CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203214Orig1s04

Trade Name: Xeljanz

Generic Name: Tofacitinib

Sponsor: PF Prism C.V.

Approval Date: 02/21/2014

This Prior Approval supplemental new drug application provides for inclusion of language in the Clinical Studies - Radiographic Response section of the package insert.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203214/S-004

SUPPLEMENT APPROVAL

PF PRISM C.V.
c/o Pfizer, Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Nickie V. Kilgore, D.V.M.
Director, Worldwide Regulatory Strategy

Dear Dr. Kilgore:

Please refer to your Supplemental New Drug Application (sNDA) dated April 22, 2013, received April 22, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xeljanz (tofacitinib) Tablets, 5 mg.

We acknowledge receipt of your amendments dated May 30 and November 21, 2013, and February 10 and 17, 2014

This Prior Approval supplemental new drug application provides for inclusion of language in the CLINICAL STUDIES – *Radiographic Response* section of the package insert.

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.

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 includes 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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

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:

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

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, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

SARAH K YIM
02/21/2014
Signing for Badrul Chowdhury, M.D., Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

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

XELJANZ ® (tofacitinib) 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 until the infection is controlled. (5.1)**
- **Prior to starting XELJANZ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ. (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)	02/2014
Dosage and Administration (2)	02/2014
Warnings and Precautions (5)	02/2014

----------INDICATIONS AND USAGE----------

- XELJANZ 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 antirheumatic drugs (DMARDs). (1.1)
- Limitations of Use: Use of XELJANZ in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1.1)

----------DOSAGE AND ADMINISTRATION----------

Rheumatoid Arthritis

- Recommended dose of XELJANZ is 5 mg twice daily. (2.1)
- Moderate and severe renal impairment and moderate hepatic impairment: Reduce dose to 5 mg once daily. (2.4, 8.6, 8.7)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 5 mg (3)

----------CONTRAINDICATIONS----------

None (4)

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

- Avoid use of XELJANZ 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. (5.5)

----------ADVERSE REACTIONS----------

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials (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. (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----------

- Potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., ketoconazole): Reduce dose to 5 mg once daily. (2 3, 7.1)
- One or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole): Reduce dose to 5 mg once daily. (2.3, 7.2)
- Potent CYP inducers (e.g., rifampin): May result in loss of or reduced clinical response. (2.3, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 2/2014

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*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 are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1) and 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 until the infection is controlled.

Reported infections include:

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

The risks and benefits of treatment with XELJANZ 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, 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

1.1 Rheumatoid Arthritis

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Rheumatoid Arthritis

- XELJANZ may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). The recommended dose of XELJANZ is 5 mg twice daily.
- XELJANZ is given orally with or without food.

2.2 Dosage Modifications due to Serious Infections and Cytopenias (See Tables 1, 2, and 3 below.)

- It is recommended that XELJANZ not be initiated 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) and Adverse Reactions (6.1)]*.
- Avoid use of XELJANZ if a patient develops a serious infection until the infection is controlled.

2.3 Dosage Modifications due to Drug Interactions

- XELJANZ dosage should be reduced to 5 mg once daily in patients:
  - receiving potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., ketoconazole).
  - receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).
- Coadministration of potent inducers of CYP3A4 (e.g., rifampin) with XELJANZ may result in loss of or reduced clinical response to XELJANZ. Coadministration of potent inducers of CYP3A4 with XELJANZ is not recommended.

2.4 Dosage Modifications in Patients with Renal or Hepatic Impairment

- XELJANZ dosage should be reduced to 5 mg once daily in patients:
  - with moderate or severe renal insufficiency.
  - with moderate hepatic impairment.
- Use of XELJANZ in patients with severe hepatic impairment is not recommended.

Table 1: Dose Adjustments for Lymphopenia

Low Lymphocyte Count *[see Warnings and Precautions (5.4)]*	
Lab Value (cells/mm^3)	**Recommendation**
Lymphocyte count greater than or equal to 500	Maintain dose
Lymphocyte count less than 500 (Confirmed by repeat testing)	Discontinue XELJANZ

Table 2: Dose Adjustments for Neutropenia

Low ANC *[see Warnings and Precautions (5.4)]*	
Lab Value (cells/mm^3)	**Recommendation**
ANC greater than 1000	Maintain dose
ANC 500-1000	For persistent decreases in this range, interrupt dosing until ANC is greater than 1000 When ANC is greater than 1000, resume XELJANZ 5 mg twice daily
ANC less than 500 (Confirmed by repeat testing)	Discontinue XELJANZ

Table 3: Dose Adjustments for Anemia

Low Hemoglobin Value *[see Warnings and Precautions (5.4)]*	
Lab Value (g/dL)	**Recommendation**
Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Maintain dose
Greater than 2 g/dL decrease or less than 8.0 g/dL (Confirmed by repeat testing)	Interrupt the administration of XELJANZ until hemoglobin values have normalized

3 DOSAGE FORMS AND STRENGTHS

XELJANZ is provided as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) tablets: White, round, immediate-release film-coated tablets, debossed with "Pfizer" on one side, and "JKI 5" on the other side.

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 rheumatoid arthritis patients receiving XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster and urinary tract infection *[see Adverse Reactions (6.1)]*. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus, and BK virus 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.

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

Avoid use of XELJANZ in patients with an active, serious infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating XELJANZ 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 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 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.

Tuberculosis

Patients should be evaluated and tested for latent or active infection prior to administration of XELJANZ.

Anti-tuberculosis therapy should also be considered prior to administration of XELJANZ 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.

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 on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials.

5.2 Malignancy and Lymphoproliferative Disorders

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

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.

5.3 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical studies with XELJANZ in rheumatoid arthritis patients, although the role of JAK inhibition in these events is not known.

XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). 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 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 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)*.

Neutropenia

Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo.

Avoid initiation of XELJANZ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3). For patients who develop a persistent ANC of 500-1000 cells/mm^3, interrupt XELJANZ dosing until ANC is greater than or equal to 1000 cells/mm^3. In patients who develop an ANC less than 500 cells/mm^3, treatment with XELJANZ is not recommended.

Monitor neutrophil counts at baseline and after 4-8 weeks of treatment and every 3 months thereafter. For recommended modifications based on ANC results *see Dosage and Administration (2.2)*.

Anemia
Avoid initiation of XELJANZ treatment in patients with a low hemoglobin level (i.e. less than 9 g/dL). Treatment with XELJANZ should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment.

Monitor hemoglobin at baseline and after 4-8 weeks of treatment and every 3 months thereafter. For recommended modifications based on hemoglobin results *see Dosage and Administration (2.2)*.

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 should be interrupted until this diagnosis has been excluded.

Lipid Elevations
Treatment with XELJANZ was associated with 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. 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 therapy.

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

5.5 Vaccinations
No data are available on the response to vaccination or on the secondary transmission of infection by live vaccines to patients receiving XELJANZ. Avoid use of live vaccines concurrently with XELJANZ.

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

6 ADVERSE REACTIONS

6.1 Clinical Trial 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.

Although other doses have been studied, the recommended dose of XELJANZ is 5 mg twice 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 4.

Table 4: Adverse Reactions Occurring in at Least 2% or More of Patients on 5 or 10 mg Twice Daily XELJANZ With or Without DMARD (0-3 months) and at Least 1% Greater Than That Observed in Patients on Placebo

	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg Twice Daily*	Placebo
Preferred Term	**N = 1336 (%)**	**N = 1349 (%)**	**N = 809 (%)**
Diarrhea	4.0	2.9	2.3
Nasopharyngitis	3.8	2.8	2.8
Upper respiratory tract infection	4.5	3.8	3.3
Headache	4.3	3.4	2.1
Hypertension	1.6	2.3	1.1
N reflects randomized and treated patients from the seven clinical trials			

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

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

Blood and lymphatic system disorders: Anemia
Metabolism and nutrition disorders: Dehydration
Psychiatric disorders: Insomnia
Nervous system disorders: Paresthesia
Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion
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
General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema

Clinical Experience in Methotrexate-Naïve Patients

Study 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 I-V.

7 DRUG INTERACTIONS

7.1 Potent CYP3A4 Inhibitors

Tofacitinib exposure is increased when XELJANZ is coadministered with potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) *[see Dosage and Administration (2.3) and Figure 3]*.

7.2 Moderate CYP3A4 and Potent CYP2C19 Inhibitors
Tofacitinib exposure is increased when XELJANZ is coadministered with medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole) *[see Dosage and Administration (2.3) and Figure 3]*.

7.3 Potent CYP3A4 Inducers
Tofacitinib exposure is decreased when XELJANZ is coadministered with potent CYP3A4 inducers (e.g., rifampin) *[see Dosage and Administration (2.3) and Figure 3]*.

7.4 Immunosuppressive Drugs
There is a risk of added immunosuppression when XELJANZ is coadministered with potent immunosuppressive drugs (e.g., azathioprine, tacrolimus, cyclosporine). Combined use of multiple-dose XELJANZ with potent immunosuppressants has not been studied in rheumatoid arthritis. Use of XELJANZ in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic effects:
Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. XELJANZ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Tofacitinib has been shown to be fetocidal and teratogenic in rats and rabbits when given at exposures 146 times and 13 times, respectively, the maximum recommended human dose (MRHD).

In a rat embryofetal developmental study, tofacitinib was teratogenic at exposure levels approximately 146 times the MRHD (on an AUC basis at oral doses of 100 mg/kg/day). 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 MRHD (on an AUC basis at oral doses of 30 mg/kg/day). In the rabbit embryofetal developmental study, tofacitinib was teratogenic at exposure levels approximately 13 times the MRHD (on an AUC basis at oral doses of 30 mg/kg/day) 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 MRHD (on an AUC basis at oral doses of 10 mg/kg/day).

Nonteratogenic effects:
In a peri- and postnatal rat study, there were reductions in live litter size, postnatal survival, and pup body weights at exposure levels approximately 73 times the MRHD (on an AUC basis at oral doses of 50 mg/kg/day). 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 MRHD (on an AUC basis at oral doses of 10 mg/kg/day).

Pregnancy Registry: To monitor the outcomes of pregnant women exposed to XELJANZ, a pregnancy registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

8.3 Nursing Mothers
Tofacitinib was secreted in milk of lactating rats. It is not known whether tofacitinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from tofacitinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug for the mother.

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

8.5 Geriatric Use
Of the 3315 patients who enrolled in 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. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

8.6 Hepatic Impairment
XELJANZ-treated patients with moderate hepatic impairment had greater tofacitinib levels than XELJANZ-treated patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Higher blood levels may increase the risk of some adverse reactions, therefore, XELJANZ dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment *[see Dosage and Administration (2.4)]*. XELJANZ has not been studied in patients with severe hepatic impairment; therefore, use of XELJANZ in patients with severe hepatic impairment is not recommended. No dose adjustment is required in patients with mild hepatic impairment. The safety and efficacy of XELJANZ have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

8.7 Renal Impairment
XELJANZ-treated patients with moderate and severe renal impairment had greater tofacitinib blood levels than XELJANZ-treated patients with normal renal function; therefore, XELJANZ dose should be reduced to 5 mg once daily in patients with moderate and severe renal impairment *[see Dosage and Administration (2.4)]*. In clinical trials, XELJANZ was not evaluated in rheumatoid arthritis patients with baseline creatinine clearance values (estimated by

the Cockroft-Gault equation) less than 40 mL/min. No dose adjustment is required in patients with mild renal impairment.

10 OVERDOSAGE

Signs, Symptoms, and Laboratory Findings of Acute Overdosage in Humans

There is no experience with overdose of XELJANZ.

Treatment or Management of Overdose

Pharmacokinetic data up to and including a single dose of 100 mg in healthy volunteers indicate that more than 95% of the administered dose is expected to be eliminated within 24 hours.

There is no specific antidote for overdose with XELJANZ. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

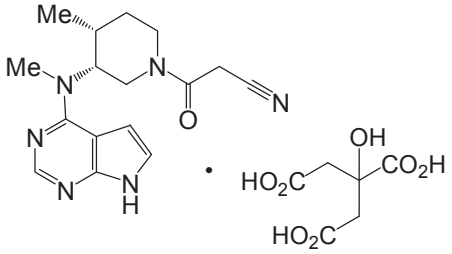
11 DESCRIPTION

XELJANZ is 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 $C_{16}H_{20}N_6O \bullet C_6H_8O_7$. The chemical structure of tofacitinib citrate is:



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

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.

12.3 Pharmacokinetics

Following oral administration of XELJANZ, peak plasma concentrations are reached within 0.5-1 hour, elimination half-life is ~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.

Absorption

The absolute oral bioavailability of tofacitinib 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.

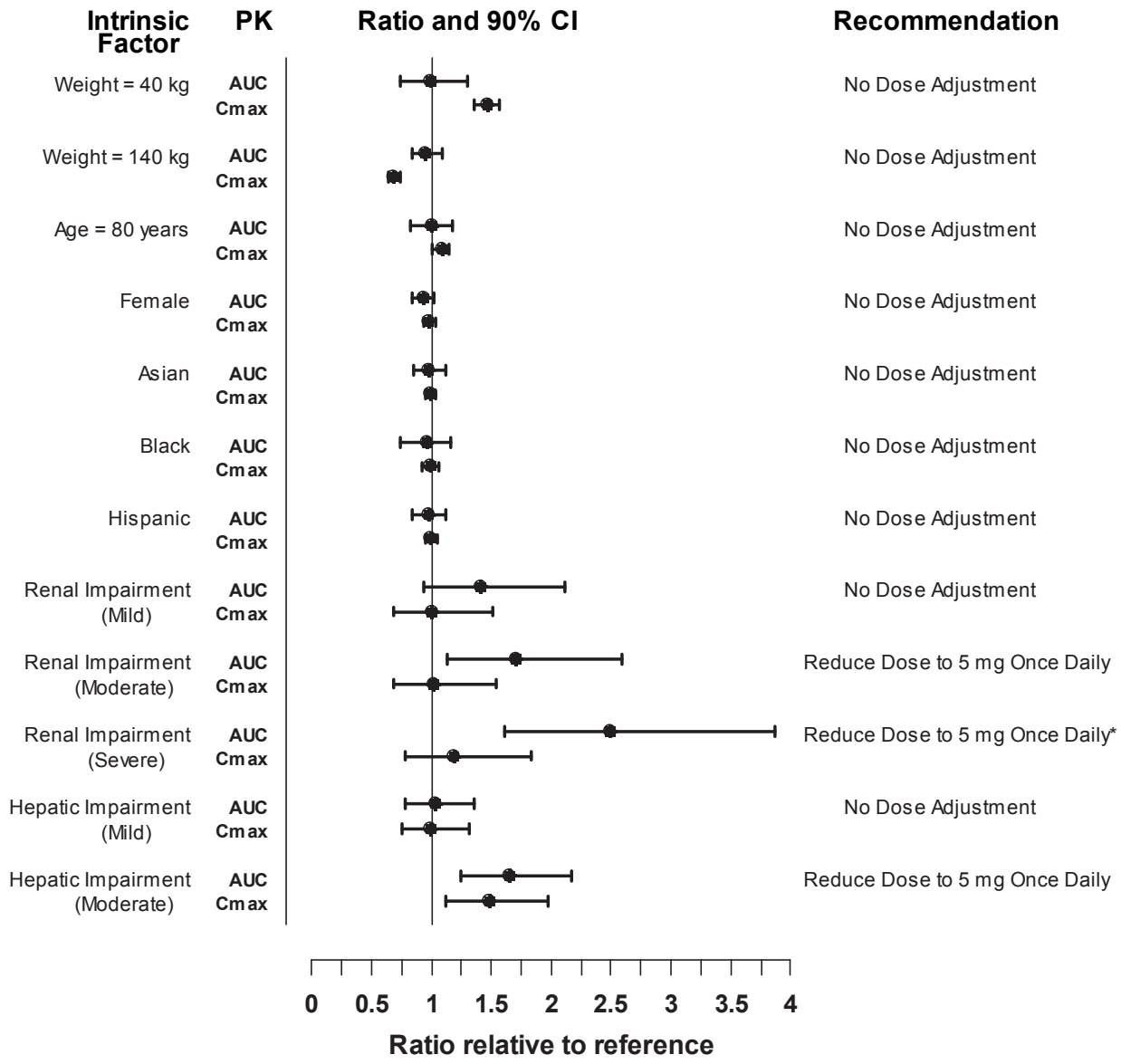
Distribution
After intravenous administration, the volume of distribution is 87 L. The protein binding of tofacitinib is ~40%. Tofacitinib binds predominantly to albumin and does not appear to bind to α1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

Metabolism and Elimination
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 Rheumatoid Arthritis Patients
Population PK analysis in rheumatoid arthritis patients 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 between-subject variability (% coefficient of variation) in AUC of tofacitinib is estimated to be approximately 27%.

Specific Populations
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



* Supplemental doses are not necessary in patients after dialysis.

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.

Drug Interactions

Potential for XELJANZ 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 exceeding 185 times the steady state C_{max} of a 5 mg

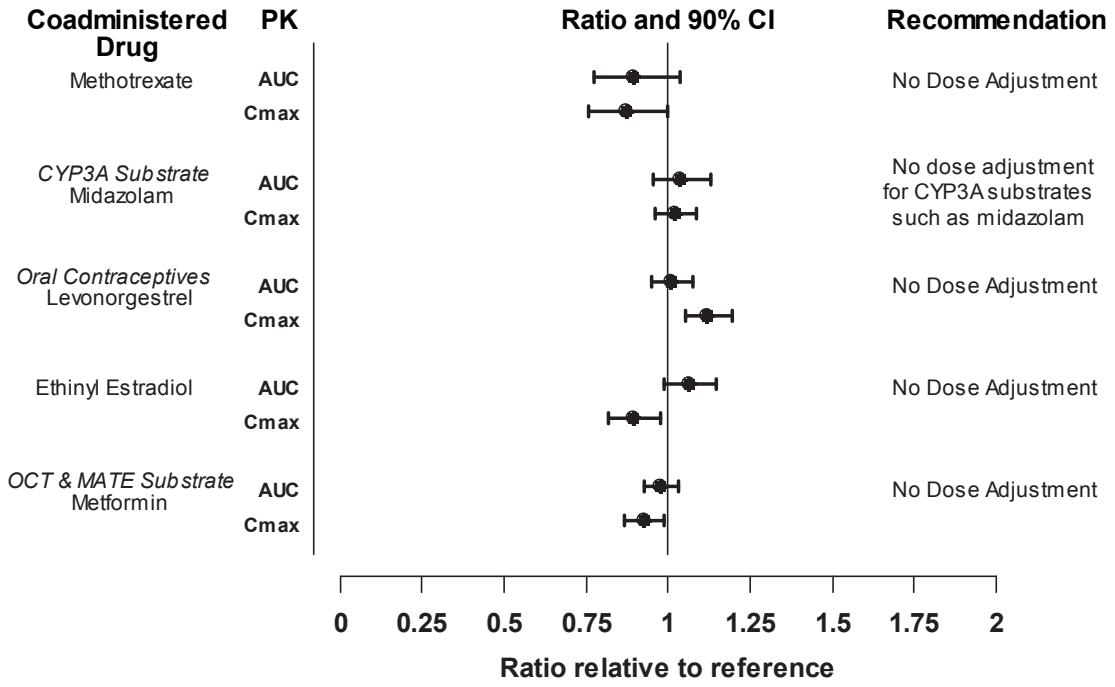
twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the PK of midazolam, a highly sensitive CYP3A4 substrate, when coadministered with XELJANZ.

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 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 are shown in Figure 2.

Figure 2. Impact of XELJANZ on PK of Other Drugs

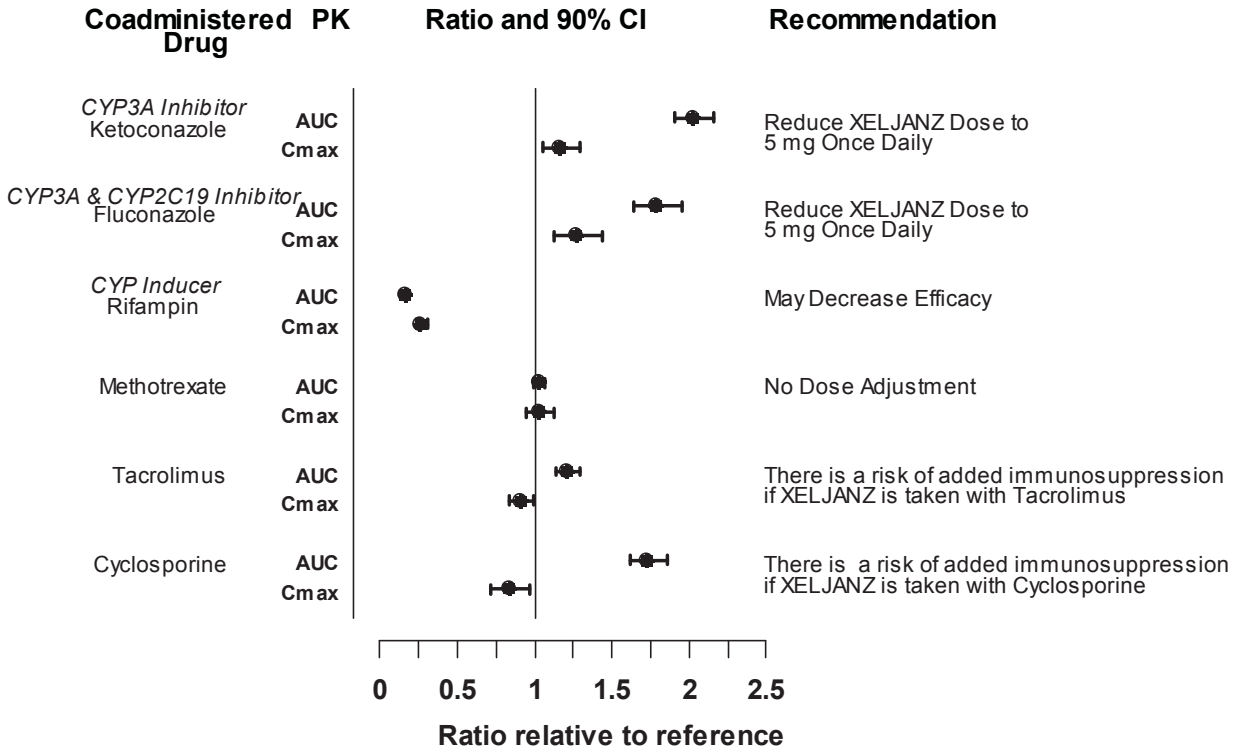


Note: Reference group is administration of concomitant medication alone; OCT = Organic Cationic Transporter; MATE = Multidrug and Toxic Compound Extrusion

Potential for Other Drugs to Influence the PK 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 PK of tofacitinib. Dosing recommendations for XELJANZ for administration with CYP inhibitors or inducers are shown in Figure 3.

Figure 3. Impact of Other Drugs on PK of XELJANZ



Note: Reference group is administration of tofacitinib alone

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 MRHD (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 MRHD (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 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.

14 CLINICAL STUDIES

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

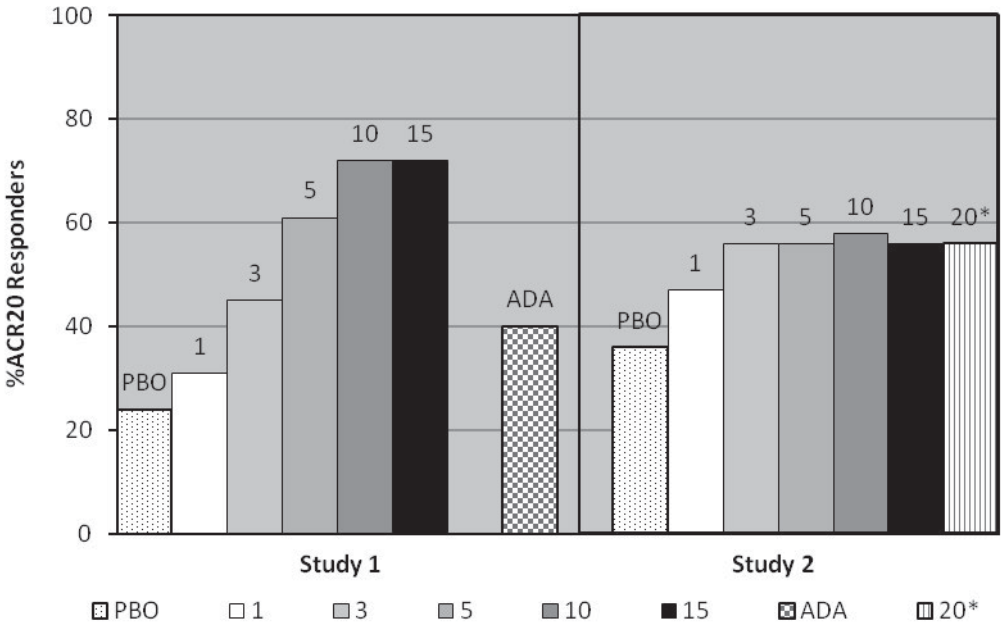
Dose selection for XELJANZ was based on two pivotal dose-ranging trials.

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 I 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 II 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 III 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 IV is an ongoing 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 V 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-inhibiting 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 VI is an ongoing 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 I, IV, and V are shown in Table 5. Similar results were observed with Studies II and III. In trials I-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 5: Proportion of Patients with an ACR Response

	Percent of Patients								
	Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders[c]			MTX Inadequate Responders[d]			TNF Inhibitor 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 inhibitor due to lack of efficacy and/or intolerance.
[f] The recommended dose of XELJANZ is 5 mg twice daily.

In Study 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 6).

Table 6: 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** **160**	**XELJANZ 5 mg Twice Daily + MTX** **321**	**XELJANZ 10 mg Twice Daily + MTX*** **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)
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 IV are shown in Table 7. Similar results were observed for XELJANZ in Studies I, II, III, V, and VI.

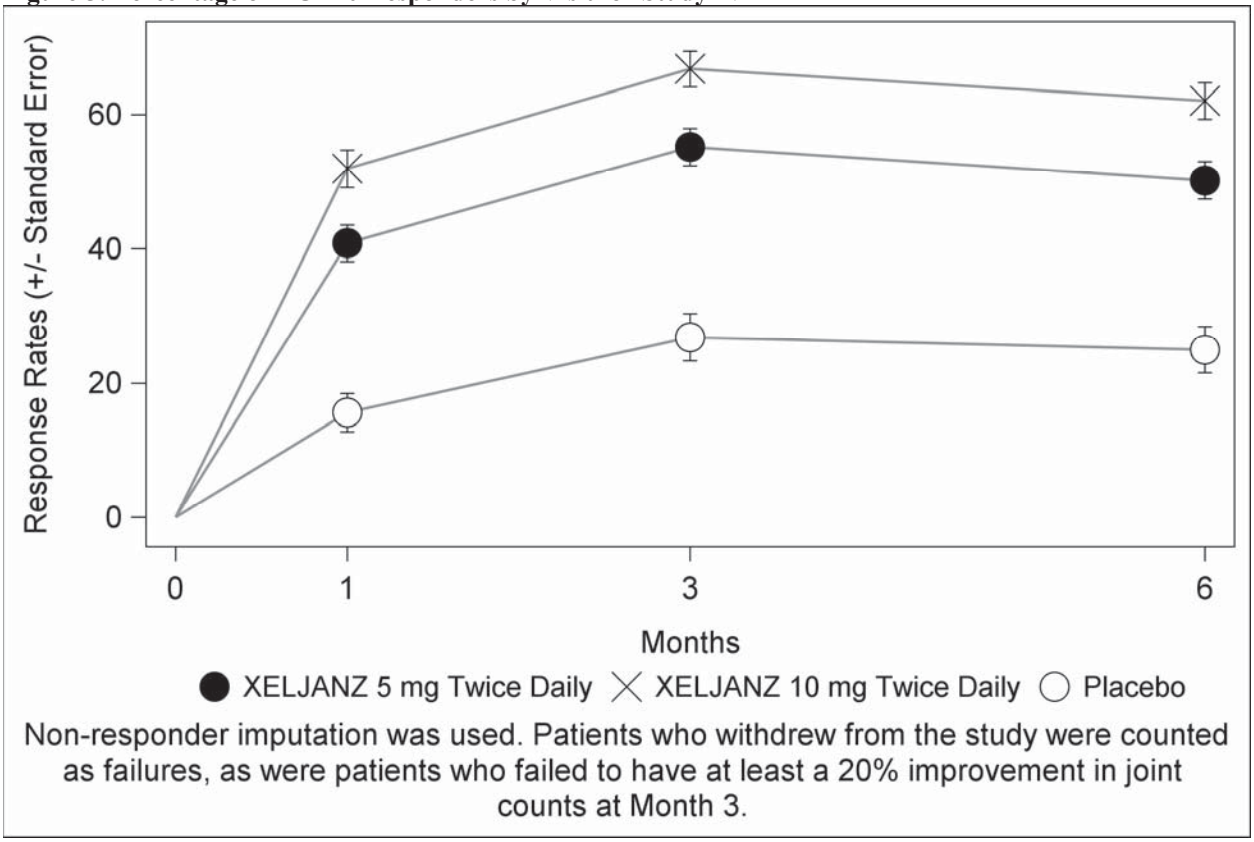
Table 7: Components of ACR Response at Month 3

	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 IV is shown in Figure 5. Similar responses were observed for XELJANZ in Studies I, II, III, V, and VI.

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



Radiographic Response

Two studies were conducted to evaluate the effect of XELJANZ on structural joint damage. In Study IV and Study 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 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 8. 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 VI, XELJANZ monotherapy inhibited the progression of structural damage compared to MTX at Months 6 and 12 as shown in Table 8. 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 8: 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 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 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 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

XELJANZ is provided as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) tablets: White, round, immediate-release film-coated tablets, debossed with “Pfizer” on one side, and “JKI 5” on the other side, and available in:

Bottles of 28:	NDC 0069-1001-03
Bottles of 60:	NDC 0069-1001-01
Bottles of 180:	NDC 0069-1001-02

Storage and Handling
Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature].

Do not repackage.

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Medication Guide).

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

Patient Counseling
Advise patients of the potential benefits and risks of XELJANZ.

Serious Infection
Inform patients that XELJANZ may lower the ability of their immune system to fight infections. Advise patients not to start taking XELJANZ 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)]*.

Malignancies and Lymphoproliferative Disorders
Inform patients that XELJANZ 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 may affect certain lab test results, and that blood tests are required before and during XELJANZ treatment *[see Warnings and Precautions (5.4)]*.

Pregnancy
Inform patients that XELJANZ should not be used during pregnancy unless clearly necessary, and advise patients to inform their doctors right away if they become pregnant while taking XELJANZ. Inform patients that Pfizer has a registry for pregnant women who have taken XELJANZ during pregnancy. Advise patients to contact the registry at 1-877-311-8972 to enroll *[see Pregnancy (8.1)]*.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.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LAB-0445-4.0

MEDICATION GUIDE

XELJANZ (ZEL' JANS')
(tofacitinib)

Read this Medication Guide before you start taking XELJANZ and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

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

1. Serious infections.

XELJANZ is a medicine that affects your immune system. XELJANZ can lower the ability of your immune system to fight infections. Some people have serious infections while taking XELJANZ, 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.
- Your healthcare provider should monitor you closely for signs and symptoms of TB infection during treatment with XELJANZ.

You should not start taking XELJANZ if you have any kind of infection unless your healthcare provider tells you it is okay.

Before starting XELJANZ, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection such as:
    - fever, sweating, or chills
    - muscle aches
    - cough
    - shortness of breath
    - blood in phlegm
    - weight loss
    - warm, red, or painful skin or sores on your body
    - diarrhea or stomach pain
    - burning when you urinate or urinating more often than normal
    - feeling very tired
- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes, 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. 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, call your healthcare provider right away if you have any symptoms of an infection. XELJANZ can make you more likely to get infections or make worse any infection that you have.

2. Cancer and immune system problems.

XELJANZ may increase your risk of certain cancers by changing the way your immune system works.

- Lymphoma and other cancers can happen in patients taking XELJANZ. 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 get tears in their stomach or intestine. 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 and while you take XELJANZ 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 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 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, and as needed after that. Normal cholesterol levels are important to good heart health.

See "What are the possible side effects of XELJANZ?" for more information about side effects.

What is XELJANZ?

XELJANZ is a prescription medicine called a Janus kinase (JAK) inhibitor. XELJANZ is used to treat adults with moderately to severely active rheumatoid arthritis in which methotrexate did not work well.

It is not known if XELJANZ is safe and effective in people with Hepatitis B or C.

XELJANZ is not for people with severe liver problems.

It is not known if XELJANZ is safe and effective in children.

What should I tell my healthcare provider before taking XELJANZ?

XELJANZ may not be right for you. Before taking XELJANZ, tell your healthcare provider if you:

- have an infection. See "What is the most important information I should know about XELJANZ?"
- 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
- have recently received or are scheduled to receive a vaccine. People who take XELJANZ should not receive live vaccines. People taking XELJANZ can receive non-live vaccines.
- have any other medical conditions
- plan to become pregnant or are pregnant. It is not known if XELJANZ will harm an unborn baby.

  Pregnancy Registry: Pfizer has a registry for pregnant women who take XELJANZ. 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, 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 or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. XELJANZ 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. You should not take tocilizumab (Actemra®), etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), rituximab (Rituxan®), abatacept (Orencia®), anakinra (Kineret®), certolizumab (Cimzia®), golimumab (Simponi®), azathioprine, cyclosporine, or other immunosuppressive drugs while you are taking XELJANZ. Taking XELJANZ 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?

- Take XELJANZ as your healthcare provider tells you to take it.

- Take XELJANZ 2 times a day with or without food.

- If you take too much XELJANZ, call your healthcare provider or go to the nearest hospital emergency room right away.

What are possible side effects of XELJANZ?

XELJANZ may cause serious side effects, including:

- See “What is the most important information I should know about XELJANZ?”

- **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. Your healthcare provider may do blood tests before you start treatment with XELJANZ and while you are using XELJANZ. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B or C infection:
    - feel very tired
    - skin or eyes look yellow
    - little or no appetite
    - vomiting
    - clay-colored bowel movements
    - fevers
    - chills
    - stomach discomfort
    - muscle aches
    - dark urine
    - skin rash

Common side effects of XELJANZ include:

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

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. 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?

Store XELJANZ at 68°F to 77°F (room temperature).

Safely throw away medicine that is out of date or no longer needed.

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

General information about the safe and effective use of XELJANZ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XELJANZ for a condition for which it was not prescribed. Do not give XELJANZ 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. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about XELJANZ that is written for health professionals.

What are the ingredients in XELJANZ?

Active ingredient: tofacitinib citrate

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

LAB-0535-1.0
Issued: November 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s04

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Division Summary Review
NDA/BLA #/ Supplement#	NDA 203214/ Supplement 0004
Applicant	Pfizer
Date of Submission	April 22, 2013
PDUFA Goal Date	February 21, 2014
Proprietary Name / Established (USAN) names	Xeljanz / Tofacitinib
Dosage forms / Strength	Tablet / 5 mg
Proposed Indication(s)	1. Moderately to severely active rheumatoid arthritis – structural damage claim
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Nikolay Nikolov, M.D.
Statistical Review	Yongman Kim, Ph.D.; Joan Buenconsejo, Ph.D.
CDTL Review	Sarah Yim, M.D.
Office of Prescription Drug Promotion (OPDP)	Adewale Adeleye, PharmD MBA, Kathleen Klemm, PharmD
Study Endpoints and Labeling Development (SEALD)	Debra Beitzell, Eric Brodsky, M.D.

1. Introduction

Xeljanz® (tofacitinib) is an oral small molecule inhibitor of Janus Kinase (JAK) which was approved on November 6, 2012 at the dose of 5 mg twice daily (BID) for the treatment of moderately to severely active rheumatoid arthritis (RA) in patients with an inadequate response or intolerance to methotrexate (MTX). At the time of the original application, Pfizer submitted data on radiographic outcomes from Study A3921044 (abbreviated hereafter as Study 1044), which was not considered adequate on its own to support inclusion in labeling. Concerns with the radiographic data were discussed in detail at May 9, 2012 Arthritis Advisory Committee meeting. The specific concerns with the data included:

- The low amount of progression in the placebo control group which limited the treatment difference that could be demonstrated,
- The small treatment difference that was observed was susceptible to and dependent on the analytical approach and missing data imputation method, and appeared to be driven by few extreme observations

- Data were not consistent with respect to dose—i.e., in some analyses 10 mg appeared to be better than 5 mg, and in other analyses 5 mg appeared to be better than 10 mg.

This supplemental New Drug application (sNDA) is to add results from a planned 1-year analysis of an additional Phase 3 clinical trial, Study A3921069 (Study 1069), which is a study in MTX-naïve RA patients who are randomized to begin MTX or tofacitinib. Results from Study 1069 were not available at the time of the original NDA. This study includes radiographic outcomes as its co-primary endpoint, and proposed as the additional evidence of efficacy needed to include radiographic results in the tofacitinib label. (b) (4)

(b) (4)

(b) (4)

2. Background

Since the late 1990's, clinical development programs evaluating the efficacy of proposed products for RA have primarily utilized American College of Rheumatology (ACR) response criteria to assess treatment effect on signs and symptoms, the Health Assessment Questionnaire-Disability Index (HAQ-DI) to assess treatment effect on physical functioning, and a standardized radiographic scoring system, such as the Sharp Score or modifications thereof, to assess treatment effect on structural damage progression.

One conundrum associated with the assessment of efficacy in RA is the possible dissociation between clinical and radiographic outcomes. Radiographic progression may occur in people who have very low apparent disease activity and patients with clinical disease activity may have no evidence of radiographic progression.[1] Thus, documentation of a benefit of treatment on structural damage progression has been an important goal of clinical development programs for new products proposed for RA, particularly if the product has a novel target. This has become an increasingly important aspect of the risk-benefit assessment for new RA treatments in light of the many approved treatments that have documented beneficial effects in inhibiting structural damage progression.

However, the many effective treatments approved for RA have also made it more difficult to demonstrate a treatment effect on radiographic outcomes:

- Background likelihood and rate of progression in RA patients is lower because Disease-Modifying Anti-Rheumatic Drugs (DMARDs) are standard of care and employed as first-line therapy after diagnosis[2]
- Placebo (even placebo added on to background therapy) control groups are ethically difficult to justify beyond 12 to 16 weeks in duration due to the concern for structural

[1] EC Keystone, "Clinical implications of understanding radiographic findings in relation to clinical outcomes in rheumatoid arthritis." J Rheumatol 2009; 36 Supple 82:11-16

[2] Singh et al., "2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis." Arthritis Care & Res 2012; 64(5):625-639.

damage occurring during the period that disease activity is not adequately controlled[3], however radiographic changes may take 6 months or more to detect. Thus by the time of the radiographic endpoint, many patients have required "escape" from assigned treatment. Their data is then missing at the time of the radiographic endpoint and must be imputed. If imputed data is the major influential factor in the overall results, then this causes uncertainty regarding the true treatment effect.

- The small changes in radiographs that are captured in a feasible clinical trial are small, and radiographic endpoints are therefore not well-suited for non-inferiority trial designs, as the small effect size results in impractically small non-inferiority margins. Reliably demonstrating superiority to an active comparator is also difficult because small changes can limit the possible treatment effect size.

Study 1044, which enrolled a patient population who were already on background DMARDs, suffered from many of these difficulties. In spite of this, results were suggestive of, though not definitive for, a beneficial effect of tofacitinib on radiographic outcomes. Study 1069, which forms the basis of this sNDA, enrolled RA patients who were MTX-naïve (patients were generally early in their disease course), and randomized patients to receive tofacitinib or optimized MTX (titrated up to 20 mg/week). The active control allowed for patients to remain in their assigned treatment groups for the full 6-month period prior to assessment of the radiographic endpoint, and no "escape" option was utilized, resulting in less missing data. This allowed for a more convincing demonstration of the effect of tofacitinib on radiographic outcomes, as will be discussed later in this memorandum.

3. CMC/Device

No new CMC data were submitted with this supplemental application. There are no outstanding issues that would preclude approval of this supplemental application.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this supplemental application and there are no outstanding issues.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology or biopharmaceutics data were submitted with this supplemental application, and there are no outstanding issues.

[3] Conference Summary: American College of Rheumatology Clinical Trial Priorities and Design Conference, July 22-23, 2010. Arthritis & Rheum 2011; 63(8):2151-2156.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Summary of Clinical Studies

Two studies incorporated radiographic outcome assessments, as summarized in Table 1 below. The results from Study 1044 were described in the reviews of the original NDA and will be briefly recapitulated here. Whereas Study 1044 evaluated RA patients with inadequate response to MTX and had a control group of patients who received placebo added to stable background medications, Study 1069 was an active-controlled study that evaluated RA patients who had not yet received MTX, and randomized patients to receive optimized MTX (titrated up to 20 mg/week) or tofacitinib. Because of this basic difference in study design, Study 1069 did not require a rescue therapy option or a cross-over to active treatment, whereas placebo group patients in Study 1044 could change treatment as early as Month 3 and were all crossed over to tofacitinib at Month 6. Therefore in Study 1069 there was less missing data and less imputed data, and most of the control group remained available for comparison at Month 6 and even Month 12.

Table 1: Tofacitinib Radiographic Studies in RA

Protocol	Patient Population	Design *Duration*	Enrolled *Randomization*	Treatment Arms (transition and escape for NR)	Primary Endpoints	Timepoint
Patients naïve to MTX						
A3921069	Moderate-to-severe RA MTX-naïve	R, DB, PC Phase 3 *Two years**	399 *2:2:1:1*	CP 5 mg BID, monotherapy CP 10 mg BID, monotherapy MTX up-titrated q 4 weeks to 20 mg/week, monotherapy	mTSS ACR70	Month 6 Month 6
Patients with incomplete response to MTX or other DMARDs						
A3921044	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 3 *Two years*	797 *4:4:1:1*	CP 5 mg BID + MTX CP 10 mg BID + MTX PBO (→CP 5 mg BID @ Mo 6 or Mo3 if NR)+ MTX PBO (→CP 10 mg BID @ Mo 6 or Mo3 if NR)+ MTX	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6

Source: Summary of Clinical Efficacy, Clinical Study Reports for studies A3921032, A3921044, A3921045, A3921046, A3921064
*-One year efficacy data submitted for Study A3921069; BID-two times daily; DMARDs-disease-modifying anti-rheumatic drugs; IR-incomplete response; MTX-methotrexate; mTSS-modified total Sharp Score; NR-non-responder defined as patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts over baseline at Month 3 visit; PBO-placebo; PC-placebo (add-on for studies A3921032, A3921044, A3921046, A3921064)-controlled; SC-subcutaneous; CP=CP-690,550/tofacitinib

Source: Table 3 of Dr. Nikolov's clinical review

Brief Description of Radiographic Endpoint

- *Van der Heijde modified Sharp Score*

The Van der Heijde-modified Sharp radiographic scoring method grades the presence of erosions in the joints of the hands and feet, and the presence of joint space narrowing (JSN) in the hands, wrists, and feet.[4] The scores for each feature for the individual joints are summed.

[4] S Boini and F Guillemin, "Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages." Ann Rheum Dis 2001; 60:817-827

Erosions are assessed at 16 locations in each hand and wrists and 12 locations in each foot, using a 6-point scale from 0 to 5. Scores are derived based on the number and size of discrete erosions in each location, but are summed to a maximum of 5. Thus the maximum erosion score for the hands/wrists is 160, and the maximum erosion score for the feet is 120, for a maximum total erosion score of 280. JSN scores are based on 15 locations in each hand and wrist and 6 locations in each foot, scored using a 5-point scale from 0 to 4: 0 = normal; 1 = focal or minimal and generalized narrowing; 2 = generalized narrowing <50%; 3 = generalized narrowing >50% or subluxation; and 4 = ankylosis or complete dislocation. The maximum total JSN for the hands/wrists is 120, and the maximum total JSN for the feet is 48, for a maximum total JSN score of 168. Therefore the theoretical maximum modified total Sharp Score (mTSS) is 448, although the actual clinical range in RA drug development trials is typically much lower because a given individual typically only has a fraction of his or her joints affected by radiographically evident damage.

Study 1044 Radiographic Results

The primary radiographic endpoint in Study 1044 was assessed at Month 6, after which all placebo control group patients were transitioned to tofacitinib. At Month 3, patients who had not experienced a 20% improvement in tender and swollen joint counts were advanced to active treatment. Approximately 49% of placebo patients left the placebo group at Month 3 for this reason, compared to 26% of patients in the tofacitinib 5 mg group and 18% of patients in the tofacitinib 10 mg group.

Patients with missing data at Month 6 or Month 12 had their data imputed using linear extrapolation from baseline to their last radiographs prior to exiting their assigned treatment group. This imputation method has been used historically in other RA development programs assessing structural damage, but has inherent limitations, particularly as the length of the extrapolation period increases and the amount of missing data increases. Binary variables (e.g., rates of patients with no progression in mTSS) were analyzed using normal approximation to the binomial. Scoring of all radiographs was done by two separate central blinded assessors.

The primary analysis of the radiographic outcome in Study 1044 excludes patients from sites with data integrity or procedural issues, as well as additional patients for whom valid post-baseline radiographs were not obtained. Thus the primary radiographic analysis excludes 21 (13%) placebo patients, 44 (14%) patients in the tofacitinib 5 mg group, and 24 (8%) patients in the tofacitinib 10 mg group. This amount of missing data is consistent with other RA development programs and is not excessive.

A primary analysis using the analysis of covariance (ANCOVA) model and a sensitivity analysis using rank-based ANCOVA were pre-specified in the protocol's statistical analysis plan. Results of the parametric primary analysis versus the non-parametric sensitivity analysis are summarized in Table 2 below. In the primary analysis, only the change from baseline in mTSS for the tofacitinib 10 mg group achieved statistical significance compared to the placebo group. The statistical significance of the findings changes when the non-parametric analysis

was used—only the tofacitinib 5 mg group results achieved statistical significance. Both doses were not significantly different from placebo at Month 12.

Table 2: Analyses of Change from Baseline in Modified Total Sharp Scores, Study A3921044

Analyses of Radiographic Outcomes: Change from Baseline in Modified Total Sharp Scores (mTSS) in Study A3921044			
	PBO + MTX	CP 5 mg BID + MTX	CP 10 mg BID + MTX
Assigned to study treatment (tx)	n = 160	n = 321	n = 319
Received at least 1 dose of study tx	n = 160	n = 321	n = 316
"Full Analysis Set"	n = 156	n = 316	n = 309
Sponsor primary analysis (FAS, LEP, parametric)			
Month 6 (Primary Endpoint)	n = 139*	n = 277*	n = 290*
mTSS LS means	0.47	0.12	0.06
p-value vs. placebo	-	0.0792	0.0376
Month 12	n = 139*	n = 286*	n = 295*
mTSS LS means	0.92	0.29	0.05
p-value vs. placebo	-	0.0558	0.0081
Pre-specified non-parametric analyses			
Month 6 (Primary Endpoint)			
ANCOVA with ranked data p-value	-	0.0237	0.1979
Month 12			
ANCOVA with ranked data p-value	-	0.0578	0.079

Sources: Summary of Clinical Efficacy Table 27; Study A3921044 CSR, Tables 11 and 14.2.15.1.6
FAS=Full Analysis Set; LEP=Linear Extrapolation method for missing data imputation
*If subjects did not have any valid post-baseline radiographs, they were excluded from this analysis

Results in Table 3 below show that fewer patients progressed in the tofacitinib 5 mg group than the tofacitinib 10 mg group. This result contrasts with the apparently larger treatment effect for the 10 mg dose in the analysis of mean change from baseline in mTSS. The apparently larger effect observed in the 10 mg group was explained by two outliers, one of which was extrapolated data. Further illustrating the lack of conclusiveness of the radiographic data, a change in the definition of "no progression" from a change in mTSS of $\leq$0.5 units to 0 units resulted in an 8% reduction in the proportion of nonprogressors in the tofacitinib 10 mg dose group and a loss of statistical significance compared to the control group.

Table 3: Rates of "No Progression" Based on Change from Baseline to Month 6 in mTSS

Treatment	N	N	Rate	Diff from PBO	P-value
No Progression defined by applicant as Change in mTSS ≤ 0.5					
CP 5 mg	277	246	89 %	11 %	**.0055**
CP 10 mg	290	252	87 %	9 %	**.0230**
PBO	139	108	78 %		
No Progression defined by FDA reviewer as Change in mTSS ≤ 0					
CP 5 mg	278	233	84 %	10 %	**.0200**
CP 10 mg	290	229	79 %	5 %	.2766
PBO	140	104	74 %		

Source: Table 20 of A3921044 Clinical Study Report; FDA analysis by Dr. Yongman Kim

In other exploratory analyses performed by FDA statisticians, when outliers (defined as a change greater than 7 units) were excluded, the difference between the tofacitinib 5 mg and placebo groups remained significant but the difference between the tofacitinib 10 mg and placebo group did not. When outliers of greater than 20 units were excluded, the difference between both tofacitinib groups and the placebo group lost statistical significance. Therefore the estimated treatment effect of tofacitinib was highly dependent on these outliers. The reader is referred to the statistical review of the original submission of NDA 203214 for details of these analyses.

In summary, the data in Study 1044 was suggestive of a treatment benefit of tofacitinib for the radiographic endpoint but was not adequate to definitively characterize the treatment effect and its relationship to dose.

Study 1069 Radiographic Results

At the time of the data cutoff for this submission, approximately 17% of patients in each of the tofacitinib groups had discontinued the study, and approximately 28% of the MTX group patients had discontinued. To be included in the radiographic endpoint assessment, patients must have had a baseline and at least one post-baseline radiograph. Patients with missing data at Month 6 or Month 12 had their data imputed using linear extrapolation from baseline to their last radiographs prior to exiting their assigned treatment group. This imputation method has been used historically in other RA development programs assessing structural damage, but has inherent limitations, particularly as the length of the extrapolation period increases and the amount of missing data increases. Scoring of all radiographs was done by central blinded assessors.

As shown in Table 4 below, both tofacitinib 5 mg and tofacitinib 10 mg were associated with a reduction in mean change from baseline in mTSS compared to MTX. The pre-specified primary analysis, using ANCOVA, was statistically significant. Although the degree of difference was slightly greater for tofacitinib 10 mg compared to 5 mg, this study was not powered for a comparison of tofacitinib 5 and 10 mg, and additionally, it is not clear whether the small difference observed would translate into a clinically meaningful difference.

The applicant pre-specified a Rank-ANCOVA analysis which was consistent with the primary analysis. Improvement in the total modified Sharp score was also reflected in the individual erosion and joint space narrowing components of the modified Sharp score (data not shown).

Table 4: Study 1069 Results for modified Total Sharp Score (mTSS)

	MTX	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
Assigned to study treatment (tx)	n = 186	n = 374	n = 398
Received at least 1 dose of study tx	n = 186	n = 371	n = 395
Full Analysis Set (FAS)*	n = 166 (89%)	n = 346 (93%)	n = 369 (93%)
Change from Baseline in modified Total Sharp Score (mTSS)			
Month 6 (Primary Endpoint)			
LS mean	0.84	0.18	0.04
Difference from MTX	--	-0.66	-0.81
95% CI of the difference		(-1.03, -0.28)	(-1.18, -0.44)
p-value (ANCOVA)		<0.001	<0.001
Month 12			
LS mean	1.3	0.4	0
Difference from MTX		-0.9	-1.3
95% CI of the difference		(-1.4, -0.4)	(-1.8, -0.8)

Source: Study A3921069 CSR Tables 11 and 15
*If subjects did not have any valid post-baseline radiographs, they were excluded from this analysis

FDA statistical reviewer Dr. Yongman Kim also conducted sensitivity analyses evaluating the sensitivity of the estimated treatment effect with respect to extreme (≥20 units) and moderate (≥7 units) outliers. Only 2 patients had a change of 20 or more units in mTSS—one patient in the tofacitinib 5 mg group and one patient in the MTX group. When these two patients were excluded, the difference in mTSS between the tofacitinib groups and the MTX group remained consistent with the primary analysis, and was also statistically significant. When 7 units was used to define outliers, 9 patients were excluded (4 from the MTX group, 4 from the 5 mg group and 1 from the 10 mg group). When these patients were excluded, the difference between the tofacitinib and MTX groups remained consistent with the primary analysis, and remained statistically significant. Therefore, unlike Study 1044, the radiographic outcome results for Study 1069 were not sensitive to the effect of outliers.

As shown in Table 5 below, tofacitinib treatment was associated with a higher proportion of patients experiencing no radiographic progression compared to MTX, whether that was defined as a change in mTSS of ≤0.5 units (the sponsor's analysis) or whether that was defined as a change in mTSS of ≤0 units (FDA analysis). Although tofacitinib 10 mg was associated with a slightly higher proportion of nonprogressors compared to the 5 mg dose, the difference between the tofacitinib groups is small, and it is not clear whether this represents a real or clinically meaningful difference.

Overall, results of Study 1069 provided conclusive evidence of the efficacy of tofacitinib for reducing structural damage as assessed by the radiographic outcome of mTSS. The numerical differences observed between the 10 mg and 5 mg dose of tofacitinib were small, and the clinical meaningfulness of those differences is unclear.

Table 5: Proportion of Patients with "No Progression" in mTSS, Study 1069

Treatment	N	n	Rate	Difference vs. MTX	95% CI
No Progression Defined by Applicant as Change in mTSS ≤ 0.5					
CP 5 mg	346	289	84 %	13 %	(5%, 21%)
CP 10 mg	369	331	90 %	19 %	(11%, 27%)
MTX	167	118	71 %		
No Progression Defined by Reviewer as Change in mTSS ≤ 0					
CP 5 mg	346	254	73 %	18 %	(9%, 27%)
CP 10 mg	369	284	77 %	21 %	(13%, 30%)
MTX	167	93	56 %		

Source: Table 7 of the FDA Statistical Review by Dr. Yongman Kim

Other Endpoints

The co-primary endpoint for Study 1069 was the proportion of ACR70 responders at Month 6. There were multiple other secondary endpoints evaluated in Study 1069, including the proportion of ACR20 and ACR50 responders, ACR response rates over time, change from baseline in the ACR core variables, the proportion of patients with a sustained ACR70 response for at least 6 months, DAS28-4(ESR), Health Assessment Questionnaire-Disability Index (HAQ-DI), and many other outcome measures. The efficacy of tofacitinib for these multiple measures of clinical response and physical functioning have been previously established in the original NDA, and the results of Study 1069 are consistent with the previously submitted studies.

8. Safety

- **Discuss the adequacy of the database, major findings/signals**

The safety data in this submission were updated data from the 6 Phase 2 studies, 6 Phase 3 studies, and two ongoing open-label long-term extension studies that comprised the tofacitinib development program in RA. Because this submission is the first for Study 1069, and this study evaluated RA patients at an earlier stage (MTX-naïve patients), safety results for Study 1069 were assessed separately, and then in the context of the other studies in the clinical development program. As of the data cutoff for this submission (April 19, 2012), the safety database included ~4800 patients across all treatment groups and ~8500 patient-years of exposure to all doses of tofacitinib (approximately 1500 additional patient-years of exposure compared to the original NDA submission). The number of patients with at least 24 months of exposure to tofacitinib has more than doubled since the original submission, from 709 patients to 2002 patients. There are still a limited number of patients who have received tofacitinib for

36 months or more (634 patients). The number of patients with a longer duration of exposure is important because of the apparent dose- and duration- dependent safety concerns noted in the original NDA submission.

At the time of the original NDA submission, potential safety issues identified included:

- Malignancy
    - The risk of malignancy appeared to increase over time in the long-term extension;
    - There appeared to be an increased risk of lymphoma in particular;
    - There was also a suggestion of increasing risk with increasing dose, based on nonclinical data and human data in RA and renal transplant patients.
- A dose-dependent increase in serious infections, including opportunistic infections and tuberculosis.
- A dose-dependent increase in a number of laboratory abnormalities, to include abnormal hematologic parameters, lipid parameter changes, and serum creatinine elevation.

Overall, the safety profile of tofacitinib in Study 1069 was consistent with the safety profile of tofacitinib demonstrated in previous studies. Updated long-term data from ongoing studies in the tofacitinib clinical development program are also consistent with the aforementioned dose- and duration- dependent safety concerns.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

Table 7 below contains a summary of the one-year safety data for Study 1069. In terms of overall adverse events (AEs), serious adverse events (SAEs), and discontinuations due to adverse events (DAEs), incidence in both tofacitinib groups was similar to MTX. This very high level summary does not adequately capture dose- and duration- dependent safety concerns, which will be described in further detail below.

Table 6: Overview of One-Year Safety Data for Study 1069

	Tofa 5 mg BID n (%)	Tofa 10 mg BID n (%)	MTX n (%)
Randomized and treated	371	395	186
Exposure for event, patient-years (PY)	331	353	152
Total number of AEs	863	1057	449
Total patients with ≥ 1 AE, n (%)	260 (70)	294 (74)	130 (70)
Incidence of AEs, event per 100 PY	155	183	197
Total patients with ≥ 1 SAE, n (%)	24 (7)	24 (6)	13 (7)
Incidence of SAEs, event per 100 PY	7.2	6.8	8.6
Total patients with ≥ 1 Severe AE, n (%)	22 (6)	21 (5)	11 (6)
Patients who discontinued due to AE, n (%)	24 (7)	31 (8)	17 (9)
Incidence discontinuations due to AE, event per 100 PY	7.2	8.8	11.2

Source: CSR A3921069, Adapted from Tables 27 and 28

Source: Table 19 of Dr. Nikolov's clinical review

Where available, the exposure-adjusted incidence of adverse events of interest over time in the tofacitinib RA clinical development program is summarized in Table 8 below. The exposure-adjusted incidence of death has remained low and consistent over time, with additional exposure. These data suggest that serious infections, tuberculosis, and lymphoproliferative disorders may be increasing over time, whereas opportunistic infections and malignancies excluding non-melanoma skin cancer (NMSC) may be relatively stable. However these data are limited in that they are not broken down by dose, and are cumulative. Further analyses to shed light on incidence by dose, and non-cumulative incidence by 6-month intervals are provided separately below.

Table 7: Cumulative Exposure-Adjusted Incidence for Safety Events of Interest

	Original Submission 29 Mar 2011 Data Cut N (Event/100 PY)	**120 Day Safety Update 29 Sep 2011 Data Cut** N (Event/100 PY)	**April 2012 Update 19 Apr 2012 Data Cut** N (Event/100 PY)]
N	4789	4791	4789
Exposure, Patient Years	5651	6922	8460
Mortality (up to 30 days of last dose)	21 (0.4)	24 (0.4)	25 (0.3)
Serious Infections	167 (2.97)	206 (3.00)	259 (3.09)
Tuberculosis (TB)	NA	11 (0.16)	16 (0.19)
Opportunistic Infections, including TB	NA	33 (0.48)	41 (0.49)
Herpes Zoster	239 (4.4)	288 (4.3)	346 (4.3)
Malignancies (excl. NMSC)	50 (0.89)	65 (0.94)	75 (0.89)
Lymphoproliferative Disorders/Lymphoma	3 (0.05)	3 (0.04)	7 (0.07)*

Source: Integrated Summary of Safety, Adapted from Tables 4 an 255.2 (* Data cutoff for lymphoma was April 16, 2012 using a different estimate number of patients/patient years -5559/9935)
Subjects exposure time is counted from first dose of tofacitinib in the index study through last known dose in the extension study. Some events may have occurred post end of treatment, these events were counted in the numerator and subjects' full tofacitinib treatment exposure was included in denominator.

Source: Table 20 of Dr. Nikolov's Clinical Review

- **Special safety concerns—Dose- and Duration- Dependent Risks**

As summarized in Table 9 below, with roughly similar exposure in the 5 mg and 10 mg cohorts, tofacitinib 10 mg BID appears to be associated with an increased risk over 5 mg BID for overall SAE, DAE, serious infections, tuberculosis, herpes zoster, and malignancy (excluding non-melanoma skin cancer). There is also an apparent dose-related increased risk of non-melanoma skin cancer (NMSC) with tofacitinib treatment. As of the April 2013 data cutoff, tofacitinib 5 mg BID was associated with an exposure-adjusted incidence of approximately 0.35 NMSC per 100 patient-years, compared to approximately 0.84 NMSC per 100 patient-years for the 10 mg BID dose regimen. There does not appear to be a dose-related increase in deaths or opportunistic infections.

Table 8: Overview of Safety by Dose (Patients who only received the assigned dose) in the Cumulative RA Development Program

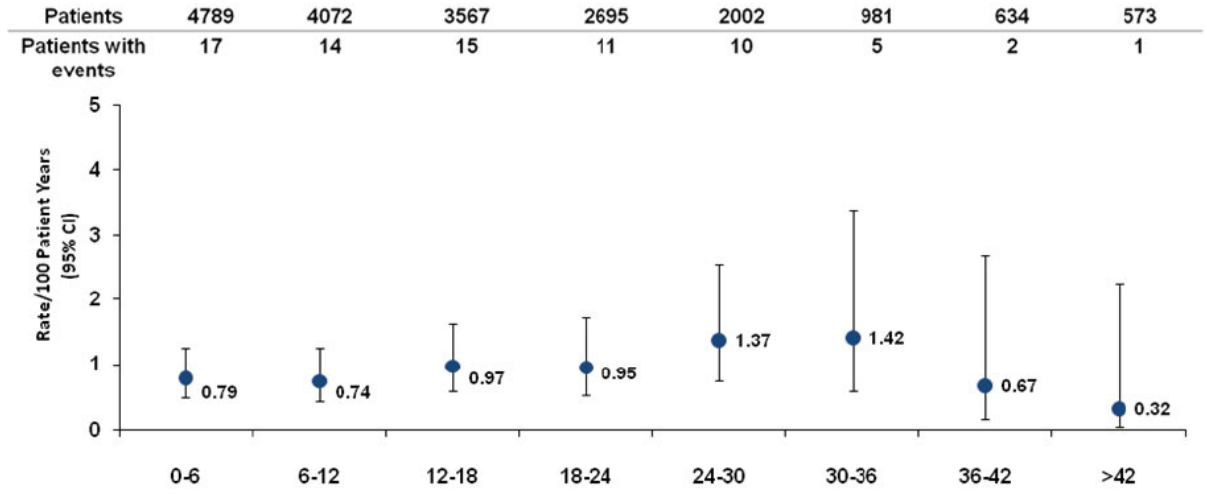
	5 mg BID cohort	10 mg BID cohort
Number of patients	1955	1846
Exposure (PY)	2174	2460
Deaths within 30 days of last dose	6	5
Rate per 100 PY (95% CI)	*0.28 (0.1, 0.6)*	*0.2 (0.1, 0.5)*
No with ≥ 1 SAE	210	261
Rate per 100 PY (95% CI)	*10.2 (8.9, 12)*	*11.1 (9.9, 12.6)*
AE leading to discontinuation	170	223
Rate per 100 PY (95% CI)	*7.9 (6.8, 9.1)*	*9.2 (8.1, 10.5)*
Serious infection, n	59	87
Rate per 100 PY (95% CI)	*2.7 (2.1, 3.5)*	*3.6 (2.9, 4.4)*
Tuberculosis (TB), n	2	9
Rate per 100 PY (95% CI)	*0.1 (0.02, 0.4)*	*0.4 (0.2, 0.7)*
Opportunistic infection, n	8	7
Rate per 100 PY	*0.4*	*0.3*
No with ≥ 1 H. zoster infection	84	113
Rate per 100 PY (95% CI)	*4.0 (3.2, 5.0)*	*4.8 (4.0, 5.7)*
No with ≥ 1 Malignancy (excl. NMSC)	18	23
Rate per 100 PY (95% CI)	*0.83 (0.5, 1.3)*	*0.94 (0.6, 1.4)*
LPD, n	1	2
Rate per 100 PY (95% CI)	*0.05 (0.01, 0.3)*	*0.08 (0.02, 0.3)*
No with ≥ 1 MACE	6	8
Rate per 100 PY (95% CI)	*0.5 (0.2, 1.1)*	*0.4 (0.2, 0.7)*

Source: Summary of Clinical Safety, Adapted from Table 5

Source: Table 21 of Dr. Nikolov's clinical review

Figures 1 and 2 below illustrate the non-cumulative rates over time, by 6-month intervals, for malignancy and serious infections, respectively. Although this submission provides additional data, the pattern is very similar to the data provided in the original NDA. Specifically, the incidence of malignancy appears to be slowly increasing over time with increasing exposure. There are too few patients at the 36-month and 42-month time points to know whether the drop off in incidence is due to a lack of a signal or due to an insufficient number of patients being exposed at those durations. For similar reasons it is not clear whether the incidence of serious infections has dropped off at these same time points. Otherwise the incidence of serious infections appears to be relatively consistent over time, with the highest incidence being in the second 6-months of exposure.

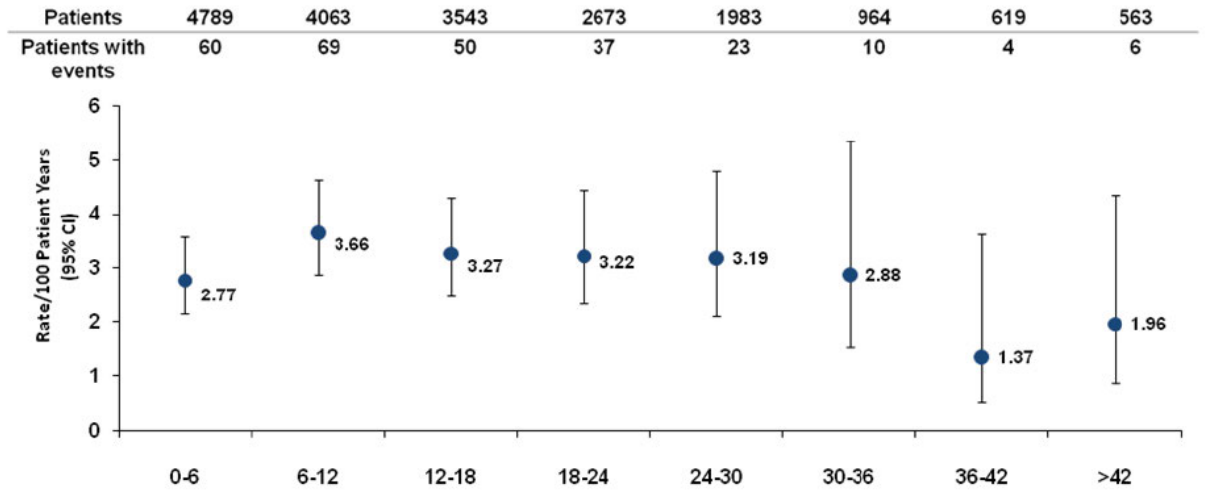
Figure 1: Non-Cumulative Incidence of Malignancy by 6-Month Intervals in the Tofacitinib RA Development Program (Excluding Non-Melanoma Skin Cancer)



Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Phase 2, Phase 3 and LTE data as of 19 April 2012

Source: Integrated Summary of Safety as of April 29, 2012

Figure 2: Non-Cumulative Incidence of Serious Infections by 6-Month Intervals in the Tofacitinib RA Development Program



Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Phase 2, Phase 3 and LTE data as of 19 April 2012

Source: Integrated Summary of Safety as of April 29, 2012, Figure 2

- **Safety Conclusions**

The safety data in this submission are consistent with the data in the original NDA submission. Tofacitinib has the safety profile of a potent immunosuppressive, and has serious dose- and duration- related safety signals, such as an increased risk of serious infection and malignancy.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this supplemental application, as no issues that would warrant discussion were identified. The original NDA for tofacitinib was discussed at the May 9, 2012 Arthritis Advisory Committee meeting.

10. Pediatrics

This sNDA does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and therefore does not trigger PREA. With the original NDA, the sponsor received a partial waiver for polyarticular juvenile idiopathic arthritis (PJIA) patients under 2 years of age and a deferral for studies in PJIA patients 2 to <18 years of age. The PREA PMR studies include a multiple dose pharmacokinetic trial (final report due in September 2014) and a randomized withdrawal efficacy and safety trial (final report due in September 2017) in PJIA patients.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues of concern**—No issues identified.
- **Financial disclosures**—No issues identified.
- **Other GCP issues**—No issues identified.
- **Office of Scientific Investigation (OSI) audits**—No clinical site inspections were deemed warranted for this submission. OSI inspections were conducted for the original NDA and did not identify major deficiencies in data quality or integrity.
- **Other outstanding regulatory issues**—There are no other unresolved relevant regulatory issues

12. Labeling

- **Proprietary name**—Already approved as Xeljanz.
- **Physician labeling**—The sponsor submitted proposed labeling changes that were primarily limited to radiographic results in Section 14. There were no major labeling issues. Refinements in the proposed labeling language and data display were recommended by the FDA review team. FDA and Pfizer have agreed upon final labeling changes to the currently approved Xeljanz prescribing information.
- **Carton and immediate container labels**—No change from the approved labeling is proposed.
- **Patient labeling/Medication guide**—No changes are proposed or warranted on the basis of this submission.

13. Decision/Action/Risk-Benefit Assessment

- **Regulatory Action**

The action on this supplemental NDA will be approval.

- **Risk Benefit Assessment**

Based on the data in this submission, the risk-benefit profile of tofacitinib 5 mg BID remains favorable for the RA indication. Study 1069 provided convincing evidence of the efficacy of tofacitinib 5 mg BID and 10 mg BID for reducing the progression of structural damage due to RA. Although tofacitinib 10 mg BID appeared to be slightly more efficacious than 5 mg BID for radiographic outcomes, the differences between these two dose regimens were small, and are of unclear clinical significance. (b) (4)

- **Postmarketing Risk Evaluation and Management Strategies**

Tofacitinib currently has an approved Risk Evaluation and Mitigation Strategy (REMS) consisting of a medication guide and communication plan. The REMS focuses on the risks of serious infections, including opportunistic infections, tuberculosis, malignancy, increase in cholesterol and decrease in blood counts. No change in the currently approved REMS is warranted on the basis of the information in this submission.

- **Other Postmarketing Requirements and Commitments**

There are three postmarketing requirements (PMR) that were associated with the original approval of tofacitinib: 2 deferred pediatric studies (as described in Section 10 above) and 1 controlled clinical trial to evaluate the long-term safety of the 5 and 10 mg BID doses of tofacitinib in comparison to an active comparator. There are no postmarketing commitments (PMC). No additional PMR or PMC are recommended on the basis of this submission.

- **Comments to Applicant**—None.

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/s/

SARAH K YIM
02/20/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s04

OFFICER/EMPLOYEE LIST

Officer/Employee List

Application: NDA 203214/S-004

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

1. Bowen, Philantha
2. Buenconsejo, Joan
3. Chowdhury, Badrul
4. Jafari, Ladan
5. Kim, Yongman
6. Nikolov, Nikolay
7. Permutt, Thomas
8. Yim, Sarah

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s04

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 31, 2014
From	Sarah Yim, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 203214 Supplement 0004
Applicant	Pfizer
Date of Submission	April 22, 2013
PDUFA Goal Date	February 21, 2014
Proprietary Name / **Established (USAN) names**	Xeljanz / Tofacitinib
Dosage forms / Strength	Tablet / 5 mg
Proposed Indication(s)	1. Moderately to severely active rheumatoid arthritis – structural damage claim
Recommended:	*Approval*

1. Introduction

Xeljanz® (tofacitinib) is an oral small molecule inhibitor of Janus Kinase (JAK) which was approved on November 6, 2012 at the dose of 5 mg twice daily (BID) for the treatment of moderately to severely active rheumatoid arthritis (RA) in patients with an inadequate response or intolerance to methotrexate (MTX). At the time of the original application, Pfizer submitted data on radiographic outcomes from Study A3921044 (abbreviated hereafter as Study 1044), which was not considered adequate on its own to support inclusion in labeling. Concerns with the radiographic data were discussed in detail at May 9, 2012 Arthritis Advisory Committee meeting. The specific concerns with the data included:

- The low amount of progression in the placebo control group which limited the treatment difference that could be demonstrated,
- The small treatment difference that was observed was susceptible to and dependent on the analytical approach and missing data imputation method, and appeared to be driven by few extreme observations
- Data were not consistent with respect to dose—i.e., in some analyses 10 mg appeared to be better than 5 mg, and in other analyses 5 mg appeared to be better than 10 mg.

This supplemental New Drug application (sNDA) is to add results from a planned 1-year analysis of an additional Phase 3 clinical trial, Study A3921069 (Study 1069), which is a study in MTX-naïve RA patients who are randomized to begin MTX or tofacitinib. Results from Study 1069 were not available at the time of the original NDA. This study includes radiographic outcomes as its co-primary endpoint, and proposed as the additional evidence of efficacy needed to include radiographic results in the tofacitinib label. (b) (4)

(b) (4)

(b) (4)

2. Background

Since the late 1990's, clinical development programs evaluating the efficacy of proposed products for RA have primarily utilized American College of Rheumatology (ACR) response criteria to assess treatment effect on signs and symptoms, the Health Assessment Questionnaire-Disability Index (HAQ-DI) to assess treatment effect on physical functioning, and a standardized radiographic scoring system, such as the Sharp Score or modifications thereof, to assess treatment effect on structural damage progression.

One conundrum associated with the assessment of efficacy in RA is the possible dissociation between clinical and radiographic outcomes. Radiographic progression may occur in people who have very low apparent disease activity and patients with clinical disease activity may have no evidence of radiographic progression.[1] Thus, documentation of a benefit of treatment on structural damage progression has been an important goal of clinical development programs for new products proposed for RA, particularly if the product has a novel target. This has become an increasingly important aspect of the risk-benefit assessment for new RA treatments in light of the many approved treatments that have documented beneficial effects in inhibiting structural damage progression.

However, the many effective treatments approved for RA have also made it more difficult to demonstrate a treatment effect on radiographic outcomes:

- Background likelihood and rate of progression in RA patients is lower because Disease-Modifying Anti-Rheumatic Drugs (DMARDs) are standard of care and employed as first-line therapy after diagnosis[2]
- Placebo (even placebo added on to background therapy) control groups are ethically difficult to justify beyond 12 to 16 weeks in duration due to the concern for structural damage occurring during the period that disease activity is not adequately controlled[3], however radiographic changes may take 6 months or more to detect. Thus by the time of the radiographic endpoint, many patients have required "escape" from assigned treatment. Their data is then missing at the time of the radiographic endpoint and must be imputed. If imputed data is the major influential factor in the overall results, then this causes uncertainty regarding the true treatment effect.
- The small changes in radiographs that are captured in a feasible clinical trial are small, and radiographic endpoints are therefore not well-suited for non-inferiority trial designs, as the small effect size results in impractically small non-inferiority margins. Reliably demonstrating superiority to an active comparator is also difficult because small changes can limit the possible treatment effect size.

[1] EC Keystone, "Clinical implications of understanding radiographic findings in relation to clinical outcomes in rheumatoid arthritis." J Rheumatol 2009; 36 Supple 82:11-16
[2] Singh et al., "2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis." Arthritis Care & Res 2012; 64(5):625-639.
[3] Conference Summary: American College of Rheumatology Clinical Trial Priorities and Design Conference, July 22-23, 2010. Arthritis & Rheum 2011; 63(8):2151-2156.

Study 1044, which enrolled a patient population who were already on background DMARDs, suffered from many of these difficulties. In spite of this, results were suggestive of, though not definitive for, a beneficial effect of tofacitinib on radiographic outcomes. Study 1069, which forms the basis of this sNDA, enrolled RA patients who were MTX-naïve (patients were likely early in their disease course), and randomized patients to receive tofacitinib or optimized MTX (titrated up to 20 mg/week). The active control allowed for patients to remain in their assigned treatment groups for the full 6-month period prior to assessment of the radiographic endpoint, and no "escape" option was utilized, resulting in less missing data. This allowed for a more convincing demonstration of the effect of tofacitinib on radiographic outcomes, as will be discussed later in this memorandum.

3. CMC/Device

No new CMC data were submitted with this supplemental application.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this supplemental application.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology or biopharmaceutics data were submitted with this supplemental application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary Clinical Reviewer: Nikolay Nikolov, M.D.
Primary Statistical Reviewer: Yongman Kim, Ph.D.
Secondary Statistical Reviewer: Joan Buenconsejo, Ph.D.

Summary of Clinical Studies

Two studies incorporated radiographic outcome assessments, as summarized in Table 1 below. The results from Study 1044 were described in the reviews of the original NDA and will be

briefly recapitulated here. Whereas Study 1044 evaluated RA patients with inadequate response to MTX and had a control group of patients who received placebo added to stable background medications, Study 1069 was an active-controlled study that evaluated RA patients who had not yet received MTX, and randomized patients to receive optimized MTX (titrated up to 20 mg/week) or tofacitinib. Because of this basic difference in study design, Study 1069 did not require a rescue therapy option or a cross-over to active treatment, whereas placebo group patients in Study 1044 could change treatment as early as Month 3 and were all crossed over to tofacitinib at Month 6. Therefore in Study 1069 there was less missing data and less imputed data, and most of the control group remained available for comparison at Month 6 and even Month 12.

Table 1: Tofacitinib Radiographic Studies in RA

Protocol	Patient Population	Design *Duration*	Enrolled *Randomization*	Treatment Arms (transition and escape for NR)	Primary Endpoints	Timepoint
Patients naïve to MTX						
A3921069	Moderate-to-severe RA MTX-naïve	R, DB, PC Phase 3 *Two years**	399 *2:2:1:1*	CP 5 mg BID, monotherapy CP 10 mg BID, monotherapy MTX up-titrated q 4 weeks to 20 mg/week, monotherapy	mTSS ACR70	Month 6 Month 6
Patients with incomplete response to MTX or other DMARDs						
A3921044	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 3 *Two years*	797 *4:4:1:1*	CP 5 mg BID + MTX CP 10 mg BID + MTX PBO (→CP 5 mg BID @ Mo 6 or Mo3 if NR)+ MTX PBO (→CP 10 mg BID @ Mo 6 or Mo3 if NR)+ MTX	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6

Source: Summary of Clinical Efficacy, Clinical Study Reports for studies A3921032, A3921044, A3921045, A3921046, A3921064
*-One year efficacy data submitted for Study A3921069; BID-two times daily; DMARDs-disease-modifying anti-rheumatic drugs; IR-incomplete response; MTX-methotrexate; mTSS-modified total Sharp Score; NR-non-responder defined as patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts over baseline at Month 3 visit; PBO-placebo; PC-placebo (add-on for studies A3921032, A3921044, A3921046, A3921064)-controlled; SC-subcutaneous; CP=CP-690,550/tofacitinib

Source: Table 3 of Dr. Nikolov's clinical review

Brief Description of Efficacy Endpoints

- *ACR Response Rates*

In 1995, the American College of Rheumatology (ACR) published a definition of improvement for clinical trials in rheumatoid arthritis, which have since been used in drug development trials to demonstrate evidence of efficacy for signs and symptoms of RA.[4] The ACR20 response is calculated as a ≥20% improvement in:

- tender joint count (of 68 joints) and
- swollen joint count (of 66 joints) and
- 3 of the 5 remaining ACR core set measures
    - Patient Global Assessment of Arthritis on a visual analog scale (VAS)
    - Physician Global Assessment of Arthritis on a VAS
    - Patient Assessment of Pain on a VAS
    - Patient Assessment of Physical Function (e.g. Health Assessment Questionnaire)
    - Acute Phase Reactant (Erythrocyte Sedimentation Rate or C-reactive protein)

[4] DT Felson, et al., Arthritis & Rheum, 1995 June, 38(6):727-735

Fifty percent and 70 percent improvement (ACR50 and ACR70) are similarly calculated using these higher levels of improvement.

- *Radiographic Outcome: Van der Heijde modified Sharp Score*

The Van der Heijde-modified Sharp radiographic scoring method grades the presence of erosions in the joints of the hands and feet, and the presence of joint space narrowing (JSN) in the hands, wrists, and feet.[5] The scores for each feature for the individual joints are summed. Erosions are assessed at 16 locations in each hand and wrists and 12 locations in each foot, using a 6-point scale from 0 to 5. Scores are derived based on the number and size of discrete erosions in each location, but are summed to a maximum of 5. Thus the maximum erosion score for the hands/wrists is 160, and the maximum erosion score for the feet is 120, for a maximum total erosion score of 280. JSN scores are based on 15 locations in each hand and wrist and 6 locations in each foot, scored using a 5-point scale from 0 to 4: 0 = normal; 1 = focal or minimal and generalized narrowing; 2 = generalized narrowing <50%; 3 = generalized narrowing >50% or subluxation; and 4 = ankylosis or complete dislocation. The maximum total JSN for the hands/wrists is 120, and the maximum total JSN for the feet is 48, for a maximum total JSN score of 168. Therefore the theoretical maximum modified total Sharp Score (mTSS) is 448, although the actual clinical range in RA drug development trials is typically much lower because a given individual typically only has a fraction of his or her joints affected by radiographically evident damage.

Radiographic Outcomes:
Summary of Study 1044 Radiographic Results

The primary radiographic endpoint in Study 1044 was assessed at Month 6, after which all placebo control group patients were transitioned to tofacitinib. At Month 3, patients who had not experienced a 20% improvement in tender and swollen joint counts were advanced to active treatment. Approximately 49% of placebo patients left the placebo group at Month 3 for this reason, compared to 26% of patients in the tofacitinib 5 mg group and 18% of patients in the tofacitinib 10 mg group.

Patients with missing data at Month 6 or Month 12 had their data imputed using linear extrapolation from baseline to their last radiographs prior to exiting their assigned treatment group. This imputation method has been used historically in other RA development programs assessing structural damage, but has inherent limitations, particularly as the length of the extrapolation period increases and the amount of missing data increases. Binary variables (e.g., rates of patients with no progression in mTSS) were analyzed using normal approximation to the binomial. Scoring of all radiographs was done by two separate central blinded assessors.

The primary analysis of the radiographic outcome in Study 1044 excludes patients from sites with data integrity or procedural issues, as well as additional patients for whom valid post-

[5] S Boini and F Guillemin, "Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages." Ann Rheum Dis 2001; 60:817-827

baseline radiographs were not obtained. Thus the primary radiographic analysis excludes 21 (13%) placebo patients, 44 (14%) patients in the tofacitinib 5 mg group, and 24 (8%) patients in the tofacitinib 10 mg group. This amount of missing data is consistent with other RA development programs and is not excessive.

A primary analysis using the analysis of covariance (ANCOVA) model and a sensitivity analysis using rank-based ANCOVA were pre-specified in the protocol's statistical analysis plan. Results of the parametric primary analysis versus the non-parametric sensitivity analysis are summarized in Table 2 below. In the primary analysis, only the change from baseline in mTSS for the tofacitinib 10 mg group achieved statistical significance compared to the placebo group. The statistical significance of the findings changes when the non-parametric analysis was used—only the tofacitinib 5 mg group results achieved statistical significance. Both doses were not significantly different from placebo at Month 12.

Table 2: Analyses of Change from Baseline in Modified Total Sharp Scores, Study A3921044

Analyses of Radiographic Outcomes: Change from Baseline in Modified Total Sharp Scores (mTSS) in Study A3921044			
	PBO + MTX	**CP 5 mg BID + MTX**	**CP 10 mg BID + MTX**
Assigned to study treatment (tx)	n = 160	n = 321	n = 319
Received at least 1 dose of study tx	n = 160	n = 321	n = 316
"Full Analysis Set"	n = 156	n = 316	n = 309
Sponsor primary analysis (FAS, LEP, parametric)			
Month 6 (Primary Endpoint)	n = 139*	n = 277*	n = 290*
mTSS LS means	0.47	0.12	0.06
p-value vs. placebo	-	0.0792	0.0376
Month 12	n = 139*	n = 286*	n = 295*
mTSS LS means	0.92	0.29	0.05
p-value vs. placebo	-	0.0558	0.0081
Pre-specified non-parametric analyses			
Month 6 (Primary Endpoint)			
ANCOVA with ranked data p-value	-	0.0237	0.1979
Month 12			
ANCOVA with ranked data p-value	-	0.0578	0.079

Sources: Summary of Clinical Efficacy Table 27; Study A3921044 CSR, Tables 11 and 14.2.15.1.6
FAS=Full Analysis Set; LEP=Linear Extrapolation method for missing data imputation
*If subjects did not have any valid post-baseline radiographs, they were excluded from this analysis

Results in Table 3 below show that fewer patients progressed in the tofacitinib 5 mg group than the tofacitinib 10 mg group. This result contrasts with the apparently larger treatment effect for the 10 mg dose in the analysis of mean change from baseline in mTSS. The apparently larger effect observed in the 10 mg group was explained by two outliers, one of which was extrapolated data.

Further illustrating the lack of conclusiveness of the radiographic data, a change in the definition of "no progression" from a change in mTSS of $\leq$0.5 units to 0 units resulted in an 8% reduction in the proportion of nonprogressors in the tofacitinib 10 mg dose group and a loss of statistical significance compared to the control group.

Table 3: Rates of "No Progression" Based on Change from Baseline to Month 6 in mTSS

Treatment	N	N	Rate	Difference from PBO	P-value
No Progression defined by applicant as Change in mTSS ≤ 0.5					
CP 5 mg	277	246	89 %	11 %	**.0055**
CP 10 mg	290	252	87 %	9 %	**.0230**
PBO	139	108	78 %		
No Progression defined by FDA reviewer as Change in mTSS ≤ 0					
CP 5 mg	278	233	84 %	10 %	**.0200**
CP 10 mg	290	229	79 %	5 %	.2766
PBO	140	104	74 %		

Source: Table 20 of A3921044 Clinical Study Report; FDA analysis by Dr. Yongman Kim

In other exploratory analyses performed by FDA statisticians, when outliers (defined as a change greater than 7 units) were excluded, the difference between the tofacitinib 5 mg and placebo groups remained significant but the difference between the tofacitinib 10 mg and placebo group did not. When outliers of greater than 20 units were excluded, the difference between both tofacitinib groups and the placebo group lost statistical significance. Therefore the estimated treatment effect of tofacitinib was highly dependent on these outliers. The reader is referred to the statistical review of the original submission of NDA 203214 for details of these analyses.

In summary, the data in Study 1044 was suggestive of a treatment benefit of tofacitinib for the radiographic endpoint but was not adequate to definitively characterize the treatment effect and its relationship to dose.

Radiographic Results of Study 1069

At the time of the data cutoff for this submission, approximately 17% of patients in each of the tofacitinib groups had discontinued the study, and approximately 28% of the MTX group patients had discontinued. To be included in the radiographic endpoint assessment, patients must have had a baseline and at least one post-baseline radiograph. Patients with missing data at Month 6 or Month 12 had their data imputed using linear extrapolation from baseline to their last radiographs prior to exiting their assigned treatment group. This imputation method has been used historically in other RA development programs assessing structural damage, but has inherent limitations, particularly as the length of the extrapolation period increases and the amount of missing data increases. Scoring of all radiographs was done by central blinded assessors.

As shown in Table 4 below, both tofacitinib 5 mg and tofacitinib 10 mg were associated with a reduction in mean change from baseline in mTSS compared to MTX. The pre-specified primary analysis, using ANCOVA, was statistically significant. Although the degree of difference was slightly greater for tofacitinib 10 mg compared to 5 mg, this study was not

powered for a comparison of tofacitinib 5 and 10 mg, and additionally, it is not clear whether the small difference observed would translate into a clinically meaningful difference.

Table 4: Study 1069 Results for modified Total Sharp Score (mTSS)

	MTX	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
Assigned to study treatment (tx)	n = 186	n = 374	n = 398
Received at least 1 dose of study tx	n = 186	n = 371	n = 395
Full Analysis Set (FAS)*	n = 166 (89%)	n = 346 (93%)	n = 369 (93%)
Change from Baseline in modified Total Sharp Score (mTSS)			
Month 6 (Primary Endpoint)			
LS mean	0.84	0.18	0.04
Difference from MTX	--	-0.66	-0.81
95% CI of the difference		(-1.03, -0.28)	(-1.18, -0.44)
p-value (ANCOVA)		<0.001	<0.001
Month 12			
LS mean	1.3	0.4	0
Difference from MTX		-0.9	-1.3
95% CI of the difference		(-1.4, -0.4)	(-1.8, -0.8)

Source: Study A3921069 CSR Tables 11 and 15
*If subjects did not have any valid post-baseline radiographs, they were excluded from this analysis

The applicant pre-specified a Rank-ANCOVA analysis which was consistent with the primary analysis. Improvement in the total modified Sharp score was also reflected in the individual erosion and joint space narrowing components of the modified Sharp score (data not shown).

FDA statistical reviewer Dr. Yongman Kim also conducted sensitivity analyses evaluating the sensitivity of the estimated treatment effect with respect to extreme ($\geq$20 units) and moderate ($\geq$7 units) outliers. Only 2 patients had a change of 20 or more units in mTSS—one patient in the tofacitinib 5 mg group and one patient in the MTX group. When these two patients were excluded, the difference in mTSS between the tofacitinib groups and the MTX group remained consistent with the primary analysis, and was also statistically significant. When 7 units was used to define outliers, 9 patients were excluded (4 from the MTX group, 4 from the 5 mg group and 1 from the 10 mg group). When these patients were excluded, the difference between the tofacitinib and MTX groups remained consistent with the primary analysis, and remained statistically significant. Therefore, unlike Study 1044, the radiographic outcome results for Study 1069 were not sensitive to the effect of outliers.

As shown in Table 5 below, tofacitinib treatment was associated with a higher proportion of patients experiencing no radiographic progression compared to MTX, whether that was defined as a change in mTSS of $\leq$0.5 units (the sponsor's analysis) or whether that was defined as a change in mTSS of $\leq$0 units (FDA analysis). Although tofacitinib 10 mg was associated with a slightly higher proportion of nonprogressors compared to the 5 mg dose, the difference between the tofacitinib groups is small, and it is not clear whether this represents a real or clinically meaningful difference.

Overall, results of Study 1069 provided conclusive evidence of the efficacy of tofacitinib for reducing structural damage as assessed by the radiographic outcome of mTSS. The numerical

differences observed between the 10 mg and 5 mg dose of tofacitinib were small, and the clinical meaningfulness of those differences is unclear.

Table 5: Proportion of Patients with "No Progression" in mTSS, Study 1069

Treatment	N	n	Rate	Difference vs. MTX	95% CI
No Progression Defined by Applicant as Change in mTSS ≤ 0.5					
CP 5 mg	346	289	84 %	13 %	(5%, 21%)
CP 10 mg	369	331	90 %	19 %	(11%, 27%)
MTX	167	118	71 %		
No Progression Defined by Reviewer as Change in mTSS ≤ 0					
CP 5 mg	346	254	73 %	18 %	(9%, 27%)
CP 10 mg	369	284	77 %	21 %	(13%, 30%)
MTX	167	93	56 %		

Source: Table 7 of the FDA Statistical Review by Dr. Yongman Kim

Results for ACR70 at Month 6 in Study 1069

The second prespecified primary endpoint for Study 1069 was the proportion of ACR70 responders at Month 6. As summarized in Table 6 below, tofacitinib treatment was associated with a higher proportion of ACR70 responders at Month 6 compared to MTX. Additionally, the 10 mg dose appeared to be associated with a numerically higher proportion of ACR70 responders than the 5 mg dose.

Table 6: Proportion of ACR70 Responders at Month 6 in Study 1069

ACR70	Tofa 5 mg BID	Tofa 10 mg BID	MTX
Randomized and treated	371	395	186
Analyzed for primary efficacy	369 (99)	393 (99)	184 (99)
ACR70 responders, n (%)	94 (25%)	148 (38%)	22 (12%)
Difference from MTX	13%	26%	-
95% CI of difference	7, 20	20, 32	-
p-value	<0.0001	<0.0001	

Source: CSR A3921069, Adapted from Tables 16 and 14.2.3.1
Abbreviations: CI=confidence interval, FAS=full analysis set, N=number of patients, n=number of patients meeting prespecified criteria, NRI=nonresponder imputation, BID=twice daily, MTX=methotrexate

Source: Table 14 of Dr. Nikolov's Clinical Review

Other Endpoints

There were multiple other secondary endpoints evaluated in Study 1069, including the proportion of ACR20 and ACR50 responders, ACR response rates over time, change from

baseline in the ACR core variables, the proportion of patients with a sustained ACR70 response for at least 6 months, DAS28-4(ESR), Health Assessment Questionnaire-Disability Index (HAQ-DI), and many other outcome measures. The efficacy of tofacitinib for these multiple measures of clinical response and physical functioning have been previously evaluated in the original NDA, and the results of Study 1069 are consistent with the previously submitted studies.

8. Safety

- **Discuss the adequacy of the database, major findings/signals**

The safety data in this submission were updated data from the 6 Phase 2 studies, 6 Phase 3 studies, and two ongoing open-label long-term extension studies that comprised the tofacitinib development program in RA. Because this submission is the first for Study 1069, and this study evaluated RA patients at an earlier stage (MTX-naïve patients), safety results for Study 1069 were assessed separately, and then in the context of the other studies in the clinical development program. As of the data cutoff for this submission (April 19, 2012), the safety database included ~4800 patients across all treatment groups and ~8500 patient-years of exposure to all doses of tofacitinib (approximately 1500 additional patient-years of exposure compared to the original NDA submission). The number of patients with at least 24 months of exposure to tofacitinib has more than doubled since the original submission, from 709 patients to 2002 patients. There are still a limited number of patients who have received tofacitinib for 36 months or more (634 patients). The number of patients with a longer duration of exposure is important because of the apparent dose- and duration- dependent safety concerns noted in the original NDA submission.

At the time of the original NDA submission, potential safety issues identified included:

- Malignancy
    - The risk of malignancy appeared to increase over time in the long-term extension;
    - There appeared to be an increased risk of lymphoma in particular;
    - There was also a suggestion of increasing risk with increasing dose, based on nonclinical data and human data in RA and renal transplant patients.
- A dose-dependent increase in serious infections, including opportunistic infections and tuberculosis.
- A dose-dependent increase in a number of laboratory abnormalities, to include abnormal hematologic parameters, lipid parameter changes, and serum creatinine elevation.

Overall, the safety profile of tofacitinib in Study 1069 was consistent with the safety profile of tofacitinib demonstrated in previous studies. Updated long-term data from ongoing studies in the tofacitinib clinical development program are also consistent with the aforementioned dose- and duration- dependent safety concerns.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

Table 7 below contains a summary of the one-year safety data for Study 1069. In terms of overall adverse events (AEs), serious adverse events (SAEs), and discontinuations due to adverse events (DAEs), incidence in both tofacitinib groups was similar to MTX. This very high level summary does not adequately capture dose- and duration- dependent safety concerns, which will be described in further detail below.

Table 7: Overview of One-Year Safety Data for Study 1069

	Tofa 5 mg BID n (%)	Tofa 10 mg BID n (%)	MTX n (%)
Randomized and treated	371	395	186
Exposure for event, patient-years (PY)	331	353	152
Total number of AEs	863	1057	449
Total patients with ≥ 1 AE, n (%)	260 (70)	294 (74)	130 (70)
Incidence of AEs, event per 100 PY	155	183	197
Total patients with ≥ 1 SAE, n (%)	24 (7)	24 (6)	13 (7)
Incidence of SAEs, event per 100 PY	7.2	6.8	8.6
Total patients with ≥ 1 Severe AE, n (%)	22 (6)	21 (5)	11 (6)
Patients who discontinued due to AE, n (%)	24 (7)	31 (8)	17 (9)
Incidence discontinuations due to AE, event per 100 PY	7.2	8.8	11.2

Source: CSR A3921069, Adapted from Tables 27 and 28

Source: Table 19 of Dr. Nikolov's clinical review

Where available, the exposure-adjusted incidence of adverse events of interest over time in the tofacitinib RA clinical development program is summarized in Table 8 below. The exposure-adjusted incidence of death has remained low and consistent over time, with additional exposure. These data suggest that serious infections, tuberculosis, and lymphoproliferative disorders may be increasing over time, whereas opportunistic infections and malignancies excluding non-melanoma skin cancer (NMSC) may be relatively stable. However these data are limited in that they are not broken down by dose, and are cumulative. Further analyses to shed light on incidence by dose, and non-cumulative incidence by 6-month intervals are provided separately below.

Table 8: Cumulative Exposure-Adjusted Incidence for Safety Events of Interest

	Original Submission 29 Mar 2011 Data Cut N (Event/100 PY)	120 Day Safety Update 29 Sep 2011 Data Cut N (Event/100 PY)	April 2012 Update 19 Apr 2012 Data Cut N (Event/100 PY)]
N	4789	4791	4789
Exposure, Patient Years	5651	6922	8460
Mortality (up to 30 days of last dose)	21 (0.4)	24 (0.4)	25 (0.3)
Serious Infections	167 (2.97)	206 (3.00)	259 (3.09)
Tuberculosis (TB)	NA	11 (0.16)	16 (0.19)
Opportunistic Infections, including TB	NA	33 (0.48)	41 (0.49)
Herpes Zoster	239 (4.4)	288 (4.3)	346 (4.3)
Malignancies (excl. NMSC)	50 (0.89)	65 (0.94)	75 (0.89)
Lymphoproliferative Disorders/Lymphoma	3 (0.05)	3 (0.04)	7 (0.07)*

Source: Integrated Summary of Safety, Adapted from Tables 4 an 255.2 (* Data cutoff for lymphoma was April 16, 2012 using a different estimate number of patients/patient years -5559/9935)
Subjects exposure time is counted from first dose of tofacitinib in the index study through last known dose in the extension study. Some events may have occurred post end of treatment, these events were counted in the numerator and subjects' full tofacitinib treatment exposure was included in denominator.

Source: Table 20 of Dr. Nikolov's Clinical Review

- **Special safety concerns—Dose- and Duration- Dependent Risks**

As summarized in Table 9 below, with roughly similar exposure in the 5 mg and 10 mg cohorts, tofacitinib 10 mg BID appears to be associated with an increased risk over 5 mg BID for overall SAE, DAE, serious infections, tuberculosis, herpes zoster, and malignancy (excluding non-melanoma skin cancer). This is consistent with the findings summarized in Table 10 below, which demonstrate a dose-related increased risk in non-melanoma skin cancer (NMSC). There does not appear to be a dose-related increase in deaths or opportunistic infections.

Figures 1 and 2 below illustrate the non-cumulative rates over time, by 6-month intervals, for malignancy and serious infections, respectively. Although this submission provides additional data, the pattern is very similar to the data provided in the original NDA. Specifically, the incidence of malignancy appears to be slowly increasing over time with increasing exposure. There are too few patients at the 36-month and 42-month time points to know whether the drop off in incidence is due to a lack of a signal or due to an insufficient number of patients being exposed at those durations. For similar reasons it is not clear whether the incidence of serious infections has dropped off at these same time points. Otherwise the incidence of serious infections appears to be relatively consistent over time, with the highest incidence being in the second 6-months of exposure.

Table 9: Overview of Safety by Dose (Patients who only received the assigned dose) in the Cumulative RA Development Program

	5 mg BID cohort	10 mg BID cohort
Number of patients Exposure (PY)	1955 2174	1846 2460
Deaths within 30 days of last dose *Rate per 100 PY (95% CI)*	6 *0.28 (0.1, 0.6)*	5 *0.2 (0.1, 0.5)*
No with ≥ 1 SAE *Rate per 100 PY (95% CI)*	210 *10.2 (8.9, 12)*	261 *11.1 (9.9, 12.6)*
AE leading to discontinuation *Rate per 100 PY (95% CI)*	170 *7.9 (6.8, 9.1)*	223 *9.2 (8.1, 10.5)*
Serious infection, n *Rate per 100 PY (95% CI)*	59 *2.7 (2.1, 3.5)*	87 *3.6 (2.9, 4.4)*
Tuberculosis (TB), n *Rate per 100 PY (95% CI)*	2 *0.1 (0.02, 0.4)*	9 *0.4 (0.2, 0.7)*
Opportunistic infection, n *Rate per 100 PY*	8 *0.4*	7 *0.3*
No with ≥ 1 H. zoster infection *Rate per 100 PY (95% CI)*	84 *4.0 (3.2, 5.0)*	113 *4.8 (4.0, 5.7)*
No with ≥ 1 Malignancy (excl. NMSC) *Rate per 100 PY (95% CI)*	18 *0.83 (0.5, 1.3)*	23 *0.94 (0.6, 1.4)*
LPD, n *Rate per 100 PY (95% CI)*	1 *0.05 (0.01, 0.3)*	2 *0.08 (0.02, 0.3)*
No with ≥ 1 MACE *Rate per 100 PY (95% CI)*	6 *0.5 (0.2, 1.1)*	8 *0.4 (0.2, 0.7)*
Source: Summary of Clinical Safety, Adapted from Table 5		

Source: Table 21 of Dr. Nikolov's clinical review

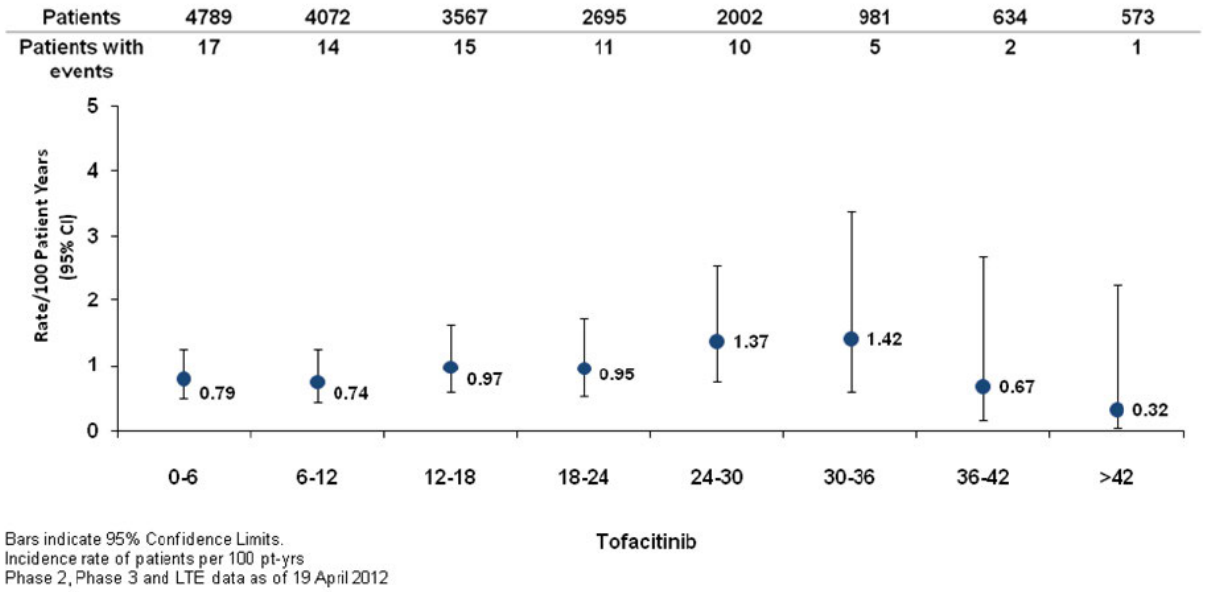
Table 10: Incidence of Non-Melanoma Skin Cancer by Dose and Duration of Tofacitinib Treatment in the RA Development Program

	Overall RA development P2P3LTE (All doses)	LTE		
		5 mg BID	10 mg BID	All doses
April 2011 (n=4789; pys=5650)	0.373 (0.243, 0.572)	0.359 (0.179, 0.717)	0.681 (0.306, 1.517)	0.450 (0.266, 0.760)
Sep 2011 (n=4791; pys=6921)	0.450 (0.316, 0.639)	0.368 (0.198, 0.684)	0.894 (0.539, 1.483)	0.569 (0.384, 0.842)
April 2012 (n=4789; pys=8460)	0.451 (0.328, 0.620)	0.310 (0.167, 0.575)	0.793 (0.522, 1.204)	0.533 (0.377, 0.753)
April 2013 (n=5671; pys=12,664)	0.525 (0.412, 0.668)	0.351 (0.208, 0.593)	0.835 (0.619, 1.126)	0.624 (0.481, 0.809)

Source: Labeling Supplement 0005, Adapted from Attachment 1, Table 1 and Efficacy Supplement 0004, Summary of Clinical Safety, Table 375.s16.1.13
*n and pys are for P2P3LTE data set
P2P3LTE through April 2012 includes Phase 2 Studies A3921019, A3921025, A3921035, A3921039, A3921040, A3921109, Phase 3 Studies A3921032, A3921044 (1-Year), A3921045, A3921046, A3921064 and LTE studies (for those patients entering from the included Phase 2/3 studies); for April 2013 data cut, P2P3LTE includes A3921044 (2-year) and also includes Study A3921069 (1-year).
LTE includes LTE Studies A3921024 and A3921041.
BID = twice daily, pys = patient years, P2P3LTE = Phase 2, Phase 3 and long-term extension

Source: Table 23 of Dr. Nikolov's clinical review

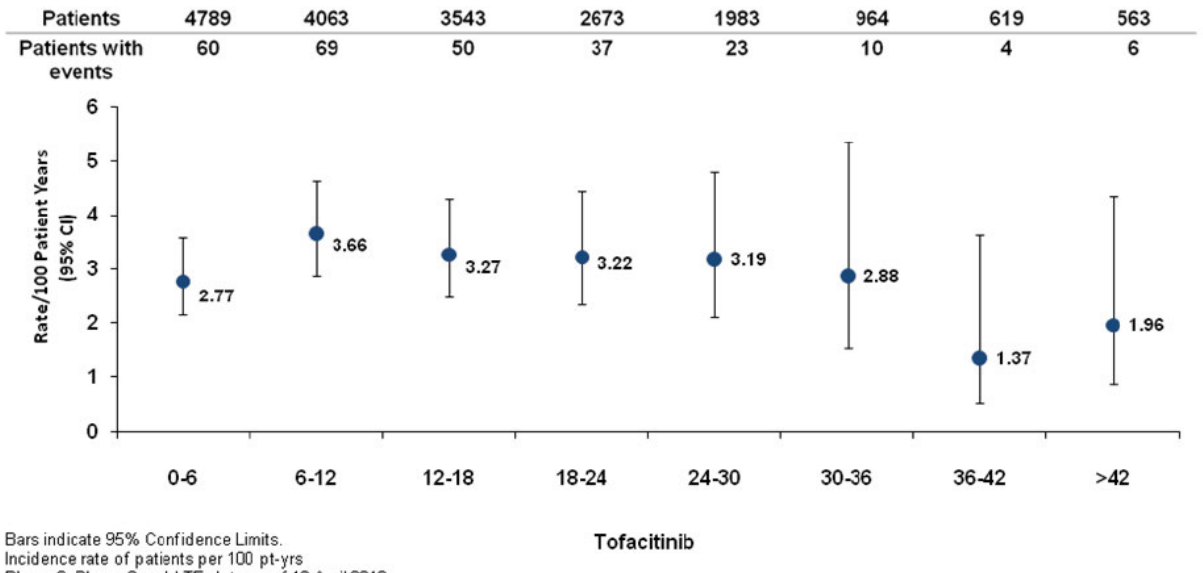
Figure 1: Non-Cumulative Incidence of Malignancy by 6-Month Intervals in the Tofacitinib RA Development Program (Excluding Non-Melanoma Skin Cancer)



Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Phase 2, Phase 3 and LTE data as of 19 April 2012

Source: Integrated Summary of Safety as of April 29, 2012

Figure 2: Non-Cumulative Incidence of Serious Infections by 6-Month Intervals in the Tofacitinib RA Development Program



Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Phase 2, Phase 3 and LTE data as of 19 April 2012

Source: Integrated Summary of Safety as of April 29, 2012, Figure 2

- **Safety Conclusions**

The safety data in this submission are consistent with the data in the original NDA submission. Tofacitinib has the safety profile of a potent immunosuppressive, and has serious dose- and duration- related safety signals, such as an increased risk of serious infection and malignancy.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this supplemental application, as no issues that would warrant discussion were identified. The original NDA for tofacitinib was discussed at the May 9, 2012 Arthritis Advisory Committee meeting.

10. Pediatrics

This sNDA does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and therefore does not trigger PREA. With the original NDA, the sponsor received a partial waiver for polyarticular juvenile idiopathic arthritis (PJIA) patients under 2 years of age and a deferral for studies in PJIA patients 2 to <18 years of age. The PREA PMR studies include a multiple dose pharmacokinetic trial (final report due in September 2014) and a randomized withdrawal efficacy and safety trial (final report due in September 2017) in PJIA patients.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues of concern**—No issues identified.
- **Financial disclosures**—No issues identified.
- **Other GCP issues**—No issues identified.
- **Office of Scientific Investigation (OSI) audits**—No clinical site inspections were deemed warranted for this submission. OSI inspections were conducted for the original NDA and did not identify major deficiencies in data quality or integrity.
- **Other outstanding regulatory issues**—No issues identified.

12. Labeling

- **Proprietary name**—Already approved as Xeljanz.
- **Physician labeling**—The sponsor submitted proposed labeling changes that were primarily limited to radiographic results in Section 14. There were no major labeling issues. Refinements in the proposed labeling language and data display were implemented by the FDA review team. Final labeling agreement with the sponsor is pending at the time of this review.
- **Carton and immediate container labels**—No change from the approved labeling is proposed.
- **Patient labeling/Medication guide**—No changes are proposed or warranted on the basis of this submission.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this supplement NDA, pending final agreement on revisions to the originally proposed labeling changes.

- **Risk Benefit Assessment**

Based on the data in this submission, the risk-benefit profile of tofacitinib 5 mg BID remains favorable for the RA indication. Study 1069 provided convincing evidence of the efficacy of tofacitinib 5 mg BID and 10 mg BID for reducing the progression of structural damage due to RA. Although tofacitinib 10 mg BID appeared to be slightly more efficacious than 5 mg BID for radiographic outcomes, the differences between these two dose regimens were small, and are of unclear clinical significance. (b) (4)

(b) (4)

(b) (4)

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(b) (4)

(b) (4).

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

Tofacitinib currently has an approved Risk Evaluation and Mitigation Strategy (REMS) consisting of a medication guide and communication plan. The REMS focuses on the risks of serious infections, including opportunistic infections, tuberculosis, malignancy, increase in cholesterol and decrease in blood counts. No change in the currently approved REMS is warranted on the basis of the information in this submission.

- **Recommendation for other Postmarketing Requirements and Commitments**

There are three postmarketing requirements (PMR) that were associated with the original approval of tofacitinib: 2 deferred pediatric studies (as described in Section 10 above) and 1 controlled clinical trial to evaluate the long-term safety of the 5 and 10 mg BID doses of tofacitinib in comparison to an active comparator. There are no postmarketing commitments (PMC). No additional PMR or PMC are recommended on the basis of this submission.

- **Recommended Comments to Applicant**—None.

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/s/

SARAH K YIM
01/31/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s04

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: **203214**

Submission Date(s): **April 22, 2013**

Applicant: Pfizer

Product: **Xeljanz (tofacitinib)**

Reviewer: **Nikolay Nikolov, M.D.**

Date of Review: **January 15, 2014**

Covered Clinical Study (Name and/or Number): **A3921069**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **867**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **13**		
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: **0** Significant payments of other sorts: **13** Proprietary interest in the product tested held by investigator: **0** Significant equity interest held by investigator in sponsor of covered study: **0**		
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) **0**		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Reviewer Comments:

The applicant has adequately disclosed financial interests and/or arrangements with clinical investigators by having submitted a signed Form FDA 3454, Form FDA 3455, a statement for steps taken to minimize bias, and a financial disclosure summary.

The sponsor certifies that the covered study, A3291069, is not funded via variable compensation and none of the investigators in the study hold any form of propriety interest in the product. Pfizer has examined its financial data regarding significant payments of other sorts made to all investigators who participated in the study and equity information as provided by those investigators, as defined in 21 CFR 54.2.

Certification:

Per US FDA Form 3454, certification is provided for 854 of the 867 investigators listed in the study report indicating:

- Certified investigators. A total of 854 of the investigators are certified as having no Financial Arrangements as defined in 21 CFR 54.4
- No Due Diligence activities were required for this covered study.

Note that all investigators are assessed for equity, significant payments of other sorts, variable compensation and propriety interest. Significant payments of other sorts and other financial arrangements are checked via internal Pfizer procedures.

Disclosure:

Per US FDA Form 3455, 13 investigators of the 867 entries listed in the study report had significant payments of other sorts as defined in 21 CFR 54.4.

All Investigator Initiated Research Grants associated with the investigators are paid directly to the Institution rather than to the individual investigator.

The sponsor has employed multiple processes to minimize potential bias, detailed in the bias statement, which are sufficient to ascertain the reliability of data and interpretation of study results.

In summary, the disclosed financial interests/arrangements, does not affect the approvability of the application.

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/s/

NIKOLAY P NIKOLOV
02/09/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203,214
Priority or Standard	Standard
Submit Date(s)	April, 22, 2013
Received Date(s)	April, 22, 2013
PDUFA Goal Date	February, 21, 2014
Division / Office	DPARP/OND
Reviewer Name(s)	Nikolay P. Nikolov, M.D.
Review Completion Date	January 15, 2014
Established Name	Tofacitinib (CP-690,550)
(Proposed) Trade Name	Xeljanz (Proposed)
Therapeutic Class	Janus kinase (JAK) inhibitor
Applicant	Pfizer
Formulation(s)	Tablets
Dosing Regimen	5 mg BID
Indication(s)	Rheumatoid Arthritis (RA)
Intended Population(s)	Moderate-to-Severe RA

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this sNDA with revisions to the proposed labeling.

1.2 Risk Benefit Assessment

Brief Overview of the Clinical Program

The current supplemental NDA is intended to provide data in support of the use of tofacitinib for the inhibition of radiographic progression in patients with moderate to severe rheumatoid arthritis (RA).

Pivotal data for this application were derived from study 1069 which was a randomized, 2-year, double-blind, international, parallel group study on the safety and efficacy of CP-690,550 at doses of 5 mg and 10 mg BID versus MTX alone in MTX-naïve patients with active, moderate-to-severe RA. This submission contains data up to Month 12. Efficacy was assessed for:

- Inhibition of progression of structural damage by change in mTSS at Month 6 as the primary timepoint, with a follow up at 12 and
- Signs and symptoms of RA by ACR70 response at Month 6 as the primary timepoint, with a follow up at 12 months.

The efficacy from study 1069 was reviewed in the context of the inconclusive radiographic endpoint results from study 1044 which was reviewed in the original NDA.

Safety data were derived from the Year 1 randomized controlled period of the study 1069 and the updated safety from the tofacitinib RA development, consisting of Phase 2, Phase 3, and long-term extension studies, with a clinical cut-off April 19, 2012.

Summary of Efficacy Review and Conclusions

The pivotal study 1069 demonstrated:

1. <u>Effects of tofacitinib on structural damage progression</u>:
   The results of study 1069 provide robust evidence of efficacy of tofacitinib at both 5 and 10 mg BID dosing regimens on the inhibition of structural progression, as measured by the mean change from baseline in mTSS and the rate of non-radiographic progression, in the relatively early, MTX-naïve RA patient population to support a claim of radiographic benefit in patients with moderate to severe RA. Sensitivity and related secondary endpoint analyses yielded consistent results. The FDA reviewer analyses were in general agreement with the sponsor's. The

results from study 1069 provide corroborating evidence of tofacitinib's radiographic benefit and address the uncertainties with the interpretation of the findings from study 1044 discussed in the original NDA application. Specifically, study 1069 was able to demonstrate a measurable treatment difference, due to the degree of radiographic progression in the control group, and consistent radiographic benefit irrespective of the missing data, outliers, or imputation method, based on the sensitivity and secondary analyses.

(b) (4)

2. Effects of tofacitinib on signs and symptoms of RA and physical function:
   The results from study 1069 provide evidence of benefit of tofacitinib at both 5 and 10 mg BID dosing regimens of (1) signs and symptoms of RA as measured by ACR20/50/70 responses and DAS28 change from baseline and over time and (2) physical function as measured by change from baseline in HAQ-DI in patients with moderate to severe RA. These findings are consistent with the observations from the original NDA and the already approved labeling claims.

In conclusion, study 1069 provided corroborating evidence of tofacitinib's radiographic benefit in patients with moderate to severe RA and addresses the uncertainties with the interpretation of the findings from the first radiographic study, 1044. While the results from study 1044 alone, did not meet the statistical rigor to support a definitive conclusion of radiographic benefit of tofacitinib as a new molecular entity as discussed in the original NDA reviews, they were indicative of potential benefit and now the data from study 1069 provides the definitive evidence of reduction of radiographic progression to support inclusion in the product labeling. Further, the applicability of the radiographic data from the MTX-naïve patient population to the indicated population of MTX incomplete responders is scientifically justified, because these patient populations represent the same disease entity, albeit in different stages.

Taken together, the results from both study 1044 and 1069 provide the evidentiary support for a radiographic benefit labeling claim in patients with moderate-to-severe RA.

While the results from study 1069 indicate a higher degree of structural preservation with tofacitinib than with MTX in the MTX-naïve patient population, the findings from the radiographic endpoint assessment should be viewed in the context of the overall risk-benefit of tofacitinib which has been associated with significant dose-dependent toxicities and has a limited long-term safety record as compared with MTX.

Summary of Safety Review and Conclusions

The safety information from the tofacitinib development program was reviewed in detail with the original NDA submission and resulted in a boxed warning for serious infections and malignancy, including:

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

The safety data from study 1069 and the updated safety data from the tofacitinib RA development program, which were comprised of some 4800 patients across all treatment groups with about 8500 patient-years of exposure to all doses, were consistent with the findings in the original NDA. No new safety signals were identified with the exception of potentially increased dose- and exposure-dependent risk of non-melanoma skin cancer which warrants inclusion in the product labeling.

Overall, the safety data from the tofacitinib RA development program is consistent with the profile of a potent immunosuppressant, with associated inherent risks, such as serious infections, including opportunistic infections and tuberculosis. Tofacitinib administration was also associated with malignancy in a manner that may be consistent with a dose- and duration of exposure- dependent manner. Gastrointestinal perforations and interstitial lung disease were observed in the clinical trials, however the relative risk and role of tofacitinib treatment in the development of these adverse events is not well defined. Treatment with tofacitinib resulted in dose-dependent changes in laboratory parameters, such as sustained neutropenia and progressive lymphopenia, sustained elevations in total, LDL, and HDL cholesterol, small but significant elevations of mean serum creatinine, and liver enzymes elevations. While most of these were not associated with clinical adverse events in the controlled setting of the clinical trials, severe lymphopenia was associated with increased risk of infections. One case of Hy's law occurred with tofacitinib treatment. Using the estimate of severe drug-induced liver injury as occurring at $1/10^{th}$ the rate of Hy's Law cases, 1 case of severe liver injury might be expected in 50,000 patients treated with tofacitinib.

To further address the potentially increased risk of malignancy, including LPD, serious infections, including TB and opportunistic infections, associated long-term tofacitinib administration, the sponsor is currently initiating a global safety post-marketing

requirement (PMR) study for which the final protocol has been reviewed by the Agency and found to be acceptable to fulfill the PMR objectives.

Risk Benefit Overview

The overall risk-benefit profile of tofacitinib in RA remains favorable, as determined at the time of the original NDA approval, and is not altered on the basis of this submission. The current submission supports the addition of the radiographic results from study 1069 in Section 14 of the prescribing information. To provide further context for the interpretation of the radiographic outcomes, inclusion of the radiographic results from study 1044 is also justified. Although the risks of tofacitinib are not minimal, these are balanced by a number of clinical benefits, which include reduction in patient's signs and symptoms and disease activity, improvement in physical functioning, general health status, and now inhibition of radiographic progression.

Dosing Recommendations

The clinical significance of the observed small incremental changes of 10 mg vs 5 mg BID dosing on radiographic endpoints in study 1069 is unclear. In addition, in study 1044, depending on the types of analyses, the pattern of the radiographic endpoints was inconsistent between the two doses, (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) Furthermore, the potential incremental benefit on signs and symptoms, physical function, and radiographic outcomes should be interpreted in the context of risk-benefit considerations in light of the significant dose-dependent safety findings, such as malignancy, serious infections and laboratory abnormalities which continue to be of concern, as discussed in detail in Section 7 Review of Safety below.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Tofacitinib currently has a REMS consisting of a Medication Guide and Communication Plan. Based on this submission, the current REMS remains adequate.

1.4 Recommendations for Postmarket Requirements and Commitments

Tofacitinib currently has a safety post-marketing requirement for which the negotiations have been completed and the final protocol agreed upon. Based on this submission, I do not have specific recommendations for additional post-marketing requirements and commitments.

2 Introduction and Regulatory Background

New Drug Application (NDA) 203214 from Pfizer for tofacitinib, Xeljanz (also known as CP-690,550), an oral small molecule inhibitor of the Janus associated kinases (JAK) was approved on November 06, 2012 for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). The product is an immediate-release tablet for oral administration in 5 mg dosage strength.

This submission is intended to provide data in support of the use of tofacitinib for the inhibition of radiographic progression in patients with moderate to severe rheumatoid arthritis (RA). At the pre-sNDA meeting, where general agreement was reached on the format and the content of the application, the Agency recommended (1) that Pfizer propose labeling including results from both study A3921069 and A3921044 and (2) submit safety data on patients who were exposed to the same tofacitinib dose without a cross-over. Based on these recommendations, Pfizer proposes labeling changes to Section 14, Clinical Studies to include radiographic results from both study A3921069 and A3921044.

2.1 Product Information

Tofacitinib is intended to be a selective inhibitor of Janus associated kinases (JAK) family of kinases, which mediate signal transduction activity through the common gamma chain family of cytokines including IL-2, -4, -7, -9, -15, and 21. These cytokines are integral to lymphocyte activation, proliferation and function.

In kinase assays, tofacitinib inhibited JAK1, JAK2, JAK3 and, to a lesser extent, TyK2. The broad effect of JAK inhibition on multiple cytokine pathways provided the rationale for developing CP-690,550 as a treatment for RA in which lymphocyte activation and proliferation play a pathogenic role.

Tofacitinib citrate film-coated tablets are an immediate-release (IR) formulation designed to disintegrate and dissolve rapidly under physiological conditions in the stomach.

2.2 Tables of Currently Available Treatments for Proposed Indications

Many effective therapies have been already approved for the treatment of patients with RA as listed in Table 1 and Table 2. The classes of drugs used for treatment of RA include: nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, corticosteroids, and disease modifying anti rheumatic drugs (DMARDs). NSAIDs and COX-2 inhibitors are utilized primarily for symptomatic relief of pain and are useful co-therapies because of their anti-inflammatory and analgesic effects. Corticosteroids are

versatile agents with potent anti-inflammatory effects, but their use is limited by long-term toxicity.

DMARDs are a diverse group of therapeutic agents that reduce signs and symptoms of RA as well as slow disease progression or produce a disease-modifying effect by retarding radiographic progression of joint damage. Methotrexate is the most commonly used DMARD because of its proven efficacy, and well-understood long term effects. Large molecule biologic products are considered to be DMARDs when they have been shown to inhibit progression of joint damage, which is the case for most of them (Table 2). In the treatment of RA, methotrexate is often the initial DMARD used and then combined with other DMARDs, commonly biologics, to enhance clinical effect.

Table 1. Small Molecule DMARDs Approved for Marketing in the United States

Product Name (Trade Name) [Sponsor]	**Mechanism of Action in RA**	**Year of First Approval for RA**
Sulfasalazine (AZULFIDINE) [Pfizer]	Anti-inflammatory and antimicrobial	1950
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	Anti-metabolite	1953
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	Interference with antigen processing (?)	1955
Azathioprine (IMURAN) [Prometheus Labs]	Cytostatic	1968
Penicillamine (CUPRIMINE) [Alton]	Unknown	1970
Auranofin (RIDAURA) [Prometheus Labs]	Unknown	1985
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]	T-cell activation inhibitor	1995, 1990
Leflunomide (ARAVA) [Sanofi-Aventis]	Anti-metabolite	1998
Tofacitinib (XELJANZ) [Pfizer]	JAK inhibitor	2012

Table 2. Biologic DMARDs Approved for Marketing in the United States

Product Name (Trade Name) [Sponsor] {year} [*]	**Presentation and *ROA*** [†]	**Description and *MOA*** [§]	**Claims for adult RA** [#]
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Vial 25 mg Prefilled syringe 25 or 50 mg/mL SureClick Autoinjector 50 mg/mL *SC injection*	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Infliximab (REMICADE) [Centocor] {1999}	Vial 10 mg/mL *IV infusion*	Chimeric IgG1 k mAb *TNF inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Anakinra (KINERET) [Amgen] {2001}	Prefilled syringe 10 mg *SC injection*	Recombinant polypeptide *IL-1 receptor antagonist*	Clinical response Physical function response Radiographic response
Adalimumab (HUMIRA) [Abbott] {2002}	Prefiled syringe 40 mg/0.8 mL Humira Pen 40 mg/0.8 mL *SC injection*	Human IgG1 k mAb *TNF inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Lyophilized powder 250 mg/vial *IV infusion*	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Vial 10 mg/mL *IV infusion*	Chimeric murine/human IgG1 k mAb *Anti CD20, B cell depletor*	Clinical response Physical function response Radiographic response
Golimumab (SIMPONI) [Centocor] {2009}	Prefiled syringe 50 mg/0.5 mL SmartJect Autoinjector 50 mg/0.5 mL *SC injection*	Humanized IgG1 k mAb *TNF inhibitor*	Clinical response Physical function response
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder 200 mg/vial *SC injection*	Humanized Fab fragment *TNF inhibitor*	Clinical response Major clinical response Radiographic response Physical function response
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Vial 20 mg/mL *IV infusion*	Humanized IgG1 k mAb *IL-6 receptor inhibitor*	Clinical response Radiographic response Physical function response

[*] Year = Year of first approval for RA
[†] ROA = Route of administration
[§] MOA= Mechanism of action
[#] Claims: Clinical response (or reducing signs and symptoms) assessed by ACR 20, 50, and 70 response over 6 month; Major clinical response defined as achieving ACR 70 response over 6 months period; Physical function response (or improving physical func ion) assessed by heal h assessment questionnaire (HAQ) over at least 6 month period; Radiographic response (or inhibi ing progression of structural damage) assessed radiographically by Total Sharp Score (TSS) and sometimes its components of erosion score (ES) or joint space narrowing (JSN) score over at least 12 months

Since the late 1990's, clinical development programs evaluating the efficacy of proposed products for RA have primarily utilized American College of Rheumatology (ACR) response criteria to assess treatment effect on signs and symptoms, the Health Assessment Questionnaire-Disability Index (HAQ-DI) to assess treatment effect on physical functioning, and a standardized radiographic scoring system, such as the Sharp Score or modifications thereof, to assess treatment effect on structural damage progression.

One conundrum associated with the assessment of efficacy in RA is the possible dissociation between clinical and radiographic outcomes. Radiographic progression may occur in people who have very low apparent disease activity and patients with clinical disease activity may have no evidence of radiographic progression.[1] Thus, documentation of a benefit of treatment on structural damage progression has been an important goal of clinical development programs for new products proposed for RA, particularly if the product has a novel target. This has become an increasingly important aspect of the risk-benefit assessment for new RA treatments in light of the many approved treatments that have documented beneficial effects in inhibiting the progression of structural damage.

2.3 Availability of Proposed Active Ingredient in the United States

Tofacitinib is currently marketed and available in the United States for the same indication, formulation, and dosing regimen.

2.4 Important Safety Issues With Consideration to Related Drugs

Tofacitinib is in the same drug class with ruxolitinib (Jakafi), which is another Janus associated kinase (JAK) inhibitor, targeting JAK1 and JAK2, approved for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in November 2011. The major warnings and precautions identified in ruxolitinib's label include thrombocytopenia, anemia, neutropenia and infections.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

At the time the investigational new drug application (IND) for tofacitinib was submitted in 2004, Phase 1 clinical data were already available. Dose-ranging study A3921019 was the initial protocol submitted to the IND, which proposed monotherapy with CP-690,550 at doses of 5, 15, and 30 mg BID for a duration of 6 weeks. Lack of nonclinical coverage for the proposed doses was noted at that time. However, because there were pre-existing human data in approximately 180 patients at doses up to 50 mg BID for 14 days, the Agency at that time made an internal decision that the clinical data were adequate to support the safety of proceeding with the study, despite the lack of nonclinical support for all of the proposed doses, which would typically be required.

In January 2007, the Agency provided written feedback regarding the proposed design of Study A3921025 and an extension study. Study A3921025 included proposed doses of 1, 3, 5, 10, 15 mg BID and 20 mg QD, to be given with stable background

1 EC Keystone, "Clinical implications of understanding radiographic findings in relation to clinical outcomes in rheumatoid arthritis." J Rheumatol 2009; 36 Supple 82:11-16

methotrexate (MTX) for a duration of 6 months. The design of the studies was considered generally acceptable, although it was noted that the nonclinical data appeared to only support chronic dosing in patients up to 5 mg BID. The review team at that time determined that previous clinical experience appeared to support the ability to proceed with the proposed studies.

In December 2008, an End of Phase 2 (EOP2) meeting took place to discuss the CP-690,550 development program. The Agency generally agreed with the proposed Phase 3 program elements and endpoints. Discussions included:

- Pure placebo control should be limited to 3 months, even if they had apparent symptomatic improvement (i.e., ACR20).
- 5 mg BID and 10 mg BID doses appear reasonable; 3 mg BID should be considered. QD regimens may warrant further study.
- The safety database proposal appeared to be adequate (1500 patients on the to-be-marketed dose for a year or more).
- Concern regarding effects on lipids and the implications for cardiovascular safety, and the need for this to be comprehensively evaluated for NDA.
- The Agency did not agree with Pfizer's proposal to use historical control data for timepoints beyond 6 months to use as a comparison for the radiographic data.

The original NDA 203,214 was approved for the treatment of patients with moderate to severe RA

However, the radiographic data from study A3921044 submitted in the original application did not meet the evidentiary standard for approval of the proposed claim for inhibition of radiographic progression due to several limitations, including the limited size of the treatment difference, no clear dose-response, reliance on extrapolated data and the effect of outliers. An additional concern was the lack of corroborating data from another study.

As part of their Phase 3 development, Pfizer has initiated a second study, A3921069, to investigate the radiographic benefit of tofacitinib as the primary endpoint, in methotrexate-naïve patients with moderate to severe RA, a population different from the original NDA. The Year 1 data from this study is now submitted to support this supplemental NDA.

At the Pre-NDA meeting for this application in February 2013, the Agency requested that the sponsor submit a summary of safety that includes updated information available from the ongoing RA development program and postmarketing data and if available, information on the safety profile by dosing regimen, 5 and 10 mg BID to aid in the assessment of dose-dependency of safety with long-term tofacitinib exposure. The sponsor was also advised to submit proposed labeling that includes the results from both radiographic studies 1044 and 1069.

2.6 Other Relevant Background Information

Tofacitinib received a negative opinion by the European Medicines Agency (EMA) on April 25, 2013, confirmed upon re-examination on July 25, 2013.[2] The EMA's major concern with Pfizer's application was that the benefits of Xeljanz did not outweigh its risks, specifically the risk and type of serious infections related to its immunosuppressive action relative. EMA also cited tofacitinib's lack of robust evidence on prevention of structural damage for the target patient population of patients with RA in whom treatment with at least two other DMARDs have been unsuccessful, i.e. a second or third line therapy, which EMA has considers as the potential target population.

3 Ethics and Good Clinical Practices

The Sponsor stated in the NDA submission that the studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed.

Written informed consent was obtained prior to the subject entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

3.1 Submission Quality and Integrity

The NDA submission was in electronic common technical document (eCTD) format and was adequately organized.

The Office of Scientific Investigations (OSI) inspections were not deemed necessary for this submission. The OSI inspections conducted for the original NDA did not identify major deficiencies in data quality and integrity.

3.2 Compliance with Good Clinical Practices

The applicant certified that all clinical investigations in the NDA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the US conducted under IND 70903 were conducted in compliance with 21 CFR Subchapter D,

2 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002542/WC500154697.pdf

part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP).

3.3 Financial Disclosures

The applicant submitted FDA Form 3454 (v.4/06) certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

There were no significant safety/efficacy issues related to CMC, clinical microbiology, preclinical pharmacology/toxicology, or clinical pharmacology in this submission.

5 Sources of Clinical Data

NDA 203,214, supplement 0004 was submitted on April 22, 2013 and can be found in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The study report including protocols, statistical analysis plan, and all referenced literature can be found in the EDR using the following path:
\\CDSESUB5\EVSPROD\NDA203214\203214.enx

The tofacitinib RA clinical development program, as of 29 March 2011 (the clinical data cut-off), consists of:

- Phase 1: 21 completed studies,
- Phase 2: 8 studies (6 completed, 2 ongoing),
- Phase 3: 6 studies (4 completed, 2 ongoing),
- Open label, long-term extension (LTE): 2 ongoing studies.

The nomenclature of all the clinical studies in the RA development consists of the prefix A392 followed by a four digit unique study number, i.e. A3921044. For simplicity, in this document, the studies will be referred to with the four digit unique study number, e.g. 1044. Also for simplicity, treatment groups of CP-690,550 5 mg BID and CP-690,550 10 mg BID may be referred to as CP5 and CP10, respectively. The terms CP-690,550 and tofacitinib are used interchangeably in this document.

Study 1069 is a 2-year study, comparing CP-690,550 monotherapy versus methotrexate in MTX-naïve RA patients with primary endpoints of ACR70 and modified Sharp Scores at Month 6 with follow up out to 12 and 24 months.

5.1 Tables of Studies/Clinical Trials

Table 3. Key Design Features of the Phase 3 Radiographic Studies in RA

Key Design Features of the Phase 3 Radiographic Studies in RA						
Protocol	**Patient Population**	**Design** ***Duration***	**Enrolled** ***Randomization***	**Treatment Arms (transition and escape for NR)**	**Primary Endpoints**	**Timepoint**
Patients naïve to MTX						
A3921069	Moderate-to-severe RA MTX-naïve	R, DB, PC Phase 3 *Two years**	399 *2:2:1:1*	CP 5 mg BID, monotherapy CP 10 mg BID, monotherapy MTX up-titrated q 4 weeks to 20 mg/week, monotherapy	mTSS ACR70	Month 6 Month 6
Patients with incomplete response to MTX or other DMARDs						
A3921044	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 3 *Two years*	797 *4:4:1:1*	CP 5 mg BID + MTX CP 10 mg BID + MTX PBO (→CP 5 mg BID @ Mo 6 or Mo3 if NR)+ MTX PBO (→CP 10 mg BID @ Mo 6 or Mo3 if NR)+ MTX	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6

Source: Summary of Clinical Efficacy, Clinical Study Reports for studies A3921032, A3921044, A3921045, A3921046, A3921064
*-One year efficacy data submitted for Study A3921069; BID-two times daily; DMARDs-disease-modifying anti-rheumatic drugs; IR-incomplete response; MTX-methotrexate; mTSS-modified total Sharp Score; NR-non-responder defined as patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts over baseline at Month 3 visit; PBO-placebo; PC-placebo (add-on for studies A3921032, A3921044, A3921046, A3921064)-controlled; SC-subcutaneous; CP=CP-690,550/tofacitin b

5.2 Review Strategy

The NDA submission was reviewed for content, format and overall data quality and integrity and found acceptable during the filing review.

Efficacy analyses were derived from study 1069 and reviewed for the primary efficacy endpoints with sensitivity analyses:

- Change from baseline in Van der Heijde modified Sharp Scores (mTSS) at Month 6 as the first primary endpoint in a sequence of two endpoints.
- ACR70 response criteria were assessed as the pre-specified second primary endpoint in study 1069.

Where appropriate, the data were discussed in the context of the findings from study 1044 and the overall RA development.

Safety data in this submission were derived from:

- Six Phase 2 studies in RA: 1019, 1039, 1040, 11109, and pivotal 1025, 1035
- All Phase 3 pivotal studies in RA: 1032, 1045, 1046, 1064, 1044, 1069
- Two ongoing, open label, long-term extensions (LTE) studies in RA: 1024, 1041

Safety was reviewed separately for study 1069, the updated safety from the ongoing RA development program, and post-marketing. Additionally, safety was reviewed from the newly defined cohorts of patients exposed to either 5 mg or 10 mg BID dosing without change in dosing regimens as requested at the pre-NDA meeting.

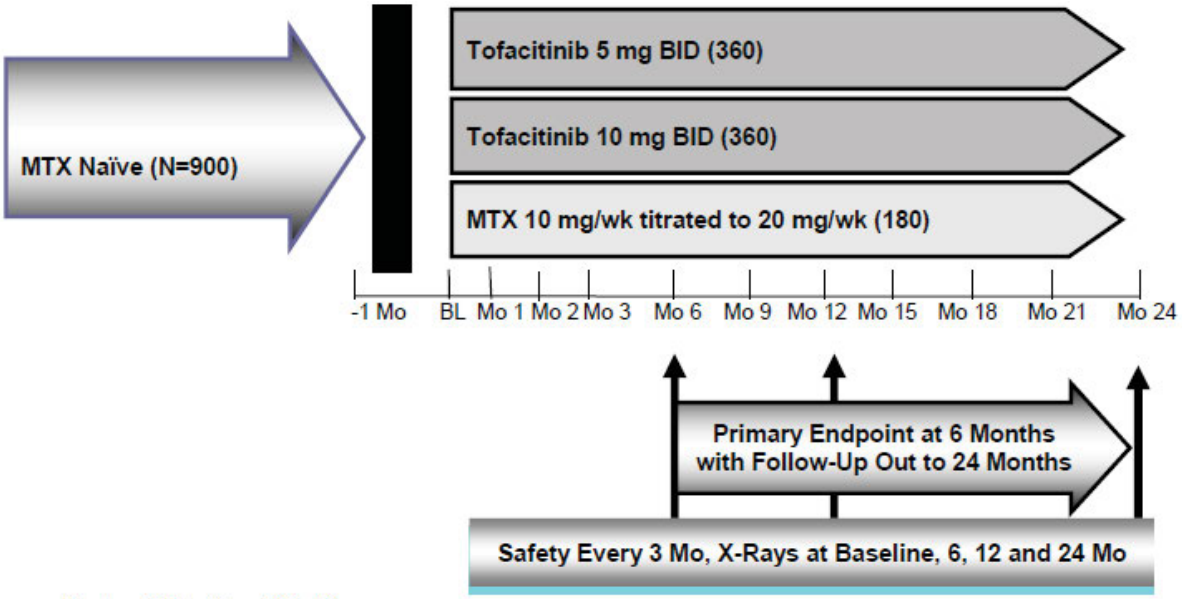
5.3 Discussion of Individual Studies/Clinical Trials

Study A3921069

Study Design

This is a Phase 3, randomized, 24-month, double-blind, international, parallel group study on the safety and efficacy of CP-690,550 at doses of 5 mg (360 patients) and 10 mg BID (360 patients) versus Methotrexate alone (180 patients) at 10 mg/week titrated to 20 mg/week in Methotrexate-naïve patients with active, moderate-to-severe RA. Efficacy is assessed for inhibition of progression of structural damage by change in mTSS and for signs and symptoms by ACR70 response at Month 6 with a follow up at 12 and 24 months. This submission contains data up to Month 12.

Figure 1. Study Design



Source: Protocol (Section 16.1.1)
Abbreviations: MTX=methotrexate, N=number of patients, wk=week, mo=month, BID=twice daily, BL=Baseline, Rand=randomization
* MTX dose started at 10 mg/wk and was titrated by 5 mg/wk every 4 weeks as tolerated to 20 mg/wk by Week 8; then maintained at the titrated dose throughout study, with one 5 mg/wk dose reduction allowed for MTX intolerance.

Key Inclusions Criteria

1. Age ≥18 years old.
2. ACR classification criteria for the diagnosis of RA

3. Active, moderate to severe RA (rheumatoid arthritis with joint erosions or positive IgM Rheumatoid Factor (RF) or antibodies to cyclic citrullinated peptide (anti-CCP).
    - ≥6 tender/painful joints on motion, and;
    - ≥6 swollen joints.
    - ESR (Westergren method) >28 mm/hr, or;
    - C-Reactive protein (CRP) >7 mg/L in the central laboratory
4. Patient has discontinued all disallowed concomitant medications for the required time prior to the first dose of study drug and is taking only those concomitant medications in doses and frequency allowed by the protocol;
5. Women of childbearing potential must test negative for pregnancy prior to enrollment in this study;
6. Sexually active women of childbearing potential and men whose partners are women of childbearing potential are required to use adequate contraceptive methods during participation in this trial, as required for men and women on methotrexate therapy;
7. No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB).
8. Patient must be at least 18 years of age or older.

Exclusions Criteria

1. Patients who have received more than 3 weekly doses of MTX or, if less than 3 weekly doses were received, MTX was stopped due to adverse event attributed to methotrexate.
2. Pregnancy or currently lactating
3. Blood dyscrasias, including confirmed:
    a. Hemoglobin <9 g/dL or Hematocrit <30%
    b. White blood cell count $<3.0 \times 10^9$/L
    c. Absolute neutrophils count $<1.2 \times 10^9$/L
    d. Platelet count $<100 \times 10^9$/L
4. Estimated GFR <60 ml/min based on the formula for estimating GFR developed by the Modification of Diet in Renal Disease (MDRD) Study Group
5. AST or ALT greater than 1.5 times the upper limit of normal at screening or any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the patient's participation in the study.
6. Severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, metabolic (including clinically significant hypercholesterolemia), endocrine, pulmonary, cardiac or neurologic disease, including pleural effusions or ascites; and conditions contraindicating treatment with MTX, including presence of severe or significant renal or significant hepatic impairment.
7. Severe, progressive or uncontrolled chronic liver disease including fibrosis, cirrhosis, or recent or active hepatitis.

8. History of any other rheumatic autoimmune disease, other than Sjogren's syndrome.
9. History of an infected joint prosthesis at any time, with the prosthesis still in situ.
10. History of any lymphoproliferative disorder, such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.
11. History of recurrent (more than one episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
12. History of any infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study drug.
13. History of any infection requiring antimicrobial therapy within 2 weeks prior to the first dose of study drug
14. Any prior treatment with non B cell-specific lymphocyte depleting agents/therapies [eg, alemtuzumab (Campath®), alkylating agents (eg, cyclophosphamide or chlorambucil), total lymphoid irradiation, etc]. Patients who have received rituximab or other selective B lymphocyte depleting agents (including experimental agents) are eligible if they have not received such therapy for at least 1 year prior to study baseline and have normal CD 19/20+ counts by FACS analysis. (Section 5.6.4. Disallowed Concomitant Medications; Biologic Response Modifiers).
15. Any patient who has been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study drug or is to be vaccinated with these vaccines at any time during treatment or within 6 weeks following discontinuation of study drug. (See Section 4.4.2. for further information regarding avoidance of household contacts who may be vaccinated).
16. A patient with any condition possibly affecting oral drug absorption, eg, gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding, that simply divide the stomach into separate chambers, are NOT exclusionary.
17. History of alcohol or substance abuse, unless in full remission for greater than 6 months prior to first dose of study drug.
18. Screening 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect patient safety.
19. A patient with a first degree relative with a hereditary immunodeficiency.
20. A patient with a malignancy or with a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
21. Significant trauma or surgery procedure within 1 month prior to first dose of study drug.
22. A patient requiring prohibited concomitant medications including prohibited dietary supplements.
23. A patient known to be infected with human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus.

24. A patient who has previously participated in any study of CP-690,550.
25. Participation in studies of investigational compounds within 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug. Patients cannot participate in studies of other investigational compounds at any time during their participation in this study. Exposure to investigational biologics should be discussed with the Pfizer Medical Monitor.

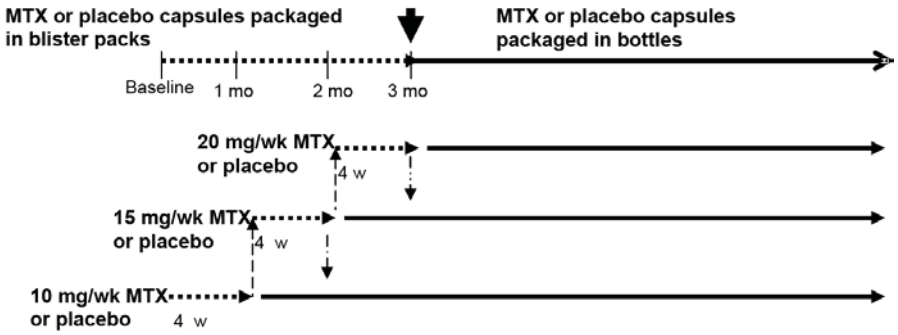
Concomitant Medications

1. Stable background pain and other arthritis therapy, was defined in the protocol. Steroids use at stable doses less than 10 mg/day.
2. Other concomitant medications, including use of herbals were detailed in the protocol.
3. Rescue therapies were detailed in the protocol. Intra-articular steroids (40 mg maximum) were allowed as a rescue therapy.
4. Disallowed concomitant medications were detailed in the protocol and included DMARDs other than MTX, oral corticosteroids over 10 mg/day, intramuscular and intraarticular and intravenous corticosteroids.

Assignment to Treatment Group

Approximately 900 patients were randomized using an automated web/telephone randomization system in a 2:2:1 ratio to:

- Treatment Arm 1: Tofacitinib 5 mg BID (tablets);
- Treatment Arm 2: Tofacitinib 10 mg BID (tablets);
- Treatment Arm 3: Methotrexate 10 mg/week (wk) to 20 mg/wk (capsules), titrated as follows:



MTX dose starts at 10 mg/wk and is titrated by 5 mg/wk every 4 weeks as tolerated to 20 mg/wk by Week 8; then maintained at the titrated dose throughout study, with one 5 mg/wk dose reduction allowed for MTX intolerance.

Patient compliance was verified by the accounting of study drug at each visit after Baseline. When study drug was administered at the research facility, it was

administered under the supervision of study personnel. Compliance of the study drug was monitored by the accounting of unused medication returned by the patient at every visit after Baseline. Compliance was documented. If compliance was <80%, the investigator or designee was to counsel the patient and ensure steps were taken to improve compliance. Patients who were less than 80% compliant with the dosage regimen for any 2 consecutive visit periods during the study were to be withdrawn from the study.

Blinding

This study was patient-, investigator-, and Sponsor-blinded.

Schedule of Assessments

A summary of the protocol-specified assessments is presented in Table 4.

AEs assessment is based on spontaneous reporting, physical examination and laboratory evaluation. Severity assessment is defined as mild, moderate, and severe.

An independent Data Safety Monitoring Board (DSMB) governed by a charter, consisted of experts external to the Sponsor who were reviewing accumulating safety data on an ongoing basis.

In addition, malignancies and cardio-vascular events were special events of interests and were adjudicated by Safety Endpoint Adjudication Committees blinded to treatment assignment.

Table 4. Schedule of Activities in Study 1069

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		Screening[a]	Visits										
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
			Baseline Day 0	1 mo	2 mo	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	21 mo	24 mo/ EOS
Informed consent, RA diagnosis, medical history[b]		X											
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination		X	X						X				X
Targeted physical examination[c]				X	X	X	X	X		X	X	X	
Vital signs, temperature		X	X	X	X	X	X	X	X	X	X	X	X
QuantiFERON-Gold®™		X											
Radiograph of chest[d]		X											
12-lead electrocardiogram		X							X				X
Radiograph of hands & feet[e]			X				X		X				X
Blood/Urine	Rheumatoid factor, anti-CCP	X	X										X
	Hematology[f], chemistry panel[g]	X	X	X	X	X	X	X	X	X	X	X	X
	Lipid profile (fasting)[h]	X	X			X	X	X	X		X		X
	CBC with differential & chemistry laboratories[i]						As appropriate for MTX Local Label						
	Urine pregnancy test (HCG) (done locally)[j]	X	X	X	X	X	X	X	X	X	X	X	X
	Urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X
	Stool examination for parasites (Brazil only)	X											
	Molecular profiling sampling[k]		X				X		X				X
	Tofacitinib pharmacokinetics*			X					X				
	HIV serology, HBsAG, HCV Ab	X											
ACR/ DAS	C-reactive protein (CRP)	X	X	X	X	X	X	X	X	X	X	X	X
	Erythrocyte sedimentation rate (ESR)[l]	X	X	X	X	X	X	X	X	X	X	X	X
	Tender/painful joint count, swollen joint count	X	X	X	X	X	X	X	X	X	X	X	X
	Patient assessment of arthritis pain		X	X	X	X	X	X	X	X	X	X	X
	Patient global assessment of arthritis		X	X	X	X	X	X	X	X	X	X	X
	Physician global assessment of arthritis		X	X	X	X	X	X	X	X	X	X	X
	Health assessment questionnaire – disability index		X	X	X	X	X	X	X	X	X	X	X
SF-36 (version 2, acute)			X	X	X	X	X	X	X	X	X	X	X
MOS sleep scale/FACIT - fatigue scale			X	X	X	X	X		X		X		X
EuroQol EQ-5D, work limitations questionnaire			X			X	X		X		X		X
RA healthcare resource utilization questionnaire			X			X	X		X		X		X

Page 2 of 2

	Screening[a]	Visits										
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
		Baseline Day 0	1 mo	2 mo	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	21 mo	24 mo/ EOS
Randomization		X										
Drug dispensing**		X	X	X	X	X	X	X	X	X	X	
Drug accountability			X	X	X	X	X	X	X	X	X	X
Adverse event reporting		X	X	X	X	X	X	X	X	X	X	X
Review entry criteria for A3921024												X

Source: Protocol (Section 16.1.1)

Abbreviations: mo=month, EOS=end of study, RA=rheumatoid arthritis, LDL=low-density lipoprotein, HDL=high-density lipoprotein, CCP=cyclic citrullinated peptide, FACIT=Functional Assessment of Chronic Illness Therapy, SF-36=Short Form-36, MOS=Medical Outcomes Study, EuroQol EQ-5D=European Quality of Life 5-dimension scale, HIV=human immunodeficiency virus, HBsAg=hepatitis B surface antigen, HCV Ab=hepatitis C virus antibody, HCG=human chorionic gonadotropin, CBC=complete blood count, IRB=institutional review board, IEC=independent ethics committee, MTX=methotrexate

[a] Baseline visit was to occur within 1 month of the completion of the screening assessments with a +10 day window. Visits 2, 3, and 4 consisted of 28-day periods with a ±2 day window, all other study visits (5 - 11) consisted of 91-day periods with a ±7 day window.

[b] Medical History included smoking status, average weekly alcohol consumption, family history of premature coronary heart disease (CHD).

[c] Targeted physical examination consisted of weight, examination of heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes.

[d] Radiograph of chest to be done unless performed and documented within 3 months of screening.

[e] Hand and foot radiographs were read and scored centrally.

[f] Hematology included red blood cell, white blood cell with differential, hemoglobin, hematocrit, and platelet count.

[g] Chemistry Panel included urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, gamma-glutamyl transferase, albumin, and creatine kinase.

[h] Lipid Profile included fasting total cholesterol, LDL, HDL, and triglycerides; apolipoprotein A-1 and B and other lipoprotein tests potentially including particle size measurements were obtained at screening (only LDL and HDL), Baseline, Months 3, 6, 9, 12, 18, and 24. The blood draws for laboratory tests requiring a fasting state may have been separated by -48 hours from the Baseline visit and ±48 hours for the other visits requiring fasting laboratory tests.

[i] Chemistry procedures as appropriate for local laboratory in patients receiving MTX; may have included hematology, creatinine, albumin, and liver function tests.

[j] Urinalysis included specific gravity, pH, protein, glucose, ketones, and blood and leukocyte esterase. Urinary pregnancy testing (HCG) was required only for women who were of childbearing potential; may have been repeated more frequently if required by local practices, IRB/IECs or local regulations if a menstrual cycle was missed, or if potential pregnancy was otherwise suspected. Pregnancy tests were to be repeated as per request of IRB/IECs or local regulations every month. (Bulgaria only).

[k] Only at sites participating in the molecular profiling research component. Refer to molecular profiling supplement (Section 16.1.1) for further details.

[l] All ESR tests performed after screening were to be done blinded. This was done only at sites where the local laboratory had the capability of reporting results only to the central laboratory and maintaining the blind.

* Pharmacokinetics at participating sites only.

** Folate supplementation prescription at Visits 1 and 7.

Study Outcomes

- Primary Endpoints:
  1. Change in mTSS from baseline to Month 6 visit (Structure preservation).
  2. ACR70 responder rate at Month 6 visit (Signs and symptoms).
- Secondary Efficacy Endpoints.
  1. Structure preservation:
     - Actual and change from Baseline of mTSS at Months 12 and 24
     - Actual and change from Baseline of 2 individual components of mTSS (erosion and joint space narrowing [JSN] scores) at Months 6, 12, and 24
     - The rate of nonprogression in mTSS change from Baseline. Nonprogression was defined as mTSS change ≤0.5 units
     - The rate of "no new erosions." The "no new erosion" was defined as an erosion score change ≤0.5
  2. Signs and Symptoms:
     - ACR70 responder rates at all time points other than Month 6.
     - ACR20 and ACR50 responder rates at all time points.
     - DAS28 at all time points.
  3. Physical Function:
     - Actual and change from Baseline in HAQ-DI

- Safety Endpoints:
  1. All AEs will be summarized descriptively to include: Incidence and severity; Incidence of adjudicated cardiovascular events; Incidence of adjudicated malignancies; Serious infections; Incidence and severity of clinical laboratory abnormalities with special attention to neutrophils counts, serum creatinine, platelet counts, liver function tests; Summary of changes in physical examination compared to baseline by subject; change from baseline in vital signs (BP, HR, and Temperature). AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA), version 15.0.

Study Conduct

The study has been conducted at 152 study centers in 29 countries in regions of United States, Europe/Canada, Latin America, and Asia/Other

Study Initiation and Completion Dates: 25 January 2010 to 24 May 2012 (data cutoff date) based on an interim data cutoff point for the 1-year analysis.

Amendments

The protocol, finalized 10 Nov 2009, was amended 6 times to provide additional safeguards to study subjects and for administrative changes. The statistical analysis

plan (SAP), finalized 06 Apr 2010, was also amended on April 02, 2012 before the data cut-off, to include:

- The interim analysis was changed from Month 6 to Month 12
- In order to conform with the typical analyses performed for mTSS and its components, missing values due to patients withdrawing were imputed using linear extrapolation (LEP) as the primary analysis, consistent with the Agency's advice
- Nonprogression for mTSS and no new erosions were added as secondary endpoints
- For mTSS, the analysis based on rank as well as a potential trimmed data analysis were added as sensitivity analyses
- Multiple imputation for mTSS was removed

The implementation of these amendments did not negatively impact the study conduct, efficacy or safety evaluations.

Baseline Demographics and Disease Characteristics

For discussion on Baseline Demographics and Disease Characteristics, refer to section6.1.2 Demographics.

Patient Disposition

For discussion on patient disposition, refer to section 6.1.3 Subject Disposition.

Efficacy Results

For discussion on efficacy, refer to section 6 Review of Efficacy.

Safety Results

For discussion on efficacy, refer to section 7 Review of Safety.

6 Review of Efficacy

6.1 Indication

The indication is the same as currently labeled. With this submission the sponsor is seeking inclusion of radiographic data in the clinical studies section to support the inhibition of structural progression claim.

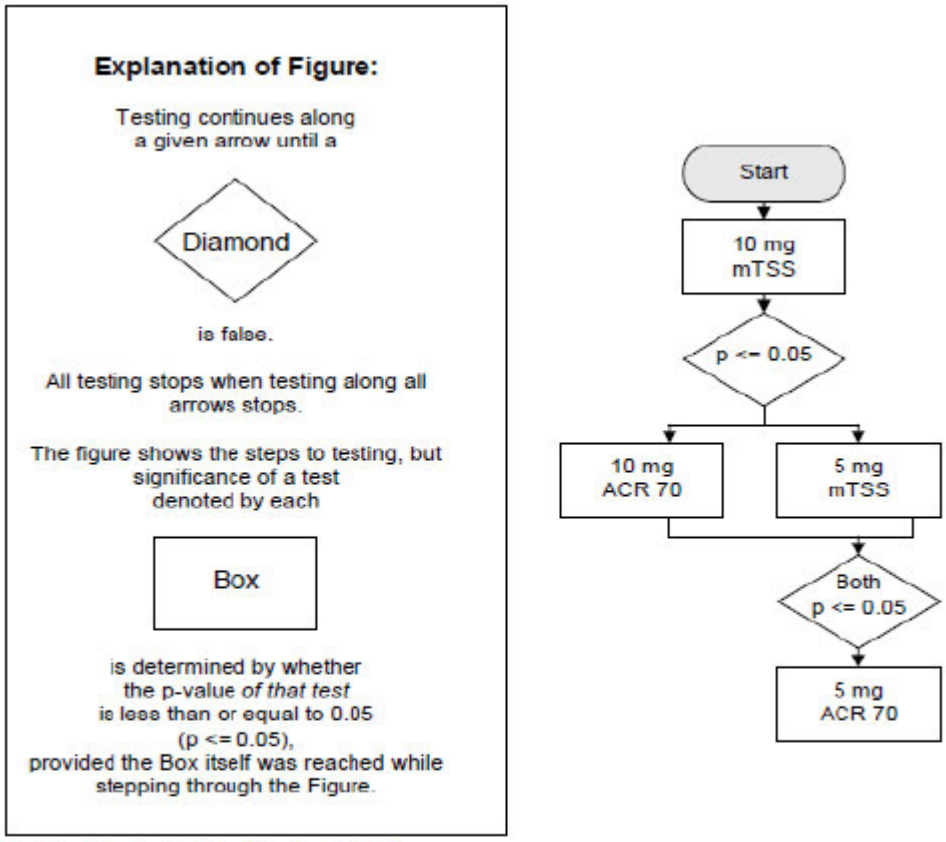
6.1.1 Methods

The efficacy data for this submission were derived from study A3921069. Additional efficacy data, submitted under the original NDA, were reviewed as needed, to provide context for the interpretation of the data from the current application.

Statistical considerations:

1. Sample size: The sample size was estimated ~900 subjects to yield a 90% power for:
    a. At least 0.9 unit difference in modified Total Sharp score (mTSS), assuming a standard deviation of 2.8.
    b. At least 15% difference in ACR70 responses, assuming 20% response to MTX.
2. Analysis of Primary Endpoints: This protocol has two primary endpoints and two investigational drug dose arms. For each endpoint and each dose group the level of statistical significance (2 sided alpha) is set at 0.05 or equivalently (1-sided) at 0.025.
    a. To preserve type I error (account for multiplicity) each objective will be assessed sequentially using gate-keeping or step-down approach where statistical significance can be claimed for each endpoint only if the first endpoint meets the significance criteria. The proposed sequence of the analysis is:
        i. Structure preservation as measured by mTSS at 6 months
        ii. Signs and symptoms as measured by ACR 70 at 6 months.
    b. To account for the two dose arms, a step-down procedure will be used where the high dose will be tested first (i.e. the lower dose can be tested only if the higher dose reaches statistical significance) for each endpoint.
    c. Analysis of variance model will be used for the first primary endpoint (change in mTSS). The baseline mTSS and the status of early RA (time since diagnosis) will be used as covariates.

Figure 2. Step-down Approach to Account for Multiplicity



Source: Statistical Analysis Plan (Section 16.1.9)
Abbreviations: mTSS=modified Total Sharp Score; ACR70=American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures

3. Analysis of major clinical response: For the major clinical response, the comparisons of these endpoints will utilize exact methods (Barnard exact test). Pair-wise testing will be used, that is, the CP-690,550 10 mg BID group to the MTX group in one test, and the CP-690,550 5 mg BID group to MTX in the other. A patient will be said to have had a Major Clinical Response if that patient has an ACR70 response at each visit spanning *any* 6 months.
4. Missing values:
    a. Sharp score will not be imputed for patient who dropout of the study prior to Month 6.
    b. Analysis of ACR70 response data from patients who dropout for any reason will use the baseline observation carried forward (BOCF).
    c. Missing ACR70 data, while the patients are enrolled, will be handled as Last observation carried forward (LOCF).

5. Interim Analysis: The 1-year analysis (interim analysis) was conducted to support regulatory filings after all patients had either completed their Month 12 visit (the primary time point) or dropped out from the study, which implied that the primary endpoint (mTSS and ACR70 at Month 6) was achieved for the patient or the patient had been discontinued from the study when the 1-year analysis was performed. Therefore, no additional adjustment was made for type I error rate, and all statistical inferences for the primary endpoints were drawn from this interim analysis. Statistical analyses performed at Month 24 (the end of the study) will be used as supportive results in addition to this analysis at Month 12 and published separately.

6.1.2 Demographics

The patient population in study 1069 consisted of adult patients with moderately-to-severely active RA or relatively short duration (mean of 3 years) who were methotrexate-naïve. The baseline demographics and disease characteristics were well balanced between the treatment groups within each study as summarized in Table 5, Table 6, and Table 7.

Compared with the study population in the original NDA, patients in study 1069 were several years younger and had significantly shorter disease duration (mean 3 years vs. about 7 to 13 years in the original NDA), which would be expected for MTX-naïve population. However, the two cohorts were comparable with respect to disease activity. With respect to the radiographic damage, patients in study 1069 had lower mTSS scores compared to patients in study 1044 from the original NDA (mean of about 20 vs. 30 in study 1044) consistent with the accumulated structural damage due to longer disease duration in study 1044.

Table 5. Summary of Demographics and Baseline Disease Characteristics in Study 1069

Summary of Demographics and Baseline Disease Characteristics in Study 1069			
	Tofa 5 mg BID n=371	Tofa 10 mg BID n=395	MTX n=186
Gender			
Females, n (%)	283 (76)	325 (82)	145 (78)
Age, years			
mean (SD)	50 (12)	49 (13)	49 (13)
Weight, kg			
mean (SD)	71 (17)	71 (19)	71 (18)
Height, cm			
mean (SD)	163 (9)	163 (10)	163 (10)
Race, n (%)			
White	239 (64)	265 (67)	127 (68)
Black	13 (4)	12 (3)	4 (2)
Asian	67 (18)	61 (15)	22 (18)
Other	52 (14)	57 (14)	22 (12)
Duration of RA, years			
mean (Range)	3 (0-44)	3 (0-34)	3 (0-30)
Rheumatoid Factor status			
% Positive	83%	82%	84%
Anti-CCP Antibody status			
% Positive	85%	82%	87%
MTX at screening			
Number of subjects, (%)	24 (7)	27 (7)	14 (8)
Prior TNF inhibitor use			
Number of subjects, n (%)	0	1	1
Prior non-biologic DMARD use			
Number of subjects, n (%)	136 (38)	156 (40)	76 (41)

Source: CSR A3921069, Adapted from Tables 12 and 13, Table 14.4.2.2.2

Table 6. Summary of Baseline Disease Activity in Study 1069

Summary of Baseline Disease Activity in Study 1069			
	Tofa 5 mg BID n=371	Tofa 10 mg BID n=395	MTX n=186
DAS28-3(CRP) mean (SD)	5.6 (1)	5.5 (1)	5.6 (1)
DAS28-4(ESR) mean (SD)	6.6 (1)	6.5 (1)	6.6 (1)
ESR, mm/h (normal ≤ 24) mean (SD)	56 (29)	53 (27)	56 (28)
CRP, mg/L (normal ≤ 7) mean (SD)	23 (27)	20 (24)	26 (31)
Tender Joint Count (0-68 joints) mean (SD)	26 (14)	25 (14)	25 (15)
Swollen Joint Count (0-66 joints) mean (SD)	16 (9)	16 (8)	17 (10)
Sharp Score (mTSS) mean (SD)	20 (41)	19 (40)	17 (29)
HAQ-DI (max 3) mean (SD)	1.5 (1)	1.5 (1)	1.5 (1)
Source: CSR A3921069, Adapted from Tables 12 and 13			

The geographic distribution summarized in Table 7, was also comparable between study 1069 and the rest of the tofacitinib RA development program as reviewed in the original NDA.

Table 7. Geographic Distribution in Study 1069

Geographic Distribution in Study 1069			
	Tofa 5 mg BID n=374 n (%)	Tofa 10 mg BID n=398 n (%)	MTX n=186 n (%)
United States	84 (22)	97 (24)	39 (21)
Latin America	63 (17)	71 (18)	28 (15)
Europe	151 (40)	158 (40)	81 (44)
Rest of the World	76 (20)	72 (18)	38 (20)
Source: CSR A3921069, Adapted from Table 14			

6.1.3 Subject Disposition

Table 8 below summarizes patient disposition by treatment assignment. Overall, more patients discontinued the methotrexate group due to both lack of efficacy and adverse events compared with the tofacitinib groups suggesting differential dropout. However the differences are small and are not likely to have a significant impact on the assessment of efficacy or safety.

Table 8. Subject Disposition in Study 1069, Year 1 Data

Subject Disposition in Study 1069, Year 1 Data			
Screened: 1540	Tofa 5 mg BID n (%)	Tofa 10 mg BID n (%)	MTX n (%)
Assigned to treatment	374	398	186
Treated	371	395	186
Ongoing at date cutoff	307 (82)	328 (82)	134 (72)
Discontinued	64 (17)	67 (17)	52 (28)
Lack of efficacy	15 (4)	17 (4)	11 (6)
Adverse event	18 (5)	23 (6)	15 (8)
Lost to follow up	7 (2)	4 (1)	3 (2)
No longer willing to participate	16 (4)	16 (4)	8 (4)
Protocol violation	3 (1)	8 (2)	4 (2)
Pregnancy	2 (1)	0	0
Other	3 (1)	7 (2)	4 (2)
Source: CSR A3921069, Adapted from Table 7			

6.1.4 Analysis of Primary Endpoints

Primary efficacy analyses were conducted on the full analysis set (FAS, Table 9) which included all patients who (1) were randomized to the study, (2) received at least 1 dose of the randomized study drug (tofacitinib) or MTX and (3) had a Baseline and at least 1 non-missing on-study assessment of the endpoint. Patients with violations that could potentially affect the efficacy analysis were excluded from FAS.

As shown in Table 9, a total of 71 patients excluded from the analysis of radiographic endpoint: 57 were excluded because they had no post-baseline data and 14 were excluded because they lacked a baseline value. The proportions of patients excluded from the primary analysis due to missing data were relatively small and overall balanced across the treatment arms.

Table 9. Full Analysis Set for the Primary Endpoints in Study 1069, Year 1 Data

Full Analysis Set for the Primary Endpoints in Study 1069, Year 1 Data			
	Tofa 5 mg BID n (%)	Tofa 10 mg BID n (%)	MTX n (%)
Randomized and treated	371	395	186
Analyzed for primary efficacy			
mTSS	346 (93)	369 (93)	166 (89)
ACR70	369 (99)	393 (99)	184 (99)
Source: CSR A3921069, Adapted from Table 11			

Change in Modified Total Sharp Score (mTSS) from Baseline

The Van der Heijde-modified Sharp radiographic scoring method grades the presence of erosions in the joints of the hands and feet, and the presence of joint space narrowing (JSN) in the hands, wrists, and feet.[3] The total maximum erosion score is 280 and the maximum total JSN score is 168. Thus the theoretical maximum modified total Sharp Score (mTSS) is 448. However, the actual mTSS range in RA drug development trials is typically much lower because a given individual typically only has a fraction of his or her joints affected by radiographically evident damage.

The primary radiographic endpoint in study 1069 was assessed at Month 6 with a follow up assessment at Month 12. Because this trial was an active comparator trial, all patients continued to receive their originally assigned treatment. Only patients who required rescue medication for active disease for more than 10 consecutive days were discontinued from the study. For this assessment, radiographs of hands and feet were obtained at Baseline (Visit 1), Month 6 (Visit 5), Month 12 (Visit 7) and Month 24 (Visit 11 or End of Study Visit).

To be included in the radiographic endpoint assessment, patients must have had a baseline and at least one post-baseline radiograph. Patients with missing data at Month 6 or Month 12 had their data imputed using linear extrapolation from baseline to their last radiographs prior to exiting their assigned treatment group. This imputation method has been used historically in other RA development programs assessing structural damage, but has inherent limitations, particularly as the length of the extrapolation period increases and the amount of missing data increases. Binary variables (e.g., rates of patients with no progression in mTSS) were analyzed using normal approximation to the binomial. Scoring of all radiographs was done by central blinded assessors.

3 S Boini and F Guillemin, “Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages.” Ann Rheum Dis 2001; 60:817-827

The primary analysis was an analysis of covariance (ANCOVA) model for change of mTSS from Baseline to Month 6. The model included Baseline mTSS and the status of early RA (measure of time since diagnosis) as covariates. The Sharp scores for patients who dropped out from the study prior to Month 6 were not otherwise imputed.

The change of mTSS from Baseline to Month 6 and Month 12 was analyzed using a linear model with Baseline mTSS and the status of early RA (measure of time since diagnosis) as covariates. The individual components of Total Sharp score were analyzed in the same way as the mTSS score.

The study met its primary endpoint of superiority of tofacitinib (5 mg and 10 mg BID) to MTX in patients with relatively early MTX-naïve RA as shown in Table 10. The results were consistent at Month 12 as shown in Figure 3. These data support tofacitinib's beneficial effect on radiographic progression and provide evidence of efficacy on the structural outcomes corroborating the findings from study 1044.

Table 10. Radiographic Primary Analysis at Month 6 (FAS, LEP, Year 1 Analysis)

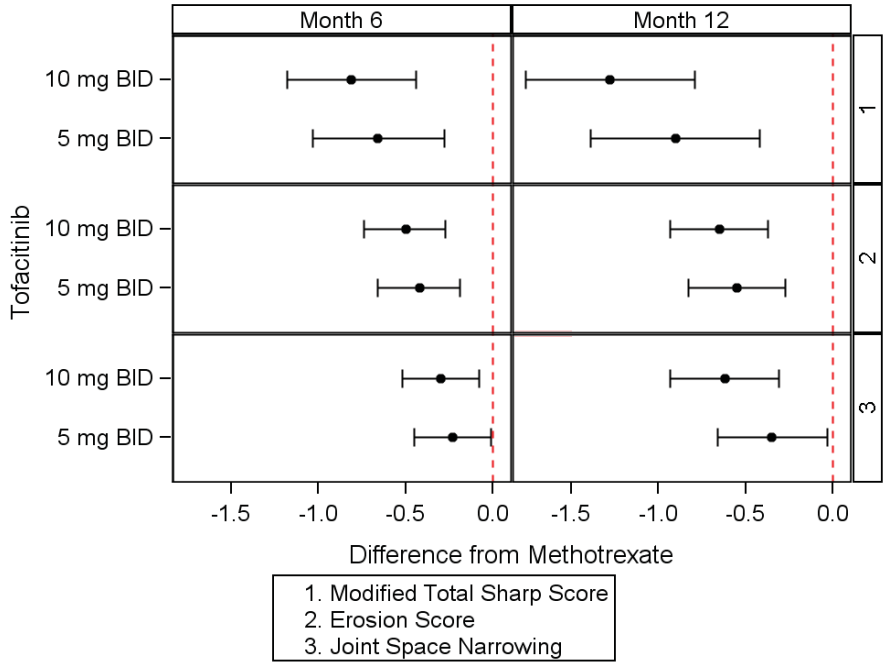
Summary of LS Mean Changes From Baseline in Modified Total Sharp Scores (mTSS) at Month 6 (FAS, LEP, Year 1 Analysis)			
mTSS	Tofa 5 mg BID	Tofa 10 mg BID	MTX
Randomized and treated	371	395	186
Analyzed for primary efficacy	346 (93)	369 (93)	166 (89)
LS Mean	0.18	0.04	0.84
LS Mean difference from MTX	-0.66	-1.18	-
95% CI of difference	-1.03, -0.28	-1.18, -0.44	-
p-value	0.0006	<0.0001	

Source: CSR A3921069, Adapted from Tables 11 and 15
If patients did not have any valid postbaseline radiographs, they were not included in this summary.
Abbreviations: BID=twice daily, CI=confidence interval, FAS=full analysis set, LS=least squares, LEP=linear extrapolation, MTX=methotrexate

Change in mTSS Components

Proportional improvements were seen in the mTSS components, joint space narrowing (JSN), and erosion score (ES) as shown in Figure 3, indicating a beneficial effect on both the cartilage damage and the bone erosions.

Figure 3. Differences From MTX in mTSS, Erosion Scores and JSN at Months 6 and 12 (FAS, LEP, 1-Year Analysis)

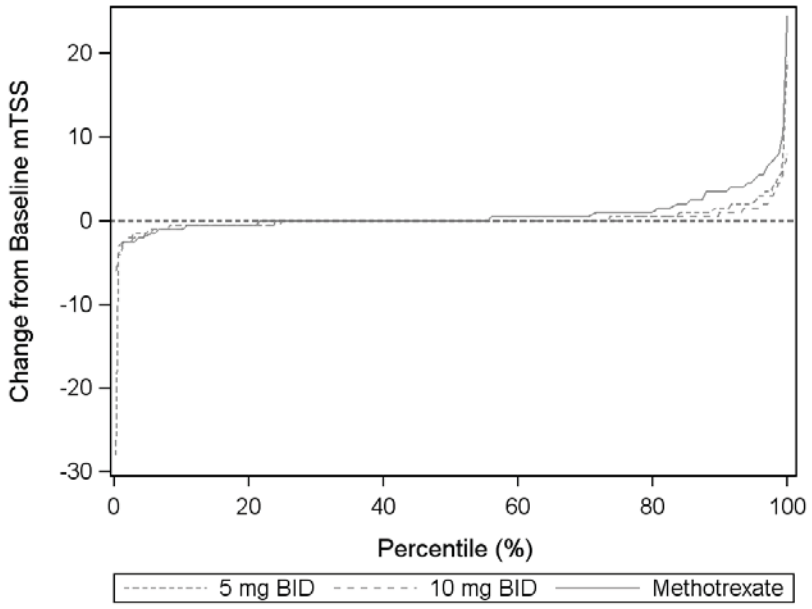


Source: CSR A3921069, Figure 14

Cumulative Radiographic Data Distribution

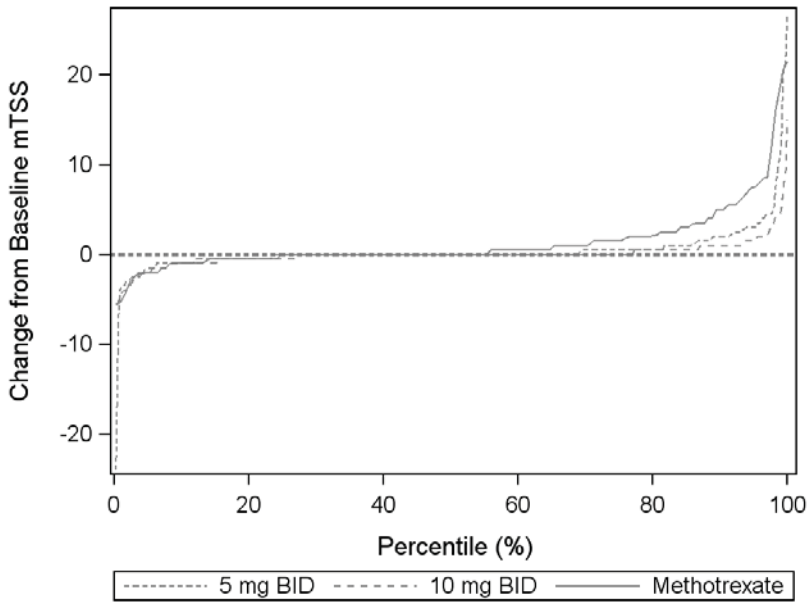
As illustrated in Figure 4 and Figure 5, which contain study 1069 results and are consistent with the distribution observed in other RA programs, only a fraction of patients experience progression (above “0” on the graphs) in the time frame of the study. However, the plots indicate a higher proportion of patients progressing on methotrexate compared to tofacitinib with a suggestion that 10 mg may be slightly better than 5 mg in reducing radiographic progression at both Month 6 and 12.

Figure 4. Cumulative Probability Plot of Changes From Baseline to Month 6 in mTSS (LEP, 1-Year Analysis)



Source: CSR A3921069, Figure 18

Figure 5. Cumulative Probability Plot of Changes From Baseline to Month 12 in mTSS (LEP, 1-Year Analysis)



Source: CSR A3921069, Figure 19

Sensitivity analyses

Sensitivity analyses on the radiographic data from study 1069 were conducted by the statistical review team to account for the amount of missing and imputed radiographic data and the potential effect of potential outliers as shown in Table 11 and Table 12 which were significant limitations in study 1044. In summary, these analyses supported the findings from the primary analysis as detailed in the statistical review.

Table 11. Radiographic Primary and Pre-Specified Secondary Analysis, Month 6, Study 1069

Treatment	N	LS Mean	Difference vs. MTX		
			LS Mean Difference	95% CI	P-value
Primary Analysis: Full Analysis Set (ANCOVA)					
CP 5 mg	346*	0.18	-0.66	(-1.03, -0.28)	<0.001
CP 10 mg	369*	0.04	-0.81	(-1.18, -0.44)	<0.001
MTX	166*	0.84			
Pre-specified Sensitivity Analysis: Rank ANCOVA					
CP 5 mg	346*	432	-73	(-117, -29)	0.001
CP 10 mg	369*	411	-94	(-137, -61)	<0.001
MTX	166*	504			

Source: Dr. Kim's statistical review

Table 12. Radiographic Endpoint Sensitivity Analysis: Excluding Patients with mTSS Greater than 7 Units Change from Baseline at Month 6, Study 1069

Treatment	N	LS Mean	Difference vs. MTX		
			LS Mean Difference	95% CI	P-value
Primary Analysis: Full Analysis Set					
CP 5 mg	346	0.18	-0.66	(-1.03, -0.28)	<0.001
CP 10 mg	369	0.04	-0.81	(-1.18, -0.44)	<0.001
MTX	166	0.84			
Excluding patients with |Δ| greater than 7 units*					
CP 5 mg	342	0.14	-0.41	(-0.63, -0.18)	0.005
CP 10 mg	368	0.01	-0.54	(-0.77, -0.32)	<0.001
MTX	162	0.55			

Source: Dr. Kim's statistical review

Analysis of Patients with No Radiographic Progression

Radiographic progression is an important categorical measure to assess structural benefit. As shown in Table 13, the proportion of patients with no radiographic progression (defined as either change in mTSS ≤ 0.5 units or change of 0) at Month 6 was greater in tofacitinib-treated compared with MTX-treated patients with numerical advantage of the higher tofacitinib dose, supporting the robustness of the radiographic data in this patient population.

Table 13. Proportion of Patients with No Radiographic Progression in Study 1069 at 6 Months (Imputation Using Linear Extrapolation, FAS Population)

Proportion of Patients with No Radiographic Progression in Study 1069 at 6 Month (Imputation Using Linear Extrapolation, FAS Population)					
	Tofa 5 mg BID	Tofa 10 mg BID	MTX	95% CI (5mg BID)	95% CI (10mg BID)
No Progression defined by applicant as Change in mTSS ≤ 0.5 units					
Total number of patients	346	369	167		
Patients with no progression, n (%)	289 (84%)	331 (90%)	118 (71%)	(5%, 21%)	(11%, 27%)
Difference from MTX	13%	19%	-	-	-
No Progression defined by FDA reviewer as Change in mTSS of 0 units					
Total number of patients	346	369	167		
Patients with no progression, n (%)	254 (73%)	284 (77%)	93 (56%)	(9%, 27%)	(13%, 30%)
Difference from placebo	18%	21%	-	-	-

Source: Source: CSR A3921069, Adapted from Tables 18 and 14.2.15.4.1
FDA Statistical review team analyses
If subjects did not have any valid post-baseline radiographs, they were excluded from this analysis

These findings address some of the limitations of the radiographic data from study 1044, where a change in the definition of "no progression" from a change in mTSS of ≤0.5 units to 0 units resulted in a loss in statistical significance for the tofacitinib 10 mg dose group and results discordant with the change in mean mTSS scores as discussed in the original NDA.

Conclusion of Radiographic Outcomes

The results of study 1069 provide robust evidence of efficacy of tofacitinib at both 5 and 10 mg BID dosing regimens for the inhibition of structural progression in the relatively early, MTX-naïve RA patient population support a claim of radiographic benefit in patients with moderate to severe RA. These results provide a corroborating evidence of tofacitinib's radiographic benefit and address the uncertainties with the interpretation of the findings from study 1044 discussed in the original NDA application. Specifically,

study 1069 was able to demonstrate a measurable treatment difference, due to the degree of radiographic progression in the control group, and consistent radiographic benefit irrespective of the missing data, outliers, or imputation method, based on the sensitivity and secondary analyses

While the results from study 1069 indicate a higher a degree of structural preservation with tofacitinib than with MTX in the MTX-naïve patient population, the findings from the radiographic endpoint assessment should be viewed in the context of the overall risk-benefit of tofacitinib which has been associated with significant dose-dependent toxicities and has a limited long-term safety record as compared with MTX.

ACR70 Response Rates

ACR70 response criteria were used to assess superiority of two doses of tofacitinib (5 mg and 10 mg BID) over MTX as the second primary endpoint.

The American College of Rheumatology's response in RA (ACR70) is calculated as a ≥70% improvement in:

- tender joint count (68) and
- swollen joint counts (66) and
- 3 of the 5 remaining ACR-core set measures:
    - patient global assessments of arthritis on a visual analog scale (VAS),
    - physician global assessment of arthritis on a VAS,
    - patient reported pain on a VAS,
    - patient assessment of physical function (e.g., Health Assessment Questionnaire-Disability Index [HAQ-DI], and
    - acute-phase reactant (e.g., CRP).

Similarly, ACR20, and 50 are calculated with the respective percent improvement and were assessed as major secondary endpoints.

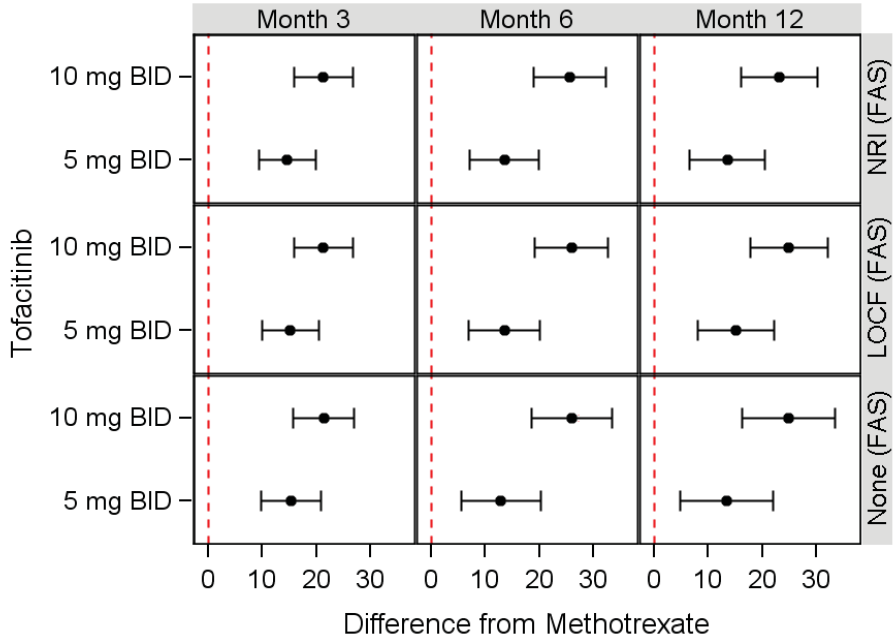
The original NDA provided the evidence to conclude that tofacitinib administration at both doses (5 mg and 10 mg BID) showed statistically significant and clinically meaningful increases in ACR20/50/70 response rates in all 5 Phase 3 studies (either Month 3 or 6) as described in the product labeling. The clinical response results from study 1069 are overall consistent with the rest of the tofacitinib RA clinical development with some dose dependence as shown in Table 14 and Figure 7 below indicating that tofacitinib administration provides clinical benefit also to patients with earlier disease who are naïve to MTX, which would not be unexpected given the disease characteristics and tofacitinib's mechanism of action.

Table 14. ACR70 Response Rates at Month 6 (FAS, NRI, 1-Year Analysis)

ACR70 Response Rates at Month 6 (FAS, NRI, 1-Year Analysis)			
ACR70	Tofa 5 mg BID	Tofa 10 mg BID	MTX
Randomized and treated	371	395	186
Analyzed for primary efficacy	369 (99)	393 (99)	184 (99)
ACR70 responders, n (%)	94 (25%)	148 (38%)	22 (12%)
Difference from MTX	13%	26%	-
95% CI of difference	7, 20	20, 32	-
p-value	<0.0001	<0.0001	

Source: CSR A3921069, Adapted from Tables 16 and 14.2.3.1
Abbreviations: CI=confidence interval, FAS=full analysis set, N=number of patients, n=number of patients meeting prespecified criteria, NRI=nonresponder imputation, BID=twice daily, MTX=methotrexate

Figure 6. ACR70 Responses at Months 3, 6, and 12, Difference from MTX in Study 1069, Sensitivity Analysis



Source: CSR A3921069, Figure 6

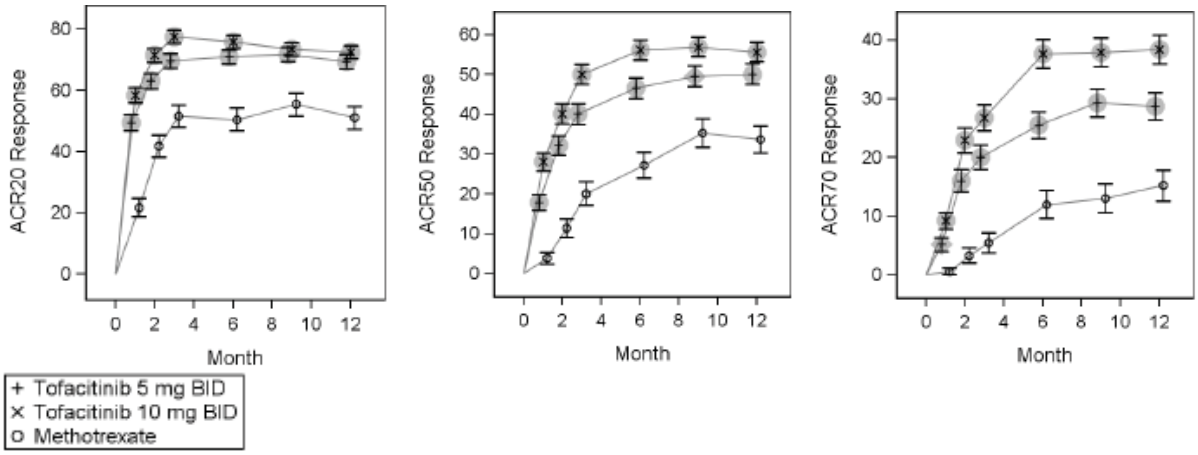
6.1.5 Analysis of Secondary Endpoints(s)

Clinical Response

ACR Response Rates and Time Course

ACR20 and ACR50 response rates were also consistent with the ACR70 rates with some numerical dose-dependence particularly for ACR70 responses over the 12-month observation period as shown in Figure 7. These results are also consistent with the clinical responses in the overall RA development program as discussed in the original NDA supporting the conclusion that tofacitinib treatment was effective up to 1 year in the randomized controlled studies.

Figure 7. ACR20/50/70 Response Rates Over Time (±SE) Through Month 12 (FAS, NRI, 1-Year Analysis)



Source: CSR A3921069, Adapted from Figures 7 and 9

ACR Core Components

Additional sensitivity analysis of mean change from baseline at Month 6 in all ACR components, demonstrated that treatment with tofacitinib resulted in greater improvement compared with MTX, in all ACR components, without a consistent dose-response (data not shown). These results are consistent with the results of the primary analysis of ACR70 response rates and the observations in the original NDA.

Major Clinical Response

The sponsor has also submitted data on the proportion of patients with sustained ACR70 responses over at least 6 months providing evidence of benefit of tofacitinib treatment (both 5 mg and 10 mg BID) over MTX as shown in Table 15.

Table 15. Proportion of Patients With ACR70 Response Sustained at Least 6 Months (FAS, No Imputation, Year 1 Analysis)

Proportion of Patients With ACR70 Response Sustained at Least 6 Months (FAS, No Imputation, Year 1 Analysis)			
Major Clinical Response	Tofa 5 mg BID	Tofa 10 mg BID	MTX
Randomized and treated	371	395	186
Analyzed for primary efficacy	369 (99)	393 (99)	184 (99)
MCR, n (%)	61 (16%)	97 (25%)	11 (6%)
95% CI for %	13, 21	10, 29	3, 10

Source: CSR A3921069, Adapted from Tables 17 and 14.2.3.7
Abbreviations: CI=confidence interval, FAS=full analysis set, N=number of patients, n=number of patients meeting prespecified criteria, NRI=nonresponder imputation, BID=twice daily, MTX=methotrexate
Major Clinical Response: ACR70 Response Sustained for at Least 6 Months

Disease Activity Score (DAS28)

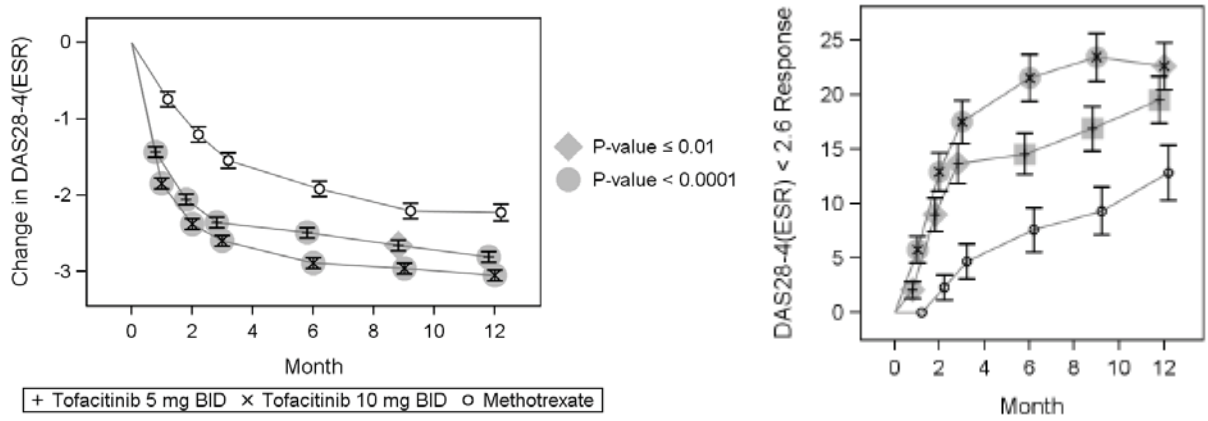
Secondary outcome in study 1069 to support tofacitinib's effect on signs and symptoms of disease included measurement of Disease Activity Score (DAS) which is a composite endpoint with differential weighting given to each component. The components of the DAS28 arthritis assessment include:

- tender joint count (28 joints to include bilateral shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees.),
- swollen joint count (28),
- an acute phase reactant (ESR or CRP)
- patient's global assessment of arthritis.

The DAS components are summed mathematically into a single numerical value ranging from 0 to 10. A DAS28 score >5.1 is indicative of high disease activity, and <2.6 of low disease activity. A change of ≥1.2 in DAS28 score is considered clinically significant. DAS28-4(ESR) uses all 4 components listed above and ESR as the acute-phase reactant. DAS28-3(CRP) uses CRP as the acute-phase reactant but does not include the Patient's Global Assessment of Arthritis.

Treatment with tofacitinib (5 mg or 10 mg BID) resulted in greater decreases (improvements) from baseline in DAS28-4(ESR), and the proportion of patients achieving low disease activity (DAS28 ≤ 2.6) through Months 12 compared with MTX as shown in Figure 8. Consistent results were reported with a variant scoring of the instrument, i.e. DAS28-3 (CRP) (data not shown).

Figure 8. Improvement in DAS28-4(ESR) Over 12 Months in Study 1069, Change from Baseline and Proportion of Patients with Clinically Meaningful Improvement, ±SE (FAS, NRI, Year 1 Data)



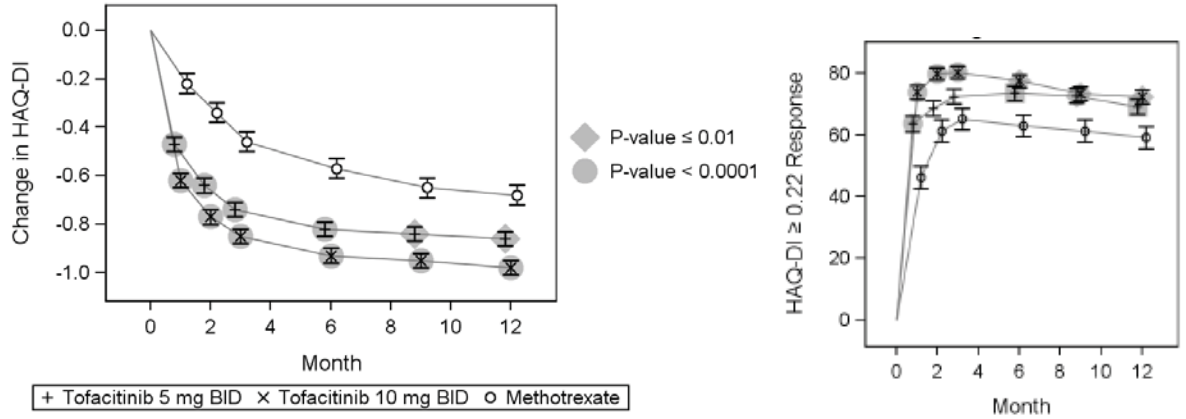
Source: CSR A3921069, Adapted from Figures 28 and 23

Physical Function (HAQ-DI)

Physical function was assessed as a secondary endpoint in study 1069 using Health Assessment Questionnaire–Disability Index (HAQ-DI). The HAQ-DI assesses the degree of difficulty a patient has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

The magnitude and kinetics of the improvement in physical functioning as measured by change from baseline in HAQ-DI scores and the proportion of patients achieving a clinically meaningful improvement (HAQ-DI ≥ 0.22 units) in study 1069 (see Figure 9) was consistent with the effect seen in the overall RA development program as discussed in the original NDA. These effects are also reflected in the currently approved labeling.

Figure 9. Improvements in HAQ-DI Over 12 Months in Study 1069, Change from Baseline and Proportion of Patients with Clinically Meaningful Improvement, ±SE (FAS, NRI, Year 1 Data)



Source: CSR A3921069, Adapted from Figures 25 and 26
Abbreviations: BID=twice daily, FAS=full analysis set, NRI=nonresponder imputation, HAQ-DI=Health Assessment Questionnaire - Disability Index, SE=standard error, MTX=methotrexate

6.1.6 Other Endpoints

Multiple additional secondary endpoints, such as SF-36, FACIT-F fatigue scale, MOS sleep scale, were included in the sponsor-provided analyses of efficacy. Since these are not proposed by the applicant to support labeling claims, and are generally not utilized by the Agency to support labeling language for RA products with the exception of SF-36 (which is already labeled claim in tofacitinib's labeling), these were not reviewed in detail in this document. However, the applicant's submitted analyses of these endpoints were consistent with the overall conclusion of treatment benefit associated with tofacitinib treatment.

6.1.7 Subpopulations

Explorations of efficacy (ACR20/50/70, DAS28-4(ESR) <2.6, HAQ-DI change from Baseline, and mTSS change from baseline) in subpopulations in study 1069 were consistent with the findings in the original NDA where the results of the subgroup analysis demonstrate a consistent benefit across a variety of different subgroups (age, gender, geographic region).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The results from study 1069 were consistent with observations form the original NDA which suggested some dose-dependency in the clinical outcomes in the domains of signs and symptoms and physical function. However, the potential added benefit of the 10 mg BID dose over the 5 mg BID dose is minimal and was not consistent across the randomized controlled studies.

In the domain of structural outcomes, the clinical significance of the observed small incremental benefit of 10 mg vs 5 mg BID dosing on radiographic endpoints in study 1069 is unclear. In addition, in study 1044, depending on the type of analysis, the pattern of the radiographic endpoints was inconsistent between the two doses, which raises further questions about the benefit of 10 mg vs 5 mg BID dosing on these endpoints (b) (4)

(b) (4)

Furthermore, the potential incremental benefit on signs and symptoms, physical function, and radiographic outcomes should be interpreted in the context of risk-benefit considerations in light of the significant dose-dependent safety findings, such as malignancy, serious infections and laboratory abnormalities which are discussed in detail in Section 7 Review of Safety below.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In study 1069, the time course of ACR20/50/70 responses, DAS28, and HAQ-DI changes as discussed in the respective sections above suggest that response rates has increased between 3 and 6 months and plateaus afterwards, supporting the conclusion that tofacitinib treatment was effective up to 1 year. This is consistent with the observations in the rest of the randomized controlled studies reviewed under the original NDA.

6.1.10 Additional Efficacy Issues/Analyses

Efficacy issues and analyses are discussed in Section 6 Review of Efficacy above.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data in this submission were derived from:

- Six Phase 2 studies in RA: 1019, 1039, 1040, 11109, and pivotal 1025, 1035
- All Phase 3 pivotal studies in RA: 1032, 1045, 1046, 1064, 1044, 1069
- Two ongoing, open label, long-term extensions (LTE) studies in RA: 1024, 1041

7.1.2 Categorization of Adverse Events

Adverse events (AEs) for study 1069 were categorized consistent with the rest of the tofacitinib RA development.

Adverse events were coded by using the MedDRA (version 15.0). SAEs were defined as any event that resulted in death, was life-threatening, resulted in a persistent or significant disability or incapacity, required in-patient hospitalization or prolongation of existing hospitalization, or resulted in a congenital anomaly or birth defect. In addition, other important medical events were considered SAEs if they jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed in this definition. 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. Severity of AEs was recorded as mild, moderate, or severe, as judged by the investigator.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety review in this document is presented separately for:

1. Study 1069 due to the different patient population, i.e. relatively early, MTX-naïve RA.

2. Updated safety from the original NDA comprising the controlled periods and the long-term extension periods of the tofacitinib RA development program:

    - P2P3LTE - This population includes any patient in the Phase 2 or Phase 3, or LTE studies (for those patients entering from the included Phase 2/3 studies), who was dosed with tofacitinib at any time (all doses combined); patient exposure was counted from the first dose of tofacitinib to the last dose of tofacitinib in any study, regardless of whether this occurred in the index study or LTE, and exposure time was summed between index and LTE studies. The P2P3LTE cohort includes all studies mentioned above.

    - LTE – This population consists of pooled safety data from all patients who enrolled in either one of the two LTE studies (A3921024 [global] and A3921041 [Japan only]). LTE exposures were limited to dosing within the LTE studies. The LTE safety is broken down into a 5 mg BID cohort, a 10 mg twice daily (BID) cohort and both doses combined. Patients were categorized into the 5 and 10 mg cohorts based on the highest dose received during the first 135 days of treatment in the LTE study. This dose definition is the same as that utilized for the original NDA submission.

Importantly, the assessment of safety in these cohorts was complicated by several factors: (1) inconsistent dosing in significant number of patients who have crossed over between the two doses; (2) the overall duration of exposure in the extension studies is highly variable within a group, (3) the duration of exposure was significantly different between the two doses, and (4) these cohorts continued to accrue patients from the

ongoing Phase 2 and Phase 3 program resulting in variable denominators for the incidence rates calculations for the different cutoff timepoints of safety reporting . All of these cohort design characteristics have limited the adequate quantification of potential dose-dependent safety signals. Therefore, the updated safety in this cohort is presented only for completeness.

3. Newly defined cohorts: To overcome some of the limitations discussed above, and to better quantify the potential dose-dependent safety concerns with longer-term tofacitinib exposure beyond the controlled periods, the sponsor has submitted safety analyses of the following two new cohorts as requested at the pre-sNDA meeting. Importantly, exposure time and events were censored if a dose change occurred when a patient went from a Phase 2 or Phase 3 index study to an LTE study:

   - P2P3LTE 5 mg BID Cohort – The P2P3LTE 5 mg BID cohort consists of all patients randomized to the tofacitinib 5 mg BID dose or advanced to the 5 mg BID dose from placebo in the P2P3LTE population; patient exposure was counted from the first dose of tofacitinib (by definition 5 mg BID) until the last dose of tofacitinib 5 mg BID in any study, regardless of whether this occurred in the index study or LTE. The dose definition for this population in the LTE studies is the same as described above for the LTE population. This cohort includes the same studies listed for the P2P3LTE cohort, above.

   - P2P3LTE 10 mg BID Cohort - The P2P3LTE 10 mg BID cohort consists of all patients randomized to the tofacitinib 10 mg BID dose or advanced to the 10 mg BID dose from placebo in the P2P3LTE population; patient exposure was counted from the first dose of tofacitinib (by definition 10 mg BID) until the last dose of tofacitinib 10 mg BID in any study, regardless of whether this occurred in the index study or LTE. The dose definition for this population in the LTE studies is the same as described above for the LTE population. This cohort includes the same studies listed for the P2P3LTE cohort, above.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As of April 19th, 2012 (clinical data cut-off date of this NDA supplement), the RA Phase 2, 3 and LTE studies included about 4800 patients across all treatment groups with about 8500 patient-years of exposure to all doses as shown in Table 16 which represents additional 1500 patient-years of exposure as compared with the original NDA.

Table 16. Exposure to Tofacitinib in Phase 2, Phase 3 and LTE Trials in RA

Exposure to Tofacitinib in Phase 2, Phase 3 and LTE Trials in RA			
Data cut-off	March 29, 2011	Sept. 29, 2011	April 19, 2012
Number of patients	4789	4791	4789
Exposure (PY)	5651	6922	8460
Exposure at any dose, by duration			
≥ 12 months	2649	3126	3567
≥ 24 months	709	941	2002
≥ 36 months	ND	567	634
Source: Summary of Clinical Safety, adapted from Table 1			

For completeness, the exposure in the LTE studies in RA is summarized in Table 17 below.

Table 17. Exposure to Tofacitinib by Dose and Duration in the LTE Studies in RA

Exposure to Tofacitinib in the LTE Studies in RA			
Duration of exposure	March 29, 2011	Sept. 29, 2011	April 19, 2012
Number of patients	3227	5315	4102
Exposure (PY)	3118	4410	6034
Source: Summary of Clinical Safety, adapted from Table 2			

To quantify potential dose-dependent major toxicities associated with tofacitinib exposures beyond the controlled periods of the pivotal studies, the sponsor has defined new cohorts of patients who were exposed to the same dose (either 5 or 10 mg BID) without cross-overs. The exposures for these newly defined cohorts is summarized in Table 18 below and indicates comparable number of patients and duration of exposure to the two doses allowing for more meaningful safety comparisons between the two dosing regimens with longer exposure.

Table 18. Exposure to Tofacitinib by Dose Cohort (Continuous Same Dose) in Phase 2, Phase 3 and LTE Trials in RA

Exposure to Tofacitinib by Dose Cohort (Continuous Same Dose) in Phase 2, Phase 3 and LTE Trials in RA		
	5 mg BID cohort	10 mg BID cohort
Number of patients	1955	1846
Exposure (PY)	2174	2460
Source: Summary of Clinical Safety, adapted from Table 5		

7.2.2 Explorations for Dose Response

To account for the differences in exposure among treatment groups, exposure-adjusted AE incidence rates are calculated as the number of patients with a new event (for that time period), divided by the total exposure in that treatment group in the pooled cohort, and multiplied by 100 (i.e., rate per 100 patient-years). This allows for a standardized comparison among treatment groups in the pooled safety analyses. This approach was used to identify potential safety signals of rare events, such as malignancy, mortality, and serious infections.[4]

To quantify potential dose-dependent major toxicities associated with tofacitinib exposures beyond the controlled periods of the pivotal studies, the sponsor has defined new cohorts of patients who were exposed to the same dose (either 5 or 10 mg BID) without cross-overs.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this submission.

7.2.4 Routine Clinical Testing

The type and frequency of routine clinical testing of patients in study 1069 was consistent with the overall RA development program and was considered adequate. For details, see section 5.3Discussion of Individual Studies/Clinical Trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable to this submission.

4 Liu GF, et al., Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials, Statist Med 2006; 25:1275-1286

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Tofacitinib is in the same drug class with ruxolitinib, which is another Janus associated kinase (JAK) inhibitor, targeting JAK1 and JAK2, approved for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in November 2011. The major warnings and precautions identified in ruxolitinib's label include thrombocytopenia, anemia, neutropenia and infections.[5]

Tofacitinib's safety data were assessed in the context of what is known about the safety profile of other traditional and biologic DMARDs. Therefore the data were evaluated with special attention to serious infections, malignancies. However JAK inhibition may pose unique risks, such as neutropenia, lymphopenia, elevated serum creatinine, and elevated lipid parameters. These potential concerns are also addressed below.

7.3 Major Safety Results

Study 1069

Table 19 provides an overview of the Year 1 safety in study 1069. The incidence rates of AEs, SAEs, Severe AEs, and AEs leading to discontinuation were comparable between the two tofacitinib dose groups and remain consistent with the rates observed in the controlled periods of the pivotal NDA studies reviewed in the original NDA. There are some numerical increases in these estimates in the MTX-treated group which may be attributed to the unequal randomization and the higher degree of uncertainty regarding the estimated rates in this group. The most frequently reported AEs were those coding to the MedDRA SOCs of Infections and infestations and Gastrointestinal disorders consistent with the original NDA.

5 USPI Jakafi (ruxolibinib), November 2011

Table 19. Overview of Safety in Study 1069 (Year 1 Data)

Overview of Safety in Study 1069 (Year 1 Data)			
	Tofa 5 mg BID n (%)	Tofa 10 mg BID n (%)	MTX n (%)
Randomized and treated	371	395	186
Exposure for event, patient-years (PY)	331	353	152
Total number of AEs	863	1057	449
Total patients with ≥ 1 AE, n (%)	260 (70)	294 (74)	130 (70)
Incidence of AEs, event per 100 PY	155	183	197
Total patients with ≥ 1 SAE, n (%)	24 (7)	24 (6)	13 (7)
Incidence of SAEs, event per 100 PY	7.2	6.8	8.6
Total patients with ≥ 1 Severe AE, n (%)	22 (6)	21 (5)	11 (6)
Patients who discontinued due to AE, n (%)	24 (7)	31 (8)	17 (9)
Incidence discontinuations due to AE, event per 100 PY	7.2	8.8	11.2
Source: CSR A3921069, Adapted from Tables 27 and 28			

Safety Update: Tofacitinib RA Development

To more accurately assess the safety of long-term tofacitinib exposure in this review, emphasis is placed on the analyses of:

- The exposure-adjusted incidence rates of major AEs of interest from the RA development program (Phase 2, Phase 3 and LTE studies).and
- The newly defined cohorts of patients with continuous same tofacitinib dose as defined in 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.

Table 20 below provides an overview of the cumulative exposure-adjusted incidence rates of the major events of special interest in the tofacitinib RA development program comparing the different data cutoff timepoints indicating that the overall rates remain stable with the exception of serious infections, tuberculosis, and lymphoma, which continue to increase slowly with prolonged tofacitinib exposure consistent with the trends observed in the original NDA. The risks of serious infections and malignancy, including LPD, with chronic immunosuppression have been recognized by the rheumatology community and have been highlighted as a boxed warning in the product labeling and included in the REMS.

Table 20. Cumulative Exposure-Adjusted Incidence Rates for Safety Events of Interest Across Data Cuts, RA Development (Phase 2, 3 and LTE Studies)

Cumulative Exposure-Adjusted Incidence Rates for Safety Events of Interest Across Data Cuts, RA Development (Phase 2, 3 and LTE Studies)			
	Original Submission 29 Mar 2011 Data Cut N (Event/100 PY)	**120 Day Safety Update 29 Sep 2011 Data Cut** N (Event/100 PY)	**April 2012 Update 19 Apr 2012 Data Cut** N (Event/100 PY)]
N	4789	4791	4789
Exposure, Patient Years	5651	6922	8460
Mortality (up to 30 days of last dose)	21 (0.4)	24 (0.4)	25 (0.3)
Serious Infections	167 (2.97)	206 (3.00)	259 (3.09)
Tuberculosis (TB)	NA	11 (0.16)	16 (0.19)
Opportunistic Infections, including TB	NA	33 (0.48)	41 (0.49)
Herpes Zoster	239 (4.4)	288 (4.3)	346 (4.3)
Malignancies (excl. NMSC)	50 (0.89)	65 (0.94)	75 (0.89)
Lymphoproliferative Disorders/Lymphoma	3 (0.05)	3 (0.04)	7 (0.07)*

Source: Integrated Summary of Safety, Adapted from Tables 4 an 255.2 (* Data cutoff for lymphoma was April 16, 2012 using a different estimate number of patients/patient years -5559/9935)
Subjects exposure time is counted from first dose of tofacitinib in the index study through last known dose in the extension study. Some events may have occurred post end of treatment, these events were counted in the numerator and subjects' full tofacitin b treatment exposure was included in denominator.

Table 21 presents the summary of safety for the newly defined patient cohorts of patients who were exposed to the same dose continuously, without being crossed-over to the other dose. The two cohorts have comparable number of patients and exposures allowing for a reasonable comparison of relative dose-related trends for major AEs and AEs of special interest with longer-term exposure to only one dose. The data indicates dose-dependent increases in the rates of SAEs, AEs leading to discontinuation, serious infections, including tuberculosis and herpes zoster infections, malignancy, including lymphoproliferative disorders, all of which are consistent with the trends observed in the original NDA.

Table 21. Overview of Safety by Dose Cohort (Continuous Same Dose) in Phase 2, Phase 3 and LTE Trials in RA

Overview of Safety by Dose Cohort (Continuous Same Dose) in Phase 2, Phase 3 and LTE Trials in RA		
	5 mg BID cohort	**10 mg BID cohort**
Number of patients Exposure (PY)	1955 2174	1846 2460
Deaths within 30 days of last dose *Rate per 100 PY (95% CI)*	6 *0.28 (0.1, 0.6)*	5 *0.2 (0.1, 0.5)*
No with ≥ 1 SAE *Rate per 100 PY (95% CI)*	210 *10.2 (8.9, 12)*	261 *11.1 (9.9, 12.6)*
AE leading to discontinuation *Rate per 100 PY (95% CI)*	170 *7.9 (6.8, 9.1)*	223 *9.2 (8.1, 10.5)*
Serious infection, n *Rate per 100 PY (95% CI)*	59 *2.7 (2.1, 3.5)*	87 *3.6 (2.9, 4.4)*
Tuberculosis (TB), n *Rate per 100 PY (95% CI)*	2 *0.1 (0.02, 0.4)*	9 *0.4 (0.2, 0.7)*
Opportunistic infection, n *Rate per 100 PY*	8 *0.4*	7 *0.3*
No with ≥ 1 H. zoster infection *Rate per 100 PY (95% CI)*	84 *4.0 (3.2, 5.0)*	113 *4.8 (4.0, 5.7)*
No with ≥ 1 Malignancy (excl. NMSC) *Rate per 100 PY (95% CI)*	18 *0.83 (0.5, 1.3)*	23 *0.94 (0.6, 1.4)*
LPD, n *Rate per 100 PY (95% CI)*	1 *0.05 (0.01, 0.3)*	2 *0.08 (0.02, 0.3)*
No with ≥ 1 MACE *Rate per 100 PY (95% CI)*	6 *0.5 (0.2, 1.1)*	8 *0.4 (0.2, 0.7)*
Source: Summary of Clinical Safety, Adapted from Table 5		

7.3.1 Deaths

Mortality in Study 1069:

No patients died within the data cutoff date for the 1-year analysis. Two deaths occurred outside of the 1-year data cutoff:

- A 61-year-old female in the tofacitinib 10 mg BID group, had an SAE of Stage IV colon cancer. The patient discontinued study medication on Day 351. On Day 378, the onset date of event was reported, which corresponded to the date of the first computed tomography scan diagnosing the mass itself. Approximately 5 months later, the patient developed cerebrovascular accident, pneumonia, nervous system disorder, and disseminated intravascular coagulation (DIC)

considered medically significant. The patient died due to Stage IV colon cancer approximately 530 days after the first dose of study medication.

- A 53-year old female in the tofacitinib 5 mg BID group, was found dead at home approximately 471 days after the first dose of study medication. The probable cause of death was myocardial infarction. The investigator reported the event term as "Death - unknown causes." An autopsy was not performed. The patient had no prior medical history of any cardiovascular disease other than systemic arterial hypertension. The patient's family history however is suggestive of premature coronary heart disease, with father who died at age 45 and sister at age 36, both from myocardial infarction.

Safety Update: Mortality in Tofacitinib RA Development

As of the clinical data cut-off, April 29, 2012, three additional deaths were reported in the tofacitinib RA clinical development program:

- Patient 1041-10031002, a 53-year-old male patient in Japan, who was treated with tofacitinib 5 mg BID and on background methotrexate (MTX), died of metastatic small cell lung cancer. The patients smoked 40 to 60 cigarettes per day for about 30 years. He had a medical history of ongoing interstitial pneumonia, pyorrhea and emphysema.

- Patient 1041-10271005, a 55-year-old female patient in Japan, who was treated with tofacitinib 5 mg BID, died of adenocarcinoma gastric stage IV with metastases and peritoneal dissemination. The patient had a family history of gastric cancer.

- Patient 1024-11451012, a 63-year-old female patient in Chile, who was treated with tofacitinib 10 mg BID on background MTX and concomitant prednisone, experienced pneumonia, multiorgan failure and cardiogenic shock and died.

The overall mortality rates, adjusted for exposure, in the tofacitinib RA development program have remained stable (see Table 20) and the causes of death are what would be expected for the background patient population. Further, the data from the two newly defined dose cohorts do not suggest a dose-dependent mortality trends as shown in Table 21.

7.3.2 Nonfatal Serious Adverse Events

An SAE was defined as any untoward medical occurrence at any dose that:

- Resulted in death;
- Was life-threatening (immediate risk of death);
- Required inpatient hospitalization or prolongation of existing hospitalization;

- Resulted in persistent or significant disability/incapacity; and/or
- Resulted in congenital anomaly/birth defect.

Study 1069

Table 22 summarizes the SAEs in study 1069 where the most common SAEs were infections with pneumonia being the most common, occurring in three tofacitinib-treated patients and herpes zoster, gastroenteritis, psychotic disorder, cataract, and deep vein thrombosis (2 patients each). Overall, the incidence and types of SAEs in study 1069 were consistent with the original NDA and no new safety signals have been identified.

Table 22. Summary of SAEs in Study 1069 (Year 1 Data)

Summary of SAEs in Study 1069 (Year 1 Data)			
	Tofa 5 mg BID n (%)	**Tofa 10 mg BID n (%)**	**MTX n (%)**
Total patients with ≥ 1 SAE, n (%)	24 (7)	24 (6)	13 (7)
Incidence of SAEs, event per 100 PY	7.2	6.8	8.6
Pneumonia	2 (0.5)	1 (0.3)	0
Herpes zoster	1 (0.3)	1 (0.3)	0
Gastroenteritis	-	1 (0.3)	1 (0.5)
Psychotic disorder	-	1 (0.3)	1 (0.5)
Abdominal injury	-	1 (0.3)	-
Arthralgia	-	1 (0.3)	-
Bone tuberculosis	-	1 (0.3)	-
Bronchitis chronic	-	1 (0.3)	-
Cardiac failure congestive	-	1 (0.3)	-
Cerebrovascular accident	-	1 (0.3)	-
Cholecystitis acute	-	1 (0.3)	-
Chronic obstructive pulmonary disease	-	1 (0.3)	-
Colonic stenosis	-	1 (0.3)	-
Compression fracture	-	1 (0.3)	-
Demyelinating polyneuropathy	-	1 (0.3)	-
Diarrhea	-	1 (0.3)	-
Gastritis	-	1 (0.3)	-
Hepatomegaly	-	1 (0.3)	-
High grade B-cell lymphoma Burkitt-like	-	1 (0.3)	-
Hydronephrosis	-	1 (0.3)	-
Joint dislocation	-	1 (0.3)	-
Noncardiac chest pain	-	1 (0.3)	-
Osteoarthritis	-	1 (0.3)	-
Pathological fracture	-	1 (0.3)	-
Pyelonephritis chronic	-	1 (0.3)	-
Rheumatoid vasculitis	-	1 (0.3)	-
Upper limb fracture	-	1 (0.3)	-
Ureteric stenosis	-	1 (0.3)	-
Uterine polyp	-	1 (0.3)	-
Wrist fracture	-	1 (0.3)	-
Cataract	2 (0.5)	-	-
Abdominal hernia	1 (0.3)	-	-
Abdominal wall hematoma	1 (0.3)	-	-
Angina pectoris	1 (0.3)	-	-
Arthritis reactive	1 (0.3)	-	-
Asthma	1 (0.3)	-	-
Carotid artery stenosis	1 (0.3)	-	-
Dengue fever	1 (0.3)	-	-
Drug ineffective	1 (0.3)	-	-

Erythema annulare	1 (0.3)	-	-
Esophageal ulcer	1 (0.3)	-	-
Fracture	1 (0.3)	-	-
Gastric ulcer	1 (0.3)	-	-
Gastrointestinal infection	1 (0.3)	-	-
Humerus fracture	1 (0.3)	-	-
Hypersensitivity	1 (0.3)	-	-
Muscle hemorrhage	1 (0.3)	-	-
Myocardial ischemia	1 (0.3)	-	-
Osteonecrosis	1 (0.3)	-	-
Pleural infection	1 (0.3)	-	-
Renal adenoma	1 (0.3)	-	-
Subcutaneous abscess	1 (0.3)	-	-
Tendon rupture	1 (0.3)	-	-
Typhoid fever	1 (0.3)	-	-
Unintended pregnancy	1 (0.3)	-	-
Unstable angina	1 (0.3)	-	-
Uterine leiomyoma	1 (0.3)	-	-
Deep vein thrombosis	-	-	2 (1.1)
Ankle fracture	-	-	1 (0.5)
Atrial flutter	-	-	1 (0.5)
Atrioventricular block first degree	-	-	1 (0.5)
Erythema multiforme	-	-	1 (0.5)
Fall	-	-	1 (0.5)
Femoral neck fracture	-	-	1 (0.5)
Hemorrhoids	-	-	1 (0.5)
Intervertebral disc protrusion	-	-	1 (0.5)
Nasopharyngitis	-	-	1 (0.5)
Musculoskeletal chest pain	-	-	1 (0.5)
Rheumatoid arthritis	-	-	1 (0.5)
Source: CSR A3921069, Adapted from Tables 27, 28, and 42			

Safety Update: Tofacitinib RA Development

The dose-dependent incidence rates (9.8 per 100 patient years of exposure for the 5 mg BID vs. 12.6 per 100 patient years of exposure for the 10 mg BID dosing) and types of SAEs in the long-term extensions studies in RA development program remained consistent with the original NDA, with pneumonia being the most common SAE, followed by osteoarthritis, urinary tract infection, and H. zoster. No new safety signals have been identified.

Malignancy

Malignancy Excluding Non-Melanoma Skin Cancer (NMSC)

Study 1069

One malignant neoplasm occurred within the 1-year data cutoff period in study 1069:

- Patient 11571001, a 65-year-old male in the tofacitinib 10 mg BID treatment group, discontinued the study due to lymph node biopsy-documented high-grade B-cell lymphoma Burkitt-like lymphoma on Day 149. The last dose of study medication was on Day 171. Staining for EBV+ cells was equivocal. On Day 185, the patient was given chemotherapy and transferred to the local hospital for palliative care.

In addition, four malignant neoplasms occurred outside of the 1-year data cutoff period:

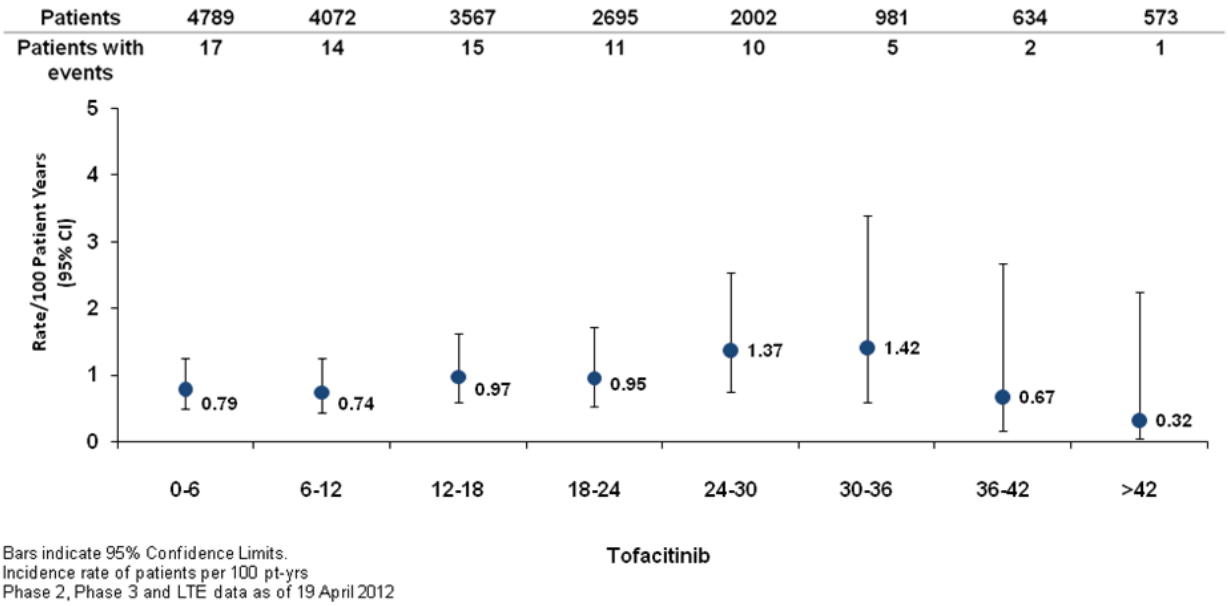
- Patient 10231006, a 61-year-old female in the tofacitinib 10 mg BID group, experienced an SAE of Stage IV colon cancer. Approximately 5 months later, the patient developed cerebrovascular accident, pneumonia, nervous system disorder, and DIC and died.
- Patient 10421001, a 65-year-old male in the tofacitinib 10 mg BID group was diagnosed with a biopsy-confirmed prostatic adenocarcinoma approximately 200 days after initiating therapy in study 1069 treated with resection.
- Patient 11931002, a 63-year-old male in the tofacitinib 5 mg BID group, developed leukocytosis approximately 3 months into treatment and experienced lymphoproliferation (T-lymphoproliferative T-cell chronic lymphocytic leukemia – Non-Hodgkin's lymphoma) approximately 6 months after the data cutoff date. Staining for EBV+ cells was reported as negative. Relevant medical history included splenectomy due to suspected Felty syndrome.
- Patient 12241006, a 61-year-old female in the MTX group, reported diagnosis of cancer of stomach confirmed by gastroscopy and treated with subtotal resection of stomach and lymph nodes.

The types of malignancies, including lymphoproliferative disorders (LPD) in study 1069 are consistent with the original NDA. Further, the risks of malignancy and LPD with tofacitinib exposure are recognized in the product labeling with a boxed warning.

Safety Update: Tofacitinib RA Development

The sponsor provided an updated figure (Figure 11) with non-cumulative incidence of malignancy, excluding NMSC, over time by 6–month intervals, which was consistent with the data in the original application. The data through month 30 suggest a slight increase in malignancy risk over time, and there are relatively few patients in the 6-month intervals over 30 months to draw conclusions. Another limitation of these data is the inability to assess dose-dependency as the figure represents the pooled data from all tofacitinib doses and many patients have crossed over between the two dosing regimens. Overall, the data are not adequate to clarify the concerns about malignancy identified in the original application, but do not raise additional concerns that would warrant additional actions or labeling changes.

Figure 10. Malignancy (Excluding Non-Melanoma Skin Cancer): Non-Cumulative Rates Over Time in Tofacitinib RA Development Program



Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Phase 2, Phase 3 and LTE data as of 19 April 2012

Source: Integrated Summary of Safety as of April 29, 2012

Non-Melanoma Skin Cancer (NMSC)

Study 1069

No cases of non-melanoma skin cancer have been reported in study 1069.

Safety Update: Tofacitinib RA Development

This supplemental NDA provided an update on the NMSC as of the clinical data cut-off, April 19, 2012. In addition, the sponsor has submitted a labeling supplement 0005 on September 25, 2013 to update the product labeling with information on NMSC due to accumulated information on the dose-dependent increasing incidence of NMSC with prolonged tofacitinib exposure as summarized in Table 23 below. The overall rates have increased over time and appear to be driven by the cases accumulating in the 10 mg BID dose group whose rates (0.6 to 0.8 per 100 patient-years) are higher than the historical control rates of 0.2 to 0.3).[6,7] This information supports the Agency's concerns, expressed in the original NDA review, with the dose and exposure-dependent

6 Askling J, et al. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Safety 2011;20:119-30.
7 Mariette X, et al. Malignancies associated with tumor necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis 2011; 70(11):1895-904

increased risk of immunosuppression and tumorigenesis with tofacitinib and warrants inclusion the labeling. Updating Section 6.1, Clinical Trials Experience with the information on NMSC is currently under review of the in-house labeling supplement 0005 and will not be included in the labeling revisions under this efficacy supplement.

Table 23. Incidence Rate of Non-Melanoma Skin Cancer in Tofacitinib Treated Patients in P2P3LTE and LTE RA Studies

Incidence Rate of Non-Melanoma Skin Cancer in Tofacitinib Treated Patients in P2P3LTE and LTE RA Studies				
	Overall RA development P2P3LTE (All doses)	LTE		
		5 mg BID	10 mg BID	All doses
April 2011 (n=4789; pys=5650)	0.373 (0.243, 0.572)	0.359 (0.179, 0.717)	0.681 (0.306, 1.517)	0.450 (0.266, 0.760)
Sep 2011 (n=4791; pys=6921)	0.450 (0.316, 0.639)	0.368 (0.198, 0.684)	0.894 (0.539, 1.483)	0.569 (0.384, 0.842)
April 2012 (n=4789; pys=8460)	0.451 (0.328, 0.620)	0.310 (0.167, 0.575)	0.793 (0.522, 1.204)	0.533 (0.377, 0.753)
April 2013 (n=5671; pys=12,664)	0.525 (0.412, 0.668)	0.351 (0.208, 0.593)	0.835 (0.619, 1.126)	0.624 (0.481, 0.809)

Source: Labeling Supplement 0005, Adapted from Attachment 1, Table 1 and Efficacy Supplement 0004, Summary of Clinical Safety, Table 375.s16.1.13
*n and pys are for P2P3LTE data set
P2P3LTE through April 2012 includes Phase 2 Studies A3921019, A3921025, A3921035, A3921039, A3921040, A3921109, Phase 3 Studies A3921032, A3921044 (1-Year), A3921045, A3921046, A3921064 and LTE studies (for those patients entering from the included Phase 2/3 studies); for April 2013 data cut, P2P3LTE includes A3921044 (2-year) and also includes Study A3921069 (1-year).
LTE includes LTE Studies A3921024 and A3921041.
BID = twice daily, pys = patient years, P2P3LTE = Phase 2, Phase 3 and long-term extension

To further address the potentially increased risk of malignancy associated long-term tofacitinib administration, the sponsor is currently initiating a safety post-marketing requirement (PMR) study for which the final protocol has been reviewed by the Agency and found to be acceptable to fulfill the PMR objectives.

Serious Infections

In tofacitinib RA development, a serious infection was defined as any infection that required hospitalization for treatment, required parenteral antimicrobial therapy, or met other criteria that required it to be classified as an SAE. A patient who experienced a serious infection was to be discontinued from the study.

Study 1069

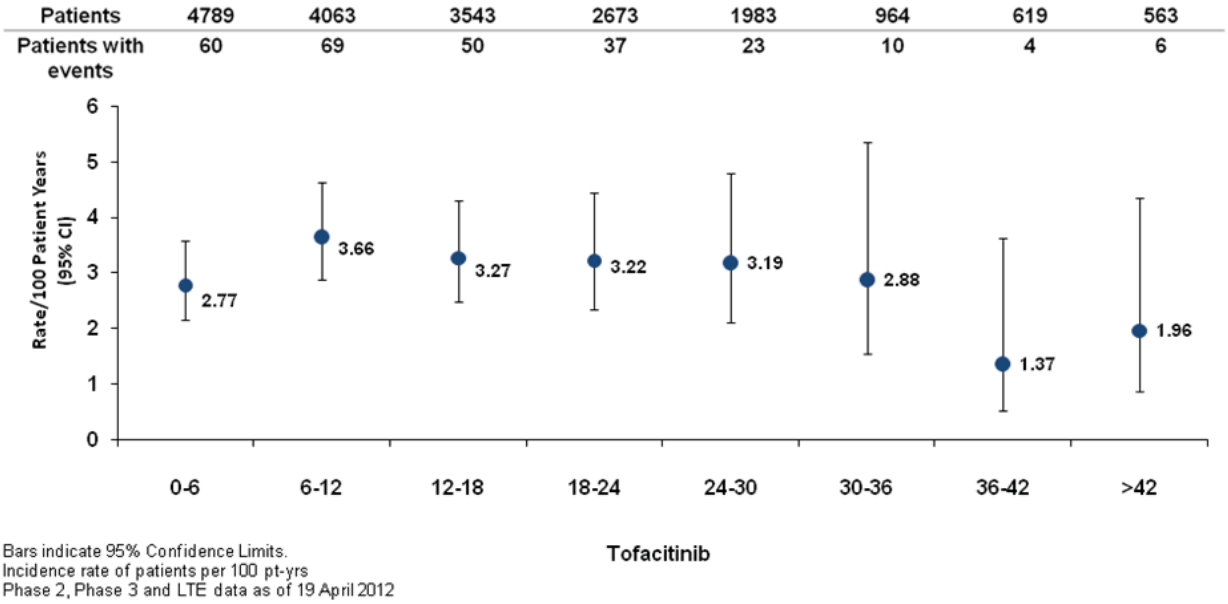
In study 1069 the reported types of serious infections were consistent with the original NDA and included:

- Tofacitinib 5 mg BID: herpes zoster, pleural infection, dengue fever, pneumonia (x2), subcutaneous abscess, gastrointestinal infection, and typhoid fever.
- Tofacitinib 10 mg BID: herpes zoster, bone tuberculosis, gastroenteritis, chronic bronchitis, chronic pyelonephritis, and pneumonia.
- Methotrexate: nasopharyngitis and gastroenteritis.

Safety Update: Tofacitinib RA Development

The sponsor provided an updated figure (Figure 11) with non-cumulative incidence of serious infections over time by 6–month intervals which is consistent with the original application. Interestingly, the rate of infections per 100 patient-years is higher later on than in the first 6 months of treatment, which suggests the rates are not due to patients otherwise having an underlying predisposition to infection, but are most likely due to chronic treatment with tofacitinib. There are relatively few patients exposed to over 30 months of treatment and no conclusions can be drawn from these later timepoints. Another limitation of these data is the inability to assess dose-dependency as the figure represents the pooled data from all tofacitinib doses and many patients have crossed over between the two dosing regimens.

Figure 11. Serious Infections: Non-Cumulative Rates Over Time in Tofacitinib RA Development Program



Source: Integrated Summary of Safety as of April 29, 2012, Figure 2

Tuberculosis (TB)

Study 1069

One case of extra-pulmonary (bone) tuberculosis occurred in a 53-year-old Asian female (patient 11661012) in the tofacitinib 10 mg BID group tofacitinib 10 mg BID dose group on Day 325. The patient was permanently discontinued in response to the event:

Safety Update: Tofacitinib RA Development

As of 19 April 2012 in the tofacitinib RA program, four new cases of TB have been reported in the global RA development program, to a total of 16 patients experienced active TB while receiving tofacitinib. Five cases have accrued in the 5 mg BID group, and 11 were diagnosed on 10 mg BID, with most of cases occurring endemic parts of the world. Ten of these patients had pulmonary TB and 6 had extra-pulmonary infection. The incidence of tuberculosis continues to be higher in the 10 mg BID dose group (Table 21), consistent with the original NDA data.

Opportunistic Infections

Study 1069

In addition to the case of bone TB described above, one case of multidermatomal Herpes zoster occurred in a 64-year-old white female patient in the tofacitinib 10 mg BID group on Day 126. A 63-year-old white female in the MTX group, experienced an AE of cytomegalovirus infection on Study Day 133.

Safety Update: Tofacitinib RA Development

As of 19 April 2012, a total of 25 cases of opportunistic infections (excluding TB) were reported in tofacitinib treated patients in the RA program including cytomegalovirus (CMV) (6), multi-dermatomal herpes zoster (2), BK encephalitis (1), Cryptococcus (3), esophageal candidiasis (8), pneumocystis pneumonia (3), and Non-TB mycobacteria (lung) (2). All three new cases of opportunistic infections (CMV pneumonia, CMV chorioretinitis, and multi-dermatomal herpes zoster) occurred in patients treated with tofacitinib 10 mg BID dosing. These results support the dose-dependent increase in the incidence of opportunistic infections related to dose-related immunosuppression with the higher tofacitinib dose. Overall, the types of new opportunistic infections are consistent with the original application.

Herpes Zoster Infections

Study 1069

A higher proportions of patients reported H. zoster infections in a tofacitinib dose-dependent manner compared with the MTX-treated patients [8 (2.2%) in the tofacitinib 5 mg BID group, 10 (2.5%) in the tofacitinib 10 mg BID group, and 2 (1.1%) in the MTX group]. This is consistent with the potent immunosuppressive properties of tofacitinib and with the data from the original NDA.

Safety Update: Tofacitinib RA Development

Cases of H. zoster continued to accumulate in the RA development program at steady rate as summarized in Table 20 with the dose-dependency seen in the original NDA as shown in Table 21.

In summary, the overall incidence and types of serious infections, including TB and opportunistic infection remain consistent with the original NDA and with previously recognized the immunosuppressive potential of tofacitinib. All of these are highlighted in the boxed warning of the product labeling and included in the REMS.

7.3.3 Dropouts and/or Discontinuations

Study 1069

The most frequent AEs resulting in discontinuation overall were blood creatinine increased (which occurred in 2, 3, and 0 patients in the tofacitinib 5 mg BID and 10 mg BID and MTX groups, respectively) and rheumatoid arthritis (which occurred in 2, 1, and 0 patients in the tofacitinib 5 mg BID and 10 mg BID and MTX groups, respectively) and nausea (which occurred in 0, 1, and 2 patients in the tofacitinib 5 mg BID and 10 mg BID and MTX groups, respectively).

7.3.4 Significant Adverse Events

Study 1069

No cases of gastrointestinal perforation or interstitial lung disease have been reported in study 1069.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission-specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 1069

The most common AEs (occurring in ≥2% in any treatment group) during the 1 year reporting period in study 1069 were in Gastrointestinal disorders, followed by Infections and infestations system organ class. The most frequently reported AEs in the tofacitinib-treated patients were nausea, headache, upper respiratory tract infection, and urinary tract infection, consistent with the original NDA. The incidence of treatment-emergent AEs was highest in the MTX group (data not shown). There were no new safety signals or trends identified.

7.4.2 Laboratory Findings

Tofacitinib treatment resulted in dose-dependent changes of certain hematologic, hepatobiliary, serum chemistry (creatinine and creatine phosphokinase) and lipid parameters. Overall, the findings from study 1069 and the updated RA development program were generally consistent with the observations from the original NDA with respect to the laboratory abnormalities.

Study 1069

Changes in laboratory parameters observed for tofacitinib 5 mg BID and 10 mg BID relative to MTX were consistent with data from previous clinical trials, including dose-dependent decreases in neutrophil counts and increases in HDL, LDL, and total cholesterol levels which are labeled events.

The reported hematologic abnormalities in study 1069 at Year 1 were consistent with the incidence and magnitude of changes reported in the original NDA.

Through Month 12 in study 1069, liver test abnormalities were comparable among the treatment groups with rates consistent with the original NDA. No patient met the Hy's law criteria during the reporting period.

The rates of patients with creatine kinase elevations were higher in the tofacitinib groups (in a dose-dependent manner) than for the MTX group as summarized in Table 24. Three patients were withdrawn from the study due to asymptomatic CPK elevations and the sponsor reports no cases of rhabdomyolysis upon standardized MedDRA query. The clinical significance of the observed CPK elevations remains unknown.

Table 24. Patients With Creatine Kinase Elevations (>2×ULN), Study 1069 (Year 1 Data)

Patients With Creatine Kinase Elevations (>2×ULN), Study 1069 (Year 1 Data)			
Patients with CPK Elevations	Tofa 5 mg BID	Tofa 10 mg BID	MTX
Randomized and treated	371	395	186
With normal baseline CPK, n/N (%)	27/363 (7)	50/381 (13)	2/179 (1)
Any CPK elevation, n/N (%)	29/369 (8)	61/395 (15)	3/184 (2)

Source: CSR A3921069, Adapted from Table 44
Abbreviations: CPK= creatine phosphokinase, BID=twice daily, N=number of patients, n=number of patients meeting prespecified criteria, ULN=upper limit of normal, MTX=methotrexate

Consistent with the original NDA, small elevations in mean serum creatinine elevations were observed in study 1069 (data not shown) with higher proportions of patients meeting the protocol-specified criteria for monitoring and discontinuation in a dose-dependent manner in tofacitinib-treated patients compared with MTX-treated as shown in Table 25. Most of these abnormalities have remained within the laboratory normal reference range and none were associated with SAE renal failure. The clinical significance of these creatinine elevations is unclear and is currently handled via the product labeling and the REMS.

Table 25. Patients With Creatinine Values Meeting Protocol Criteria for Monitoring and Discontinuation, Study 1069 (Year 1 Data)

Patients With Creatinine Values Meeting Protocol Criteria for Monitoring and Discontinuation, Study 1069 (Year 1 Data)			
Patients with Serum Creatinine Elevations	Tofa 5 mg BID	Tofa 10 mg BID	MTX
Randomized and treated	371	395	186
Increase of ≥ 33% of the average screening and Baseline value, n (%)	3 (<1)	9 (2)	1 (<1)
Increase of ≥ 33% of the average screening and Baseline value, n (%)	5 (1)	7 (2)	0

Source: CSR A3921069, Adapted from Table 44
Abbreviations: CPK= creatine phosphokinase, BID=twice daily, N=number of patients, n=number of patients meeting prespecified criteria, ULN=upper limit of normal, MTX=methotrexate

The reported lipid abnormalities in study 1069 were also consistent with lipid changes seen in the original NDA. To further address the potentially increased risk of cardio-vascular adverse outcomes associated with these lipid abnormalities, the sponsor is currently initiating a safety post-marketing requirement (PMR) study for which the final

protocol has been reviewed by the Agency and found to be acceptable to fulfill the PMR objectives.

7.4.3 Vital Signs

Study 1069

Vital signs changes were minimal in study 1069 and were overall consistent with the original NDA. No new trends were observed.

7.4.4 Electrocardiograms (ECGs)

Study 1069

Twelve-lead ECGs were obtained for all patients at the screening, Month 12, and Month 24 visits. No ECG abnormalities were reported in this study.

7.4.5 Special Safety Studies/Clinical Trials

To address the potentially increased risk of cardio-vascular adverse outcomes associated with these lipid abnormalities, serious infections, including TB and opportunistic infections and malignancy, including lymphoproliferative disorders, the sponsor is currently initiating a safety post-marketing requirement (PMR) study for which the final protocol has been reviewed by the Agency and found to be acceptable to fulfill the PMR objectives.

7.4.6 Immunogenicity

Use of tofacitinib, as an oral small molecule, is not expected to be associated with induction of immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Study 1069

Through Month 12 in study 1069, the numbers of major events of interest were small to make definitive conclusions regarding dose-dependency.

P2P3LTE 5 mg and 10 mg BID Cohorts

To better quantify the dose-dependency of the potential major safety risks associated with long-term tofacitinib administrations, the sponsor has submitted data on two newly

defined patients cohorts as requested at the pre-sNDA meeting as discussed in detail in sections 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence and 7.3 Major Safety Results. As seen in Table 21, The data indicates dose-dependent increases in the rates of SAEs, AEs leading to discontinuation, serious infections, including tuberculosis and herpes zoster infections, malignancy, including lymphoproliferative disorders, all of which are consistent with the concerns expressed by the Agency during the original NDA review.

7.5.2 Time Dependency for Adverse Events

Overall, the time dependency of AEs in study 1069 and the safety update for the RA development were consistent with the original NDA.

7.5.3 Drug-Demographic Interactions

Overall, the drug-demographic interactions in study 1069 and the safety update for the RA development were consistent with the original NDA.

7.5.4 Drug-Disease Interactions

Overall, the drug-disease interactions in study 1069 and the safety update for the RA development were consistent with the original NDA.

7.5.5 Drug-Drug Interactions

No new drug-drug interactions were reports in this submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Safety data on malignancy and neoplasms is discussed in detail in section 7.3.2 Nonfatal Serious Adverse Events above.

7.6.2 Human Reproduction and Pregnancy Data

A total of 4 cases of exposure in utero were reported in study 1069 with either a normal pregnancy and delivery of a healthy infant, or limited data on the pregnancy outcomes. This small cohort of patients in the tofacitinib RA development is not sufficient to draw definitive conclusions about the possible effect of tofacitinib on human reproduction and pregnancy. To further address the potential impact of tofacitinib exposure in utero, the sponsor has voluntarily initiated a pregnancy registry.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable for this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Sponsor has not reported cases of drug abuse or dependence, withdrawal and rebound or other information relevant to the potential for drug abuse in these studies.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Tofacitinib has been approved in the US since November 2012. This efficacy supplement was submitted shortly after the approval of tofacitinib and does not contain information on the post-marketing experience. The review of the Periodic Adverse Drug Experience Report submitted under the NDA revealed safety findings consistent the already known safety profile of tofacitinib, with AEs coded to Gastrointestinal disorders and Infections and infestation SOC being the most common; no new safety signals were identified with the exception of potentially increased dose- and exposure-dependent risk of non-melanoma skin cancer which warrants inclusion in the product labeling as discussed in sections 7.3.2Nonfatal Serious Adverse Events. Updating the product labeling with information on NMSC however, will be addressed under a separate review of an in-house labeling supplement.

9 Appendices

9.1 Literature Review/References

EC Keystone, "Clinical implications of understanding radiographic findings in relation to clinical outcomes in rheumatoid arthritis." J Rheumatol 2009; 36 Supple 82:11-16

Askling J, et al. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Safety 2011;20:119-30.

Mariette X, et al. Malignancies associated with tumor necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis 2011; 70(11):1895-904

USPI Jakafi (ruxolibinib), November 2011

Liu GF, et al., Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials, Statist Med 2006; 25:1275-1286

S Boini and F Guillemin, "Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages." Ann Rheum Dis 2001; 60:817-827

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002542/WC500154697.pdf

9.2 Labeling Recommendations

I recommend the following major revisions to the proposed labeling (New text in ***Bold***, deleted text in ~~strikethrough~~):

9.2.1 Safety:

- Since efficacy data from study 1069 will be included in section 14, the proposed summary statement on the safety of this study in Section 6.1, Clinical Trials Experience, is generally acceptable.
- NMSC was identified as potential safety concern as discussed in this review. However, updating Section 6.1, Clinical Trials Experience with that information is currently under review of the in-house labeling supplement 0005 and will not be included in the labeling revisions under this efficacy supplement.

9.2.2 Efficacy:

I agree with the sponsor's proposal to include the description of study 1069 and the results of both study 1044 and 1069 in the product labeling. The data from study 1069 provides a robust evidence of tofacitinib's efficacy on the inhibition of radiographic progression addressing the limitations seen with the study 1044 data. On the other hand, the radiographic data from study 1044 provides further context for the interpretation of the radiographic benefit in the patient population with the already approved indication. Therefore, my recommendation is to present the data from both study 1044 and 1069 with the focus on the pre-specified primary analyses and the proportions of non-progressors defined by mTSS change from baseline of 0, consistent with the labeling of already approved RA products with radiographic response data. The internal discussions on the optimal presentation of the data are ongoing at the time of this review.

9.2.3 Labeling changes recommended by SEALD Labeling team

Labeling revisions were suggested by the SEALD labeling team to ascertain consistency across labels and compliance with applicable guidances. These should be implemented to the extent possible.

9.3 Advisory Committee Meeting

There was not Advisory Committee meeting for this application. However, an Arthritis Advisory Committee was convened on May 09, 2012 for the discussion of the original NDA. At that meeting the majority of the committee did not agree that the study 1044 data provided substantial evidence for the efficacy of tofacitinib for radiographic outcomes (voting Yes=2 to No=8) even though they considered the radiographic data encouraging. The committee stated that the data were lacking in quality and did not meet the FDA standards for substantial evidence and corroborating evidence for a new study would be needed. Despite the concerns with the radiographic data from study 1044, the committee voted for approval of tofacitinib (voting Yes=8 to No=2) based on the substantial evidence of efficacy in the clinical response and physical function domains with the recommendation to collect more long-term safety data.

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/s/

NIKOLAY P NIKOLOV
01/15/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s04

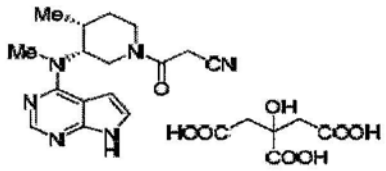
CHEMISTRY REVIEW(S)

Chemist Review: # 1	**1. Division:** DPARP	2. **NDA Number**: 203214

3. Name and Address of Applicant: Pfizer Inc. 445 Eastern Point Road Groton, CT 06340	**4. Supplement Number**: S004 Date(s): 04/22/2013
5. Name of Drug: XELJANZ™	**6. Nonproprietary name:** Tofacitinb Citrate

7. Efficacy Supplement managed by OND.		**8. Amendment(s): N/A**
9. Pharmacological Category: Treatment of Rehumatoid Arthritis	**10. How Dispensed:** R_x	**11. Related Documents: N/A**
12. Dosage Form: Tablet	**13. Potency:** 5 mg	

14. Chemical Name and Structure: The chemical name of Tofacitinib Citrate is (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) ., and structure is as follows:



15. Comments: This efficacy supplemental New Drug application (sNDA) is submitted to add results from a planned 1-year analysis of a Phase 3 clinical trial, study A3921069, including the co-primary endpoint measuring effects of XELJANZ 5 and 10 mg BID on structural preservation. No CMC changes are proposed.
Minor clarification under Description regarding the solubility is proposed as follows:

The solubility of tofacitinib citrate in water is 2.9 mg/mL. (NDA 203, 214; Section 3.2.S.1.3; Table 1) ~~It is freely soluble in water.~~

16. Conclusions and Recommendations: Referenced solubility information is from the Table provided in the original NDA. Therefore, the proposed description change is considered as approved editorial change. Recommend approval from the CMC standpoint.

17. Name:	**Signature:**	**Date:** 02-21-2014
Mamta Gautam-Basak, Ph.D., Chemist		
18. Concurrence:	**Signature:**	**Date:**
Ramesh Raghavachari, Ph.D., Branch Chief **ONDQA/DNDQA III/Branch IX**		

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

/s/

MAMTA GAUTAM BASAK
02/21/2014
Recommend approval from the CMC standpoint.

RAMESH RAGHAVACHARI
02/21/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s04

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	sNDA 203,214/004
Drug Name:	Xeljanz (tofacitinib) (b) (4)
Indication(s):	Treatment of Rheumatoid Arthritis (supplement claim: inhibition of progression of structural damage)
Applicant:	Pfizer Inc.
Date(s):	Submitted: April 22, 2013
	PDUFA: February 21, 2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Yongman Kim, Ph.D.
Concurring Reviewers:	Joan Buenconsejo, Ph.D.
	Thomas Permutt, Ph.D.
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Nikolay Nikolov, M.D.
	Sarah Yim, M.D.
Project Manager:	Philantha Bowen

Keywords: NDA, clinical studies, missing data, outliers, linear extrapolation

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1 EXECUTIVE SUMMARY

In this supplemental new drug application (sNDA), Pfizer Inc. is seeking to add the claim of inhibition of structural damage progression of tofacitinib (CP-690,550) 5 mg (b) (4) orally administered twice a day (BID) in rheumatoid arthritis (RA) patients in the product label. To support the claim, the applicant employed radiographic data from two Phase 3 studies – study A3921044 (hereafter referred to as 1044) from the original NDA in 2011 and study A3921069 (hereafter referred to as 1069) from this application. Statistics review of the radiographic data from study 1044 was completed as part of the original submission. Therefore, only pertinent information from that study is summarized in this review. The focus of this statistical review is on the new study 1069.

Study 1044 was a 2-year, phase 3, randomized, double-blind, placebo-controlled study designed to demonstrate efficacy of tofacitinib (CP-690,550) 5 mg BID and 10 mg BID over placebo added to background methotrexate (MTX) in active RA patients who had an inadequate response to MTX. The design of this trial included early escape at month 3 for non-responding placebo patients who did not have at least a 20% improvement from baseline levels in both the tender/painful and swollen joint counts at the month 3 visit. These non-responding placebo patients were advanced to a second pre-determined treatment of tofacitinib 5 or 10 mg BID. At month 6, all placebo patients were advanced to their second predetermined treatment. One of the four primary efficacy endpoints in this study was on the structural preservation measured by the change from baseline in van der Heijde modified Sharp score at month 6. In my review of the radiographic data, I concluded that there was evidence that tofacitinib 10 mg and tofacitinib 5 mg might have some activity on radiographic progression. However, there was uncertainty associated with the results including: (1) less progression in the placebo group, (2) only a minority (<40%) had some change from baseline, (3) magnitude of effect was sensitive to outliers in the tofacinitib 10 mg group, (4) the impact of excluded and missing data was unclear, (5) inconsistent results with respect to dose, and most importantly, (6) there was lack of corroborative evidence from another study. Therefore, the inclusion of this claim in the label was denied in the original cycle.

Study 1069 was a 2-year, phase 3, randomized, double-blind, active-controlled study designed to demonstrate efficacy of tofacitinib (CP-690,550) 5 mg BID and 10 mg BID over methotrexate (MTX) in MTX-naïve RA patients. The design of this trial did not include early escape for non-responding patients at month 3. Like Study 1044, one of the two primary efficacy endpoints in this study was on the structural preservation measured by the change from baseline in van der Heijde modified Sharp score at month 6. In this study, there was strong evidence that both tofacitinib 10 mg and tofacitinib 5 mg reduced radiographic progression in the patient population studied based on the following results:

1. A statistically significant difference in mTSS change from baseline was observed in patients treated with tofacitinib 5 mg or tofacitinib 10 mg compared to methotrexate.

2. A statistically significantly higher proportion of patients in the tofacitinib group (5 mg or 10 mg) experienced 'No Progression' compared to methotrexate.

3. The magnitude of effect in tofacitinib group was not sensitive to outlying observations.

This finding was also supported by other efficacy endpoints including ACR70, HAQ-DI and DAS28 confirming the effect of tofacitinib on signs and symptoms, as well as on disease activity.

In conclusion, there was strong evidence that both tofacitinib 10 mg and tofacitinib 5 mg reduces structural damage progression in MTX-naïve RA patients. Studies 1044 and 1069 taken together, there was evidence that tofacitinib reduces structural damage progression in patients with moderate to severe rheumatoid arthritis.

Further, there was substantial evidence of efficacy of tofacitinib 5 mg or 10 mg for the treatment of rheumatoid arthritis based on consistent findings in the domains of reducing signs and symptoms of RA as measured by ACR70 and DAS28 responses and improving physical function as measured by HAQ-DI.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Tofacitinib (CP-690,550) immediate-release tablets for oral administration in 5 mg dosage strength were approved for the treatment of rheumatoid arthritis. In this supplemental NDA, the applicant is seeking to add the claim of inhibition of structural damage progression of tofacitinib (CP-690,550) 5 mg and 10 mg in the Clinical Section (Section 14) of the product label.

2.1.2 History of Drug Development and Regulatory Interactions

The tofacitinib clinical development program was first introduced to the Division of Anesthesia, Analgesia and Rheumatology Products in 2004 under IND 70,903. The IND was later moved to the Division of Pulmonary, Allergy and Rheumatology Products in 2010. Communication with the applicant regarding their development plan is documented under this IND. Pertinent parts of the statistical portion of those communications are summarized herein.

In December 2008, the applicant had an EOP2 meeting with the division, where input was received regarding the proposed Phase 3 program. All Phase 3 protocols (A3921032, A3921045, A3921044, A3921046, A3921064, and A3921069) were amended following the meeting.
On October 21, 2011, the NDA was submitted for tofacitinib (CP-690,550) 5 mg (b) (4) orally administered twice a day (BID) for the proposed treatment of rheumatoid arthritis. In that

submission, the applicant was also seeking to include the claim of inhibition of structural damage progression in the label based on a single 2-year, randomized, placebo+MTX controlled trial (study A3921044). In my original review on radiographic data from this trial, I concluded that there was evidence that tofacitinib 10 mg and tofacitinib 5 mg might have some activity on radiographic progression. However, there was uncertainty associated with the results for the following reasons:

1. There was less progression in the placebo control group than presumed when the applicant powered the study, therefore, the observed treatment effect size was smaller than anticipated;
2. Less than 40% of patients had some change in mTSS from baseline and only 16% of patients' radiographic scores improved;
3. Data were not consistent with respect to dose;
4. The magnitude of effect in tofacitinib 10 mg group was sensitive to outliers;
5. It was unclear how excluded data might affect the overall conclusion;
6. The evidence for an effect in radiographic progression was from a single study.

The Arthritis Advisory Committee convened on May 9, 2012 to discuss the efficacy and safety of tofacitinib 5 mg and 10 mg doses. The 10-member committee discussed the efficacy of treatment on signs and symptoms, quality of life, and radiographic structural damage progression, as well as potential safety signals including malignancy, serious infections and laboratory abnormalities. The committee voted 8 to 2 that that the available radiographic data were not adequate but voted 10 to 0 that efficacy has been demonstrated for signs and symptoms and quality of life in patients with rheumatoid arthritis. The committee voted 7 to 2 that the available data for safety (particularly in the 5 mg dose group) were adequate, but asked for long term postmarketing data. Overall, they voted 8 to 2 for approval (5 mg dose) with changes to the indication. On November 16, 2012, tofacitinib 5 mg dose was approved for the treatment of rheumatoid arthritis without granting the claim for inhibition of structural damage progression by the Agency.

On April 22, 2013, this supplemental new drug application was submitted with new radiographic data from study A3921069 for the claim.

2.1.3 Specific Study Reviewed

The focus of this review is on the radiographic data from efficacy studies, 1069 and 1044. I conducted additional analyses on the new radiographic data from study 1069 and took the analysis results from study 1044 radiographic data from my original NDA review.

2.1.4 Major Statistical Issues

Following is a list of statistical issues found in the submission:

1. Robustness of efficacy data – potential outlier issues and statistical analysis models (parametric vs. nonparametric analysis on mTSS)

2. Missing data on HAQ-DI –mixed-effect repeated measures (MMRM) analysis based on missing at random (MAR) assumption

These issues will be further discussed in detail in section 5.1.

2.2 Data Sources

NDA 203,214 was submitted on October 21, 2011 and current supplemental NDA 203,214/004 was submitted on April 22, 2013 and can be found in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The study report including protocols, statistical analysis plan, and all referenced literature can be found in the EDR. The program codes used in statistical analyses and the electronic data sets with raw and derived variables and data definitions were provided in the EDR using the following path:

\\CDSESUB5\EVSPROD\NDA203214\203214.enx

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted efficacy data were acceptable in terms of quality and integrity. I was able to reproduce the primary and secondary efficacy endpoints analyses. No noticeable deviations between the case report forms and analysis datasets relevant to primary and secondary endpoints were identified.

Study seemed to be conducted properly based on the submission when I assessed the history of regulatory interactions, protocol revisions/amendments, study report, study datasets, and internal consistency among those components.

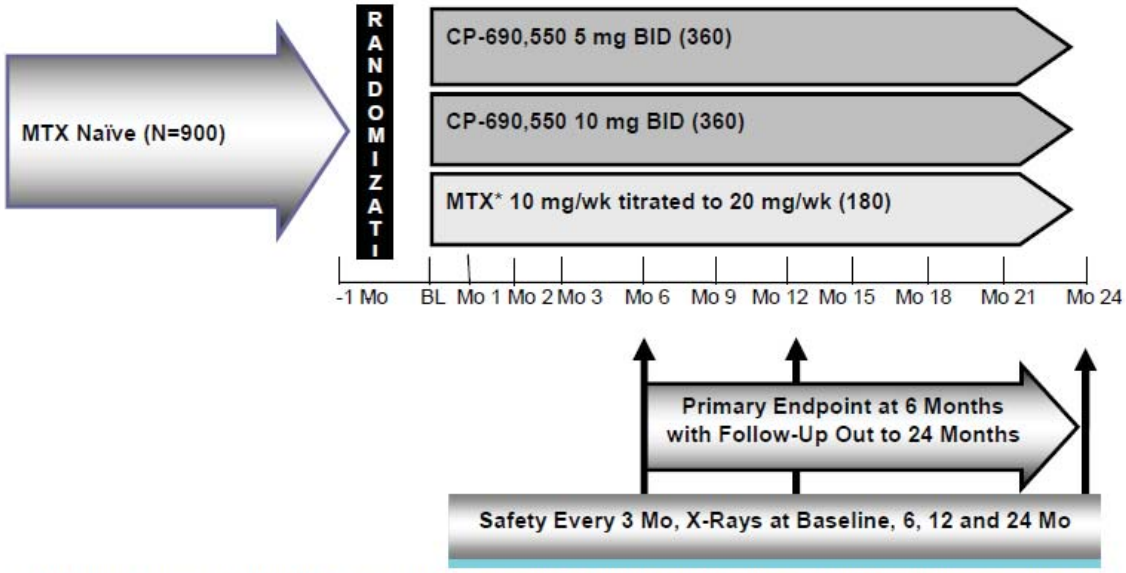
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 1069 was a phase 3, randomized, double-blind, active-controlled study designed to demonstrate efficacy of tofacitinib (CP-690,550) 5 mg BID and 10 mg BID (hereafter referred to as CP5 and CP10) over methotrexate in the domains of reducing signs and symptoms of RA as measured by ACR70 response criteria, reducing the progression of structural damage, as

measured by change from baseline in van der Heijde modified Sharp score, and improving physical function as measured by HAQ-DI. The applicant also planned to evaluate the disease activity by comparing the rate of achieving DAS28-4 (ESR)<2.6 response. Methotrexate-naïve patients were included in this study, in contrast to study 1044 that included patients with active RA who had an inadequate response to MTX.

A schematic of study design for A1032069 is shown below.



** MTX dose starts at 10 mg/wk and is titrated by 5 mg/wk every 4 weeks as tolerated to 20 mg/wk by Week 8; then maintained at the titrated dose throughout study, with one 5 mg/wk dose reduction allowed for MTX intolerance.*

Source: Excerpted from the statistical analysis plan v2.0 (page 9).

A summary of the study design and endpoints is presented in Table 1. The table also includes the design of study 1044 for better understanding of the study results provided in the appendix. In study 1069, patients randomized to methotrexate were given 10 mg/wk at the start and were titrated up to 20 mg/wk over two months and then, one 5 mg/wk reduction was allowed for lack of tolerance. In study1044, patients originally randomized to placebo were advanced to either CP5 or CP10 at 3 or 6 months. In study 1044, placebo nonresponders were advanced at Month 3, and all remaining placebo patients were advanced at Month 6. Nonresponders were defined as those patients who did not have at least a 20% improvement from baseline levels in both the tender/painful and swollen joint counts at the Month 3 visit.

Table 1: Summary of Study Design

Study ID	Study Design	Population and Sample Size	Supplemental Claims
A3921069	A 2-year, placebo-controlled, 3-arm parallel study of CP-690550 5 or 10 mg BID or MTX	MTX-naïve RA patients 958 randomized (planned 900)	***M6 Change from baseline modified Total Sharp Score*** *M6 ACR70 response*
A3921044	A 2-year, placebo-controlled, 3-arm parallel study of CP-690550 5 or 10 mg BID or placebo added to background MTX At M3, non-responding placebo patients are advanced to a second pre-determined treatment of CP-690550 5 or 10 mg BID. At M6, all placebo patients are advanced to their second predetermined treatment.	Subjects with active RA who had an inadequate response to MTX 797	*M6 ACR20 response* ***M6 Change from baseline in modified Total Sharp Score*** *M3 Change from baseline in HAQ-DI* *M6 DAS28-4(ESR) < 2.6*

Study 1069 had two primary efficacy endpoints (in sequence):

1. Structural preservation as measured by modified Total Sharp score (mTSS) at Month 6;
2. Signs and symptoms as measured by ACR70 at Month 6.

Study 1044 had four primary efficacy endpoints (in sequence):

1. Signs and symptoms as measured by ACR20 at Month 6;
2. Structural preservation as measured by modified Total Sharp score (mTSS) at Month 6;
3. Physical function as measured by the HAQ-DI change from baseline at Month 3;
4. Incidence of DAS <2.6 at Month 6.

3.2.2 Statistical Methodologies

The study A3921069 was designed to establish superiority of two doses (5 mg and 10 mg BID) of tofacitinib (CP-690,550) to methotrexate for the radiographic and other efficacy endpoints. The following are the protocol-specified analytical approach for the primary endpoints:

- For the change from baseline in the modified Sharp score at Month 6, the analysis of covariance (ANCOVA) with treatment, status of early RA (duration of disease <2 years from time of diagnosis versus ≥2 years), and site (US, Europe/Canada, Latin America, Asia/Other) as fixed effects and actual baseline value as a covariate was pre-specified as the primary analysis. Month 6 measurements for patients with missing values due to patient dropout were imputed using a linear extrapolation based on the baseline radiographs and post baseline radiographs prior to withdrawal. Of note, post-withdrawal radiographic data were not collected making it difficult to know what happened to these patients after they discontinued treatment.

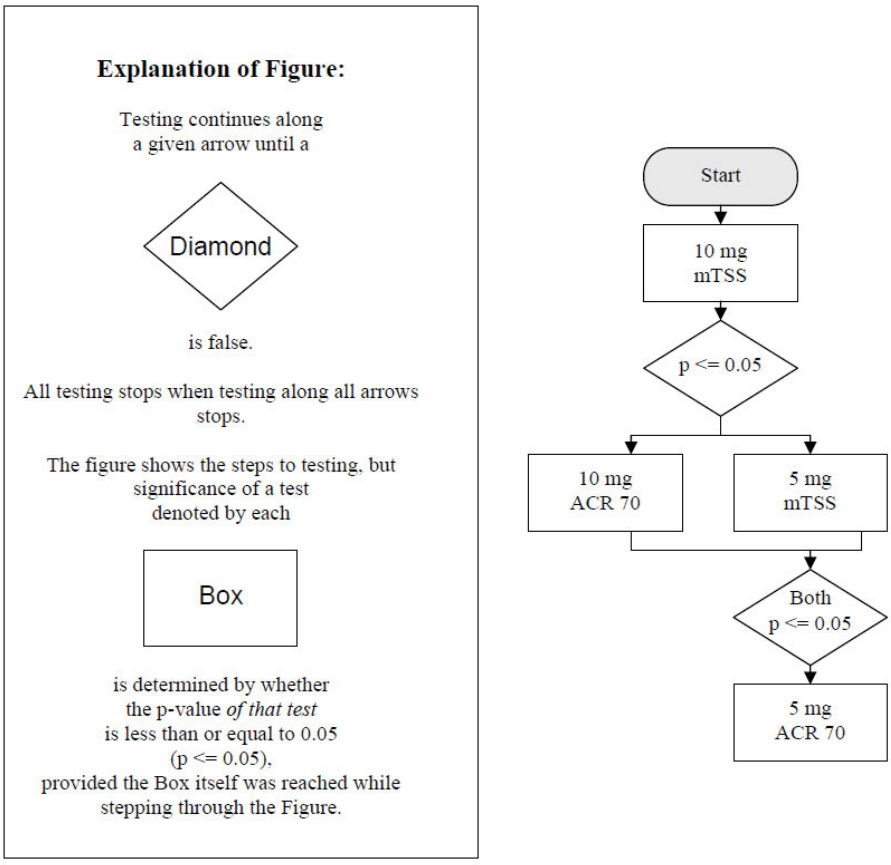
- For the binary endpoints such as ACR70 at Month 6, the normal approximation for the difference in binomial proportions was used to compare treatment difference. Missing values due to a patient dropping from the study for any reason (e.g., lack of efficacy or adverse event) were handled by setting the ACR value (ACR20, ACR50, and ACR70) to nonresponsive (that is, baseline observation carried forward, BOCF) from that visit onward. This also goes by the name Non Responder Imputation (NRI).

- For HAQ-DI at Month 3 or at Month 6, the mixed-effect model with repeated measures including treatment, status of early RA (duration of disease <2 years from time of diagnosis versus ≥2 years), site (US, Europe/Canada, Latin America, Asia/Other), baseline value, visit, and treatment-by-visit interaction as fixed effects and patient as random effect was pre-specified to compare treatment difference. Compound symmetry was assumed (though the applicant proposed to check the robustness of the results by fitting other structured covariance matrices, e.g., autoregressive 1, and unstructured. as well). It was also pre-specified that no imputation will be applied to missing data.

Several sensitivity analyses for each of the primary endpoint (i.e. ACR70 and mTSS) were pre-specified in the protocol to support the interpretation of the primary analyses. Specifically, for the change from baseline in the modified Sharp score, ANCOVA model on the ranks with treatment as factor, and rank baseline modified Sharp score as covariate was pre-specified as a sensitivity analysis. Missing values were imputed by linear extrapolation like above, and the resulting imputed data were ranked.

Because there were multiple doses and multiple endpoints being tested, a gatekeeping or step-down approach was pre-specified to control the probability of type 1 error. Using this approach, statistical significance can be claimed for the second endpoint only if the first endpoint in the sequence meets the requirements for significance. Additionally, as there were two doses within each endpoint, the gatekeeping or step-down approach was also applied. The applicant presented a flow chart to show the procedure in more detail (Figure 1).

Figure 1: Primary Analysis Stepdown Procedure – Study 1069



Source: Excerpted from the statistical analysis plan v2.0 (page 13).

For study 1069, one interim analysis was planned. The interim analysis was performed at 100% accrual at the completion of Month 12, which included all the primary analyses. All the inferences were based on year 1 interim analyses.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

More patients in the tofacitinib treated groups completed the study compared to the control group (MTX alone). The most frequent reason for discontinuation was due to adverse event, followed by lack of efficacy, and these occurred more often in the control group compared to the tofacitinib treated group. This suggests some efficacy of tofacitinib compared to MTX alone. The patient disposition can be summarized as follows:

- Completion rates:
  82-83% in active groups; 72% in control group

- Dropout rates due to adverse events (AE):
  5-6% in active groups; 8% in control group

- Dropout rates due to lack of efficacy (LOE):
  2-4% in active groups; 10% in control group

The detail of disposition can be found from Table 12 in the appendix.

There were no noticeable imbalances of the demographics and baseline characteristics between treatment groups as shown again Table 13 and Table 14 in the appendix. Following list summarizes demographic and baseline characteristics from the study 1069.

- Female 79% (753/952 patients)
- White 66% (631/952 patients)
- Mean age: 49.5 years (range 18 years to 83 years)
- Mean weight: 71 kg (range 31.4 kg to 183.2 kg)
- Region: 23% US, 17% Latin America, 41% Europe, 19% ROW
- Median time from diagnosis of RA to enrollment was 0.7 years
- Mean mTSS scores at Baseline: 20.3 tofacitinib 5 mg; 18.9 tofacitinib 10 mg; 16.5 MTX
- Mean CRP values at Baseline: 22.7 mg/L tofacitinib 5 mg; 20.2 mg/L tofacitinib 10 mg; 25.9 mg/L MTX

The efficacy analysis was conducted on the Full Analysis Set (FAS) population. The applicant defined FAS to include all randomized participants who received at least one study drug, which is usually called the Intent-To-Treat (ITT) population.

In the analyses of radiographic data, patients who have both the baseline data and at least one post-baseline data were included since they are needed for linear extrapolation of missing 6 or 12 month data. I defined the analysis set as radiographic ITT (rITT) which agrees with applicant's FAS.

The following table summarizes FAS analyzed for mTSS and ACR70 (Table 2).

Table 2: Analysis sets for efficacy analyses – Study 1069

	MTX	CP 5 mg	CP 10 mg
FAS	186	371	395
mTSS	166 (89%)	346 (93%)	369 (93%)
ACR70	184 (99%)	369 (99%)	393 (99%)

3.2.4 Results and Conclusions

In this presentation of the results, the results from study 1069 regarding mTSS, ACR70, HAQ-DI, and DAS28-4(ESR) less than 2.6 are summarized. Both the applicant's and my analyses are presented. A discussion of the results from study 1044 is also included.

3.2.4.1 Radiographic Endpoint

In this section, the analyses of radiographic data from study 1069 are summarized. The analyses of radiographic data from study 1044 are presented in the appendix.

Below is the table summarizing the applicant's primary and sensitivity analyses on mTSS. Both tofacitinib 5mg or 10 mg dose groups were statistically significantly different from methotrexate group in terms of mTSS. There was a small numerical difference between the two tofacitinib doses favoring the 10 mg group. The significant results were supported by the rank-based ANCOVA analyses on mTSS (Table 3). There were also statistically significant differences between tofacitinib and methotrexate in terms of component scores of mTSS – Erosion & Joint Space Narrowing scores (Table 4). Similarly, there was a small numerical difference between the two tofacitinib doses favoring the 10 mg group.

Table 3: Applicant's Primary and Pre-specified Sensitivity Analysis on mTSS – Study 1069

Treatment	N	LS Mean	Difference vs. MTX		
			LS Mean Difference	95% CI	P-value
Primary Analysis: Full Analysis Set (ANCOVA)					
CP 5 mg	346*	0.18	-0.66	(-1.03, -0.28)	<0.001
CP 10 mg	369*	0.04	-0.81	(-1.18, -0.44)	<0.001
MTX	166*	0.84			

*CP5 93%, CP10 93%, MTX 89% of the ITT population
P-value from pre-specified Rank-ANCOVA for CP5 vs. MTX is 0.001 and p-value for CP10 vs. MTX is less than 0.001.
Source: Adapted from Clinical Study Report, Tables 14.2.15.1.6 & 14.2.15.1.7 (pages 572 & 574)

Table 4: Applicant's Analyses on Components of mTSS – Study 1069

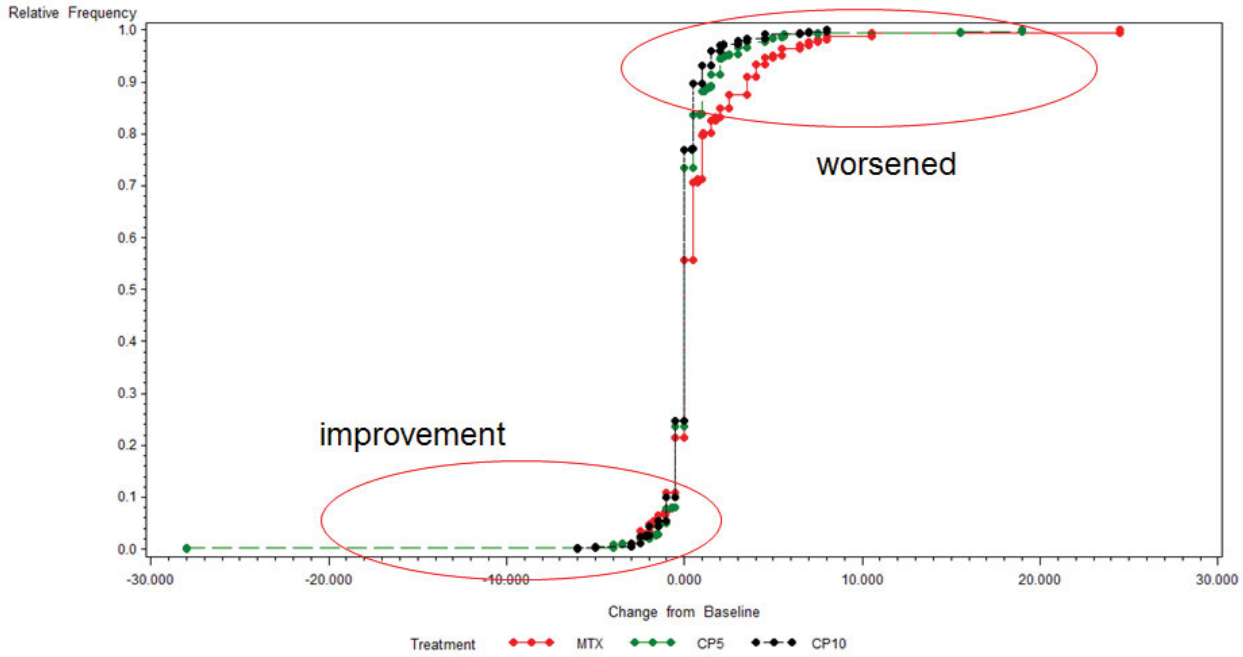
Treatment	N	LS Mean	Difference vs. MTX		
			LS Mean Difference	95% CI	P-value
Erosion					
CP 5 mg	346	0.07	-0.42	(-0.66, -0.19)	<0.001
CP 10 mg	369	-0.01	-0.50	(-0.74, -0.27)	<0.001
MTX	166	0.50			
JSN					
CP 5 mg	346	0.12	-0.23	(-0.45, -0.01)	0.039
CP 10 mg	369	0.05	-0.30	(-0.52, -0.08)	<0.007
MTX	166	0.35			

Source: Adapted from Clinical Study Report, Tables 14.2.15.2.6 & 14.2.15.3.6 (pages 621 & 626)

Examining the cumulative distribution functions by treatment group, there appeared to be a dose-response relationship among treatment groups especially in the region of 'worsened' of the curves with more patients in the MTX group experiencing progression (i.e., worse mTSS score) at month 6 compared to those in the tofacinitib groups (Figure 2). This is consistent with what

was observed in the primary analysis. Since there were a number of patients with no changes from baseline and there appeared to be potential outliers with one CP5 patient and one MTX patients experiencing a change of at least 20 points, rank-based analysis appeared to be more appropriate.

Figure 2: Cumulative Distribution of mTSS – Study 1069



In order to assess the sensitivity of estimated treatment effect with respect to potential outliers, I conducted a couple of additional analyses, first excluding extreme outliers with change from baseline greater than 20 units and then excluding outliers with change from baseline greater than 'clinically meaningful criterion' of 7 units (Figures 3-4). Both analyses results supported the primary analysis with a significant difference between tofacitinib and methotrexate (Tables 5-6). However, there was at least a 19% and 35% reduction in the estimated treatment effect for CP10 and CP5, respectively when extreme outliers (20 units or more) were excluded from the analysis. Additional reduction was observed when outliers (7 units or more) were excluded from the analysis.

Figure 3: Reviewer's mTSS plot (patients with $|\Delta| \geq 20$ units) – Study 1069

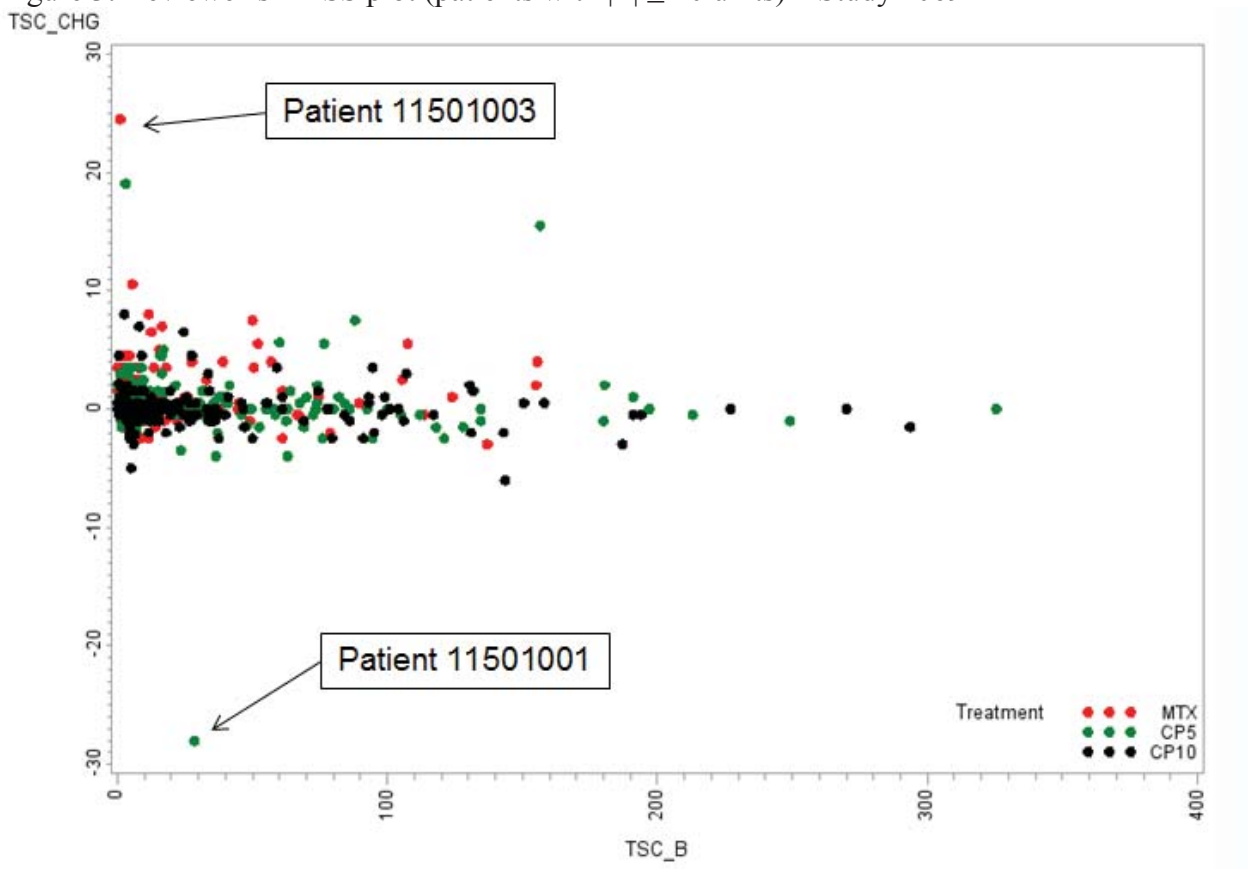


Table 5: Reviewer's Sensitivity Analysis # 1: Excluding patients with $|\Delta| \geq 20$ units – Study 1069

Treatment	N	LS Mean	Difference vs. MTX		
			LS Mean Difference	95% CI	P-value
Primary Analysis: Full Analysis Set					
CP 5 mg	346	0.18	-0.66	(-1.03, -0.28)	<0.001
CP 10 mg	369	0.04	-0.81	(-1.18, -0.44)	<0.001
MTX	166	0.84			
Excluding Patients 11501001* & 11501003* from CP5 & MTX group, respectively					
CP 5 mg	345	0.26	-0.43	(-0.73, -0.14)	0.004
CP 10 mg	369	0.03	-0.66	(-0.95, -0.37)	<0.001
MTX	165	0.69			

*Patient 11501001's baseline score is 28.5. At Month 6, patient's change score is -28. Patient 11501003's baseline score is 1. At Month 6, patient's change score is 24.5.

Figure 4: Reviewer's mTSS plot (patients with $|\Delta| > 7$ units) – Study 1069

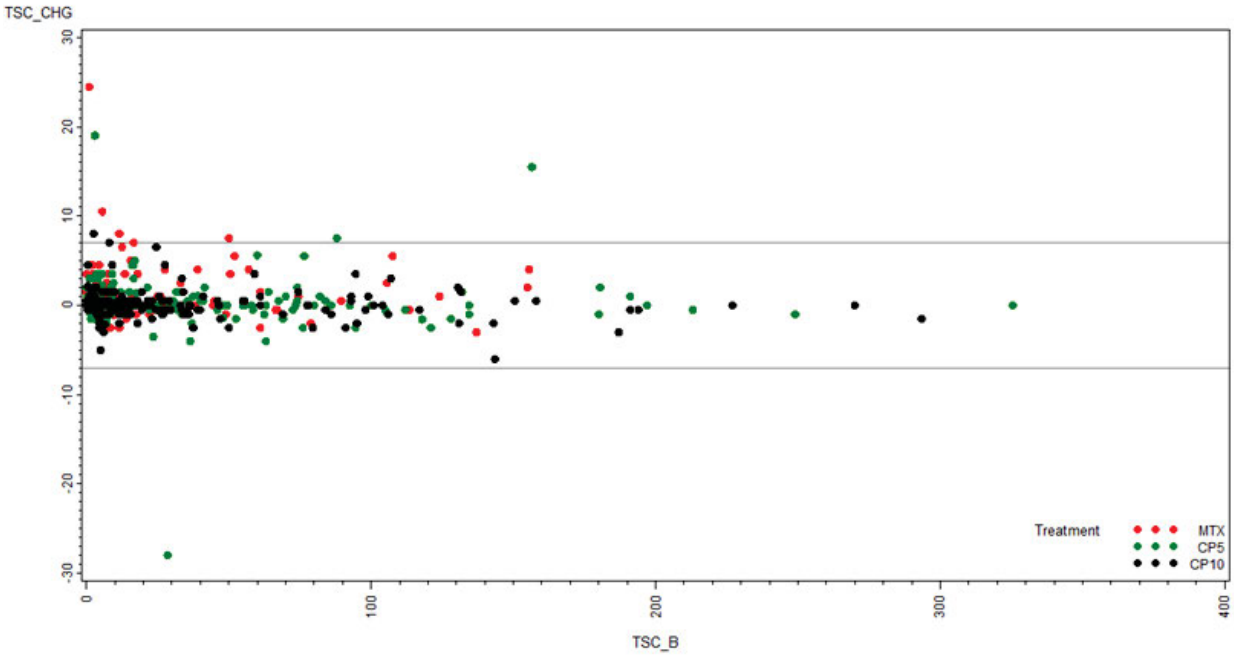


Table 6: Reviewer's Sensitivity Analysis # 2: Excluding patients with |Δ| > 7 units – Study 1069

Treatment	N	LS Mean	Difference vs. MTX		
			LS Mean Difference	95% CI	P-value
Primary Analysis: Full Analysis Set					
CP 5 mg	346	0.18	-0.66	(-1.03, -0.28)	<0.001
CP 10 mg	369	0.04	-0.81	(-1.18, -0.44)	<0.001
MTX	166	0.84			
Excluding patients with |Δ| greater than 7 units*					
CP 5 mg	342	0.14	-0.41	(-0.63, -0.18)	0.005
CP 10 mg	368	0.01	-0.54	(-0.77, -0.32)	<0.001
MTX	162	0.55			

*9 patients were excluded, 4 from MTX, 4 from CP5, and 1 from CP10 group, respectively.

Table 7 gives an inferential result using a definition of "no progression," one by the applicant (defined as Change in mTSS ≤ 0.5) and the other by me (defined as Change in mTSS ≤ 0). Applying each of the definitions, both doses were significantly different from methotrexate with tofacinitib 10 mg favoring slightly over tofacitinib 5 mg group.

Table 7: Rates of 'No Progression' based on mTSS – Study 1069

Treatment	N	n	Rate	Difference vs. MTX	95% CI
No Progression Defined by Applicant as Change in mTSS ≤ 0.5					
CP 5 mg	346	289	84 %	13 %	(5%, 21%)
CP 10 mg	369	331	90 %	19 %	(11%, 27%)
MTX	167	118	71 %		
No Progression Defined by Reviewer as Change in mTSS ≤ 0					
CP 5 mg	346	254	73 %	18 %	(9%, 27%)
CP 10 mg	369	284	77 %	21 %	(13%, 30%)
MTX	167	93	56 %		

In summary, both tofacitinib 5mg or 10 mg dose groups were statistically significantly different from methotrexate group in terms of mTSS in study 1069. There was a small numerical difference between the two tofacitinib doses favoring the 10 mg group, suggesting a dose-response relationship which was not evident in study 1044. These findings were consistent when we examined the cumulative distribution function by treatment groups and the proportion of patients who experienced no progression, as defined by the change in mTSS ≤ 0. While the statistical significance was not affected by outliers, there was some reduction in treatment effects when potential outliers were excluded in the analysis.

Given that different patient population was studied in these trials, cross-study comparison of the estimated treatment difference can potentially be misleading. However, there were some differences in the radiographic outcome measures worth noting. For example, in study 1069, more than 50% of patients had some change in mTSS from baseline compared to less than 40% in study 1044, and 24% of patients' radiographic scores improved in study 1069 compared to only 16% in study 1044. These observations may be the consequence of differing patient population studied in these trials.

Nonetheless, there was evidence from study 1069 that tofacitinib 10 mg and 5 mg had activity on radiographic progression and this evidence was supported by study 1044 despite some of its limitations.

3.2.4.2 ACR70 Endpoint

There were statistically significant differences between tofacitinib doses and methotrexate in terms of ACR70 at Month 6 as another primary endpoint (Table 8).

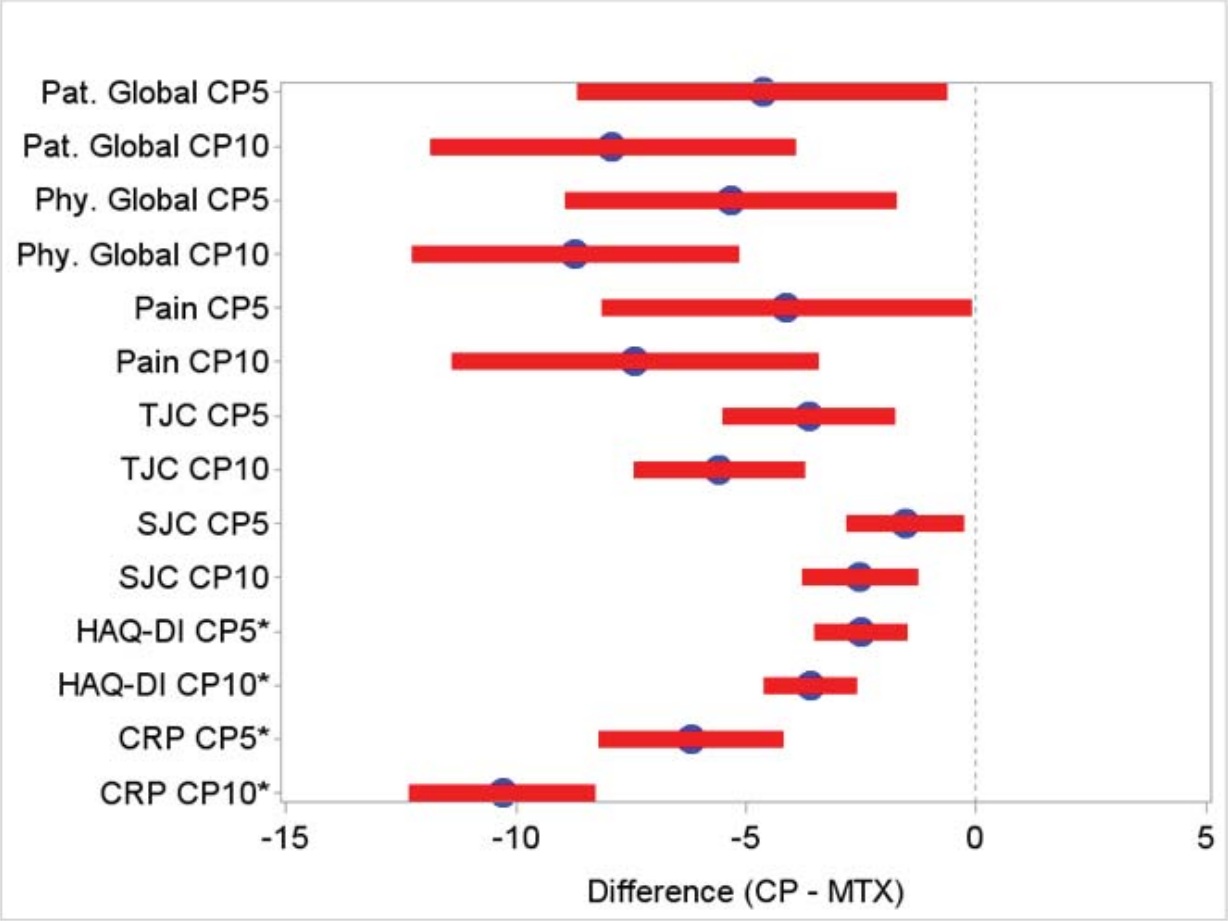
Table 8: Applicant's Primary Analysis on ACR70 Response – Study 1069

Treatment	N	n	Response Rate	Difference vs. MTX		
				Difference	95% CI	P-value
Primary Analysis: Full Analysis Set						
CP 5 mg	369	94	26%	14%	(7%, 20%)	<0.001
CP 10 mg	393	148	38%	26%	(19%, 32%)	<0.001
MTX	184	22	12%			

Source: Adapted from Clinical Study Report, Table 14.2.3.1 (page 366)

A graphical summary of results on ACR components at Month 6 is given below (Figure 5).

Figure 5: Applicant's Analyses on Components of ACR – Study 1069



* HAQ-DI and CRP were multiplied by 10.
Source: Analyses results excerpted from the clinical study report A3921069: Tables 14.2.8.5, 14.2.9.5, 14.2.10.5, 14.2.4.5, 14.2.5.5, 14.2.11.5, 14.2.6.5 (pages 415, 421, 423, 399, 403, 435, 407)

Following table is the corresponding results on ACR components at Month 6 (Table 9).

Table 9: Applicant's Analyses on ACR components - Study 1069

Treatment	N	LS Mean	LS Mean Difference vs. MTX	95% CI
Patient Global Assessment (mm) Change from Baseline at Month 6				
CP 5 mg	341	-32	-5	(-9, -1)
CP 10 mg	365	-35	-8	(-12, -4)
MTX	157	-27		

Physician Global Assessment (mm) Change from Baseline at Month 6				
CP 5 mg	337	-40	-6	(-9, -2)
CP 10 mg	362	-43	-9	(-12, -5)
MTX	156	-34		
Pain VAS (mm) Change from Baseline at Month 6				
CP 5 mg	341	-32	-4	(-8, -0)
CP 10 mg	365	-35	-7	(-11, -3)
MTX	157	-28		
Tender Joint Counts Change from Baseline at Month 6				
CP 5 mg	341	-16.3	-3.6	(-5.5, -1.8)
CP 10 mg	366	-18.3	-5.6	(-7.4, -3.7)
MTX	157	-12.7		
Swollen Joint Counts Change from Baseline at Month 6				
CP 5 mg	341	-11.0	-1.6	(-2.8, -0.3)
CP 10 mg	366	-12.0	-2.5	(-3.8, -1.3)
MTX	157	-9.5		
HAQ-DI Change from Baseline at Month 6				
CP 5 mg	341	-0.82	-0.25	(-0.35, -0.15)
CP 10 mg	364	-0.93	-0.36	(-0.46, -0.26)
MTX	157	-0.57		
CRP Change from Baseline at Month 6				
CP 5 mg	340	-16.9	-7.1	(-9.4, -4.8)
CP 10 mg	365	-18.7	-8.9	(-11.1, -6.6)
MTX	158	-9.8		

Source: Analyses results excerpted from the clinical study report A3921069: Tables 14.2.8.5, 14.2.9.5, 14.2.10.5, 14.2.4.5, 14.2.5.5, 14.2.11.5, 14.2.6.5 (pages 415, 421, 423, 399, 403, 435, 407)

3.2.4.3 Other Efficacy Endpoints

Following are results from the analyses of secondary efficacy endpoints including HAQ-DI and DAS-28(ESR)<2.6 (Tables 10-11).

For the HAQ-DI endpoint, the applicant assumed missing-at-random mechanism for missing data due to dropout and employed the mixed model repeated measures analysis when analyzing HAQ-DI. In general, we find that this approach may not be reasonable given that the reasons many of these patients discontinue treatment are often treatment-related (i.e., adverse events or lack of efficacy). I applied a baseline observation carried forward approach (BOCF) as a sensitivity analysis to assess the robustness of the primary result. While this approach is not perfect since this does not account for the variance and potentially overstates the statistical significance of results, in general this approach does provide a conservative point estimate of the treatment effect.

The results observed applying MMRM and BOCF were consistent. There were statistically significant differences between tofacitinib doses and methotrexate in terms of HAQ-DI at Month 6 in both applicant's MMRM analysis and my ANCOVA analysis with BOCF imputation for missing data.

Table 10: Analyses on HAQ-DI – Study 1069

Treatment	N	LS Mean	LS Mean Difference vs. MTX	95% CI
HAQ-DI at Month 6 (Applicant's based on FAS)				
CP 5 mg	341	-0.82	-0.25	(-0.35, -0.15)
CP 10 mg	381	-0.93	-0.36	(-0.46, -0.26)
MTX	157	-0.57		
HAQ-DI at Month 6 (Reviewer's ITT BOCF)				
CP 5 mg	371	-0.78	-0.22	(-0.33, -0.11)
CP 10 mg	395	-0.90	-0.34	(-0.45, -0.23)
MTX	186	-0.56		

Source: Applicant's analyses results excerpted from the clinical study report A3921069: Table 14.2.11.5 (page 435)

There were statistically significant differences between tofacitinib doses and methotrexate in terms of DAS response at Month 6 in both applicant's analysis with available data and my ITT analysis with non-responder imputation for missing data.

Table 11: Analyses on DAS28-4(ESR)<2.6 Response – Study 1069

Treatment	N	n	Response rate	Difference vs. MTX 95% CI
DAS28-4(ESR)<2.6 at Month 6 (Applicant's based on FAS)				
CP 5 mg	343	50	15%	7 % (2%, 13%)
CP 10 mg	371	80	22%	14 % (8%, 20%)
MTX	171	13	8%	
DAS28-4(ESR)<2.6 at Month 6 (Reviewer's based on ITT)				
CP 5 mg	371	50	14%	7 % (1%, 12%)
CP 10 mg	395	80	20%	13 % (8%, 19%)
MTX	186	13	7%	

Source: Analyses results excerpted from the clinical study report A3921069: Table 14.2.13.19.2 (page 503)

In summary,

- Results on mTSS:
  - Study 1069: both CP5 and CP10 won (compared to MTX)
    - Supported by various robustness checking sensitivity & outlier analyses
    - Analyses on components were consistent
    - Subgroup analyses were consistent
  - Study 1044: CP5 failed and CP10 won (compared to PBO)
    - Not supported by various robustness checking sensitivity & outlier analyses

Also data from study 1069 provides evidence of efficacy in the domains of reducing signs and symptoms of RA seen from ACR70 and DAS28-4(ESR)<2.6 responses and HAQ-DI.

3.3 Evaluation of Safety

The assessment of the safety of the study drug was mainly conducted by the reviewing medical team.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The following analyses are graphical presentation of the subgroup analyses by demographics in terms of mTSS. The subgroup analyses were consistent with the results from the overall population in terms of mTSS (Figures 6-7).

Figure 6: Reviewer's Subgroup Analyses on mTSS (demographics) – Study 1069

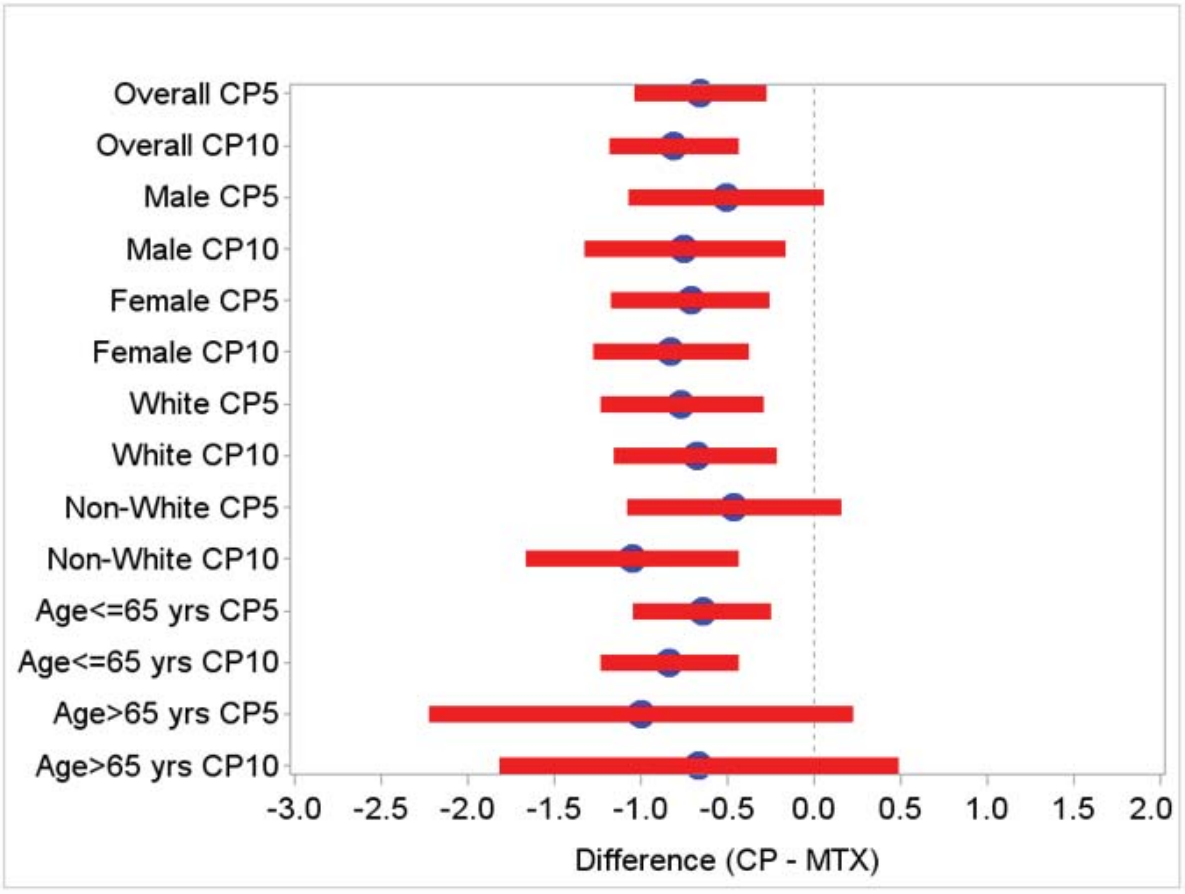
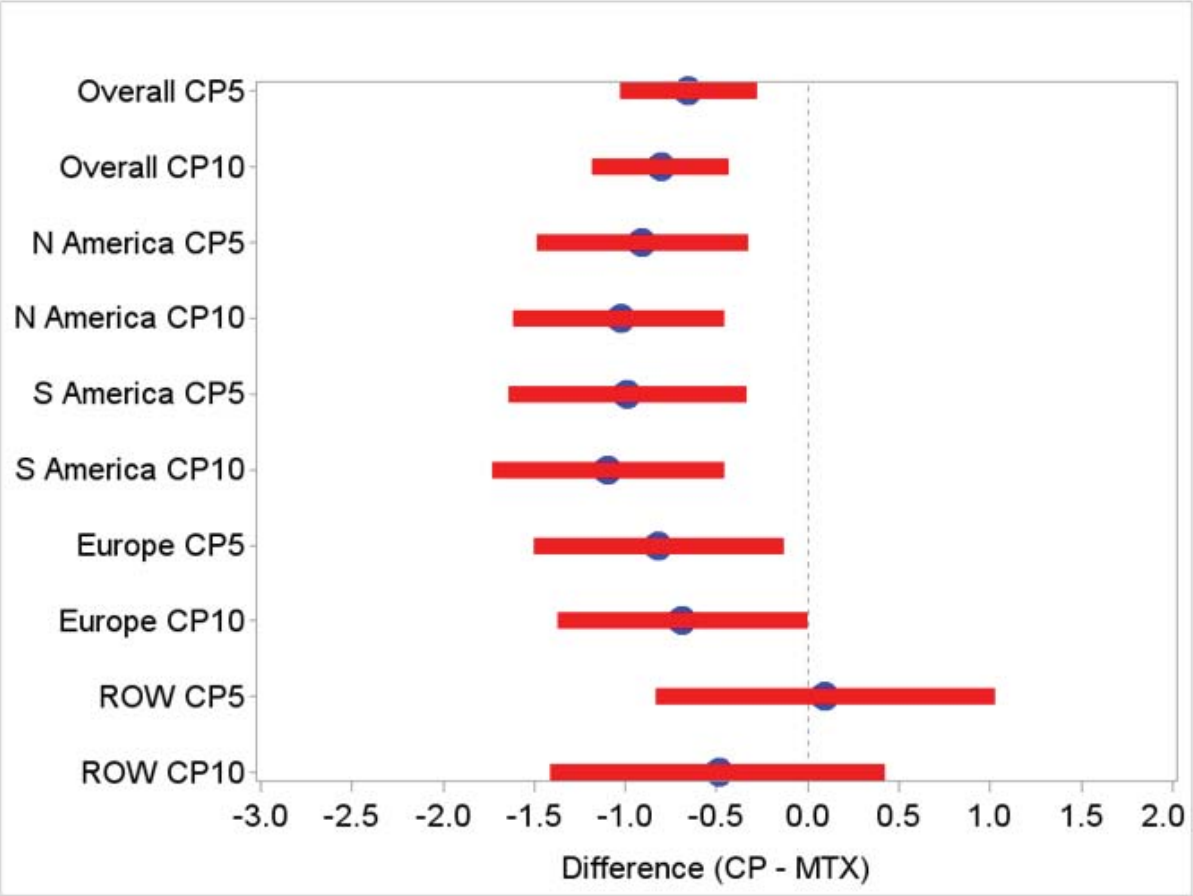


Figure 7: Reviewer's Subgroup Analyses on mTSS (region) – Study 1069

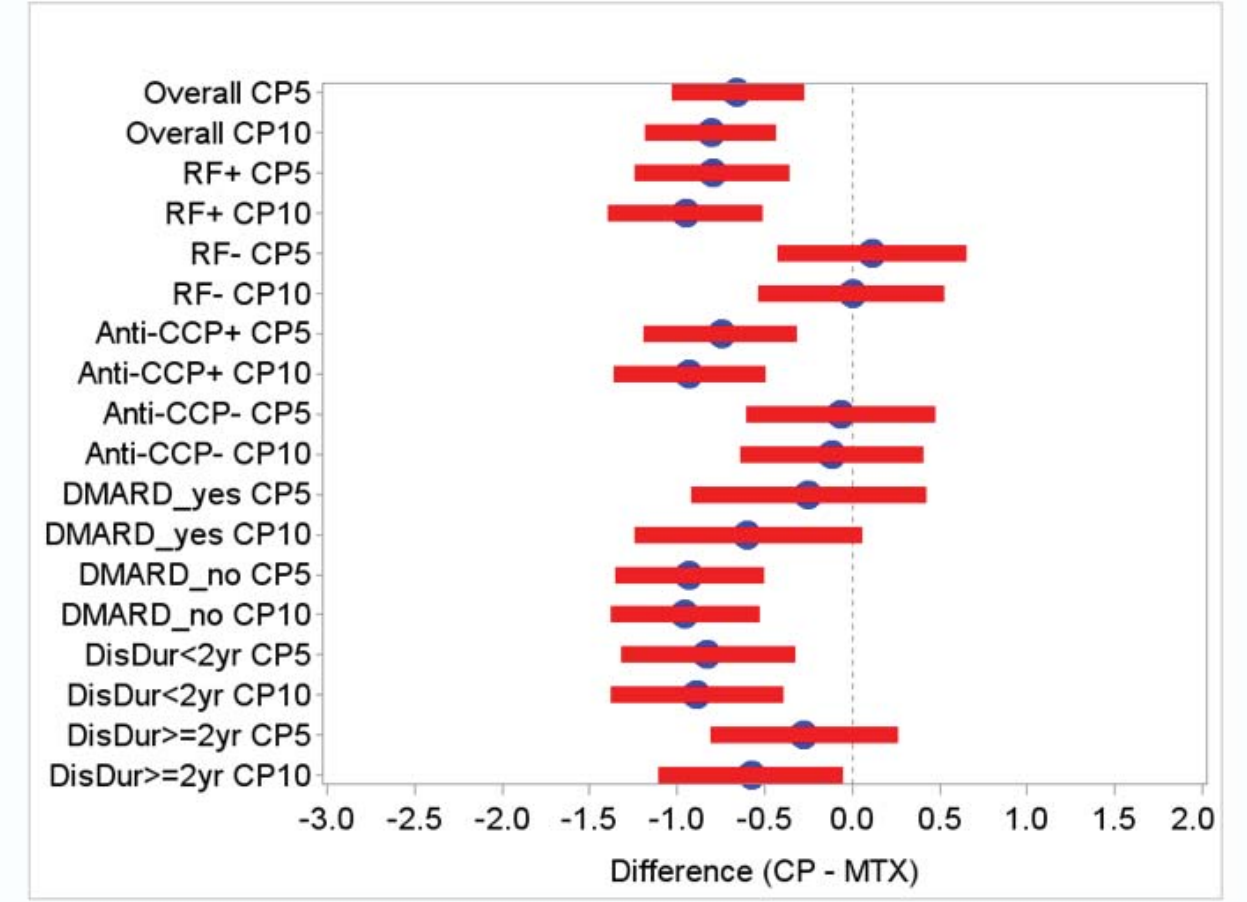


4.2 Other Special/Subgroup Populations

The following analyses are graphical presentation of the subgroup analyses by baseline characteristics in terms of mTSS.

There was no noticeable difference in terms of mTSS between groups regarding use of DMARD (yes or no) and duration of disease (<2 years or ≥2 years), but there appeared to exist some differences regarding RF(+/-) and anti-CCP (+/-) (Figure 8).

Figure 8: Reviewer's Subgroup Analyses on mTSS (baseline characteristics) – Study 1069



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In study 1069, the primary parametric analysis and the pre-specified secondary non-parametric analysis on radiographic endpoint were consistent. This is in contrast to what was observed in study 1044 in which there was a lack of consistent finding when different statistical models were applied. Consistent findings were also observed when examining the distribution of the radiographic data and the impact of some potential outliers in study 1069. This confirms that both tofacitinib 5 mg and 10 mg have activity on radiographic progression in the patient population studied in study 1069.

The applicant assumed missing-at-random mechanism for missing data due to dropout and employed the mixed model repeated measures analysis when analyzing HAQ-DI. In general, we find that this approach may not be reasonable given that the reasons many of these patients

discontinue treatment are often treatment-related (i.e., adverse events or lack of efficacy). I applied a baseline observation carried forward approach (BOCF) as a sensitivity analysis to assess the robustness of the primary result. While this approach is not perfect since this does not account for the variance and potentially overstates the statistical significance of results, in general this approach does provide a conservative point estimate of the treatment effect. Results from the two analyses were consistent.

5.2 Collective Evidence

The new radiographic data from study 1069 provided strong evidence in reducing structural damage progression of tofacitinib 5mg and 10 mg doses compared to methotrexate. Along with data from study 1044, I conclude that tofacitinib 5mg and 10 mg doses provide evidence of efficacy in terms of reducing structural damage progression in RA patients.

5.3 Conclusions and Recommendations

The efficacy data from study 1069 gave an additional evidence of tofacitinib 5 mg and 10 mg for treatment of signs and symptoms based on ACR and improvement in physical function based on HAQ-DI. While radiographic data from study 1044 showed that tofacitinib 5 mg and 10 mg may have some activity on radiographic progression and statistical significance was sensitive to the outliers and the statistical methods applied, new radiographic data from study 1069 provided statistically robust and significant difference between tofacitinib 5 mg and 10 mg doses and methotrexate.

5.4 Labeling Recommendations

Following is an excerpt from the relevant clinical studies section in the proposed label. I generally agree with the study description and primary analysis results and their interpretation. I recommend removing the (b) (4) (b) (4) (b) (4) From an internal labeling meeting, clinical and statistical teams recommended that (1) the primary model-based analyses on mTSS from two studies 1044 and 1069 should be (b) (4) (b) (4) (b) (4)

(b) (4)

Following this page 2 pages have been withheld in full due to draft labeling (b) (4)

APPENDICES

Table 12: Patient Disposition

Study 1069:

No. (%) of Patients	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Methotrexate
Screened: 1540			
Assigned to study treatment	374	398	186
Treated	371	395	186
Ongoing at date of cutoff	307 (82.1)	328 (82.4)	134 (72.0)
Discontinued	64 (17.1)	67 (16.8)	52 (28.0)
Related to study drug	28 (7.5)	24 (6.1)	29 (15.6)
Adverse event	13 (3.5)	17 (4.3)	11 (5.9)
Lack of efficacy	15 (4.0)	7 (1.8)	18 (9.7)
Not related to study drug	36 (9.7)	43 (10.9)	23 (12.4)
Adverse event	5 (1.3)	8 (2.0)	4 (2.2)
Lost to follow-up	7 (1.9)	4 (1.0)	3 (1.6)
Patient no longer willing to participate in study	16 (4.3)	16 (4.1)	8 (4.3)
Other	8 (2.2)	15 (3.8)	8 (4.3)
Pregnancy	2 (0.5)	0	0
Protocol violation	3 (0.8)	8 (2.0)	4 (2.2)
Other	3 (0.8)[a]	7 (1.8)[b]	4 (2.2)[c]

Source: Excerpted from the clinical study report, table 7 (page 102).

Table 13: Baseline Demographics

Study 1069:

	Tofacitinib 5 mg BID N=371	Tofacitinib 10 mg BID N=395	Methotrexate N=186
Gender, n			
Male	88	70	41
Female	283	325	145
Age (years), n (%)			
18-44	102 (27.5)	130 (32.9)	67 (36.0)
45-64	231(62.3)	220 (55.7)	99 (53.2)
≥65	38 (10.2)	45 (11.4)	20 (10.8)
Mean	50.4	49.2	48.8
Standard deviation	12.3	12.7	13.3
Range	18-83	18-79	20-80
Race, n (%)			
White	239 (64.4)	265 (67.1)	127 (68.3)
Black	13 (3.5)	12 (3.0)	4 (2.2)
Asian	67 (18.1)	61 (15.4)	33 (17.7)
Other	52(14.0)	57 (14.4)	22 (11.8)
Weight (kg)			
Mean	70.5	71.3	70.9
Standard deviation	16.5	18.6	18.2
Range	33.0-143.0	34.1-183.2	31.4-129.0
Height (cm)			
Mean	163.0	162.6	162.8
Standard deviation	9.4	9.5	10.4
Range	142.5-198.0	136.0-190.0	127.0-198.0

Source: Excerpted from the clinical study report, table 12 (page 108).

Table 14: Baseline Characteristics

Study 1069:

Baseline Characteristic Parameter	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Methotrexate
Disease duration (rheumatoid arthritis) (duration since first diagnosis, years)			
N	371	395	185[a]
Mean	2.9	3.3	2.6
Median	0.7	0.7	0.7
Range	0.0-44.0	0.0-34.0	0.0-30.0
Rheumatoid factor, n (%)			
N	371	395	186
Negative	65 (17.5)	73 (18.5)	29 (15.6)
Positive	306 (82.5)	322 (81.5)	157 (84.4)
Anti-CCP antibodies, n (%)			
N	371	395	186
Negative (<20 units)	56 (15.09)	75 (18.99)	25 (13.44)
Weak Positive 20-39 units	6 (1.62)	7 (1.77)	10 (5.38)
Moderate Positive 40-59 units	170 (45.82)	170 (43.04)	86 (46.24)
Strong Positive ≥60 units	139 (37.47)	143 (36.20)	65 (34.95)
DAS28-3(CRP)			
N	371	395	186
Mean (SD)	5.55 (0.92)	5.45 (0.94)	5.61 (0.95)
Range	3.16 - 7.80	2.27 - 7.82	3.61 - 7.91
DAS28-4(ESR)			
N	370	395	186
Mean (SD)	6.61 (0.99)	6.54 (0.95)	6.60 (1.02)
Range	3.23 - 8.89	3.90 - 9.00	4.24 - 9.04
Sharp Scores (mTSS)			
N	346	370	170
Mean (SD)	20.30 (40.45)	18.85 (39.29)	16.51 (29.33)
Range	0.00 - 325.50	0.00 - 293.50	0.00 - 155.50
Health Assessment Questionnaire - Disability Index			
N	371	394	186
Mean (SD)	1.54 (0.65)	1.50 (0.67)	1.52 (0.65)
Range	0.00 - 3.00	0.00 - 3.00	0.00 - 3.00
Tender joint counts			
N	371	395	186
Mean (SD)	25.61 (13.83)	25.13 (13.52)	25.41 (15.03)
Range	5.00 - 68.00	1.00 - 68.00	6.00 - 67.00

Swollen joint counts			
N	371	395	186
Mean (SD)	16.28 (9.25)	15.58 (8.39)	16.76 (10.27)
Range	2.00 - 55.00	1.00 - 49.00	6.00 - 58.00
Erythrocyte sedimentation rate (mm/hr)			
N	370	395	186
Mean (SD)	55.68 (28.89)	53.45 (27.31)	56.04 (27.50)
Range	5.00 - 140.00	5.00 - 140.00	1.00 - 125.00
C-reactive protein (mg/L)			
N	371	395	186
Mean (SD)	22.73 (27.14)	20.21 (23.96)	25.92 (30.94)
Range	0.20 - 170.00	0.20 - 159.00	0.23 - 190.00

Source: Excerpted from the clinical study report, table 13 (pages 109-110).

Results from Studies 1044 excerpted from my review on the original NDA

The primary analysis of radiographic data (mTSS) was ANCOVA (parametric analysis). Based on the applicant's analyses, the difference between tofacitinib 10 mg and placebo was statistically significant for mTSS score, while the difference was not statistically significant between 5 mg and placebo, at Month 6 and Month 12 (Table 3).

Table 3: Applicant's Analysis on mTSS (FAS)

Treatment	N	LS Mean	Difference vs. PBO		
			LS Mean Difference	95% CI	P-value
Study 1044 (primary at Month 6)					
CP 5 mg	278	0.12	-0.34	(-0.73, 0.04)	.0792
CP 10 mg	290	0.06	-0.40	(-0.79, -0.02)	.0376
PBO	140	0.47			
Study 1044 (Month 12)					
CP 5 mg	286	0.29	-0.63	(-1.27, 0.02)	.0558
CP 10 mg	295	0.05	-0.87	(-1.51, -0.23)	.0081
PBO	139	0.92			

Excerpted from the clinical study report A3921044.

The results from my analyses of radiographic data produced similar results from that of the applicant's analyses using ANCOVA, and therefore were not presented here. As noted, a sensitivity analysis was pre-specified in the protocol to evaluate treatment difference using ANCOVA model on the ranks with treatment as factor, and rank baseline modified Sharp score as covariate (a non-parametric analysis). The results from this analysis suggest no significant difference between tofacitinib 10 mg and placebo on mTSS at Month 6, while the difference was significant between tofacitinib 5 mg and placebo (Table 4). This is in reverse to what was shown

in the primary (parametric) analysis. Both doses were not significantly different from placebo at Month 12. Other variations of rank sum test gave consistent results (Table 4).

Table 4: Analyses on mTSS based on the Ranks (FAS)

	N	**ANCOVA with ranked data P-value***	Wilcoxon test P-value†	Van der Waerden test P-value†	Van Elteren test P-value**†
Study 1044 (primary 6 months)					
CP 5 mg	278	.0237	.0216	.0283	.0245
CP 10 mg	290	.1979	.1751	.1410	.1710
PBO	140				
Study 1044 (12 months)					
CP 5 mg	286	.0790	.0665	.0721	.0772
CP 10 mg	295	.0578	.0594	.0488	.0675
PBO	139				

*Source: Study Report Table 14.2.15.1.7
**van Elteren's test adjusted for the same covariates as in rank ANCOVA model.
† Reviewer's analyses

The inferential results using a definition of "no progression," by the applicant (defined as Change in mTSS ≤ 0.5) and by me (defined as Change in mTSS ≤ 0) are presented. With the applicant's definition of "no progression," both doses were significantly different from placebo while only 5 mg dose was different from placebo when my definition was applied. This further illustrates the lack of conclusiveness of the radiographic data when change in the definition of no progression resulted in a loss in statistical significance for the tofacitinib 10 mg dose group.

Table 5: Rates of 'No Progression' based on mTSS (rITT)

Treatment	**N**	**N**	**Rate**	**Difference vs. PBO**	**P-value**
No Progression defined by applicant as Change in mTSS ≤ 0.5					
CP 5 mg	278	246	88 %	11 %	.0028
CP 10 mg	290	252	87 %	9 %	.0167
PBO	140	108	77 %		
No Progression defined by reviewer as Change in mTSS ≤ 0					
CP 5 mg	278	233	84 %	10 %	.0200
CP 10 mg	290	229	79 %	5 %	.2766
PBO	140	104	74 %		

The cumulative distribution plot of mTSS at Month 6 is presented in Figure 2, without any specific cut-off for defining "no progression." The x-axis represents change from baseline and the y-axis represents cumulative percentage. Left of zero means improvement and right of zero means worsening. There appears to be a separation of curves between the tofacitinib doses and placebo (Figure 2). As shown in Table 6, a numerically higher proportion of patients in the tofacitinib group appears to improve compared to the placebo group. Likewise, a numerically smaller proportion of patients in the tofacitinib group appears to worsen compared to placebo group, suggesting some benefit of tofacitinib on structural damage score. However, the 5 mg dose

appears to be numerically better than the 10 mg dose. This is consistent with the findings from the non-parametric analysis.

Figure 2: Cumulative Distribution of mTSS (rITT)

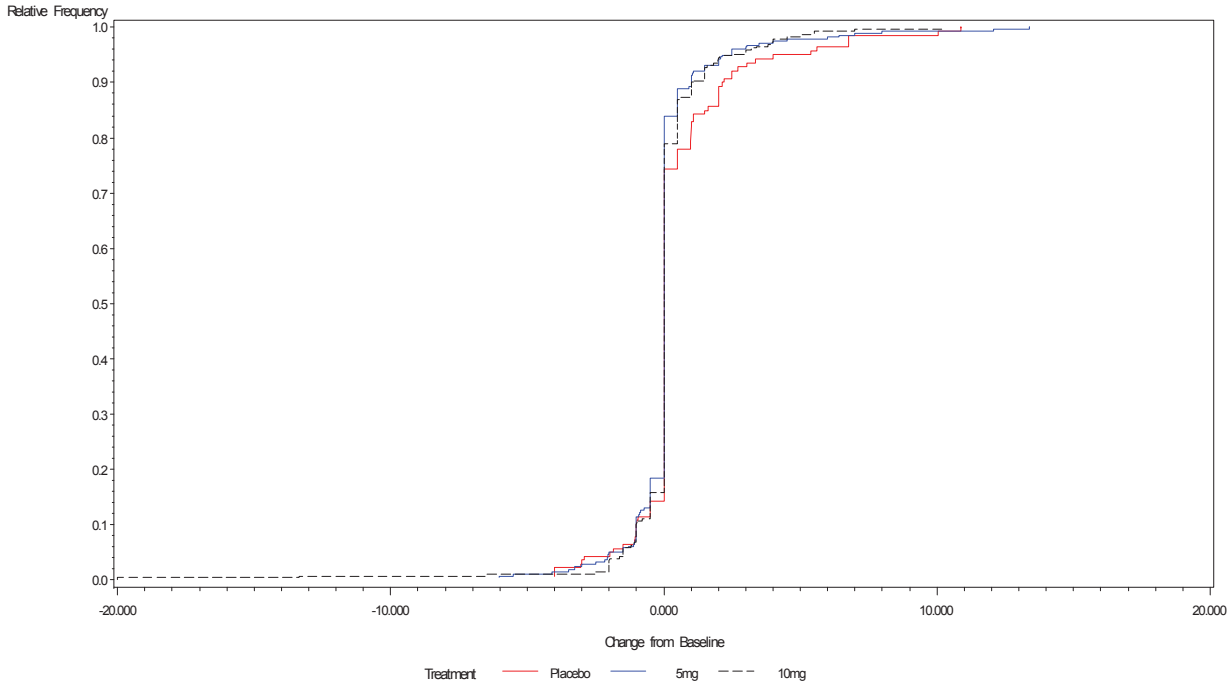


Table 6: Proportion of "Improved" or "No Change" or "Worsened" (rITT)

	PBO (N=140)	CP 5 mg (N=278)	CP 10 mg (N=290)
Improved (change in mTSS < 0)	20 (14%)	51 (18%)	46 (16%)
No Change	84 (60%)	182 (66%)	183 (63%)
Worsened (change in mTSS > 0)	36 (26%)	45 (16%)	61 (21%)

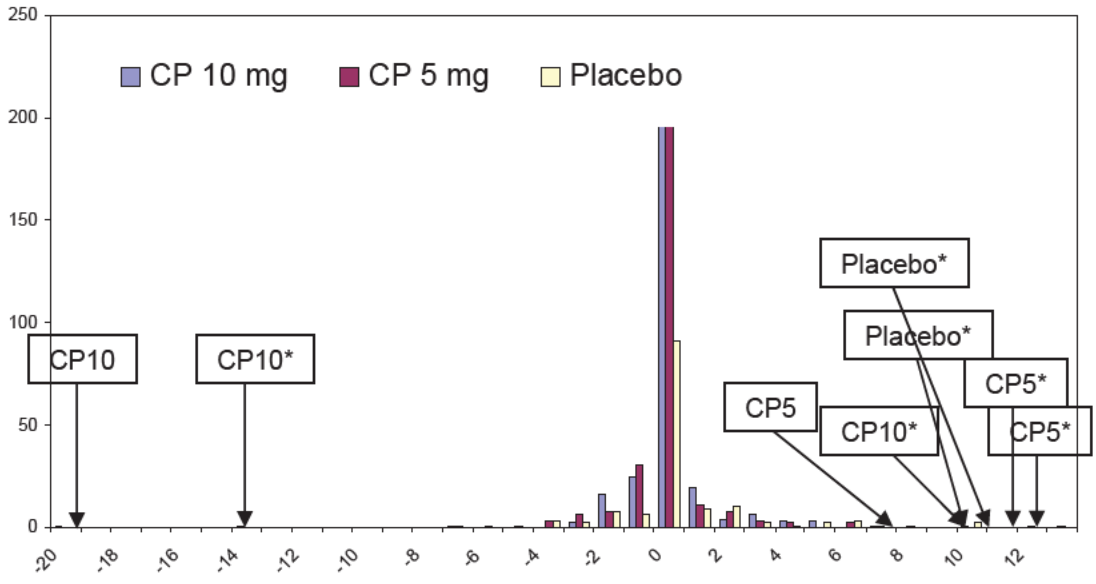
As noted in Table 6, about 63% of subjects had zero change from baseline, which implies that comparison between group means could be problematic because conclusion could be driven by a few outlying or extreme values.

Following are exploratory analyses on mTSS at Month 6 including outlier analyses conducted by me. This allows one to assess the impact of outliers or extreme observations on the applicant's analyses. Frequency distributions by treatment group are presented (Figure 3). The diagrams suggest that there were potential outliers especially in the tofacitinib groups. In consultation with the clinical team, extreme observations with absolute change greater than 7 units were identified with randomized treatment and extrapolated values were marked with asterisks (Figure 3). Of note, some outliers at Month 6 are observed data and others are linearly extrapolated due to missing data at Month 6. The same parametric ANCOVA model was applied to the new data after excluding the outlying observations. In contrast with the results from the full ANCOVA model, the results from this new analysis showed no statistically significant differences between tofacitinib 10 mg and placebo, while the difference between tofacitinib 5 mg and placebo was statistically significant (Table 15). As expected, the same conclusion applies to nonparametric

analyses regardless of whether outliers were excluded or not (data not shown). Similar analyses were conducted by excluding a patient with the most extreme observation. The results from the same ANCOVA model showed no statistically significant differences between tofacitinib groups and placebo (Table 16). The outlier analyses suggest that the significant findings based on group means using ANCOVA may be driven by a few extreme observations.

We acknowledge that inclusion or exclusion of outliers from data analysis can be done in many ways, and that it also depends on the reason why the case is an outlier. In this study, some of these values were not the actual observed values given that they were extrapolated values. There were also others that could be due to measurement errors. In summary, there is lack of consistent findings in the two tofacitinib dose groups when different statistical models were applied. Furthermore, based on the responder analysis (Table 6), 5 mg appears to be better than 10 mg.

Figure 3: Frequency Distribution of Change from Baseline in mTSS at Month 6



*Extrapolated data

Table 7: ANCOVA on mTSS excluding outlying subjects (|Δ| greater than 7 units)

Treatment	N	LS Mean	Difference from PBO		
			LS Mean Difference	95% CI	P-value
Study 1044 (primary at Month 6)					
CP 5 mg	275	-0.003	-0.32	(-0.59, -0.05)	0.021
CP 10 mg	287	0.14	-0.17	(-0.44, 0.09)	0.203
PBO	138	0.32			

Table 8: ANCOVA on mTSS excluding outlying subjects (|Δ| greater than 20 units)

Treatment	N	LS Mean	Difference from PBO		
			LS Mean Difference	95% CI	P-value
Study 1044 (primary at Month 6) excluding patient 10421014 from CP 10 mg group					
CP 5 mg	278	0.11	-0.34	(-0.69, 0.01)	0.056
CP 10 mg	287	0.12	-0.33	(-0.68, 0.02)	0.061
PBO	138	0.45			

*Patient 10421014's baseline score is 42.5. At Month 6, her score is 22.5.

In summary, based on the statistical assessment of radiographic data from study 1044, there is lack of consistent findings when different statistical models were applied to the radiographic data. In the primary analysis using parametric model, the difference between tofacitinib 10 mg and placebo was statistically significant for mTSS, while the difference was not statistically significant between 5 mg and placebo, at Month 6. In contrast, when non-parametric model was applied, the difference between tofacitinib 10 mg and placebo was not statistically significant for mTSS score, while the difference was statistically significant between 5 mg and placebo. In addition, based on the responder analysis, 5 mg appears to be numerically better than 10 mg, with lower proportion of patients experienced worsening and higher proportion of patients experienced improvement in the 5 mg group compared to 10 mg group.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Yongman Kim, Ph.D.

Date: January 17, 2014

Concurring Reviewer(s): Joan Buenconsejo, Ph.D.

Statistical Team Leader: Joan Buenconsejo, Ph.D.

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Joan Buenconsejo, Ph.D.
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Lillian Patrician

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

/s/

YONGMAN KIM
01/17/2014

JOAN K BUENCONSEJO
01/17/2014
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s04

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title[1]	**XELJANZ (tofacitinib) tablets, for oral use**
Applicant	PF Prism C.V.
Application/Supplement Number	NDA 203214/S-004
Type of Application	Efficacy supplement
Indication(s)	Treatment of rheumatoid arthritis
Office/Division	ODEII/DPARP
Division Project Manager	Philantha Bowen
Date FDA Received Application	April 22, 2013
Goal Date	February 22, 2014
Date PI Received by SEALD	February 11, 2014
SEALD Review Date	February 12, 2014
SEALD Labeling Reviewer	Debra Beitzell
Acting SEALD Division Director	Sandra Kweder

1 Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word "must" denotes that the item is a regulatory requirement, while the word "should" denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item **(deficiency)**.
- **YES:** The PI meets the requirement for this item **(not a deficiency)**.
- **N/A**: This item does not apply to the specific PI under review (**not applicable**).

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *HL is one-half page without the BW.*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *Remove white space in between product title and Initial U.S. Approval date.*

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Under D&A heading, second bulleted item, insert cross reference to subsection 2.4 (i.e., "(2.4, 8.6, 8.7)").*

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

YES 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

YES 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
1.1 [text]
1.2 [text]
2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]
6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]
7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 [text]
14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

DEBRA C BEITZELL
02/12/2014

ERIC R BRODSKY
02/12/2014
I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 203214/S-002 and 203214/S-004

Application Type: Efficacy Supplement

Name of Drug: Xeljanz (tofacitinib) Tablets

Applicant: Pfizer

Submission Date: January 18, 2013; April 22, 2013

Receipt Date: January 18, 2013; April 22, 2013

1.0 Regulatory History and Applicant's Main Proposals

Pfizer submitted efficacy supplements dated January 18 and April 22, 2013, (labeling supplements with clinical data) which propose changes to the CLINICAL STUDIES – *Physical Function Response* and the CLINICAL STUDIES – *Radiographic Response* section of the package insert, respectively.

The purpose of supplement 002 is to update the language in the package insert regarding the improvement in functional health status. Supplement 004 is intended to provide language in label pertaining to the inhibition of progression of structural damage.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 3, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment: *Space is needed before each of the headings.*

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Reference is needed for the DOSAGE AND ADMINISTRATION*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

NO 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment: *Statement is not centered*

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

NO 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *Title is absent.*

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

PHILANTHA M BOWEN
05/22/2013

LADAN JAFARI
05/22/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s04

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Debarment Certification

DEBARMENT CERTIFICATION

[FD&C Act 306(k)(l)]

Pfizer hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Nickie Kilgore

Signature of Company Representative

19 April 2013

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203214 BLA #	NDA Supplement # 004 BLA Supplement #	If NDA, Efficacy Supplement Type: SE-8
Proprietary Name: Xeljanz Established/Proper Name: tofacitinib Dosage Form: Tablets, 5 mg		Applicant: P.F. Prism CV Agent for Applicant (if applicable):
RPM: Philantha Bowen		Division: DPARP

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is *February 21, 2014*	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 10/30/2013

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	February 21, 2014
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP: February 21, 2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	2/17/14
• Original applicant-proposed labeling	4/22/13
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None – *previously approved, no changes*
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	N/A – *previously approved, no changes*
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	*N/A – Trade Name established and approved previously*
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM *5/22/13* ☐ DMEPA ☐ DMPP/PLT (DRISK) ☒ OPDP (DDMAC) *2/14/14* ☒ SEALD *2/12/14* ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	N/A (SE-8)
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: ***Application does not trigger PREA.*** • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☐ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	5/7/13, 2/5/14; 2/14/14
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☐ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg February 19, 2013
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 2/20/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 1/31/14
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	1/15/14
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	2/9/14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None *See concurrence on primary review*
Statistical Review(s) *(indicate date for each review)*	☐ None 1/17/14
Clinical Pharmacology ☒ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☒ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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

/s/

PHILANTHA M BOWEN
02/21/2014

EXCLUSIVITY SUMMARY

NDA # **203214** SUPPL # **004** HFD # **570**

Trade Name: Xeljanz

Generic Name: Tofacitinib

Applicant Name: P.F. Prism C.V.

Approval Date, If Known: February 21, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

This supplement proposed to include language to the package insert regarding the inhibition of progression of structural damage.

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# **203214**

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study #1: A3921069

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐
Investigation #3	YES ☐	NO ☐
Investigation #4	YES ☐	NO ☐
Investigation #5	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐
Investigation #3	YES ☐	NO ☐

Investigation #4 YES ☐ NO ☐
Investigation #5 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
Investigation #2
Investigation #3
Investigation #4
Investigation #5

IND # ***70903*** YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES ☐ ! NO ☐

Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: *Philantha Bowen, MPH*
Title: *Sr. Regulatory Project Manager, DPARP*
Date: *February 21, 2014*

Name of Office/Division Director signing form: *Badrul A. Chowdhury, M.D., Ph.D.*
Title: *Division Director, DPARP*

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

PHILANTHA M BOWEN
02/21/2014

SARAH K YIM
02/21/2014
Signing for Badrul Chowdhury, M.D., Ph.D.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 14, 2014

To: Philantha Bowen, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Adewale Adeleye, Pharm. D., MBA, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm. D., Team Leader, OPDP

Subject: NDA# 203214/S-004 - XELJANZ® (tofacitinib) tablets for oral administration (Xeljanz)

Reference is made to DPARP's consult request dated January 17, 2014, requesting review of the proposed Package Insert (PI) for Xeljanz. The PI has been updated to include language regarding the inhibition of progression of structural damage.

OPDP has reviewed the proposed PI entitled, "sNDA 203214(S-004) – FDA Label (clean)/ (2-4-14).doc" that was sent via e-mail from DPARP to OPDP on February 4, 2014. OPDP has no comments on the proposed PI at this time.

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

Following this page 35 pages have been withheld in full due to draft labeling (b) (4)

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/s/

ADEWALE A ADELEYE
02/14/2014

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: February 14, 2014

To: Nickie Kilgore, DVM
Director, Worldwide Regulatory Strategy

Company: PF PRISM C.V.

Fax: 860-686-7545

Phone: 860-441-5030

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: **NDA 203214/S-004** (Xeljanz) – Request #2 for Labeling Revisions

# of Pages including cover: 40

Thank you.

NDA 203214/S-004
Tofacitinib Tablets
PF Prism C.V.

Dear Dr. Kilgore:

Your labeling submission dated February 10, 2014, to sNDA 203214/S-004 is currently under review. The enclosed label contains FDA comments that clarify the rationale for the revision requests in the package insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these comments are not all-inclusive and we may have additional recommendations as we continue our review of the label.

Submit a clean copy and a tracked-change version of the label incorporating the recommendations in the attached package insert by Tuesday, February 18, 2014, at 12 NN EST to the NDA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

_____

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert

Following this page 37 pages have been withheld in full due to draft labeling (b) (4)

NDA 203214/S-004
Tofacitinib Tablets
PF Prism C.V.

Drafted: Bowen/2-14-14

Clearance: Jafari/2-14-14

Finalized: Bowen/2-14-14

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/s/

PHILANTHA M BOWEN
02/14/2014

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: February 5, 2014

To: Nickie Kilgore, DVM
Director, Worldwide Regulatory Strategy

Company: PF PRISM C.V.

Fax: 860-686-7545

Phone: 860-441-5030

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: **NDA 203214/S-004** (Xeljanz) – Request for Labeling Revisions

# of Pages including cover: 42

Thank you.

NDA 203214/S-004
Tofacitinib Tablets
PF Prism C.V.

Dear Dr. Kilgore:

Your labeling submission dated November 21, 2013, to sNDA 203214/S-004 is currently under review. The enclosed label contains FDA comments that clarify the rationale for the changes made in the package insert, as well as revision requests. The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these comments are not all-inclusive and we may have additional recommendations as we continue our review of the label.

Submit a clean copy and a tracked-change version of the label incorporating the recommendations in the attached package insert by Monday, February 10, 2014, to the NDA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

_____

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert

NDA 203214/S-004
Tofacitinib Tablets
PF Prism C.V.

Drafted: Bowen/2-4-14

Clearance: Jafari/2-4-14
Yim/2-4-14
Davi/2-4-14
Nikolay/2-4-14
Kim/2-3-14

Finalized: Bowen/2-4-14

Following this page 38 pages have been withheld in full due to draft labeling (b) (4)

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/s/

PHILANTHA M BOWEN
02/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Philantha Bowen, RPM DPARP 301-796-2466

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
January 17, 2014		**203214/S-004**	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Xeljanz (tofacitinib)			February 3, 2014

NAME OF FIRM:	
PF Prism C.V.	PDUFA Date: February 21, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission: Labeling submission dated November 21, 2013

EDR Location: \\CDSESUB1\evsprod\NDA203214\203214.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS: This efficacy supplement is a labeling supplement with clinical data. The PI has been updated to include language regarding the inhibition of progression of structural damage. We are requesting review of the package insert for any recommendations/comments you may have regarding this proposed change. There were no changes to the MG. No carton/container labeling was submitted.

PDUFA Date: February 21, 2014

SIGNATURE OF REQUESTER
See appended electronic signature

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check all that apply) ☐ eMAIL ☑ DARRTS ☐ HAND

06/18/2013

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/s/

PHILANTHA M BOWEN
01/17/2014

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: May 23, 2013

To: Nickie Kilgore, DVM
Director, Worldwide Regulatory Strategy

Company: Pfizer, Inc.

Fax: 860-686-7545

Phone: 860-441-5030

From: Philantha Bowen, MPH, RN
Senior Program Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: sNDA 203214/S-002 and 203214/S-004 – Format Labeling Request

# of Pages including cover: 3

Thank you.

NDA 203214/S-002
NDA 203214/S-004
Tofacitinib Tablets
Pfizer

Dear Dr. Kilgore:

Your submissions dated January 18 and April 22, 2013, to NDA 202314/S-002 and NDA 203214/S-004, respectively are currently under review. During our preliminary review of your submitted labeling, we have identified the following labeling format issues which pertain to the HIGHLIGHTS (HL) Section of the package insert:

1. White space must be present before each major heading in HL.

   Comment: *Space is needed before each of the headings.*

2. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

   Comment: *A reference is needed for the DOSAGE AND ADMINISTRATION*

3. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

   Comment: *This statement is not centered.*

4. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

   Comment: *The Boxed Warning title is absent in the TOC.*

We request that you resubmit labeling that addresses these issues by June 3, 2013 The resubmitted labeling will be used for further labeling discussions.

Submit a clean copy and a tracked-change version of the label to both sNDA applications.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

_____

Philantha Montgomery Bowen
Sr. Program Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

NDA 203214/S-002
NDA 203214/S-004
Tofacitinib Tablets
Pfizer

Drafted: Bowen/5-22-13
Clearance: Jafari/5-22-13
Finalized: Bowen/5-23-13

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/s/

PHILANTHA M BOWEN
05/23/2013

Food and Drug Administration
Center for Drug Evaluation and Research
ODE II / DPARP / HFD-570
10903 New Hampshire Ave.
Silver Spring, MD 20993

Memo to File

Filing/Planning Meeting

NDA: 203,214

Supplement: 0004

Reviewer: Nikolay P. Nikolov, M.D., CDER/OND/DPARP

Received: April 22, 2013

Reviewed: May 20, 2013

Product: Tofacitinib (CP-690,550), a selective inhibitor of Janus kinase (JAK) family of kinases

Proposed use: Treatment of rheumatoid arthritis (RA)

Sponsor: Pfizer

Submission: Efficacy Supplement to the NDA to Support an Inhibition of Radiographic Progression Claim (clinical data from study A3921069)

Summary: Pfizer has submitted a one-year efficacy and safety data from study A3921069 (A Phase 3 Randomized, Double-Blind Study of the Efficacy and Safety of 2 Doses of CP-690,550 Compared to Methotrexate in Methotrexate-Naïve Patients With Rheumatoid Arthritis) including the co-primary endpoint measuring effects of XELJANZ 5 and 10 mg BID on structural preservation. While the study has collected ACR70 response rates at Week 24 as the other co-primary endpoint and multiple other secondary endpoints, the sponsor has proposed to only include the efficacy data on the radiographic endpoints in the product labeling. As requested by the Division, the proposed labeling also includes structure data from study A3921044. The results of study A3921069 appear consistent with the overall efficacy of tofacitinib in RA and provides evidence of the benefit on the radiographic progression for both tested doses, 5 mg BID and 10 mg BID as monotherapy over methotrexate alone. The adequacy of the efficacy assessments will be subject to review. The safety information from study A3921069 is also consistent with the previously identified safety profile of tofacitinib in this patient population. As requested at the pre-sNDA meeting on February 19, 2013, the sponsor has also provided updated safety information from the global RA development program with a clinical data cut-off date of April 19, 2012 which appears to be consistent with the safety in the original application. The sponsor has also provided as requested new safety analyses of patients being exposed continuously on either 5 mg or 10 mg BID dose. These analyses suggest a consistent dose-dependent (5 mg vs. 10 mg BID) numerical increase in the exposure-adjusted estimated incidence of major events of interest.

Details on the regulatory history, clinical development, study design and efficacy and safety results are summarized in the attached Filing/Planning meeting presentation.

Action Taken: The application is fileable as a standard review.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Received: April 22, 2013
PDUFA Goal: February 21, 2014

sNDA 203,214/0004
Tofacitinib for Treatment of RA Radiographic Claim

MO: Nikolay P. Nikolov, M.D.
Filing/Planning Meeting
May 20, 2013

1

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Executive Summary

- Product: tofacitinib (JAK3 inhibitor)
- Dosing: 5 mg BID, oral tablets
- Population: Adults with mod-to-severe active RA
- Approved on 11.06.2012 for:
  - Improvement of signs and symptoms of RA
  - Improvement in physical function
- New efficacy claim (same indication):
  - Inhibition of Radiographic Progression
- Updated safety

2

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Regulatory History

- October 13, 2004: IND 70,903 submitted
- December 16, 2008: EOP2 Meeting:
  - Single radiographic study would be sufficient
- February 16, 2011: Pre-NDA Meeting
- May 09, 2012: Advisory Committee:
  - No substantial evidence of radiographic benefit (Study 1044)
- August 2012: New safety analyses as a major amendment with extended review clock
- November 6, 2012: Approval of 5 mg BID:
  - Improvement of signs and symptoms of RA
  - Improvement in physical function

3

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Confirmatory Studies

Protocol	Design	N	Treatment Arms	Primary EP	Timepoint
Patients with TNF-Incomplete Response (IR)					
1032	R, DB, PC 6 months *Background MTX*	399	CP 5 mg BID CP 10 mg BID PBO	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
Patients with DMARD (MTX)-IR					
1044	R, DB, PC 2 years* *Background MTX*	797	CP 5 mg BID CP 10 mg BID PBO	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6
1046	R, DB, PC 1 year *Background DMARD*	792	CP 5 mg BID CP 10 mg BID PBO	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
1064	R, DB, AC 1 year *Background MTX*	717	CP 5 mg BID CP 10 mg BID PBO Adalimumab	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
1045	R, DB, PC 6 months *Monotherapy*	610	CP 5 mg BID CP 10 mg BID PBO	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3

EP = endpoint

4

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Summary of Efficacy: Original NDA

- Confirmatory studies provided consistent evidence of a treatment benefit with tofacitinib 5 mg and 10 mg BID for
  - ***Signs and symptoms*** of RA, based on:
    - ACR20, 50, and 70 response rates and
    - Proportion of patients achieving DAS28-4(ESR)<2.6
  - ***Physical function***, based on change from baseline in HAQ-DI scores
- ***Structural damage progression:*** Uncertainties about the treatment effect of tofacitinib due to:
  - Low degree of progression in placebo control
  - Different results are driven by outliers
  - Differences depending on the analysis used
  - Data not consistent with respect to dose
  - No corroboration from another study

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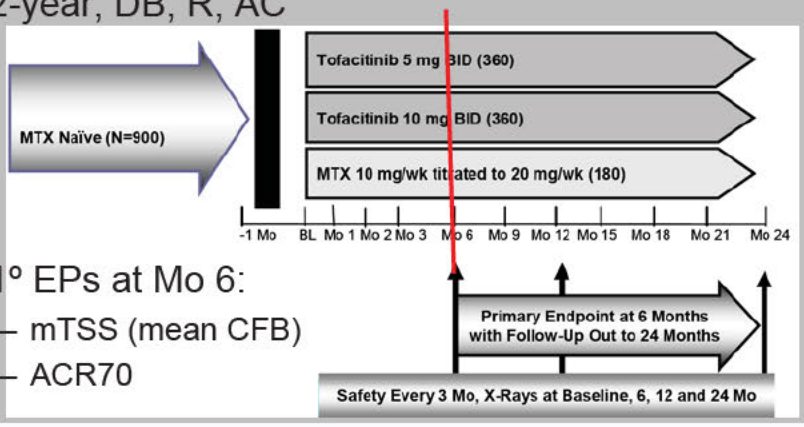
Study 1069: Design

- Monotherapy in 952 MTX-naïve RA patients
- 2-year, DB, R, AC



- 1º EPs at Mo 6:
  - mTSS (mean CFB)
  - ACR70

6

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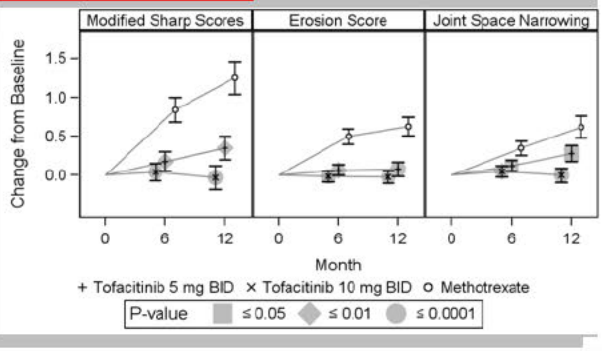
Study 1069: Efficacy, mTSS

Treatment	N	LS Mean	Differences From MTX			
			LS Mean Difference	95% CI for Difference		p-value
				Lower	Upper	
Tofacitinib 5 mg BID	346	0.18	-0.66	-1.03	-0.28	0.0006
Tofacitinib 10 mg BID	369	0.04	-0.81	-1.18	-0.44	<0.0001
Methotrexate	166	0.84				

- Superiority to MTX at all time points
- 10 mg BID numerically better than 5 mg BID



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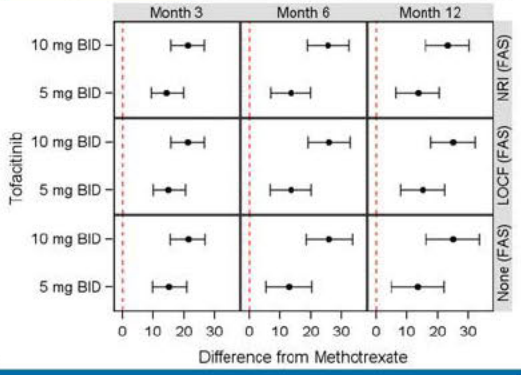
Study 1069: Efficacy, ACR70

Treatment	N	n	%	Difference From MTX			
				Difference of %	95% CI for Difference		p-value
					Lower	Upper	
Tofacitinib 5 mg BID	369	94	25.47	13.51	7.05	19.97	<0.0001
Tofacitinib 10 mg BID	393	148	37.66	25.70	18.99	32.40	<0.0001
Methotrexate	184	22	11.96				

- ACR70:
  - Superiority to MTX at all time points
  - 10 mg BID numerically better than 5 mg BID
- Consistent 2º EPs:
  - ACR20, ACR50,
  - HAQ-DI



8

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Study 1069: Safety

- Similar rates of AEs, SAEs, Sever AEs, DAEs
- Safety profile consistent with original NDA:
  - Infections, SIE, Opportunistic, TB
  - Malignancies, 1 lymphoma
  - Laboratory, most dose-dependent:
    - Neutropenia
    - Lymphopenia
    - Dyslipidemia
    - ↑Serum creatinine
    - Liver abnormalities (more in MTX group), No Hy's law cases
    - ↑Serum CK
  - Hypertension AEs higher in tofacitinib groups

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Safety Update

- P2P3LTE as of April 19, 2012:
  - Consistent safety with original NDA
- Overall exposure:

Data Cut	29 March 2011*	29 September 2011†	19 April 2012‡
Number of Patients	4789§	4791§	4789
Exposure (pt-yr)	5651	6922	8460
Duration of Exposure	**Number of Patients**	**Number of Patients**	**Number of Patients**
> 12 Months	2649	3126	3567
> 24 Months	709	941	2002
> 36 Months	ND	567	634

** Data-cut for the original NDA*
† Data-cut for data provided in the 120 Day Safety Update
‡Data cut for data provided in this sNDA

- New cohorts with constant exposure at the dose:
  - P2P3LTE 5 mg BID
  - P2P3LTE 10 mg BID

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Safety Update: 5 vs 10 mg

Parameter	**5 mg BID Cohort** N = 1955 Exposure = 2174 pt-yr Incidence Rate (95% CI) [number of pts with event]	**10 mg BID Cohort** N = 1846 Exposure = 2460 pt-yr Incidence Rate (95% CI) [number of pts with event]
Serious Adverse Events	10.16 (8.87, 11.63) [210]	11.13 (9.86, 12.57) [261]
Adverse Events Resulting in Discontinuation	7.87 (6.77, 9.14) [170]	9.18 (8.05, 10.47) [223]
Mortality (deaths within 30 days of last dose)	0.28 (0.12, 0.61) [6]	0.20 (0.09, 0.49) [5]
Serious Infections	2.73 (2.11, 3.52) [59]	3.56 (2.88, 4.39) [87]
Tuberculosis	0.092 (0.023, 0.37) [2]	0.37 (0.19, 0.70) [9]
Opportunistic Infections*	0.46 (0.25, 0.86) [10]	0.65 (0.40, 1.06) [16]
Herpes Zoster	4.00 (3.23, 4.95) [84]	4.75 (3.95, 5.71) [113]
Malignancies (excl. NMSC)	0.83 (0.52, 1.32) [18]	0.94 (0.62, 1.41) [23]
Lymphoproliferative Disorders/Lymphoma	0.046 (0.006, 0.33) [1]	0.081 (0.020, 0.33) [2]
Composite MACE (adjudicated)†	0.50 (0.22, 1.11) [6]	0.36 (0.18, 0.72) [8]

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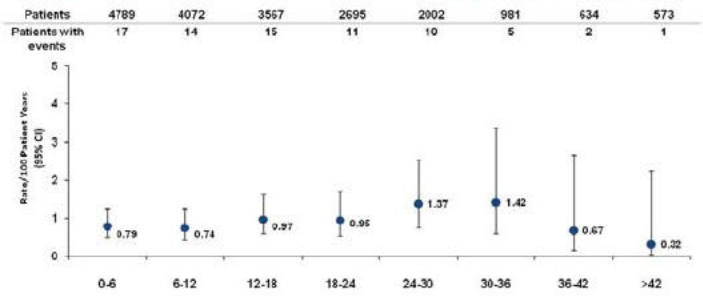
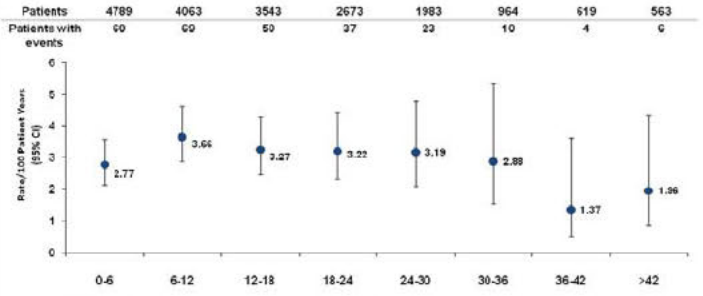
Non-Cumulative Rates Over Time

Malignancy



Serious Infections



Bars indicate 95% Confidence Limits
Incidence rate of patients per 100 pt-yrs
Phase 2, Phase 3 and LTE data as of 19 April 2012

Tofacitinib

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Proposed Labeling, Section 14

(b) (4)

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Proposed Labeling, Section 14

(b) (4)

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Proposed Labeling, Section 14

(b) (4)

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Proposed Labeling, Section 14

(b) (4)

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Proposed Labeling, Section 6.1

Section 6.1, Clinical Trials Experience:

- "Clinical Experience in Methotrexate-Naïve Patients: Study 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 I-V."

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Filing and Planning

- Clinical Filing Checklist:
  - Completed, no omissions
- Advisory Committee:
  - Not recommended
- OSI Audit:
  - Not Recommended

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Conclusions and Mid-Cycle Deliverables

- Application is fileable, as a Standard NDA
- Mid-cycle deliverables: Complete review of:
  1. Efficacy EPs proposed for labeling
  2. Safety:
     - Deaths, SAE, SIE, malignancy, LPD
     - Adverse Events of Interest:
       - Laboratory abnormalities (Lipids, Renal, Hepatic)
       - Cardiovascular AE,
       - Opportunistic infections,
       - Hepatotoxicity

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Other disciplines

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Back up slides

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Safety Update

Parameter	*Tofacitinib 5 mg BID* Incidence Rate (95% CI)			*Tofacitinib 10 mg BID* Incidence Rate (95% CI)		
	29 Mar 2011 *N = 1321 Exposure = 2236*	***29 Sep 2011*** *N = 1370 Exposure = 2726*	***19 Apr 2012*** *N = 1421 Exposure =3243*	***29 Mar 2011*** *N = 1906 Exposure =882*	***29 Sep 2011*** *N = 2145 Exposure = 1684*	***19 Apr 2012*** *N = 2681 Exposure =2791*
SAE	10.28 (9.00, 11.74)	9.65 (8.52, 10.93)	9.80 (8.75, 10.99)	13.96 (11.67, 16.69)	12.32 (10.73, 14.16)	12.60 (11.32, 14.03)
Adverse Events Resulting in Discontinuation	6.66 (5.67, 7.82)	6.39 (5.50, 7.41)	6.55 (5.72, 7.49)	8.54 (6.81, 10.71)	8.67 (7.36, 10.20)	8.15 (7.15, 9.28)
Mortality (up to 30 days of last dose)	0.36 (0.18, 0.72)	0.37 (0.20, 0.68)	0.31 (0.17, 0.57)	0.23 (0.06, 0.91)	0.18 (0.06, 0.55)	0.14 (0.05, 0.38)
Serious Infections	2.25 (1.71, 2.97)	2.33 (1.82, 2.99)	2.62 (2.11, 3.24)	4.89 (3.63, 6.60)	4.06 (3.20, 5.15)	3.60 (2.96, 4.38)
Tuberculosis	0.045 (0.006, 0.32)	0.073 (0.018, 0.29)	0.154 (0.064, 0.37)	0.113 (0.016, 0.81)	0.178 (0.057, 0.55)	0.179 (0.075, 0.43)
Opportunistic Infections*	0.36 (0.18, 0.72)	0.37 (0.20, 0.68)	0.40 (0.23, 0.69)	0.57 (0.24, 1.36)	0.54 (0.28, 1.03)	0.50 (0.30, 0.85)
Herpes Zoster	4.25 (3.46, 5.22)	4.09 (3.38, 4.95)	4.18 (3.51, 4.97)	4.95 (3.67, 6.67)	4.74 (3.79, 5.91)	4.50 (3.77, 5.38)
Malignancies (excluding NMSC)	1.03 (0.68, 1.55)	1.07 (0.74, 1.53)	1.02 (0.72, 1.43)	1.36 (0.77, 2.40)	1.25 (0.81, 1.91)	0.97 (0.66, 1.41)
LPD/ Lymphoma	0.089 (0.022, 0.36)	0.073 (0.018, 0.29)	0.062 (0.015, 0.25)	0	0	0.036 (0.005, 0.25)
Composite MACE	0.17 (0.056, 0.53)	0.18 (0.067, 0.48)	0.29 (0.15, 0.58)	0.23 (0.057, 0.91)	0.30 (0.12, 0.72)	0.29 (0.14, 0.58)

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CLINICAL FILING CHECKLIST FOR NDA Supplement

NDA Number: 203,214/4 **Applicant: Pfizer** **Stamp Date: 04/22/2013**

Drug Name: tofacitinib **NDA Type: Standard** **MO: Nikolay P. Nikolov, M.D.**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD Format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	The efficacy data are derived from a single study
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	X			Previously reviewed under the original NDA
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? • Pivotal Study #1: A3921069 for the Indication of: - Inhibition of Radiographic Progression	X			There was an agreement at the Pre-sNDA meeting for sponsor to cross-reference the previously submitted study report
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the	X			

CLINICAL FILING CHECKLIST FOR NDA Supplement

	Content Parameter	Yes	No	NA	Comment
	Division) for approvability of this product based on proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			The study was global and included 20% US patients
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			The NDA format and content were discussed at Pre-sNDA meeting, February 19, 2013
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	Reviewed with the original NDA
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Reviewed with the original NDA

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA Supplement

	Content Parameter	Yes	No	NA	Comment
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Nikolay P. Nikolov, M.D.	May 20, 2013
Reviewing Medical Officer	Date
Sarah Yim, M.D.	May 20, 2013
Clinical Team Leader	Date

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

/s/

NIKOLAY P NIKOLOV
05/21/2013

SARAH K YIM
05/21/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203214/S-004

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Nickie V. Kilgore, D.V.M.
Director
Worldwide Regulatory Strategy

Dear Dr. Kilgore:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 203214

SUPPLEMENT NUMBER: 004

PRODUCT NAME: XELJANZ (Tofacitinib) Tablets, 5 mg

DATE OF SUBMISSION: April 22, 2013

DATE OF RECEIPT: April 22, 2013

This supplemental application provides for revisions to the CLINICAL STUDIES – *Radiographic Response* section of the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 21, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Philantha M. Bowen, M.P.H., RN
Senior Program Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

PHILANTHA M BOWEN
05/07/2013