear dose related increase in overall incidence of AE in the dose range of 0.5-15 mg BID dosing, and overall incidence of AEs were similar between tofacitinib and placebo treatments. Based on the results of this phase 2 study dose-ranging study, the Applicant selected 10 mg and 15 mg BID dose levels to be further evaluated in the phase 3 induction studies. However, shortly after the initiation of phase 3 trials, the Applicant discontinued 15 mg BID dose from the phase 3 induction trials.

Furthermore, when the relationship between induction of clinical remission at week 8 and systemic exposure were explored, the model predicted that probability of achieving clinical remission increased with increasing plasma concentration and reached a plateau at a concentration that corresponds to 10 mg BID dose, supporting the selection of 10 mg BID dose as the induction dose for phase 3 trials (Figure 1). In conclusion, the observed dose-response and exposure-response relationship in phase 2 dose-ranging trial supported the selection of 10 mg BID dose for induction of remission in phase 3 trials.

Figure 1: Exposure-Response for Induction of Clinical Remission at Week 8 from Dose-Ranging Phase 2 Induction Trial (Study 1063)



Source: Adopted from Figure 13 on page 64 of Applicant's exposure-response analysis report PMAR-EQDD-A392i-sNDA-512

Note: Observed (closed circle) and model predicted probabilities (line) with 95% CI is (shaded area) based on a logistic Emax model were plotted at the median of individual Cavg values by dose in phase 2 (0 mg, 3 mg, 10 mg, and 15 mg).

Although 10 mg appears to be the lowest effective dose among the evaluated doses in this dose-ranging phase 2 study based on the clinical remission, it was not clear if 10 mg dose was truly the lowest effective dose as 5 mg dose was not evaluated in this phase 2 dose-ranging study. Given the prior safety concern with tofacitinib 10 mg BID dose with other previously approved indications, it was explored whether 5 mg BID dose would have been as efficacious as 10 mg dose for induction of UC remission. Based on the predicted efficacy at 5 mg BID by developing an exposure-response model for efficacy using pooled data from phase 3 induction studies, the predicted remission rate at 5 mg BID dose was 12.8% while the remission rate at 10 mg BID would be 19.1% (**Table 6**). The model-predicted remission rates for placebo and 10 mg BID dose were similar to observed data, confirming the validity of the model. As the difference between the predicted remission rate at 5 mg and 10 mg doses was considered to be clinically meaningful, it was concluded that 10 mg dose is likely to result in better clinical outcome than 5 mg BID dose. Therefore, the Applicant's selection of 10 mg dose for the phase 3 induction trials was further supported by the modeling and simulation of remission rate at 5 mg BID.

Table 6: Predicted Induction of Remission Rate at Week 8 for 5 mg BID from Exposure - Response Analysis using Pooled Phase 3 Data

Probability (%) (95% CI)	Placebo	5 mg BID (C_{avg}=16.8 ng/mL)	10 mg BID (C_{avg}=33.6 ng/mL)
Observed Remission	6.5 (3.6-10.6)		18.8 (16.3-21.6)
Model-Predicted Remission	6.4 (3.2-9.7)	12.8 (9.2-16.4)	19.1 (16.3-21.9)

Source: Table 12 and Table A10.1 of Applicant's exposure-response analysis report PMAR-EQDD-A392i-sNDA-512

Maintenance

The Applicant did not conduct a separate dose-ranging phase 2 study to find the optimal dose for maintenance of UC. Nonetheless, in phase 3 maintenance of UC remission study, the Applicant evaluated two dose levels, 5 mg BID and 10 mg BID versus placebo. Based on the result of phase 3 study, the Applicant is proposing 5 mg BID dose for maintenance of UC remission and 10 mg BID dose for UC patients who failed prior TNF inhibitor therapy.

Biomarkers

Two biomarkers, C-Reactive Protein (CRP) and fecal calprotectin, were measured as secondary endpoints in phase 2 dose-ranging study. Both biomarkers demonstrated treatment effect of tofacitinib (CP-690,550), supporting the clinical outcome; and largest decrease from the baseline to week 8 versus placebo was observed with 15 mg dose group. However, there was no clear dose-response relationship observed with either biomarker.

Table 7: Baseline and Change from Baseline in C-Reactive Protein by Visit

Visit / Parameter	Placebo	CP-690,550 BID			
		0.5 mg	3 mg	10 mg	15 mg
Baseline, N	**48**	**31**	**33**	**32**	**49**
Geometric mean (SD) (mg/L)	4.53 (12.84)	6.60 (29.43)	6.34 (13.21)	4.74 (16.45)	5.70 (26.44)
Natural log-transformed data:					
Arithmetic mean (SD)	1.51 (1.40)	1.89 (1.58)	1.85 (1.38)	1.56 (1.44)	1.74 (1.67)
Week 4, N	**38**	**22**	**25**	**30**	**46**
Change from baseline:					
Geometric mean	0.82	0.88	0.47	0.31	0.24
Natural log-transformed data:					
Arithmetic mean (SD)	-0.20 (1.01)	-0.13 (1.04)	-0.76 (1.24)	-1.17 (1.47)	-1.42 (1.21)
Week 8, N	**37**	**21**	**27**	**28**	**44**
Change from baseline:					
Geometric mean	0.73	0.75	0.41	0.59	0.27
Natural log-transformed data:					
Arithmetic mean (SD)	-0.31 (1.02)	-0.28 (1.37)	-0.89 (1.29)	-0.53 (1.50)	-1.31 (1.62)

Source: Study A3921063 CSR, Table 29 (page 96)

Table 8: Baseline and Change from Baseline in Fecal Calprotectin by Visit

Visit / Parameter	Placebo	CP-690,550 BID			
		0.5 mg	3 mg	10 mg	15 mg
Baseline, N	**46**	**29**	**31**	**32**	**49**
Geometric mean (SD) (mg/kg)	635.4 (2596)	664.6 (1623)	718.1 (2182)	366.6 (2001)	720.3 (2575)
Natural log-transformed data:					
Arithmetic mean (SD)	6.45 (1.56)	6.50 (1.49)	6.58 (1.26)	5.90 (1.75)	6.58 (1.24)
Week 2, N	**39**	**24**	**28**	**31**	**47**
Change from baseline:					
Geometric mean	1.29	1.38	0.62	0.83	0.39
Natural log-transformed data:					
Arithmetic mean (SD)	0.25 (1.35)	0.33 (1.72)	-0.48 (2.05)	-0.18 (1.25)	-0.95 (1.66)
Week 4, N	**37**	**22**	**27**	**28**	**45**
Change from baseline:					
Geometric mean	1.01	1.06	0.65	0.72	0.29
Natural log-transformed data:					
Arithmetic mean (SD)	0.01 (1.36)	0.06 (1.64)	-0.44 (2.04)	-0.32 (1.17)	-1.25 (1.48)
Week 8, N	**40**	**25**	**28**	**31**	**43**
Change from baseline:					
Geometric mean	0.81	0.72	0.46	0.50	0.24
Natural log-transformed data:					
Arithmetic mean (SD)	-0.21 (1.64)	-0.34 (1.48)	-0.78 (1.67)	-0.70 (1.85)	-1.41 (1.78)
Week 12, N	**33**	**19**	**24**	**28**	**42**
Change from baseline:					
Geometric mean	0.61	1.17	0.67	0.59	0.39
Natural log-transformed data:					
Arithmetic mean (SD)	-0.49 (1.67)	0.16 (1.18)	-0.41 (1.92)	-0.53 (1.55)	-0.95 (1.36)

Source: Study A3921063 CSR, Table 31 (page 98)

Serum high sensitivity C-reactive protein (hsCRP) was also measured in all three phase 3 induction and maintenance trials, and supported the efficacy of tofacitinib with noticeable decrease from the baseline compared to placebo (See **Table 9** and **Table 10**).

Table 9: Change from Baseline (arithmetic mean (SD)) in High Sensitivity C-Reactive Protein (hsCRP) (mg/L) at Week 8 in Phase 3 Induction Studies

	Tofacitinib 10 mg BID	**Placebo**
Study A3921094	-4.0 (19.9)	-0.2 (16.2)
Study A3921095	-6.2 (18.4)	-2.5 (14.4)

Source: Study A3921094 CSR, table 38 (page 115) and Study A3921095 CSR, table 38 (page 115)

Table 10: Change from Baseline (arithmetic mean (SD)) in High Sensitivity C-Reactive Protein (hsCRP) (mg/L) in Phase 3 Maintenance Study (Study A3921096)

	Tofacitinib 10 mg	**Tofacitinib 5 mg**	**Placebo**
Week 8	0.7 (11.5)	0.8 (6.3)	4.6 (13.6)
Week 24	-0.5 (6.2)	1.2 (7.2)	2.2 (7.8)
Week 52	-0.6 (6.9)	1.1 (6.7)	2.0 (8.0)

Source: Study A3921096 CSR, table 14.3.4.1.8 (page 3627)

5.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Renal/Hepatic impairment

The Applicant proposed the following dosing instructions for patients with renal or hepatic impairment.

In UC patients with:

- moderate or severe renal insufficiency, or moderate hepatic impairment, the recommended dose is as follows:
  - 5 mg QD when original dose in patients without impairment is 5 mg twice daily.
  - 5 mg twice daily when original dose in patients without impairment is 10 mg twice daily.
- Use of XELJANZ in patients with severe hepatic impairment is not recommended.
- No dose adjustment is required in patients with mild hepatic or renal impairment.

The Applicant's proposal is acceptable based on the available data in the current XELJANZ's label. No new studies were conducted to support the dosage adjustment in patients with hepatic or renal impairment.

The recommended dose reduction for 5 mg BID is consistent with the currently available label for XELJANZ for previously approved indications. As 10 mg BID dose will be a new dose in UC indication compared to other previously approved indications for XELJANZ, the label will be updated regarding the recommended dose reduction for 10 mg BID dose.

Effects of other intrinsic factors:
Population PK analysis in patients with UC showed that there were no clinically relevant effects of age, body weight, sex, and race on the exposure of tofacitinib.

5.3.3 TNF-α refractory patients

The application proposes to consider 10 mg BID dosing for maintenance of UC remission in patients who failed prior TNF inhibition therapy. Based on the subgroup analysis, the Applicant's proposal appears to be reasonable from the efficacy standpoint. However, the long-term use of 10 mg BID dose was associated with greater risk of some adverse events, relative to the 5 mg BID dose. Refer to the safety review below for additional discussion of dose-dependent risks.

For maintenance of UC remission, two dose levels, 5 mg BID and 10 mg BID, versus placebo were evaluated in the phase 3 maintenance study (A3921096). A significantly greater proportion of patients in both the XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily treatment groups achieved the primary endpoint of remission at week 52 compared to placebo, while the treatment difference compared to placebo for 5 mg versus 10 mg doses were similar (23.2% for 5 mg dose versus 29.5% for 10 mg dose). Based on this result, the Applicant is proposing 5 mg BID dosing for maintenance of UC remission.

However, in a subgroup analysis, patients with prior TNF blocker failure, the observed treatment difference compared to placebo was much greater for XELJANZ 10 mg (25.3%) compared to XELJANZ 5 mg (12.9%) for the primary endpoint of remission at week 52. Based on the subgroup analysis, the Applicant's proposal appears to be reasonable from the efficacy standpoint. In UC patients, there was an exposure-dependent increase in the rate of AEs such as HZ. For the cumulative proportion of patients with a given AE of interest over time, refer to discussion in **Section 7**. The benefits of 10 mg BID dose as maintenance treatment should be

considered in context of safety. In all patients (regardless of prior TNF blocker failure) the lowest effective dose to maintain adequate efficacy should be selected for long-term use.

5.3.3.1 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No new food effect trials are submitted in this sNDA and no dose adjustments based on meal status are recommended for the treatment of UC, which is consistent with the current approved tofacitinib label for other indications.

When tofacitinib is co-administrated with potent inhibitor of CYP3A4 or when it is co-administrated with one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 in UC patients, the Applicant has proposed to reduce the dose to 5 mg twice daily when original recommended dose without above concomitant medications is 10 mg twice daily, and to reduce the dose to 5 mg QD when original recommended dose without above concomitant medications is 5 mg twice daily. The Applicant's proposal appears to be acceptable. The recommended dose reduction for 5 mg BID is consistent with the currently available label for XELJANZ for previously approved indications. As 10 mg BID dose will be a new dose in UC indication compared to other previously approved indications for XELJANZ, the label will be updated regarding the recommended dose reduction for 10 mg BID dose.

Food

According to XELJANZ's current label, co-administration of XELJANZ with high fat meal has no significant effect on the extent of absorption ($AUC_{0-\infty}$) but reduces the C_{max} by 32%. XELJANZ is proposed to be given orally with or without food for the treatment of UC, which is consistent with the current approved tofacitinib label for other indications. The Applicant's proposal is acceptable.

DDI

The Applicant did not submit any new *in-vitro* or *in-vivo* drug interaction studies in this efficacy sNDA. All *in-vitro and in-vivo* DDI studies were submitted and reviewed previously and reflected accordingly in the current label. The current XELJANZ label recommends that the tofacitinib dose should be reduced by half when tofacitinib is co-administrated with potent inhibitor of CYP3A4 (e.g., ketoconazole) or when it is co-administrated with one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

5.3.3.2 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?)?

The formulation(s) used in the UC clinical trials (phase 2B tablets and phase 3 tablets) were previously shown to be bioequivalent to the to-be-marketed (TBM) commercial formulation (commercial tablets) in Study A3921075, which was submitted and reviewed during the original NDA review cycle. While phase 3 formulation contains only 5 mg strength tablet, commercial (TBM) formulation include the 5 mg and 10 mg strength tablet. According to the Biopharmaceutics review by Dr. John Duan, dated June 19, 2012, the commercial 5 mg and 10 mg strengths can be considered similar from the Biopharmaceutics perspective.

No new phase 1 studies were included in this sNDA as the formulation(s) used in the UC program have the same qualitative and quantitative composition as the commercial tablets.

Table 11: Formulations Used in Phase 2 and Phase 3 Studies in UC Patients

Protocol	Dosage Formulation	Strength
A3921063	Phase 2B Tablet	0.5 mg, 1 mg and 5 mg
A3921094, A3921095, A3921096,	Phase 3 Tablet	5 mg
A3921139	Commercial tablets*	5 mg

*Formulation 1100272 is a commercial formulation equivalent to the registration commercial formulation; it only differs in debossing.
Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 1, (page 6)

The phase 2 dose-ranging study in UC patients (A3921063) used the same phase 2B tablets that were used in RA program; UC phase 3 studies A3921094, A3921095, and A3921096 used the same phase 3 tablet used in the RA program. Study A3921075 which demonstrated the bioequivalence of Phase 2B tablets (10 mg administered as 2 x 5 mg tablet) versus phase 3 tablet (10 mg administered as 2 x 5 mg tablet) versus commercial tablets (1 x 10 mg tablet) was reviewed and found to be acceptable by Office of Clinical Pharmacology previously. Please see Clinical Pharmacology review for NDA 203214 by Dr. Lokesh Jain, dated June 25, 2012.
While the phase 3 formulation contains only 5 mg strength tablet, commercial (TBM) formulation include the 5 mg and 10 mg strength tablets. According to the Biopharmaceutics review by Dr. John Duan, dated June 19, 2012, the commercial 5 mg and 10 mg strengths can

be considered similar from the Biopharmaceutics perspective based on the following observations:

- The formulations of the 5 mg and 10 mg commercial tablets are compositionally similar. The 5 mg tablet uses the same blend as the 10 mg commercial tablet.
- The two strengths share the same manufacturing process.
- Both the 5 mg and the 10 mg tablets dissolve rapidly ([(b) (4)]% in 15 minutes using mild conditions, such as basket at 100 rpm in 0.1N HCl).

Therefore, the clinical and the to-be-marketed formulations are adequately bridged.

6. Statistical and Clinical Evaluation - Study Design and Efficacy Results

6.1 Study Overview

This application contained data from the following 3 trials that provide substantial evidence of efficacy and controlled safety in support of approval: two phase 3 induction trials (Studies 1094 and 1095 – identical 9-week studies) and a single phase 3 maintenance trial (Study 1096 – a 53-week study of patients who completed Study 1094 or 1095 and were in at least clinical response).

In addition, the submission contained data from a phase 2 dose ranging study (Study 1063, which is discussed in the clinical pharmacology section) and an open-label extension study (Study 1139). These two studies provided supportive safety and efficacy data. The key features of these studies will be discussed in detail below.

Table 12, **Table 13**, and **Figure 2** summarize these studies.

Table 12: Listing of Controlled Clinical Trials in Support of Approval

Trial Design	Doses Studied	Study Endpoints	Treatment Duration & Follow Up	Patients Enrolled	Study Population	Centers and Countries
Study 1094 DB, R, PC, PG, MC	Tofacitinib 10 mg BID (n=476) Placebo (n=122) Tofacitinib 15 mg BID (n=16)[c]	**Primary (week 8):** • Remission[a] **Key secondary (week 8):** • Mucosal healing	9 weeks (followed by a 4-week safety follow-up for patients not enrolled in Study 1096 or Study 1139)	N=598	Adults with moderately to severely active UC (Mayo score >=6 & endoscopic subscore >=2) with prior intolerance or failure to at least one of the following: IV or oral corticosteroids, AZA/6-MP, infliximab or adalimumab	113 centers in 28 countries
Study 1095 DB, R, PC, PG, MC	Tofacitinib 10 mg BID (n=429) Placebo (n=112) Tofacitinib 15 mg BID (n=6)[d]	**Primary (week 8):** • Remission[a] **Key secondary (week 8):** • Mucosal healing	9 weeks (followed by a 4-week safety follow-up for patients not enrolled in Study 1096 or Study 1139)	N=541	Adults with moderately to severely active UC (Mayo score >=6 & endoscopic subscore >=2) with prior intolerance or failure to at least one of the following: IV or oral corticosteroids, AZA/6-MP, infliximab or adalimumab	124 centers in 29 countries
Study 1096 DB, R, PC, PG, MC	Tofacitinib 5 mg BID (n=198) Tofacitinib 10 mg BID (n=197) Placebo (n=198)	**Primary (week 52):** • Remission[a] **Key secondary (week 52):** • Mucosal healing • Sustained steroid-free remission (among patients in remission at baseline of Study 1096)	53 weeks (followed by a 4-week safety follow-up for patients who did not enroll in Study 1139)	N=593	Patients who completed the 9-week induction treatment from Study 1094 or Study 1095 and who achieved clinical response[b] in their enrolled study	195 centers in 31 countries

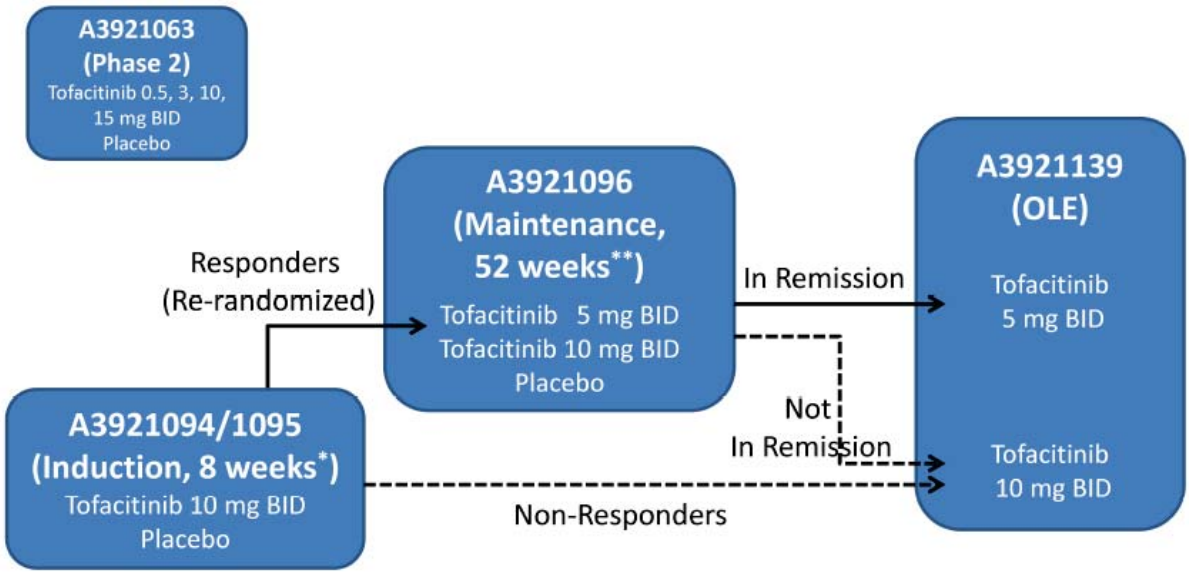
Source: Reviewer's table. DB = Double-blind, R = Randomized, PC = Placebo Controlled, PG = Parallel Group, MC = Multi-center, OL= Open-label, LTE= Long-term Extension study. [a] Remission is defined by a total Mayo score of 2 points, with no individual subscore >1 point, and a rectal bleeding subscore of 0. [b] Clinical response is defined by a decrease from baseline in Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1. [c] 16 patients randomized to tofacitinib 15 mg BID before initiation of Protocol Amendment 3 were not included in the analysis datasets. [d] 6 additional patients were randomized to tofacitinib 15 mg BID prior to Protocol Amendment 2 and were not included in the analysis datasets.

Table 13: Listing of Additional Supportive Trials

Trial Design	Doses Studied	Study Endpoints	Treatment Duration & Follow Up	Patients Enrolled	Study Population	Centers and Countries
Study 1063 DB, R, PC, PG, MC	Tofacitinib 0.5 mg BID (n=31) Tofacitinib 3 mg BID (n=33) Tofacitinib 10 mg BID (n=33) Tofacitinib 15 mg BID (n=49) Placebo (n=48)	Primary (week 8): • Clinical response[a] Key secondary (week 8): • Clinical remission • Endoscopic response • Endoscopic remission	8 weeks (followed by a 4-week safety follow-up)	N=194	Adults with moderately to severely active UC (Mayo score >=6 & endoscopic subscore >= 2)	51 centers in 17 countries
Study 1139 OL, LTE	Tofacitinib 5 mg BID (n=175) Tofacitinib 10 mg BID (n=769) Protocol specified dose adjusment permitted	Long-term durability of efficacy and long-term safety	Ongoing; Up to first global marketing authorization	N=944	Patients completing 52 weeks maintenance treatment or withdrawn due to treatment failure in Study 1096; or non-responders after completion in induction Studies 1094 and 1095	298 centers in 30 countries

Source: Reviewer's table. DB = Double-blind, R = Randomized, PC = Placebo Controlled, PG = Parallel Group, MC = Multi-center, OL= Open-label, LTE= Long-term Extension study. [a] Clinical response is defined by a decrease from baseline in Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1.

Figure 2: Tofacitinib Phase 2 and 3 UC Program



Source: Applicant's study PMAR-EQDD-A392i-sNDA-514 submission dated May 4, 2017

The overall program design is notable for the following features, which affect the subsequent efficacy and safety analyses:

- Induction randomization (Study 1094, 1095) was 4:1 tofacitinib to placebo. Patients who achieved clinical response (rather than remission) entered Study 1096 as induction responders. Induction non-responders were eligible to enter open-label extension (Study 1139), and all such patients received a dose of 10 mg BID long-term. This design results in a much greater proportion of patients with long-term exposure to 10 mg BID, compared with 5 mg BID, as discussed further in the safety section below.

- For the induction, non-responder population (IndNR subgroup), an efficacy assessment that includes centrally read endoscopy was repeated 8 weeks into Study 1139 (after a total of 16 weeks of total trial participation). The exploratory efficacy assessment of this "IndNR" subgroup compares patients who received placebo in a phase 3 induction trial for 8 weeks followed by tofacitinib treatment for 8 weeks in the open-label extension study, against those who received a total of 16 weeks of tofacitinib induction therapy (8 weeks in a phase 3 induction trial + 8 additional weeks in the open-label extension study). The Applicant proposed to utilize this exploratory analysis, which was not subject to multiplicity control, to support the

proposal to extend induction dosing to 16 weeks for patients with inadequate therapeutic response at week 8.

- Patients who demonstrated clinical response at week 8 were re-randomized 1:1:1 at the start of Study 1096 to tofacitinib 10 mg BID, 5 mg BID, or placebo. In Study 1096, the primary assessment of remission at week 52 was conducted on the population of patients who were induction responders (those who achieved clinical response or remission at week 8 of Study 1094/1095). The Applicant utilized a key secondary endpoint ("sustained corticosteroid-free remission") to assess long-term efficacy in maintaining remission (among those who were in remission at the start of Study 1096), which is a clinically important endpoint, and is discussed further below. Because patients must have demonstrated some clinical improvement (achieved clinical response) to be eligible to enter Study 1096, the baseline Mayo score for this study was lower (mean 3.4) than that of patients entering the induction studies (mean 9.0). This difference in severity may be relevant for the safety comparisons.

- Patients who were not in remission at the completion of Study 1096 (week 52) were eligible to enter the open-label extension at a dose of 10 mg BID. Those who achieved remission at week 52 were eligible to enter the open-label extension at a dose of 5 mg BID (regardless of treatment allocation in Study 1096). Additionally, patients who met a specific protocol defined definition of treatment failure during Study 1096 (i.e., increase in Mayo score of at least 3 points from baseline of maintenance study, accompanied by an increase in rectal bleeding subscore of 1 point and increase in endoscopic subscore of 1 point, yielding an absolute endoscopic subscore of at least 2 after minimum of 8 weeks in study) were eligible to enter the open-label extension at a 10 mg BID dose. However, patients with other clinical scenarios that may be construed as worsening or treatment failure (such as requiring new therapy for UC, requiring surgery for UC, or requiring prednisone exceeding 15 mg per day after week 15) that may have occurred at any time during Study 1096 were not eligible to enter the open-label extension. Thus, the patient population enrolled in the open-label extension study is skewed. In particular, the Mayo score at baseline of the open-label extension was higher in those who received 10 mg BID long-term treatment in Study 1139 (mean 8.2) compared with those who received 5 mg BID long-term treatment in Study 1139 (mean 1.2).

6.2 Data Sources and Quality

Data Sources

The clinical study reports, protocols, SAPs, Statistical Analysis System transport datasets, Statistical Analysis System codes, and dataset reviewer's guides for the three studies were submitted

electronically. The network path for the submissions is \\cdsesub1\evsprod\NDA203214\0323\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5351-stud-rep-contr. The network path for the analysis datasets is \\cdsesub1\evsprod\NDA203214\0323\m5\datasets.

All submitted analysis datasets and case report form tabulation datasets were in legacy format. A group of safety-related datasets were submitted in Study Data Tabulation Model format as a response to an information request dated May 31, 2017. The Applicant provided Statistical Analysis System programs for safety and efficacy datasets and for analysis of the primary efficacy endpoints.

Data and Analysis Quality

In general, the data submitted by the Applicant to support the efficacy and safety of tofacitinib for the proposed indication were acceptable.

6.3 Efficacy Evaluation for Pivotal Phase 3 Induction Trials (Studies 1094 and 1095)

6.3.1 Trial Objective, Design, and Efficacy Endpoints

The Applicant conducted two identical phase 3 induction trials (Studies 1094 and 1095) whose primary objective was to demonstrate the efficacy and safety of tofacitinib 10 mg BID in inducing remission in adult patients with moderately to severely active UC who had intolerance to or inadequate response to prior conventional therapy (corticosteroids, azathioprine, or 6-mercaptopurine) or TNF blocker treatment (infliximab or adalimumab).

Studies 1094 and 1095 were multi-center, randomized, double-blind, placebo-controlled 9-week clinical trials followed by a 4-week safety follow-up for patients who were not participants in a maintenance study (Study 1096) or an open-label study (Study 1139). The induction trials randomized patients to tofacitinib 10 mg BID or placebo at a 4:1 ratio. Randomization was stratified by prior treatment with anti-TNF therapy, corticosteroid use at baseline, and geographic region. The treatment allocation reflected a change implemented with Protocol Amendment 3 and Protocol Amendment 2 in Study 1094 and Study 1095, respectively, which removed the 15 mg BID arm from the study (patients who were enrolled prior to those protocol amendments had been randomly assigned to receive either tofacitinib 10 mg BID, tofacitinib 15 mg BID, or matched placebo BID at a 2:2:1 allocation ratio). Patients who were randomized under the prior protocols and who were still active in the study at the time of the approval of the protocol amendments continued to receive blinded treatment assigned at baseline for the treatment period.

For both studies, the main inclusion criteria that defined the study population were as follows:

- At least 18 years of age
- A diagnosis (endoscopic or radiographic and histological) of UC ≥ 4 months prior to entry into the study
- Have moderately to severely active UC as defined by a total Mayo score of ≥ 6, with a rectal bleeding score of ≥ 1 and an endoscopic subscore of ≥ 2 on the Mayo score determined within 10 days of baseline visit (visit 2)
- Failure or intolerance (discontinued the medication due to an adverse event as determined by the investigator) of at least one of the following treatments for UC:
    - Oral or intravenous corticosteroids
    - Azathioprine or 6-mercaptopurine (6-MP)
    - Anti-TNF-alpha therapy: infliximab or adalimumab.

For both studies, the primary and key secondary endpoints were as follows:

- Primary efficacy endpoint: the proportion of patients in remission at week 8. Remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0.
- Key secondary endpoint: the proportion of patients achieving a Mayo endoscopic subscore of 0 or 1 (referred to as “mucosal healing” in the Applicant’s protocol) at week 8.

The Mayo score is comprised of 4 individual subscores, each scored from 0 to 3. The total score ranges from 0 to 12 (most severe). Moderate to severe UC is defined as a score of 6 to 12.

Table 14: Mayo Score

	0	1	2	3
Physician Global Assessment	Normal	Mild	Moderate	Severe
Endoscopic Appearance	Normal or inactive	Mild disease (erythema, decreased vascular pattern)	Moderate disease (marked erythema, absent vascular pattern, **any friability**, erosions)	Severe disease (spontaneous bleeding, ulcerations)
Stool Frequency	Normal number of stools per day for patient	1 to 2 more stools per day than normal	3 to 4 more stools per day than normal	>-5 more stools per day than normal
Rectal Bleeding*	No blood seen	Streaks of blood with stool less than half the time	Obvious blood with stool most of the time	Passing blood alone

Source: Reviewer's table, adapted from Mayo score as utilized in this program
*The daily bleeding score represents the most severe bleeding of the day

The scores for stool frequency and rectal bleeding are patient-reported data derived and collected from a daily diary administered for 3 days prior to the evaluation time point. The endoscopic score is assessed based on sigmoidoscopy. Note that within this development program, the definition of a score of "1" for endoscopic appearance excludes any friability. The endoscopic component of primary endpoint assessments (week 8 in Study 1094/1095, and weeks 24 and 52 in Study 1096) were conducted based on centrally read endoscopy.

The Applicant uses the term "mucosal healing" to describe the results of visual inspection of mucosa by endoscopy at week 8 (Study 1094/1095) and week 52 (Study 1096), and defined as achieving an endoscopy subscore of 0 or 1, where 1 does not include any friability. As described in the regulatory history above, the Agency indicated that assessment of the mucosa limited to appearance (not incorporating histology) will not support a labeling claim of "mucosal healing" and instead will be described as "improvement in endoscopic appearance of the mucosa." For the purposes of this review, the term "mucosal healing" is retained as it appears in the SAPs and protocol.

The following UC treatments were allowed provided they were stable for the specified period prior to the first dose of study medication and were not permitted to change (dose reduction or increase) during the study treatment period:

- Oral 5-ASA or sulfasalazine were allowed provided that the dose was stable for at least 4 weeks prior to baseline
- Chronic treatment for UC with antibiotics (e.g., metronidazole, rifaximin) was allowed provided that the dose was stable for at least 2 weeks prior to baseline
- Oral corticosteroids were allowed during the study up to the dose of 25 mg per day of oral prednisone or equivalent, and up to 9 mg per day of budesonide, provided that the dose was stable within 2 weeks of baseline. [23]

If a patient required initiation of a new therapy for UC, the patient was withdrawn from the study and appropriate treatment was provided at the discretion of the investigator.

6.3.2 Statistical Analysis Plan

Statistical analyses of efficacy endpoints for both trials utilized the full analysis set (FAS), which was defined as all patients who were randomly assigned to tofacitinib 10 mg BID or placebo. Some sensitivity analyses were conducted using the per-protocol analysis set (PPAS), which was defined as a subset of the FAS who had no major protocol violations. Specifically, the SAPs defined the PPAS as all randomized patients except those:

- Who received prohibited medications or treatments during the treatment period
- Whose compliance with study drug was <80% or >120% over the treatment

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[23] Note: For patients taking >20 mg per day oral corticosteroids, the dose may have been decreased down to 20 mg per day at the investigator's discretion starting at week 4/visit 4 and stayed at this reduced dose thereafter for the remainder of the induction study, provided their partial Mayo score was ≤ 2, with no individual subscore >1 and rectal bleeding subscore of 0 at week 4. If a patient subsequently experienced worsening of UC signs or symptoms, in the opinion of the investigator, due to reduction in corticosteroid daily dose, the daily corticosteroid dosage for the patient could have been reverted to the preceding daily dosage instructed by the investigator; however, in that case, no further dose decrease was allowed for the remainder of the induction study.

period
- Who were randomized but took/received incorrect treatment
- Who withdrew for an administrative reason.

Analysis for the Primary Endpoint
The primary endpoint, the proportion of patients in remission at week 8, was analyzed with a Cochran-Mantel-Haenszel (CMH) test stratified by prior treatment with TNF inhibitor (TNF blocker), corticosteroid use at baseline, and geographical region. The analysis also included a normal approximation for the difference in binomial proportions, along with the 95% confidence interval (CI) for the difference in proportions.

Analysis for the Key Secondary Endpoint
The key secondary endpoint, the proportion of patients achieving an endoscopic subscore of 0 or 1 ("mucosal healing") at week 8, was analyzed in the same manner as the primary efficacy endpoint. Non-responder imputation (NRI) was utilized to handle missing endpoint data.

Multiple Testing Approach
The protocol specified that the fixed sequence procedure was used to preserve Type I error. The primary endpoint was tested at the two-sided significance level of 0.05 first. The key secondary endpoint was to be tested at the two-sided significance level of 0.05 if the primary endpoint was significant. Statistical significance was to be claimed for the key secondary endpoint only if the primary endpoint was also significant.

Handling of Missing Data
NRI was the primary method specified in the protocols for handling missing efficacy endpoint values. With NRI, patients with missing efficacy endpoint values were treated as non-responders.

Sensitivity Analyses
The protocols indicated five types of sensitivity analyses for the primary and key secondary endpoints. Those methods were: (i) use the PPAS; (ii) include only the patients randomized after Protocol Amendment 3 for Study 1094 and Protocol Amendment 2 for Study 1095; (iii) use the last observation carried forward (LOCF) method; (iv) use an observed-case analysis, where missing values were excluded; and (v) use remission data based on locally-read endoscopic scores. In the LOCF method for the primary endpoint, each Mayo individual score was considered first. The total Mayo score was then calculated based on the LOCF data of the subscores, and the primary endpoints were derived based on LOCF data of total Mayo score and LOCF data of subscores. The statistical reviewer performed an additional sensitivity analysis using responder imputation.

6.4 Efficacy Evaluation for Phase 3 Maintenance Trial (Study 1096)

6.4.1 Trial Objective, Design, and Efficacy Endpoints

The Applicant conducted a single phase 3 maintenance trial (Study 1096); the primary objective was to demonstrate the efficacy and safety of tofacitinib 5 mg BID and 10 mg BID as maintenance therapy in adult patients with moderately to severely active UC who had an inadequate response to prior conventional therapy or TNF blocker treatment.

Study 1096 was a multi-center, randomized, double-blind, placebo-controlled 53-week clinical trial for patients who completed one of the induction trials (Study 1094 or Study 1095) and demonstrated clinical response. Clinical response was defined as a decrease from induction study baseline in Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. The eligibility of a patient for the study was assessed based on study data collected at the week 8 visit of Study 1094 or Study 1095, which was considered and recorded as the baseline visit for Study 1096. This maintenance trial randomized patients to tofacitinib 10 mg BID, tofacitinib 5 mg BID, or placebo at a 1:1:1 ratio. Randomization was stratified by induction study treatment assignment and baseline remission status.

The double-blind treatment period was followed by a 4-week safety follow-up for patients who did not participate in Study 1139 (open-label extension study).

For Study 1096, the primary and key secondary endpoints were as follows:

- Primary efficacy endpoint: the proportion of patients in remission at week 52. Remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0.

- Key secondary endpoints (included in the multiple testing procedure):
    - The proportion of patients achieving a Mayo endoscopic subscore of 0 or 1 (referred to as “mucosal healing” in the protocol) at week 52.
    - The proportion of patients with sustained steroid-free remission among patients in remission at baseline of Study 1096. Sustained steroid-free remission was defined as being in remission and steroid-free at both week 24 and week 52. Steroid-free remission was defined as being in remission (a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0) in

addition to not requiring any treatment with corticosteroid for at least 4 weeks prior to the visit. A full Mayo score (including sigmoidoscopy) was collected at week 24 and week 52.

6.4.2 Statistical Analysis Plan

Statistical analyses for the efficacy endpoints used the FAS, which was defined as all patients who were randomly assigned to tofacitinib 5 mg BID, tofacitinib 10 mg BID, or placebo. Some sensitivity analyses were conducted using the mFAS, which was defined as a subset of FAS including only patients that received tofacitinib in the induction studies. Some sensitivity analyses were conducted using the PPAS, which was defined as a subset of the FAS who had no major protocol violations. Specifically, in the SAP, the PPAS was defined as all randomized patients except those:

- Who received prohibited medications or treatments during the treatment period
- Who were randomized but took/received incorrect treatment.

Analysis for the Primary Endpoint
The primary endpoint, the proportion of patients in remission at week 52, was analyzed using a CMH test stratified by induction study treatment assignment and remission at baseline. The analysis also included a normal approximation for the difference in binomial proportions, along with the 95% CI for the difference in proportions. NRI was utilized to handle missing endpoint data.

Analysis for the Key Secondary Endpoints
The key secondary endpoints, the proportion of patients achieving "mucosal healing" at week 52, and the proportion of patients with sustained steroid-free remission among patients in remission at baseline of Study 1096, were analyzed in the same manner as the primary efficacy endpoint. NRI was utilized to handle missing endpoint data.

Multiple Testing Approach
The protocol specified that the family-wise Type I error was controlled at a 5% level using a sequentially rejective Bonferroni-based iterative multiple test procedure. There were six null hypotheses of interest for the comparison of each tofacitinib dose group versus placebo:

H_{11}: No difference in the remission at week 52 for tofacitinib 10 mg BID versus placebo.
H_{12}: No difference in the "mucosal healing" at week 52 for tofacitinib 10 mg BID versus placebo.
H_{13}: No difference in the sustained steroid-free remission among patients in remission at

baseline for tofacitinib 10 mg BID versus placebo.
H_{21}: No difference in the remission at week 52 for tofacitinib 5 mg BID versus placebo.
H_{22}: No difference in the "mucosal healing" at week 52 for tofacitinib 5 mg BID versus placebo.
H_{23}: No difference in the sustained steroid-free remission among patients in remission at baseline for tofacitinib 5 mg BID versus placebo.

The multiple testing procedure was to first test the null hypothesis of no treatment effect between the tofacitinib 10 mg BID dose group and placebo on remission at week 52 at a significance level of 0.05. If the null hypothesis was rejected, the remaining 5 hypotheses were to be tested in two sequences as follows:

- Test the null hypothesis of no treatment effect between tofacitinib 5 mg BID and placebo for remission at week 52 at a significance level of 0.025. If it is rejected, continue to test the null hypothesis of no treatment effect between tofacitinib 5 mg BID and placebo for "mucosal healing" at week 52 at a significance level of 0.025. If it is rejected, continue to test the null hypothesis of no treatment effect between tofacitinib 5 mg BID and placebo for sustained steroid-free remission among remitters at a significance level of 0.025. If it is rejected, continue to test the null hypothesis of no treatment effect between tofacitinib 10 mg BID and placebo for "mucosal healing" at week 52 at an updated significance level of 0.05. If it is rejected, continue to test the null hypothesis of no treatment effect between tofacitinib 10 mg BID and placebo on the sustained steroid-free remission on remitters at the updated significance level of 0.05.

- Test the null hypothesis of no treatment effect between tofacitinib 10 mg BID and placebo for "mucosal healing" at week 52 at a significance level of 0.025. If it is rejected, continue to test the null hypothesis of no treatment effect between tofacitinib 10 mg BID and placebo for sustained steroid-free remission among remitters at a significance level of 0.025. If it is rejected, continue to test the null hypothesis of no treatment effect between tofacitinib 5 mg BID and placebo for remission at week 52 at an updated significance level of 0.05. If it is rejected, continue to test the null hypothesis of no treatment effect between tofacitinib 5 mg BID and placebo for "mucosal healing" at week 52 at the updated significance level of 0.05. If it is rejected, continue to test the null hypothesis of no treatment effect between tofacitinib 5 mg BID and placebo for sustained steroid-free remission among remitters at the

updated significance level of 0.05.

If a hypothesis failed to be rejected at the specified level in a sequence, the subsequent hypotheses in that sequence were not to be tested and were not rejected. If a hypothesis was rejected in any sequence, the associated treatment effect was to be claimed as statistically significant.

Handling of Missing Data

NRI was the primary method specified in the protocol for handling missing efficacy endpoint values.

Sensitivity Analyses

The SAP specified that sensitivity analyses for the primary endpoint were analyzed using a generalized linear mixed-effect model (GLMM) using a logit link, assuming the mechanism of the missing data was missing at random. An additional sensitivity analysis of the primary endpoint was based on remission derived from locally read endoscopic scores. Using the mFAS was another sensitivity analysis method for the key binary efficacy endpoints; that method analyzes the effects of the study drug in patients who had drug-induced remission in the induction studies rather than placebo-induced remission.

Sensitivity analyses under the missing not at random mechanism were performed for key binary efficacy endpoints at week 52 for the FAS and mFAS. These analyses assumed that all patients with missing data had a common proportion of response. Two separate analyses assuming the following common proportions were performed: 1) the observed proportion based on the non-missing data from the placebo group (copy the control); 2) the observed proportion based on the non-missing data from the tofacitinib group ((copy the active (tofacitinib 10 mg BID))). A multiple imputation approach was used under those assumptions to capture the imputation variability and combine the estimates.

In addition, the SAP specified that other sensitivity analyses for key binary efficacy endpoints at week 52 were performed for the FAS and mFAS: 1) all patients with missing data were assumed as responders; 2) all patients with missing data were assumed as responders except for patients with missing data due to withdrawal, indicated with a reason of insufficient clinical response on the patient summary case report form (those patients were considered as non-responders); and 3) the primary endpoint and key secondary endpoint analyses were performed using the PPAS. All sensitivity analyses were conducted for the FAS and the mFAS, except for the analysis that utilized the PPAS.

The statistical reviewer added a sensitivity analysis to examine a possible withdrawal effect. In that analysis, patients who discontinued from the study at or before week 8 were excluded.

6.4.3 Protocol and SAP Amendments

The SAP for Study 1096 was amended on June 27, 2016. The SAP Amendment V2 was based on Protocol Amendment 6 and comments from the FDA. Pertinent changes in the amended SAP were the inclusion of the mFAS in the analysis set section, and the use of the mFAS in the analyses of several efficacy endpoints.

6.5 Patient Characteristics for Study 1094

6.5.1 Patient Disposition

Study 1094 enrolled patients from 113 study sites in Europe, North America, and other countries, such as Japan, Australia, Colombia, and South Africa.

Of the 598 patients in the FAS (all patients who were randomized), 35 (5.9%) patients discontinued, and 563 (94.1%) patients completed the study. The proportion of patients who discontinued the study was higher in the tofacitinib 10 mg BID group compared to the placebo group (6.5% vs 3.3%).

Table 15 summarizes patient disposition by treatment group for this study.

Table 15: Patient Disposition for Study 1094

	Placebo N (%)	**Tofacitinib 10 mg BID N (%)**
Patients randomized	122	476
Prior to Protocol Amendment 3*	8	14
After Protocol Amendment 3*	114	462
FAS patients	122 (100.0)	476 (100.0)
PPAS patients	117 (95.9)	443 (93.1)
Safety analysis set patients	122 (100.0)	476 (100.0)
Patients treated	122	476
Patients completed	118 (96.7)	445 (93.5)
Patients discontinued	4 (3.3)	31 (6.5)
Primary reason for discontinuation		
Patient died	0	1 (0.2)
Related to study drug	2 (1.6)	19 (4.0)
Adverse event	1 (0.8)	8 (1.7)
Insufficient clinical response	1 (0.8)	11 (2.3)
Not related to study drug	2 (1.6)	11 (2.3)
Adverse event	0	1 (0.2)
No longer willing to participate in study	1 (0.8)	4 (0.8)
Protocol violation	1 (0.8)	4 (0.8)
Other	0	2 (0.4)

Source: Study 1094 CSR Table 7 (p. 74)

*Protocol Amendment 3 removed the tofacitinib 15 mg BID arm from the study, these patients were not included in the analysis sets.

6.5.2 Demographic and Baseline Clinical Characteristics

The demographic characteristics of Study 1094 are summarized by treatment group in **Table 16**. Most patients were male (59%) and white (82%). The mean age was approximately 42 years, ranging from 18 to 81 years, and the mean weight was approximately 73 kg, ranging from 37 to 157 kg. Demographic characteristics were generally similar between treatment groups.

Table 16: Demographic Characteristics for Study 1094 (FAS)

	Placebo (N=122)	Tofacitinib 10 mg BID (N=476)
Age (years)		
Mean (SD)	41.8 (15.3)	41.3 (14.1)
Median	42	39
Min, Max	19, 81	18, 77
Age group		
< 65 years	111 (91.0)	440 (92.4)
≥ 65 years	11 (9.0)	36 (7.6)
Gender, n (%)		
Male	77 (63.1)	277 (58.2)
Female	45 (36.9)	199 (41.8)
Race, n (%)		
White	98 (80.3)	395 (83.0)
Black	3 (2.5)	3 (0.6)
Asian	14 (11.5)	54 (11.3)
Other	3 (2.5)	15 (3.2)
Unspecified	4 (3.3)	9 (1.9)
Ethnicity, n (%)		
Hispanic/Latino	5 (4.1)	23 (4.8)
Not Hispanic/Latino	113 (92.6)	444 (93.3)
Unspecified	4 (3.3)	9 (1.9)
Weight (kg): Mean (SD)	72.7 (16.7)	72.9 (16.8)
Height (cm): Mean (SD)	172.4 (10.4)	171.4 (9.6)
BMI: Mean (SD)	24.4 (4.7)	24.7 (5.0)

Source: Study 1094 CSR Table 13 (p. 84)

Baseline Clinical Characteristics

Baseline clinical characteristics of Study 1094 were generally similar between treatment groups. See **Table 17.**

Table 17: Baseline Clinical Characteristics for Study 1094 (FAS)

	Placebo (N=122)	Tofacitinib 10 mg BID (N=476)
Duration of disease (years):		
Mean (SD)	8.4 (7.6)	8.3 (7.1)
Median (Min, Max)	6.0 (0.5, 36.2)	6.5 (0.3, 42.5)
Time since start of most recent UC flare (months):		
Mean (SD)	7.8 (12.8)	6.9 (13.5)
Median (Min, Max)	3.4 (0.0, 86.9)	2.9 (0.0, 154.4)
Number of UC flares in the last 12 months:		
Mean (SD)	1.8 (1.1)	1.9 (1.4)
Median (Min, Max)	1.5 (0.0, 9.0)	2 (0.0, 12.0)
Total Mayo score at baseline:		
Mean (SD)	9.1 (1.4)	9.0 (1.4)
Median (Min, Max)	9 (6.0, 12.0)	9 (5.0, 12.0)
Partial Mayo score at baseline:		
Mean (SD)	6.5 (1.2)	6.3 (1.2)
Median (Min, Max)	7 (4.0, 9.0)	6 (3.0, 9.0)

Source: Study 1094 CSR Table 14 (p. 86-87)
Partial Mayo score is the Mayo score without endoscopy.

6.5.3 Concomitant Medications

In Study 1094, the most frequent concomitant drug treatments for UC were aminosalicylates (tofacitinib 10 mg BID: 70.6%; placebo: 73.8%) and corticosteroids (tofacitinib 10 mg BID: 45.0%; placebo: 47.5%). The mean dose of corticosteroids at baseline was 15.8 mg/day for the tofacitinib 10 mg BID group, and 17.0 mg/day for the placebo group. Refer to **Table 18** below.

Table 18: Study 1094 Concomitant Drug Treatments for UC

	Tofacitinib 10 mg BID (N = 476) n (%)	Placebo (N = 122) n (%)	Total (N = 598) n (%)
Aminosalicylates	336 (70.6)	90 (73.8)	426 (71.2)
Antibiotics	1 (0.2)	0	1 (0.2)
Corticosteroids	214 (45.0)	58 (47.5)	272 (45.5)
Immunosuppressants	2 (0.4)	0	2 (0.3)

Source: Applicant's Study 1094 CSR p. 82/954, source Table 14.4.2.5.2 submission dated May 4, 2017

In addition, at baseline, 8.9% of patients were receiving concomitant lipid modifying agents.

6.6 Patient Characteristics for Study 1095

6.6.1 Patient Disposition

Study 1095 enrolled patients at 124 study sites in Europe, North America, and other countries, such as Korea, Australia, Colombia, and South Africa.

Of the 541 patients in the FAS, 47 (8.7%) patients discontinued, and 494 (91.3%) patients completed the study. The proportion of patients who discontinued the study was higher in the placebo group compared to the tofacitinib 10 mg BID group (13.4% versus 7.5%).

Table 19 summarizes patient disposition by treatment group for this study.

Table 19: Patient Disposition for Study 1095

	Placebo N (%)	Tofacitinib 10 mg BID N (%)
Patients randomized	112	429
Prior to Protocol Amendment 2*	4	8
After Protocol Amendment 2*	108	421
FAS patients	112 (100.0)	429 (100.0)
PPAS patients	102 (91.1)	406 (94.6)
Safety analysis set patients	112 (100.0)	429 (100.0)
Patients treated	112	429
Patients completed	97 (86.6)	397 (92.5)
Patients discontinued	15 (13.4)	32 (7.5)
Primary reason for discontinuation		
Related to study drug	12 (10.7)	21 (4.9)
Adverse event	1 (0.9)	4 (0.9)
Insufficient clinical response	11 (9.8)	17 (4.0)
Not related to study drug	3 (2.7)	11 (2.6)
Adverse event	1 (0.9)	3 (0.7)
No longer willing to participate in study	2 (1.8)	2 (0.5)
Protocol violation	0	5 (1.2)
Other	0	1 (0.2)

Source: Study 1095 CSR Table 7 (p. 75)

*Protocol Amendment 2 removed the tofacitinib 15 mg BID arm from the study, these patients were not included in the analysis sets.

6.6.2 Demographic and Baseline Clinical Characteristics

The demographic characteristics of Study 1095 are summarized by treatment group in **Table 20**. Most patients were male (58%) and white (77%). The mean age was approximately 41 years, ranging from 18 to 80 years, and the mean weight was approximately 74 kg, ranging from 42 to 136 kg. Demographic characteristics were generally similar between treatment groups.

Table 20: Demographic Characteristics for Study 1095 (FAS)

	Placebo (N=112)	**Tofacitinib 10 mg BID (N=429)**
Age (years)		
Mean (SD)	40.4 (13.2)	41.1 (13.5)
Median	38	40
Min, Max	18, 70	18, 80
Age group		
< 65 years	107 (95.5)	404 (94.2)
≥ 65 years	5 (4.5)	25 (5.8)
Gender, n (%)		
Male	55 (49.1)	259 (60.4)
Female	57 (50.9)	170 (39.6)
Race, n (%)		
White	88 (78.6)	331 (77.2)
Black	0	3 (0.7)
Asian	14 (12.5)	60 (14.0)
Other	4 (3.6)	18 (4.2)
Unspecified	6 (5.4)	17 (4.0)
Ethnicity, n (%)		
Hispanic/Latino	3 (2.7)	11 (2.6)
Not Hispanic/Latino	103 (92.0)	401 (93.5)
Unspecified	6 (5.4)	17 (4.0)
Weight (kg): Mean (SD)	73.2 (16.2)	74.4 (16.8)
Height (cm): Mean (SD)	171.1 (9.8)	172.0 (9.5)
BMI: Mean (SD)	24.9 (4.7)	25.1 (5.0)

Source: Study 1095 CSR Table 13 (p. 85)

The Applicant provided a summary of the primary efficacy endpoint in Studies 1094, 1095 and 1096 by sex, race, age, and geographic region. Results were generally consistent with the primary analysis

results for the overall population and indicated higher proportions of patients in remission in the tofacitinib 10 mg BID group compared to placebo for the induction studies, and a higher proportion of patients in remission for both 10 mg BID and 5 mg BID groups against placebo in the maintenance study, with the notable exception of race and ethnicity.

There was underrepresentation of Black patients in the controlled trials for UC, which resulted in an inability to adequately assess for similarity or differences in efficacy or safety based on this race in comparison to others. Only 0.8% (n=10/1220) of Black patients were enrolled across the pooled induction studies (cohort 1 is defined as studies 1094, 1095, and 1063), although the prevalence of UC in Blacks in the United States is approximately 25 to 150 per 100,000 persons.[24,25]

The percentage of Black patients enrolled in the tofacitinib UC program does not match the proportion of the general population that would be expected to be enrolled based on the relative prevalence of UC in Black patients in the US (~13%) in comparison to patients of other races and ethnicities enrolled (excluding patients that are designated as "other"). The prevalence of UC in White patients is approximately 89 per 100,000 persons (~47%) and this group comprised 85% of Cohort 1. Additionally, the representation of other ethnic minorities was underrepresented based on their estimated prevalence of UC in the United States, as follows: the prevalence of UC in Hispanic/Latino patients is approximately 35 per 100,000 (~19%) persons and this group comprised 3.4% (42/1220) of Cohort 1, and the prevalence of UC in Asian patients is approximately 40 per 100,000 (~21%) persons and this group comprised 11.6% (142/1220) of Cohort 1 .[20]

Baseline Clinical Characteristics

Baseline clinical characteristics of Study 1095 were generally similar between treatment groups. See Table 21.

[24] Wang YR, Loftus EV Jr, Cangemi JR, Picco MF. Racial/Ethnic and regional differences in the prevalence of inflammatory bowel disease in the United States. Digestion. 2013;88(1):20-5.

[25] Castaneda G, Liu B, Torres S, Bhuket T, Wong RJ. Race/Ethnicity-Specific Disparities in the Severity of Disease at Presentation in Adults with Ulcerative Colitis: A Cross-Sectional Study. Dig Dis Sci. 2017 Oct;62(10):2876-2881.

Table 21: Baseline Clinical Characteristics for Study 1095 (FAS)

	Placebo (N=112)	Tofacitinib 10 mg BID (N=429)
Duration of disease (years):		
Mean (SD)	7.7 (6.3)	8.0 (6.9)
Median (Min, Max)	6.2 (0.4, 27.9)	6.0 (0.4, 39.4)
Time since start of most recent UC flare (months):		
Mean (SD)	5.8 (9.9)	6.9 (13.9)
Median (Min, Max)	2.9 (0.0, 88.7)	3.3 (0.0, 143.1)
Number of UC flares in the last 12 months:		
Mean (SD)	1.7 (1.3)	2.0 (2.3)
Median (Min, Max)	1 (1.0, 12.0)	1 (0.0, 36.0)
Total Mayo score at baseline:		
Mean (SD)	8.9 (1.5)	9.0 (1.5)
Median (Min, Max)	9 (5.0, 12.0)	9 (6.0, 12.0)
Partial Mayo score at baseline:		
Mean (SD)	6.4 (1.2)	6.4 (1.3)
Median (Min, Max)	6.0 (3.0, 9.0)	6.5 (3.0, 9.0)

Source: Study 1095 CSR Table 14 (p. 87-88)
Partial Mayo score is the Mayo score without endoscopy.

6.6.3 Concomitant Medications

In Study 1095, the most frequent concomitant drug treatments for UC were aminosalicylates (tofacitinib 10 mg BID: 72.7%; placebo: 67.9%) and corticosteroids (tofacitinib 10 mg BID: 47.1%; placebo: 50.0%). The mean dose of corticosteroids at baseline was 16.4 mg/day for the tofacitinib 10 mg BID group, and 16.2 mg/day for the placebo group. Refer to **Table 22** below.

Table 22: Study 1095 Concomitant Drug Treatments for UC

	Tofacitinib 10 mg BID (N = 429) n (%)	Placebo (N = 112) n (%)	Total (N = 541) n (%)
Aminosalicylates	312 (72.7)	76 (67.9)	388 (71.7)
Antibiotics	5 (1.2)	0	5 (0.9)
Corticosteroids	202 (47.1)	56 (50.0)	258 (47.7)
Immunosuppressants	5 (1.2)	0	5 (0.9)

Source: Applicant's Study 1095 CSR p 83/938, source Table 14.4.2.5.2 submission dated May 4, 2017

6.7 Efficacy Results for Studies 1094 and 1095

6.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of patients in remission at week 8, defined as achieving a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding score of 0. The Applicant's results for the primary efficacy endpoint based on the FAS are displayed in **Table 23**. In Studies 1094 and 1095, statistically significantly higher proportions of patients in remission at week 8 were observed in the tofacitinib group relative to the placebo group (p-values of 0.0070 and 0.0005, respectively). The observed differences between the treatment groups in the proportion of patients in remission were 10.3% and 13.0% in Study 1094 and Study 1095, respectively. These results were confirmed by the statistical reviewer.

Table 23: Applicant's Primary Efficacy Endpoint Analysis: Proportion of Patients in Remission at Week 8* (FAS)

			Difference from Placebo	
Study	Placebo N=122 (1094) N=112 (1095) n (%) [95% CI]	Tofacitinib 10 mg BID N=476 (1094) N=429 (1095) n (%) [95% CI]	Difference (95% CI)[a]	P-value[b]
1094	10 (8.2) [3.3, 13.1]	88 (18.5) [15.0, 22.0]	10.3 (4.3, 16.3)	0.0070
1095	4 (3.6) [0.1, 7.0]	71 (16.6) [13.0, 20.1]	13.0 (8.1, 17.9)	0.0005

Source: Study 1094 CSR Table 16 (p. 90), Study 1095 CSR Table 16 (p. 91), statistical reviewer's analysis

*Analyzed with non-responder imputation (NRI) for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by prior treatment with TNF blocker, corticosteroid use at baseline, and geographical region.

Sensitivity Analyses

Table 24 and **Table 25** show results from the Applicant's sensitivity analyses of the primary efficacy endpoint in Studies 1094 and 1095, respectively. The results were consistent with those of the primary analysis. Results based on locally read endoscopies indicated slightly larger differences in the proportions of patients who achieved remission in the tofacitinib group compared to placebo. Results using responder imputation were the same as the primary efficacy endpoint results.

Table 24: Applicant's Sensitivity Analyses for Primary Efficacy Endpoint in Study 1094: Proportion of Patients in Remission at Week 8

	Placebo		**Tofacitinib 10 mg BID**		**Difference from Placebo**	
Method	N1	n (%)	N1	n (%)	Difference (95% CI)[a]	P-value[b]
PPAS, NRI	117	9 (7.7)	443	82 (18.5)	10.8 (4.8, 16.9)	0.0047
FAS, LOCF	122	10 (8.2)	476	88 (18.5)	10.3 (4.3, 16.3)	0.0070
FAS, observed	118	10 (8.5)	447	88 (19.7)	11.2 (5.0, 17.4)	0.0039
FAS, NRI, based on locally read endoscopy	122	14 (11.5)	476	118 (24.8)	13.3 (6.5, 20.2)	0.0017
FAS, NRI among patients randomized after Protocol Amendment 3	114	10 (8.8)	462	85 (18.4)	9.6 (3.3, 15.9)	0.0131

Source: Study 1094 CSR Table 14.2.2.2 (p. 272)

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by prior treatment with TNF blocker, corticosteroid use at baseline, and geographical region.

Table 25: Applicant's Sensitivity Analyses for Primary Efficacy Endpoint in Study 1095: Proportion of Patients in Remission at Week 8

	Placebo		Tofacitinib 10 mg BID		Difference from Placebo	
Method	N1	n (%)	N1	n (%)	Difference (95% CI)[a]	P-value[b]
PPAS, NRI	102	4 (3.9)	406	70 (17.2)	13.3 (8.1, 18.6)	0.0006
FAS, LOCF	112	4 (3.6)	429	71 (16.6)	13.0 (8.1, 17.9)	0.0005
FAS, observed	98	4 (4.1)	397	71 (17.9)	13.8 (8.4, 19.2)	0.0007
FAS, NRI, based on locally read endoscopy	112	6 (5.4)	429	89 (20.7)	15.4 (9.7, 21.1)	0.0002
FAS, NRI among patients randomized after Protocol Amendment 2	108	4 (3.7)	421	70 (16.6)	12.9 (7.9, 18.0)	0.0008

Source: Study 1095 CSR Table 14.2.2.2 (p. 263)

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by prior treatment with TNF blocker, corticosteroid use at baseline, and geographical region.

6.7.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint was the proportion of patients with "mucosal healing" at week 8, and it was defined as achieving a Mayo endoscopic subscore of 0 or 1 (where a score of 1 excludes friability). The Applicant's results for the key secondary efficacy endpoint based on the FAS are shown in **Table 26**. In Studies 1094 and 1095, statistically significantly higher proportions of patients achieved "mucosal healing" at week 8 in the tofacitinib group relative to the placebo group (p-values of 0.0005 and 0.0002, respectively). The observed differences between the treatment groups in the proportion of patients with "mucosal healing" were 15.7% and 16.8% in Study 1094 and Study 1095, respectively. These results were confirmed by the statistical reviewer.

Table 26: Applicant's Key Secondary Efficacy Endpoint Analysis: Proportion of Patients with Endoscopy Subscore of 0 or 1 ("Mucosal Healing") at Week 8* (FAS)

Study	Placebo N=122 (1094) N=112 (1095) n (%) [95% CI]	Tofacitinib 10 mg BID N=476 (1094) N=429 (1095) n (%) [95% CI]	Difference from Placebo	
			Difference (95% CI)[a]	P-value[b]
1094	19 (15.6) [9.1, 22.0]	149 (31.3) [27.1, 35.4]	15.7 (8.1, 23.4)	0.0005
1095	13 (11.6) [5.7, 17.5]	122 (28.4) [24.2, 32.7]	16.8 (9.5, 24.1)	0.0002

Source: Study 1094 CSR Table 18 (p. 92), Study 1095 CSR Table 18 (p. 92), statistical reviewer's analysis
*Analyzed with NRI for missing data
[a] 95% CI was based on the normal approximation for the difference in binomial proportions.
[b] P-value was based on CMH Chi-squared test stratified by prior treatment with TNF blocker, corticosteroid use at baseline, and geographical region.

Sensitivity Analyses

Table 27 and **Table 28** show results from the Applicant's sensitivity analyses for the key secondary efficacy endpoints in Study 1094 and Study 1095, respectively. The results were consistent with those of the key secondary endpoint analysis. Results based on locally read endoscopies indicated slightly larger differences in the proportions of patients in remission in the tofacitinib group compared to placebo.

Table 27: Applicant's Sensitivity Analysis for Key Secondary Efficacy Endpoint in Study 1094: Proportion of Patients with "Mucosal Healing" at Week 8

	Placebo		Tofacitinib 10 mg BID		Difference from Placebo	
Method	N1	n (%)	N1	n (%)	Difference (95% CI)[a]	P-value[b]
PPAS, NRI	117	17 (14.5)	443	141 (31.8)	17.3 (9.6, 25.0)	0.0001
FAS, LOCF	122	19 (15.6)	476	150 (31.5)	15.9 (8.3, 23.6)	0.0004
FAS, observed	118	19 (16.1)	447	149 (33.3)	17.2 (9.3, 25.2)	0.0002
FAS, NRI, based on locally read endoscopy	122	28 (23.0)	476	202 (42.4)	19.5 (10.8, 28.2)	<0.0001
FAS, NRI among patients randomized after Protocol Amendment 3	114	19 (16.7)	462	145 (31.4)	14.7 (6.7, 22.8)	0.0017

Source: Study 1094 CSR Table 14.2.3.2 (p. 280)

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by prior treatment with TNF blocker, corticosteroid use at baseline, and geographical region.

Table 28: Applicant's Sensitivity Analysis for Key Secondary Efficacy Endpoint in Study 1095: Proportion of Patients with "Mucosal Healing" at Week 8

	Placebo		Tofacitinib 10 mg BID		Difference from Placebo	
Method	N1	n (%)	N1	n (%)	Difference (95% CI)[a]	P-value[b]
PPAS, NRI	102	12 (11.8)	406	119 (29.3)	17.5 (9.9, 25.2)	0.0002
FAS, LOCF	112	13 (11.6)	429	123 (28.7)	17.1 (9.7, 24.4)	0.0001
FAS, observed	98	13 (13.3)	398	122 (30.7)	17.4 (9.3, 25.5)	0.0004
FAS, NRI, based on locally read endoscopy	112	17 (15.2)	429	156 (36.4)	21.2 (13.1, 29.2)	<0.0001
FAS, NRI among patients randomized after Protocol Amendment 2	108	13 (12.0)	421	121 (28.7)	16.7 (9.2, 24.2)	0.0003

Source: Study 1095 CSR Table 14.2.3.2 (p. 268)

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by prior treatment with TNF blocker, corticosteroid use at baseline, and geographical region.

6.7.3 Additional Efficacy Analyses

The Applicant performed primary and secondary endpoint subgroup analyses for Studies 1094, 1095, and 1096 by refractory disease status, which was defined as those who had a history of TNF blocker failure, and primary endpoint subgroup analyses by gender, race, age, and geographic region. Also, per the Agency's request, the Applicant performed an analysis of the modified symptomatic remission endpoint in Studies 1094 and 1095. The definition of modified symptomatic remission is most consistent with the Agency's current thinking on how best to strictly define remission in UC. Since these endpoints were not prespecified with a suitable multiplicity adjustment, their results are considered exploratory. Results by refractory disease status for the primary endpoint are discussed further in the "Key Subgroup Analyses of Interest" section.

Table 29 contains the Applicant's summary of the modified symptomatic remission endpoint in Studies 1094 and 1095. Modified symptomatic remission was defined as a stool frequency subscore of 0, rectal bleeding subscore of 0, and a Mayo endoscopic subscore of 0 or 1, where 1 does not include friability. In both studies, the proportions of patients who met the endpoint were smaller than the proportions in the primary analysis, and the differences in proportions in the tofacitinib group compared to placebo were smaller than the differences in the primary analysis.

Table 29: Applicant's Analysis: Proportion of Patients in Modified Symptomatic Remission at Week 8* (FAS)

			Difference from Placebo	
Study	**Placebo N=122 (1094) N=112 (1095) n (%)**	**Tofacitinib 10 mg BID N=476 (1094) N=429 (1095) n (%)**	**Difference (95% CI)[a]**	**P-value[b]**
1094	7 (5.7)	56 (11.8)	6.0 (1.0, 11.1)	0.0601
1095	3 (2.7)	46 (10.7)	8.0 (3.9, 12.2)	0.0090

Source: Study 1094 Table 2.3.1.a, Study 1095 Table 2.3.1.a

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by prior treatment with TNF blocker, corticosteroid use at baseline, and geographical region.

Table 30 contains the Applicant's summary of the modified symptomatic remission endpoint in Studies 1094 and 1095 stratified by prior TNF blocker failure. The differences in proportions were larger for the subgroup without prior TNF blocker failure.

Table 30: Applicant's Analysis: Proportion of Patients in Modified Symptomatic Remission at Week 8 by Prior TNF Blocker Failure* (FAS)

Study **Prior TNF Blocker Failure**	**Placebo** **N=122 (1094)** **N=112 (1095)**		**Tofacitinib 10 mg BID** **N=476 (1094)** **N=429 (1095)**		**Difference from Placebo**
	N1	n (%)	N1	n (%)	(%)
1094					
Yes	64	1 (1.6)	243	13 (5.3)	3.8
No	58	6 (10.3)	233	43 (18.5)	8.1
1095					
Yes	60	0 (0.0)	222	17 (7.7)	7.7
No	52	3 (5.8)	207	29 (14.0)	8.2

Source: Study 1094 Table 229a.28.1, Study 1095 Table 229a.28.2
*Analyzed with NRI for missing data

Table 31 through **Table 34** contain the Applicant's summary of the exploratory analyses of the primary efficacy endpoint in Studies 1094 and 1095 by gender, race (White, Black, Asian, and Other), age (18-64 and 65+ years) and geographic region (Europe, North America, and Other) subgroups. Results were generally consistent with the primary analysis results for the overall population and indicated higher proportions of patients in remission in the tofacitinib 10 mg BID group compared to placebo except for the Black subgroup in both studies, which had a small sample size (0 or 3 patients in each treatment group).

Table 31: Applicant's Primary Endpoint Subgroup Analysis by Gender: Proportion of Patients in Remission at Week 8* (FAS)

Study Gender	Placebo N=122 (1094) N=112 (1095)		Tofacitinib 10 mg BID N=476 (1094) N=429 (1095)		Difference from Placebo
	N1	n (%)	N1	n (%)	(%)
1094					
Male	77	4 (5.2)	277	49 (17.7)	12.5
Female	45	6 (13.3)	199	39 (19.6)	6.3
1095					
Male	55	3 (5.5)	259	33 (12.7)	7.3
Female	57	1 (1.8)	170	38 (22.4)	20.6

Source: Study 1094 IR Table 219a.1.1, Study 1095 IR Table 219a.2.1

*Analyzed with NRI for missing data

Table 32: Applicant's Primary Endpoint Subgroup Analysis by Race: Proportion of Patients in Remission at Week 8* (FAS)

Study Race	Placebo N=122 (1094) N=112 (1095)		Tofacitinib 10 mg BID N=476 (1094) N=429 (1095)		Difference from Placebo
	N1	n (%)	N1	n (%)	(%)
1094					
White	98	8 (8.2)	395	71 (18.0)	9.8
Black	3	1 (33.3)	3	1 (33.3)	0
Asian	14	1 (7.1)	54	12 (22.2)	15.1
Other	3	0	15	4 (26.7)	26.7
1095					
White	88	4 (4.5)	331	55 (16.6)	12.1
Black	0	0	3	0	NE
Asian	14	0	60	10 (16.7)	16.7
Other	4	0	18	3 (16.7)	16.7

Source: Study 1094 IR Table 219a.1.1, Study 1095 IR Table 219a.2.1

*Analyzed with NRI for missing data

NE=not evaluable

Table 33: Applicant's Primary Endpoint Subgroup Analysis by Age: Proportion of Patients in Remission at Week 8* (FAS)

Study Age Category	Placebo N=122 (1094) N=112 (1095)		Tofacitinib 10 mg BID N=476 (1094) N=429 (1095)		Difference from Placebo
	N1	n (%)	N1	n (%)	(%)
1094					
< 65 years	111	8 (7.2)	440	78 (17.7)	10.5
≥ 65 years	11	2 (18.2)	36	10 (27.8)	9.6
1095					
< 65 years	107	4 (3.7)	404	69 (17.1)	13.3
≥ 65 years	5	0	25	2 (8.0)	8.0

Source: Study 1094 IR Table 219a.1.1, Study 1095 IR Table 219a.2.1

*Analyzed with NRI for missing data

Table 34: Applicant's Primary Endpoint Subgroup Analysis by Geographic Region: Proportion of Patients in Remission at Week 8* (FAS)

Study Region	Placebo N=122 (1094) N=112 (1095)		Tofacitinib 10 mg BID N=476 (1094) N=429 (1095)		Difference from Placebo
	N1	n (%)	N1	n (%)	(%)
1094					
Europe	72	7 (9.7)	285	49 (17.2)	7.5
North America	30	1 (3.3)	102	17 (16.7)	13.3
Other	20	2 (10.0)	89	22 (24.7)	14.7
1095					
Europe	63	2 (3.2)	249	48 (19.3)	16.1
North America	23	2 (8.7)	85	11 (12.9)	4.2
Other	26	0 (0.0)	95	12 (12.6)	12.6

Source: Study 1094 CSR Table 17 (p. 91), Study 1095 CSR Table 17 (p. 91)

*Analyzed with NRI for missing data

Additionally, the SAP indicated that all endpoint results that used the stool frequency subscore were based on the average number (rounded to integer) of stools during the prior 3 days minus the normal

number of stools per day reported by a patient. Endpoint results that used the rectal bleeding subscore were based on the average number (rounded to integer) of the 3 days' rectal bleeding scores prior to a study visit. **Table 35** contains the Applicant's additional analysis of the primary efficacy endpoint in Studies 1094 and 1095 using the worst stool frequency and rectal bleeding subscores. The results were consistent with those of the primary analysis.

Table 35: Applicant's Primary Endpoint Analysis: Proportion of Patients in Remission at Week 8 Using the Worst Stool Frequency and Rectal Bleeding Subscores* (FAS)

			Difference from Placebo	
Study	**Placebo N=122 (1094) N=112 (1095) n (%)**	**Tofacitinib 10 mg BID N=476 (1094) N=429 (1095) n (%)**	**Difference (95% CI)[a]**	**P-value[b]**
1094	6 (4.9)	76 (16.0)	11.0 (6.0, 16.1)	0.0019
1095	1 (0.9)	58 (13.5)	12.6 (9.0, 16.3)	0.0002

Source: Study 1094 Table 2.3.3.a, Study 1095 Table 2.3.3.a

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by prior treatment with TNF blocker, corticosteroid use at baseline, and geographical region.

6.8 Patient Characteristics for Study 1096

6.8.1 Patient Disposition

Study 1096 enrolled patients at 196 study sites in Europe, North America, and other countries, such as Japan, Australia, Colombia, and South Africa.

Of the 592 patients in the safety analysis set, 302 (51.0%) patients discontinued, and 290 (49.0%) completed the study. The proportion of patients who discontinued the study was higher in the placebo group compared to the tofacitinib groups (73.2% in the placebo group compared to 43.9% and 35.7% in the tofacitinib 5 mg BID and tofacitinib 10 mg BID groups, respectively).

Table 36 summarizes patient disposition by treatment group for this study.

Table 36: Patient Disposition for Study 1096

	Placebo N (%)	Tofacitinib 5 mg BID N (%)	Tofacitinib 10 mg BID N (%)
Patients randomized	198	198	197
FAS patients	198 (100.0)	198 (100.0)	197 (100.0)
PPAS patients	188 (94.9)	183 (92.4)	186 (94.4)
mFAS patients	174 (87.9)	176 (88.9)	173 (87.8)
Safety analysis set patients	198 (100.0)	198 (100.0)	196 (99.5)
Patients treated	198	198	196
Patients completed	53 (26.8)	111 (56.1)	126 (64.3)
Patients discontinued	145 (73.2)	87 (43.9)	70 (35.7)
Primary reason for discontinuation			
Related to study drug	134 (67.7)	74 (37.4)	61 (31.1)
Adverse event	2 (1.0)	4 (2.0)	8 (4.1)
Insufficient clinical response	132 (66.7)	70 (35.4)	53 (27.0)
Not related to study drug	11 (5.6)	13 (6.6)	9 (4.6)
Adverse event	5 (2.5)	1 (0.5)	1 (0.5)
No longer willing to participate in study	5 (2.5)	6 (3.0)	3 (1.5)
Protocol violation	0	0	1 (0.5)
Lost to follow-up	1 (0.5)	3 (1.5)	2 (1.0)
Discontinued due to pregnancy	0	1 (0.5)	1 (0.5)
Other	0	2 (1.0)	1 (0.5)

Source: Study 1096 CSR Table 6 (p. 88)

6.8.2 Demographic and Baseline Clinical Characteristics

The demographic characteristics of Study 1096 are summarized by treatment group in **Table 37**. Most patients were male (56%) and white (80%). The mean age was approximately 43 years, ranging from 18 to 80 years, and the mean weight was approximately 75 kg, ranging from 31 to 155 kg. Demographic characteristics were generally similar across treatment groups.

Table 37: Demographic Characteristics for Study 1096 (FAS)

	Placebo (N=198)	Tofacitinib 5 mg BID (N=198)	Tofacitinib 10 mg BID (N=197)
Age (years)			
Mean (SD)	43.4 (14.0)	41.9 (13.7)	42.9 (14.4)
Median	42.0	41.0	40.0
Min, Max	19, 80	18, 79	18, 79
Age group			
< 65 years	180 (90.9)	185 (93.4)	180 (91.4)
≥ 65 years	18 (9.1)	13 (6.6)	17 (8.6)
Gender, n (%)			
Male	116 (58.6)	103 (52.0)	110 (55.8)
Female	82 (41.4)	95 (48.0)	87 (44.2)
Race, n (%)			
White	155 (78.3)	164 (82.8)	153 (77.7)
Black	3 (1.5)	2 (1.0)	0
Asian	26 (13.1)	23 (11.6)	25 (12.7)
Other	9 (4.5)	5 (2.5)	9 (4.6)
Unspecified	2 (2.5)	4 (2.0)	10 (5.1)
Ethnicity, n (%)			
Hispanic/Latino	7 (3.5)	5 (2.5)	7 (3.6)
Not Hispanic/Latino	186 (93.9)	189 (95.5)	180 (91.4)
Unspecified	5 (2.5)	4 (2.0)	10 (5.1)
Weight (kg): Mean (SD)	76.2 (16.7)	73.4 (17.8)	74.6 (15.1)
Height (cm): Mean (SD)	171.5 (10.0)	170.7 (9.5)	171.0 (9.5)
BMI: Mean (SD)	25.8 (4.9)	25.1 (5.1)	25.5 (4.8)

Source: Study 1096 CSR Table 13 (p. 98)

Baseline Clinical Characteristics

Baseline clinical characteristics of Study 1096 were generally similar across treatment groups. See **Table 38**. The majority (64.8%) of patients had Mayo scores ≥ 3 at baseline; the median baseline Mayo score was 3.3, ranging from 0.0 to 10.0.

Table 38: Baseline Clinical Characteristics for Study 1096 (FAS)

	Placebo (N=198)	Tofacitinib 5 mg BID (N=198)	Tofacitinib 10 mg BID (N=197)
Treatment assignment in induction study, n (%)			
Placebo	24 (12.1)	22 (11.1)	24 (12.2)
Tofacitinib 10 mg and 15 mg	174 (87.9)	176 (88.9)	173 (87.8)
Tofacitinib 10 mg	167 (84.3)	170 (85.9)	167 (84.8)
Remission at baseline, n (%)			
Yes	59 (29.8)	65 (32.8)	55 (27.9)
No	139 (70.2)	133 (67.2)	142 (72.1)
"Mucosal healing" at baseline, n (%)			
Yes	101 (51.0)	105 (53.0)	89 (45.2)
No	97 (49.0)	93 (47.0)	108 (54.8)
Mayo score, n (%)			
< 3	74 (37.4)	71 (35.9)	64 (32.5)
≥ 3	124 (62.6)	127 (64.1)	133 (67.5)
Mayo score: Mean (SD) Median (Min, Max)	 3.3 (1.8) 3 (0.0-8.0)	 3.3 (1.8) 3 (0.0-10.0)	 3.3 (1.8) 3 (0.0-7.0)
Partial Mayo score, n (%)			
< 2	85 (42.9)	89 (44.9)	88 (44.7)
≥ 2	113 (57.1)	109 (55.1)	109 (55.3)
Partial Mayo score: Mean (SD) Median (Min, Max)	 1.8 (1.4) 2 (0.0-7.0)	 1.8 (1.3) 2 (0.0-7.0)	 1.8 (1.3) 2 (0.0-6.0)

Source: Study 1096 CSR Table 15 (p. 101)

"Mucosal healing" is defined by a Mayo endoscopic subscore of 0 or 1.

Partial Mayo score is the Mayo score without endoscopy.

6.8.3 Concomitant Medications

In Study 1096, the most frequent concomitant drug treatments for UC were aminosalicylates (tofacitinib 5 mg BID: 72.7%; tofacitinib 10 mg BID: 72.4%; placebo: 74.7%) and corticosteroids

(tofacitinib 5 mg BID: 52%; tofacitinib 10 mg BID: 46.4%; placebo: 53%). The mean prednisone equivalent dose of oral corticosteroids at baseline was 14.9 mg/day for the tofacitinib 5 mg BID group, 14.4 mg/day for the 10 mg BID group, and 15.8 mg/day for the placebo group. Refer to **Table 39** below.

Table 39: Study 1096 Concomitant Drug Treatments for UC

	Tofacitinib 5 mg BID (N = 198) n (%)	Tofacitinib 10 mg BID (N = 196) n (%)	Placebo (N = 198) n (%)	Total (N = 592) n (%)
Aminosalicylates	144 (72.7)	142 (72.4)	148 (74.7)	434 (73.3)
Antibiotics	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.3)
Oral corticosteroids	103 (52.0)	91 (46.4)	105 (53.0)	299 (50.5)
Probiotics/Bacterial therapy	5 (2.5)	3 (1.5)	6 (3.0)	14 (2.4)

Source: Applicant's Study 1096 CSR p. 96/3827, source Table 14.4.2.5.2 submission dated May 4, 2017

6.9 Efficacy Results for Study 1096

6.9.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of patients in remission at week 52 for patients with UC who completed one of the induction studies (Study 1094 or Study 1095) and demonstrated a clinical response. The Applicant's results for the primary efficacy endpoint based on the FAS are shown in **Table 40**. Statistically significantly higher proportions of patients in remission at week 52 were observed in each tofacitinib group relative to the placebo group (p-values < 0.0001 for both tofacitinib groups). The observed differences between the tofacitinib treatment groups and placebo in the proportion of patients in remission were 23.2% and 29.5% for the tofacitinib 5 mg BID group and tofacitinib 10 mg BID group, respectively. These results were confirmed by the statistical reviewer.

Table 40: Applicant's Primary Efficacy Endpoint Analysis: Proportion of Patients in Remission at Week 52* (FAS)

Placebo N=198 n (%) [95% CI]	Tofacitinib 5 mg BID N=198 n (%) [95% CI]	Difference from Placebo		Tofacitinib 10 mg BID N=197 n (%) [95% CI]	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
22 (11.1) [6.7, 15.5]	68 (34.3) [27.7, 41.0]	23.2 (15.3, 31.2)	<0.0001	80 (40.6) [33.8, 47.5]	29.5 (21.4, 37.6)	<0.0001

Source: Study 1096 CSR Table 21 (p. 109), statistical reviewer's analysis

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment and remission at baseline.

Both the tofacitinib 5 mg BID and 10 mg BID doses are efficacious for the primary endpoint of remission at week 52 of treatment in comparison to placebo. There appears to be numerically greater efficacy in patients treated with the tofacitinib 10 mg BID dose, in comparison to the tofacitinib 5 mg BID dose; however, the observed difference in proportions between the tofacitinib 10 mg BID group and the tofacitinib 5 mg BID group was 6.3% (95% CI: (-3.3, 15.8)), and the CMH test comparing the proportions between the tofacitinib groups was not statistically significant (p-value = 0.1534). As a result, the relative safety of tofacitinib 10 mg BID vs tofacitinib 5 mg BID should be considered when selecting a dose for long-term use. The potential incremental benefit of use of tofacitinib 10 mg BID over 5 mg BID long-term was also discussed at the GIDAC meeting held on March 8, 2018 (refer to summary of AC discussion below).

Maintenance of Remission

Although not prespecified as a key secondary endpoint, the Agency considered an analysis of "maintenance of remission", defined as remission at week 52 among patients in remission at baseline, and results were as follows: among a total of 165 patients in remission at baseline of Study 1096, 28 patients (46.7%) in the tofacitinib 5 mg BID group and 30 patients (56.6%) in the tofacitinib 10 mg BID group were in remission at week 52. The differences in proportions relative to placebo were 37.1% and 47.0% for the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group, respectively. This analysis includes only patients who received active treatment in induction Study 1094/1095 (i.e., excludes placebo responders). Results for this secondary endpoint are shown in Table 41.

Table 41: Applicant's Secondary Efficacy Endpoint Analysis: "Maintenance of Remission" – Remission Among Patients in Remission at Baseline* (mFAS)

Visit	Placebo		Tofacitinib 5 mg BID			Tofacitinib 10 mg BID		
	N1	n (%)	N1	n (%)	Difference from Placebo (95% CI)[a]	N1	n (%)	Difference from Placebo (95% CI)[a]
Week 52	52	5 (9.6)	60	28 (46.7)	37.1 (22.1, 52.0)	53	30 (56.6)	47.0 (31.4, 62.6)

Source: Study 1096 CSR Table 14.2.5.1.2 (p. 723)
*Analyzed with NRI for missing data
[a] 95% CI was based on the normal approximation for the difference in binomial proportions.
N1 = number of patients in the analysis set.
p-values for differences at week 52 are both <0.0001.

As noted in the Agency's recent Draft Guidance on UC, it is important to determine whether the population of patients in remission at week 8 and week 52 remained in remission during the intervening time. Ideally, "maintenance of remission" would be supported by data at some interval visits in between the start and end of the study, demonstrating that patients did in fact stay well between week 8 and week 52, and that the measure is not erroneously capturing patients who had flares sometime between week 8 and week 52 but recovered by week 52. The Agency explored this concept with what the Applicant has defined as "sustained remission." This exploratory analysis defined "sustained remission" as remission at both week 24 and week 52, among patients in remission at baseline of Study 1096. Results were as follows: among patients in remission at baseline of Study 1096, 24 patients (36.9%) in the tofacitinib 5 mg BID group and 26 patients (47.3%) in the tofacitinib 10 mg BID group were in sustained remission at week 52. The differences in proportions relative to placebo were 31.8% and 42.2% for the tofacitinib 5 mg BID group and tofacitinib 10 mg BID group, respectively. Results for this secondary endpoint are shown in Appendix **Table 90**. Very small numbers and lack of multiplicity control for this analysis limit the ability to draw firm conclusions from this exploratory analysis. However, this concept was also further explored using a more stringent definition (sustained corticosteroid-free remission) which was a key secondary endpoint and is discussed further below.

Sensitivity Analyses

Sensitivity analysis results for the primary efficacy endpoint were generally consistent with the primary analysis results. Results based on locally read endoscopies, as well as results based on GLMMs, indicated larger differences in the proportions of patients in remission in the tofacitinib groups

compared to placebo. Results based on responder imputation indicated slightly smaller differences in the proportions of patients in remission in the tofacitinib groups compared to placebo. Results from the analysis that examined a possible withdrawal effect were similar to those for the primary efficacy endpoint; this suggests that the occurrence of patient discontinuation at or before week 8 did not have a large impact on the study's primary efficacy endpoint. Sensitivity analysis results are shown in **Table 91** through **Table 99** in the Appendix.

6.9.2 Key Secondary Efficacy Endpoints

"Mucosal Healing" and Sustained Steroid-Free Remission

Study 1096 had two key secondary endpoints: the proportion of patients achieving endoscopic subscore of 0 or 1 ("mucosal healing") at week 52, and the proportion of patients with sustained steroid-free remission among patients in remission at baseline of Study 1096. Statistically significantly higher proportions of patients were observed in each tofacitinib group relative to the placebo group for both endpoints (p-values < 0.0001 for both tofacitinib groups in both key secondary endpoints). The Applicant's results for the key secondary efficacy endpoints based on the FAS are shown in **Table 42** and **Table 43**.

"Mucosal Healing"

The observed differences between the tofacitinib treatment groups and placebo in the proportion of patients with "mucosal healing" were 24.2% and 32.6% for the tofacitinib 5 mg BID group and tofacitinib 10 mg BID group, respectively. These results were confirmed by the statistical reviewer.

Table 42: Applicant's Key Secondary Efficacy Endpoint Analysis: Proportion of Patients with "Mucosal Healing" at Week 52* (FAS)

Placebo N=198 n (%) [95% CI]	Tofacitinib 5 mg BID N=198 n (%) [95% CI]	Difference from Placebo		Tofacitinib 10 mg BID N=197 n (%) [95% CI]	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
26 (13.1) [8.4, 17.8]	74 (37.4) [30.6, 44.5]	24.2 (16.0, 32.5)	<0.0001	90 (45.7) [38.7, 52.6]	32.6 (24.2, 41.0)	<0.0001

Source: Study 1096 CSR Table 24 (p. 115), statistical reviewer's analysis

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment and remission at baseline.

Sustained Steroid-free Remission

The observed differences between the tofacitinib treatment groups and placebo in the proportion of patients in sustained steroid-free remission were 30.3% and 42.2% for the tofacitinib 5 mg BID group and tofacitinib 10 mg BID group, respectively. The analysis of the specified key secondary endpoint was conducted in the FAS based on all patients in remission at baseline of Study 1096, as specified in the SAP. These results were confirmed by the statistical reviewer.

Table 43: Applicant's Key Secondary Efficacy Endpoint Analysis: Proportion of Patients in Sustained Steroid-Free Remission Among Patients in Remission at Baseline* (FAS)

Placebo N=198		**Tofacitinib 5 mg BID N=198**		**Difference from Placebo**		**Tofacitinib 10 mg BID N=197**		**Difference from Placebo**	
N1	n (%) [95% CI]	N1	n (%) [95% CI]	Difference (95% CI)[a]	P-value[b]	N1	n (%) [95% CI]	Difference (95% CI)[a]	P-value[b]
59	3 (5.1) [0.0, 10.7]	65	23 (35.4) [23.8, 47.0]	30.3 (17.4, 43.2)	<0.0001	55	26 (47.3) [34.1, 60.5]	42.2 (27.9, 56.5)	<0.0001

Source: Study 1096 CSR Table 27 (p. 121), statistical reviewer's analysis

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment.

N1 = number of patients in each group at week 52, and used as the denominator in the percentage calculation.

Sustained corticosteroid-free remission is the most stringent and clinically important of the endpoints achieved in this program, as it reflects that patients were able to achieve remission, discontinue corticosteroids, and remain in remission through 52 weeks, confirmed with the 24-week interim time point. Adverse reactions associated with long-term treatment with systemic corticosteroids are significant and therapy which results in remission, but does not enable patients to wean from corticosteroid treatment, may be of limited utility. Thus, success on this endpoint is supportive of the overall benefit of treatment with tofacitinib.

In addition to the analysis described in the table above, an alternate approach is to consider only those who achieved sustained steroid-free remission, out of the population of patients who were on steroids and in remission on entry to Study 1096. These data are presented in Table 44 for the mFAS (limited to those who received active treatment in Study 1094/1095). A very small sample size limits the utility of this exploratory analysis, but the trends are consistent with those seen in the prespecified key secondary endpoint analysis presented in **Table 43**.

Table 44: Applicant's Exploratory Analysis: Proportion of Patients in Sustained Steroid-Free Remission Among Patients in Remission at Baseline of Study 1096 Who Were Receiving Steroids at Baseline* (mFAS)

Placebo N=174		**Tofacitinib 5 mg BID N=176**		**Difference from Placebo[a]**	**Tofacitinib 10 mg BID N=197**		**Difference from Placebo[a]**
N1	n (%)	N1	n (%)	Difference (95% CI)	N1	n (%)	Difference (95% CI)
27	2 (7.4)	26	4 (15.4)	8.0 (-9.0, 25.0)	20	5 (25.0)	17.6 (-3.8, 39.0)

Source: Reviewer's table created from tables provided in Applicant's response to IR received 5 Feb 2018 (Table 243a.21.1, Table 243a.21.2)

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

N = number of patients in remission at baseline regardless of steroid use at baseline.

N1 = number of patients in each group at both week 24 and week 52, and used as the denominator in the percentage calculation.

Sensitivity Analyses

Sensitivity analysis results for the key secondary endpoints were consistent with those of the key secondary endpoint analysis. Results based on locally read endoscopies indicated larger differences in the proportions of patients who met the key secondary endpoints in the tofacitinib groups compared to placebo. Results from the analyses that examined a possible withdrawal effect were similar to those for the key secondary efficacy endpoints; this suggests that the occurrence of patient discontinuation at or before week 8 did not have a large impact on the study's key secondary efficacy endpoints. Sensitivity analysis results are shown in **Table 100** through **Table 105** in the Appendix.

6.9.3 Additional Efficacy Analyses

Table 45 contains the Applicant's summary of the modified symptomatic remission endpoint (defined as a stool frequency subscore of 0, rectal bleeding subscore of 0, and a Mayo endoscopic subscore of 0 or 1, where 1 does not include friability). The proportions of patients who met this endpoint were smaller than the proportions in the primary analysis, and the differences in proportions in the tofacitinib groups compared to placebo were smaller than the differences in the primary analysis.

Table 45: Applicant's Analysis: Proportion of Patients in Modified Symptomatic Remission at Week 52* (FAS)

Placebo N=198 n (%)	Tofacitinib 5 mg BID N=198 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=197 n (%)	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
14 (7.1)	45 (22.7)	15.7 (8.8, 22.5)	<0.0001	53 (26.9)	19.8 (12.7, 27.0)	<0.0001

Source: Study 1096 Table 2.3.1.b

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment and remission at baseline.

Table 46 contains the Applicant's summary of the modified symptomatic remission endpoint stratified by prior TNF blocker failure. The differences in proportions were larger for the subgroup without prior TNF blocker failure.

Table 46: Applicant's Analysis: Proportion of Patients in Modified Symptomatic Remission at Week 52 by Prior TNF Blocker Failure* (FAS)

Prior TNF Blocker Failure	Placebo		Tofacitinib 5 mg BID			Tofacitinib 10 mg BID		
	N1	N=198 n (%)	N1	N=198 n (%)	Difference from Placebo (%)	N1	N=197 n (%)	Difference from Placebo (%)
Yes	89	7 (7.9)	83	15 (18.1)	10.2	93	18 (19.4)	11.5
No	109	7 (6.4)	115	30 (26.1)	19.7	104	35 (33.7)	27.2

Source: Study 1096 Table 229a.29.2

*Analyzed with NRI for missing data

6.9.4 Demographic and Regional Subgroup Analyses

Table 47 through **Table 50** contain the Applicant's exploratory summary of the primary efficacy endpoint in Study 1096 by gender, race (White, Black, Asian, and Other), age (18-64 and 65+ years), and geographic region (Europe, North America, and Other) subgroups. Results were generally consistent with the primary analysis results for the overall population and indicated higher proportions of patients in remission in the tofacitinib groups compared to placebo except for the Black subgroup, which had a small sample size (0, 2, or 3 patients in each treatment group).

Table 47: Applicant's Primary Endpoint Subgroup Analysis by Gender: Proportion of Patients in Remission at Week 52* (FAS)

	Placebo		Tofacitinib 5 mg BID			Tofacitinib 10 mg BID		
Gender	N1	N=198 n (%)	N1	N=198 n (%)	Difference from Placebo (%)	N1	N=197 n (%)	Difference from Placebo (%)
Male	116	11 (9.5)	103	40 (38.8)	29.4	110	40 (36.4)	26.9
Female	82	11 (13.4)	95	28 (29.5)	16.1	87	40 (46.0)	32.6

Source: Study 1096 CSR Table 23 (p. 112)

*Analyzed with NRI for missing data

Table 48: Applicant's Primary Endpoint Subgroup Analysis by Race: Proportion of Patients in Remission at Week 52* (FAS)

	Placebo		**Tofacitinib 5 mg BID**			**Tofacitinib 10 mg BID**		
Race	N1	N=198 n (%)	N1	N=198 n (%)	Difference from Placebo (%)	N1	N=197 n (%)	Difference from Placebo (%)
White	155	18 (11.6)	164	53 (32.3)	20.7	153	60 (39.2)	27.6
Black	3	0	2	0	NE	0	0	NE
Asian	26	4 (15.4)	23	11 (47.8)	32.4	25	11 (44.0)	28.6
Other	9	0	5	2 (40.0)	40.0	9	6 (66.7)	66.7

Source: Study 1096 Table 219a.3.1

*Analyzed with NRI for missing data

NE=not evaluable

Table 49: Applicant's Primary Endpoint Subgroup Analysis by Age: Proportion of Patients in Remission at Week 52* (FAS)

	Placebo		Tofacitinib 5 mg BID			Tofacitinib 10 mg BID		
Age Category	N1	N=198 n (%)	N1	N=198 n (%)	Difference from Placebo (%)	N1	N=197 n (%)	Difference from Placebo (%)
< 65 years	180	21 (11.7)	185	63 (34.1)	22.4	180	72 (40.0)	28.3
≥ 65 years	18	1 (5.6)	13	5 (38.5)	32.9	17	8 (47.1)	41.5

Source: Study 1096 Table 219a.3.1

*Analyzed with NRI for missing data

Table 50: Applicant's Primary Endpoint Subgroup Analysis by Geographic Region: Proportion of Patients in Remission at Week 52* (FAS)

	Placebo		Tofacitinib 5 mg BID			Tofacitinib 10 mg BID		
Region	N1	N=198 n (%)	N1	N=198 n (%)	Difference from Placebo (%)	N1	N=197 n (%)	Difference from Placebo (%)
Europe	112	14 (12.5)	113	39 (34.5)	22.0	121	47 (38.8)	26.3
North America	45	4 (8.9)	39	10 (25.6)	16.8	44	19 (43.2)	34.3
Other	41	4 (9.8)	46	19 (41.3)	31.5	32	14 (43.8)	34.0

Source: Study 1096 CSR Table 23 (p. 112)

*Analyzed with NRI for missing data

Table 51 contains the Applicant's additional analysis of the primary efficacy endpoint using the worst stool frequency and rectal bleeding subscores. The results were consistent with those of the primary analysis.

Table 51: Applicant's Primary Endpoint Analysis: Proportion of Patients in Remission at Week 52 Using the Worst Stool Frequency and Rectal Bleeding Subscores* (FAS)

Placebo N=198 n (%)	Tofacitinib 5 mg BID N=198 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=197 n (%)	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
18 (9.1)	64 (32.3)	23.2 (15.6, 30.9)	<0.0001	73 (37.1)	28.0 (20.1, 35.8)	<0.0001

Source: Study 1096 Table 2.3.3.b

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment and remission at baseline.

6.10 Key Subgroup Analyses of Interest Relevant to Dosing Recommendations

The Applicant conducted subgroup analyses for the purposes of supporting alternative dosing regimens/recommendations. Specifically, additional exploratory efficacy analyses were conducted in the IndNR subgroup (patients in Study 1094/1095 who did not achieve clinical response by week 8, and who were then treated with an additional 8 weeks of 10 mg BID open-label tofacitinib in the open-label extension (Study 1139)). Additionally, exploratory efficacy analyses were submitted based on refractory disease status.

Table 52 contains the Applicant's summary of the exploratory analyses of the primary efficacy endpoint (remission) in induction Studies 1094 and 1095 by prior (yes/no) TNF blocker failure. **Table 53** contains a similar summary for Study 1096. In all three studies, results were generally consistent with the primary analysis results for the overall population. In Studies 1094 and 1095, the differences in proportions in the tofacitinib groups compared to placebo were similar between the two TNF blocker subgroups, and the differences in proportions of patients who were in remission at week 8 compared to placebo were smaller in the subgroup with prior TNF blocker failure compared to the subgroup without prior TNF blocker failure.

Table 52: Applicant's Study 1094 and Study 1095 Primary Efficacy Endpoint Exploratory Subgroup Analysis by Prior TNF Blocker Failure: Proportion of Patients in Remission at Week 8* (FAS)

Study Prior TNF Blocker Failure	Placebo N=122 (1094) N=112 (1095)		Tofacitinib 10 mg BID N=476 (1094) N=429 (1095)		Difference from Placebo (95% CI)[a]
	N1	n (%)	N1	n (%)	
1094					
Yes	64	1 (1.6)	243	27 (11.1)	9.5 (4.6, 14.5)
No	58	9 (15.5)	233	61 (26.2)	10.7 (-0.2, 21.6)
1095					
Yes	60	0 (0.0)	222	26 (11.7)	11.7 (7.5, 15.9)
No	52	4 (7.7)	207	45 (21.7)	14.0 (4.9, 23.2)

Source: Study 1094 CSR Table 17 (p. 91), Study 1095 CSR Table 17 (p. 91)
*Analyzed with NRI for missing data
[a] 95% CI was based on the normal approximation for the difference in binomial proportions.
N1 = number of patients in each group at week 8.

As summarized in **Table 53**, for both tofacitinib dose levels in Study 1096, the differences in proportions of patients who were in remission at week 52 compared to placebo were smaller in the subgroup with prior TNF blocker failure compared to the subgroup without prior TNF blocker failure. The differences in proportions compared to placebo in the subgroup of patients who did not have prior TNF blocker failure were numerically very similar between tofacitinib dose levels. In contrast, in the subgroup with prior TNF blocker failure, the difference in proportion of patients in remission at week 52 compared to placebo in the tofacitinib 10 mg BID arm was nearly numerically double that in the 5 mg BID arm; however, this apparent difference between dose levels observed in this exploratory analysis was not nominally statistically significant (nominal p-value = 0.07). These exploratory results cannot establish a difference of treatment effect for the dose levels in the TNF blocker failure subgroup. They also suggest insignificant differences between the two tofacitinib doses in the subgroup of patients who are not TNF blocker failures. The apparent trend in the nominal p-value in the TNF blocker failure subgroup might be hypothesized to reflect an inadequate sample size; however, given that this subgroup analysis had no adjustment for multiplicity, the observation can only be viewed as hypothesis generating.

Table 53: Applicant's Study 1096 Primary Efficacy Endpoint Exploratory Subgroup Analysis by Prior TNF Blocker Failure: Proportion of Patients in Remission at Week 52* (FAS)

Prior TNF Blocker Failure	Placebo		Tofacitinib 5 mg BID			Tofacitinib 10 mg BID		
	N1	N=198 n (%)	N1	N=198 n (%)	Difference from Placebo (95% CI)[a]	N1	N=197 n (%)	Difference from Placebo (95% CI)[a]
Yes	89	10 (11.2)	83	20 (24.1)	12.9 (1.6, 24.2)	93	34 (36.6)	25.3 (13.5, 37.1)
No	109	12 (11.0)	115	48 (41.7)	30.7 (20.0, 41.5)	104	46 (44.2)	33.2 (22.0, 44.4)

Source: Study 1096 CSR Table 23 (p. 112)
*Analyzed with NRI for missing data
[a] 95% CI was based on the normal approximation for the difference in binomial proportions.
N1 = number of patients in each group at week 52, and used as the denominator in the percentage calculation.

Despite the limitations described above, the issue of potential added benefit of tofacitinib 10 mg BID compared to tofacitinib 5 mg BID in TNF failure patients was discussed at length at the GIDAC meeting and is further discussed below in **Section 9**. The Committee members noted that the numerically greater remission rate for tofacitinib 10 mg BID vs 5 mg BID may be of clinical importance for refractory patients who have failed other advanced therapies, despite not reaching statistical significance in this analysis.

The following tables (**Table 54** and **Table 55**) created by the Division summarize exploratory efficacy results for the IndNR subgroup. This subgroup consists of patients who did not achieve clinical response at week 8 (Study 1094/1095) and subsequently enrolled in the open-label extension (Study 1139) and received 8 weeks of 10 mg BID open-label therapy. The following analysis includes only patients who initially received active treatment in Study 1094/1095 (i.e., only the patients who received 16 weeks of active therapy, due to failure to meet clinical response at week 8). This approach was chosen because patients with initial non-response to placebo may not be comparable to those who had non-response to active treatment. The goal of this analysis was to explore whether the Applicant's proposal to continue induction dosing to 16 weeks for those who fail to respond initially is adequately supported.

Table 54: Exploratory Binary Efficacy Endpoints Based on FMS for IndNR Subgroup in Study 1139

	Remission (FMS)		Clinical Response	
	Baseline	After 16 Weeks Tofacitinib Treatment	Baseline	After 16 Weeks Tofacitinib Treatment
Overall*	0/295	25/291 (8.6%)	0/295	149/291 (51.2%)
Prior TNF blocker failure	0/181	11/178 (6.2%)	0/181	86/178 (48.3%)

*This population includes only the patients in the IndNR subgroup who were previously randomized to active treatment in Study 1094/1095 (i.e., patients who received a total of 16 weeks active treatment)
FMS=full Mayo score
Source: Reviewer's table, created from Applicant's Tables 229a.27.1 and 229a.27.2, analyzed with NRI for missing data.
Denominators are numbers of patients who based on their enrollment dates and last non-missing full Mayo score (for ongoing patients) could have reached the specified timepoint, at the July 8, 2016, data cut-off date. Endoscopy results are based on central read.

This analysis, though exploratory and uncontrolled, suggests that for patients failing to respond after 8 weeks induction therapy, continuing therapy for 8 additional weeks resulted in rates of remission at month 2 of approximately 9%. The Division notes that this is open-label treatment. To provide context, estimates of placebo remission rates for induction in controlled clinical trials for UC vary, but are in the range of 5 – 12%[26,27,28]; thus, these data do not convincingly support the Applicant's assertion that extended induction therapy will result in clinical remission by Week 16. However, the Division also notes that 51% of these induction non-responders demonstrated some

[26] Results from controlled clinical trials which supported approval of adalimumab for treatment of UC include a placebo remission rate of 9% at week 8 (see FDA prescribing information available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125057s403lbl.pdf)
[27] Results from controlled clinical trials for other biologics (noting the earlier week 6 timepoint) noted induction placebo remission rates of 5% for vedolizumab and 6% for golimumab (see FDA Prescribing Information available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125289s133lbl.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125476s000lbl.pdf)
[28] Results from Cochrane review (which did include trials for agents used for less severe disease, as well as biologics) suggested pooled placebo remission rate for induction of 12%. Jairath V, Zhou GY, et al. Placebo response and remission rates of induction and maintenance therapy for ulcerative colitis. Cochrane Library 2017. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011572.pub2/epdf

degree of improvement (protocol defined clinical response) at the Week 16 assessment. In patients who are unable to achieve remission at an early timepoint, a clinical response that results in some improvement in patients' symptoms and functioning may be considered beneficial and may warrant consideration of continuing treatment.

It is then necessary to consider the long-term outcomes of patients who did not respond by Week 8. When this population as a whole is followed longer term, results suggest low proportions of patients in remission by 12 and 24 months. **Table 55** highlights that remission rates at 12 and 24 months are approximately 25%, where analysis was limited to only the patients with non-missing values. Again, though comparisons to placebo response rates in UC at 1 year in other development programs are somewhat limited by differences in the study populations, design, and conduct, available data suggest that placebo remission rates at 52 weeks are still substantial in clinical trials for UC (ranging from 8.5% to 17% in various estimates)[29,30,31]. Thus, a clear benefit to patients of this long-term exposure to tofacitinib 10 mg BID in patients who have not experienced a clinical response after 8 weeks of treatment has not been demonstrated. In addition, these results are based on local endoscopy reads, rather than central reads (as these endoscopies were not protocol mandated to have central reading). While the Agency's experience with local versus central readings is limited to date, within the tofacitinib UC program, overall response rates were noted to be slightly higher based on local reads, when compared to central, for the timepoints where both evaluations were available.

[29] Results from controlled clinical trials which supported approval of adalimumab for treatment of UC included 52 week placebo clinical remission rate of 8.5% (see FDA prescribing information available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125057s403lbl.pdf).

[30] Results from controlled clinical trials for vedolizumab noted 52 week placebo remission rate of 16% (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125476s000lbl.pdf)

[31] Results from Cochrane review (which did include trials for agents used for less severe disease, as well as biologics) suggested pooled estimate of placebo remission in maintenance trials was 17%, and noted that biologics generally have higher rates of placebo response than non-biologic therapies. Jairath V, Zhou GY, et al. Placebo response and remission rates of induction and maintenance therapy for ulcerative colitis. Cochrane Library 2017. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011572.pub2/epdf

Table 55: Exploratory Binary Efficacy Endpoints, Based on FMS with Local Endoscopic Read, for IndNR Subgroup in Study 1139

	Remission (FMS)				**Clinical Response**			
	Baseline	Month 2	Month 12	Month 24	Baseline	Month 2	Month 12	Month 24
Induction 10 mg x 16 weeks*	1/295 (0.3%)	42/293 (14.3%)	72/289 (24.9%)	40/164 (24.4%)	22/295 (7.5%)	155/293 (52.9%)	121/289 (41.9%)	55/164 (33.5%)

*Includes only patients who received tofacitinib 10 mg BID in Study 1094/1095 and failed to demonstrate clinical response at week 8 (i.e., patients who received ongoing 10 mg BID therapy through 24 months). Denominators are numbers of patients in the specified category with non-missing values.
FMS=full Mayo score
Analyzed with NRI for missing data
Source: Reviewer's table, created from Applicant's Study 1139 CSR Table 27 (p. 111)

During the AC meeting held on March 8, 2018, the Applicant provided an additional post-hoc analysis, aimed at describing the potential benefit of continuing therapy in patients who did not respond by Week 8. In this analysis, the Applicant considers the population of patients who did not initially respond by Week 8, received the additional 8 weeks of 10 mg BID, and then achieved at least a clinical response by Week 16. Specifically, there were 149 patients who were induction non-responders at Week 8, and then achieved at least clinical response after an additional 8 weeks (16 weeks total treatment). Of this population, at 1 year, 144 had available data and 65 of them were in remission. All of the aforementioned limitations also apply to this assessment, including the lack of multiplicity control, lack of concurrent control, and open label nature of treatment. However, considering patients with moderately to severely active UC may have been refractory to all other available therapies, these results are considered informative in this clinical situation, and are described in the label. In other words, tofacitinib 10 mg BID can be continued for an additional 8 weeks in patients without adequate response in the first 8 weeks, provided that patients and providers are aware that therapy should be permanently discontinued if no benefit is achieved by 16 weeks.

Given the limitations of these analyses, the uncertainty regarding any incremental benefit of the long term use of 10 mg vs 5 mg as described for study 1096, as well as the serious risks associated with long-term use of tofacitinib, the decision to continue patients on 10 mg BID long term must be made with caution and in consideration of the risks and benefits of tofacitinib versus other options, which may include the need for colectomy. In the overall risk-benefit assessment, the Agency acknowledges

that while the strength of the evidence in support of continued dosing beyond 8 weeks in patients who were initial non-responders is very limited, this dosing regimen could be considered as an option in the best interest of patients who have failed other available medical therapies.

7. Review of Safety

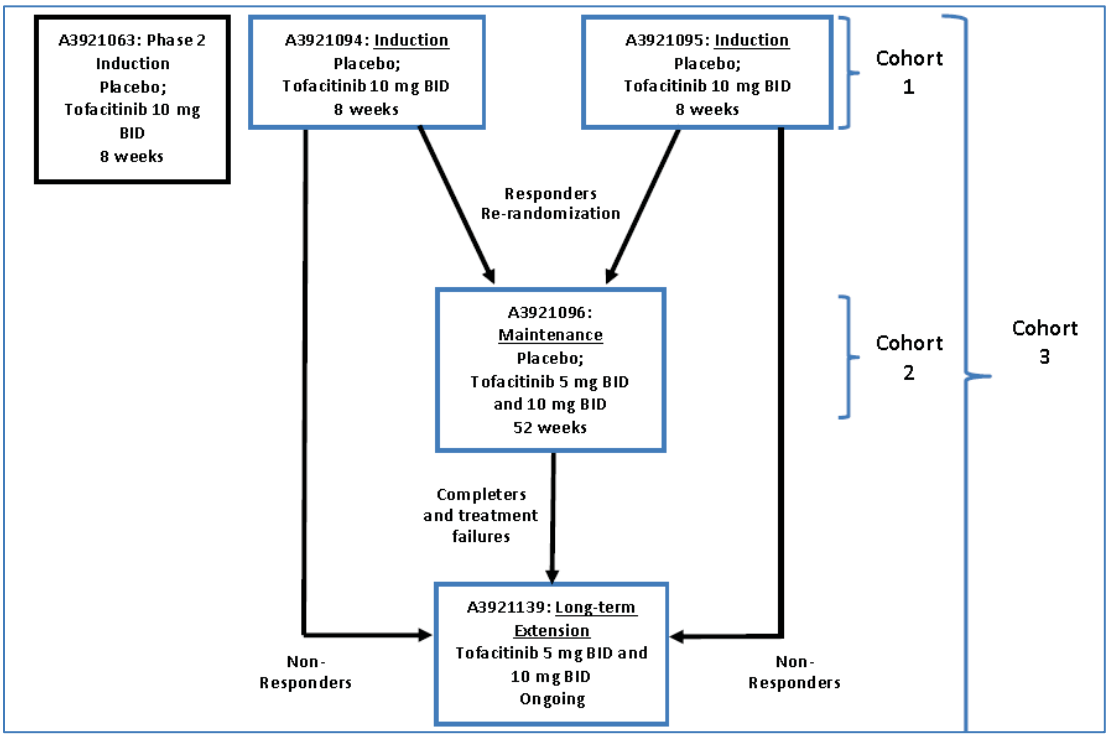
7.1 Safety Review Approach

The assessment of clinical safety in patients with UC focused on the integrated data from the three phase 3 trials (1094, 1095, and 1096), one phase 2 trial (1063), and a long-term extension (LTE) study (1139). In general, the safety data were analyzed as three cohorts, as created by the Applicant. Data from Cohort 1 (phase 2 and phase 3 induction trials) and Cohort 2 (phase 3 maintenance trial) were analyzed from data submitted at the time of sNDA submission. Cohort 3 included data from the following UC program trials: the phase 2 and 3 induction trials, the phase 3 maintenance trial, and the LTE study.

Data from patients in the LTE Study 1139 were included in the initial sNDA submission if patients were enrolled in this study at least 2 months before July 8, 2016. The 120-day safety update provided an update of the Cohort 3 data based on safety data available after July 8, 2016, through December 16, 2016. At the time of this review, Study 1139 was the only ongoing study in the UC program. In addition, safety data accrued from inquiry request responses from the Applicant have been incorporated into this safety review. A later data cut-off date of September 29, 2017, was created by the Applicant for the reporting and analysis of select adverse events of special interest (AESIs) data in response to inquiries sent by the Division.

For the purposes of the evaluation of the tofacitinib UC program, the Applicant created and defined the integrated safety analyses cohorts and subgroups, shown in the figure below. See **Figure 3** for a schema showing the cohorts that were created by the Applicant and used for the integrated analyses and for this safety review.

Figure 3: Schema of the Assignment of Studies to Cohorts for the Integrated Analyses



Source: Applicant's figure from the May 4, 2017 submission, Summary of Clinical Safety, page 30/292

The clinical reviewer evaluated the select cohorts, studies, and subgroups, as follows:

Cohort 1 is referred to as the phase 2 and phase 3 "Induction Studies" in this review. This cohort provides comparison data of tofacitinib 10 mg BID vs placebo treatment over a short duration time (8 weeks). This cohort is useful to evaluate the overall short-term safety of tofacitinib 10 mg BID.

Extended Induction Therapy (IndNR) 2 Months Cohort describes the safety profile of patients who received tofacitinib 10 mg BID in the phase 3 induction studies and did not achieve clinical response and were rolled over into the LTE study to receive an additional 8 weeks of tofacitinib 10 mg BID therapy (total of 16 weeks of tofacitinib 10 mg BID induction treatment). The IndNR subgroup safety data were censored at 2 months into the LTE study to compare the risks of additional (subsequent) 8 weeks of tofacitinib 10 mg BID versus the initial 8 weeks of treatment in the phase 2 and 3 induction studies (Cohort 1).

Cohort 2 is referred to as the phase 3 "Maintenance Study" in this review. This cohort provides comparison data between doses of tofacitinib 5 mg and 10 mg BID versus placebo over 52 weeks. This cohort data allowed analyses to assess whether specific AEs demonstrated dose-dependent relationship over a 52-week time-period.

IndNR 12 Months Cohort is a subgroup of safety data focusing on the induction non-responders who entered the LTE study to receive an additional 8 weeks of tofacitinib 10 mg BID, and then continued treatment with 10 mg BID through 53 weeks. (This group includes patients who received placebo in an induction trial.) The safety data of this induction non-responder subgroup of the LTE study was captured through 53 weeks into LTE study and were censored at 12 months. These data supplement the assessment of the safety profile of the tofacitinib 10 mg BID group administered continuously over a year's time.

Cohort 3 is referred to as the "tofacitinib UC program" in this review and includes patients in the phase 2 and 3 induction trials, the phase 3 maintenance trial, and the LTE study. This cohort provides an overall view of the tofacitinib UC program. Patients in the LTE study were included in the submission if they were enrolled in the LTE study at least 2 months before a database lock date. The patient safety events related to the dosage of tofacitinib were analyzed base on the patients' predominant (average) dosage (PD) or first post-induction dose (PInd) in the maintenance or LTE study.

a. Predominant Dose (PD) tofacitinib 5 mg BID cohort refers to patients in the tofacitinib program who received an average tofacitinib dose of <15 mg/day over the course of their treatment.

b. Predominant Dose (PD) tofacitinib 10 mg BID cohort refers to patients in the tofacitinib program who received an average tofacitinib dose of ≥15 mg/day over the course of their treatment.

Post-Induction dose (PInd) analyses groups include patients who were treated with tofacitinib or placebo in induction and tofacitinib after induction (on maintenance trial and/or LTE study). The PInd groups are separated into subgroups based on the first tofacitinib dose level they received after participating in the induction trial(s). These analyses groups are smaller than the predominant dose (PD) analyses groups since all patients, regardless of placebo treatment in the induction and maintenance studies, required tofacitinib treatment for at least 8 weeks in the tofacitinib program to be included.

The purpose of this supplemental analysis is to evaluate the relationship between longer-term AEs and the constant tofacitinib dose levels administered after induction treatment.

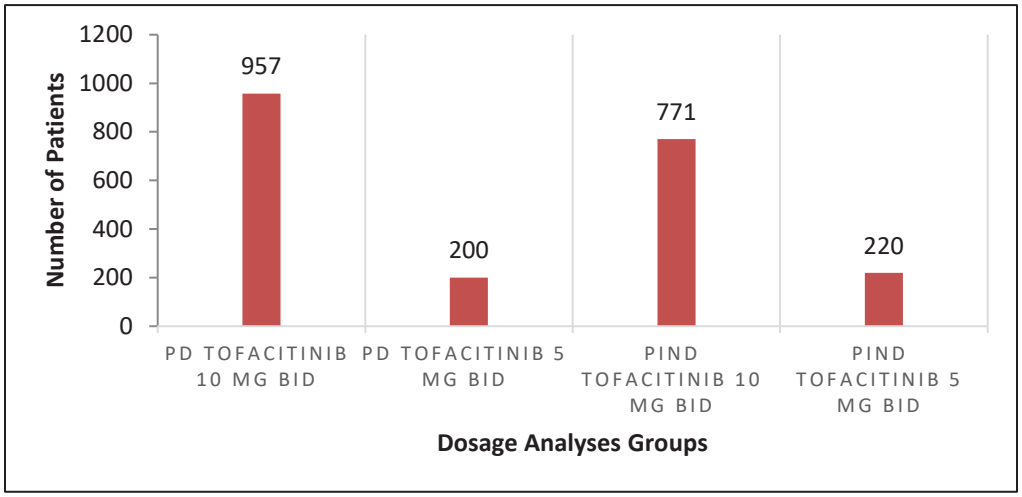
Prior TNF blocker treatment failure subgroup of each of the above cohorts were characterized as having history of prior TNF failure if they had inadequate therapeutic response (prior primary or secondary failure), or prior intolerance to TNF blockers (any adverse reaction requiring discontinuation).

In general, the primary safety analyses in this review evaluate the AESIs, treatment emergent adverse events (TEAEs), SAEs, AEs leading to discontinuation, and laboratory abnormalities based on the treatment arm, predominant dose (PD) or post-induction (PIND) of tofacitinib administered. In particular, the AESIs were chosen based on concerning AEs seen in rheumatoid arthritis (RA), psoriasis (PsO), and psoriatic arthritis (PsA) patients in the tofacitinib drug development program and with comparable UC products. For select AEs, additional safety analyses evaluated specific subpopulations of patients based on prior history of TNF inhibitor failure.

Cohort 3 Allocation of Patients

In both the predominant dose (PD) and post-induction dose (PInd) analyses groups of Cohort 3, there were more patients in the higher, 10 mg BID dosage group in comparison to the lower, 5 mg BID dosage group. The disparity in the number of patients in the dosage analyses groups limits the ability to make direct comparisons of safety events and laboratory evaluations. Another potential limitation of the PInd group analyses is that not all tofacitinib-treated patients in the UC program were included, since data capture was censored when there was a change in post-induction dose. In the UC program, change in tofacitinib dose from 5 mg BID to 10 mg BID occurred in 13% of patients, and a decrease in dose from 10 mg BID to 5 mg BID occurred in 5% of patients in the LTE study. See **Figure 4** below for the allocation of patients to the Pharmacodynamics and PInd analyses groups by tofacitinib dosage.

Figure 4: Cohort 3 Tofacitinib Patient Populations by Dosage Analyses Groups



Source: Reviewer's table. PD = predominant dose, Pind = post-induction dose, 29 September 2017 Update cut-off date

7.2 Review of the Safety Database

Overall, there appears to be adequate exposure to tofacitinib in the UC program for the evaluation of common AEs and safety events with short latency. However, the evaluation of rare or infrequent AEs of special interest and/ or those that may occur after a long duration of tofacitinib treatment and are of longer latency may not be adequately assessed with exposure in this program. Additionally, there were fewer patients with exposure to the lower tofacitinib 5 mg BID dosage used long-term, in comparison to the higher tofacitinib 10 mg BID dosage. This presents a potential limitation in the ability to adequately compare the relative safety of the tofacitinib 5 mg in comparison to the 10 mg BID dosage for long-term use.

The total exposure of tofacitinib in patients with UC was 1986 patient-years (PYs; N=1157), based upon a cut-off date of September 29, 2017 (based on inquiries by the Division). As mentioned, due to the design of the UC program, most of the patients were categorized in the tofacitinib UC program (Cohort 3) as predominant dose (PD) tofacitinib 10 mg BID: 83% (957/ 1157) versus PD tofacitinib 5 mg BID group 17% (200/ 1157). As expected, a large proportion of patients discontinued the tofacitinib UC program studies, across both placebo and treatment arms, which further limits tofacitinib exposure of tofacitinib and safety assessment relative to placebo in the tofacitinib UC program. The most common reason for discontinuation was insufficient clinical response (i.e., lack of efficacy).

Moreover, in comparison to the exposure of patients in the previously evaluated tofacitinib indications of RA and PsO, the duration of tofacitinib exposure in the UC program is much less. The tables below present summaries of the clinical trial exposure and duration of treatment at the September 29, 2017, data cut-off in the tofacitinib UC program compared to the non-UC programs. See

Table 56, **Table 57**, and**Table 58** below for further details.

Table 56: Tofacitinib UC Exposure by Cohort 1, 2, and IndNR Subgroup Per Treatment group

	Cohort 1 (Phase 2 and 3 UC Induction Studies)		**Cohort 2 (Phase 3 UC Maintenance Study)**			**IndNR 12 Months**
Treatment Dose	Placebo	Tofacitinib 10 mg BID	Placebo	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib 10 mg BID
Number of Patients (N)	282	938	198	198	196	429
Total Patient-Years (PY)	44.8 PY	156.2 PY	100.4 PY	146.2 PY	154.3 PY	286.5 PY

Source: Reviewer's table based on Applicant's safety tables response to 26 September 2017 Inquiry Response; 29 September 2017 data cut-off IndNR group includes patients who did not achieve clinical response in phase 3 induction studies 1094/1095, and subsequently received open- label 10 mg BID for an additional 8 weeks induction therapy, followed by 10 mg BID long-term "maintenance" therapy if response occurred.

Table 57: Tofacitinib UC Cohort 3 Duration of Drug Administration per Predominant Dose (PD) Group

	PD Tofacitinib 10 mg BID (N=957)	PD Tofacitinib 5 mg BID (N=200)	Tofacitinib All (N=1157)
Total Patient-Years	1496	490	1986
Median Duration (days)	427	970	606
Mean (days)	572	894	627
Standard Deviation (days)	498	408	499
Range (days)	1-1779	52-1774	1-1779

Source: Reviewer's table based on Applicant's safety tables response to 26 September 2017 Inquiry Response; 29 September 2017 data cut-off

Table 58: Comparative Duration of Tofacitinib Exposure in the UC, PsA, RA, and PsO

Duration of Exposure	Ulcerative Colitis (UC) Cohort 3	Rheumatoid Arthritis (RA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)
At least 1 dose, N, PYs	N=1157 1613 PYs*	6300 (21886)	3662 (8537)	783 (775 PYs)
At least 6 months, n	762	5406	3027	665
At least 12 months, n	653	4904	2648	437
At least 24 months, n	359	4158	2044	44

Source: Reviewer's table, adapted from Applicant's FDA Advisory Committee (AC) Presentation slides 03 August 2017 AC Meeting on Tofacitinib for the treatment of PsA for sNDA 203214/s-017; *UC data as of 16 Dec 2016 data cut-off, RA and PsO data as of 10 May 2016 data-cut off

Although there generally appear to be adequate numbers of patients in the tofacitinib UC safety database, concerns exist that the occurrence of rare AEs of special interest may not apparent due to

the limitations of the exposure. This is always a concern for IBD development programs, as it is not feasible to study a sufficiently large population to truly quantify some of these rare events, in the context of a phase 3 program. Notably, AEs of special interest that occur infrequently, such as malignancies and major adverse cardiovascular events (MACE), have been noted in the tofacitinib RA and psoriasis programs. In these other indications, some of these rare events were seen with extensive duration of drug exposure. A long-term safety outcome trial in RA patients is ongoing to assess the incidence rates of rare of adverse events. In general, the demographics of the study population are representative of the target population, with the notable exception of under-representation of certain racial and ethnic groups as in the demographic sections above.

7.3 Categorization of Adverse Events (AEs)

AEs were categorized by system-organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA version 19.0 was used in the initial supplement submission dated May 4, 2017. In the updated safety data, submitted July 28, 2017, version 19.1 was used. The coding of adverse events in the tofacitinib UC sNDA submission appeared adequate, and allowed for accurate estimation of AE risks.

The Applicant defined an AE as “any untoward medical occurrence in a clinical study patient administered a medicinal product”, unrelated to whether it was considered to be study drug related. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Study investigators monitored each patient regularly for AEs or SAEs occurring throughout the trial.

Investigators also categorized AE for intensity, seriousness, causality, duration, and action taken with study drug. All AEs were categorized according to severity:

- Mild: does not interfere with the patient’s usual function
- Moderate: interferes to some extend with the patient’s usual function
- Severe: interferes significantly with the patient’s usual function.

Of note, a severe event was not necessarily a SAE. SAEs were defined as any events that:

- Resulted in death
- Was life-threatening
- Resulted in a persistent or significant disability or incapacity

- Required patient hospitalization or prolongation of existing hospitalization
- Resulted in a congenital anomaly or birth defect.

The reporting of SAEs began at the time the patient provided informed consent through 28 days after the last study dose, or at any time after the last dose if a causal relationship to study medication was suspected by the investigator. In addition, other important medical events were considered SAEs if the AE jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed in this definition. In association with SAEs, an AE in the infections and infestations system organ class (SOC) that met SAE criteria was classified as a serious infection.

AEs and SAEs were recorded and reported from the time of signed and dated informed consent form (ICF) was obtained until completion of the patient's last study related procedure (which may have included contact for follow-up of safety). All AEs or SAEs were followed until satisfactory resolution or a clinically stable or baseline status. The Applicant reported AEs to be TEAEs if the AEs occurred after the first dose of treatment. The general categorization of the AEs and the methods of adjudication for AEs of special interest were appropriate.

Adjudication of Select Adverse Events

In the phase 3 studies of the tofacitinib UC program, select AEs of special interest underwent adjudication by qualified experts in order to apply a consistent approach to interpreting these AEs. Charters for the adjudication committees were provided in the submission. Since the conduct of the phase 2 Study 1063 predated the establishment of the adjudication committees, Study 1063 was not included in the adjudication process. Standardized AE review and adjudication were implemented for the following:

- Opportunistic infections (OIs)
- Malignancies
- Cardiovascular safety including major adverse cardiovascular events (MACE)
- Gastrointestinal (GI) perforations
- Interstitial lung disease (ILD)
- Hepatic injury.

Routine Clinical Tests

Appropriate safety evaluations were performed as a part of the drug development program. The clinical testing performed as part of routine safety assessments was deemed adequate. The evaluation

of safety was conducted during visits to the clinic. In the induction studies of Cohort 1, scheduled visits occurred at screening, weeks 0, 2, 4, and 8 (or early termination), and follow-up at week 13 (for patients without further enrollment into Study 1096 or 1139). In the maintenance study (Cohort 2), scheduled visits occurred at screening, weeks 0, 4, and 8, followed by every 8 weeks through week 40, and then at week 52. The safety assessment consisted of:

- Monitoring of all spontaneous AEs and SAEs, with their severity and relationships to study drug, and pregnancies
- Hematology, blood chemistry, urine testing, pregnancy testing, assessments of vital signs, physical examinations, electrocardiograms (ECGs), and evaluation for tuberculosis (TB) infection.

7.4 Deaths

As of March 7, 2017, there were five (5) deaths in the tofacitinib UC program. Each of the deaths occurred in patients whose predominant tofacitinib dose was 10 mg BID. The causes of death were aortic dissection, hepatic angiosarcoma, acute myeloid leukemia (AML), pulmonary embolism in a patient with metastatic cholangiocarcinoma, and cutaneous malignant melanoma. In most of the cases, the investigator assessed the event as related or probably related to study drug. With the exception of the patient with aortic dissection, all of these patients had a prior history of TNF blocker failure. The aortic dissection death occurred in the induction studies and three additional deaths occurred, ranging from Day 168 to 1518 of study enrollment, in the LTE study. The fifth death occurred approximately 5 months after the last dose of tofacitinib in the LTE study. Analyses of incidence rate of death were performed by the Applicant and FDA incorporating all deaths reported in the UC program. See Table 59 below for summary characteristics of the death cases.

Deaths in the tofacitinib UC program (though rare) were clustered in those patients who received the 10 mg BID dosage as their predominant treatment over time, vs those who predominately took the lower, tofacitinib 5 mg dosage over a long duration of therapy. The majority of the deaths were related to malignancy, which also occurred primarily in patients treated with the 10 mg BID dosage long-term. However, as described above, most patients in the program were predominantly treated with 10 mg BID long-term, vs 5 mg BID, which limits the ability to determine whether death and malignancy represent true dose-dependent risks. See **Table 59** below for a summary of the patients who died.

Table 59: Summary of Deaths in Tofacitinib UC Program

Case Number	Study / Patient ID, Treatment Group (days of listed treatment)	Age+ (years) / Gender	Day of Diagnosis of Etiology of Death	Day of Death (in last study enrolled)	Last Known Dose Day (in given study)	Total Days received Tofacitinib	Cause of Death / Additional Details
1*	**A3921094 /** (b) (6) Tofacitinib 10 mg BID (64 days) **A3921096 /** (b) (6) Placebo (180 days) **A3921139 /** (b) (6) PD 10 mg BID (123 days)	52 / Male	120	168	123 (study 1139)	187	Hepatic Angiosarcoma History of visceral Leishmaniasis Prior history of TNF blocker failure
2	**A3921094 /** (b) (6) PD 10 mg BID (31 days)	39 / Male	24	31	31 (study 1094)	31	Aortic dissection (aortic aneurysm) History of Cushing's syndrome
3*	**A3921095 /** (b) (6) Tofacitinib 10 mg BID (64 days) **A3921096 /** (b) (6) Placebo (112 days) **A3921139 /** (b) (6) PD 10 mg BID (283 days)	52 / Male	Leukopenia and neutropenia: 267 Acute myeloid leukemia: 310 (post-therapy day 27)	334 (post-therapy day 51)	283 (study 1139)	347	Acute myeloid leukemia Diagnosed with leukopenia and neutropenia while on tofacitinib treatment Prior history of TNF blocker failure

Case Number	Study / Patient ID, Treatment Group (days of listed treatment)	Age+ (years) / Gender	Day of Diagnosis of Etiology of Death	Day of Death (in last study enrolled)	Last Known Dose Day (in given study)	Total Days received Tofacitinib	Cause of Death / Additional Details
4	**A3921094 /** (b) (6) Tofacitinib 15 mg BID (64 days) **A3921096 /** (b) (6) Placebo (175 days) **A3921139 /** (b) (6) PD 10 mg BID (378 days)	68 / Male	Cholangio-carcinoma: 368 Peritoneal Carcinomatosis: 383	384	378 (study 1139)	442	Pulmonary embolism (after the development of cholangiocarcinoma and peritoneal carcinomatosis while on tofacitinib treatment) History of primary sclerosing cholangitis Prior history of TNF blocker failure
5*	**A3921094 /** (b) (6) Placebo **A3921139 /** (b) (6) PD 10 mg BID (1359 days)	62 / Male	1359	1518	1359 (study 1139)	1359	Malignant melanoma of finger, metastases of tumors in lungs, brain, and colon History of basal cell carcinoma Prior history of TNF blocker failure

*Patients died >28 days post-therapy, +Age of patient at baseline of induction study

Source: Reviewer's table, adapted from the Applicants' submission page 60/292 of the Summary of Clinical Safety and submitted patient narratives (29 September 2017 data cut-off)

Although there is insufficient information available to conclude if the event of aortic dissection was related in any way to tofacitinib, this event was unlikely to be related to tofacitinib treatment, given the unrelated mechanism of action the drug to the pathophysiology of aortic dissection. In contrast, since tofacitinib is recognized as a potent immunosuppressant, it is possible that tofacitinib may have increased the risks of the development of malignancy in those who died secondary to malignancy-related issues. Therefore, it is plausible that these deaths may have stemmed from the onset and/ or growth of malignancies secondary to tofacitinib immunosuppression of patients' innate immunity that would otherwise protect against malignancy development.

For more detailed narratives of cases resulting in death, refer to **Appendix D**.

7.5 Serious Adverse Events (SAEs)

For each cohort and select subgroups, the types and proportions SAEs were evaluated. The relationship of the occurrence of SAEs to the treatment or the predominant dosage of tofacitinib is discussed below.

In each of the tofacitinib UC program studies, the most frequently reported serious adverse events (SAE) was the Preferred Term (PT) "Colitis Ulcerative", in the System Organ Classification (SOC) Gastrointestinal disorder category.

Induction Trials (Cohort 1) and Extended Induction Therapy Cohort (IndNR 2 months)

The percentages of patients experiencing any SAEs during the placebo-controlled induction trial or during extended induction (8 additional weeks of 10 mg BID in the setting of the LTE study) were similar. The proportion of patients experiencing an SAE was higher in the placebo group (6%, 16/282) than in the tofacitinib 10 mg BID group (4%, 36/938). In the extended induction therapy cohort (IndNR 2 months), SAEs occurred in 4% (11/295) of patients; SAEs experienced by patients in this IndNR group within the first 8 weeks of treatment would have been captured in the tofacitinib 10 mg BID treatment group in cohort 1 in this analysis. In Cohort 1, the most frequently reported System Organ Classification (SOC) for SAEs was Gastrointestinal disorder: 3% placebo group (9/ 282) and 2% tofacitinib 10 BID group (21/938). The breakdown of AEs by System Organ Class (SOC) was similar for IndNR 2 Months group. Additional details can be found in **Table 106** and **Table 107** in the Appendix.

Maintenance Trial (Cohort 2) and IndNR 12 Months

Among the patients in the phase 3 maintenance trial who had received tofacitinib 10 mg BID in the induction trial (i.e., excluding the patients who received placebo or tofacitinib 15 mg BID in the induction trial and were qualified to be randomized in the maintenance trial), SAEs were reported in 7% (12/167), 7% (11/167), and 6% (10/170) of the placebo, tofacitinib 10 mg BID groups, and tofacitinib 5 mg BID groups, respectively.

The tofacitinib 10 mg BID induction treatment non-responders (IndNR 12 Months, patients who did not enter the maintenance trial but continued treatment with tofacitinib 10 mg BID in the LTE study), had a numerically higher rate of SAEs over the subsequent 12-month treatment period than those who responded to tofacitinib 10 mg BID induction treatment and were treated in the maintenance study; this difference was driven by GI system related AEs, likely due to the severity of underlying UC and/or lack of efficacy of the drug in those patients. See **Table 59** for further details.

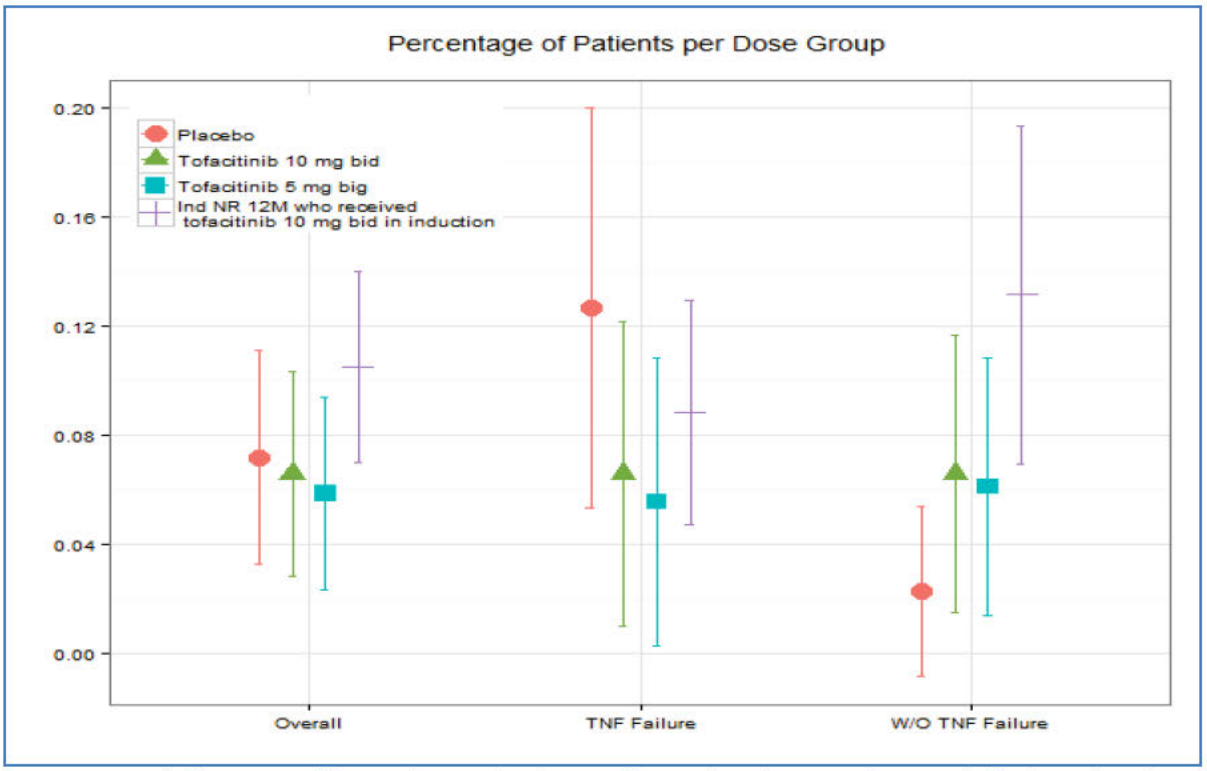
Maintenance Trial (Cohort 2): Prior TNF Blocker failure versus Non-TNF Blocker Failures Subgroup

Overall, the rates of SAEs for those randomized to a tofacitinib treatment group (5 mg or 10 mg) in the phase 3 maintenance trial were generally comparable between those with or without a history of failure to prior TNF therapy. In the maintenance study, the highest proportions of SAEs occurred in the placebo group, in both the overall maintenance trial population and within the TNF inhibitor failure subgroup of the maintenance trial. SAEs were reported less frequently in the tofacitinib 5 mg BID arm than in the tofacitinib 10 mg BID arm.

The IndNR 12 Months group includes patients who were initially randomized to treatment, failed to have clinical response by week 8 in the phase 3 induction studies, and then continued treatment with 10 mg BID in the open-label LTE study. This group is included to explore the safety experience in this nonrandomized group (without a concurrent control) to that observed in the maintenance study.

The SAE experience of the prior TNF blocker failure subgroup is included as it represents the clinical course of patients most likely to continue 10 mg BID longer term. Direct comparison between this IndNR subgroup and those randomized to the maintenance trial should be made with caution, due to differences in baseline severity of these 2 groups (IndNR patients were initial non-responders, whereas all those randomized to Study 1096 demonstrated clinical response in the induction trial by week 8). See **Figure 5** and corresponding **Table 60** below for further details.

Figure 5: Rates of SAEs in Maintenance Trial (Cohort 2) and in the IndNR 12 Months Cohort, Analyses Limited to Patients Who Received Tofacitinib 10 mg BID in Induction Trials*



Source: Reviewer's figure, created from Cohort 2 and IndNR 12 subgroup data. *Patients who received placebo in the induction trial are not included in these analyses.

Table 60: Rates of SAEs in Maintenance Trial (Cohort 2) and in the IndNR 12 Months Cohort, Analyses Limited to Patients Who Received Tofacitinib 10 mg BID in Induction Trial*

	Placebo % (n/N)	Tofacitinib 10 mg BID % (n/N)	Tofacitinib 5 mg BID % (n/N)	IndNR 12 Months who Received 10 mg in Induction % (n/N)
Overall SAEs	7% (12/167)	7% (11/167)	6 % (10/170)	11% (31/295)
Prior TNF Blocker Failure SAEs	13% (10/79)	7% (5/76)	6% (4/72)	9% (16/181)
Without prior TNF Blocker Failure SAEs	2% (2/88)	7% (6/91)	6% (6/98)	13% (15/114)

Source: Reviewer's table, created from Cohort 2 and IndNR12 subgroup data. *Patients who received placebo in the induction trial are not included in these analyses.

Long-Term Extension (LTE) Study

For patients who received the induction tofacitinib 10 mg BID dose, SAEs in the LTE study were reported in 13% (77/587) and 9% (13/146) of patients eventually treated in the tofacitinib 10 and tofacitinib 5 mg BID groups of the LTE study, respectively.

The patients in the higher dose group experienced mostly GI related SAEs in comparison to the lower dose group. Due to the program design (where patients who had inadequate response at week 8, or who met protocol specified disease worsening criteria during the maintenance study, could enroll in the LTE at 10 mg BID), the patients treated with 10 mg BID in the LTE had more severe disease, in general, than those treated with 5 mg BID in this study. Only patients who were in remission at conclusion of maintenance study, or in rare cases due to adverse event that required dose modification, enrolled in LTE at the dose of 5 mg BID.

LTE Study: Prior TNF Blocker Failure vs Non-TNF Blocker Failures Subgroup

Patients with a history of TNF blocker failure in the LTE study had higher rates of SAEs overall than patients who did not have this history. Moreover, the highest rates of SAEs within the prior TNF blocker failure subgroup occurred in patients who had been exposed to the tofacitinib 10 mg BID dose for the entire duration of induction, maintenance, and LTE. In **Table 61**, the data for the prior TNF failure subgroup and non-TNF failure subgroup within the LTE are summarized to facilitate comparison of SAE rates across these subgroups.

Table 61: Rates of SAEs in the LTE Study by History of Tofacitinib Treatment in Patients Who Received Tofacitinib 10 mg BID in Induction Trials*

	Induction 10 mg/ Maintenance 10 mg/ LTE Study 10 mg % (n/N)	Induction 10 mg/ Maintenance 10 mg/ LTE Study 5 mg % (n/N)	Induction 10 mg/ Maintenance 5 mg/ LTE Study 10 mg % (n/N)	Induction 10 mg/ Maintenance 5 mg/ LTE Study 5 mg % (n/N)
Overall SAEs	16% (11/68)	7% (5/71)	8% (7/89)	10% (6/58)
Prior TNF Blocker Failure SAEs	19 % (7/36)	14% (4/28)	6% (3/45)	13% (2/16)
Prior without (non) TNF Blocker Failure SAEs	13% (4/32)	2% (1/43)	9% (4/44)	10% (4/42)

Source: Reviewer's table based on data from LTE study. *Patients who received placebo in the induction trial are not included in these analyses.

7.6 Common Adverse Events

Induction Studies (Cohort 1) and Extended Induction Therapy Cohort (IndNR 2 months)

The most common system organ class (SOC) of AEs reported in the randomized, controlled induction trials was the Gastrointestinal SOC, and was experienced in 7% (20/282) of patients in the placebo group vs 3% (30/938) in the tofacitinib 10 mg BID group. In the non-randomized, extended induction therapy (IndNR 2 months) group, 8% (24/295) of patients had an AE of colitis ulcerative.

Table 62 displays the common AEs that occurred more frequently in the tofacitinib treatment arm of the pooled phase 3 induction trials compared to placebo, and occurred in at least 2% of the overall study population. Data from the induction trials are displayed in comparison to the AE data from the group of patients who received non-randomized, extended induction therapy.

Table 62: AEs That Occurred in the Induction trials (Cohort 1) and Extended Induction Therapy Group, in at Least 2% of the Patients and at Least 1% Greater than that Observed in Placebo

Preferred Terms	Placebo (N=282)	Tofacitinib 10 mg BID (8 Weeks Induction) (N=938)	Tofacitinib 10 mg BID Extended Induction* (Total 16 Weeks) (N=295)
Nasopharyngitis	14 (5%)	56 (6%)	21 (7%)
Headache	19 (7%)	73 (8%)	8 (3%)
Blood creatinine phosphokinase increased	3 (1%)	25 (3%)	7 (2%)
Pyrexia	5 (2%)	27 (3%)	4 (1%)
Elevated Cholesterol Levels**	0 (0%)	29 (3%)	4 (1%)
Acne	1 (0.4%)	25 (3%)	5 (2%)

Source: Reviewer's table produced by J Review 12.0. *IndNR subgroup patients who received a total of 16 weeks of tofacitinib 10 mg BID induction treatment; **Combined Preferred Terms for "Elevated Cholesterol Levels": hypercholesterolemia, blood cholesterol increased, lipids increased, lower density lipoprotein (LDL) increased, or hyperlipidemia

Maintenance Trial (Cohort 2)

In the entire phase 3 randomized, controlled maintenance trial, the most common AE was colitis ulcerative: 36% (71/198) in the placebo group, 15% (29/196) in the tofacitinib 10 mg BID group, and 18% (36/198) in the tofacitinib 5 mg BID group. Likewise, 15% (45/295) of patients in the non-randomized IndNR 12 months cohort of the LTE study, who initially received tofacitinib 10 mg BID in the induction studies, experienced AEs of colitis ulcerative.

Of note, in the phase 3 maintenance trial, HZ infections occurred more frequently in patients receiving tofacitinib 10 mg BID in comparison to the placebo and 5 mg BID groups. Similar to the induction trials, a higher proportion of patients experienced elevated cholesterol levels in both tofacitinib treatment

arms compared to placebo. There appears to be a dose-related increase in the proportion of patients experiencing elevated lipids in the tofacitinib 10 mg vs the 5 mg BID group. Per the Applicant, the increase in elevated cholesterol levels is consistent with the known effect of tofacitinib on serum lipids.

Table 63 below displays the adverse reactions that occurred more frequently in either of the tofacitinib treatment groups than placebo group, and in ≥ 4% of Cohort 2 (maintenance trial).

Table 63: Maintenance Study AEs Occurring in ≥ 4 % or More of Patients and at Least 1% Greater than Observed in UC Patients on Placebo

Preferred Term	Placebo (n=198)	Tofacitinib 10 mg BID (n=196)	Tofacitinib 5 mg BID (n=198)
Nasopharyngitis	11 (6%)	27 (14%)	19 (10%)
Elevated cholesterol levels**	3 (1%)	18 (9%)	9 (5%)
Headache	12 (6%)	6 (3%)	17 (9%)
Upper respiratory tract infection	7 (4%)	12 (6%)	13 (7%)
Blood creatine phosphokinase increased	4 (2%)	13 (7%)	6 (3%)
Rash	8 (4%)	11 (6%)	6 (3%)
Diarrhea	5 (3%)	9 (5%)	3 (2%)
Herpes zoster	1 (1%)	10 (5%)	3 (2%)
Gastroenteritis	5 (3%)	8 (4%)	6 (3%)
Anemia	3 (2%)	4 (2%)	8 (4%)
Nausea	5 (3%)	8 (4%)	1 (1%)

Source: Reviewer table, JReview v. 11.0, *IndNR subgroup patients who received 10 mg BID in induction studies; ** Combined Preferred Terms for "Elevated Cholesterol Levels": hypercholesterolemia, hyperlipidemia, blood cholesterol increased, low density lipoprotein increased, blood triglycerides increased, or lipids increased.

Maintenance Trial (Cohort 2): Prior TNF Blocker Failure subgroup

Patients within the phase 3 maintenance trial who had a history of prior TNF blocker failure, had the following AEs reflected in **Table 64** below.

Table 64: Maintenance Study (Cohort 2) AEs Occurring in at ≥ 5 % of Patients, and at Least 1% Greater than Observed in UC Patients on Placebo, Prior TNF Blocker Failure Subgroup

Preferred Term	Placebo (n=89)	Tofacitinib 10 mg BID (n=92)	Tofacitinib 5 mg BID (n=83)
Nasopharyngitis	7 (8%)	20 (22%)	11 (13%)
Arthralgia	11 (12%)	14 (15%)	8 (10%)
Herpes Zoster	0 (0%)	9 (10%)	1 (1%)
Gastroenteritis	4 (5%)	8 (9%)	5 (6%)
Elevated Cholesterol Levels*	1 (1%)	7 (8%)	4 (5%)
Pyrexia	3 (3%)	6 (7%)	3 (4%)
Upper respiratory tract infection	4 (5%)	6 (7%)	3 (4%)
Influenza	1 (1%)	6 (7%)	0 (0%)
Blood creatine phosphokinase increased	2 (2%)	5 (5%)	2 (2%)

Source: Reviewer table, JReview v. 11.0, *Combined Preferred Terms for "Elevated Cholesterol Levels": hypercholesterolemia, hyperlipidemia, blood cholesterol increased, low density lipoprotein increased, blood triglycerides increased, or lipids increased.

The common AEs noted in the UC program were generally comparable to what is already included in the prescribing information for RA and PsA. There are a few differences noted. Common AEs that occurred in patients treated with tofacitinib in the UC program that were not observed as common AEs in the RA program included acne. Additionally, the AE of "elevated cholesterol levels", constituted by multiple cholesterol related AEs, shows that there is a possible dose-dependency of this observation in patients treated with tofacitinib in the induction and maintenance trials.

Tofacitinib UC Controlled Studies AEs

As reflected in the tables above, adverse reactions reported in ≥ 5% of patients treated with either 5 mg or 10 mg twice daily of tofacitinib, and ≥ 1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials, were the following: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

Tofacitinib UC Program (Cohort 3)

Most of the most common AEs in the tofacitinib UC program have been recognized in the tofacitinib RA program and are already reflected in the Xeljanz (tofacitinib) labeling. In addition to the common AEs that have been included in the Xeljanz labeling, AEs of elevated cholesterol levels were reported at a frequency which constitutes inclusion into labeling based on the results of the tofacitinib controlled induction and maintenance studies. In contrast to the randomized, controlled maintenance trial, within the overall tofacitinib UC program (Cohort 3), a dose-dependent increase in elevated cholesterol levels was not apparent. The types and proportions of common AES within the subgroup of patients with a history of prior TNF failure were similar to the overall patient population.

Discontinuations Due to Adverse Effects

In the tofacitinib UC studies, trial sites were instructed to select insufficient clinical response if a lack of efficacy from the study treatment was the primary reason the patient was withdrawn from the study.

Induction Trials (Cohort 1) and Non-Randomized Extended Induction Therapy (IndNR 2 months) Cohort

In the Induction Trials (Cohort 1), a total of 7% (65/938) of patients in the tofacitinib 10 mg BID group and 11% (32/282) of patients in the placebo group discontinued therapy. In the non-randomized, extended induction therapy (IndNR 2 months) cohort, a total of 16% (46/295) discontinued therapy.

As shown in **Table 65** below, the most frequent reason for the study discontinuation in the induction phase of treatment was insufficient clinical response, which included the AE of "Worsening UC." This reason accounted for approximately half of the discontinuations in each treatment group of the induction study. A comparable and nominal number of patients in the tofacitinib 10 mg BID group (0.4%, 4/938) and placebo group (0.4%, 1/282) had surgical intervention for their disease after discontinuation. In the non-randomized, extended induction therapy (IndNR 2 months) cohort, 11% (31/295) discontinued the LTE study due to insufficient clinical response, which included AEs related to worsening UC. In addition, one patient discontinued due to AE of worsening abdominal pain and another patient required surgery for UC.

Table 65: Adverse Event-Related Discontinuation in Induction Trials (Cohort 1) and Non-Randomized Extended Induction Therapy (IndNR 2 Months) Cohort

DISCONTINUATION REASON	Placebo (N=282)	Tofacitinib 10 mg BID 8 Weeks (N=938)	Extended Induction Therapy* Total 16 Weeks (N=295)
ADVERSE EVENT (does not includes AEs of worsening UC)	6 (2%)	16 (2%)	1 (0.3%)
INSUFFICIENT CLINICAL RESPONSE (includes AEs of worsening UC)	17 (6%)	30 (3%)	31 (11%)
Overall Total Discontinuation	32 (11%)	65 (7%)	46 (16%)

Source: Reviewer's table, JReview 11.0, *IndNR 2 Months subgroup are patients who received 10 mg BID in induction studies and an additional 8 weeks in the LTE study **Per the Applicant's IR response for 08 September 2017

Temporary Discontinuation due to AEs in the Induction Trials (Cohort 1) and Non-Randomized Extended Induction Therapy (IndNR 2 months) Cohort

In both the induction and maintenance studies, temporary discontinuation of study drug was permitted for non-serious infections at the investigator's discretion. In this situation, treatment could be withheld for up to 5 days while the infection was treated. In addition, due to identified increased risk of interstitial pneumonia in Japanese patients, a country specific protocol amendment was instituted at Japanese sites, such that if a patient developed signs/symptoms consistent with possible interstitial pneumonia (cough, fever, dyspnea), temporary discontinuation should be considered, while evaluation for pneumonia, TB, PCP, and invasive fungal infection was completed. Temporary discontinuation for non-serious infection did not affect efficacy assessment.

In the induction trials, a total of 21 patients had an AE that led to temporary discontinuation of study treatment. No patients underwent tofacitinib dose reduction, as this was not permitted in induction. A similar proportion of patients temporarily discontinued the trial due to AEs in the placebo, tofacitinib 10 mg BID dose, and extend induction therapy (IndNR 2 Months) groups: 2% (5/282), 2% (16/938), and 2% (5/295), respectively. The most common AE that led to temporary discontinuation was HZ, which occurred in three (3) patients in the tofacitinib 10 mg BID group.

Maintenance Trial (Cohort 2)

In the maintenance trial, the proportion of patients who discontinued from the study was similar between the tofacitinib 5 mg BID and tofacitinib 10 mg BID groups. There was no apparent dose dependency in the risk of discontinuation due to AEs in the trial.

There was a notably larger proportion of placebo group patients who discontinued the trial due to AEs, in comparison to patients receiving either dose of tofacitinib. This observation was attributed to worsening UC-related AEs. When AEs related to worsening UC are excluded, study discontinuation due to AEs in placebo-controlled induction and maintenance studies occurred in similar proportion of patients among the placebo and tofacitinib groups. No patients in a tofacitinib arm of the maintenance trial discontinued and underwent surgery for UC. In contrast, 3 patients in the placebo group (3/198) discontinued for this reason. See **Table 66** below for further details.

Table 66: Adverse Event-Related Discontinuations in the Maintenance Trial (Cohort 2) and in the Non-randomized IndNR 12 Months Cohort

Discontinuation Reason	Placebo (N=198)	Tofacitinib 10 mg BID (N=196)	Tofacitinib 5 mg BID (N=198)	IndNR 12 Months* (N=295)
Adverse Event (does not include AEs of worsening UC)	7 (4%)	9 (5%)	5 (3%)	11 (4%)
Insufficient Clinical Response (includes AEs of worsening UC)	132 (67%)	53 (27%)	70 (35%)	132 (45%)
Patient Subtotal	145 (73%)	70 (36%)	87 (44%)	166 (56%)

Source: Reviewer's table, JReview v. 11.0; *IndNR subgroup patients who received 10 mg BID in induction studies and continue to receive tofacitinib treatment in the LTE study

Temporary Discontinuation due to AEs in the Maintenance Trial (Cohort 2)

For the maintenance study, a total of 21 patients had an AE that led to temporary discontinuation of study treatment. A larger proportion of patients temporarily discontinued the trial due to AEs in the tofacitinib 10 mg BID dose group compared to the tofacitinib 5 mg BID and placebo groups: 7.7% (15/196), in comparison to 3% (6/198) and 2% (4/198), respectively. The most common AE that led to

temporary discontinuation was HZ, which occurred in three (3) patients in the tofacitinib 10 mg BID group. No patients underwent tofacitinib dose reduction, as this was not permitted in the maintenance trial.

Concomitant Corticosteroids in Maintenance Studies

In the randomized, controlled maintenance trial, 48% (287/592) of patients reported concomitant corticosteroids use at baseline. Among this subgroup, the proportion of patients who discontinued from the study was similar between the tofacitinib treatment groups. In this subgroup of patients, there was a higher percentage of discontinuation due to AEs (that do not include AEs of worsening UC) in the tofacitinib 10 mg BID group (8%, 7/86), in comparison to the lower dose tofacitinib 5 mg BID (3%, 3/101), and placebo group (3%, 3/100).

LTE Study

In all groups, the most common reason for discontinuation was insufficient clinical response related to UC. In this study, patients were assigned to the higher tofacitinib dosage due to poor response at the lower dose, and therefore, may have had more severely active disease than those on the lower dosage at the baseline of the LTE study. Overall, from the 120-day safety update, 52% (399/769) of patients in the tofacitinib 10 mg BID dose group discontinued, compared to 17% (29/175) of the tofacitinib 5 mg BID dose group. However, in the prior TNF inhibitor failure subgroup of the LTE study, the proportion of patients who discontinued from the 10 mg BID dose group was numerically lower than in the 5 mg BID dose group: 25% (16/64) as compared to 34% (21/61). Nine patients (1.2%, 9/769) in the tofacitinib 10 mg BID group discontinued the study and underwent surgery for UC, in comparison to none in the tofacitinib 5 mg BID group.

Tofacitinib UC Program (Cohort 3)

In the overall tofacitinib UC program, the adverse event-related discontinuation reasons and the proportions in each dose and category mirrored those presented in the above cohorts and, patients with prior TNF blocker failures had similar proportions of discontinuation in each treatment group. Refer to Table 67 for additional detail.

Table 67: Adverse Event-Related Discontinuations in the Overall Tofacitinib UC Program (Cohort 3), by Tofacitinib Predominant Dose

Discontinuation Reason	PD Tofacitinib 10 mg BID (N=971)	PD Tofacitinib 5 mg BID (N=186)
Adverse Event (does not include AEs of worsening UC)	64 (7%)	14 (8%)
Overall Patient Discontinuation	483 (50%)	63 (34%)

Source: Reviewer's table, JReview v. 11.0, data cut off- 16 December 2017

In the overall tofacitinib UC program, among the 78 patients who were reported to have discontinued from studies due to AEs that were "not related to worsening UC", six of these patients may have had AEs that could be considered UC related and possibly were misclassified. These AEs included verbatim terms of: upper abdominal pain, nausea, abdominal pain, worsening abdominal pain, rectal bleeding, and worsening of UC. However, the exclusion of these potentially misclassified AEs as those "not related to worsening UC" does not change the overall conclusions described above.

7.7 Adverse Events of Special Interest (AESIs)

AESIs were chosen based on AEs of concern seen with tofacitinib in the previously studied indications and in other UC development programs. These AESIs included those listed in the current labeling for tofacitinib, which includes a boxed warning for (1) serious infections leading to hospitalization or death, including tuberculosis, invasive fungal, viral, and other opportunistic infections; and (2) malignancies (including lymphomas and other malignancies). The Warnings and Precautions section of labeling includes the following:

- Serious infections, including tuberculosis and viral reactivation
- Malignancies, lymphoproliferative disorders, and non-melanoma skin cancers
- Gastrointestinal (GI) perforations
- Laboratory abnormalities, including lymphocyte abnormalities, neutropenia, anemia, liver enzyme elevations, and lipid elevations
- Avoidance of live immunizations

External adjudication committees independent and external to the Applicant were established for review of potential adverse events of opportunistic infections, malignancies, cardiovascular events,

hepatic events, and GI perforations. Evaluation and qualification of potential malignancies consisted of a central laboratory pathologist review of biopsies (Histopathology Review) and review of clinical information including central pathologist assessment by a Malignancy Adjudication Committee (MAC). Since the conduct of the phase 2 trial A3921063 predated the establishment of the adjudication committees, Study A3921063 was not included in the adjudication process.

The numbers and percentages of patients with an adverse event and incidence rate (IR) estimates per 100 patient-years (PYs) of exposure (for Cohort 2 and 3) were calculated with the inclusion of events occurring up to 28 days beyond the last dose (or to the data cut-off date for ongoing studies). AESIs that occurred more than 28 days post last dose were also assessed by the clinical reviewer and in sensitivity analyses by the Applicant, since some of these events, such as malignancies and deaths, may have been study drug related but often have a long latency period.

7.7.1 Serious Infections

Induction Trials (Cohort 1) and Extended Induction Therapy Cohort (IndNR 2 months)

Serious infections are defined as those infections that meet the serious adverse event (SAE) reporting criteria as predetermined in the trial protocol(s), and consistent with US regulatory reporting requirements.

There were nine patients with serious infections in the induction trials. All of these infections occurred in the tofacitinib 10 mg BID group [1% (9/938)]; none were in the placebo group. In the non-randomized, extended induction therapy (IndNR 2 Month) cohort, in which patients received 8 additional weeks of tofacitinib 10 mg BID (for a total of 16 weeks), serious infections occurred in 0.7% (2/295) of patients, similar to the rate seen for the first 8 weeks of induction treatment. The types of serious infections and the number of patients are summarized in the **Table 68** below.

Table 68: Types of Serious Infections in the Randomized, Controlled Induction Trials (Cohort 1) and in the Non-randomized, Extended Induction Therapy Cohort

Dosage Groups	Tofacitinib 10 mg BID Group (N=938)	Extended Induction Therapy IndNR 2 Months Tofacitinib 10 mg BID* (N=295)
Serious Infection Types (number of patients)	Anal abscess (2)	Gastroenteritis (1)^
	Cellulitis (1)	Pilonidal cyst (1)
	Clostridium difficile infection (1)	
	Febrile infection (1)	
	Furuncle (1)	
	Otitis externa (1)	
	Pneumonia (1)	
	Postoperative abscess (1)	

Reviewer's table, JReview v 11. * IndNR 2 Months group received tofacitinib 10 mg BID in induction studies and 8 additional weeks of tofacitinib 10 mg BID in the LTE study; ^ In patients with prior TNF blocker failure

Maintenance Trial (Cohort 2)

In the maintenance trial, there were nominal serious infections in each treatment group. See **Table 69** below. The data from the non-randomized cohort of patients treated with tofacitinib for 12 months is included for purposes of exploratory comparisons.

Table 69: Types of Serious Infections Observed in the Randomized, Controlled Maintenance Trial (Cohort 2) and in the Non-Randomized LTE Group Exposed to Tofacitinib for 12 Months, IndNR 12 Months

Dosage Groups	Placebo (N=198)	Tofacitinib 10 mg BID Group (N=196)	Tofacitinib 5 mg BID Group (N=198)	IndNR 12 Months Tofacitinib 10 mg BID* (N=295)
Serious Infections Types (number of patients)	Diverticulitis (1)^	Bacterial diarrhea (1)^	Peritonsillar abscess (1)^	Atypical pneumonia (1) ^
	Subcutaneous abscess (1)^		Urinary tract infection (1)^	Cytomegalovirus hepatitis (1)
				Gastroenteritis (1) ^
				Pilonidal cyst (1)

Reviewer's table. * IndNR 12 months received tofacitinib 10 mg BID in induction studies and 8 additional weeks of tofacitinib 10 mg BID in the LTE study and continued tofacitinib treatment; ^ In patients with prior TNF blocker failure

Overall Tofacitinib UC Studies (Cohort 3)

Possible dose dependency in the risk of serious infection was observed in the overall tofacitinib UC program (Cohort 3). The incidence rate ratio (IRR) for the tofacitinib Predominant Dose 10 mg BID vs the Predominant Dose 5 mg BID in Cohort 3 was: 1.4 (95% CI 0.6-3.2). These results are evaluated in the context that most patients in the tofacitinib UC program were predominantly treated with the 10 mg BID dose. Hence, a smaller number of patients were treated predominantly with the 5 mg BID dosage. No serious infection resulted in death. See **Table 70** below for further details.

Table 70: Serious Infections Exposure and Incidence Rates (IR) (per 100 PYs) in Overall Tofacitinib UC Studies (Cohort 3), Presented by Predominant Dose Exposure

Treatment Group	PD Tofacitinib 10 mg BID	PD Tofacitinib 5 mg BID	PD Tofacitinib All
Number of patients with exposure	957	200	1157
Number of patient with events, n (%)	31 (3.2%)	7 (3.5%)	38 (3.3%)
Total drug exposure (PY)	1540.2	496.8	2037.0
Incidence Rates (95% CI)	2.01 (1.37, 2.86)	1.41 (0.57, 2.90)	1.87 (1.32, 2.56)

Source: Applicant's submission dated 26 October 2017, Database lock 29 September 2017

The risk for serious infection was explored in association with the patients' absolute lymphocyte count (ALC). At the time of the July 8, 2016, database cut-off, any baseline or post-baseline ALC $<1 \times 10^9$/L was observed in 543 patients. ALC $<1 \times 10^9$/L after baseline, as confirmed by 2 consecutive observations, was observed in 188 patients. Serious infections occurred in 6/188 (3.2%) patients who had post-baseline confirmed ALC $<1x10^9$/L, compared to 23/960 (2.4%) in patients who did not have post-baseline confirmed low ALC $<1x10^9$/L. Opportunistic infections occurred in 5/183 (2.7%) patients who had post-baseline confirmed ALC $<1x10^9$/L, compared to 12/932 (1.3%) in patients who did not have post-baseline confirmed low ALC $<1x10^9$/L. Likewise, HZ infections occurred in 12/184 (6.5%) patients who had post-baseline confirmed ALC $<1x10^9$/L, compared to 47/964 (4.9%) in patients who did not have post-baseline confirmed low ALC $<1x10^9$/L.

In the RA program, a post-baseline confirmed nadir ALC $<0.5 \times 10^9$/L was identified as a risk factor for serious infections. The labeling of Xeljanz (tofacitinib) recommends that treatment is stopped for ALC $<0.5 \times 10^9$/L. Hence, patients with screening ALC $<0.5 \times 10^9$/L were excluded from the phase 3 UC induction studies, and patients with confirmed ALC $<0.5 \times 10^9$/L during treatment were required to be discontinued from the UC studies. Thus, it was not possible to assess if the relationship between confirmed ACL $< 0.5 \times 10^9$ /L and serious infection was also present within the UC data.

Serious infections occurred at a higher rate (based on calculated incidence rates) in patients who were treated predominately with the tofacitinib 10 mg BID dose, in comparison to the tofacitinib 5 mg BID dose. Within the UC program, a low post-baseline ALC count ($<1 \times 10^9$) was associated with a slightly increased risk of serious infection. This is consistent with the experience from the RA program, where patients with developed a low ALC (post-baseline) may have higher risks for developing serious infections.

7.7.2 Herpes Zoster (HZ) Infections

In general, HZ infection (shingles) has been recognized and labeled as a risk associated with tofacitinib use. As evident across multiple tofacitinib developmental programs, HZ infections occur in a dose-dependent fashion. Descriptions of opportunistic HZ infections are included in this section and data relating to all opportunistic infections occurring in the tofacitinib UC program are included in **Section 7.7.3**.

Induction Trials (Cohort 1) and Extended Induction Therapy Cohort (IndNR 2 months)

In the induction trials, there were 6 cases (0.6%) of HZ in the tofacitinib 10 mg BID treatment group and 1 (0.4%) case of HZ in the placebo group. For the extended induction therapy (IndNR 2 months) subgroup of the LTE, in which tofacitinib 10 mg BID was continued for an additional 8 weeks beyond the initial 8-week induction period, two more cases occurred (2 cases, 0.5%). There were no serious or severe cases of HZ in either cohort.

Maintenance Trial (Cohort 2)

In the randomized, controlled maintenance trial, there were 10 patients (5%, 10/196) in the tofacitinib 10 mg BID group, 3 patients in the tofacitinib 5 mg BID (2%, 3/198), and 1 patient in the placebo group (0.5%, 1/198) who had HZ infection. In the maintenance trial, there is a dose-dependent increase in the rate of HZ infections for those treated with tofacitinib 10 mg BID, compared with tofacitinib 5 mg BID. There were no HZ SAEs in the maintenance study.

Tofacitinib UC Program (Cohort 3)

In the overall tofacitinib program, the incidence rate ratio (IRR) for the Predominant Dose (PD) tofacitinib 10 mg BID versus the PD tofacitinib 5 mg BID in Cohort 3 was 1.0, 95% CI 0.6-1.6. Refer to **Table 71** below for additional details.

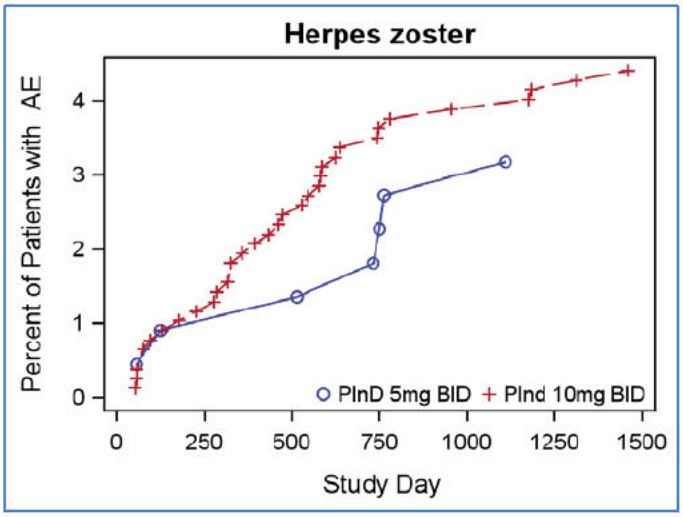
Table 71: Herpes Zoster AEs in Cohort 3 by Tofacitinib Predominant Dose and Incidence Rates (per 100 PYs)

Treatment Group	PD Tofacitinib 5 mg BID	PD Tofacitinib 10 mg BID	PD Tofacitinib All
Number of patients with exposure	200	957	1157
Number of patient with events, n (%)	18 (9.0%)	56 (5.9%)	74 (6.4%)
Total drug exposure (PY)	465.1	1480.6	1945.7
IR (95% CI)	3.87 (2.29, 6.12)	3.78 (2.86, 4.91)	3.80 (2.99, 4.77)

Source: Applicant's submission dated 26 October 2017, Database lock 29 September 2017

Figure 6 below shows the cumulative incidence of HZ infections by post-induction dose (PInd) analysis groups for Cohort 3. The cumulative percentage of patients with HZ infections increased over time and HZ infection occurred at a greater rate in patients allocated to the 10 mg BID post-induction dose group, in comparison with the 5 mg BID post-induction dose group.

Figure 6: Cumulative Incidence of Herpes Zoster (HZ) Infections in the Tofacitinib UC Population (Cohort 3) by Post Induction Dose (PInd) Analysis Group



Source: Reviewer's figure, created from the integrated summary of safety dataset "advers.xpt" and "pinfo.xpt" by post induction dose provided by the Applicant to FDA in response to an information request by the Agency on December 7, 2017. AE events were from patients in Phase 3 studies A3921094, A3921095, A3921096, and the LTE study A3921139. Post induction doses (PInd) are treatment doses in study A3921096 and LTE study A3921139. Herpes zoster infections: Cohort 3 PInd

tofacitinib 10 mg BID analyses group, n=34 cases; Cohort 3 PInd tofacitinib 5 mg BID analyses group, n=7 cases.

Overall Characteristics of HZ Infections

The median age of patients who developed HZ infections in Cohort 3 was 53.4 years, with an overall age range of 19.8 to 82.3 years. At the time of the 120-day safety update, a total of 69 events of HZ were reported in 65 patients. Four percent (3/69) of these events were considered as "severe" AEs and 6% (4/69) were SAEs. The SAEs of HZ infection occurred in the LTE study and involved patient hospitalization. Most of the HZ cases (74%, 51/69) were limited to cutaneous involvement of 1 or 2 adjacent dermatomes. Most were not associated with post-herpetic neuralgia, with post-herpetic neuralgia occurring in 5% (3/65) patients who developed HZ. Most of the events (87%, 60/69) of HZ were reported as resolved. HZ infections leading to discontinuation of tofacitinib occurred in 8% (5/65) of the patients. As of July 16, 2016, HZ infection led to dose reduction or temporary withholding of treatment in 1% (16/1157) of all patients in the UC program.

HZ Opportunistic Infections

HZ infections that were confirmed as opportunistic infections (OIs) were classified into 2 categories:

1. HZ, disseminated (meeting any of the following criteria): diffuse rash (>6 dermatomes), encephalitis, pneumonia, other non-skin organ involvement
2. HZ, multi-dermatomal (nonadjacent or >2 adjacent dermatomes that is not classified as disseminated)

The majority of the reported OIs were HZ infections, accounting for 18 (82%) out of the 22 OI events. Most of these 18 HZ infections (12 events in 11 patients) were cutaneous multi-dermatomal HZ infections. As aforementioned, 6 patients with HZ infection had disseminated HZ, consisting of: 1 event of HZ encephalitis, 2 events of ophthalmic HZ, and 3 events of cutaneous HZ.

Events of HZ dissemination resulting in HZ encephalitis (1 case) and ophthalmologic HZ disease (2 cases) were seen in the tofacitinib UC program. These most severe forms of HZ occurred within the LTE study, in patients who received PD 10 mg, with onset ranging from 344 to 1066 days on treatment.

These types of events have not been previously included as opportunistic infections in the labeling. Based on the analysis of the controlled portion of the program (induction and maintenance studies), it appears that there is a dose-dependent risk of developing HZ infection in patients who predominantly took 10 mg BID in comparison to the lower 5 mg BID dosage. These results have been evaluated in the context that most patients in the tofacitinib UC program were predominantly treated with the 10 mg BID dose, in comparison to the 5 mg BID dose.

Concomitant Oral Corticosteroids and Risk of HZ Infection

In general, patients who used concomitant oral corticosteroids had similar risks of developing HZ than those who did not use concomitant oral corticosteroids. The risk of developing HZ when taking concomitant oral corticosteroids did not appear to increase with increasing dose of tofacitinib. At the data cut-off of September 29, 2017, a similar proportion of patients who took concomitant oral corticosteroids had HZ infection in the PD tofacitinib 10 mg BID (2.4%, 23/957) and PD tofacitinib 5 mg BID (3.5%, 7/200) groups.

Varicella Zoster (Shingles) Vaccine

Based on the data provided by the Applicant, it is unclear whether VZV vaccine for shingles prevents the development of HZ infection in patients treated with tofacitinib. The Applicant states that the case report form for prior shingles vaccinations was introduced after the phase 3 UC program was started. Therefore, this history was not collected from every patient enrolled in the phase 3 program and was not available from the phase 2 induction trial, Study 1063. Hence, in the overall tofacitinib UC program (Cohort 3), among the 1124 patients who participated in at least one phase 3 UC study, the status of prior shingles vaccination was unknown or missing in 16% (178 /1124) of patients. Moreover, only 1% (12/ 1124) of patients reported having received prior shingles vaccinations. None of these 12 patients developed shingles. Notably, at the time of initiation of these studies, the only approved vaccination for shingles was Zostavax (zoster vaccine live). Many UC patients would be ineligible to receive this vaccination due to risk of live vaccination in patients receiving immunosuppressing medications. Since that time, a newer, recombinant adjuvanted vaccine (Shingrix) was approved in the US, which is not contraindicated in patients receiving concomitant immunosuppressive medications. Use of this new vaccine may represent a strategy to mitigate treatment related HZ risk in the future. A post-marketing

commitment will be issued to further assess the potential use of this vaccine to mitigate the risk of HZ associated with tofacitinib treatment.

7.7.3 Opportunistic Infections (Including HZ and non-HZ OIs) and Tuberculosis

Because of the lack of universal definition of OIs in the literature, the tofacitinib UC program used an external, independent Opportunistic Infection Review Committee (OIRC) for adjudication for the determination of these potential events. Infections considered in-scope for committee review were prespecified in the OIRC Charter and included specific viral, bacterial, fungal and parasitic infections. Although the OIRC evaluated reports of tuberculosis, this diagnosis was not included as an opportunistic infection in the calculation of proportion and incidence rates in the tofacitinib UC program. Additionally, all OIs reported as SAEs were adjudicated.

Overall Tofacitinib UC Program (Cohort 3)

In the overall tofacitinib UC program, a total of 22 OIs (excluding a case of tuberculosis) were reported in 21 patients. As aforementioned, 18 of these 22 OIs were HZ infections; please see **Section 7.7.2** Herpes Zoster (HZ) Infections for more information regarding overall HZ infections. There were four remaining opportunistic infections that were non-HZ; three of which occurred in the PD tofacitinib 10 mg group. These cases included one event each: cytomegalovirus (CMV) colitis, which occurred in an induction study; and pulmonary cryptococcosis, pulmonary histoplasmosis, and CMV hepatitis in the LTE study. Three of these cases occurred in the PD tofacitinib 10 mg group, and one occurred in the PD tofacitinib 5 mg group. In the LTE study, a case of active tuberculosis was identified in a patient from the PD tofacitinib 10 mg BID group. The opportunistic infection AEs in Cohort 3 are summarized by PD tofacitinib dose in the **Table 72** below. The incidence rate ratio (IRR) for the PD tofacitinib 10 mg BID vs the PD tofacitinib 5 mg BID in Cohort 3 was: 0.8, 95% CI 0.3-2.2.

Overall, five (23%) of the 22 OI events were serious infections, and none resulted in death. Most (77%, 17/22) of the OI events were reported as resolved, including the events of CMV hepatitis and CMV colitis. Among the 21 tofacitinib-treated patients with OIs, 5 were discontinued from the studies due to their infections.

Table 72: Opportunistic Infection AEs in the Overall Tofacitinib UC Studies (Cohort 3) by Predominant Tofacitinib Dose and Incidence Rates (per 100 PYs)*

Treatment Group	PD Tofacitinib 10 mg BID	PD Tofacitinib 5 mg BID	Tofacitinib All
Number of patients with exposure	924	200	1124
Number of patient with events, n (%)	16 (1.7%)	6 (3.0%)	22 (2.0%)
Total drug exposure (PY)	1525.6	485.1	2010.7
IR	1.05 (0.60, 1.70)	1.24 (0.45, 2.69)	1.09 (0.69, 1.66)

Source: Applicant's submission dated 26 October 2017; Database lock 29 September 2017
*Endpoints based on adjudicated Opportunistic Infections data from A3921094, A3921095, A3921096 and A3921139; Excludes one case of tuberculosis and cases of herpes zoster with two adjacent dermatomes

Overall, there is no clear dose dependency in the risk of opportunistic infections in the tofacitinib UC program, and no opportunistic infections resulted in death.

7.7.4 Malignancy Excluding Non-Melanoma Skin Cancer (NMSC)

Malignancy was recognized as an AESIs for the tofacitinib UC program. The currently approved tofacitinib labeling includes a boxed warning for malignancy, including lymphoma. In the overall tofacitinib UC program, 15 events of malignancy (excluding NMSC) were reported in 13 patients, per the Malignancy Adjudication Committee (MAC) adjudication. The number of patient and events are based on the data cut-off date of September 29, 2017 in a response from the Applicant to an FDA inquiry dated February 18, 2018. Two patients had two events of malignancy each. None of the malignancies occurred during the induction studies. All malignancy events occurred in tofacitinib-treated patients during the LTE study. One event of breast cancer occurred in a placebo-treated patient in the maintenance study.

Of note, most patients with malignancies had a history of prior azathioprine and/or 6-MP treatment (92%, 12/13) and a history of TNF blocker failure (76.9%, 10/13 patients), both of which are known to increase the risk of malignancies. Two patients had adenocarcinoma of the colon, which is known to be associated with UC itself. Two out of the 13 patients were diagnosed with malignancies 57 and 104

days after treatment initiation, which suggests that malignancy did not occur exclusively after a long duration of tofacitinib treatment. Malignancies occurred almost exclusively in patients treated with 10 mg BID long-term. Additionally, there appears to be a trend toward an increased risk of malignancy in patients with a history of TNF inhibitor failure as compared to non-failures.

As discussed previously, three of the malignancies resulted in death: (1) Patient (b) (6), who had confirmed hepatic angiosarcoma; (2) Patient (b) (6), who had confirmed acute myeloid leukemia (AML), and (3) Patient (b) (6), who had confirmed cholangiocarcinoma and died from pulmonary embolism. See Error! Reference source not found. in the Appendix for a description of the cases. These patients were treated with the PD and PInd tofacitinib 10 mg BID in the tofacitinib UC program (Cohort 3).

Based on the available data, the risk of the development of malignancies appears to be higher in the PD tofacitinib 10 mg BID dose group in comparison to the PD tofacitinib 5 mg BID group, and in those treated previously with immunosuppressants or with prior TNF blocker. However, because Cohort 3 included multiple sequential studies in which patients may have received varying tofacitinib dosages, and the fact that most patients were treated with PD tofacitinib 10 mg BID dosage (83%, 9571/1157), there were a very limited number of patients with long-term exposure to 5 mg BID. Given that malignancies, in general, are a rare occurrence within a clinical trial, this imbalance in exposure to long-term 5 mg BID compared with 10 mg BID limits the ability to conclude that lower dosage of tofacitinib is safer than the higher dosage, in regards to malignancy risk.

Incidence Rates

Per the Applicant, the cumulative IR per 100 patient-years (95% CI) of malignancies (excluding NMSC) in the PD Tofacitinib 10 mg BID group in Cohort 3 is 0.84 (0.45, 1.44) at the September 29, 2017, data cut-off. See **Table 73** below for further details.

Table 73: Cohort 3 Tofacitinib UC Program Adjudicated Malignancies (Excluding NMSC) and Incidence Rates (per 100 PYs) by Tofacitinib Predominant Dose

Treatment Group	PD Tofacitinib 10 mg BID	PD Tofacitinib 5 mg BID	Overall Tofacitinib UC Program
Number (N) of patients with exposure, (%) of Tofacitinib All group	924 (82%)	200 (18%)	1124 (100%)
Number of patient with events, n (%)	13 (1.4)	0	13 (1.2%)
Total drug exposure (PY)	1541.28	498.78	2040.60
IR (95% CI)	0.84 (0.45, 1.44)	0 (0, 0.74)	0.64 (0.34, 1.09)

Source: Applicant's submission dated 26 October 2017, pg. 8/30, Database lock 29 September 2017;
Note: Includes events that occurred more than 28 days after the last dose; Number of patients with exposure include those in phase 3 UC studies; adjudication was not performed in the phase 2 induction study

A higher IR of malignancies in patients treated with PD tofacitinib 10 mg group, compared with PD tofacitinib 5 mg group was observed. However, given the rare nature of malignancies, even if there was an increased risk of malignancy from 5 mg compared to placebo, cases may not have occurred in the small population (200 patients) who were exposed to 5 mg BID long-term. Thus, the comparison of the incidence rate of zero in 5 mg group, compared to that reported (0.84) in the much larger population of patients exposed long-term to 10 mg (924 patients), as well as the fact that there was no control arm for the full duration of treatment, it is difficult to determine whether the numeric IR differences signify a true increased risk of malignancy associated with the tofacitinib 10 mg BID dose.

Comparison Cohort: Truven MarketScan Database

To put the reported incidence rates of malignancy associated with each dose into context, the Applicant attempted to compare the risks of malignancy in patients treated with tofacitinib, to those expected in a population of patients with moderate to severe UC who may have received, or continue to be treated, with biologics and/or other immunosuppressant agents.

The MarketScan claims databases contain 143 million unique patients since 1996. Based on data from 2015, MarketScan claims databases contain data on 50 million covered lives. This database contains nationally representative data sample of Americans with employer-provided health insurance and Medicaid, and contains complete information on outpatient prescriptions and diagnoses.

Constructed from the Truven database, "trial-criteria cohort" (n=6366) was used by the Applicant. This comparison cohort consisted of adult patients (≥18 years of age) with moderate to severe UC. Additionally, to identify moderate to severe UC patients, the cohort was restricted to the following:

- Patients who are receiving or have received biologics (TNF-blocker [including infliximab, adalimumab, and golimumab] or vedolizumab),
- Patients who are receiving or have received AZA, 6-MP, methotrexate, tacrolimus (oral or intravenous) or cyclosporine (oral or intravenous), or
- Patients who received more than 4000 mg of prednisone-equivalent oral, systemic glucocorticoids in the 6 months prior to the start of follow-up (calculated based on the cumulative dose as of the index date when they would otherwise qualify for cohort entry based on the diagnosis and coverage requirements).

In addition, patients in this Truven Marketscan comparison cohort also met nine exclusion criteria from the tofacitinib global phase 3 UC studies, which could be reasonably operationalized in Truven Marketscan data. These exclusion criteria included, but were not limited to, exclusion of patients with solid organ or autologous bone marrow transplantation, infection with human immunodeficiency virus, hepatitis B virus or hepatitis C virus, advanced kidney disease, advanced liver disease, history of colectomy, presence of Crohn's Disease (CD), prior surgery for UC and recent bowel surgery (within 6 months), and cancer diagnoses within a 365-day baseline period prior to each new exposure episode. The purpose of the "trial-criteria" cohort is to closely match for comparison to the population in the tofacitinib global phase 3 UC studies.

The incidence rate of malignancies (excluding NMSC) in the health claims comparison cohort was 0.63/100 PY, with 95% CI (0.43, 0.90), which was very similar to the reported IR for malignancies excluding NMSC for the overall tofacitinib program (0.64, (0.34- 1.09)). However, the incidence rate in the PD tofacitinib 10 mg group (Cohort 3) was 0.84/100 PY (95% CI: 0.45-1.44), which is numerically greater than the incidence rate of malignancies (excluding NMSC) in the Truven MarketScan comparison cohort of 0.63/100 PY (95% CI: 0.43, 0.90).

There are multiple limitations to this type of comparison between claims based data and clinical trial data. For example, adverse events will not be reported using standardized case definitions in the

claims data, there are differences in methodology for the evaluation and confirmation of AEs (such as clinical care vs adjudication committee), and timing and quality of patient follow-up may differ. However, this analysis is summarized here for the purposes of providing context as to how the identified tofacitinib related risks may compare with those associated with having active UC and utilizing other available therapies. Note the relatively tight CI associated with the large sample size from the claims database, in comparison to the relatively wide CI associated with the estimates in the tofacitinib program. This comparison is purely exploratory, and limitations in the quality of data obtained from claims databases may be important. For further information regarding the Agency's interpretation of the Truven MarketScan Database results, please see the review by Joel Weissfeld, MD MPH, of the Office of Surveillance and Epidemiology (OSE), dated September 29, 2017.

7.7.5 Non-Melanoma Skin Cancer (NMSC)

Induction Trials (Cohort 1) and Maintenance Trial (Cohort 2)

In the randomized, controlled induction trials, there were two cases of NMSC in the tofacitinib 10 mg treatment group. One case was basal cell cancer (BCC) and the other was squamous cell cancer (SCC). There were no NMSC cases in the placebo group. In the maintenance trial, there were a total of four cases of NMSCs. There were two patients with basal cell carcinoma, including one patient in the tofacitinib 10 mg BID and one patient in the placebo group. Two patients in the tofacitinib 10 mg BID developed squamous cell carcinoma. There were no NMSC events in the tofacitinib 5 mg BID group.

Tofacitinib UC Program (Cohort 3)

As of September 29, 2017, the adjudicated cases of NMSC were reported among 15 patients. Among the 15 patients who reported NMSC, 12 (80%) were in the PD tofacitinib 10 mg BID group and 3 (20%) were in the PD Tofacitinib 5 mg BID group. The incidence rate ratio (IRR) for the PD tofacitinib 10 mg BID vs the tofacitinib 5 mg BID in Cohort 3 was: IRR 1.3, 95% CI 0.4-4.6.

Nine of these 15 patients with NMSC events were diagnosed with BCC and 9 patients had SCC, with 3 patients reporting both BCC and SCC. None of these NMSC events resulted in discontinuation of tofacitinib. Three events out of 16 NMSC AEs (19%) were considered SAEs. Seven (47%) of 15 patients had a prior history of NSMC, 14 (93%) patients had prior exposure to azathioprine or 6-mercaptopurine, and 13 (87%) patients had prior TNF blocker failure. Among patients with prior TNF

blocker history, of the 11 patients who reported NMSC, 10 of them were in the PD 10 mg BID group and one patient was in the 5 mg BID group.

Of the aforementioned, adjudicated patients with NMSC, prior history of NMSC was reported in 6 patients, prior use of AZA or 6-MP was reported in 10 patients, and 10 had prior treatment failure with TNF blocker agents. Ten events of squamous cell cancers (SCC) were reported in 7 patients, and 8 events of basal cell carcinoma (BCC) were reported in 6 patients. All of the SCC events occurred in the PD 10 mg BID group. See **Table 74** below for further details. See Error! Reference source not found. in the Appendix for the NMSC case descriptions.

Table 74: Adjudicated NMSC in Cohort 3 Tofacitinib UC Program Patients by Tofacitinib Predominant Dose, Incidence Rates (per 100 PYs)

Treatment Group	PD Tofacitinib 10 mg BID	PD Tofacitinib 5 mg BID	Overall Tofacitinib UC Program
Number (N) of patients with exposure	924	200	1124
Number of patient with events, n (%)	12 (1.3%)	3 (1.5%)	15 (1.3%)
Total drug exposure (PY)	1522.89	495.54	2017.94
IR (95% CI)	0.79 (0.41, 1.38)	0.61 (0.12, 1.77)	0.74 (0.42, 1.23)
Median (Days)	463.5	609.0	515.0
Range (Days)	16 – 1311	329 – 690	16 – 1311

Source: Reviewer's Table per Applicant's submission dated 26 October 2017 and 21 December 2017; Database lock 29 September 2017; Note: Includes events that occurred more than 28 days after the last dose; Number of patients with exposure include those in phase 3 UC studies; adjudication was not performed in the phase 2 induction Study 1063

Within the UC program, NMSC occurred more frequently in patients treated with PD 10 mg BID compared to PD 5 mg BID, suggesting a dose-dependent risk. In addition, the majority of patients who had adjudicated NMSC had prior exposure to other medications that can increase the risk of NMSC, so it is difficult to determine how much of the risk is attributed to tofacitinib or prior therapies. Nonetheless, it will be important to communicate to patients and providers the importance of measures to detect and prevent skin cancers, including consideration of regular dermatologic examinations (as is recommended with other drugs/biologics associated with this risk). This information is included in the Warnings and Precautions section of the label.

7.7.6 Major Cardiovascular Adverse Events (MACE)

The Cardiovascular Event Adjudication Committee (CV-EAC) evaluated possible Major Adverse Cardiovascular Events (MACE). MACE is defined by the Applicant within this program as a composite endpoint consisting of the following components:

1. Cardiovascular death: death due to acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, death due to other cardiovascular causes: e.g., peripheral artery disease
2. Non-fatal myocardial infarction
3. Non-fatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischemia or hemorrhage

The CV-EAC committee also adjudicated cardiovascular-related events other than MACE, such as non-fatal congestive heart failure cases. In addition, all fatal events, regardless of cause of death, were reviewed by CV-EAC. These cases were evaluated to determine whether these events should or should not be categorized as MACE. Adjudicated non-MACE cases, such as malignancy related deaths, that were evaluated by the committee, were not categorized as MACE events.

In the tofacitinib UC program, as of September 29, 2017, there were a total of five patients who had events that were eventually adjudicated as MACE. Each patient with MACE had a history of CV risk factors. Four of the five cases predominantly received tofacitinib 10 mg BID dosage, prior to the onset of the MACE event. See
Table 75 for further details of the tofacitinib UC program MACE cases.

Table 75: Overall Tofacitinib UC Program (Cohort 3) Patients with MACE

Case	Study, Patient ID, Treatment Dose at Event Onset	Induction Study Dose (1094 or 1095), Maintenance Study Dose (1096)	Age (years), Gender, Race	Adjudicated Event Type	CV Risk Factors	Cumulative Onset Day Number/ Last Known Dose Day	Outcome
1*	A3921094 (b) (6) Tofacitinib 10 mg BID	1094: Tofacitinib 10 mg BID (60 days)	66, Male, white	Acute Coronary Syndrome	Medical history of angina pectoris, arrhythmia, myocardial infarction, diabetes, hypertension, hypercholesterolemia and obesity	28/ 60	Resolved
2	A3921096 (b) (6) Tofacitinib 5 mg BID	1095: Tofacitinib 10 mg BID (65 days), 1096: Tofacitinib 5 mg BID (78 days)	74 Male, white	Myocardial Infarction	Medical history of hyperlipidemia, atrial fibrillation, intraventricular conduction delay, bradycardia, hypertension, and deep vein thrombosis	142/ 143	Resolved
3	A3921096 (b) (6) Tofacitinib 10 mg BID	1094: Tofacitinib 10 mg BID (63 days) 1096: Tofacitinib 10 mg BID (85 days)	55 Female, White	Hemorrhagic stroke	Medical history of hypertension, headache, hypercholesterolemia, and diabetes mellitus	148/ 148	Still present
4	A3921094 (b) (6) Tofacitinib 10 mg BID	1094: Tofacitinib 10 mg BID (31 days)	39 Male, White	Aortic Dissection	Medical history of Anemia and Cushing's syndrome	24/ 31	Patient died

Case	Study, Patient ID, Treatment Dose at Event Onset	Induction Study Dose (1094 or 1095), Maintenance Study Dose (1096)	Age (years), Gender, Race	Adjudicated Event Type	CV Risk Factors	Cumulative Onset Day Number/ Last Known Dose Day	Outcome
5**	A3921139 (b) (6) Tofacitinib 10 mg BID	1095: Tofacitinib 10 mg BID 1096: placebo	56 Male, White	Cerebrovascular insult: Occipital infarction	Hypertension, Diabetes mellitus	858	resolved

Source: Reviewer's Table per Applicant's SCS pg. 128/292, *In the analyses by predominant dose (PD), this patient is categorized as PD 5 mg for the overall program. However, at the time of MACE event, patient was receiving 10 mg BID. **Event occurred on 27 May 2017, and was adjudicated on 21 November 2017. The CV-EAC committee did not adjudicate this case as MACE.

There were two adjudicated cardiovascular events that occurred in the induction studies. Both patients were treated in the tofacitinib 10 mg group. One case was discussed above under **Section 7.4** Deaths, regarding a fatal case of aortic dissection in a 39-year-old male. The second case was a 78-year-old patient with acute coronary syndrome. In the maintenance study, two cases of MACE were identified (noted in the
Table 75).

There was one additional case of ischemic stroke, (listed as case 5 in
Table 75) which was not adjudicated as a MACE event. However, the rationale for excluding this case is unclear / is not considered sufficient to the clinical reviewer. The details of this case are summarized in **Appendix D**. and consideration is given to the fact that the true number of MACE cases may be 5 rather than 4.

In summary, there is insufficient information available in UC patients to make a conclusion regarding any potential risk of MACE incurred from treatment with tofacitinib. As described in the regulatory history section above, (b) (4)

(b) (4)

7.7.7 Gastrointestinal Perforations

The Gastrointestinal Perforation Review Committee (GI PRC) provided adjudication of potential GI perforation events. The definition of GI perforation was revised during the course of the tofacitinib UC program in order to exclude the following PTs of Perirectal abscess, Rectal abscess, Anal abscess, Perineal abscess, Pilonidal cyst, and any PTs containing the term fistula regardless of the location of the fistula. In regards to diagnosed abscesses, this definition only included abscesses occurring above the level of peritoneal reflection at the rectouterine or recto-vesical pouch.

Cohort 3 (Tofacitinib UC Program)

In the entire UC program, GI perforation (revised definition) was reported in three tofacitinib-treated patients. Two events (0.2%, 2/924) occurred in the PD tofacitinib 10 mg BID group vs one case (0.5%, 1/200) in the PD tofacitinib 5 mg BID group. The IR of GI perforation (revised definition) in the Tofacitinib All group in the Overall Cohort was 0.18/100 PY. In the 47-year-old patient treated with tofacitinib 10 mg BID, the intestinal perforation occurred while the patient was lifting a heavy object, 24 days after an unscheduled endoscopy procedure that showed worsening of UC inflammation. See the **Table 76** below for details regarding these three cases.

Table 76: Gastrointestinal Perforations (Revised Definition) in Cohort 3, as of December 16, 2016

PD Treatment Group in the Overall Cohort	Age (Years)[a], Gender, Race	Preferred Term / Location	Concomitant Oral Corticosteroids / Concomitant NSAIDs / Concurrent Diverticulitis	Relatedness to Study Drug as Assessed by Investigator	Other Potential Risk Factors	Onset Day	Last Known Dose Day	Study Drug Action	Outcome
PD 5 mg BID	26, Male, White	Appendicitis / Large bowel, excluding anus and rectum	No / Yes / No	Unrelated	Ulcerative colitis	430	456	Permanently discontinued	Resolved
PD 10 mg BID	47, Male, White	Intestinal perforation / Large bowel, excluding anus and rectum	Yes / No / No	Related	Mechanical stress, ulcerative colitis, and concomitant prednisone	40	39	Permanently discontinued	Resolved
PD 10 mg BID	52, Male, White	Gastrointestinal perforation / Large bowel, excluding anus and rectum	Yes / No / No	Unrelated	Ulcerative colitis or lymphoma	103	98	No action taken	Resolved

Source: Applicant's FDA AC Meeting Briefing Document, pg.92/176; NSAID = nonsteroidal anti-inflammatory drug

Unlike other conditions where tofacitinib is used (such as RA or PsA), in UC patients, active disease itself and concomitant medications that may be used, can predispose patients to colonic perforation. Thus, a rare case of colonic perforation would not be unexpected in a UC development program.

Thrombosis-Related Events

Events of thromboembolism occurred in the tofacitinib UC program and have been noted to occur with other drugs in the same class as JAK inhibitors. In the induction and maintenance studies, venous thromboses that were non-deep vein were identified in patients treated with tofacitinib and placebo. In the LTE study, four patients had events of pulmonary embolism (PE) and were predominantly treated with tofacitinib 10 mg BID. These patients had known risk factors for the development of PE in their medical history, including two patients with a medical history of venous thromboembolic events prior to the start of tofacitinib treatment. One of these patients, who had associated malignancy, died.

In the overall tofacitinib UC program, potential thromboembolic events were identified in a total of 15 patients. Additional events included the following: three MACE events (reported above), an individual case of an ischemic stroke (adjudicated as a non-MACE event), thrombophlebitis, bone infarction, intermittent amaurosis fugax, and hemorrhoid thrombosis.

The occurrence of concerning thrombosis and/or thromboembolism was infrequent in UC patients, and it is unclear if there is a possible dose-dependent relationship with these events. Since these thromboembolic events may represent emergent class effect for JAK inhibitors, it is worth noting their occurrence in this drug development program.

7.7.8 Hepatic Injury, Hepatic Enzyme Abnormalities, and Drug Induced Liver Injury (DILI)

Abnormal Hepatic Enzyme Levels

In the tofacitinib UC induction trials, patients with screening alanine aminotransferase (ALT), aspartate aminotransferase (ALT) or total bilirubin > 1.5 x upper limit of normal (ULN) were excluded from enrollment. Overall, treatment with tofacitinib was associated with small mean increases in transaminases and bilirubin that were not clinically meaningful. The proportion of patients with

increases in transaminases of AST or ALT ≥3 or 5x ULN was nominal and comparable between the tofacitinib treatment groups and the placebo group in the controlled induction and maintenance trials. No overt dose dependencies in relation to liver biochemistry abnormalities were observed. See **Table 113** in the Appendix.

Hepatic Injury Adjudication

The Hepatic Event Review Committee (HERC) included an expert panel of hepatologists who performed an independent review of the suspected drug induced liver injury (DILI) cases using a prespecified, consistent set of criteria within the UC program and across the various indications of the broader tofacitinib development program.

Suspected events of hepatic injury could have been identified by the investigator or the Applicant, by searches of clinical, safety or laboratory databases that included the following:

- Hy's Law (ALT or AST ≥3 × ULN, bilirubin≥2 × ULN) cases
- ALT or AST ≥5 × ULN
- All events meeting hepatic discontinuation criteria per protocol (laboratory-based portions)
- SAEs coding to MedDRA Hepatobiliary SOC, serious and non-serious AEs coding to MedDRA Liver infections SMQ, serious and non-serious AEs coding to MedDRA Infectious biliary disorders SMQ, AEs coding to MedDRA Drug-induced liver injury preferred term (PT)
- Any death in a patient with, or a report of jaundice

In the UC program, select cases of possible "hepatic injury," meeting criteria above were adjudicated for DILI. A total of 5 cases were adjudicated as "possible" DILI by the HERC. Each of these patients were part of the PD tofacitinib 10 mg BID group. They had abnormalities of liver biochemistry results, but did not meet all the Hy's law criteria. In each of these cases, the HERC concluded that DILI was "possible" (but not probable, highly likely or definite) as each of these patients had other reasons, besides tofacitinib treatment, to potentially have developed an increase in hepatic enzymes. Overall, there was a low incidence (0.4%, 5/1157) of cases of suspected DILI in the tofacitinib UC program. Moreover, in the UC program, there were no AEs that contained the term "hepatic failure". There was one SAE in the hepatobiliary disorders SOC which was an event of acute cholecystitis.

The potential for DILI is reflected in the current label for Xeljanz as a less common adverse event. (b) (4)

(b) (4)

(b) (4)
(b) (4). In addition, per labeling, 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.

In the induction studies, there were no potential Hy's law cases. However, in the maintenance and LTE studies, there were two patients who met the screening criteria for potential Hy's law, though neither was concluded to be a DILI case. Patient A3921139 (b) (6) had a hepatic angiosarcoma, and the second patient with potential Hy's law case was found to have elevated liver biochemistry tests (at different time periods) secondary to strenuous exercise (Patient A3921096 (b) (6)).

7.7.9 Interstitial Lung Disease (ILD)

In the tofacitinib UC program, there were no cases of ILD.

7.8 Laboratory Findings

Tofacitinib is associated with changes in certain hematologic, hepatobiliary, and lipid parameters. Tofacitinib treatment in the UC program was associated with decreases in absolute lymphocyte count (ALC) and increases in transaminases and creatinine kinase (CK). Treatment with tofacitinib also 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. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

The increases in transaminases, CK and lipids returned to baseline values within 4 weeks after tofacitinib withdrawal. However, a mixed effect of treatment withdrawal on recovery from abnormally low lymphocytes cell counts was observed. Among the 6 patients who discontinued due to decreased ALC, recovery of ALC appeared to be variable with some patients demonstrating partial/complete recovery and some patients not showing recovery within 30 days after the last dose. The current product labeling reflects notable changes in laboratory parameters based on the findings from patients treated with tofacitinib in the RA trials.

7.9 Vital Signs

In general, treatment with tofacitinib was not associated with increases in heart rate or blood pressure. Changes in blood pressure were small and comparable in all treatment group of each cohort.

In the LTE study, there were no SAEs due to vital sign abnormalities. Two patients in the tofacitinib 10 mg BID group had AEs due to vital sign abnormalities (hypertension, pyrexia) that led to temporary discontinuation or dose reduction. No patients had AEs due to vital sign abnormalities that led to permanent study drug or study discontinuation.

7.10 Electrocardiograms (ECGs)

As reported in the original tofacitinib NDA, a thorough QT study (Study A3921028) was performed and confirmed the lack of association between tofacitinib and clinically significant changes in ECG waveform or QT/QTc interval. In the UC studies, no meaningful difference was observed in the proportions of patients in various categories of potentially clinical concerning maximum QTc interval (both Bazett's and Fridericia's) or maximum change from baseline in QTc interval.

7.11 Immunogenicity

Not applicable.

7.12 Dose Dependency of Adverse Events

Despite the limitations noted previously (small number of patients exposed to 5 mg BID long-term, compared to 10 mg), based on available data in UC patients, the 10 mg BID dose showed a greater incidence in HZ, malignancies, NMSC, and serious infections when compared to the 5 mg BID dose. A greater magnitude of change in laboratory parameters related to hematology, liver function, and immune function was also observed in patients taking the tofacitinib 10 mg BID dose in comparison to the 5 mg BID dose.

In addition to the analysis of AEs by dose administered, the applicant also conducted exposure-response analysis for safety. The results of the exposure response analysis for safety are consistent with those described above, demonstrating an increased risk of certain AEs of interest with higher drug

exposures. The methods used and results of this exposure-response analysis of adverse events and laboratory parameters are summarized by the pharmacometrics reviewer in **Section A.**3.2. Dose/Exposure Response Analysis for Safety below.

The dose-related safety signals seen in the UC trials can be explained by the mechanism of action by tofacitinib. The findings are consistent with what was seen previously in the RA and psoriasis study populations.

7.13 Safety Analyses by Demographic Subgroups

7.13.1 Age

Per the Applicant, geriatric subgroup analyses were based on the following age categories: < 65 and ≥ 65 years. Patients who were ≥ 65 years of age were not further categorized into additional geriatric subgroups because a low proportion of patients in the UC program were ≥ 65 years old at the time of enrollment in the induction studies, and only a few patients were ≥ 75 years of age.
Among the 1156 patients in Cohort 3, which consists of all patients who received at least 1 dose of tofacitinib 5 mg BID or 10 mg BID in the UC development program, the age distribution at the time of first dose of tofacitinib was as follows: 18 to < 65 years: 1079 patients (93%); ≥ 65 to < 75 years: 69 patients (6.0%), and ≥ 75 years: 8 patients (0.7%).

Overall, the proportions of patients with AEs, SAEs or AEs leading to discontinuation were numerically higher in patients who are ≥ 65 years of age compared with younger patients, regardless of whether the patients received tofacitinib or placebo. Per the Applicant, increasing age was associated with an increased risk in developing OIs and HZ infection in the multivariate analysis.

7.13.2 Gender

In general, the proportion of patients with AEs was numerically higher in female patients than in male patients, regardless of whether the patient received tofacitinib or placebo. However, there did not appear to be an effect of gender on the proportion of patients with SAEs or AEs leading to discontinuation in tofacitinib-treated patients.

7.13.3 Race

As described in the demographics section above, the majority (81%) of patients in the induction trials were White. The other racial categories were Asian (12%), Black (0.8%), other (4%), and unspecified (3%).

Per **Table 77** below, it appears that White patients had a numerically and proportionally higher number of SAEs, severe AEs, and discontinuations due to AEs, in comparison to Asian patients. The proportions of Black and other races were too small to determine attributable safety risks adequately.

Table 77: Cohort 1 TEAEs based on Race Subgroup

	Placebo		Tofacitinib 10 mg BID	
Age (years)	White	Asian	White	Asian
Number (%) of subjects				
Subjects evaluable for AEs	229	28	756	114
Subjects with AEs	125 (54.6)	14 (50.0)	404 (53.4)	62 (54.4)
Subjects with SAEs	15 (6.6)	1 (3.6)	31 (4.1)	2 (1.8)
Subjects with severe AEs	14 (6.1)	0	33 (4.4)	2 (1.8)
Subjects discontinued due to AEs[a]	13 (5.7)	0	31 (4.1)	4 (3.5)
Subjects with dose reduced or temporary discontinuation due to AEs	5 (2.2)	0	12 (1.6)	1 (0.9)

Abbreviations: AE = adverse event; BID = twice daily; P2= Phase 2; P3 =Phase 3; SAE = serious adverse event.
a. Includes discontinuation due to worsening ulcerative colitis
Sources: 5.3.5.3 Table 222a.3.3

Source: Table from IR response from Sponsor dated 8/16/17

Per the Applicant's multivariate analysis, there appears to be an increased risk of developing HZ infections in Asian patients in the tofacitinib UC program. Data from the RA and PsO programs suggest that patients from Japan and Korea have an increased risk of developing HZ infection compared with patients enrolled from other geographic regions. This information is reflected in currently approved labeling.

7.13.4 Prior TNF Blocker Failure

In the maintenance study, there were trends toward increased rates of serious infections, HZ infections, opportunistic infections in patients who had previously failed TNF blocker therapy, compared to those without prior TNF blocker failure, regardless of the tofacitinib dose. Further, within the predominant 10 mg group, NMSC rates were higher in patients with history of prior TNF blocker failure, compared to those without. However, with the exception of HZ, the number of cases of each

of these AEs was very low, thus limiting the precision of these incident rates and the strength of any conclusion that can be drawn. See **Table 112** in the Appendix.

Similar trends are noted in the Cohort 3 data, summarized in **Table 78** below.

Table 78: Effect of the TNF-inhibitor Failure Subgroup on Incidence Rates of Adverse Events of Special Interest in the Tofacitinib All Group in Cohort 3

AEs of special interest	Cohort 3, Tofacitinib All			
	Non-TNFi failure N = 541 Exposure = 698.0 PY		TNFi failure N = 582 Exposure = 662.6 PY	
	n	IR (95% CI)	n	IR (95% CI)
Serious infection	14	1.95 (1.07, 3.28)	13	1.89 (1.01, 3.24)
Opportunistic infection	8	1.12 (0.48, 2.20)	9	1.33 (0.61, 2.52)
Non-herpes zoster OI	2	0.28 (0.03, 1.00)	2	0.29 (0.04, 1.05)
Herpes zoster (all)	23	3.28 (2.08, 4.92)	35	5.35 (3.72, 7.44)
Malignancy (excluding NMSC)	1	0.14 (0.00, 0.77)	6	0.87 (0.32, 1.89)
NMSC	0	0.00 (0.00, 0.51)	10	1.47 (0.70, 2.70)
MACE	3	0.42 (0.09, 1.22)	1	0.15 (0.00, 0.81)
GI perforation (revised definition)	1	0.14 (0.00, 0.77)	2	0.29 (0.04, 1.05)

Source: Table from Applicant's SCS, submitted 04 May 2017, pg 281/292

7.14 Additional Tofacitinib Safety Studies: Long-Term RA Safety Study for MACE risk and HZ Vaccine (Zostavax) Study

Additional evaluations regarding the safety of tofacitinib have been, or continue to be, conducted in the post-marketing setting (b) (4) (b) (4)

Trial A3921237 (Completed)

The Applicant conducted Study A3921237, a vaccine study to evaluate the humoral and cell-mediated responses to immunization with a Zostavax (live HZ vaccine), which is indicated for the prevention of HZ infection. This study was a randomized, double-blind, placebo-controlled study evaluating the immune response following administration of Zostavax to RA patients receiving tofacitinib or placebo

with background methotrexate treatment. A total of 112 eligible patients received immunization with zoster vaccination 2-3 weeks prior to initiating treatment with a 12-week course of tofacitinib 5 mg BID or placebo in a 1:1 ratio. Six weeks after immunization with the zoster vaccine, tofacitinib and placebo recipients exhibited similar humoral and cell mediated responses. These responses were similar to those observed in healthy volunteers aged 50 years and older. There were no deaths in the study. No SAEs were reported in the placebo group. Three SAEs were reported in the tofacitinib group including one case of disseminated zoster which resolved. See the details regarding this study in the DPARP review by Juwaria Waheed, MD, dated August 21, 2017.

(b) (4)

7.15 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies on the use of tofacitinib in pregnant women, however, embryofetal toxicity, including malformations, occurred in embryofetal development studies in rats and rabbits. In one of the animal reproduction studies, tofacitinib at AUC multiples of 13 times the recommended dose of 5 mg twice daily and 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings. However, there is uncertainty as to how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. It is recommended that pregnancy planning and prevention for females of reproductive potential are considered.

In the tofacitinib UC program, there were 24 cases of exposure during pregnancy with tofacitinib in the Phase 3 clinical trials as of February 2018. Of these 24 cases, 13 (54%) were cases of maternal exposure and 11 (46%) were cases of paternal exposure. The outcomes of the 13 maternal exposure cases were: 5 normal newborns (38%), 2 (15%) spontaneous abortion, 2 (15%) therapeutic abortions, 2 (15%) lost to follow-up, and 2 (15%) outcomes pending. In these maternal exposure cases, the doses of tofacitinib were: 10 mg BID in 11 cases and 5 mg BID in 2 cases. In regards to the 11 cases of paternal exposure to tofacitinib, the exposure events occurred in the first trimester. The doses of tofacitinib were: 10 mg BID in 9 cases, 5 mg BID in 1 case, and not reported in 1 case. The outcomes of the 11 cases were: 5 normal newborns (45%), and 6 outcomes pending (55%).

In the RA program, there were a total of 43 cases of tofacitinib exposure (36 maternal, 7 paternal) during pregnancy from clinical trials as of May 15, 2016. MTX was allowed as a concomitant medication with tofacitinib in some clinical trials; therefore, in 21 (49%) of the 43 cases (17 female, 4 male), the patient may have been taking MTX before or at the time of pregnancy. In all 36 (100%) maternal cases, exposure to tofacitinib occurred in the first trimester, and the dose of tofacitinib was: 5 mg BID in 16 (44%) cases, 10 mg BID in 19 (53%) cases, and 15 mg BID in 1 (3%) case. The outcomes of these 36 cases were: 17 normal newborns, 2 premature births (gestational ages at birth 35 and 37 weeks), 6 spontaneous abortions, 4 medical terminations, 1 congenital malformation of pulmonary valve stenosis, 2 pending, 1 unknown, and 3 lost to follow-up. The outcomes of the 7 paternal exposure cases were: 3 normal newborns, 1 premature birth (gestational age at birth 36 weeks), 2 spontaneous abortions, and 1 outcome pending.

Refer to Jane Liedtka, MD review from the Division of Pediatric and Maternal Health (DPMH) dated March 21, 2018 for further information regarding tofacitinib effects on human reproduction and pregnancy data. Per this review, human pregnancy outcome data for tofacitinib are limited in the

published literature, and the Applicant's pharmacovigilance database (PVDB) is insufficient to inform a benefit/ risk assessment. Since the adverse developmental outcomes that were seen in animals were at relatively high multiples of the MRHD [6.3 x (in rabbit) and 73x (in rat)], it is unclear whether tofacitinib will cause harm in the fetus.

In addition, tofacitinib has no effects on male fertility, sperm motility, or sperm concentration. No contraceptive measures are required in males treated with tofacitinib.

7.16 Pediatrics and Assessment of Effects on Growth

As part of a Proposed Pediatric Study Request (PPSR) for RA, Pfizer has proposed studies in patients with JIA. Tofacitinib PK characteristics in pediatric patients in Study A3921103, which is currently ongoing, will inform dose selection for the efficacy study in pediatric patients with UC. Available PK data from the efficacy study in patients with JIA may also be utilized to inform dose selection for the efficacy study in pediatric UC.

An agreed iPSP for UC studies was submitted with this application (agreement letter from the FDA dated March 18, 2014).

The Applicant proposes to defer the studies in children with moderate to severe UC until after confirmation of the benefit: risk in adults with UC, and completion of review of the pediatric juvenile idiopathic arthritis (JIA) PK study. This timeline will allow the Applicant to have more data to inform the appropriate use of tofacitinib in the UC pediatric population. The Applicant will be issued requirements to conduct post-marketing studies in pediatric UC under the Pediatric Research Equity Act (PREA). The planned pediatric UC program will include a single PK, safety, and efficacy study in patients 2 to <18 years of age with moderately to severely active UC, as well as an open-label long-term extension study. Refer to approval letter for details of PREA-required PMRs.

7.17 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Excluding cases of sporadic non-compliance, there were no reports of overdose (accidental overdose or intentional overdose) in the UC program. Tofacitinib has been administered in phase 1 studies in doses as high as 100 mg in a single dose to healthy patients (Studies A3921002 and A3921028) and 50 mg BID for 14 days to healthy patients with PsO (Study A3921003).

In patients with UC, the highest dose used was tofacitinib 15 mg BID for up to 9 weeks (71 patients total, including 49 patients in Study A3921063, 16 patients in Study 1094 and 6 patients in Study 1095). There were no reports of drug abuse or dependence or other information relevant to the potential for drug abuse in the UC studies. There were no reports of impairment of the senses, coordination or other factors that would result in diminished ability to drive a vehicle, operate machinery or would impair mental ability.

In regards to potential withdrawal and rebound effects of tofacitinib, the design of the UC program included conversion from active (tofacitinib) treatment to placebo in some patients during re-randomization at the time of entry into the maintenance study. There were no reports of pharmacological effects of withdrawal or rebound in the UC program.

7.18 Comparison of Safety of Tofacitinib Across Indications

Given the relatively small number of events in the UC safety database for select AEs of special interest and the relatively limited time of patient follow-up, the Applicant performed an evaluation of adverse events of special interest in the tofacitinib RA, PsA and PsO datasets. The incidence rates for selected safety events of interest in patients treated with tofacitinib 5 mg and tofacitinib 10 mg in UC, RA, and PsO are presented in the table below. Roughly similar rates are noted on tofacitinib across the indications for many events. However, there are wide CIs around many of these incidence rates given limited number of events. Of note, there are significant limitations to comparisons across patient populations given differences in the disease, demographics, concomitant medications, and comorbidities. In addition, there are limitations given the fewer patient-years of exposure in the tofacitinib UC program as compared to the tofacitinib RA and PsO programs.

Considering the totality of data across indications in the broad tofacitinib development program, including IRs of AESIs in placebo-controlled randomized phase 3 studies and long-term extension studies, the Applicant has ascertained that there is dose-dependency in the IRs of serious infection, HZ and NMSC, but no discernable evidence of dose-dependency in the long-latency AESIs of malignancy (excluding NMSC) or major adverse cardiovascular events (MACE).

Per the Applicant, the databases for death and relevant adjudicated AESIs and incidence rates (IRs) have been updated for all tofacitinib-treated patients in UC Cohort 3 Tofacitinib by PD group, and all studies in the RA and psoriasis (PsO) programs (all exposure) as follows:

(1) UC Cohort 3 Tofacitinib, cutoff date of September 29, 2017
(2) RA (all exposure), cutoff date of March 2, 2017
(3) PsO (all exposure), final database date of August 18, 2016.

See Table 79 below for further detail.

Table 79: Cumulative Incidence Rates (per 100 Patient-Years) for Death and Select Safety Events in Patients Treated with Tofacitinib (All Doses Combined) in the UC Cohort 3, Rheumatoid Arthritis (All Exposure), and Psoriasis (All Exposure) Programs

Safety Event	Ulcerative Colitis Tofacitinib UC Program (Cohort 3) * N= 1157 PY=1986		Rheumatoid Arthritis (All Exposure) N=7061 PY=22,875		Plaque Psoriasis (All Exposure) N=3663 PY=8955	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Death (all cause)	5 (0.4%)	0.24 (0.08, 0.57)	59 (0.8%)	0.25 (0.19,0.32)	17 (0.5%)	0.18 (0.11, 0.29)
Serious infection	38 (3.3%)	1.87 (1.32, 2.56)	576 (8.2%)	2.48 (2.28,2.69)	119 (3.2%)	1.29 (1.07, 1.54)
Opportunistic infection	22 (2.0%)	1.09 (0.69, 1.66)	90 (1.3%)	0.39 (0.31,0.47)	29 (0.8%)	0.31 (0.21, 0.45)
Non-herpes zoster opportunistic infection	4 (0.4%)	0.20 (0.05, 0.50)	34 (0.5%)	0.15 (0.10,0.20)	4 (0.1%)	0.04 (0.01, 0.11)
Herpes zoster infection	74 (6.4%)	3.80 (2.99, 4.77)	782 (11.1%)	3.63 (3.38,3.90)	209 (5.7%)	2.35 (2.04, 2.69)
Serious herpes zoster infection	5 (0.4%)	0.24 (0.08, 0.57)	57 (0.8%)	0.24 (0.18,0.32)	11 (0.3%)	0.12 (0.06, 0.21)
Malignancy (excluding NMSC)*	13 (1.2%)	0.84 (0.45, 1.44)	177 (2.5%)	0.76 (0.65,0.88)	60 (1.6%)	0.65 (0.49, 0.83)
Colorectal cancer	2 (0.2%)	0.10 (0.01, 0.35)	11 (0.2%)	0.05 (0.02,0.08)	3 (0.1%)	0.03 (0.01, 0.09)
Lymphoma	1 (0.1%)	0.05 (0.00, 0.27)	12 (0.2%)**	0.05 (0.03,0.09)	2 (0.1%)	0.02 (0.00, 0.08)
NMSC	15 (1.3%)	0.74 (0.42, 1.23)	129 (1.8%)	0.56 (0.46,0.66)	63 (1.7%)	0.69 (0.53, 0.88)
MACE	5 (0.4%)	0.25 (0.08, 0.57)	85 (1.3%)	0.38 (0.30,0.47)	23 (0.6%)	0.25 (0.16, 0.37)
GI perforation (all cases)	4 (0.4%)	0.20 (0.05, 0.50)	28 (0.4%)	0.12 (0.08,0.17)	7 (0.2%)	0.08 (0.03, 0.16)

Source: Reviewer's table, adapted from the Applicant's submission dated 26 October 2017, Database lock 29 September 2017. UC Cohort 3 data cutoff date 29 September, 2017; RA data cutoff date 02 March 2017; PsO final database date 18 August 2016. *For Malignancies (excluding NMSC), the incidence rate is based on the PD Tofacitinib 10 mg BID analysis group (PY 1521.28), since these events in the 13

patients did not occur in the PD Tofacitinib 5 mg BID group. The combined IR for the PD tofacitinib 5 and 10 mg BID dosages was 0.64 (0.34, 10.9). Except for death and malignancies and NMSC in the UC Cohort 3, events occurring within 28 days (based on adjudication) following the last dose were included. **Note, per the Applicant: The number of patients with lymphoma decreased from 13 to 12 in the updated RA database. After the 10 May 2016 data cutoff, the start date of 1 lymphoma event was revised such that the start date was outside the 28-day risk period following the last dose. This event was not counted for IR calculation in the updated database, resulting in a decrease of the number of patients with lymphoma by one (1).

Data broken down by predominant dose (PD) were available for UC and RA for the updated databases. For PsO, data broken down by PD were not available for the final database but were available for the data cutoff of May 10, 2016, used in the initial UC submission. In the final PsO database, tofacitinib exposure increased by only 4.9% from the data cutoff of May 10, 2016, used in the initial UC submission (from 8537 patient-years [PY] to 8955 PY). The small percent increase in PY is not expected to affect assessment of dose-relationship in this mature database. See **Table** 80, **Table 81**, and **Table 82** below for incidence rates of select safety events by dose group in UC, RA, and PsO respectively.

Table 80: Incidence Rates (per 100 Patient-Years) for Select Safety Events by Predominant Dose (PD) Group in Overall Tofacitinib UC Program (Cohort 3)

	Tofacitinib PD 5 mg BID[b] N = 200 Exposure = 489.5 PY		Tofacitinib PD 10 mg BID[b] N = 957 Exposure = 1496.3 PY	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Death (all cause)	0 (0.0)	0.00 (0.00, 0.74)	5 (0.5)	0.32 (0.10, 0.75)
Serious infection	7 (3.5)	1.41 (0.57, 2.90)	31 (3.2)	2.01 (1.37, 2.86)
Opportunistic infection[a]	6 (3.0)	1.24 (0.45, 2.69)	16 (1.7)	1.05 (0.60, 1.70)
Non-herpes zoster opportunistic infection[a]	1 (0.5)	0.20 (0.01, 1.12)	3 (0.3)	0.19 (0.04, 0.57)
Herpes zoster	18 (9.0)	3.87 (2.29, 6.12)	56 (5.9)	3.78 (2.86, 4.91)
Malignancy (excluding non-melanoma skin cancer)[a,c]	1 (0.5)	0.20 (0.01, 1.12)	14 (1.5)	0.91 (0.50, 1.53)
Colorectal cancer[a]	0 (0.0)	0.00 (0.00, 0.74)	2 (0.2)	0.13 (0.02, 0.47)
Lymphoma[a]	0 (0.0)	0.00 (0.00, 0.74)	1 (0.1)	0.06 (0.00, 0.36)
Non-melanoma skin cancer (NMSC)[a,d]	4 (2.0)	0.81 (0.22, 2.07)	13 (1.4)	0.85 (0.45, 1.46)
Major Adverse Cardiovascular Event (MACE)[a,e]	2 (1.0)	0.40 (0.05, 1.46)	3 (0.3)	0.19 (0.04, 0.57)
GI perforation (all cases)[a]	1 (0.5)	0.20 (0.01, 1.12)	3 (0.3)	0.19 (0.04, 0.57)

Source: Information per Applicant as of 29 September 2017; Applicant's Inquiry Response Submission 28 February 2018 and UC Table 229a.1; Table 229a.2.1; Table 229a.3; Table 229a.4; Table 229a.4.2; Table 229a.4.3; Table, 229a.5.1; Table 229a.6.1.

a. Adjudicated events. Percentage (%) was calculated based on the number of patients in studies in which adjudication was performed.

b. PD group categorization was based on the average total daily dose received by the patients during tofacitinib treatment. c. Patients [redacted] (b) (6) (Breast cancer) and [redacted] (b) (6) (Cervical dysplasia) were pending adjudication review as of 29 September 2017 and have been counted in the numerator of incidence rates for malignancy (excluding NMSC). d. Patients [redacted] (b) (6) (Basal cell carcinoma), and [redacted] (b) (6) (Bowen's disease) were pending adjudication review as of 29 September 2017 have been counted in the numerator of incidence rates of NMSC. e. Patients [redacted] (b) (6) (Cerebrovascular accident) was pending adjudication review as of 29 September 2017 and has been counted in the numerator of incidence rates for MACE.

Table 81: Incidence Rates (per 100 Patient-Years) for Select Safety Events by Predominant Dose (PD) Group in the Rheumatoid Arthritis (RA) Program

	Tofacitinib PD 5 mg BID[b] N = 3066 Exposure = 8171.30 PY		Tofacitinib PD 10 mg BID[b] N = 3995 Exposure = 14703.22 PY	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Death (all cause)	29 (0.9)	0.34 (0.23, 0.49)	30 (0.8)	0.20 (0.13, 0.28)
Serious infection	233 (7.6)	2.81 (2.46, 3.19)	343 (8.6)	2.30 (2.07, 2.56)
Opportunistic infection[a]	28 (0.9)	0.33 (0.22, 0.48)	62 (1.6)	0.41 (0.32, 0.53)
Non-herpes zoster opportunistic infection[a]	20 (0.7)	0.24 (0.15, 0.37)	14 (0.4)	0.09 (0.05, 0.16)
Herpes zoster	269 (8.8)	3.48 (3.07, 3.92)	513 (12.8)	3.72 (3.41, 4.06)
Malignancy (excluding NMSC)[a]	64 (2.1)	0.76 (0.59, 0.97)	113 (2.8)	0.75 (0.62, 0.91)
Colorectal cancer[a]	6 (0.2)	0.07 (0.03, 0.16)	5 (0.1)	0.03 (0.01, 0.08)
Lymphoma[a]	1 (0.0)	0.01 (0.00, 0.07)	11 (0.3)	0.07 (0.04, 0.13)
NMSC[a]	36 (1.2)	0.43 (0.30, 0.60)	93 (2.3)	0.63 (0.51, 0.77)
MACE[a]	31 (1.1)	0.41 (0.28, 0.58)	54 (1.4)	0.37 (0.27, 0.48)
GI perforation (all cases)[a]	6 (0.2)	0.07 (0.03, 0.16)	22 (0.6)	0.15 (0.09, 0.22)

Source: Information per Applicant as of 05 March 2017; Applicant's Inquiry Response Submission 28 February 2018 and RA Table 1295.1; Table 1295.1.3.1; Table 1295.1.3.2; Table 1295.1.3.3; Table 1295.1.3.4; Table 1295.1.3.5; Table 1295.1.3.6; Table 1295.1.3.7; Table 1295.1.3.8; Table 1295.1.3.9; Table 1295.3.1.3; Table 1295.4.9.1; Table 1295.5.2.3.1; Table 1403.1.1; Table 1403.2.1; Table 1403.3.1.

a. Adjudicated events. Percentage (%) was calculated based on the number of patients in studies in which adjudication was performed.

b. PD group categorization was based on the average total daily dose received by the patient during tofacitinib treatment. For RA, PD was identified as Average dose in the source tables.

Table 82: Incidence Rates (per 100 Patient-Years) for Select Safety Events by Predominant Dose (PD) Group in the Plaque Psoriasis (PsO) Program

	Tofacitinib PD 5 mg BID[b] N = 923 Exposure = 1413.61 PY		Tofacitinib PD 10 mg BID[b] N = 2739 Exposure = 7123.53 PY	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Death (all cause)	8 (0.9)	0.54 (0.23,1.07)	9 (0.3)	0.12 (0.06,0.23)
Serious infection	23 (2.5)	1.56 (0.99, 2.34)	88 (3.2)	1.21 (0.97, 1.49)
Opportunistic infection[a]	5 (0.5)	0.34 (0.11, 0.79)	21 (0.8)	0.29 (0.18, 0.44)
Non-herpes zoster opportunistic infection[a]	3 (0.3)	0.20 (0.04, 0.59)	1 (0.0)	0.01 (0.00, 0.08)
Herpes zoster	20 (2.2)	1.38 (0.84, 2.13)	181 (6.6)	2.59 (2.23, 3.00)
Malignancy (excluding NMSC)[a]	17 (1.8)	1.15 (0.67, 1.85)	39 (1.4)	0.54 (0.38, 0.73)
Colorectal cancer[a]	1 (0.1)	0.07 (0.00, 0.38)	2 (0.1)	0.03 (0.00, 0.10)
Lymphoma[a]	0 (0.0)	0.00 (0.00, 0.25)	1 (0.0)	0.01 (0.00, 0.08)
NMSC[a]	8 (0.9)	0.55 (0.24, 1.08)	43 (1.6)	0.60 (0.43, 0.80)
MACE[a]	8 (0.9)	0.54 (0.23, 1.07)	13 (0.5)	0.18 (0.10, 0.31)
GI perforation (all cases)[a]	3 (0.3)	0.20 (0.04, 0.59)	3 (0.1)	0.04 (0.01, 0.12)

Source: Information per Applicant as of 10 May 2016; Applicant's Inquiry Response Submission received 28 February 2018 and PsO Table 198.1.2; Table 198.2.2.1; Table 198.2.2.2; Table 198.2.2.3; Table 198.2.2.6; Table 198.2.2.7; Table 198.5.2.

a. Adjudicated events. Percentage (%) was calculated based on the number of patients in studies in which adjudication was performed.

b. PD group categorization was based on the average total daily dose received by the patients during tofacitinib treatment

c. Patients (b) (6) (Breast cancer) and (b) (6) (Cervical dysplasia) were pending adjudication review as of 29 September 2017 and have been counted in the numerator of incidence rates for malignancy (excluding NMSC). d. Patients (b) (6) (Basal cell carcinoma), and (b) (6) (Bowen's disease) were pending adjudication review as of 29 September 2017 have been counted in the numerator of incidence rates of NMSC. e. Patients (b) (6) (Cerebrovascular accident) was pending adjudication review as of 29 September 2017 and has been counted in the numerator of incidence rates for MACE.

Limitations to the evaluation of potential dose-dependent risks are acknowledged as previously described in this review. In addition, multiple factors, such as age, race, comorbidities, prior treatments and concomitant treatment with corticosteroids or other immunomodulatory agents, could influence the assessment of dose-dependency of individual AESIs. For example, in the RA program (all exposure), despite similar IRs of serious infection between PD 5 mg BID and PD 10 mg BID (2.81 vs 2.30 / 100 PY), Cox multivariate regression indicated dose-dependency in the risk of serious infection with tofacitinib treatment.[33] As a result, the above potential dose-dependent risks of certain AEs are noted, but the data should be interpreted with caution.

7.19 Comparison of Tofacitinib Safety to Ulcerative Colitis (UC) trials of Approved Biologic Therapies

As previously described, the Applicant provided estimates of the risk of various adverse events of special interest within the UC population from the Truven Marketscan claims database, based on a constructed "trial-criteria cohort" intended to match the characteristics of patients enrolled in the tofacitinib clinical trials for UC (details of methodology described under **Section 7.7.4**. The following table presents the incidence rates for select AESIs noted in the tofacitinib program (Cohort 3) and the Truven estimates. See **Table 83** for further details.

[33] Cohen S, Radominski SC, Gomez-Reino JJ, et al. Analysis of infections and all-cause mortality in Phase II, Phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. Arthritis Rheum 2014;66:2914-37.

Table 83: Incidence Rates (IRs) per 100 PYs of AEs of Special Interest in Tofacitinib UC Program in Comparison to Truven Comparison Cohort Data

Safety Event	Tofacitinib UC Program (Cohort 3) N= 1157 PY=1986 IR (95% CI)	Observational Data Truven Comparison Cohort N=6,366 IR (95% CI)
Serious infection	1.87 (1.32, 2.56)	3.33 (2.73, 4.02)
Herpes zoster	3.80 (2.99, 4.77)	1.77 (1.34, 2.29)
Malignancy (excluding NMSC)*	0.84 (0.45, 1.44)	0.63 (0.43, 0.90)
NMSC	0.74 (0.42, 1.23)	1.69 (1.35, 2.10)
MACE	0.20 (0.05, 0.50)	0.51 (0.31, 0.79)
GI perforation (all cases)	0.20 (0.05, 0.50)	0.23 (0.11, 0.44)

Sources: Reviewer's table, adapted from Applicant's Submission, Clinical Overview Table 15 (pg.70/118), for Cohort 3 data; Pfizer, 2016 data on file for Truven cohort data. UC Cohort 3 data cutoff date 29 September, 2017. *For Malignancies (excluding NMSC), the incidence rate is based on the PD Tofacitinib 10 mg BID analysis group (PY 1521.28), since these events in the 13 patients did not occur in the PD Tofacitinib 5 mg BID group. The combined IR for the PD tofacitinib 5 and 10 mg BID dosages was 0.64 (0.34, 10.9). Except for malignancies and NMSC in the UC Cohort 3, events occurring within 28 days (based on adjudication date) following the last dose were included.

These comparison data provide context to the IR estimates that were discussed in more detail in the section above. Given the differences in methodology, and potential differences in patient population, follow-up, etc. between claims based data and clinical trial data, a direct comparison may not be valid. Noting these limitations and uncertainties, these data may suggest treatment with tofacitinib confers an increased risk of HZ infection. These data also suggest that treatment with PD tofacitinib 10 mg IBD confers an increased risk of malignancies (excluding NMSC) in comparison to the Truven external cohort; however, wide and overlapping CIs were observed.

7.20 Safety in the Postmarket Setting

7.20.1 Safety Concerns Identified Through Postmarket Experience

On November 6, 2012, tofacitinib received its first regulatory approval in the United States at a dose of 5 mg BID for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to MTX. The post-marketing data for RA includes serious and non-serious AEs from voluntarily reported sources, as well as SAEs from noninterventional studies and other non-interventional solicited sources.

As of May 5, 2016, cumulatively, there have been approximately 45,410 PY of exposure to tofacitinib from marketing experience. A total of 13,574 case reports were received by Pfizer during the 3.5-year reporting period from November 6, 2012 through May 5, 2016. The most common SAEs reported in the 13,574 cases (≥ 1%) were rheumatoid arthritis, (5%), condition aggravated (4%), and pneumonia (2%). Among common AEs reported in the 13574 cases (≥2%), drug ineffective (14%) and HZ (3%) were present.

Lymphopenia

Of note, the Applicant completed a Cox regression analysis (based on the March 31, 2015, data cut) to evaluate the risk of infections in association with degrees of lymphopenia in RA patients treated with tofacitinib. In addition to confirming the risk of serious infection associated with confirmed lymphocyte count less than 500 cells/mm3 (HR = 2.65, 95, CI = 1.18 to 5.98), the updated analysis further indicates that confirmed lymphocyte count less than 1000 cells/mm3 is associated with a modest increased risk of serious infections (HR = 1.28, 95% CI = 1.03 to 1.61).

Herpes Zoster Infections

An increase in the rate of HZ is an identified risk associated with tofacitinib. When the rates of HZ are examined by geographic region, the rate of HZ in Asia (5.9/100 patient-year [PY]) is significantly higher than that observed in non-Asian regions (3.3/100 PY). Similarly, the rate of 5.9/100 PY observed in the Asian region is higher compared to the rate in each individual non-Asian geographic region (incidence rate point estimates ranged from 2.5 - 4.3/100 PY).

To determine whether this increased rate is due to a broad regional effect or due to higher rates in individual countries within the Asia region (i.e., a country level effect), the rate of HZ was assessed

for individual Asian countries. The HZ rates in Japan and Korea (8.1 - 8.2/ 100 PY) were shown to be higher than in non-Asian regions and higher than the rate noted in other Asian countries (range 2.7-5.3/100 PY). It is unclear if the observed difference was due to race, genetic predisposition, or medical practices in the diagnosis of HZ among different countries and/or regions.

Pancreatic Cancer

A cluster of cases of pancreatic cancer have been identified in patients administered tofacitinib in the tofacitinib PsO clinical program and the JPMS (Japanese Post Marketing Study) study. As of May 2016, a total of 12 cases were reported, of which 10 cases reported (suspected or confirmed) pancreatic cancer described in tofacitinib studies (5 cases reported in the tofacitinib PsO (psoriasis) program, 4 cases in RA patients, and 1 psoriatic arthritis (PsA) patient). The remaining 2 cases were spontaneous reports of pancreatic lesions potentially representing pancreatic cancer in patients with RA from post marketing surveillance reports received by the Applicant. While the reported proportion for pancreatic cancer is low, it is considered an important medical event and "pancreatic cancer" was added to the list of malignancies observe in the tofacitinib development and post-marketing program under the Warning and Precautions **Section 5.2** of the tofacitinib labeling.

In summary, while there are limitations of post-marketing surveillance reports which include the nature of spontaneously reporting and containing limited information, the types and frequencies of AE reports from post-marketing data are consistent with the known safety profile of tofacitinib characterized in the RA clinical development program.

7.20.2 Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the tofacitinib safety data identified signals that are currently included in the labeling of tofacitinib. However, additional data are needed to characterize the safety profile of the proposed product in special populations (pregnant and lactating females and the pediatric population age ≥ 2 years of age) and to assess the risk of adverse events associated with long latency periods such as malignancy. Refer to **Section 12** of this review for the post-marketing requirements and commitments.

8. Integrated Assessment of Efficacy and Safety

The efficacy of tofacitinib for the treatment of moderately to severely active UC was demonstrated in induction Studies 1094 and 1095, and maintenance Study 1096. Those three phase 3 trials had positive results with very small p-values for the primary endpoints and all key secondary endpoints. However, only tofacitinib 10 mg BID was studied in the two induction studies; consequently, whether a lower tofacitinib dose is effective as an induction treatment is unknown.

In induction studies 1094 and 1095, the primary endpoint was remission at Week 8. Remission was defined as a Mayo score of 2 or less, with no individual sub-score of greater than 1 and a rectal bleeding subscore of 0. Tofacitinib 10 mg BID for 8 weeks was superior to placebo in inducing remission (treatment difference of 10% and 13% in Studies 1094 and 1095, respectively). The key secondary endpoint for induction was "mucosal healing," which was defined as Mayo endoscopic sub-score of 0 or 1, excluding any friability, and is more appropriately described as "improvement in the endoscopic appearance of the mucosa." The treatment difference from placebo for "mucosal healing" was 16% and 17% in Study 1094 and 1095, respectively.

In the maintenance study 1096, the primary endpoint was remission at Week 52. Both tofacitinib 10 mg BID and 5 mg BID were demonstrated to be superior to placebo in achieving remission (treatment difference of 30% and 23%, respectively). The key secondary endpoints were sustained corticosteroid-free remission (defined as being in remission at week 24 and week 52 of treatment among patients in remission at week 8) and "mucosal healing". Both tofacitinib 10 mg and 5 mg BID proved to be effective in achieving sustained corticosteroid-free remission, with a treatment difference from placebo of 42% and 30% for 10 mg BID and 5 mg BID, respectively. Tofacitinib 10 mg BID or 5 mg BID treatment in Study 1096 both resulted in "mucosal healing" (treatment difference from placebo of 33% and 24%, respectively). Exploratory analyses comparing the efficacy of 10 mg BID to 5 mg BID after induction suggest that the effect of tofacitinib 10 mg BID may not be significantly different from tofacitinib 5 mg BID over 52 weeks; this was based on evaluations of the primary and all key secondary endpoints. Taken together, the results of these three controlled clinical trials provide convincing evidence of the effectiveness of tofacitinib in the treatment of UC.

Patients who did not achieve at least clinical response by Week 8 had the option to enroll in the open label extension study (1139) and receive an additional 8 weeks of open label 10 mg BID tofacitinib treatment. The Applicant provided descriptive information on the long-term outcomes for these patients (referred to as induction non-responders "IndNR"). There are limitations to the conclusions

that can be drawn from the long-term experience of this cohort (lacking any concurrent control, and who were not randomized). However, in the context of a patient population who may already have failed the other available therapies, the review team concluded that it may be reasonable to permit those with inadequate response by Week 8 an additional 8 weeks of induction therapy. If there is still no response by Week 16, therapy should be discontinued.

The exploratory subgroup analyses by prior TNF blocker failure status (Studies 1094, 1095, 1096) consistently suggested that patients without history of TNF blocker failure do better (higher rates of response and remission compared to patients with prior TNF blocker failure).

In summary, the primary and key secondary endpoints in this submission's three phase 3 studies were statistically significant. The totality of evidence support that tofacitinib is effective in the treatment of moderately to severely active UC. For most patients, the recommended dosage of 10 mg BID for 8 weeks, followed by 5 mg BID is appropriate. Alternate dosing regimens including the option to continue 10 mg BID long term may be considered in certain circumstances, where the disease severity and overall benefit-risk assessment for the individual patient may support a trial of longer term use of 10 mg BID.

Overall, the safety profile of tofacitinib in moderate to severe UC appears to be consistent with the labeled safety profile of tofacitinib for the treatment of moderate to severe RA. Identified risks include, but are not limited to, serious and opportunistic infections, including HZ infection, malignancies, NMSC, thromboembolic events, and various laboratory abnormalities (including alterations in hematologic and lipid profiles).

The short-term treatment with tofacitinib induction therapy of tofacitinib 10 mg BID for 8 weeks showed low risk of SAEs in comparison to placebo therapy. In general, patients who received a total of 16 weeks extended induction therapy (as non-responders to tofacitinib 10 mg BID in the 8-week induction phase 3 trials and then received additional 8 weeks of tofacitinib 10 mg BID treatment in the long-term extension study), had a similar safety profile to those who received the 8-week, tofacitinib 10 mg BID induction treatment. The common AEs were generally mild and potentially mitigatable, including laboratory changes of decreased absolute lymphocyte count and elevated levels of cholesterol, liver biochemistry tests, and creatinine phosphokinase levels.

In contrast, concern exists regarding the long-term use of tofacitinib 10 mg BID dosage for maintenance therapy in comparison to the lower, tofacitinib 5 mg BID dosage. Dose-dependent risks were identified for NMSC, HZ infections, serious infections, and elevated cholesterol levels.

Specifically, given the size, design, and duration of the UC program, uncertainty remains regarding whether dose-dependent relationships for deaths, malignancies, and other laboratory abnormalities with long-term use of tofacitinib exists.

There are limitations of the safety evaluation provided from the UC development program. Because most patients who were followed long-term were predominantly exposed to the tofacitinib 10 mg BID vs the tofacitinib 5 mg BID dosages, the ability to directly compare the safety of these two doses for long-term use is challenging. The level of response to treatment (i.e., response in induction studies or remission in the maintenance study) dictated the subsequent dosage received in the long-term extension (LTE) study, which adds complexity to the evaluation of the tofacitinib safety by dosage. Furthermore, many patients discontinued from the tofacitinib UC program in the maintenance and LTE studies. Although the proportion of discontinuations may be consistent with that seen in UC trials of other approved drugs, this ultimately led to relatively less exposure of patients to tofacitinib over time.

In consideration of the GIDAC's recommendations (see **Section 8**), and given the demonstrated efficacy of both tofacitinib 5 mg and 10 mg BID dosages for the long-term treatment of UC, the Division agrees with Applicant's proposal to provide options for the long-term use of tofacitinib 10 mg BID or 5 mg BID for all patients, based on the clinician's assessment of disease severity (regardless of TNF blocker failure status). While some of the serious risks of shorter latency associated with tofacitinib therapy (i.e., infection and laboratory parameter changes) may be managed or potentially mitigated, other longer-term latency risks (i.e., malignancy and death) may not be. For this reason, the dosage and administration recommendation includes the recommendation to use the lowest effective dose.

In conclusion, the application contains adequate evidence of efficacy, and the safety data support that the benefit-risk assessment of tofacitinib favors approval.

9. Advisory Committee (AC) Meeting

A GIDAC meeting was convened on March, 8, 2018, to discuss this sNDA. The following section summarizes the Committee's discussion on the topics and voting questions. Please refer to official transcript for full details.

1. **DISCUSSION:** The Applicant has proposed an induction dosing regimen of 10 mg BID for a total for 16 weeks in patients who have not achieved "adequate therapeutic benefit" by week 8 based on exploratory analyses of trial data in patients who continued induction treatment when they had not achieved clinical response defined as a decrease from baseline in Mayo score of ≥3 points and ≥ 30%, with an accompanying decrease in the subscore of rectal bleeding of ≥ 1 point or absolute subscore for rectal bleeding of 0 or 1.

    a. Please discuss the adequacy of the efficacy data to support the use of the 10 mg BID dosing for extended induction therapy for a total of 16 weeks in patients who have not achieved "adequate therapeutic benefit" by week 8.
    b. Please discuss the adequacy of the safety data to support the use of the 10 mg BID dosing for induction for a total of 16 weeks in patients who have not achieved "adequate therapeutic benefit" by week 8.

Committee Discussion: The Committee discussed that although the data from the extended induction group (those without initial response at week 8 but who continued on 10 mg BID for an additional 8 weeks) were not placebo controlled, 50% of patients were observed to have responded to tofacitinib therapy after an additional 8 weeks of treatment (16 weeks total), which favors an efficacy benefit of the product. Issues discussed include lack of a diverse patient population enrolled in clinical trials compared to those diagnosed with UC in the natural setting; especially since the African-American population may experience a more severe course of UC compared to other ethnic groups. Overall, the Committee generally agreed that the benefits outweigh risks and in general supported 10 mg BID being efficacious in treating UC in this patient population.

Regarding safety, there was a consensus that the benefits of tofacitinib treatment outweigh the potential safety issues identified from clinical trial data in the short term (8 to 16 weeks). Patients with UC have limited treatment options, and extension of treatment with this product might serve as a better alternative than performing a complete colectomy. The Committee was generally in agreement that the extended induction regimen was reasonable to consider.

2. **VOTE:** Do you recommend the inclusion of this dosing regimen for this population in the product label? If you recommend inclusion of this dosing regimen in the product label, please discuss how inadequate therapeutic benefit that merits extension of induction treatment should be distinguished from inadequate therapeutic benefit that should prompt discontinuation of tofacitinib therapy?

Vote: Yes= 15 No = 0 Abstain = 0

c. If you recommended inclusion of this dosing regimen in the product label, please discuss how inadequate therapeutic benefit that merits extension of induction treatment should be distinguished from inadequate therapeutic benefit that should prompt discontinuation of tofacitinib therapy.

Committee Discussion: The Committee unanimously recommended inclusion of the 10 mg BID dosing regimen for the proposed patient population in the product label. The panel stressed the importance of a patient and provider discussion regarding the benefits vs risks of the product. The panel further commented that patients with UC are a patient population desperate for new treatment options, and it would be better to provide an option for extended induction treatment with this drug to ensure that they truly could not benefit from its use, before permanently discontinuing and seeking out other therapies. Some members noted that they did not have confidence that 10 mg BID for the second 8 weeks was any better than 5 mg BID for the second 8 weeks, as this was not studied. The Committee noted that the Applicant does not have information that compares the group of patients who received 16 weeks of 10 mg BID due to inadequate initial response at Week 8, with the group of patients who received 10 mg BID for 8 weeks, failed to respond, and then continued on 5 mg BID for an additional 8 weeks. Thus, it is unclear if the improvement in the patients who initially failed to respond at Week 8 but received extended induction therapy is due to the continued use of high dose for those subsequent 8 weeks, or if those patients might have improved with time anyway if they had switched to 5 mg BID after the first 8 weeks (if the issue is simply that it may take longer than 8 weeks to see a full effect from therapy). Moving forward, these data would be helpful. Multiple members acknowledged that determining a level of adequate therapeutic benefit that would merit continuing tofacitinib treatment for the additional 8 weeks would be challenging, and would be a provider level decision that would be informed over time by increasing experience gained by IBD specialists using the drug.

3. **DISCUSSION**: For adult patients with moderately to severely active UC with an inadequate response, loss of response, or intolerance to TNF blocker therapy:

d. Please discuss the adequacy of the efficacy data to support the use of the 10 mg BID dosing as continuous maintenance treatment.

e. Please discuss the adequacy of the safety data to support the use of the 10 mg BID dosing as continuous maintenance treatment.

Committee Discussion: The Committee discussed that the effect size difference was impressive, despite limitations in the statistical analyses, and that it makes sense mechanistically that those who have failed TNF-inhibitor therapy may require a higher dose of tofacitinib. Some members raised concerns that prior TNF failure may not be the best surrogate for "severe disease;" patients may have severe or refractory disease but may not have access to a TNF blocker or may choose not to use one for various reasons. There was also discussion regarding the difference between intolerance and lack of efficacy to prior therapy. There was discussion surrounding issues of third party payors, and not wanting the indication language to result in providers being unable to get tofacitinib 10 mg BID for their patients, if they feel the situation warrants it, due to not having failed a prior TNF blocker, or other restrictions.
Overall, there was general support of the 10 mg BID dose. Please see the transcript details of the committee discussion.

4. **VOTE**: Do you recommend inclusion of this dosing regimen for this population in the product label?

Vote: Yes= 15 No = 0 Abstain = 0

Committee Discussion: The Committee unanimously recommended including this dosing regimen and stated that the benefits of having tofacitinib 10 mg BID as an option outweigh the safety risks observed in clinical trials. While safety concerns may exist with the higher dose in this population, in general the Committee voiced that clinical judgement is needed to determine which patients truly require long-term therapy with 10 mg BID. There were questions regarding how a clinician might determine which refractory patients need long-term 10 mg BID, and which may be successful if treated with 5 mg BID. To this end, it was discussed that it would be helpful if the Applicant could provide information in the near future (not yet presented by the Applicant) regarding when the 5 mg BID dosing regimen is appropriate for long- term use.

5. **VOTE**: Do you recommend that the Applicant conduct a post-marketing efficacy trial in this population comparing a 10 mg BID continuous dosing regimen vs a regimen of 10 mg induction and 5 mg BID as maintenance?

Vote: Yes= 7 No = 8 Abstain = 0

Committee Discussion: Some members indicated that this type of controlled clinical trial data would be highly informative for future use of the drug (given that the Applicant currently does not have sufficient data to predict who will require long-term 10 mg BID vs who may do equally well with 5 mg BID). Other members indicated that the totality of the program contains sufficient data to support approval, and that the use of 10 mg BID vs 5 mg BID will be a clinical decision at the provider level, and that future research should focus on other, more pressing scientific questions.

6. **DISCUSSION:** Please discuss if additional post-marketing evaluation of safety is warranted, and the mechanism(s) you recommend (e.g., registry, observational study, etc.) for such evaluation.

Committee Discussion: The Committee discussed the strong need for post-marketing evaluation to identify any safety signals that may show up. Pros and cons were identified for both a registry system and study. There was no consensus as to the optimal approach to collecting additional post-marketing safety data.

7. **DISCUSSION:** Please discuss the following:
    a. Any unique characteristics of the pediatric UC population that should be taken into account when planning the tofacitinib pediatric development program. Please consider the ontogeny of the immune system and the described mechanism of action of tofacitinib.

    b. Given the safety concerns (malignancy and serious infections) described with long-term use of 10 mg BID and the severity of UC in the pediatric population, please recommend the maximum dose that should be targeted for evaluation for long-term treatment in pediatric UC.

    c. Please discuss whether you recommend limiting enrollment in the pediatric trials (and subsequent pediatric indications) to patients who have failed other biologic therapies.

Committee Discussion: The Committee discussed that a formal definition of pediatric population should be identified (e.g., 2 years vs 4 years of age). It was mentioned that in younger patients (especially those less than 5-6 years) the immune system is still developing; it is unclear to what degree this may affect the safety of potential tofacitinib use in this age group. One panel member expressed that the mechanism of action of tofacitinib is more broad and affects more effector pathways than, for example, a TNF blocker – so this may be a reason to limit the enrollment of the youngest aged patients. Members suggested that data be collected on EBV status at screening, and to exclude monogenetic disorders in the youngest pediatric patients. Some members commented that this treatment may represent an option of interest to patients and parents as initial (first line) therapy and the design of the pediatric program should account for this possibility, rather than only including those with treatment failure. Others discussed that until the GI community has more experience using tofacitinib, limiting its pediatric use to those who have failed approved therapies may be appropriate.

The Committee did not express concern regarding targeting exposures to match 10 mg BID dosing in adults.

10. Pediatric Development Program

A need exists for additional therapies to treat pediatric patients with UC.

The Agreed iPSP letter dated (March 18, 2014, under Investigational New Drug 11294) includes a plan to conduct pharmacokinetics (PK), safety and efficacy studies in pediatric patients 4 years to <18 years of age with moderate to severe UC. The Applicant has requested a deferral of studies for pediatric patients 4 years and older as the drug is ready for approval in adults, and has requested a waiver of the requirement for study of patients <4 years of age. The stated reasons for the requested waiver are that the studies would be impossible or highly impracticable, due to the low incidence of UC in the youngest patients, difficulties in confirming the diagnosis in the youngest patients (between IBD subtypes) and potential additional risks of JAK inhibition in the youngest aged patients due to immaturity of the immune system.

The Division currently requires study of pediatric UC patients down to 2 years of age, unless there is a strong safety reason not to study patients in the youngest age group. While the risks of JAK inhibition in a less developed / immature immune system may possibly be increased, this increased risk is theoretical in nature, and the Division does not find this reason compelling not to study younger pediatric patients. An orally available, effective therapy for UC would be a desirable therapeutic option for more severely affected young UC patients, and including these patients in the pediatric studies will permit a better understanding of the safety, efficacy and potential for differences in safety profile in younger pediatric patients. As a result, the Division will grant the waiver for patients < 2 years, but include patients 2 to <18 years of age in the pediatric assessment plan. It should also be noted that a study is ongoing at this time to assess the safety and efficacy of tofacitinib in patients with juvenile idiopathic arthritis (JIA) 2 years and older.

The following pediatric post-marketing requirements will be issued under the PREA:

3400-1: A one-year, multi-center, randomized, controlled trial to evaluate the safety, efficacy and pharmacokinetics of XELJANZ (tofacitinib) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

The study will include an open-label induction period, followed by a randomized, controlled maintenance period. This study will include staggered enrollment by age (starting with oldest patients) and an initial PK confirmation period in a subset of patients in each cohort, prior to opening

enrollment to the subsequent (younger) cohort. The final protocol review is ongoing at the time of completion of this review.

3400-2: A multi-center, open-label long-term extension study to evaluate the long-term safety of XELJANZ (tofacitinib) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in PMR 3400-1.

This study will provide continued access to tofacitinib to patients who have participated in study 3400-1, and permit collection of additional long-term safety and efficacy data in this population.

These proposed studies were discussed with the Pediatric Research Committee (PeRC) on April 25, 2018, who generally agreed with the proposed pediatric plan. For milestone dates, please refer to the approval letter.

11. Labeling Recommendations

The Applicant's proposed label was reviewed, and revisions and comments have been communicated to the Applicant during labeling negotiations. The final approved labeling will be appended to the approval letter. The major clinical issues related to the label and DGIEP proposed changes include the following, with rationale provided below each section where applicable:

(1) Section 1 Indication and Usage:

(b) (4)

Moving forward, the Division recommends a simple, broad indication statement that is easily understood by providers and patients. More detailed discussion of trial design and specific endpoints achieved will be included in Section 14 of the labelling, as appropriate.

(2) Section 2.3 Dosing and Administration:

a. (b) (4) . The option to use 5 mg or 10 mg twice daily, depending on therapeutic response, after the initial 8 weeks of 10 mg treatment was added. The recommendation to use the lowest effective dose to maintain response was added.
b. A table was created for recommended daily dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, with moderate or severe renal impairment or moderate hepatic impairment, with lymphopenia, neutropenia or anemia.

(b) (4) . From a clinical perspective, providers are looking to see that a patient is starting to improve quickly after initiating treatment, and it may be reasonable to continue therapy even if a patient has not responded fully or is not completely in remission at an early timepoint (such as week 8 in this program), provided that the patient appears to be having an acceptable degree of improvement in the short term. The expectation is that patients may need longer duration of treatment than the studied "induction period" for disease to reach a state of full remission. As a result, the dosing recommendations should provide flexibility to providers to adjust the dose according, in part, to the clinical response of individual patient.

(3) Section 5.1 Serious Infections: Recognition of the dose-dependent risk of serious infections was included and specific opportunistic infections observed in the UC population were added.

Section 5.2: Revisions to the Malignancy and Lymphoproliferative Disorders section included that the majority of reported malignancies occurred in patients who received XELJANZ 10 mg twice daily. Also, dose-dependent risk of non-melanoma skin cancer (NMSC) in UC patients was included.

(4) Section 6.1 Adverse Reactions, Clinical Trial Experience:

a. The adverse reactions for the controlled induction studies were amended. Specifically, the term "increased cholesterol levels" was added to the Applicant's proposal, because it reached the threshold of common AE, based on the analysis done by the clinical reviewer which grouped together the related terms of hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal or lipids increased.
b. The dose dependent adverse reactions for the maintenance study and overall UC program (HZ infections, serious infections, and NMSC) were added.
c. Pulmonary embolism was added as an adverse event of special interest.

(5) Section 7 Drug Interactions: A table was created for Clinical Relevant Interactions Affecting XELJANZ and XELJANZ XR When Co-administered with Other Drugs. This table includes information on clinical impact (e.g., increased/decreased exposure to tofacitinib) and recommended intervention (e.g., dosage adjustment) when co-administering tofacitinib with other drugs, such as CP3A4 inhibitors and inducers, CYP2C19 inhibitors and immunosuppressive drugs.

(6) *Section 8 Use in Specific Population:* Multiple revisions were made to the section, including the following:

a. Section 8.1 Pregnancy: Revisions were made to the risk summary human and nonclinical data to align with current Pregnancy and Lactation Labeling Rule guidelines. The exposure margins for fetal harm in the animal studies based on the 10 mg BID dose (rather than 5 mg BID dose) were added, as this is the first approval for the 10 mg BID dose for any indication.
b. Section 8.2 Lactation: Revisions were made regarding breastfeeding. The period of time that women should consider avoiding breastfeeding after ingestion of tofacitinib (18hrs

for immediate release or 36 hrs for extended release) was added, based on the elimination half-life of the drug.

c. Section 8.3 Females and Males of Reproductive Potential: Contraception information was modified. The AUC multiples for the recommended maximal dose of 10 mg BID were added to describe adverse embryo-fetal outcomes. Previously included language recommending contraception during and for 4 weeks after tofacitinib use was modified. The new language states "Consider pregnancy planning and prevention for females of reproductive potential," rather than stating contraception should be used. The reason for this change is that the ability to directly translate the animal findings at multiples of 6.3X to 13X the recommended dose is limited. Since it is unclear if this represents a true risk to pregnant women, the review team determined that available data did not require a contraception requirement and warning/precaution at this time.
d. 8.7 Renal Impairment and 8.8. Hepatic Impairment: Formatting clarifications were made.

The summarized changes to section 8.3 and related content in section 8.1 reflect the current recommendations of the Division of Pediatric and Maternal Health (DPMH) and were discussed with the PLLR working group, as well as clinical and non-clinical teams from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP). Based on the non-clinical data pertaining to pregnancy, fertility and fetal anomalies, the pharmacology/toxicology team noted that the safety margin was <10x, which may be cause for concern of the potential for embryo-toxic effects in human patients. The lowest safety margin was seen in the rabbit, where teratogenic effects were noted at 6.3x the maximal recommended dose of 10 mg BID (based on AUC). Because there is uncertainty as to how these animal findings may related to risk in females of reproductive potential, there is some degree of concern. However, because there is some safety margin, there is no signal from the available post-marketing data (although limited) from 6 years of post-market use of the product in RA, and because the safety margins were highly variable across species (much higher margin in rodents), it was determined that a requirement for contraception, pregnancy testing prior to treatment and related warning and precaution were not indicated based on the strength of the available data. Instead, the findings are listed in Sections 8.1 and 8.3, and a statement was included that females of reproductive potential should "consider pregnancy planning and prevention."

(7) Section 12.3 Pharmacokinetics: (b) (4) table was added.

The Applicant had proposed (b) (4)
(b) (4)
(b) (4) the Division

recommended to consolidate the PK information and covariate analysis results in patients with rheumatoid arthritis, psoriatic arthritis and ulcerative colitis as there was no major difference in analysis results between these different disease populations.

- AUC information in each disease population at respective approved doses was added in a table format.

(8) Section 14.3 Clinical Studies Ulcerative Colitis:

a. Primary and clinically important secondary endpoint results were included in tabular format. The endpoint of "mucosal healing" was described as "improvement in the endoscopic appearance of the mucosa".

b. Descriptive subgroup analyses by TNF blocker failure status were included. For the subgroup analyses (b) (4)

c. All text providing results from exploratory analyses were discussed descriptively (b) (4) (b) (4) including results for the TNF blocker failure subgroups.

d. (b) (4)

A brief summary of open-label extension study results was included. Despite lack of controlled data in the OLE study, these data influenced the Advisory Committee's recommendation and the Division's decision to permit longer term treatment with 10 mg BID in patients who do not respond by 8 weeks; therefore, it was considered important to describe the outcomes that were observed in these patients (induction non-responders who continued therapy with 10 mg BID longer term).

The Applicant is also proposing to add wording to the 10 mg bottle label and the "How Supplied" section of the labeling to reinforce the Dosage and Administration section, which is proposed to state that the "Recommended dose" of 10 mg is for use in UC patients only and to be consistent with the Risk Management Plan (see below). The Applicant states that, at this time, Xeljanz XR 11 mg would not be recommended for dosage and administration in patients with UC (in place of the 5 mg IR twice a day).

In addition, Medication Guide was updated to reflect revisions described above.

12. Risk Evaluation and Mitigation Strategies (REMS)

A formal REMS program will not be required for this supplement.

The Applicant's proposed risk management plan, which encompasses both risk mitigation and pharmacovigilance components, is designed to ensure effective detection, assessment, mitigation, and communication of safety risks. Noting there are no new risks, outside of identified pulmonary embolism events, seen in the UC program based on the completed studies, the Division has concluded that risk mitigation measures beyond professional labeling are not required for tofacitinib for use in UC.

However, Applicant acknowledges that gastroenterologists represent a group of providers without prior experience prescribing tofacitinib and acknowledges that the 10 mg BID dose is not recommended for RA or PsA. Additional risk mitigation is therefore proposed by the Applicant as follows:

- A one-time letter will be sent to gastroenterologists within 60 days of approval.
- The letter will state the approved indication and recommended doses.
- The letter will inform the recipients of the risk of serious and other important infections, including HZ, and malignancy, including NMSC.
- Package labeling for the 10 mg bottles will clearly state that 10 mg is for UC only.
- Outreach to prescribers will emphasize use of tofacitinib consistent with approved indications and corresponding recommended dosages and reinforce the point that 10 mg is for UC only.

Pharmacovigilance

(b) (4)

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(b) (4)

[redacted]

13. Post-marketing Requirements and Commitments

Clinical post-marketing requirements are intended to characterize the risks of tofacitinib use in special populations and address the long- term safety of this drug (a novel mechanism of action in UC) in the target population.

Post-Marketing Required study under FDCA

A long-term, observational study to assess the long-term safety of tofacitinib 5 mg BID or 10 mg BID vs other therapies used in the treatment of adults with moderately to severely active UC. The study's primary outcome is malignancy. Secondary outcomes of interest include, but are not limited to, opportunistic infections, thromboembolic events, and hepatic injury. Specify concise case definitions, and provide outcome validation for both primary and secondary outcomes. Describe and justify choice of appropriate comparator population(s) and estimated background rates relative to tofacitinib-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate, with a pre-specified statistical analysis method. For the tofacitinib-exposed and comparator(s), the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure adequate number of patients with at least 18 months of tofacitinib exposure at the end of the study. Follow for a period of at least 7 years.

Post-Marketing Required studies under PREA

Please refer above to the section on Pediatric **Development Program** for details.

(1) A one-year, multi-center, randomized, controlled trial to evaluate the safety, efficacy and pharmacokinetics of XELJANZ (tofacitinib) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

(2) A multi-center open-label extension study to evaluate the long-term safety of XELJANZ (tofacitinib) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in PMR 3400-1.

Post-Marketing Commitments

The Applicant has agreed to conduct the following post-marketing commitment studies to generate additional safety and efficacy information as follows:

(1) A double-blind, randomized, controlled clinical trial to assess the relative efficacy of XELJANZ (tofacitinib) 5 mg BID versus 10 mg BID for maintaining remission in patients with moderate to severe ulcerative colitis who are in stable remission for at least 6 months on XELJANZ (tofacitinib) 10 mg BID therapy.

(2) A controlled clinical trial to assess both the clinical and immunological responses to Shingrix vaccination in adult patients with moderately to severely active ulcerative colitis treated with XELJANZ (tofacitinib).

14. Appendices

Appendix A. Clinical Pharmacology Appendices

A.1. Summary of Bioanalytical Method Validation and Performance

Question 1. How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

The plasma concentration of tofacitinib (CP-690,550) from phase 2 study (Protocol A3921063) for UC indication were analyzed at (b) (4) using the same validated HPLC/MS/MS bioanalytical method that was used to support the NDA approval for RA. The validation of this bioanalytical method was documented in Pfizer method validation reports 1000-071073, 1000-071073-2, 1000-071073-3, and 1000-071073-4 (A3929011). For further details on validation parameters for this bioanalytical method, please see clinical pharmacology review for NDA 203214 by Dr. Lokesh Jain dated 06/25/2012.

The plasma concentration of tofacitinib (CP-690,550) from phase 3 studies (Protocol A3921094: Protocol A3921095, Protocol A3921096) for UC indication were analyzed at (b) (4) (b) (4) using the validated HPLC/MS/MS bioanalytical method. The validation of this bioanalytical method was documented in Pfizer method validation report A3929023 titled "The Validation of an HPLC-MS/MS Assay Method for the Determination of CP-690550 in Human Heparin Sodium Plasma".

Question 2. Which metabolites have been selected for analysis and why?

No metabolites were measured in any of the studies. Although tofacitinib is extensively metabolized, primarily by CYP3A4 enzyme with minor contribution from CYP2C19, all metabolites have less than <8% of total drug exposure and their potency was reported to be ≤10% of the potency of tofacitinib for JAK1/3 inhibition. Therefore, absence of metabolite measurement in this submission was acceptable.

Question 3. What bioanalytical methods are used to assess concentrations of the measured moieties?

Table 84: Summary of the Validated Analytical Methods for Tofacitinib in Sodium Heparin Plasma

Protocol No.	Bioanalytical Site:	Pfizer Method Validation Report No.	Assay Method	Sensitivity (ng/mL)
A3921063	(b) (4)	A3929011	HPLC/MS/MS	0.100
A3921094 A3921095 A3921096		A3929023	HPLC/MS/MS	0.100

Source: Reviewer's Table per Bioanalytical reports

Question 4. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used? What are the lower and upper limits of quantitation?

Study repot	Matrix	Bioanalytical Site:	Validation report	Range of Standard Curve	LLOQ	ULOQ	Dilution factor
A3921063	Plasma	(b) (4)	A3929011	0.100 to 350 ng/mL	0.1 ng/mL	350 ng/mL	5 and 10
A3921094 A3921095 A3921096	plasma		A3929023	0.100 to 350 ng/mL	0.1 ng/mL	350 ng/mL	10 fold

Source: Reviewer's Table per Bioanalytical validation reports

All studies (phase 2 study A3921063 analyzed at (b) (4) and phase 3 studies analyzed at (b) (4)) used weighted (l/concentration2) quadratic regression curve fitting technique. All measured concentrations in all studies were below ULOQ of 350 ng/mL.

Question 5. What are the accuracy, precision, and selectivity at these limits?

Matrix	Validation report		Intra-assay	Inter-Assay
Plasma	A3929023	Precision (CV%)	< 17.2 %	< 13.1 %
		Accuracy	-6.0 % to 16.0 %	1.0 % to 8.0 %

Source: Reviewer's Table per Bioanalytical validation reports A3929023 (page 5)

The selectivity was evaluated by extracting and analyzing blank human plasma from six individual sources both with and without addition of internal standard. All 6 lots were free from significant interfering peaks in the drug and internal standard regions.

Question 6. What is the sample stability under conditions used in the study?

All PK plasma samples from both phase 2 and phase 3 studies were stored at approximately -20°C until the analysis and analyzed within the time-period for which the long-term stability has been established during the method validation except for one subject in phase 3 study. The long-term stability of tofacitinib in plasma matrix at -20°C was established for 693 days for the bioanalytical method conducted at (b) (4) for phase 2 study and for 1274 days conducted at (b) (4) for all phase 3 studies.

Table 85: Stability of Tofacitinib (CP-690550) in Human Heparin Sodium Plasma

Validation report	Freeze-thaw -70ºC (Cycles)	Freeze-thaw -20ºC (Cycles)	At Room temperature (benchtop)	At 4°C (autosampler)	At -20°C	At -70°C
A3929023	5	5	92 hr	74.5 hr	1274 days	1274 days

Source: Reviewer's Table per Bioanalytical validation reports A3929023 and its addendums

The primary stock solution stability (0.100 mg/mL in 50%ACN) was established for 91 days at 2-8ºC and 22 hours at room temperature (15-30ºC).

Table 86: Storage Period of Tofacitinib in Plasma

Study repot	Study Start Date	Study End Date	Bioanalytical analysis start date	Bioanalytical analysis end date	Applicant reported maximum storage	Worst case scenario maximum storage [1]	Samples Analyzed within Stability Limits
A3921063	01/19/2009	09/06/2010	6/2/2009	9/23/2010	539	612	Yes
A3921094	4/18/2012	5/22/2015	7/31/2013	7/8/2015	1142	1176	Yes
A3921095	6/21/2012	6/9/2015	8/2/2013	7/23/2015	1102	1127	Yes
A3921096 [2]	7/20/2012	5/27/2016	7/30/2013	7/06/2016	1121	1447	Yes except for 1 subject

Source: Reviewer's Table per Bioanalytical Reports

[1]Reviewer estimated worst case scenario for maximum storage based on the first day of clinical study and last day of bioanalytical analysis.

[2]In study A3921096, the Applicant states that the maximum time from collection to analysis for all PK plasma samples are in 1121 days for all subjects except for1325 days for subject (b) (6).

Question 7. What is the plan for the QC samples and for the reanalysis of the incurred samples?

The concentration of Quality Control (QC) in all studies (phase 2 study A3921063 analyzed at (b) (4) and phase 3 studies analyzed at (b) (4)) were 0.300, 4.00, 40.0, 280 ng/mL.

All studies had at least 7% of the samples re-analyzed as the incurred samples reanalysis (ISR) to demonstrate the reproducibility of quantification in all studies. The incurred sample repeats from all 4 studies met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20% in all studies.

Table 87: Assay Performance of Tofacitinib in Sodium Heparin Plasma in Each Clinical Study

Clinical Study	Compound Analyzed	Matrix	QCs Inter-run Precision (CV%)	QCs Inter-run Accuracy (%RE)	% of samples for ISR	Passed ISR
A3921063	Tofacitinib	Plasma	≤ 8.5%	-9.3% to 0%	7.7% (187/2413)	Yes
A3921094	Tofacitinib	Plasma	≤ 7.0%	-1.0% to 2.5%	8.3% (191/2295)	Yes
A3921095	Tofacitinib	Plasma	≤ 7.0%	-1.0% to 2.9%	8.7% (174/1994)	Yes
A3921096	Tofacitinib	Plasma	≤ 6.7%	1.0% to 2.0%	7.0% (186/2671)	Yes

Source: Reviewer's Table per Bioanalytical Reports

A.2. Population PK Analyses

Sparse PK samples were collected in the phase 2 study and phase 3 studies in UC patients. Population PK analysis was conducted using the nonlinear mixed-effects modeling approach to characterize the PK of tofacitinib in patients with moderately to severely active UC and to identify intrinsic and extrinsic factors (covariate) that may impact the PK of tofacitinib in these patients. A total of 1096 patients with 6230 plasma concentrations were included in the analysis.

Table 88: Summary of Source of Data used for Population PK Analysis in UC patients

Studies	Phase	Treatment Duration	PK Sampling Schedule/period	Dose	Number of subject in final PK dataset
A3921063	Phase 2 Induction	8-week	Baseline (Day 1) & Week 8: Pre-dose, 0.25, 0.5, 1, 2-3 hr post-dose Week 2 &4: 2 samples greater than 1 hour apart	0.5 mg BID 3 mg BID 10 mg BID 15 mg BID placebo BID	31 33 31 48
A3921094 & A3921095	Phase 3 Induction	8-weeks	Week 2: Pre-dose and 0.5 hr (0.25-1.5hr) post-dose; Week 8: Pre-dose and 2 hr (1-3hr) post-dose	10 mg BID 15 mg BID placebo BID	890 20
A3921096	Phase 3 Maintenance	52 weeks	Baseline (Day 1) & week 24: Pre-dose and 2 hr (1-3hr) post-dose Week 8 & 52: Pre-dose and 0.5 hr (0.25- 1.5hr) post-dose	5 mg BID 10 mg BID placebo BID	191 189

Source: Reviewer's table adopted from Table S2 in Population Modeling Analysis Report: PMAR-EQDD-A392i-sNDA-513 (page 5)

The population PK of tofacitinib in UC patient population was described by a one-compartment disposition model with first order absorption with an absorption lag time. The parameter estimates of the final model for tofacitinib is summarized in **Table 89**.

Table 89: Parameter Estimates for the Final Population Pharmacokinetic Model

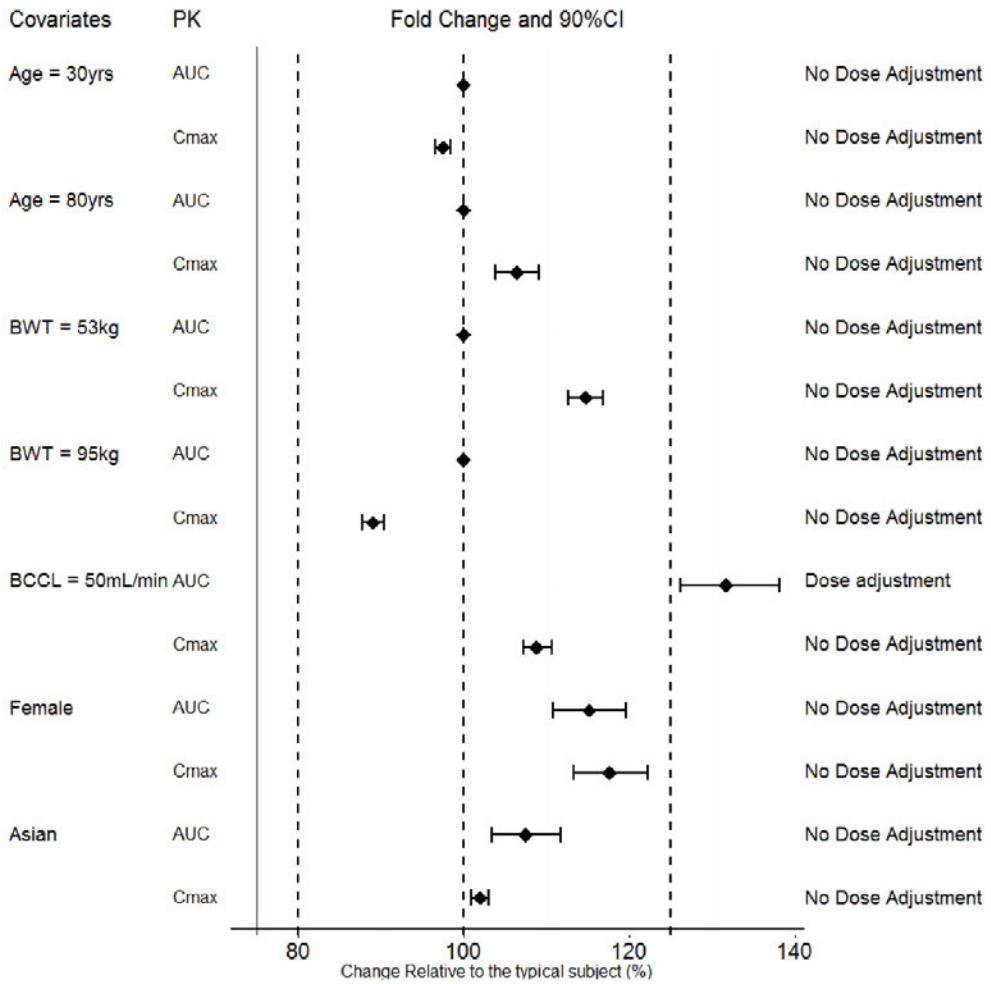
Parameter	Final model (run 72)				Bootstrap*
	Estimates (RSE %)	IIV (RSE %)	IOV (RSE%)	Median (IIV %)	95%CI (95%CI for IIV)
CL/F (L/hr)	26.3 (1.24)	22.2 (7.72)	--	26.3 (22.2)	25.5~ 27.2 (19.0 ~ 24.5)
V/F (L)	115.8 (1.09)	--		115.5	111.5~120.6
Ka (hr^{-1})	9.85 (7.1)	--	191.8 (7.04)	9.86 (191.9)#	7.9~10.8 (179~205)#
Prop Error (TAD≤8hr, %)	41.6 (2.58)	58 (6.28)		41.3 (58)	38.6 ~ 44.4 (54.0 ~ 62.2)
Prop Error (TAD>8hr, %)	68.9 (2.61)	58 (6.28)		68.6 (58)	64.1 ~ 73.5 (54.0 ~ 62.2)
Lag (hr)	0.236 (0.52)	--		0.236	0.218 ~ 0.238
Scale Parameter	0.392 (7.19)	--		0.399	0.305 ~ 0.481

Source: Table 10 on page 39 of Applicant's population PK report PMAR-EQDD-A392i-sNDA-513

Based on the population PK analysis, tofacitinib apparent clearance (CL/F) in UC patients (26.3 L/h) was similar to that of PSO (26.7L/h) and PsA patients (20.4L/h) and 45% higher than in RA patients (18.4L/h) and 25% lower than that of healthy subjects (34.9L/h). Tofacitinib exposure in UC patients (423 ng•h/mL), as measured by the steady-state AUC_{0-24} after 5 mg BID, was comparable with that of patient with PsO (404 ng•h/mL) and PsA (419 ng•h/mL) and about 20% lower than in patient with RA (504 ng•h/mL).

Based on the covariate analysis results, tofacitinib does not require dose modification or restrictions based on age, body weight, sex, and race (Asian vs others) in the adult patients with ulcerative colitis (**Figure 7**). This is consistent with the result of covariate analysis in PsA, RA and PsO patient populations. Population PK analysis in UC patients indicated that baseline creatinine clearance (BCCL) significantly affected the apparent clearance of tofacitinib in consistent with the previous findings.

Figure 7: Impact of Covariates on Tofacitinib PK in UC Patients



Dotted line represents limits of a range from 80% to 125%. A typical (reference) patient is represented as: Male, non-Asian, Body weight 72 kg, BCCL (baseline creatinine clearance) 108.7 mL/min, Age 40 years. Weights of 53 and 95 kg are the 10th and 90th percentiles of body weight in this analysis dataset. BCCL of 50 mL/min with reference to the typical patient reported above (40.75 mL/min was the lowest BCCL in the analysis dataset). AUC = Area under the concentration-time curve over a dosing interval; C_{max} = Maximum concentration; PK = Pharmacokinetics; CI = Confidence interval; kg = kilogram; Magnitude of change is presented in reference to a typical patient

Source: Figure S2 on page 10 of Applicant's population PK report PMAR-EQDD-A392i-sNDA-513

A.3. Exposure-Response Analyses

A.3.1. Dose/Exposure-response relationship for efficacy

The Applicant submitted an exposure-response analysis report for efficacy entitled *"Exposure-Response Analysis of CP-690,550 (Tofacitinib) for Binary Endpoints in Patients with Ulcerative Colitis"*. The objectives of the analysis were:

2. Characterize the exposure-response (E-R) relationship between tofacitinib exposure and binary clinical efficacy endpoints at week 8 during induction treatment and identify patient-specific factors that are important determinants of induction efficacy.
3. Characterize the E-R relationship between tofacitinib exposure and binary clinical efficacy endpoints at week 24 and 52 during maintenance treatment and identify patient-specific factors that are important determinants of maintenance efficacy.

Results of the analyses were summarized as followed.

Induction of Remission

In the phase 2 trial, a positive exposure-response relationship between C_{avg} and efficacy, assessed as clinical remission[34] based on locally read endoscopy (CREMLR), was apparent during the first 8 weeks of treatment **(Figure 8**). The rate of clinical remission plateaued at systemic exposure greater than those of 10 mg BID.

In phase 3 trials, induction was studied mainly at 10 mg BID, as a 15 mg BID dose arm was discontinued early in the trial.

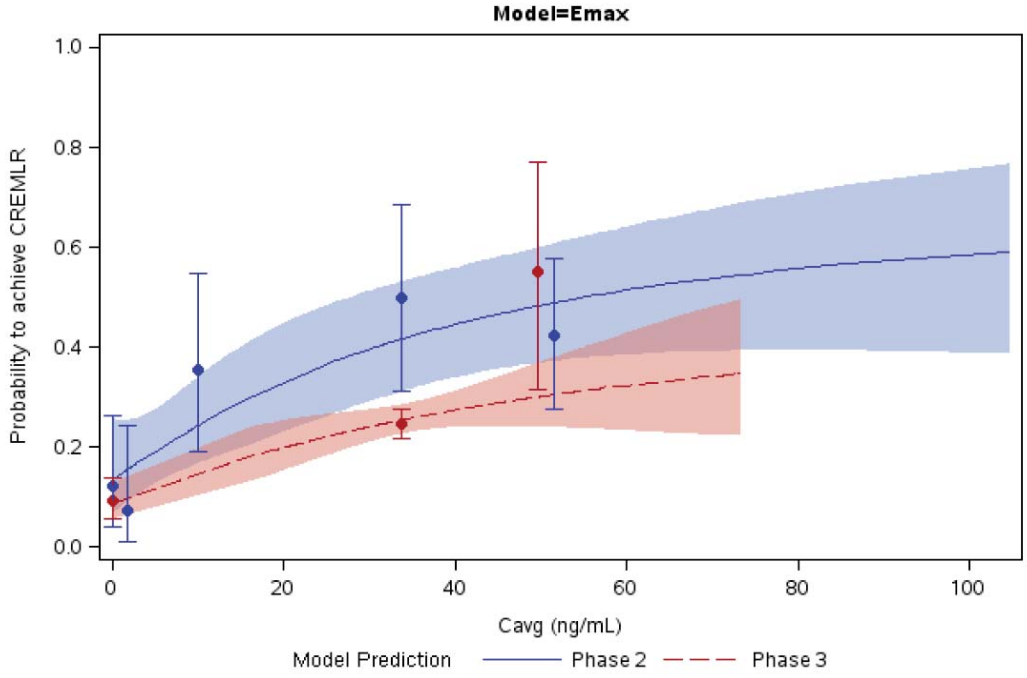
The proportion of patients achieving clinical remission was lower in phase 3 trials than in the phase 2 trial. This could be due to the differences in baseline previous treatment status; in phase 3 trials more than half (51.6%) of patients were prior TNF-inhibitor non-responders, and 73.9% were prior

[34] Clinical remission: total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point

users of immunosuppressants. In the phase 2 trial, fewer patients were either prior TNF inhibitor non-responders (40.7%) or prior users of immunosuppressants (18.5%).

When the treatment response was predicted for 5 mg BID based on a logistic Emax model, the model-predicted probability of clinical remission (CREMLR) in phase 3 populations at 5 mg BID and 10 mg BID was 18.3% (95% CI: 12.9-23.7%) and 25.4% (95% CI: 22.4 to 28.3%), respectively. The model-predicted clinical remission at 10 mg BID was similar to the observed clinical remission rate, 24.8% and 20.7% in Studies A3921094 and A3921095, respectively.

Figure 8: Observed and Model Predicted Probabilities of Patients Achieving Clinical Remission in Phase 2 and Phase 3 Trials after 8 Weeks of Induction Treatment



Source: Figure 13 on page 64 of Applicant's exposure-response analysis report PMAR-EQDD-A392i-sNDA-512

Note: Observed (closed circle) and model predicted probabilities (line) with 95% CI is (shaded area) based on a logistic Emax model were plotted (blue circle: Phase 2, red circle: Phase 3) at the median of individual Cavg values by dose in phase 2 (0 mg, 3 mg, 10 mg, and 15 mg) and phase 3 trials (0, 10 mg and 15 mg); CREMLR: clinical remission based on local read endoscopy

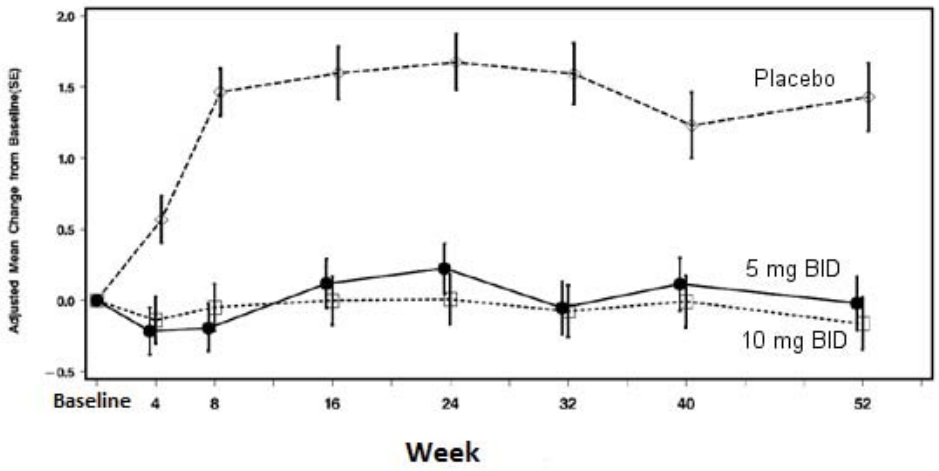
Overall, the dose / exposure-response analysis for efficacy in the dosing finding phase 2 study in patients with moderately to severely active UC supported the selection of the 10 mg BID as the induction dose in the phase 3 trials.

Maintenance Treatment

Following the 8-week induction treatment, patients who responded (clinical response defined by a decrease from baseline in Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1), were randomized to placebo, 5 mg BID, or 10 mg BID and treated for additional 52 weeks.

During the 52-week maintenance treatment, both 10 mg BID and 5 mg BID demonstrated statistically significant ($p<0.0001$) treatment benefit (difference in the proportion of remitters from placebo (95% CI): 5 mg BID: 23.2(15.3, 31.2); 10 mg BID: 29.5 (21.4, 37.6) relative to placebo. As shown in the time-course of partial Mayo score change from baseline (**Figure 9**), both tofacitinib 5 mg and 10 mg doses consistently maintained the partial Mayo score achieved following 8-week treatment for induction, over 52 weeks. In contrast, the partial Mayo score increased over time (uppermost curve in the Figure 9) following the induction period in patients randomized to placebo. There was no clear difference in the efficacy between 5 mg BID and 10 mg BID for maintenance treatment.

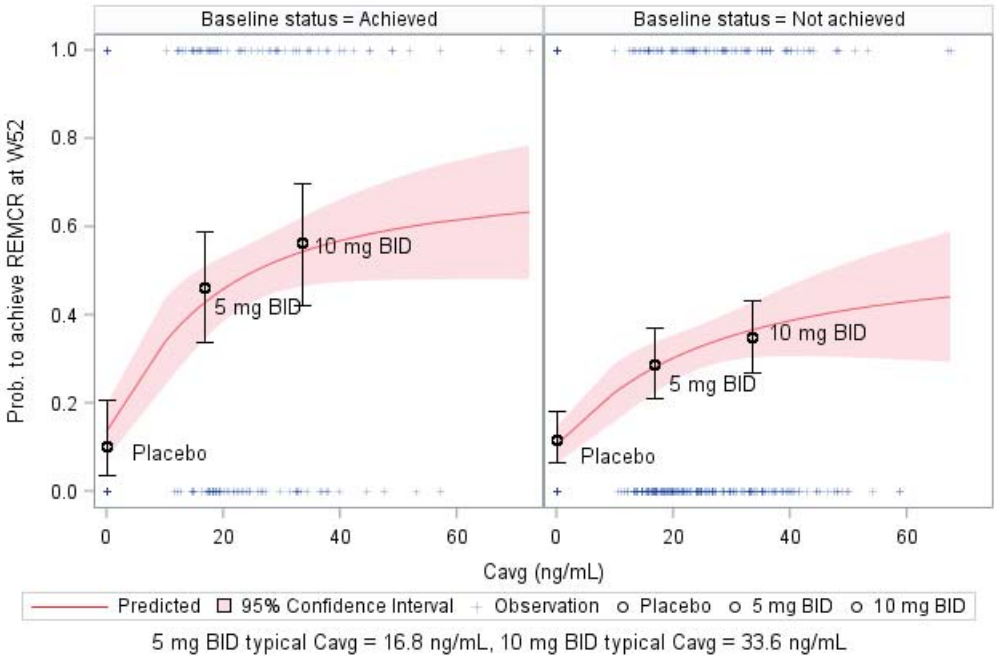
Figure 9: Mean (±SE) Change from Baseline for Partial Mayo Score by Week



Source: Figure 3 of Applicant's clinical study report A3921096. The analysis was conducted with linear mixed model using full analysis dataset (Observed cases). BID=twice a day; FAS=full analysis set; SE=standard error

The analysis of exposure-response relationship between individual average plasma concentrations (Cavg) and the proportion of patients who achieved remission (remitters)[35] (REMCR[36]) at week 52 indicated that treatment effect of tofacitinib in maintenance plateaued at systemic exposure associated with 5 mg BID (**Figure 10**). The proportion of patients who achieved remission at week 52 after 10 mg BID dose was numerically higher in both baseline remitters and non-remitters (10 mg BID vs 5 mg BID in remitters: 56.4% vs 46.2%; in non-remitters: 34.8% vs 28.6%) with overlapping 95% CI.

Figure 10: Relationship between Plasma Concentrations (Cavg) and Probability to Achieve Remission at Week 52 by Baseline Remission Status (Left Panels: Remitters; Right Panels: Non-remitters)



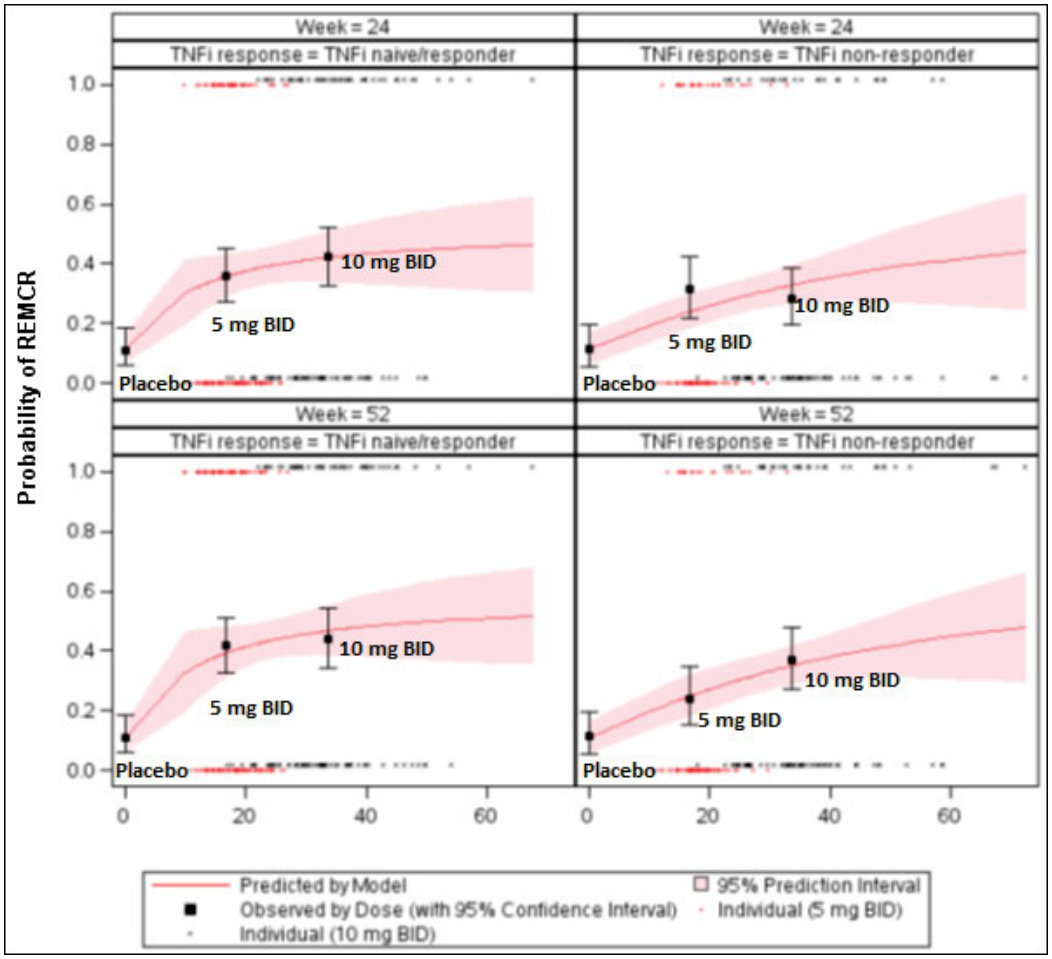
[35] Remission: total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0

[36] REMCR: Remission based on central endoscopy read

Source: Adapted from Figure 27 of Applicant's Exposure-Response analysis report based on data from study A3921096 and analysis with a Markov transition model; C_{avg} values were predicted individual average concentration under steady state using a population PK model. 5 mg BID typical C_{avg}=16.8 ng/mL; 10 mg BID typical C_{avg} =33.6 ng/mL. REMCR: Remission based on central endoscopy read

The relationship between Cavg and the proportion of remitters (REMCR) among patients who were TNF Blocker non-responder subgroup indicated no clear difference between 5 mg and 10 mg BID treatment at week 24 (top right panel in Figure 5). At week 52 in this subgroup, the proportion of patients who achieved REMCR remission in the 10 mg BID dose arm was predicted to be approximately 10% (35.0 % vs 24.9%) higher than in the 5 mg BID dose arm (bottom right panel in Figure 11) with overlapping 95% CI.

Figure 11: Relationship between Plasma Concentrations (Cavg) and Probability to Achieve Remission by TNF Blocker Non-responder Status at Baseline (Left Panels: TNF Blocker Responders; Right Panels: TNF blocker non-responders) and Treatment Duration (Top Panels: Assessment at Week 24; Bottom Panels: Assessment at Week 52)



Source: Adapted from Figure 46 of Applicant's Exposure-Response analysis report based on maintenance data and analysis with a logistic E_{max} model; probabilities and 95% CI by dose (black symbols) are shown at C_{avg} corresponding to 5 mg (16.8 ng/mL) and 10 mg BID (33.6 ng/mL) doses. C_{avg} values were predicted individual average concentration under steady state using a population PK model. REMCR: Remission based on central endoscopy read.

In summary, dose/exposure response analysis supported the proposed 5 mg BID dose in maintenance treatment. Overall, the use of 10 mg BID dose for 52 weeks achieved a similar rate of remission as the 5 mg BID dose. The Applicant proposes that TNF blocker non-responders might benefit from the use of 10 mg BID as a maintenance dose. As shown in 4.4.1-4, treatment with 10

mg BID for 24 weeks did not demonstrate better efficacy than the 5 mg BID dose in TNF blocker non-responders. At week 52, the exploratory exposure-response analyses estimated that the remission rate was about 10% higher at 10 mg BID than 5 mg BID in TNF blocker non-responders compared to 6.5% difference between 10 mg and 5 mg in overall population. However, the CIs overlapped.

A.3.2. Dose/Exposure Response Analysis for Safety

The Applicant submitted an exposure-response analysis report for safety entitled *"Exposure-Response Analysis of Tofacitinib Adverse Events and Laboratory Data in Patients with Ulcerative Colitis (UC)"*. The objectives of the analysis were:

1. To characterize the relationship between tofacitinib exposure and occurrence of specific adverse events (AEs) of special interest, such as serious infections, herpes zoster, non-melanoma skin cancer (NMSC) and malignancies (excluding NMSC) in subjects with moderate to severe ulcerative colitis (UC).
2. To evaluate the exposure-response relationships for selected hematology and liver function laboratory endpoints

Results of the Applicant's analyses were summarized as followed.

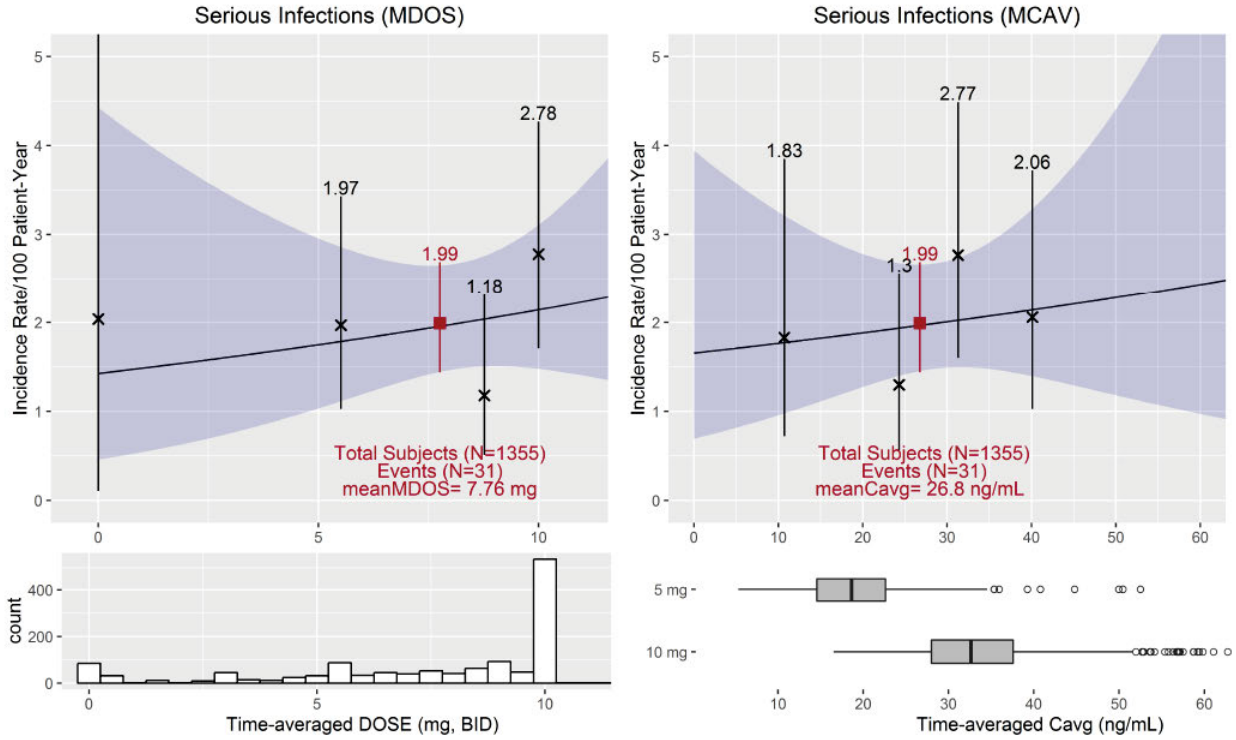
Data for Analysis: The pooled data from all Phase 2 and 3 UC studies (Studies A3921063, A3921094, A3921095, A3921096, and A3921139) including a total of 1355 patients were used in the analysis of AE of special interest; Evaluation of laboratory endpoints included separate analyses for pooled data from induction studies (A3921063, A3921094, A3921095), and data from the maintenance study (A3921096).

Methods: Poisson regression analysis was conducted to characterize exposure-response relationships between exposure metrics and AE of special interest that had a sufficient number of reported events to inform the analysis. In addition to tofacitinib exposure metrics (time-weighted average dose (MDOS) or time-weighted average concentration (MCAV)) as the primary predictor of the AE of interest, various other clinically relevant covariates such as age, gender, race, baseline disease status, TNF inhibitor failure status etc. were evaluated as additional predictors in both univariate and multivariate models

Results: Exposure response analyses with pooled data from Phase 2 and 3 UC Studies (A3921063, A3921094, A3921095, A3921096, and A3921139) were conducted using Poisson regression to assess the risk of serious infections, opportunistic infections, herpes zoster, and NMSC. Other adverse events of interest (malignancies excluding NMSC, gastrointestinal perforation, MACE, tuberculosis) were also captured in the dataset but analyses of these endpoints were not conducted due to small number of events (<10).

Serious Infections: As shown in Figure 12, the model predicted incidence rates (events/100 PYR) and associated 90% prediction intervals for placebo, 5 and 10 mg tofacitinib were 1.43 [0.460-4.43], 1.75 [1.04-2.96] and 2.14 [1.48-3.11] for MDOS, or 1.66 [0.695-3.95], 1.84 [1.17-2.90] and 2.06 [1.49-2.84] for MCAV (corresponding to 0, 16.8 and 33.6 ng/mL), respectively. The risk ratio of 10 mg BID vs 5 mg BID doses of tofacitinib for serious infections was estimated to be 1.12 with 95% CI [0.642, 1.95] including 1.0 (predicted from the MCAV model). The model-predicted Incidence Rates (IRs) with 90% CIs for placebo, tofacitinib 5 mg BID (Cavg 16.8 ng/mL), and tofacitinib 10 mg BID (Cavg 33.6 ng/mL) from the time-weighted average concentration (MCAV) model were 1.66 [0.695, 3.95], 1.84 [1.17,2.90], and 2.06 [1.49, 2.84], respectively.

Figure 12: Model-Predicted Mean and 90% Prediction Intervals for Serious Infections (Left Panel: by MDOS, Right Panel: by MCAV)



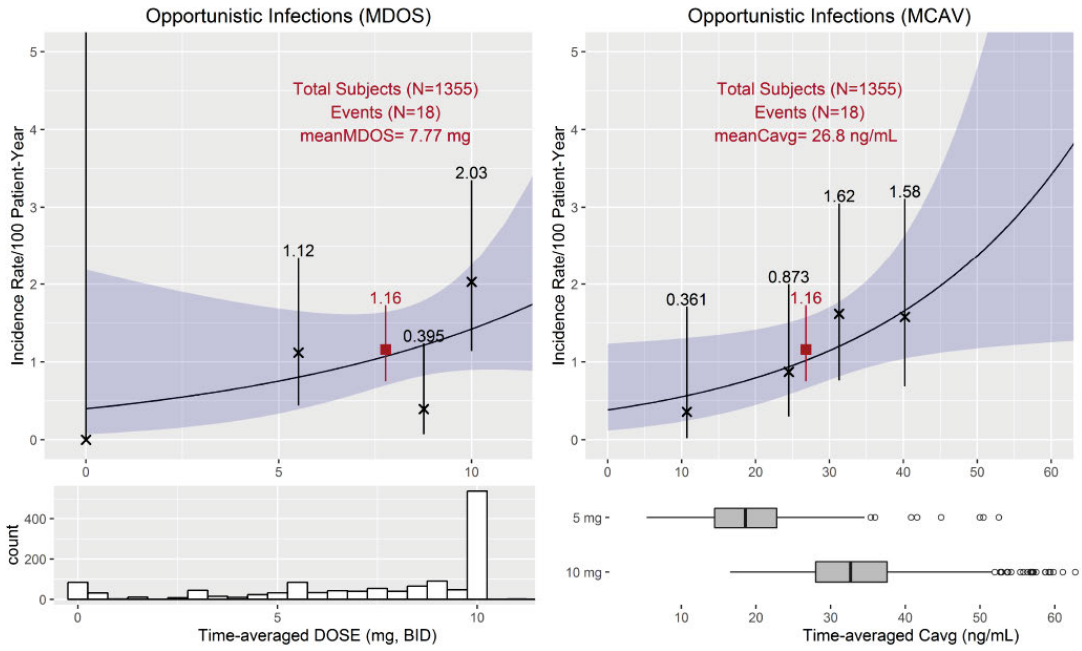
Source: Figure 3 on page 22 of Applicant's clinical study report PMAR-EQDD-A392i-sNDA-514

Note: Model predictions and associated 90% prediction intervals are shown by solid black lines and the shaded area. Observed Incidence rates (IRs) in the left panel are calculated by binning MDOS (time-averaged dose) by [0-2.5), [2.5-7.5), [7.5-10), [10-15] (mg BID) and overlaid on the plot. The count for number of patients by MDOS is also shown as a histogram below the left panel. Right panel is created by binning MCAV (time-averaged Cavg) into quartiles and calculating the IRs for the respective quartiles. The distribution of MCAV values corresponding to 5 mg and 10 mg BID is shown as a horizontal box-plot below the right panel. The individual points in the boxplot are outliers, which fall below Q1 - 1.5 × IQR (Inter quartile range) or above Q3 + 1.5 × IQR.

The exposure-response relationship for serious infections is shallow as shown in the figure above. Higher exposure was only associated with slightly higher incidence rate of serious infections.

Opportunistic Infections: Model predicted mean and 90% CIs for opportunistic infections is shown in **Figure 13**. The risk ratio of 10 mg BID vs 5 mg BID doses of tofacitinib for opportunistic infections was estimated to be 1.85 with 95% CI [0.857, 3.98] including 1.0 (predicted from the MCAV model). The model-predicted Incidence Rates (IRs) with 90% CIs for placebo, tofacitinib 5 mg BID (Cavg _ 16.8 ng/mL), and tofacitinib 10 mg BID (Cavg _ 33.6 ng/mL) from the time-weighted average concentration (MCAV) model were 0.384 [0.120, 1.24], 0.709 [0.366, 1.37], and 1.31 [0.886, 1.93], respectively.

Figure 13: Model Predicted Mean and 90% Prediction Intervals for Opportunistic Infections (Left Panel: by MDOS, Right Panel: by MCAV)



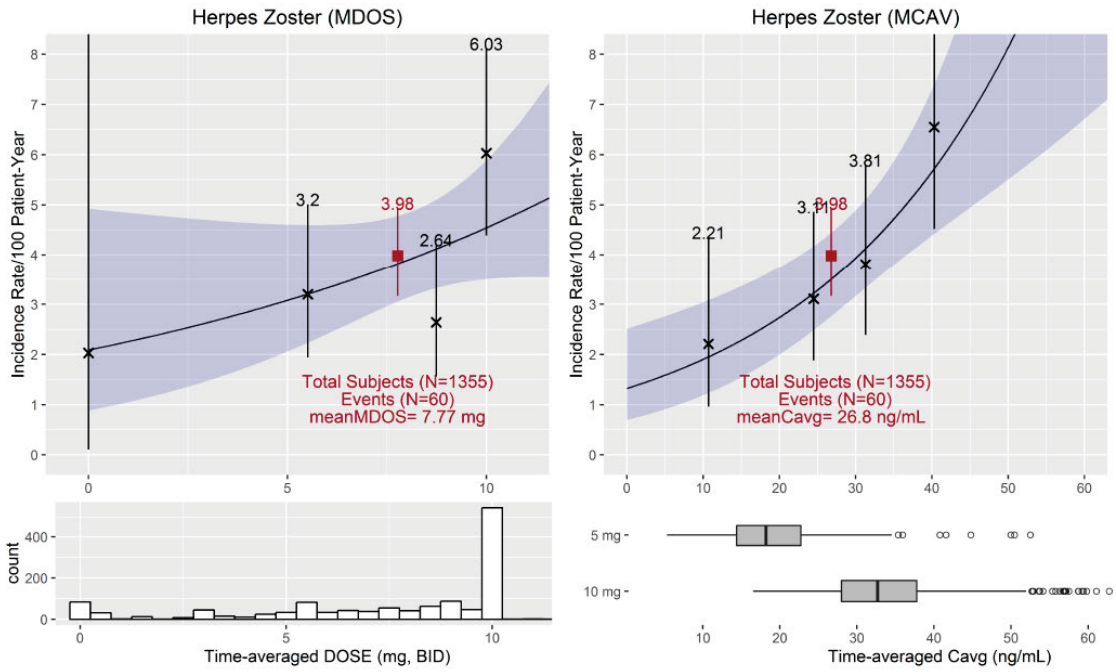
Source: Figure 3 on page 22 of Applicant's clinical study report PMAR-EQDD-A392i-sNDA-514

Note: Model predictions and associated 90% prediction intervals are shown by solid black lines and the shaded area. Observed Incidence rates (IRs) in the left panel are calculated by binning MDOS (time-averaged dose) by [0-2.5), [2.5-7.5), [7.5-10), [10-15] (mg BID) and overlaid on the plot. The count for number of patients by MDOS is also shown as a histogram below the left panel. Right panel is created by binning MCAV (time-averaged Cavg) into quartiles and calculating the IRs for the respective quartiles. The distribution of MCAV values corresponding to 5 mg and 10 mg BID is shown

as a horizontal box-plot below the right panel. The individual points in the boxplot are outliers, which fall below Q1 - 1.5 × IQR (Inter quartile range) or above Q3 + 1.5 × IQR.

Herpes zoster: Model predicted mean and 90% CIs for herpes zoster is shown in Figure 14. Age was identified as a statistically significant covariate (p<0.005) in all models (univariate, multivariate, and full model). The tofacitinib exposure (MCAV) was significant in the univariate setting but not significant in the full multivariate model. Asian and anti-TNF treatment status (failure TNF-Yes or No) were identified as potential covariates (p<0.1) in univariate setting, but neither of them were significant in multivariate or final model. The risk ratio of 10 mg BID vs 5 mg BID doses of tofacitinib for herpes zoster was estimated to be 1.84 with 95% CI [1.21, 2.79] excluding 1.0 (predicted from the MCAV model). The model-predicted Incidence Rates (IRs) with 90% CIs for placebo, tofacitinib 5 mg BID (Cavg _ 16.8 ng/mL), and tofacitinib 10 mg BID (Cavg _ 33.6 ng/mL) from the time-weighted average concentration (MCAV) model were 1.32 [0.696, 2.51], 2.44 [1.70,3.49], and 4.48 [3.62, 5.55], respectively.

Figure 14: Model Predicted Mean and 90% Prediction Intervals for Herpes Zoster (Left Panel: by MDOS, Right Panel: by MCAV)

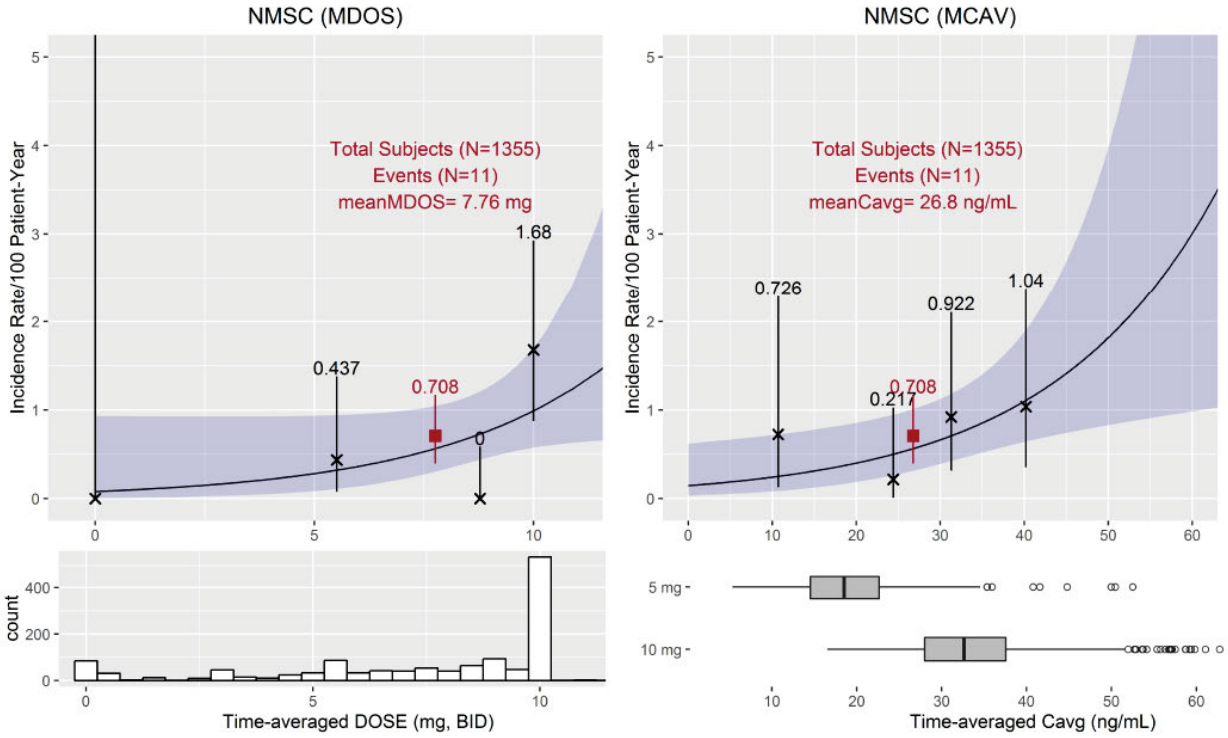


Source: Figure 4 on page 23 of Applicant's clinical study report PMAR-EQDD-A392i-sNDA-514

Note: Model predictions and associated 90% prediction intervals are shown by solid black lines and the shaded area. Observed Incidence rates (IRs) in the left panel are calculated by binning MDOS (time-averaged dose) by [0-2.5), [2.5-7.5), [7.5-10), [10-15] (mg BID) and overlaid on the plot. The count for number of patients by MDOS is also shown as a histogram below the left panel. Right panel is created by binning MCAV (time-averaged Cavg) into quartiles and calculating the IRs for the respective quartiles. The distribution of MCAV values corresponding to 5 mg and 10 mg BID is shown as a horizontal box-plot below the right panel. The individual points in the boxplot are outliers, which fall below Q1 - 1.5 × IQR (Inter quartile range) or above Q3 + 1.5 × IQR.

NMSC: As shown in **Figure 15**, the model predicted incidence rates (events/100 PYR) and associated 90% prediction intervals for placebo, 5 and 10 mg tofacitinib were 0.0807 [0.00698-0.935], 0.283 [0.0855-0.936] and 0.991 [0.576-1.71] for MDOS, or 0.147 [0.0345-0.623], 0.342 [0.145-0.805] and 0.796 [0.484-1.31] for MCAV (corresponding to 0,16.8 and 33.6 ng/mL), respectively. The risk ratio of 10 mg BID vs 5 mg BID doses of tofacitinib for NMSC was estimated to be 2.33 with 95% CI [0.863, 6.28] including 1.0 (predicted from the MCAV model). The wider CI could have resulted from relatively fewer number of NMSC (N=11) in the UC program. The model-predicted Incidence Rates (IRs) with 90% CIs for placebo, tofacitinib 5 mg BID (Cavg _ 16.8 ng/mL), and tofacitinib 10 mg BID (Cavg _ 33.6 ng/mL) from the time-weighted average concentration (MCAV) model were 0.147 [0.0345, 0.623], 0.342 [0.145, 0.805], and 0.796 [0.484, 1.31], respectively.

Figure 15: Model Predicted Mean and 90% Prediction Intervals for NMSC (Left Panel: by MDOS, Right Panel: by MCAV)



Source: Figure 4 on page 23 of Applicant's clinical study report PMAR-EQDD-A392i-sNDA-514

Note: Model predictions and associated 90% prediction intervals are shown by solid black lines and the shaded area. Observed Incidence rates (IRs) in the left panel are calculated by binning MDOS (time-averaged dose) by [0-2.5), [2.5-7.5), [7.5-10), [10-15] (mg BID) and overlaid on the plot. The count for number of patients by MDOS is also shown as a histogram below the left panel. Right panel is created by binning MCAV (time-averaged Cavg) into quartiles and calculating the IRs for the respective quartiles. The distribution of MCAV values corresponding to 5 mg and 10 mg BID is shown as a horizontal box-plot below the right panel. The individual points in the boxplot are outliers, which fall below Q1 - 1.5 × IQR (Inter quartile range) or above Q3 + 1.5 × IQR.

Safety Laboratory Data: Visual inspection of ALT and AST concentrations suggested time and tofacitinib exposure dependent increases in liver enzymes. Simple linear models that included the effect of time and tofacitinib Cavg were developed to describe these relationships. For each (ALT and AST), a small, positive relationship between enzyme concentration and tofacitinib exposure was detected. The estimated mean difference [95% CI] from placebo in ALT was 1.86 IU/L [0.84, 2.88]

and 3.72 IU/L [1.68, 5.76] at steady-state Cavg corresponding to 5 and 10 mg BID doses, respectively. Similarly, the estimated mean difference from placebo in AST was 1.98 IU/L [1.21, 2.75] and 3.95 IU/L [2.41, 5.50] at steady-state Cavg corresponding to 5 and 10 mg BID doses, respectively.

Reviewer's Comments:
The reviewer generally agrees with the Applicant's exposure-response analysis for AE of special interest (serious infections, opportunistic infections, herpes zoster, and NMSC). An increased incidence rate of adverse events (opportunistic infections, herpes zoster and NMSC) was observed with increasing tofacitinib exposure. This trend is consistent with that observed in other development programs (RA, PSO).

The safety of 10 mg BID dose as maintenance treatment of UC patients was not sufficiently characterized due to the small safety database and high rate of discontinuation of therapy in the UC program. Treatment of UC with tofacitinib is associated with safety risks such as infections and malignancy. In the development program for UC, all patients received 10 mg BID or placebo for 8 weeks as induction treatment in Study 1094 and 1095 and patients who achieved clinical response were randomized to either placebo, 5 mg BID or 10 mg BID for additional 52-week treatment. This experimental design does not allow us to compare the risk of long-term treatment with 5 mg BID or 10 mg BID without the confounding effect of initial treatment at 10 mg BID for 8 weeks. Moreover, after completion of maintenance treatment, patients were rolled over to an open-label extension study (Study 1139) at 5 mg BID if they were remitters at the completion of maintenance treatment, or at 10 mg BID if non-remitters. In addition, patients who did not respond to the initial induction treatment were also enrolled to OLE and treated at 10 mg BID. Therefore, the E-R analysis for safety by dose level is confounded. However, the difference in the risk of 5 mg BID and 10 mg BID after induction was analyzed by the incidence of adverse events for all trials (cohort 3 population) based on post induction (Pind) doses.

A.4 Enrichment, Stratification, and/or Biomarker-based Assessment

Not applicable.

A.5. Mechanistic Safety Assessment

Not applicable.

Appendix B. Supplemental Efficacy Tables

Table 90: Secondary Efficacy Endpoint: Sustained Remission (Remission at Week 24 and Week 52) Among Patients in Remission at Baseline* (FAS)

	Placebo		Tofacitinib 5 mg BID			Tofacitinib 10 mg BID		
Visit	N1	n (%)	N1	n (%)	Difference from Placebo (95% CI)[a]	N1	n (%)	Difference from Placebo (95% CI)[a]
Both week 24 and 52	59	3 (5.1)	65	24 (36.9)	31.8 (18.8, 44.8)	55	26 (47.3)	42.2 (27.9, 56.5)

Source: Study 1096 CSR Table 14.2.5.1 (p. 707)

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

N1 = number of patients in the analysis set.

Table 91: Applicant's Sensitivity Analysis for Primary Efficacy Endpoint: Proportion of Patients in Remission at Week 52* (mFAS)

Placebo N=174 n (%)	Tofacitinib 5 mg BID N=176 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=173 n (%)	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
18 (10.3)	57 (32.4)	22.0 (13.8, 30.3)	<0.0001	71 (41.0)	30.7 (22.1, 39.3)	<0.0001

Source: Study 1096 CSR Table 22 (p. 109)

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by remission at baseline.

Table 92: Applicant's Sensitivity Analysis for Primary Efficacy Endpoint: Proportion of Patients in Remission at Week 52* (FAS and mFAS, Locally-Read Endoscopic Scores)

Pop-ulation	Placebo N=198 (FAS) N=174 (mFAS) n (%)	Tofacitinib 5 mg BID N=198 (FAS) N=176 (mFAS) n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=197 (FAS) N=173 (mFAS) n (%)	Difference from Placebo	
			Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
FAS	26 (13.1)	78 (39.4)	26.3 (18.0, 34.5)	<0.0001	94 (47.7)	34.6 (26.2, 43.0)	<0.0001
mFAS	19 (10.9)	68 (38.6)	27.7 (19.2, 36.3)	<0.0001	82 (47.4)	36.5 (27.7, 45.2)	<0.0001

Source: Study 1096 CSR Table 21 (p. 109), Table 22 (p. 109)

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment and remission at baseline for the FAS and by remission at baseline for the mFAS.

Table 93: Applicant's Sensitivity Analysis for Primary Efficacy Endpoint: Adjusted Estimates of Treatment Effects Based on GLMM (FAS, Observed Centrally Read Endoscopic Scores)

		Observed Data		Adjusted Estimates		Adjusted Difference from Placebo	
Visit	Treatment	N	n (%)	%	95% CI	Difference (95% CI)	P-value
Baseline	Tofacitinib 5 mg BID	198	65 (32.8)				
	Tofacitinib 10 mg BID	197	55 (27.9)				
	Placebo	198	59 (29.8)				
Week 52	Tofacitinib 5 mg BID	169	68 (40.2)	49.6	(39.6, 59.5)	(19.1, 41.9)	<0.0001
	Tofacitinib 10 mg BID	163	80 (49.1)	60.6	(50.9, 70.4)	(29.9, 53.2)	<0.0001
	Placebo	155	22 (14.2)	19.1	(11.0, 27.1)		

Source: Study 1096 CSR Table 14.2.2.6.2 (p. 503)

The adjusted estimates of treatment effects (population-averaged), p-values, and 95% CIs are obtained using a GLMM with treatment assignment in the induction study, remission at baseline, treatment group, visit, and treatment group by visit interaction as fixed effects, and patient as a random effect.

Table 94: Applicant's Sensitivity Analysis for Primary Efficacy Endpoint: Adjusted Estimates of Treatment Effects Based on GLMM (mFAS, Observed Centrally Read Endoscopic Scores)

		Observed Data		Adjusted Estimates		Adjusted Difference from Placebo	
Visit	Treatment	N	n (%)	%	95% CI	Difference (95% CI)	P-value
Baseline	Tofacitinib 5 mg BID	176	60 (34.1)				
	Tofacitinib 10 mg BID	173	53 (30.6)				
	Placebo	174	52 (29.9)				
Week 52	Tofacitinib 5 mg BID	150	57 (38.0)	40.4	(31.6, 49.1)	(16.2, 37.0)	<0.0001
	Tofacitinib 10 mg BID	144	71 (49.3)	54.0	(45.0, 63.0)	(29.0, 51.5)	<0.0001
	Placebo	141	18 (12.8)	13.8	(7.2, 20.3)		

Source: Study 1096 CSR Table 14.2.2.6.3 (p. 504)

The adjusted estimates of treatment effects (population-averaged), p-values, and 95% CIs are obtained using a GLMM with remission at baseline, treatment group, visit, and treatment group by visit interaction as fixed effects, and patient as a random effect.

Table 95: Applicant's Sensitivity Analysis for Primary Efficacy Endpoint: Proportion of Patients in Remission at Week 52 Based on Multiple Imputation Approach (FAS, mFAS)

		Tofacitinib 5 mg BID vs Placebo		Tofacitinib 10 mg BID vs Placebo	
Population	Method	Difference (95% CI)[a]	P-value	Difference (95% CI)[a]	P-value
FAS	Copy to Placebo	22.37 (13.7, 31.1)	<0.0001	28.70 (19.9, 37.5)	<0.0001
FAS	Copy to Tofacitinib 10 mg BID	19.95 (10.1, 29.8)	<0.0001	26.91 (17.1, 36.7)	<0.0001
mFAS	Copy to Placebo	21.56 (12.6, 30.5)	<0.0001	30.01 (20.8, 39.2)	<0.0001
mFAS	Copy to Tofacitinib 10 mg BID	20.06 (9.7, 30.4)	<0.0001	29.30 (19.0, 39.7)	<0.0001

Source: Study 1096 CSR Table 14.2.5.1.9 (p. 739), Table 14.2.5.1.10 (p. 740)

Copy to Placebo and Copy to Tofacitinib 10 mg BID assume all missing data had the same response as the observed proportion calculated based on non-missing data from the placebo group and from the tofacitinib 10 mg BID group, respectively. Differences are obtained by averaging the difference from 10 multiple imputation datasets.

[a] 95% CI was based on the normal approximation of the estimated differences.

Table 96: Applicant's Sensitivity Analysis for Primary Efficacy Endpoint: Proportion of Patients in Remission at Week 52 Based on Responder Imputation (FAS)

Method	Placebo N=198 n (%)	Tofacitinib 5 mg BID N=198 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=197 n (%)	Difference from Placebo	
			Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
Responder imputation	65 (32.8)	97 (49.0)	16.2 (6.6, 25.7)	0.0009	114 (57.9)	25.0 (15.5, 34.5)	<0.0001
Responder imputation for all patients except withdrawal due to insufficient clinical response	36 (18.2)	83 (41.9)	23.7 (15.0, 32.5)	<0.0001	99 (50.3)	32.1 (23.3, 40.9)	<0.0001

Source: Study 1096 CSR Table 14.2.5.1.5 (p. 735), Table 14.2.5.1.7 (p. 737)

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment and remission at baseline.

Table 97: Applicant's Sensitivity Analysis for Primary Efficacy Endpoint: Proportion of Patients in Remission at Week 52 Based on Responder Imputation (mFAS)

Method	Placebo N=174 n (%)	Tofacitinib 5 mg BID N=176 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=173 n (%)	Difference from Placebo	
			Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
Responder imputation	51 (29.3)	83 (47.2)	17.8 (7.8, 27.9)	0.0007	100 (57.8)	28.5 (18.5, 38.5)	<0.0001
Responder imputation for all patients except withdrawal due to insufficient clinical response	27 (15.5)	71 (40.3)	24.8 (15.8, 33.8)	<0.0001	88 (50.9)	35.3 (26.2, 44.5)	<0.0001

Source: Study 1096 CSR Table 14.2.5.1.6 (p. 736), Table 14.2.5.1.8 (p. 738)

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by remission at baseline.

Table 98: Applicant's Sensitivity Analysis for Primary Efficacy Endpoint: Proportion of Patients in Remission at Week 52* (PPAS)

Placebo N=188 n (%)	Tofacitinib 5 mg BID N=183 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=186 n (%)	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
22 (11.7)	66 (36.1)	24.4 (16.0, 32.7)	<0.0001	79 (42.5)	30.8 (22.3, 39.2)	<0.0001

Source: Study 1096 CSR Table 14.2.5.1.4 (p. 730)

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment and remission at baseline.

Table 99: Reviewer's Sensitivity Analysis for Primary Efficacy Endpoint: Proportion of Patients in Remission at Week 52* (FAS, Withdrawal Effect)

Placebo N=120 n (%)	Tofacitinib 5 mg BID N=164 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=166 n (%)	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
22 (18.3)	68 (41.5)	23.1 (12.9, 33.4)	<0.0001	80 (48.2)	29.9 (19.6, 40.1)	<0.0001

Source: Statistical reviewer's analysis, FAS

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment and remission at baseline.

Table 100: Applicant's Sensitivity Analysis for Key Secondary Efficacy Endpoint: Proportion of Patients with "Mucosal Healing" at Week 52* (mFAS)

Placebo N=174 n (%)	Tofacitinib 5 mg BID N=176 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=173 n (%)	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
22 (12.6)	63 (35.8)	23.2 (14.5, 31.8)	<0.0001	80 (46.2)	33.6 (24.7, 42.5)	<0.0001

Source: Study 1096 CSR Table 14.2.5.1.2 (p. 724)

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by remission at baseline.

Table 101: Applicant's Sensitivity Analysis for Key Secondary Efficacy Endpoint: Proportion of Patients in Sustained Steroid-Free Remission Among Patients in Remission at Baseline* (mFAS)

Placebo N=174 n (%)	Tofacitinib 5 mg BID N=176 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=173 n (%)	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
3 (5.8)	22 (36.7)	30.9 (17.2, 44.6)	<0.0001	25 (47.2)	41.4 (26.5, 56.3)	<0.0001

Source: Study 1096 CSR Table 14.2.5.1.2 (p. 726)

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test.

Table 102: Applicant's Sensitivity Analysis for Key Secondary Efficacy Endpoint: Proportion of Patients with "Mucosal Healing" at Week 52* (FAS and mFAS, Locally-Read Endoscopic Scores)

Pop-ulation	Placebo N=198 (FAS) N=174 (mFAS) n (%)	Tofacitinib 5 mg BID N=198 (FAS) N=176 (mFAS) n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=197 (FAS) N=173 (mFAS) n (%)	Difference from Placebo	
			Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
FAS	31 (15.7)	89 (44.9)	29.3 (20.7, 37.9)	<0.0001	106 (53.8)	38.2 (29.5, 46.8)	<0.0001
mFAS	24 (13.8)	79 (44.9)	31.1 (22.1, 40.1)	<0.0001	93 (53.8)	40.0 (30.9, 49.0)	<0.0001

Source: Study 1096 CSR Table 14.2.5.1.1 (p. 719), Table 14.2.5.1.3 (p. 728)

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment and remission at baseline for the FAS and by remission at baseline for the mFAS.

Table 103: Applicant's Sensitivity Analysis for Key Secondary Efficacy Endpoint: Proportion of Patients in Sustained Steroid-Free Remission Among Patients in Remission at Baseline* (FAS and mFAS, Locally-Read Endoscopic Scores)

Pop-ulation	Placebo N=59 (FAS) N=52 (mFAS) n (%)	Tofacitinib 5 mg BID N=65 (FAS) N=60 (mFAS) n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=55 (FAS) N=53 (mFAS) n (%)	Difference from Placebo	
			Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
FAS	7 (11.9)	31 (47.7)	35.8 (21.1, 50.5)	<0.0001	32 (58.2)	46.3 (30.9, 61.7)	<0.0001
mFAS	5 (9.6)	29 (48.3)	38.7 (23.7, 53.7)	<0.0001	30 (56.6)	47.0 (31.4, 62.6)	<0.0001

Source: Study 1096 CSR Table 14.2.5.1.1 (p. 720), Table 14.2.5.1.3 CSR (p. 729)

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment for the FAS.

Table 104: Reviewer's Sensitivity Analysis for Key Secondary Efficacy Endpoint: Proportion of Patients with "Mucosal Healing" at Week 52* (FAS, Withdrawal Effect)

Placebo N=120 n (%)	Tofacitinib 5 mg BID N=164 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=166 n (%)	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
26 (21.7)	74 (45.1)	23.4 (12.9, 34.1)	<0.0001	90 (54.2)	32.6 (22.0, 43.1)	<0.0001

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment and remission at baseline.

Table 105: Reviewer's Sensitivity Analysis for Key Secondary Efficacy Endpoint: Proportion of Patients in Sustained Steroid-Free Remission Among Patients in Remission at Baseline* (FAS, Withdrawal Effect)

Placebo N=120 n (%)	Tofacitinib 5 mg BID N=164 n (%)	Difference from Placebo		Tofacitinib 10 mg BID N=166 n (%)	Difference from Placebo	
		Difference (95% CI)[a]	P-value[b]		Difference (95% CI)[a]	P-value[b]
3 (7.7)	23 (40.4)	32.7 (17.4, 47.9)	0.0005	26 (54.2)	46.5 (30.1, 62.9)	<0.0001

*Analyzed with NRI for missing data

[a] 95% CI was based on the normal approximation for the difference in binomial proportions.

[b] P-value was based on CMH Chi-squared test stratified by induction study treatment assignment.

Appendix C. Supplemental Safety Tables

Table 106: Serious Adverse Events (SAEs) by SOC in Induction Studies (Cohort 1)

System Organ Classification (SOC)	Preferred Terms
Blood and lymphatic system disorders	Anemia
Cardiac disorders	Acute coronary syndrome
	Cardiac failure congestive
Gastrointestinal disorders	Abdominal pain
	Anal fistula
	Colitis ulcerative
	Gastrointestinal perforation
	Constipation
	Crohn's disease
	Diarrhea
	Intestinal perforation
	Proctalgia
	Vomiting
General disorders and administration site conditions	Asthenia
	Chills
	Malaise
Immune system disorders	Drug hypersensitivity

Infections and infestations	Anal abscess
	Cellulitis
	Clostridium difficile infection
	Febrile infection
	Furuncle
	Otitis externa
	Pneumonia
Injury, poisoning and procedural complications	Animal bite
	Femur fracture
	Hip fracture
	Joint injury
Metabolism and nutrition disorders	Dehydration
Musculoskeletal and connective tissue disorders	Arthralgia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Colon adenoma
	Colon neoplasm
Reproductive system and breast disorders	Vulva cyst
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism
Skin and subcutaneous tissue disorders	Drug eruption
Vascular disorders	Aortic dissection
	Hypertension
	Temporal arteritis

Source: Reviewer's Table, JReview v. 11.0

Table 107: Serious Adverse Events (SAEs) by SOC in Extension Therapy Cohort (IndNR 2 Months)

System Organ Classification (SOC)	Preferred Terms
Cardiac disorders	Pericarditis
Gastrointestinal disorders	Colitis ulcerative
	Gastrointestinal perforation
	Hemorrhoids
Infections and infestations	Gastroenteritis
	Pilonidal cyst
Injury, poisoning and procedural complications	Spinal compression fracture
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Epstein-Barr virus associated lymphoma
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous

Source: Reviewer's Table, JReview v. 11.0

Table 108: Maintenance Study (Cohort 2) Serious Adverse Events (SAEs) by SOC in Patients Who Received Tofacitinib 10 mg BID Treatment in the Induction Studies

SYSTEM ORGAN CLASS (SOC)	Placebo (N=167)	Tofacitinib 10 mg BID (N=167)	Tofacitinib 5 mg BID (N=170)	IndNR 12 Months (N=295)
Gastrointestinal disorders	9 (5.4%)	3 (1.8%)	3 (1.8%)	16 (5.4%)
Infections and infestations	2 (1.2%)	1 (0.6%)	2 (1.2%)	4 (1.4%)
Vascular disorders	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions	1 (0.6%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.0%)	1 (0.6%)	0 (0.0%)	2 (0.7%)
Cardiac disorders	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
Pregnancy, puerperium and perinatal conditions	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
Injury, poisoning and procedural complications	0 (0.0%)	1 (0.6%)	2 (1.2%)	2 (0.7%)
Hepatobiliary disorders	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	0 (0.0%)	1 (0.6%)	1 (0.6%)	0 (0.0%)
Skin and subcutaneous tissue disorders	0 (0.0%)	2 (1.2%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	0 (0.0%)	3 (1.8%)	0 (0.0%)	0 (0.0%)
Subtotal	12 (7.2%)	11 (6.6%)	10 (5.9%)	31 (10.5%)

Reviewer Table, JReview v. 11.0, Patient population in this table are from the maintenance and LTE study population who received Tofacitinib 10 mg BID treatment in the Induction Studies

Table 109: Listing of Adjudicated Malignancies (Excluding NMSC) in Cohort 3 Including Events with Onset as of 29 September 2017

Case Number	SSID in Study at Event Onset / Treatment Group at Event Onset	PD Treatment Group in Cohort 3	Induction Study SSID	Country	Age (Years)[a], Gender, Race	Preferred Term	Malignancy Classification	Prior TNFi / Prior AZA or 6-MP	Onset Day / Last Known Dose Day	Subject Action	Study Drug Action	Outcome
1	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	Australia	36, Female, White	Cervical dysplasia	Cervical cancer	No / Yes	610 / 624	LLETZ procedure performed	No action taken	Resolved
2	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	Italy	52, Male, White	Hepatic angiosarcoma	Soft tissue sarcoma	Yes / Yes	228 / 187	Patient previously withdrawn from the study for liver function tests elevation	Permanently discontinued	Subject died
3	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	United States	68, Male, White	Cholangiocarcinoma	Gallbladder and extrahepatic bile duct cancer	Yes / Yes	381 / 378	Discontinued study	Permanently discontinued	Subject died
	A3921139 (b) (6) / Tofacitinib 10 mg BID					Metastases to peritoneum	Cancer of the liver (excluding intrahepatic bile ducts)		381 / 378	No action	No action taken	Subject died
4	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	United States	81, Male, White	Leiomyosarcoma	Soft tissue sarcoma (cutaneous)	Yes / Yes	556 / 647	Surgical excision of lesion	Permanently discontinued	Resolved
5	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	United States	52, Male, White	Epstein-Barr virus associated lymphoma	Lymphoma / Non-Hodgkin lymphoma	Yes / Yes	104 / 98	No action	No action taken	Resolved

Table 109 - Continued from previous page (2/3)

Case Number	SSID in Study at Event Onset / Treatment Group at Event Onset	PD Treatment Group in Cohort 3	Induction Study SSID	Country	Age (Years)[a], Gender, Race	Preferred Term	Malignancy Classification	Prior TNFi / Prior AZA or 6-MP	Onset Day / Last Known Dose Day	Subject Action	Study Drug Action	Outcome
6	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	United States	62, male, white	Malignant melanoma	Melanoma / Melanoma of the skin	Yes / No	1345 / 1359	Treatment given, surgery on right finger, discontinued study	Permanently discontinued	Subject died
7	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	Canada	45, Female, White	Renal cell carcinoma	Renal cancer	Yes / Yes	323 / 285	Discontinued study	Permanently discontinued	Resolved
8	A3921139 (b) (6) / Tofacitinib 5 mg BID	PD 10 mg BID	A3921095 (b) (6)	Australia	73, male, white	Pulmonary mass	Lung cancer	No / Yes	695 / 663	Treatment given, discontinued study	Permanently discontinued	Still present
9	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921095 (b) (6)	Korea	43, female, Asian	Invasive ductal breast carcinoma	Breast cancer	No / Yes	705 / 711	Treatment given, surgery, discontinued study	Permanently discontinued	Still present
10	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921095 (b) (6)	Netherlands	32, male, white	Adenocarcinoma of colon	Colorectal cancer	Yes / Yes	745 / 778	Surgery, discontinued study	Permanently discontinued	Resolved
	A3921139 (b) (6) / Tofacitinib 10 mg BID					Metastases to liver	Colorectal cancer		745 / 778	Surgery / other	No action taken	Resolved
11	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921095 (b) (6)	Slovakia	29, Female, White	Essential thrombocythaemia	Myeloproliferative neoplasms	Yes / Yes	343 / 875	Discontinued study	Permanently discontinued	Still present

Table 109 - Continued from previous page (3/3)

Case Number	SSID in Study at Event Onset / Treatment Group at Event Onset	PD Treatment Group in Cohort 3	Induction Study SSID	Country	Age (Years)[a], Gender, Race	Preferred Term	Malignancy Classification	Prior TNFi / Prior AZA or 6-MP	Onset Day / Last Known Dose Day	Subject Action	Study Drug Action	Outcome
12	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921095 (b) (6)	United States	52, Male, White	Acute myeloid leukaemia	Acute myeloid leukemia (AML) and related precursor neoplasms	Yes / Yes	374 / 347	Treatment given	No action taken	Subject died
13	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921095 (b) (6)	Germany	47, Male, White	Adenocarci-noma of colon	Colorectal cancer	Yes / Yes	57 / 50	No action	No action taken	Resolved
14	A3921139 (b) (6) / Tofacitinib 5 mg BID	PD 5 mg BID	A3921095 (b) (6)	US	79, Female, White	Breast cancer	Malignant neoplasm of the breast	No / Yes	1476	Treatment given	Permanent-ly discontinued	Still present
15	A3921139 (b) (6) / Tofacitinib 5 mg BIDb	PD 10 mg BID	A3921094 (b) (6)	Austria	31, Female, White	Cervical dysplasia	Not available	Yes / No	755	Treatment given	No action taken	Resolved

Sources: Table 3 of response to FDA 26 September 2017 information request; Response to request #1 in FDA 31 January 2018 information request; A3921139 Table 14.1.1.3.3

Abbreviations: 4MSU = 4-month safety update; AE = adverse event; AZA = azathioprine; BID = twice daily; LLETZ = large loop excision of the transformation zone of the cervix; 6-MP = 6-mercaptopurine; NMSC = nonmelanoma skin cancer; P2P3LTE = Phase 2, Phase 3, long-term extension; PD = predominant dose; SSID = study subject identification; TNFi = tumor necrosis factor inhibitor.

Event onset day was determined by the Malignancy Adjudication Committee based on all available data related to the event.

a. At baseline of induction study.

b. Subject (b) (6) had an AE of cervical dysplasia but is under review by the Malignancy Adjudication Committee as of 01 March 2018. This event was included as a cervical dysplasia for analysis.

Source: Applicant's Table 7, received in response to FDA information request dated February 28, 2018 (received 3/7/18)

Table 110: Listing of Patients with Adjudicated Malignancies (Excluding NMSC) in Cohort 3 with Onset after 29 September 2017

SSID in Study at Event Onset / Treatment Group at Event Onset	PD Treatment Group in Cohort 3	Induction Study SSID	Country	Age (Years)[a], Gender, Race	Preferred Term	Malignancy Classification	Prior TNF Blockers / Prior AZA or 6-MP	Onset Day
A3921139 (b) (6) Tofacitinib 5 mg BID	PD 5 mg BID	A3921094 (b) (6)	Canada	54, Male, White	B-cell lymphoma	Lymphoma	Yes / No	Approximately 910
A3921139 (b) (6) Tofacitinib 5 mg BID	PD 5 mg BID	A3921094 (b) (6)	Serbia	54, Female, White	Breast cancer	Breast cancer	No / Yes	Approximately 1080

Sources: Applicant's table from IR response received 7 March 2018, A3921139 Table 14.1.1.3.3

Abbreviations: AZA = azathioprine; BID = twice daily; 6-MP = 6-mercaptopurine; P2P3LTE = Phase 2, Phase 3, long-term extension; PD = Predominant dose; SSID = study patient identification; TNF blockers = tumor necrosis factor inhibitor.

Event onset day was determined by the Malignancy Adjudication Committee based on all available data related to the event.

a. At baseline of induction study

Table 111: Listing of NMSC in Cohort 3 (P2P3LTE Tofacitinib) with Onset as of 29 September 2017

Case Number	SSID in Study at Event Onset / Treatment Group at in Study at Event Onset	PD Treatment Group in Cohort 3	Induction Study SSID	Country	Age (Years)[a], Gender, Race	Prior History of NMSC[a] / Prior AZA or 6-MP	Prior TNFi Treatment / Prior TNFi Failure	Malignancy Classification	Onset Day / Last Known Dose Day	Subject Action	Study Drug Action	Outcome
1	A3921139 (b) (6) / Tofacitinib 5 mg BID	PD 5 mg BID	A3921094 (b) (6)	Hungary	46, Female, White	No / Yes	Yes / Yes	Basal cell carcinoma	690 / 1115	Excision	No action taken	Resolved
2	A3921139 (b) (6) / Tofacitinib 5 mg BID	PD 5 mg BID	A3921094 (b) (6)	United States	70, Male, White	Yes / Yes	No / No	Basal cell carcinoma	609 / 975	No action	No action taken	Resolved
	A3921139 (b) (6) / Tofacitinib 5 mg BID							Cutaneous squamous cell carcinoma	609 / 975	Excision	No action taken	Resolved
	A3921139 (b) (6) / Tofacitinib 5 mg BID							Basal cell carcinoma	609 / 975	No action	No action taken	Resolved
	A3921139 (b) (6) / Tofacitinib 5 mg BID							Cutaneous squamous cell carcinoma	672 / 975	NAb	NAb	NAb
3	A3921096 (b) (6) / Tofacitinib 10 mg BID	PD 5 mg BID	A3921094 (b) (6)	United States	44, Female, White	Yes / Yes	Yes / Yes	Cutaneous squamous cell carcinoma	329 / 875	Excision	No action taken	Resolved
	A3921139 (b) (6) / Tofacitinib 5 mg BID							Basal cell carcinoma	511 / 875	Excision scheduled	No action taken	Resolved
	A3921139 (b) (6) / Tofacitinib 5 mg BID							Basal cell carcinoma	553 / 875	NAb	NAb	NAb

Table 111- continued from previous page (2/5)

Case Number	SSID in Study at Event Onset / Treatment Group at in Study at Event Onset	PD Treatment Group in Cohort 3	Induction Study SSID	Country	Age (Years)[a], Gender, Race	Prior History of NMSC[a] / Prior AZA or 6-MP	Prior TNFi Treatment / Prior TNFi Failure	Malignancy Classification	Onset Day / Last Known Dose Day	Subject Action	Study Drug Action	Outcome
	A3921139 (b) (6) / Tofacitinib 5 mg BID							Cutaneous squamous cell carcinoma	693 / 875	Excision	No action taken	Resolved
4	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	Australia	63, Female, Other (Middle Eastern)	No / No	Yes / Yes	Basal cell carcinoma	611 / 1414	Removal of BCC from forehead	No action taken	Resolved
5	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	Belgium	72, Male, White	No / Yes	Yes / Yes	Basal cell carcinoma	106 / 1063	NA	No action taken	Still present
	A3921139 (b) (6) / Tofacitinib 10 mg BID							Basal cell carcinoma	638 /1063	NA	No action taken	Still present
	A3921139 (b) (6) / Tofacitinib 10 mg BID							Basal cell carcinoma	730 / 1063	NA	No action taken	Still present
	A3921139 (b) (6) / Tofacitinib 10 mg BID							Basal cell carcinoma	884 /1063	NA	No action taken	Still present
6	A3921096 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	France	64, Male, ---	Yes / Yes	Yes / Yes	Cutaneous squamous cell carcinoma	263 / 295	Excision	No action taken	Resolved
7	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	United States	67, Male, White	Yes / Yes	Yes / Yes	Basal cell carcinoma	580 / 1246	No action	No action taken	Resolved

Table 111 – continued from previous page (3/5)

Case Number	SSID in Study at Event Onset / Treatment Group at in Study at Event Onset	PD Treatment Group in Cohort 3	Induction Study SSID	Country	Age (Years)[a], Gender, Race	Prior History of NMSC[a] / Prior AZA or 6-MP	Prior TNFi Treatment / Prior TNFi Failure	Malignancy Classification	Onset Day / Last Known Dose Day	Subject Action	Study Drug Action	Outcome
8	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	United States	64, Male, White	No / Yes	Yes / Yes	Cutaneous squamous cell carcinoma	75 /456	NAb	NAb	NAb
	A3921139 (b) (6) / Tofacitinib 10 mg BID							Cutaneous squamous cell carcinoma	64 / 456	Excision	No action taken	Resolved
	A3921139 (b) (6) / Tofacitinib 10 mg BID							Cutaneous squamous cell carcinoma	64 / 456	Excision	No action taken	Resolved
9	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	United States	65, Male, White	Yes / Yes	Yes / Yes	Cutaneous squamous cell carcinoma	515 / 1408	Excision	No action taken	Resolved
	A3921139 (b) (6) / Tofacitinib 10 mg BID							Cutaneous squamous cell carcinoma	1058 / 1408	Excision	No action taken	Resolved
	A3921139 (b) (6) / Tofacitinib 10 mg BID							Cutaneous squamous cell carcinoma	1062 / 1408	Excision	No action taken	Resolved
10	A3921094 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	United States	63, Male, White	Yes / Yes	Yes / Yes	Cutaneous squamous cell carcinoma	52 / 1450	Excision	No action taken	Resolved
11	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921094 (b) (6)	United States	58, Male, White	No / Yes	Yes / Yes	Basal cell carcinoma	1311 / 1593	Treatment given	No action taken	Resolved

Table 111 – continued from previous page (4/5)

Case Number	SSID in Study at Event Onset / Treatment Group at in Study at Event Onset	PD Treatment Group in Cohort 3	Induction Study SSID	Country	Age (Years)[a], Gender, Race	Prior History of NMSC[a] / Prior AZA or 6-MP	Prior TNFi Treatment / Prior TNFi Failure	Malignancy Classification	Onset Day / Last Known Dose Day	Subject Action	Study Drug Action	Outcome
12	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921095 (b) (6)	Australia	48, male, white	No / Yes	No / No	Cutaneous squamous cell carcinoma	621 / 854	Excision	No action taken	Resolved
13	A3921096 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921095 (b) (6)	United States	76, Male, White	Yes / Yes	Yes / Yes	Basal cell carcinoma	412 / 1604	Excision	No action taken	Still present
	A3921139 (b) (6) / Tofacitinib 10 mg BID							Basal cell carcinoma	454 / 1604	NAb	NAb	NAb
	A3921139 (b) (6) / Tofacitinib 10 mg BID							Cutaneous squamous cell carcinoma	924 / 1604	Excision	No action taken	Resolved
	A3921139 (b) (6) / Tofacitinib 10 mg BID							Cutaneous squamous cell carcinoma	888 / 1604	Excision	No action taken	Resolved
14	A3921139 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921095 (b) (6)	United States	46, Female, White	No / Yes	Yes / Yes	Cutaneous squamous cell carcinoma	569 / 1145	Shaved and treatment given	No action taken	Resolved
15	A3921095 (b) (6) / Tofacitinib 10 mg BID	PD 10 mg BID	A3921095 (b) (6)	Hungary	66, Male, White	No / Yes	Yes / Yes	Basal cell carcinoma	16 / 73	Excision	No action taken	Resolved
16	A3921139 (b) (6) / Tofacitinib 5 mg BID	PD 5 mg BID	A3921095 (b) (6)	United States	54, Female, White	No / No	No / No	Basal cell carcinoma	Approximately 1408 / Not available	Excision	No action taken	Resolved

Table 111 – continued from previous page (5/5)

Case Number	SSID in Study at Event Onset / Treatment Group at in Study at Event Onset	PD Treatment Group in Cohort 3	Induction Study SSID	Country	Age (Years)[a], Gender, Race	Prior History of NMSC[a] / Prior AZA or 6-MP	Prior TNFi Treatment / Prior TNFi Failure	Malignancy Classification	Onset Day / Last Known Dose Day	Subject Action	Study Drug Action	Outcome
17	A3921139 (b) (6) / Tofacitinib 10 mg BIDc	PD 10 mg BID	A3921095 (b) (6)	Netherlands	67, Male, White	No / Yes	Yes / Yes	Not available	Approximately 1027 / Not available	Treatment given	No action taken	Still present

Sources: Table 6 of response to FDA 26 September 2017 information request; Response to request #1 in FDA 31 January 2018 information request; A3921139 Table 14.1.1.3.3

Abbreviations: AZA = azathioprine; BID = twice daily; 6-MP = 6-mercaptopurine; NA = not applicable; NMSC = nonmelanoma skin cancer; P2P3LTE = Phase 2, Phase 3, long-term extension; PD = predominant dose; SSID = study subject identification; TNFi = tumor necrosis factor inhibitor.

a. At baseline of induction study.

b. There were no AEs corresponding to these entries. The onset days corresponded to biopsies or excisions.

c. Subject (b) (6) had an AE of Bowen's disease that is under review by the Malignancy Adjudication Committee as of 01 March 2018. This event was included as a cutaneous squamous cell carcinoma for analysis.

Analysis of NMSC data was based on the malignancy classification reported by the Malignancy Adjudication Committee.

Three (3) subjects in the Tofacitinib All group reported both basal cell carcinoma and squamous cell carcinoma event terms.

Source: Table 8, Applicant's response to information request, received 3/7/18; A3921139 Table 14.1.1.3.3

Table 112: Effect of the TNF blocker Failure Subgroup on Incidence Rates of Adverse Events of Special Interest in the Tofacitinib Treatment Groups in the Maintenance Study and the IndNR Subgroup

	Cohort 2 Tofacitinib 5 mg BID				Cohort 2 Tofacitinib 10 mg BID				IndNR Subgroup Tofacitinib 10 mg BID			
AEs of Special Interest	Non-TNFi failure N = 115 Exposure = 89.2 PY		TNFi failure N = 83 Exposure = 57.0 PY		Non-TNFi failure N = 104 Exposure = 83.6 PY		TNFi failure N = 92 Exposure = 70.6 PY		Non-TNFi failure N = 168 Exposure = 124.4 PY		TNFi failure N = 261 Exposure = 160.7 PY	
	n	IR (95% CI)	n	IR (95% CI)	n	IR (95% CI)	n	IR (95% CI)	n	IR (95% CI)	n	IR (95% CI)
Serious infection	0	0.00 (0.00, 4.07)	2	3.46 (0.42, 12.49)	0	0.00 (0.00, 4.32)	1	1.39 (0.04, 7.76)	3	2.32 (0.48, 6.77)	2	1.16 (0.14, 4.20)
Opportunistic infection	1	1.11 (0.03, 6.21)	1	1.75 (0.04, 9.74)	1	1.18 (0.03, 6.56)	3	4.35 (0.90, 12.70)	2	1.54 (0.19, 5.55)	1	0.58 (0.01, 3.23)
Non-herpes zoster OI	0	0.00 (0.00, 4.07)	0	0.00 (0.00, 6.34)	0	0.00 (0.00, 4.32)	0	0.00 (0.00, 5.13)	1	0.77 (0.02, 4.27)	0	0.00 (0.00, 2.13)
Herpes zoster (all)	1	1.11 (0.03, 6.21)	2	3.55 (0.43, 12.83)	1	1.18 (0.03, 6.56)	9	13.74 (6.28, 26.08)	5	3.92 (1.27, 9.14)	6	3.52 (1.29, 7.66)
Malignancy (excluding NMSC)	0	0.00 (0.00, 4.07)	0	0.00 (0.00, 6.34)	0	0.00 (0.00, 4.32)	0	0.00 (0.00, 5.13)	0	0.00 (0.00, 2.82)	2	1.16 (0.14, 4.18)
NMSC	0	0.00 (0.00, 4.07)	0	0.00 (0.00, 6.34)	0	0.00 (0.00, 4.32)	3	4.20 (0.87, 12.28)	0	0.00 (0.00, 2.82)	0	0.00 (0.00, 2.13)
MACE	1	1.11 (0.03, 6.21)	0	0.00 (0.00, 6.34)	1	1.17 (0.03, 6.53)	0	0.00 (0.00, 5.13)	0	0.00 (0.00, 2.82)	0	0.00 (0.00, 2.13)
GI perforation (revised definition)	0	0.00 (0.00, 4.07)	0	0.00 (0.00, 6.34)	0	0.00 (0.00, 4.32)	0	0.00 (0.00, 5.13)	0	0.00 (0.00, 2.82)	1	0.58 (0.01, 3.22)

Source: table from Applicant's SCS, submitted 04 May 2017, pg 280/292

Table 113: Cohort 3 Incidence of Liver Enzyme Parameters (Multiples of ULN)

Parameter	Criteria	PD Tofacitinib 10 mg BID (n=971)	PD Tofacitinib 5 mg BID (n=186)	Tofacitinib All (n=1157)
		n (%)	n (%)	n (%)
ALT	≥ 1 x ULN	282 (29.0%)	47 (25.3%)	329 (28.4%)
	≥ 2 x ULN	57 (5.9%)	12 (6.5%)	69 (6.0%)
	≥ 3 x ULN	22 (2.3%)	4 (2.2%)	26 (2.2%)
	≥ 5 x ULN	4 (0.4%)	0 (0.0%)	4 (0.3%)
	≥ 10 x ULN	1 (0.1%)	0 (0.0%)	1 (0.1%)
AST	≥ 1 x ULN	200 (20.8%)	48 (25.8%)	248 (21.4%)
	≥ 2 x ULN	37 (3.8%)	10 (5.4%)	47 (4.0%)
	≥ 3 x ULN	16 (1.6%)	2 (1.1%)	18 (1.5%)
	≥ 5 x ULN	10 (1.0%)	0 (0.0%)	10 (0.8%)
	≥ 10 x ULN	2 (0.2%)	0 (0.0%)	2 (0.2%)
Total bilirubin	≥ 1 x ULN	98 (10.1%)	28 (15.1%)	126 (10.9%)
	≥ 2 x ULN	15 (1.5%)	6 (3.2%)	21 (1.8%)
	≥ 3 x ULN	2 (0.2%)	1 (0.5%)	3 (0.3%)
	≥ 5 x ULN	2 (0.2%)	0 (0.0%)	2 (0.2%)

Source: Reviewer's table. JReview v.11.0. Note: A patient can contribute to multiple rows per lab result.
Only post-baseline data are summarized in the table.

Appendix D. Relevant Clinical Narratives

D.1. Narratives of Deaths in UC Program

(1) Patient ID: A3921139 (b) (6) *Hepatic Angiosarcoma*

A 52-year-old white male patient from Italy died in the LTE Study 1139 due to hepatic angiosarcoma. This patient received tofacitinib 10 mg BID in the induction Study 1094 for 64 days, then received placebo in the maintenance Study 1096 for 180 days, and subsequently entered the LTE Study 1139 to receive tofacitinib 10 mg BID. The patient had relevant past medical history of visceral leishmaniasis. On Day 120 in Study 1139, the patient developed hepatic angiosarcoma. Tofacitinib was discontinued on Day 123 of Study 1139 (total duration of tofacitinib treatment 187 days). On Day 164, the patient underwent a repeat liver biopsy and developed persistent bleeding after the liver biopsy. The patient died on Day 168 of Study 1139. The investigator considered the AE of hepatic angiosarcoma related to the study drug. The Applicant considered the event hepatic angiosarcoma possibly related to medical history of visceral leishmaniasis and considered the study drug to play a contributory role in the development of hepatic angiosarcoma.

(2) Patient ID: A3921094 (b) (6) *Aortic Dissection*

This 39-year-old male from Ukraine died while participating in the induction Study 1094 due to dissecting aortic aneurysm. This patient received tofacitinib 10 mg BID in the induction Study 1094. The patient had no relevant past medical history or known risk factors for aortic dissection. No AEs related to increased blood pressure and no elevated blood pressures of potential clinical concern were reported in Study 1094. The patient developed the SAE of dissecting aortic aneurysm on Day 25 of Study 1094, and died on Day 31, the last day of tofacitinib dosing. The autopsy confirmed aortic aneurysm dissection and cardiac tamponade, and the SAE and resulting death were considered unrelated to the study treatment by the investigator and the Applicant. The event of dissecting aortic aneurysm was confirmed by adjudication cardiovascular committee as meeting the criteria as a major adverse cardiovascular event (MACE). According to the Applicant, the event dissecting aortic aneurysm was not related to the study drug, concomitant medication or clinical trial procedure.

(3) *Patient ID: A3921139* (b) (6) *Acute Myeloid Leukemia*

A 52-year-old white male patient from the United States died in the LTE Study 1139 due to AML. This patient received tofacitinib 10 mg BID in the induction Study 1095 for 64 days, then received placebo in the maintenance Study 1096 for 112 days, and subsequently entered the LTE Study 1139 to receive tofacitinib 10 mg BID. On Day 267 the patient developed leukopenia and neutropenia. Tofacitinib was discontinued on Day 283 of Study 1139 (total duration of tofacitinib treatment was 347 days). On Day 310 of Study 1139 (post-therapy Day 27), the patient was diagnosed with AML based upon bone marrow biopsy. The patient died on Day 334 of Study 1139. The investigator and the Applicant considered the AE of AML not related to the study drug.

(4) *Patient ID: A3921139* (b) (6) *Pulmonary Embolism; Cholangiocarcinoma, Peritoneum Metastasis*

A 68-year-old white male patient from the United States died in the LTE Study 1139 due to pulmonary embolism. This patient received tofacitinib 15 mg BID in the induction Study 1094 for 64 days, then received placebo in the maintenance Study 1096 for 175 days, and subsequently entered the LTE Study 1139 to receive tofacitinib 10 mg BID. The patient had no known history of primary sclerosing cholangitis. On Day 368 of Study 1139, the patient was diagnosed with cholangiocarcinoma. Tofacitinib was discontinued on Day 378 of Study 1139. On Day 383 of Study 1139, the patient was found to have metastases to peritoneum and experienced pulmonary embolism. The patient died on Day 384 of Study 1139. The event onset was adjudicated by the Malignancy Adjudication Committee (MAC) to be Day 381 of cumulative tofacitinib exposure. The investigator and the Applicant considered the AEs of cholangiocarcinoma and metastases to peritoneum related to the study drug, but considered the event pulmonary embolism unrelated to the study drug.

(5) *Patient ID: A3921139* (b) (6) *Malignant Melanoma (Metastatic)*

This 62-year-old male, with a history of basal cell carcinoma, received placebo in the induction Study 1094 and then enrolled directly in the LTE Study 1139 to receive tofacitinib 10 mg BID. The patient developed cutaneous melanoma of the right index finger while receiving tofacitinib 10 mg BID, which was discontinued on Day 1359 and the patient withdrew from the study on Day 1377. On (b) (6) (b) (6) (Study Day 1345 of Study 1139), the patient had biopsy of lesion on right index finger which came back as "malignant melanoma". Study drug was permanently discontinued in response to the

event on (b) (6) (Study Day 1359). On (b) (6) (Study Day 1361), the patient had excision of his right index fingertip, and the biopsy revealed "invasive malignant melanoma". In October 2016, the patient had a PET scan which revealed tumors in lungs, brain, and colon. As of November 1, 2016, the event cutaneous melanoma was under review by the Malignancy Adjudication Committee (MAC). Death occurred approximately 5 months after the last dose of tofacitinib due to multi-organ failure secondary to cancer. No autopsy was performed.

D.2. Narrative of Potential MACE Case (not adjudicated as MACE)

Patient A3921139 (b) (6) *Ischemic Stroke*

> This was a 49-year-old male with a history of hypertension and vertebral algic syndrome, who on Study Day 621 experienced the event of ischemic stroke and was hospitalized on the same day. The investigator considered the event to be mild in severity. No action was taken with the study drug in response to ischemic stroke. The patient was discharged from hospital on (b) (6) (Study Day 623), and the patient received paynocil for the prevention of ischemic stroke. The event was ongoing at the time of last report. Relevant AEs included facial paresis (starting Study Day 621) of mild severity, facial paralysis (Study Day 621 to Study Day 799) of mild severity.

In the opinion of the investigator, ischemic stroke was related to the study medication but not related to a clinical trial procedure or concomitant medication. Per the Applicant, there was not a reasonable possibility that the event of ischemic stroke was related to study drug or clinical trial procedure, but more likely represented an intercurrent illness relating to underlying hypertension.

Appendix E. Financial Disclosure/Good Clinical Practice

The Applicant certified that all clinical investigations comprising the tofacitinib UC clinical development program were performed in compliance with the principles of the Declaration of Helsinki, and in compliance with the US FDA regulations for informed consent and protection of patient rights as described in 21 CFR 50, 56, and 312.

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for tofacitinib.

Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were Trials 1063, 1094, 1095, 1096 and Study 1139 which provided the primary data to establish effectiveness and safety of this product. See **Table 114** for further details.

Table 114: Financial Disclosure for Covered Clinical Studies

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 9,996		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 5		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 240		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: ___ Significant payments of other sorts: 240 Proprietary interest in the product tested held by investigator: ___ Significant equity interest held by investigator in S Applicant of covered study: ___		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 34		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Of the total 9,996 investigators, the Applicant states that 9,722 had no financial information to disclose. Five investigators were full-time or part-time employees. Due diligence was required on 34 of the 9,996 investigators. Of the total number of investigators, 240 (2.4%) had financial information to disclose. Some investigators participated in more than one study, and multiple financial disclosure forms may have been collected for one investigator. The Applicant has adequately disclosed financial interests and/or arrangements with clinical investigators by having submitted a signed Form FDA 3454. The Applicant's justification (Form 3455) is reasonable.

Appendix F. Signature Pages

Designated Signatory Authority - Associate Division Director, DGIEP

I concur with the recommendation of the review team to approve XELJANZ (tofacitinib) for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). Tofacitinib will be the first oral product to be approved for chronic use in this indication. The recommended dosage is 10 mg twice daily for at least 8 weeks, followed by 5 mg or 10 mg twice daily. Data submitted in the supplemental NDA support the conclusion that the benefits of treatment with tofacitinib in the intended population outweigh the identified risks. The adequacy of submitted data was also discussed at a Gastrointestinal Drugs Advisory Committee (GIDAC) meeting during the review cycle, and the Committee unanimously recommended inclusion of a dosing option to continue 10 mg twice daily in patients who may benefit from extended treatment with the higher dose. However, treatment with tofacitinib should be discontinued after 16 weeks if adequate therapeutic benefit is not achieved, and the lowest effective dose should be used to maintain response.

The risks associated with tofacitinib treatment in UC are generally comparable to those associated with other potent immunosuppressive and biologic therapies currently used to treat this condition. Product labeling with a boxed warning and a Medication Guide will adequately communicate these benefits and risks to healthcare providers and patients, respectively. A REMS will not be required. Post-marketing required studies will assess: 1) the long-term safety of tofacitinib, including but are not limited to, malignancy, opportunistic infections, thromboembolic events, and hepatic injury; 2) the safety, efficacy and pharmacokinetics of tofacitinib in pediatric patients 2 to 17 years of age with moderately to severely active UC; and 3) the long-term safety of tofacitinib in these pediatric patients. In addition, the Applicant will assess the relative efficacy of tofacitinib 5 mg BID versus 10 mg BD for maintaining remission in patients who are in stable remission for at least 6 months on 10 mg BID therapy, and clinical and immunological responses to Shingrix vaccination in adult patients with UC treated with tofacitinib, as post-marketing commitment studies.

Jessica J Lee, MD
Associate Director, DGIEP

Multidisciplinary Review Team Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Regulatory Affairs/ Project Management	Kelly Richards	OND/ODEIII/DGIEP	**Sections: All**	**Select up to two:** ☐Authored ☒ Acknowledged ☐Cleared
	Signature: Kelly D. Richards -S	Digitally signed by Kelly D. Richards -S DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=0011049090, cn=Kelly D. Richards -S Date: 2018.05.29 17:47:34 -04'00'		
Division Signatory	Jessica J. Lee	OND/ODEIII/DGIEP	**Sections: All**	**Select up to two:** ☐Authored ☐Acknowledged ☒Cleared
	Signature: Jessica J. Lee -S	Digitally signed by Jessica J. Lee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica J. Lee -S, 0.9.2342.19200300.100.1.1=2000596373 Date: 2018.05.29 20:48:39 -04'00'		
Clinical Team Leader	Tara Altepeter	OND/ODEIII/DGIEP	**Sections: authored 1, Reviewed/cleared all**	**Select up to two:** ☒Authored ☐Acknowledged ☒Cleared
	Signature: Tara Altepeter -S	Digitally signed by Tara Altepeter -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tara Altepeter -S, 0.9.2342.19200300.100.1.1=2001813963 Date: 2018.05.29 16:19:57 -04'00'		
Clinical Reviewer	Lesley S. Hanes	OND/ODEIII/DGIEP	**Sections: Authored Sections 2, 3, 4, 6.1, 6.5.3, 6.6.2, 6.6.3, 6.8.3, Section 7, 8, 9, 11, 12, 13, Appendix C, D, E; Acknowledged all**	**Select up to two:** ☒Authored ☒Acknowledged ☐Cleared
	Signature: Lesley A. Hanes -S	Digitally signed by Lesley A. Hanes -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001672394, cn=Lesley A. Hanes -S Date: 2018.05.29 16:13:27 -04'00'		

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Clinical Pharmacology Reviewer	Dilara Jappar	OTS/OCP/DCPIII	**Sections: 5** **Appendix A**	**Select up to two:** ☒Authored ☐ Acknowledged ☐Cleared
	Signature: Dilara Jappar -S Digitally signed by Dilara Jappar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Dilara Jappar -S, 0.9.2342.19200300.100.1.1=2000371317 Date: 2018.05.29 16:27:19 -04'00'			
Clinical Pharmacology Team Leader	Insook Kim	OTS/OCP/DCPIII	**Sections 5** **Appendix A**	**Select up to two:** ☒Authored ☐Acknowledged ☒Cleared
	Signature: Insook Kim -S Digitally signed by Insook Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Insook Kim -S, 0.9.2342.19200300.100.1.1=1300416436 Date: 2018.05.29 15:54:47 -04'00'			
Pharmacometrics Reviewer	Fang Li	OTS/OCP/DPM	**Sections 5** **Appendix A**	**Select up to two:** ☒Authored ☐Acknowledged ☐Cleared
	Signature: Fang Li -S Digitally signed by Fang Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Fang Li -S, 0.9.2342.19200300.100.1.1=1300430137 Date: 2018.05.29 16:02:15 -04'00'			
Division Director	Yaning Wang	OTS/OCP/DPM	**Sections 5** **Appendix A**	**Select up to two:** ☐Authored ☐Acknowledged ☒Cleared
	Signature: Yaning Wang -S Digitally signed by Yaning Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yaning Wang -S, 0.9.2342.19200300.100.1.1=1300220171 Date: 2018.05.29 17:04:34 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Division Director (Acting)	Jingyu Luan	OTS/OB/DBIII	**Sections: 6, 8**	**Select up to two:** ☐Authored ☐ Acknowledged ☒Cleared
	Signature: Jingyu J. Luan -S Digitally signed by Jingyu J. Luan -S Date: 2018.05.29 15:40:18 -04'00'			
Statistical Reviewer	Sara Jimenez	OTS/OB/DBIII	**Sections: 6, 8**	**Select up to two:** ☒Authored ☐Acknowledged ☐Cleared
	Signature: Sara Jimenez -S Digitally signed by Sara Jimenez -S Date: 2018.05.29 15:04:44 -04'00'			
Statistical Team Leader	Yeh-Fong Chen	OTS/OB/DBIII	**Sections: 6,8**	**Select up to two:** ☒Authored ☐Acknowledged ☒Cleared
	Signature: Yehfong Chen -S Digitally signed by Yehfong Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yehfong Chen -S, 0.9.2342.19200300.100.1.1=1300157970 Date: 2018.05.29 15:15:45 -04'00'			
			Sections:	**Select up to two:** ☐Authored ☐Acknowledged ☐Cleared
	Signature:			

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/s/

JESSICA J LEE
05/29/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s018

STATISTICAL REVIEW(S)

Re: **The Division of Epidemiology II's assessment of the evidence for differences in risks for adverse events of special interest (AESIs) by tofacitinib dose**
Date: **January 22, 2018**
From: **Jessica Kim, Clara Kim (TL), Division of Biometrics 7**
NDA #: **SNDA 203214**
Name of drug: **tofacitinib (Xeljanz®)**
Classification of drug: **An orally administered inhibitor of Janus kinases under consideration for approval for ulcerative colitis**

This memo is in response to the consult request from the Division of Epidemiology II (DEPI-II) for the Division of Biometrics VII. DEPI conducted a nested case-control study using data from tofacitinib clinical trials to assess the risk of adverse events of special interest (AESI) in patients with ulcerative colitis by tofacitinib dose to support the Division of Gastroenterology and Inborn Error Product in preparation of the March 8th advisory committee meeting. DEPI requested DB7 to provide statistical input on the methods, assumptions, and identify fundamental flaws or major violations of the nested case-control study. DEPI provided four specific questions they shared via e-mails (see below).

The four questions are listed below followed by DB7's responses.

1. Use of PHREG to generate odds ratios and 95% Cis

DB7: Procedure PHREG can be used for both Cox regression for survival data and conditional logistic regression for matched case-control studies. Hence, the use of PHREG to generate odds ratios and corresponding 95% confidence intervals is acceptable.

2. Any concerns with "the robust sandwich method specified for estimating the covariance matrix"?

DB7: The use of the robust sandwich method for estimating the covariance matrix is a commonly accepted procedure. This reviewer does not have any concerns on this matter.

3. The review states that "Each risk set included only patients followed event free over an at-risk period matching *or exceeding follow-up time in the indexed case*." For risk set sampling, should the follow-up period be the same across cases and controls because we are matching on study time? The discussion states "Incidence density sampling individually matches controls to cases on time at risk."

DB7: The description, "or exceeding follow-up time in the indexed case" should not be explicitly stated in the definition of a risk set of the incidence density sampling method. In general, a risk set of an incidence density sampling is defined as a set of subjects who could have developed the case, but did not at the time when a case occurred. For incidence density sampling (or risk set sampling), the follow-up period will be the same for cases and time-matched controls.

4. Any comment on the following statements:
    a. "Therefore, DEPI interpreted case-control differences in average post-induction dose as representations of case-control differences in cumulative post-induction dose."

DB7: DEPI determined (1) dose on AESI index date, (2) maximum dose between first post-induction exposure and AESI index date, and (3) average post-induction dose between first post-induction exposure and AESI index date for a case-control study. They also define, "cumulative dose equals the product of average dose and time at risk." However, it is not clear 1) how the "average post-induction dose" is calculated and 2) whether the case-control study objective is to identify the cause of the AESI risk by using cumulative-dose instead of the received dose (e.g., 5 mg or 10mg).

b. "Conditional logistic regression, separately adjusting for immunosuppressant treatment history, TNFα treatment history, and maintenance trial participation, moderated this ANY AESI risk, estimated after adjustment at OR 1.47 (95% CI 0.83-2.62), 1.50 (95% CI 0.85-2.66), 1.45 (95% CI 0.78-2.70), respectively." Should multivariate adjustments be conducted, assuming sample size would be an issue?

DB7: If there are not enough number of events for each additional variable, multivariable adjustment might cause overfitting, which will yield unreliable confidence intervals. Whether to adjust the three variables separately or under a single model depends on the clinical interest of the considered variables, which should be determined prior to the conduct of the study. There is no to little statistical meaning to conduct exploratory analysis with separate adjustment or multivariate adjustment. The adjusted OR estimated separately using conditional logistic regression is reasonable.

c. "Finally, DEPI violated new-user principles to form a post-induction cohort for nested case-control analysis."

DB7: It is not clear whether "new-user principle" is applicable to this situation where the inception cohort was defined using the non-missing baseline Mayo scores and exposure to tofacitinib post induction. Since the original study was a randomized withdrawal design, the patients at the post induction had already been exposed to either to 10mg dose or placebo. Responders were, then, randomized to either 10mg or 5 mg at the maintenance stage. A nested case-control analysis from a considered post-induction cohort can be conducted but needs a detailed description of the analysis population with respect to the entry criteria of the inception cohort: baseline Mayo scores and exposure status.

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/s/

JEONGSOOK L KIM
02/01/2018

CLARA KIM
02/01/2018

STATISTICAL REVIEW AND EVALUATION

SAFETY RESPONSES TO FDA INFORMATION REQUEST

NDA/SN:	sNDA203214/SN 018
Drug Name:	Xeljanz (tofacitinib)
Indication(s):	Treatment of ulcerative colitis
Applicant:	Pfizer
Date(s):	October 20, 2017 (consult date) December 6, 2017 (completion date)
Safety Outcome(s):	Malignancy, nonmelanoma skin cancer
Item Reviewed:	Safety response to FDA information request (September 26, 2017)
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Jessica (Jeongsook) Kim, Ph.D.
Concurring Reviewers:	Clara Kim, Ph.D., Team Lead
Consulting Division:	CDER/OND/ODEIII/DGIEP
Consulting Team:	Lesley Hanes, M.D. Tara Altepeter, M.D. (Team Lead)
Project Manager:	Kelly Richards
Keywords:	Malignancy, Ulcerative Colitis

This review is in response to the Division of Gastroenterology and Inborn Errors Products' consult request for the Division of Biometrics VII to review the sponsor's (Pfizer) response to the clinical (safety) FDA information request (IR) dated September 26, 2017.This review states the FDA's request, summary of the sponsor's response, followed by this reviewer's comments in bolded italic.

FDA Clinical Request 1
Currently, we are aware of 13 adjudicated cases of patients with malignancies (excluding NMSC) in the entire Tofacitinib UC program. We request that you confirm the number, patient IDs, and updated narratives of adjudicated cases of malignancies (excluding NMSC) in the entire Tofacitinib UC program, to date as of 9/22/17. In addition:

a. Provide information on new, adjudicated cases of malignancies (excluding NMSC) that have not been reported to the Division. Accordingly, provide an update to the following tables of the 2.7.4. Summary of Clinical Safety (SCS):
b. Table 31: Proportions and Incidence Rates of Malignancies (excluding NMSC) in Cohort 3 (P2P#LTE Tofacitinib), page 107/292.
c. Table 32: Listing of Subjects with Adjudicated Malignancies (excluding NMSC) in Cohort 3 (P2P3LTE Tofacitinib), pages 110-111/292.

Sponsor's Response
The sponsor updated their database by a new cutoff date of September 29, 2017, including all malignancies (excluding nonmelanoma skin cancer [NMSC]) adjudicated by the Malignancy Adjudication Committee (MAC).

The sponsor updated proportions and incidence rates (IRs) of malignancies (excluding NMSC) in Table 1, and compared to those of the 120-day safety update report in Table 2. They also provided a listing of subjects with malignancies (excluding NMSC), including study subject identification, malignancy classification, preferred term (PT) and other relevant information.

Response to Sub-part a.
The two subjects in Cohort 3 with adjudicated malignancies (excluding NMSC) after December 16, 2016 were the same two subjects with potential malignancies that were under review by the MAC:

- Melanoma/ Melanoma of the skin (PT Malignant melanoma) in subject A3921094 (b) (6)
- Colorectal cancer (PT adenocarcinoma of colon) in subject A3921095 (b) (6)

Response to Sub-part b.
The sponsor provided Table 1 based on the updated database. The primary analysis excluded events that occurred after 28 days of the last dose, which yielded 10 subjects with an event and an IR of malignancies (excluding NMSC) in the Tofacitinib ALL group in Cohort 3 of 0.49/ 100 PY.

Table 1. Proportions and Incidence Rates of Malignancies (Excluding NMSC) in Cohort 3 (P2P3LTE Tofacitinib) as of 29 September 2017

	Tofacitinib All (N = 1124)	Predominant Dose Tofacitinib 5 mg BID (N = 200)	Predominant Dose Tofacitinib 10 mg BID (N = 924)	Post-Induction Dose Tofacitinib 5 mg BID (N = 220)	Post-Induction Dose Tofacitinib 10 mg BID (N = 771)
All malignancies (excluding NMSC)					
Exposure (PY)	2039.98	498.78	1541.20	349.79	1344.27
Number (%) of subjects with events	10 (0.9)	0	10 (1.1)	0	8 (1.0)
IR (95% CI)	0.49 (0.24, 0.90)[a]	0.00 (0.00, 0.74)	0.65 (0.31, 1.19)	0.00 (0.00, 1.05)	0.60 (0.26, 1.17)
Colorectal cancer					
Exposure (PY)	2042.24	498.78	1543.46	349.79	1346.41
Number (%) of subjects with events	2 (0.2)	0	2 (0.2)	0	1 (0.1)
IR (95% CI)	0.10 (0.01, 0.35)	0.00 (0.00, 0.74)	0.13 (0.02, 0.47)	0.00 (0.00, 1.05)	0.07 (0.00, 0.41)
Lymphoma					
Exposure (PY)	2042.40	498.78	1543.62	349.79	1346.51
Number (%) of subjects with events	1 (0.1)	0	1 (0.1)	0	1 (0.1)
IR (95% CI)	0.05 (0.00, 0.27)	0.00 (0.00, 0.74)	0.06 (0.00, 0.36)	0.00 (0.00, 1.05)	0.07 (0.00, 0.41)

Abbreviations: BID = twice daily; CI = confidence interval; IR = incidence rate; NMSC = nonmelanoma skin cancer; P2P3LTE = Phase 2, Phase 3, long-term extension; PY = patient-years.

N = Number of subjects in Phase 3 UC studies. Adjudication was not performed in the Phase 2 induction study A3921063.

a. Data shown is the IR from primary analysis, which excludes events that occurred more than 28 days after the last dose. The IR from sensitivity analysis #2 that includes all 13 subjects with malignancies (excluding NMSC) is 0.64 (95% CI: 0.34, 1.09) / 100 PY in the Tofacitinib All group.

Sources: 5.3.5.3 Table 229a.4; Table 229a.4.1; Table 229a.15.

Source: Sponsor's safety response, page 7, Table 1

Table 2. Proportions and Incidence Rates of Malignancy (Excluding NMSC) in Cohort 3 (P2P3LTE Tofacitinib) in the 120-Day Safety Update Report and the Updated Database as of 29 September 2017

	120-Day Safety Update Cumulative Data as of 16 December 2016			Updated Database as of 29 September 2017		
	Tofacitinib All	PD 5 mg BID	PD 10 mg BID	Tofacitinib All	PD 5 mg BID	PD 10 mg BID
N	1124	186	938	1124	200	924
Primary analysis						
Exposure in patient-years	1659.64	369.14	1290.50	2039.98	498.78	1541.20
Number (%) of subjects with events	8 (0.7)	0	8 (0.9)	10 (0.9)	0	10 (1.1)
IR (95% CI)	0.48 (0.21, 0.95)	0.00 (0.00, 1.00)	0.62 (0.27, 1.22)	0.49 (0.24, 0.90)	0.00 (0.00, 0.74)	0.65 (0.31, 1.19)
Sensitivity analysis #2						
Exposure in patient-years	1659.71	369.14	1290.57	2040.06	498.78	1541.28
Number (%) of subjects with events	11 (1.0)	0	11 (1.2)	13 (1.2)	0	13 (1.4)
IR (95% CI)	0.66 (0.33, 1.19)	0.00 (0.00, 1.00)	0.85 (0.43, 1.53)	0.64 (0.34, 1.09)	0.00 (0.00, 0.74)	0.84 (0.45, 1.44)

Abbreviations: BID = twice daily; CI = confidence interval; IR = incidence rate; NMSC = nonmelanoma skin cancer; P2P3LTE = Phase 2, Phase 3, long-term extension; PD = predominant dose; SUR = safety update report.

N = Number of subjects in Phase 3 UC studies. Adjudication was not performed in the Phase 2 induction study A3921063.

Primary analysis excludes events that occurred more than 28 days after the last dose.

Sensitivity analysis #2 includes events that occurred more than 28 days after the last dose.

Sources: 120-day SUR Table 15; 5.3.5.3 Table 229a.4; Table 229a.4.1.

Source: Sponsor's safety response, page 8, Table 2

The sponsor explained that all 13 subjects who reported malignancies (excluding NMSC) were in the predominant dose (PD) 10 mg twice daily (BID) group of Cohort 3 (P2P#LTE Tofacitinib). They explained that there could be issues in evaluating a potential dose-response relationship from these data, since Cohort 3 includes multiple sequential studies, such as i) the experience of tofacitinib treatment is not based on a pre-specified dose; and ii) subjects could have switched treatments.

The sponsor stated that the analysis using PD groups should be considered supplemental to the primary analysis based on the tofacitinib ALL group. The sponsor also stated the following to argue against a dose response risk:

1. The tofacitinib rheumatoid arthritis (RA) randomized Phase 3 program (n=3800) showed similar IRs for malignancy (excluding NMSC) in the 5 mg BID and 10 mg BID arms, 0.63 and 0.72/ 100PY, respectively.
2. The cumulative IR of malignancies (excluding NMSC) in the Tofacitinib ALL group in Cohort 3 (0.49/ 100PY) was similar to that reported among UC patients receiving any tumor necrosis factor (TNF) inhibitor in a claims database (0.63/ 100PY).

Reviewer's comment: The sponsor stated that all 13 subjects who reported malignancies (excluding NMSC) were in the PD 10 mg BID group of Cohort 3 (P2P3LTE Tofacitinib). In the updated database, as of September 29, 2017, 13 malignancies (excluding NMSC) were identified, yielding an IR of 0.64/100PY and 0.84/ 100PY in the tofacitinib ALL and in the predominant dose of 10 mg group, respectively, where two events occurred after 28 days of the last dose.

1. ***The sponsor's explanation about the dose response results should be carefully investigated to understand the safety profile of tofacitinib 10 mg. A well-designed long-term safety study is needed to identify the causal effect of 10 mg tofacitinib on the malignancies (excluding NMSC).***
2. ***We defer to the clinical reviewers to assess the distribution of subjects between the two PD groups that might provide reasons for the higher IR among the 10 mg users compared to the 5 mg users.***
3. ***The IRs from the RA and UC patients might not be comparable to this study's safety results because of differences in the study designs and study populations. The results of post-hoc comparisons might not be reliable.***
4. ***We calculated the 95% confidence interval of the rate difference between 5 mg and 10 mg groups as (0.34, 1.09) per 100 PY, which excludes zero, which implies difference between the groups (Byar's method, OpenEpi).***

Response to Sub-part c.

The sponsor provided updated listing of subjects with adjudicated malignancies (excluding NMSC) in Cohort 3 as of September 29, 2017. They stated that most (10/13, 77%) of the subjects who reported malignancies (without NMSC) had received prior TNF inhibitor treatment, and that all malignancies occurred in the long-term extension study A3921139. The sponsor stated that there was no evidence of clustering into specific cancer types.

Reviewer's comment: Two out of the 13 patients' disease onset day was at 104 and 57 days, which suggests that the malignancy was not exclusively due to the long-term use.

FDA Clinical Request 2

Currently, we are aware of 11 adjudicated cases of patients with NMSC (with 16 adverse events) in the entire Tofacitinib UC program. We request that you confirm the number, patient IDs, and updated narratives of adjudicated cases of NMSC in the entire Tofacitinib UC program to date, as of September 22, 2017. In addition:

a. Provide information on new, adjudicated cases of NMSC that have not been reported to the Division.
b. Table 35: Proportions and Incidence Rates of NMSC in Cohort 3 (P2P3LTE Tofacitinib), page 117/292.
c. Table 36: Listing of Subjects with NMSC in Cohort 3 (P2P3LTE Tofacitinib), pages 119-120/292

Sponsor's Response
The sponsor updated their database with a new cutoff date of September 29, 2017, including all malignancies adjudicated by the MAC.

Response to Sub-part a.
The sponsor provided information on new, adjudicated cases of NMSC that have not been reported to the Division.

Reviewer's comment: We defer to the clinical reviewers to assess the sponsor's response.

Response to Sub-part b.
The sponsor updated database: 15 subjects with an event (cutoff date September 29, 2017) yielded a cumulative IR of NMSC in the Tofacitinib ALL group in Cohort 3 of 0.74/ 100PY.

Reviewer's comment: Table 3 below is generated based on the summary statistics included in Table 4 of the sponsor's safety responses (page 16). All comparisons do not show statistical significance between 5 mg BID and 10 mg BID at both predominant dose and post-induction dose except for the squamous cell carcinoma at post-induction dose. However, the data consistently show higher risks in the 10 mg BID group compared to the 5 mg BID group. Because of the smaller sample size and shorter follow-up time of the 5 mg BID compared to 10 mg BID, Table 3 should be considered as descriptive.

Table 3. Incidence Rates of NMSC (95% CI) in Tofacitinib ALL Group and Rate Difference (95% CI) between 5 mg BID and 10 mg BID groups

	Tofacitinib ALL (n=1124)	PD Tofacitinib CI of RD between 5 mg (n=200) and 10 mg (n=924)	PI Tofacitinib CI of RD between 5 mg (n=220) and 10 mg (n=771)
All NMSC	15/2017.94 PY 0.74/100PY (0.42, 1.23)	0.182/100PY (-0.636, 0.999)	0.54/100PY (-0.204, 1.288)
Basal cell carcinoma	9/2028.31 PY 0.44/100PY (0.20, 0.84)	-0.214/100PY (-0.967, 0.539)	0.087/100PY (-0.563, 0.738)
Squamous cell carcinoma	9/2028.31 PY 0.44/100PY (0.20, 0.84)	0.054/100PY (-0.599, 0.707)	0.052/100PY (0.136, 0.913)

Source: Reviewer's calculation
CI: Confidence Interval, RD: Rate Difference; PD: Predominant Dose; PI: Post-Induction Dose; BID: twice daily; PY: patient-year; NMSC: nonmelanoma skin cancer

Response to Sub-part c.
The sponsor provided updated information on Summary of Clinical Safety.

Reviewer's comment: We defer to the clinical reviewers to assess the sponsor's response.

FDA Clinical Request 3

In addition to the above requests specific to the UC program, please provide an updated version of Table 67: Cumulative Incidence rates (per 100 Patient-Years) for Select Safety Events in Subjects Treated with Tofacitinib (All Doses Combined) in the UC Cohort 3, Rheumatoid Arthritis (All exposure), and Psoriasis (All Exposures) Programs (From the Summary of Clinical Safety, 2.7.4, page 200/292), based on your most up-todate adjudicated numbers for these events of interest, and indicate the cut-off date used.

Sponsor's Response

The sponsor updated their database and provided summary statistics in Table 4 and Table 5 for death and relevant adjudicated AEs of special interest for all tofacitinib-treated subjects in UC Cohort 3 and all studies in the RA and psoriasis (PsO) program (all exposure). The new cutoff dates for each database are as follows:

- UC Cohort 3: September 29, 2017
- RA (all exposure): March 2, 2017
- PsO (all exposure): August 18, 2016

Table 4. Numbers and Exposures of Subjects Treated with Tofacitinib (All Doses Combined) in UC Cohort 3 (P2P3LTE Tofacitinib), Rheumatoid Arthritis (All Exposure) and Psoriasis (All Exposure) in the UC Summary of Clinical Safety or 120-Day Safety Update Report and in the Most Up-to-date Databases

	UC Cohort 3		Rheumatoid arthritis (all exposure)		Psoriasis (all exposure)	
	Cumulative data in 120-day safety update report	Updated data	Data in SCS	Updated data	Data in SCS	Updated data
Cutoff date	16 December 2016	29 September 2017	10 May 2016	02 March 2017	10 May 2016	18 August 2016[a]
Number of subjects	1157	1157	6300	7061	3662	3663
Exposure (PY)	1613	1986	21886	22875	8537	8955
% increase in PY from SCS or 120-day safety update report	NA	23.1	NA	4.5	NA	4.9

Abbreviations: NA = not applicable; P2P3LTE = Phase 2, Phase 3, long-term extension; PsO = psoriasis; PY = patient-years; RA = rheumatoid arthritis; SCS = summary of clinical safety; SUR = safety update report; UC = ulcerative colitis.

a. For psoriasis (all exposure), the updated database is the final database, with a date of 18 August 2016.

Sources: SCS Table 67; 120-day SUR Table 3; 5.3.5.3 Table 229a.1; 5.3.5.3 RA Table 1295.1; 5.3.5.3 PsO Table 198c.1.1.

Source: Sponsor's safety response, pg. 26

Table 5. Updated Cumulative Incidence Rates (per 100 Patient-Years) for Death and Select Safety Events in Subjects Treated With Tofacitinib (All Doses Combined) in the UC Cohort 3 (P2P3LTE Tofacitinib), Rheumatoid Arthritis (All Exposure), and Psoriasis (All Exposure) Programs

Safety Event	UC (Cohort 3) N = 1157 Exposure = 1986 PY		RA (All Exposure) N = 7061 Exposure = 22,875 PY		Psoriasis (All Exposure) N = 3663 Exposure = 8955 PY	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Death (all cause)	2 (0.2)	0.10 (0.01, 0.35)[b]	59 (0.8)	0.25 (0.19,0.32)	17 (0.5)	0.18 (0.11, 0.29)
Serious infection	38 (3.3)	1.87 (1.32, 2.56)	576 (8.2)	2.48 (2.28,2.69)	119 (3.2)	1.29 (1.07, 1.54)
Opportunistic infection[a]	22 (2.0)	1.09 (0.69, 1.66)	90 (1.3)	0.39 (0.31,0.47)	29 (0.8)	0.31 (0.21, 0.45)
Non-herpes zoster opportunistic infection[a]	4 (0.4)	0.20 (0.05, 0.50)	34 (0.5)	0.15 (0.10,0.20)	4(0.1)	0.04 (0.01, 0.11)
Herpes zoster	74 (6.4)	3.80 (2.99, 4.77)	782 (11.1)	3.63 (3.38,3.90)	209 (5.7)	2.35 (2.04, 2.69)
Serious herpes zoster	5 (0.4)	0.24 (0.08, 0.57)	57 (0.8)	0.24 (0.18,0.32)	11 (0.3)	0.12 (0.06, 0.21)
Malignancy (excluding NMSC)[a]	10 (0.9)	0.49 (0.24, 0.90)	177 (2.5)	0.76 (0.65,0.88)	60 (1.6)	0.65 (0.49, 0.83)
Colorectal cancer[a]	2 (0.2)	0.10 (0.01, 0.35)	11 (0.2)	0.05 (0.02,0.08)	3 (0.1)	0.03 (0.01, 0.09)
Lymphoma[a]	1 (0.1)	0.05 (0.00, 0.27)	12[c] (0.2)	0.05 (0.03,0.09)	2 (0.1)	0.02 (0.00, 0.08)
NMSC[a]	15 (1.3)	0.74 (0.42, 1.23)	129 (1.8)	0.56 (0.46,0.66)	63 (1.7)	0.69 (0.53, 0.88)
MACE[a]	4 (0.4)	0.20 (0.05, 0.50)	85 (1.3)	0.38 (0.30,0.47)	23 (0.6)	0.25 (0.16, 0.37)
GI perforation (all cases)[a]	4 (0.4)	0.20 (0.05, 0.50)	28 (0.4)	0.12 (0.08,0.17)	7 (0.2)	0.08 (0.03, 0.16)

Abbreviations: CI = confidence interval; GI =gastrointestinal; IR = incidence rate; MACE = major adverse cardiovascular event; N = number of evaluable subjects; n = number of subjects with events; NMSC = nonmelanoma skin cancer; P2P3LTE = Phase 2, Phase 3, long-term extension; PsO = psoriasis; PY = patient-years; RA = rheumatoid arthritis; UC = ulcerative colitis.

Includes RA Studies A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044, A3921045, A3921046, A3921064, A3921068, A3921069, A3921073, A3921109, A3921129, A3921130, A3921152, and A3921237.

Includes psoriasis Studies A3921078, A3921079, A3921080, A3921111, A3921047, A3921147, and A3921061.

Events occurring within 28 days following the last dose were included.

UC Cohort 3 data cutoff date 29 September, 2017; RA data cutoff date 02 March 2017; PsO final database date 18 August 2016.

a. Adjudicated events. Percentage (%) was calculated based on the number of subjects in studies in which adjudication was performed.

b. Based on the sensitivity analysis of all 5 deaths in UC Cohort 3, the n (%) was 5 (0.4%), and the IR (95% CI) was 0.24 (0.08, 0.57).

c. The number of subjects with lymphoma decreased from 13 to 12 in the updated RA database. After the 10 May 2016 data cutoff, the start date of 1 lymphoma event was revised such that the start date was outside the 28-day risk period following the last dose. This event was not counted for IR calculation in the updated database, resulting in a decrease of the number of subjects with lymphoma by 1.

Sources: 5.3.5.3 Table 229a.1; Table 229a.2; Table 229a.2.1; Table 229a.3; Table 229a.4; Table 229a.5; Table 229a.6.1; 5.3.5.3 RA Table 1295.1; Table 1295.1.3.1; Table 1295.1.3.2; Table 1295.1.3.3; Table 1295.1.3.4; Table 1295.1.3.5; Table 1295.1.3.6; Table 1295.1.3.7; Table 1295.1.3.8; Table 1295.1.3.9; Table 1295.5.2.3.1; Table 1403.1.1; Table 1403.2.1; 5.3.5.3 PsO Table 198c.1.1; Table 198c.2.1.1; Table 198c.2.1.2; Table 198c.2.1.3; Table 198c.2.1.6; Table 198c.2.1.7; Table 198c.5.1.

Source: Sponsor's safety response, pg. 27

Reviewer's comment: The total number of subjects of UC in Tables 4 and 5 is n = 1157, and n = 1124 in Tables 1 and 2. We defer to the clinical reviewers to comment on such discrepancy.

The IR (95% CI) of safety events in the UC Cohort 3 included in Table 5 are slightly different from this reviewer's results. Though the discrepancies are ignorable (Table 6), the sponsor should clarify the method they used for CI calculation.

Table 6. Updated Cumulative Incidence Rates (per 100 Patient-Years) for Death and Select Safety Events in Subjects Treated With Tofacitinib (All Doses Combined) in the UC Cohort 3 (P2P3LTE Tofacitinib): Discrepancies Between The Sponsor's Results (Table 5) and DB7

		UC (Cohort 3) N = 1157 Exposure = 1986 PY IR (95% CI)	
	n(%)	Sponsor	DB7 reviewer
Death (all cause)	2 (0.2)	0.1; (0.01, 0.35)	0.1; (0.01, 0.36)
Serious infection	38 (3.3)	1.87; (1.32, 2.56)	1.91; (1.35, 2.63)
Opportunistic infection	22 (2.0) 22 (1.9)	1.09; (0.69, 1.66)	1.11; (0.69, 1.68)
Non-herpes zoster opportunistic infection	4 (0.4) 4 (0.3)	0.2; (0.05, 0.50)	0.2; (0.05, 0.52)
Herpes zoster	74 (6.4)	3.80; (2.99, 4.77)	3.73; (2.93, 4.68)
Serious herpes zoster	5 (0.4)	0.24; (0.08, 0.57)	0.25; (0.08, 0.59)
Malignancy (excluding NMSC)	10 (0.9)	0.49; (0.24, 0.90)	0.50; (0.24, 0.93)
Colorectal cancer	2 (0.2)	0.10; (0.01, 0.35)	0.10; (0.01, 0.36)
Lymphoma	1 (0.1)	0.05; (0.00, 0.27)	0.05; (0.001, 0.28)
NMSC	15 (1.3)	0.74; (0.42, 1.23)	0.76; (0.42, 1.25)
MACE	4 (0.4) 4 (0.3)	0.20; (0.05, 0.50)	0.20; (0.05, 0.52)
GI perforation (all cases)	4 (0.4) 4 (0.3)	0.20; (0.05, 0.50)	0.20; (0.05, 0.52)

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/s/

JEONGSOOK L KIM
12/06/2017

CLARA KIM
12/06/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s018

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 21, 2018

To: Kelly Richards, RN, MSN, Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for XELJANZ® (tofacitinib) tablets, for oral use

NDA: 203214/Supplement 018

In response to Division of Gastroenterology and Inborn Errors Products' (DGIEP) labeling consult request dated June 19, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for XELJANZ® (tofacitinib) tablets, for oral use (Xeljanz). This supplement (S018) is for the addition of ulcerative colitis indication to the PI.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DGIEP (Kelly Richards) on May 7, 2018, and are provided below. We do not have any comments on the proposed PI.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on May 16, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DGIEP (Kelly Richards) on May 16, 2018, and we do not have any comments

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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/s/

ADEWALE A ADELEYE
05/21/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 16, 2018
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	XELJANZ (tofacitinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 203214
Supplement Number:	S-018
Applicant:	Pfizer Inc., authorized U.S. Agent for PF Prism C.V.

1 INTRODUCTION

On May 4, 2017, Pfizer Inc., authorized U.S. Agent for PF Prism C.V., submitted for the Agency's review a Prior Approval Supplement to their New Drug Application (NDA) 203214/S-018 for XELJANZ (tofacitinib) tablets. This efficacy supplement provides for the proposed indication of XELJANZ for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have demonstrated an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-meracptopurine (6-MP) or TNF inhibitor therapy based on data generated from the tofacitinib UC development program. XELJANZ (tofacitinib) tablets and XELJANZ XR (tofacitinib) extended release tablets NDA 208246 share common labeling.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on June 16, 2017 and June 19, 2017, respectively for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for XELJANZ (tofacitinib) tablets.

2 MATERIAL REVIEWED

- Draft XELJANZ (tofacitinib) tablets MG received on December 22, 2017, and received by DMPP and OPDP on May 7, 2018.
- Draft XELJANZ (tofacitinib) tablets Prescribing Information (PI) received on December 22, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 7, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
05/16/2018

LASHAWN M GRIFFITHS
05/16/2018

ADEWALE A ADELEYE
05/16/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Memorandum

Date: March 20, 2018 **Date Consulted:** June 5, 2017

From: Jane Liedtka M.D., Medical Officer (MO), Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Kelly Richards, RPM
Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Xeljanz (tofacitinib) Tablet

Indications:
Approved

- Xeljanz /Xeljanz XR is an inhibitor of Janus kinases (JAKs) 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 anti-rheumatic drugs (DMARDs).
- For the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other DMARDs.

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

Proposed

- Xeljanz is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis with an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine (6-MP) or TNF inhibitor therapy (b) (4)

(b) (4)

Limitations of Use: Use of Xeljanz in combination with biological therapies for ulcerative colitis (UC) or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

NDA: NDA 203214 S-18

Applicant: PF PRISM CV

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- Applicant's background package for NDA 203214, Supplement #18 (S-018) submitted as supporting document (SD) # 954 on May 4, 2017.
- Applicant's background package for NDA 203214, Supplement #17 (S-017) submitted as SD# 925 on February 22, 2017.
- Applicant's "Clinical Overview" and "Summary of Literature Search on Pregnancy, Lacation and Reproductive Potential" and revised labeling to include Pregnancy and Lactation Labeling Rule (PLLR) language for NDA 203214, Supplement #14 (S-014) submitted as supporting document (SD)# 909 on January 13, 2017.
- DPMH consult request dated June 5, 2017, DARRTS Reference ID 4107190

Consult Question: Review section 8 to ensure its compliance with PLLR

INTRODUCTION

On June 5, 2017, DGIEP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of Xeljanz (tofacitinib) labeling to be in compliance with the PLLR format.

REGULATORY HISTORY

- On May 4, 2017, PF PRISM C.V. submitted an efficacy supplement to propose an additional indication for Xeljanz (tofacitinib), NDA 203214 S-18 to treat adult patients with moderately to severely active ulcerative colitis (UC) who have demonstrated an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine (6-MP) or TNF inhibitor therapy.
- While S-018 was in house, on August 22, 2017, DPARP approved supplements S-014 and S-016 to NDA 203214 and S-001 and S-002 to NDA 208246 which included revisions to update the labeling for Xeljanz (NDA 203214) and Xeljanz XR (NDA 208246) to the PLLR format.

BACKGROUND

Tofacitinib and Drug Characteristics[1]

- Tofacitinib is a JAK inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.
- Treatment with tofacitinib is associated with dose-dependent reductions of circulating CD16/56+ natural killer cells, with estimated maximum reductions occurring at approximately 8-10 weeks after initiation of therapy. These changes generally resolve within 2-6 weeks after discontinuation of treatment. Treatment with XELJANZ is associated with dose-dependent increases in B cell counts.
- The absolute oral bioavailability of tofacitinib is 74%.
- Following oral administration of Xeljanz, the elimination half-life is ≈ 3 hours.
- Following oral administration of Xeljanz XR, the elimination half-life is ≈ 6 hours.
- The protein binding of tofacitinib is ~40%, predominantly to albumin.
- The molecular weight of tofacitinib is ≈ 505 Daltons (or 312 Daltons as the tofacitinib free base).
- The most commonly reported adverse reactions during the first 3 months in controlled clinical trials [Psoriatic and Rheumatoid Arthritis] (occurring in greater than or equal to 2% of patients treated with XELJANZ monotherapy or in combination with DMARDs) were upper respiratory tract infections, headache, diarrhea and nasopharyngitis.
- Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral and other opportunistic pathogens have been reported in patients treated with tofacitinib. In addition, there have been reports of malignancies, gastrointestinal perforations, neutropenia, anemia, and liver enzyme elevations in adults who have used tofacitinib.

Inflammatory Bowel Disease and Pregnancy

Women with inflammatory bowel disease (IBD) have been reported to have higher risks of adverse pregnancy outcomes, such as spontaneous abortion (SAB), preterm birth (PTB), infants who are small for gestational age (SGA), low birth weight (LBW) babies and stillbirth. In addition, complications of labor and delivery are increased compared with the age-matched general population, even when their disease is inactive.[2,3,4,5, 6] Active disease is

[1] Xeljanz (tofacitinib) label approved August 22, 2017
[2] Mahadevan U *et al*. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: pregnancy and pediatrics. Am J Gastroenterol. 2011 Feb; 106(2):214-23.
[3] Getahun D *et al*. Association between maternal inflammatory bowel disease and adverse perinatal outcomes. J Perinatol. 2014; 34:435–440.

associated with a further increase in preterm birth and miscarriage. Stopping effective medications for IBD can lead to a high risk of flare within a year. IBD clinical practice guidelines recommend continuing maternal drug therapy during pregnancy.[2] See Table 1 below for the pregnancy outcomes reported in a number of studies.

Table 1: Pregnancy outcomes in inflammatory bowel disease

Outcome	Study population	Odds	95% CI	Reference
Adverse pregnancy outcome	CD and UC	OR 1.54	1 00–2.38	[4]
	CD and UC	No increase		[13]
SGA birth	CD and UC	OR 1.46	1.14–1.88	[14]
	UC	POR 1.27	1 05–1.54	[15]
Spontaneous preterm birth	CD and UC	OR 1.32	1.0–1.76	[14]
	CD and UC	No increase		[13]
	CD	aOR 1.65	1 33–2.06	[16]
	(Active disease)	aOR 2.66	1 89–3.74	[16]
	UC	aOR 1.78	1.49–2.13	[16]
	(Active disease)	aOR 2.72	2.12–3.4	[16]
	UC	POR 1.77	1 54–2.05	[15]
Preterm birth 32–36 weeks	CD	POR 1.76	1 51–2.05	[17]
	UC	POR 1.41	1 02–1.96	[15]
	CD	POR 1.86	1 38–2.52	[17]
Preterm birth <32 weeks				
Low birth weight	UC	aOR 1.64	1 31–2.04	[16]
	(Active disease)	aOR 2.10	1 51–2.90	[16]
	CD	aOR 1.86	1.46–2.38	[16]
	(Active disease)	aOR 3.30	2 29–4.74	[16]
	CD and UC	No increase		[13]
Adverse conception outcome	CD and UC	OR 1.63	1 09–2.48	[4]
	CD and UC	No increase		[13]
Neonatal death	UC	POR 1.93	1 04–3.60	[15]
stillbirth	CD	aOR 2.93	1 57–5.47	[16]
	(Active disease)	aOR 4.48	1.67–11.90	[16]

CD, Crohn's disease; UC, ulcerative colitis; CI, confidence interval; OR, odds ratio; SGA, small for gestational age; POR, prevalence odds ratio; aOR, adjusted odds ratio, adjusted for maternal age, parity, body mass index, smoking status, and comorbidities.

Source: Gaidos *et al* (2016)[7]

The majority of the studies reported increased adverse conception outcomes (SAB, therapeutic abortion [TAB]) and adverse pregnancy outcomes (PTB, SGA, stillbirth). The authors of the Mahadevan[3] study (#4 in above table) did not find a statistically significant difference in adverse neonatal outcomes (major congenital malformations [MCM], LBW, intrauterine growth restriction [IUGR], neonatal intensive care unit admission, newborn seizure or infant mortality) between cases and controls. Similarly, a large retrospective study reviewing the medical records of 1703 children born to mothers with IBD and 384,811 children born to mothers without IBD reported no increased risk of major congenital

[4] Stephansson O *et al*. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. Inflamm Bowel Dis. 2011; 17:795–801.
[5] Mahadevan U, Sandborn W, Li D, et al. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. Gastroenterology. 2007; 133:1106–1112.
[6] Broms G *et al*. Birth Outcomes in Women with Inflammatory Bowel Disease: Effects of Disease Activity and Drug Exposure. Inflamm Bowel Dis.2014; 20:1091-8.
[7] Jill K. J. Gaidos & Sunanda V. Kane. Overcoming challenges of treating inflammatory bowel disease in pregnancy, Expert Review of Clinical Immunology.2016; 12:8, 871-878.

anomalies (OR: 0.98; 95% CI: 0.73–1.31).[8] Multiple recent population-based studies failed to detect an increased risk of congenital anomalies in IBD pregnancies.[9]

Fertility is not decreased in inflammatory bowel disease patients with inactive disease who have not undergone surgical treatment.[10] In women with IBD, fertility is decreased in the setting of active disease and following surgery within the pelvis.[11]

Current State of the Labeling

- Current labeling for Xeljanz, revised in August of 2017, is in Physician Labeling Rule (PLR) and PLLR format.
- There is a boxed warning for serious infections and malignancy.
- There are warnings and precautions for avoiding use during active infection, gastrointestinal perforations, need for monitoring of blood counts, liver enzymes and lipids and to avoid live vaccines.
- No interaction with contraceptive pills was noted in the current labeling.
- Section 8.1 Pregnancy includes notification about the Xeljanz Pregnancy registry. The **Risk Summary** reads:

  There are no adequate and well-controlled studies of XELJANZ/XELJANZ XR use in pregnant women.

  The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. The background risks in the U.S. general population of major birth defects and miscarriages are 2-4% and 15-20% of clinically recognized pregnancies, respectively.

  Based on animal studies, XELJANZ/XELJANZ XR has the potential to affect a developing fetus. Fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 146 times and 13 times the human dose of 5 mg twice daily, respectively *[see Data]*. Further, in a peri and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73 times the human dose of 5 mg twice daily.

  Under *Human Data* it states, "In the tofacitinib clinical development program (b) (4) (b) (4) birth defects and miscarriages were reported".

- Section 8.2 **Lactation** reads

[8] Ban L, Tata L *et al*. Limited risks of major congenital anomalies in children of mothers with IBD and effects of medications. Gastroenterology. 2014; 146:76–84.
[9] Stephansson O *et al*. Congenital Abnormalities and Other Birth Outcomes in Children Born to Women with Ulcerative Colitis in Denmark and Sweden. Inflamm Bowel Dis. 2011; 17:795-801.
[10] Tavernier N *et al*. Systematic review: fertility in non-surgically treated inflammatory bowel disease. Aliment Pharmacol Ther. 2013; 38:847–853.
[11] Jill K. J. Gaidos & Sunanda V. Kane. Sexuality, Fertility, and Pregnancy in Crohn's Disease. Gastroenterol Clin N Am. 2017;46 :531–546

It is not known whether tofacitinib is excreted in human milk. Additionally, there are no data to assess the effects of the drug on the breastfed child. However, tofacitinib is excreted in rat milk at concentrations higher than in maternal serum *[see Data]*. Women should not breastfeed while treated with XELJANZ/XELJANZ XR. A decision should be made whether to discontinue breastfeeding or to discontinue XELJANZ/XELJANZ XR.

- Section 8.3 **Females and Males of Reproductive Potential** contains headings for "Contraception" and "Infertility" in females that state:

  Contraception
  Females
  Embryofetal toxicity including malformations occurred in embryofetal development studies in rats and rabbits *[see Use in Specific Populations (8.1)]*.

  Females of reproductive potential should be advised to use effective contraception during treatment with XELJANZ/XELJANZ XR and for at least 4 weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with XELJANZ/XELJANZ XR.

  Infertility
  Females
  Based on findings in rats, treatment with XELJANZ/XELJANZ XR may result in reduced fertility in females of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

REVIEW

Pregnancy

Nonclinical Experience

Fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73-times and 6.3-times the human dose of 10 mg twice daily, respectively. Further, in a peri and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73-times the human dose of 5 mg twice daily.

For further details, the reader is directed to the Nonclinical Review by Lawrence S Leshin[12], PhD.

Applicant's Review of Literature

[12] Pharmacology/Toxicology Labeling Review by Lawrence S Leshin, PhD. July 7, 2017. DARRTS Reference ID # 4121279.

The Applicant performed a literature search from January 1900 through September 7, 2016 in LactMed, OVID MEDLINE and OVID MEDLINE(R), In-Process, BIOSIS Previews, Embase Daily Alerts, and Embase on the use of tofacitinib in pregnant and lactating women. A total of nine articles were identified by the Applicant to be relevant but only a few of these were actually referenced in their summary of the literature. Details from the article by Clowse[13] *et al.* (2016) are included in the section of this review entitled "DPMH's Review of the Literature." The majority of the other publications cited by the Applicant did not contribute additional information and are therefore not discussed further.

The Applicant cited a report from a "European League against Rheumatism (EULAR) task force"[14] which was established to define points to consider on use of anti-rheumatic drugs before pregnancy, and during pregnancy and lactation. Based on a systematic literature review and pregnancy exposure data from several registries, statements on the compatibility of anti-rheumatic drugs during pregnancy and lactation were developed. With regard to tofacitinib, the authors noted

> Insufficient documentation in regard to fetal safety implies the discontinuation of leflunomide, tofacitinib as well as abatacept, rituximab, belimumab, tocilizumab, ustekinumab and anakinra before a planned pregnancy.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase on December 13, 2017 using the search terms "tofacitinib and pregnancy," "tofacitinib and pregnant women," "tofacitinib and pregnancy and birth defects," "tofacitinib and pregnancy and congenital malformations," "tofacitinib and pregnancy and stillbirth," "tofacitinib and spontaneous abortion" and "tofacitinib and pregnancy and miscarriage." No reports of adequate and well-controlled studies of tofacitinib use in pregnant women were found. No published case reports involving pregnancy in tofacitinib patients were identified.

An article reporting the results of a cohort study examining the use of tofacitinib in pregnancy in Rheumatoid Arthritis (RA) patients was identified but is not described further since the indication for this review is UC. Several review articles regarding the treatment of inflammatory bowel disease in pregnancy were identified and are referenced in the section of this review entitled "Inflammatory Bowel Disease and Pregnancy". In addition, several published reports outlining the findings regarding pregnancy and lactation from Pfizer's pharmacovigilance database (the previous owner of Xeljanz) were identified. Some details of the publication by Clowse[12] *et al.* (2016) are provided below.

[13] Clowse ME *et al*. Pregnancy Outcomes in the Tofacitinib Safety Databases for Rheumatoid Arthritis and Psoriasis. Drug Safety. 2016; 39(8):755-62.
[14] Götestam Skorpen C, et al. The EULAR points to consider for use of anti-rheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016; 0:1–16.

Table 2: Publications Summarizing the Pfizer Tofacitinib Pregnancy Database

Characteristic	RA	Psoriasis
Patients with reports of pregnancy (*n*/*N* of female patients aged 18–44[a])	31/1309 (2.4 %)	16/512 (3.1 %)
Median age (range), years[b]	31 (22–40)	27 (19–40)
Study medication (*n*; % of identified cases)	Tofacitinib monotherapy (18; 58.1 %)	Tofacitinib monotherapy (16; 100 %)
	Tofacitinib + MTX (13; 41.9 %)	
Pregnancy outcomes, *n* (% of identified cases)		
Fetal death	0 (0.0 %)	0 (0.0 %)
Congenital malformation	1 (3.2 %)	0 (0.0 %)
Spontaneous abortion	6 (19.4 %)	1 (6.3 %)
Healthy newborn	16 (51.6 %)	9 (56.3 %)
Medical termination	4 (12.9 %)	4 (25.0 %)
Lost/pending to follow-up	4 (12.9 %)	2 (12.5 %)
Range of total time on study medication at time of pregnancy identification, range, days[c]	28–1344	21–349
Duration of in utero study medication exposure, days[d]		
Range	7–244	14–43
≤90 days	29 cases	16 cases
>90 and ≤180 days	1 case	0 case
>180 days	1 case	0 case

MTX methotrexate, *RA* rheumatoid arthritis

[a] Enrolled in RA or psoriasis clinical trials

[b] Based on 30 and 15 patients with data, respectively

[c] Data available for $n = 26$ and $n = 10$ patients in the RA and psoriasis clinical trials, respectively

[d] Based on when pregnancy occurred and when the subject was discontinued from the study drug

Source: Clowse[12]et al (2016), page 757

The author's conclusions regarding pregnancy outcomes described in the above table are:

> Based on these limited clinical data, unintentional exposure to tofacitinib during conception/pregnancy does not appear to be associated with an increased risk to the fetus when compared with risks identified in the general population and specifically reported in RA and psoriasis patients. However, definitive conclusions cannot be drawn….

The authors go on to acknowledge that:

> There are limitations to the currently reported data. Although results were drawn from relatively large clinical trial databases, this was not a prospective analysis and a relatively small number of pregnancies were identified. Additionally, outcomes were not available for six (12.8 %) of the reported pregnancies after maternal exposure, and limited information is available on

the exact date of conception and gestational age in several cases. Finally, clear cut associations between the effects of tofacitinib on pregnancy outcomes cannot be drawn because of confounders, such as underlying RA and psoriasis disease activity, concomitant treatments, and other concurrent medical conditions.

Additional publications by Marren[15] *et al.* (2015) and Feldman[16] *et al.* (2014) provided essentially the same data, with earlier cutoff dates, for the Pfizer tofacitinib pregnancy database.

In Micromedex,[17] the authors note that "Fetal risk cannot be ruled out" and to "Administer tofacitinib during pregnancy only if the potential maternal benefit outweighs the potential fetal risk."

In Reprotox,[18] the authors "Quick take" states "Tofacitinib interfered with embryo viability and structural development in experimental animals. We have not located human data."

The "pregnancy recommendation" in Briggs[19] *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk* states that "No human data. Animal data suggest risk (Contraindicated if combined with Methotrexate)."

Results from the Ongoing Pregnancy Registry

Established in 2013, the Sponsor's tofacitinib Pregnancy Exposure Registry is a US-based registry conducted by the OTIS Research Group as an integrated project within the existing OTIS Autoimmune Diseases in Pregnancy Project based at the University of California, San Diego. The registry is designed to monitor planned or unplanned pregnancies exposed to tofacitinib and other comparator treatments when used to treat RA. The cohort study sample size goal is 100 pregnant women in each of 3 groups: 100 women with RA who have been exposed to tofacitinib in pregnancy, 100 women with RA who have not been exposed to tofacitinib at any time in pregnancy, and 100 healthy women who have no diagnosis of autoimmune disease and have not taken tofacitinib nor other RA therapies in pregnancy.

As of May 1, 2016, a total of 3 tofacitinib-exposed pregnancies among women with RA were enrolled in the registry. One pregnancy resulted in a live birth to a 39 year old woman on tofacitinib for Rheumatoid Arthritis (RA). Concomitant medications included prenatal vitamins, albuterol, oxycodone/paracetamol, hydrocodone/paracetamol, fentanyl patch, acetylsalicylic acid, metformin, diphtheria/tetanus/acellular pertussis (TDAP Vaccine) and measles, mumps and rubella vaccine/varicella virus vaccine, live (MMR W/Varicella Live). Additional diagnoses included asthma, gestational diabetes, migraines, fibromyalgia and multiple joint replacement surgeries. The

[15] Marren A *et al*. Arthritis Rheum. 2014; 66(11): S5840 abs 1908
[16] Feldman S *et al*. Pregnancy outcomes in the tofacitinib psoriasis safety database up to April 2014 Journal of Investigative Dermatology 2015 135 SUPPL. 3 (S9).
[17] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 1/17/18.
[18] www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 1/17/18.
[19]Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

baby was delivered full-term and weighed 3433grams. APGAR Scores were 3 and 1 at one and five minutes. A third, APGAR Score 3 was not provided. No additional information regarding this infant is available.

The outcomes of the remaining two pregnancies are still pending.

Pharmacovigilance Database Summary

The following are cases of congenital malformation in infants exposed to tofacitinib described in the Applicant's "Clinical Overview" To Support Proposed Updates to Section 8 (Subsections 8.1, 8.2, and 8.3) and Section 17 of the United States Prescribing Information to be Consistent with the Pregnancy and Lactation Labeling Rule (PLLR) submitted in January of 2017.

- 3.15 kg male infant with pulmonary valve stenosis and atrial septal defect born via cesarean section at week 38 to a 32-year old woman with rheumatoid arthritis and gestational diabetes on tofacitinib, losartan and methyldopa. The infant's weight was 3155 g, length was 48 cm and head circumference was 33 cm at birth. Apgar score was 8 at 1 minute and 9 at 5 minutes. The diagnoses of congenital pulmonary valvar stenosis (mild to moderate) and congenital interatrial communication (small) were confirmed by echocardiography. Estimated duration of *in utero* tofacitinib exposure was 35 days from conceptions to diagnosis of pregnancy at ≈ 5 weeks estimated gestational age (EGA).
- 3.70 kg female infant with a small intraventricular septal defect born at 37 weeks to a 38-year old female smoker with rheumatoid arthritis on tofacitinib, paracetamol, citalopram and clorazepate. Estimated duration of *in utero* tofacitinib exposure was 3-4 weeks from conceptions to diagnosis of pregnancy at 3-4 weeks EGA when patient self-discontinued the medication. This was reported during post-marketing and no other information is available.
- No information was found regarding a third "congenital malformation" reported to the Pfizer PVDB born to a woman who was treated with tofacitinib for an unknown indication (see table 4 below).

The following tables describe the small amount of information available regarding pregnancy outcomes from the Applicant's PVDB for Clinical Trials Exposures (Table 3) and for Post-marketing reported exposures (Table 4).

Table 3: Tofacitinib Exposed Pregnancies in Clinical Trials

# of Exposed Infants per Indication/ Maternal or Paternal	Normal Newborns	PTB[1]	SAB[2]	TAB[3]	CM[4]	Pending	Unknown	Lost to Follow-up	Refused Consent to Follow-up
RA[5]-maternal 36	17 (47%)	2 (6%)	6 (17%)	4 (11%)	1 (3%)	2 (6%)	1 (3%)	3 (8%)	
PsA[6]-maternal			1	1		1			

Comment [LJ1]: The Sponsor was asked to update this information They only provided updated information on the cohort of pending patients with UC See #'s below in yellow highlights

3			(33%)	(33%)		(33%)			
Ps[7]-maternal 20	10 (50%)		1 (5%)	5 (25%)		3 (15%)		1 (5%)	
UC[8]-maternal 5 Updated to 13[9]	2 (40%) 5 (38%)		1 (20%)	1 (20%) 2 (15%)		1 (20%) 2 (15%)		2 (15%)	
RA-paternal 7	3 (42%)		2 (28%)			1 (14%)			
TOTAL maternal 71 Updated to 79	**32 (45%) 35 (44%)**	**2 (2.8%)**	**11 (15%)**	**11 (15%)**	**1 (1.4%)**	**8 (11.3%)**	**1 (1.4%)**	**4 (5.6%)**	
PsA-paternal 2						1 (50%)	1 (50%)		
Ps-paternal 59	35 (57%)	2* (3%)	4 (7%)			9 (15%)		3 (5%)	
Crohns-paternal 6	2 (33%)					22 (33%)	1 (17%)		1 (17%)
UC-paternal 11	5 (45%)					6 (55%)			
Transplant-paternal 3	3 (100%)								
TOTAL Paternal 81	**45 (55.6%)**	**2 (2.5%)**	**4 (5%)**			**38 (46.9%)**	**2 (2.5%)**	**3 (3.7%)**	**1 (1.23%)**

[1]PTB=preterm birth, [2]SAB=spontaneous abortion, [3]TAB=therapeutic abortion, [4] CM=congenital malformation, [5]RA=rheumatoid arthritis, [6]PsA=psoriatic arthritis, [7] Ps=psoriasis, [8] UC=ulcerative colitis, 9updated as of Feb 2018, *one of the two infants died
Source: Reviewer's Table

Table 4: Tofacitinib Exposed Pregnancies in Post-Marketing Reports

# of Exposed Infants per Indication/ Maternal or	Normal	PTB[1]	SAB[2]	TAB[3]	CM[4]	Pending	Unknown	Lost to Follow-up	Refused Consent to Follow-up

Paternal	Newborns								
Post-marketing cases-RA maternal 15	1 (7%)	2 (13%)	2 (13%)		1 (7%)	6 (40%)	3 (20%)		
Post-marketing cases-unknown indication-maternal 6	1 (16.6%)				1 (16.6%)	1 (16.6%)	3 (50%)		
Post-marketing cases-unknown indication- paternal 2						1 (50%)	1 (50%)		

Source: Reviewer's Table

Summary

Human pregnancy outcome data for tofacitinib are limited in the published literature, and the Applicant's PVDB is insufficient to inform a benefit/ risk assessment. Since the adverse developmental outcomes that were seen in animals were at relatively high multiples of the MRHD [6.3 x (in rabbit) and 73x (in rat)], it is unclear whether tofacitinib will cause harm in the fetus. A comment under *Clinical Considerations* with the subheading *Disease-Associated Maternal and/or Embryo/Fetal Risk* regarding the increased maternal and fetal risks associated with Rheumatoid arthritis (RA) and ulcerative colitis (UC) will be included in Section 8. DPMH recommends labeling language for 8.1 which conveys the paucity of data. See DPMH proposed labeling for details.

Lactation

Nonclinical Experience

Following administration of tofacitinib to lactating rats, concentrations of tofacitinib in milk over time paralleled those in serum, and were approximately 2-times higher in milk relative to maternal serum at all time points measured.

For further details, the reader is directed to the Nonclinical Review by Lawrence S Leshin[12], PhD.

Applicant's Review of Literature

The Applicant stated that "The review of clinical literature as of 07 September 2016 did not identify relevant published data or information on the effects of tofacitinib on lactation".

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*[20], Micromedex[19], and of published literature in PubMed and Embase using the search terms "tofacitinib and lactation" and "tofacitinib and breastfeeding." No relevant data was found.

In Briggs[19] *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*, the notation regarding tofacitinib and lactation states "No human data. Potential toxicity (Contraindicated if combined with Methotrexate)". In addition, the authors' state:

> No reports describing the use of tofacitinib during human lactation have been located. The molecular weight (about 312 for the free base), moderate plasma protein binding (about 40%), and elimination half-life (about 3 hours) suggest that the drug will be excreted into breast milk. The effect of this exposure on a nursing infant is unknown. However, because tofacitinib has been associated with severe adverse effects in adults, including infections that have resulted in death, the drug is best avoided during breastfeeding.

Tofacitinib is referenced in *Medications and Mother's Milk*[20]. The author notes "No data. Possibly hazardous" and "Because of serious side effects that may occur in nursing infants, it is advised to not use during breastfeeding".

In a published article by Götestam Skorpen C[21], *et al*. (2014), the authors' state, "No data exist regarding tofacitinib in breast milk; therefore, tofacitinib should be avoided in breastfeeding."

Summary

There are no data on the use of tofacitinib during lactation. Pharmacokinetic variables such as molecular weight (≈312 Daltons for the free base) and protein binding (≈ 40%) suggest that tofacitinib is likely to be found in breastmilk. Tofacitinib is found in the milk of lactating rats. Given the serious adverse events seen in adults treated with tofacitinib, such as increased risk of serious infections, patients should be advised that breastfeeding is not recommended during treatment with Xeljanz/Xeljanz XR and for 6 half-lives after the last dose.

Use in Females and Males of Reproductive Potential

Nonclinical Experience

In a 39-week toxicology study in monkeys, tofacitinib at exposure levels approximately 6-times the maximum recommended human dose (MRHD) (on an area-under-the-curve (AUC) basis at oral doses of 5 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1-time the MRHD (on an AUC basis at oral doses of 1 mg/kg twice daily).

[20] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, pg. 422-423.
[21] Götestam Skorpen C, et al. The EULAR points to consider for use of anti-rheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016; 75(5): 795-810.

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib, at exposure levels approximately 34-times the MRHD (on an AUC basis at oral doses of 200 mg/kg/day) was not carcinogenic in mice.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hibernomas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 30 mg/kg/day (approximately 42-times the exposure levels at the MRHD on an AUC basis). The relevance of benign Leydig cell tumors to human risk is not known.

Tofacitinib was not mutagenic in the bacterial reverse mutation assay. It was positive for clastogenicity in the in vitro chromosome aberration assay with human lymphocytes in the presence of metabolic enzymes, but negative in the absence of metabolic enzymes. Tofacitinib was negative in the in vivo rat micronucleus assay and in the in vitro CHO-HGPRT assay and the in vivo rat hepatocyte unscheduled DNA synthesis assay.

In rats, tofacitinib at exposure levels approximately 17-times the MRHD (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the MRHD (on an AUC basis at oral doses of 1 mg/kg/day). Tofacitinib exposure levels at approximately 133-times the MRHD (on an AUC basis at oral doses of 100 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration.

For further details, the reader is directed to the Nonclinical Review by Lawrence S Leshin[12], PhD.

Applicant's Review of Literature

The Applicant performed a literature search from January 1900 through September 7, 2016 in LactMed, OVID MEDLINE and OVID MEDLINE(R), In-Process, BIOSIS Previews, Embase Daily Alerts, and Embase on the effect of tofacitinib on fertility. No relevant publications were identified.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding tofacitinib and its effects on fertility and found no relevant literature.

Summary

In the currently approved label for Xeljanz there is a recommendation for contraception in Subsection 8.3, Females and Males of Reproductive Potential. DPMH does not agree with the inclusion of required contraception for this product. Although there is evidence of embryofetotoxicity in the animal studies, they are at high multiples (73 and 6.3 times the MRHD). There have been < 100 reported pregnancies with exposure to tofacitinib and for

these cases there are very few details available. However, in this initial exposed group there have only been three reported congenital anomalies (one in clinical trial of RA and two reported in post-marketing). The number of congenital anomalies is not outside the expected range for the US population. Without more human data indicating a risk to the fetus, DPMH recommends that the Contraception recommendation and subheading is not included in Xeljanz labeling.

There is information regarding the effect of tofacitinib on female fertility which will be included in Subsection 8.3 of labeling. See DPMH proposed labeling for details.

CONCLUSIONS

Based on the literature review and review of the pharmacovigilance database, DPMH has the following PLLR labeling recommendations for Xeljanz (tofacitinib) labeling: [22]

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of Xeljanz (tofacitinib) labeling was structured in the PLLR format to include the "Risk Summary," "Clinical Considerations" and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" subsection of Xeljanz (tofacitinib) labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" sections.
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential" subsection of Xeljanz (tofacitinib) labeling was formatted in the PLLR format to include the "Infertility" section.[23]

LABELING RECOMMENDATIONS

DPMH revised the HPI and subsections 8.1, 8.2, 8.3and 17 of Xeljanz (tofacitinib) labeling for compliance with the PLLR (see below). DPMH discussed the labeling recommendations with the division on 3/19/18. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Xeljanz (tofacitinib) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)

FULL PRESCRIBING INFORMATION
8 Use in Specific Populations

[22] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.
[23] *Guidance for Industry Pregnancy, Lactation, and Reproductive Potential Labeling for Human Prescription Drug and Biological Products-Content and Format.* December 2014. Part IV Specific Subsection C-8.3 Females and Males of Reproductive Potential.

All information provided in this section is applicable to XELJANZ and XELJANZ XR as they contain the same active ingredient (tofacitinib).

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to XELJANZ/XELJANZ XR during pregnancy. Patients should be encouraged to enroll in the XELJANZ/XELJANZ XR pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call the toll-free number 1-877-311-8972.

Risk Summary

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 (RA) and ulcerative colitis (UC) in pregnancy (*see Clinical Considerations*). In animal reproduction studies, fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73-times and 6.3-times the recommended dose of 10 mg twice daily, respectively. Further, in a peri and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73- times the recommended dose of 5 mg twice daily and approximately 36 times the recommended dose of 10 mg twice daily, respectively. (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. (b) (4)

(b) (4)

(b) (4)

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest (b) (4)

(b) (4)

Data

Animal Data

In a rat embryofetal developmental study, in which pregnant rats received tofacitinib during (b) (4)

rats). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively; and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and

hemicentric thoracic centrum). In addition, there was an increase in post-implantation loss, consisting of early and late resorptions, resulting in a reduced number of viable fetuses. Mean fetal body weight was reduced. No developmental toxicity was observed in rats at exposure levels approximately 58-times the recommended dose of 5 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in pregnant rats).

In a rabbit embryofetal developmental study in which pregnant rabbits received tofacitinib during the period of organogenesis, tofacitinib was teratogenic at exposure levels approximately 13-times the recommended dose of 5 mg twice daily (b) (4) doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3-times the recommended dose of 5 mg twice daily (b) (4)

In a peri- and postnatal development study in pregnant rats that received tofacitinib from gestation day 6 through day 20 of lactation, there were reductions in live litter size, postnatal survival, and pup body weights at exposure levels approximately 73 times the recommended dose of 5 mg twice daily (on an AUC basis at oral doses of 50 mg/kg/day in rats). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels (b) (4)

8.2 **Lactation**

Risk Summary

There are no data on the presence of tofacitinib in human milk, the effects on a breastfed infant, or the effects on milk production. Tofacitinib is present in the milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adults treated with XELJANZ/XELJANZ XR, such as increased risk of serious infections, (b) (4)
(b) (4)

Data

Following administration of tofacitinib to lactating rats, concentrations of tofacitinib in milk over time paralleled those in serum, and were approximate 2-times higher in milk relative to maternal serum at all time points measure.

8.3 Females and Males of Reproductive Potential

(b) (4)

Based on findings in rats, treatment with XELJANZ/XELJANZ XR may result in reduced fertility in females of reproductive potential. It is not known if this effect is reversible. [*see Nonclinical Toxicology (13.1)]*

17 PATIENT COUNSELING INFORMATION

Pregnancy

(b) (4)

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/s/

JANE E LIEDTKA
03/20/2018

MIRIAM C DINATALE
03/20/2018

LYNNE P YAO
03/21/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 2, 2017
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 203214/S-018
Product Name and Strength:	Xeljanz (Tofacitinib) Tablets, 5 mg and 10 mg (proposed)
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pfizer, Inc.
Submission Dates:	May 4, 2017 September 5, 2017
OSE RCM #:	2017-865
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review evaluates the label and labeling for Xeljanz supplemental NDA (sNDA 203214/S-018) submitted on May 4, 2017. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed label and labeling for areas of vulnerability that may lead to medication errors. The sponsor submitted the revised Prescribing Information (PI) to the sNDA on September 5, 2017.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C– N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F– N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Pfizer Inc. submitted a supplemental NDA for Xeljanz (Tofacitinib) on May 4, 2017, to propose a new indication for treatment of adult patients with moderately to severely active ulcerative colitis with an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine (6-MP) or TNF inhibitor therapy [redacted (b) (4)] In this submission, they are also proposing a new strength (10 mg) to be used for the new indication.

DMEPA evaluated the introduction of a new strength of Xeljanz and reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. Given the dosing of this product, we find the addition of the 10 mg tablet appropriate. Additionally, we did not identify any medication error concerns from our search of the previous DMEPA reviews or ISMP Newsletters.

We find the proposed changes to the PI and container labels are acceptable and we have no further comments at this time.

4 CONCLUSION & RECOMMENDATION

DMEPA concludes that the proposed PI and the container labels are acceptable from a medication error perspective and we have no further comments at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xeljanz that Pfizer, Inc. submitted on May 4, 2017 and September 5, 2017.

Table 2. Relevant Product Information for Xeljanz (Tofacitinib) (proposed additions for a NDA 203214/S-018 are highlighted below)	
Product Name	Xeljanz
Initial Approval Date	November 6, 2012
Active Ingredient	Tofacitinib
Indication	Rheumatoid Arthritis (RA): 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). Ulcerative Colitis (proposed) Treatment of adult patients with moderately to severely active ulcerative colitis with an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine (6-MP) or TNF inhibitor therapy (b) (4) (b) (4)
Route of Administration	oral
Dosage Form	immediate-release Tablets
Strength	5 mg and 10 mg (proposed)
Dose and Frequency	**Rheumatoid Arthritis** Recommended dose of XELJANZ is 5 mg twice daily. Recommended dose in patients with moderate and severe renal impairment and moderate hepatic impairment is XELJANZ 5 mg once

	daily. **Ulcerative Colitis** Recommended dose of XELJANZ is 10 mg twice daily for induction for at least 8 weeks and 5 mg given twice daily for maintenance. Induction therapy should be discontinued in patients who show no improvement in ulcerative colitis signs and symptoms by Week 16. For refractory patients, such as patients who failed prior TNF inhibitor therapy, consideration should be given to continue 10 mg twice daily. For patients with moderate or severe renal impairment or with moderate hepatic impairment the recommended dose is half the total daily dose recommended for patients with normal renal and hepatic function.
How Supplied	5 mg tablets: White, round, immediate-release film-coated tablets available in bottles of 28, 60 or 180 count. 10 mg tablets: Blue, round, immediate-release film-coated tablets available in bottles of 28, 60 or 180 count.
Storage	Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On September 28, 2017, we searched the L: drive and AIMS using the terms, Xeljanz, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified four previous reviews[abcd] and we confirmed our previous recommendations were implemented.

[a] McMillan, T. Label and Labeling review for Xeljanz (NDA 203214/S-017) and Xeljanz XR (NDA 208246) Silver Spring (MD). Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Sept 22 p.32 OSE RCM No.: 2017-482

[b] McMillan, T. Label and Labeling review for Xeljanz XR (NDA 208246) Silver Spring (MD). Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jan 14 p.32 OSE RCM No.: 2015-1084

[c] McMillan, T. Label and Labeling review for Xeljanz (NDA 203214/S-010) Silver Spring (MD). Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 June 19 p.32 OSE RCM No.: 2015-1391

[d] Mena-Grillasca, C. Label and Labeling review for Xeljanz (b) (4) Silver Spring (MD). Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); (b) (4)

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 28, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	**Acute care**
Search Strategy and Terms	**Match Exact Word or Phrase: Xeljanz**

D.2 Results

Our search identified no cases that were associated with the current labels and labeling for Xeljanz tablets.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Xeljanz labels and labeling submitted by Synergy Pharmaceuticals on December 11, 2014, May 4, 2017 and September 5, 2017.

- Container labels
- Prescribing information (image not pictured)

G.2 Label and Labeling Images

Container labels:

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHERLY ABRAHAM
10/02/2017

SARAH K VEE
10/02/2017