CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-3214/S002

Trade Name: XELJANZ®

Generic Name: tofactinib

Sponsor: PF PRISM C.V. c/o Pfizer, Inc.

Approval Date: 11/18/2013

Indication: 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).

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203214/S-002

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 January 18, 2013, received January 18, 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 February 6, May 2, 21, 28, and 30, June 21, October 28, and November 12, 2013.

This Prior Approval supplemental new drug application provides the inclusion of language in the package insert regarding the improvement in general health status, assessed by the Short Form health survey (SF-36).

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.

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, Senior Regulatory Project Management Officer at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
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/

BADRUL A CHOWDHURY
11/18/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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)**

----------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)
- XELJANZ should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine. (1.1)

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

Rheumatoid Arthritis

The recommended dose of XELJANZ is 5 mg twice daily. (2.1)

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

- Tablets: 5 mg (3)

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

None (4)

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

- Serious Infections – Do not administer XELJANZ during an active infection, including localized infections. If a serious infection develops, interrupt XELJANZ until the infection is controlled. (5.1)
- Lymphomas and other malignancies have been reported in patients treated with XELJANZ. (5.2)
- 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 should not be given concurrently with XELJANZ. (5. 5)
- Severe hepatic impairment–Not recommended (5.6)

----------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. (2.1, 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. (2.1, 7.2)
- Potent CYP inducers (e.g., rifampin): May result in loss of or reduced clinical response. (2.2, 7.3)

----------USE IN SPECIFIC POPULATIONS----------

Moderate and severe renal impairment and moderate hepatic impairment: Reduce dose to 5 mg once daily. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS
Patients treated with XELJANZ 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).
- XELJANZ should not be used in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine.

2 DOSAGE AND ADMINISTRATION

XELJANZ is given orally with or without food.

2.1 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.

- Dose interruption is recommended for management of lymphopenia, neutropenia and anemia *[see Dosage and Administration (2.3), Warnings and Precautions (5.4), and Adverse Reactions (6.1)]*.
- XELJANZ dosage should be reduced to 5 mg once daily in patients:
  - with moderate or severe renal insufficiency
  - with moderate hepatic impairment
  - 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).

2.2 General Considerations for Administration

- XELJANZ should not be used in patients with severe hepatic impairment.
- It is recommended that XELJANZ not be initiated in patients with a 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.
- Coadministration of XELJANZ with potent inducers of CYP3A4 (e.g., rifampin) may result in loss of or reduced clinical response to XELJANZ.

2.3 Dosage Modifications

XELJANZ treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

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, cryptococcus, 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).

XELJANZ should not be initiated in patients with an active 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 Disorder
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 Parameters

Lymphocytes
Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean 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 (2.3)*.

Neutrophils
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 (2.3)*.

Hemoglobin
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 (2.3)*.

Liver Enzymes
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.

Lipids
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. Live vaccines should not be given concurrently with XELJANZ.

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

5.6 Hepatic Impairment
Treatment with XELJANZ is not recommended in patients with severe hepatic impairment *[see Adverse Reactions (6.1) and Use in Specific Populations (8.6)]*.

6 ADVERSE REACTIONS
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.

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.

6.1 Clinical Trial Experience
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 Tests

Lymphocytes
In the controlled clinical trials, confirmed decreases in 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)]*.

Neutrophils
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 Tests
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.

Lipids
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
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			

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

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 (2.1) 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 (2.1) 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 (2.1) 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 immunosuppressives has not been studied in rheumatoid arthritis.

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
No dose adjustment is required in patients with mild hepatic impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment. The safety and efficacy of XELJANZ have not been studied in patients with severe hepatic impairment or in patients with positive hepatitis B virus or hepatitis C virus serology *[see Dosage and Administration (2.1) and Warnings and Precautions (5.6)]*.

8.7 Renal Impairment
No dose adjustment is required in patients with mild renal impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with moderate and severe renal impairment *[see Dosage and Administration (2.1)]*. 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.

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.

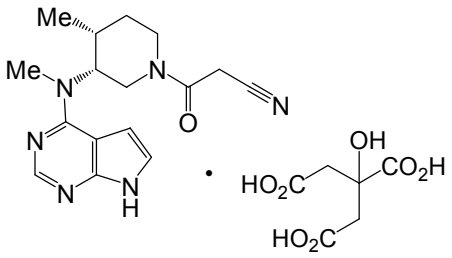
There is no specific antidote for overdose with XELJANZ. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

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) .
It is freely soluble in water.

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.

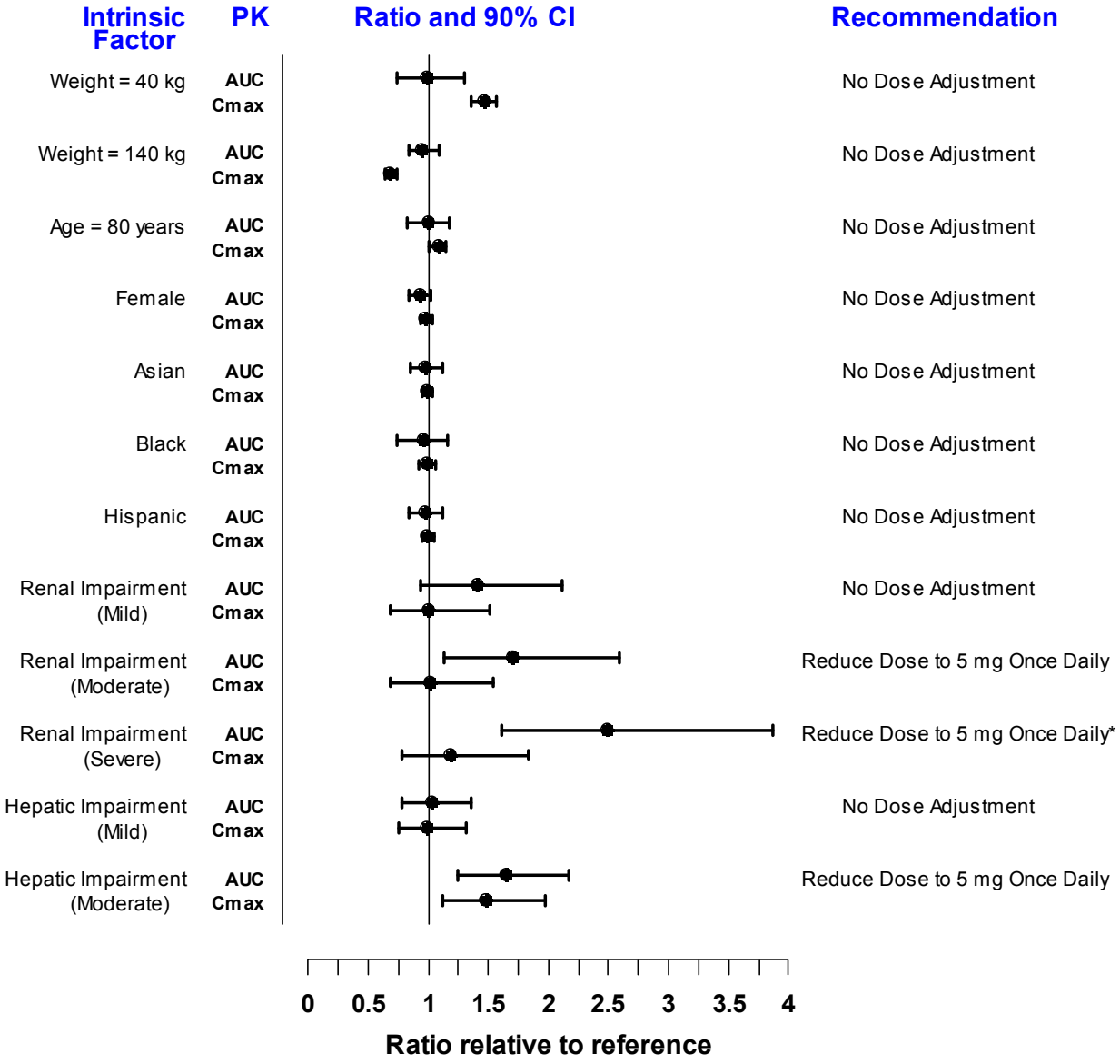
Pharmacokinetics in Rheumatoid Arthritis Patients

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

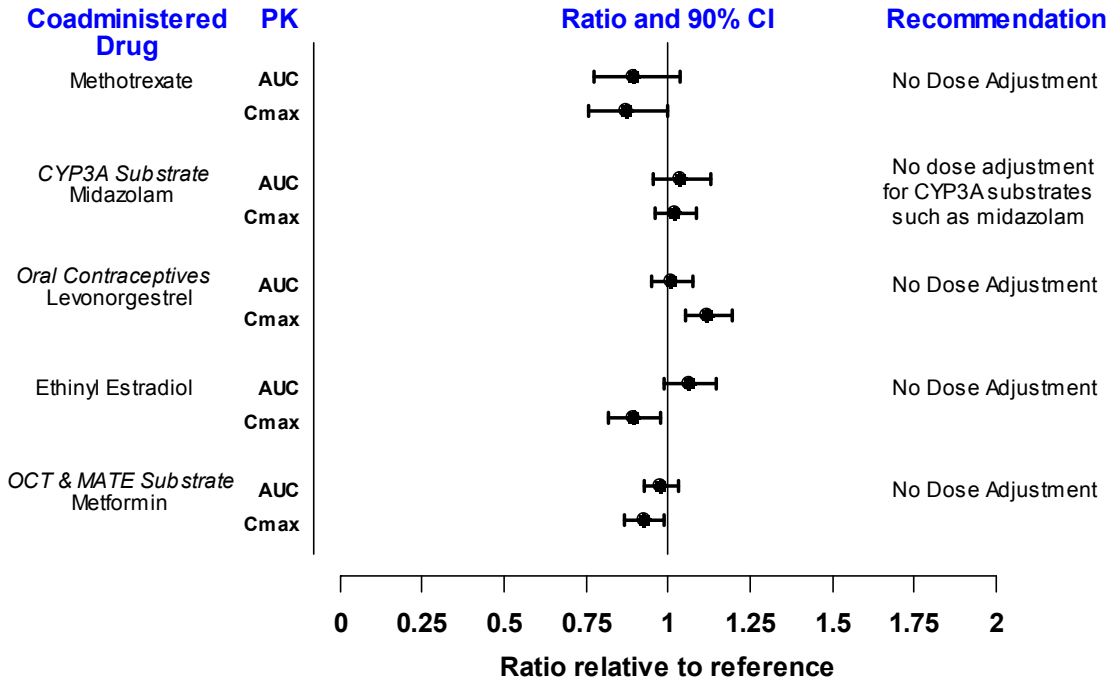
major human drug-metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations exceeding 185 times the steady state C_{max} of a 5 mg twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the PK of midazolam, 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

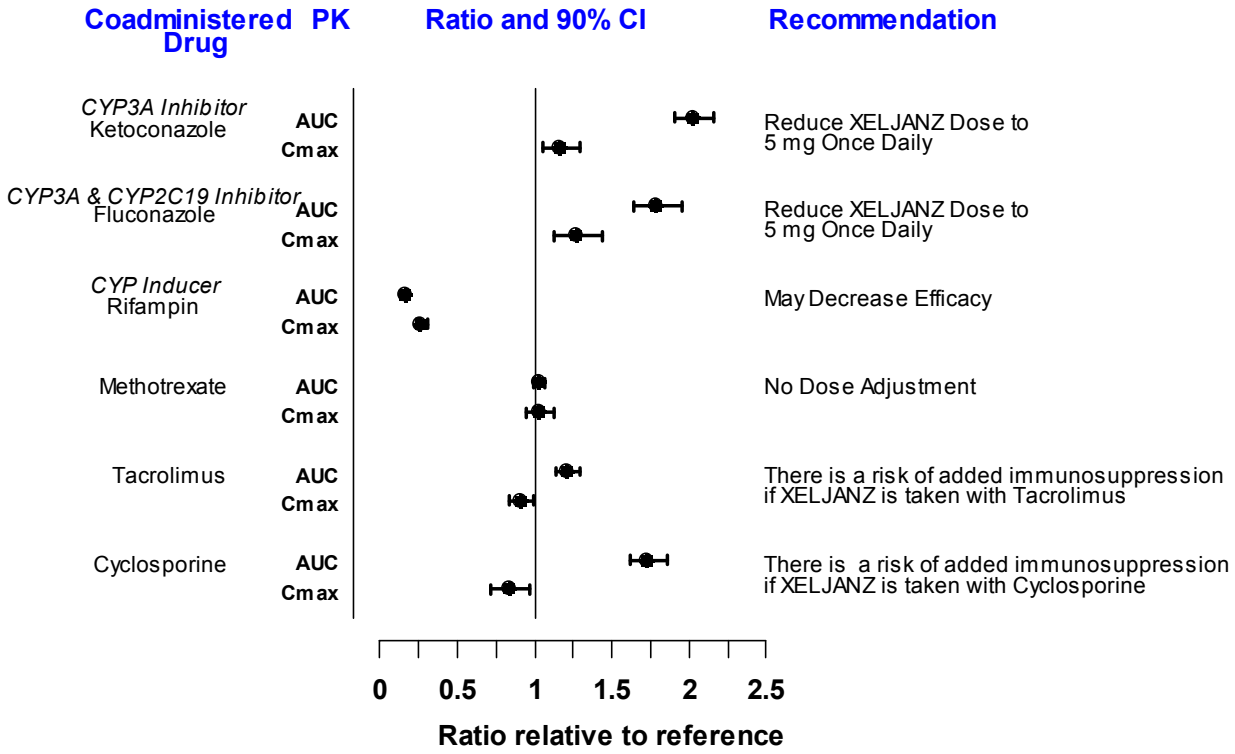


Note: Reference group is administration of concomitant medication alone; OCT = Organic Cationic Transporter; MATE = Multidrug and Toxic Compound Extrusion

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.

DOSE-RANGING TRIALS

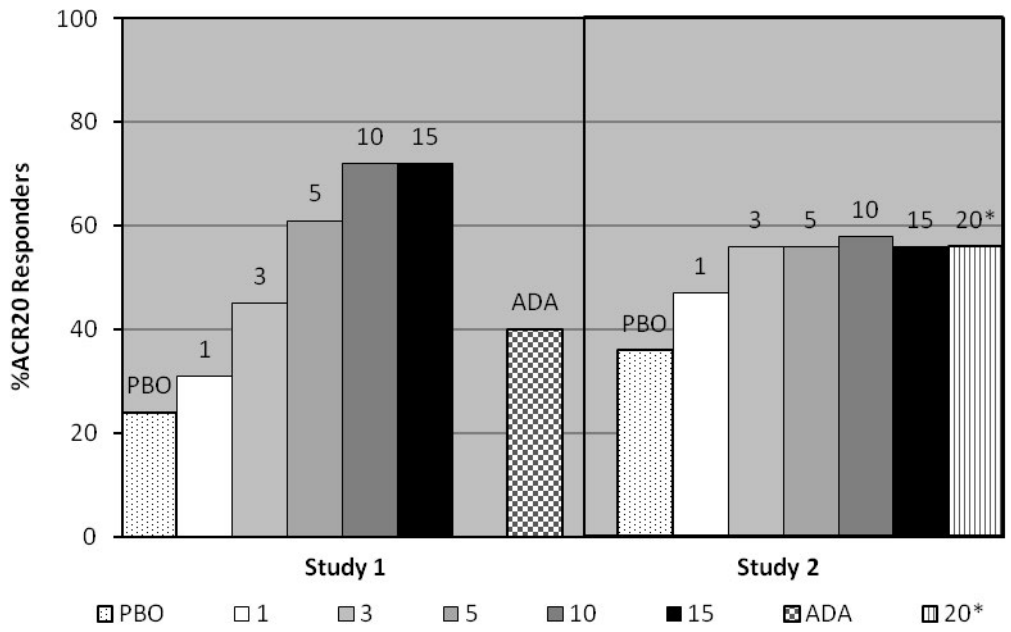
Dose selection for XELJANZ was based on two pivotal dose-ranging trials.

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.

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 all trials, 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	PBO + MTX	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX	PBO + MTX	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX
	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.

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 results of the components of the ACR response criteria for Study IV are shown in Table 7. Similar results were observed in Studies I, II, III, and V.

Table 7: Components of ACR Response at 3 Months

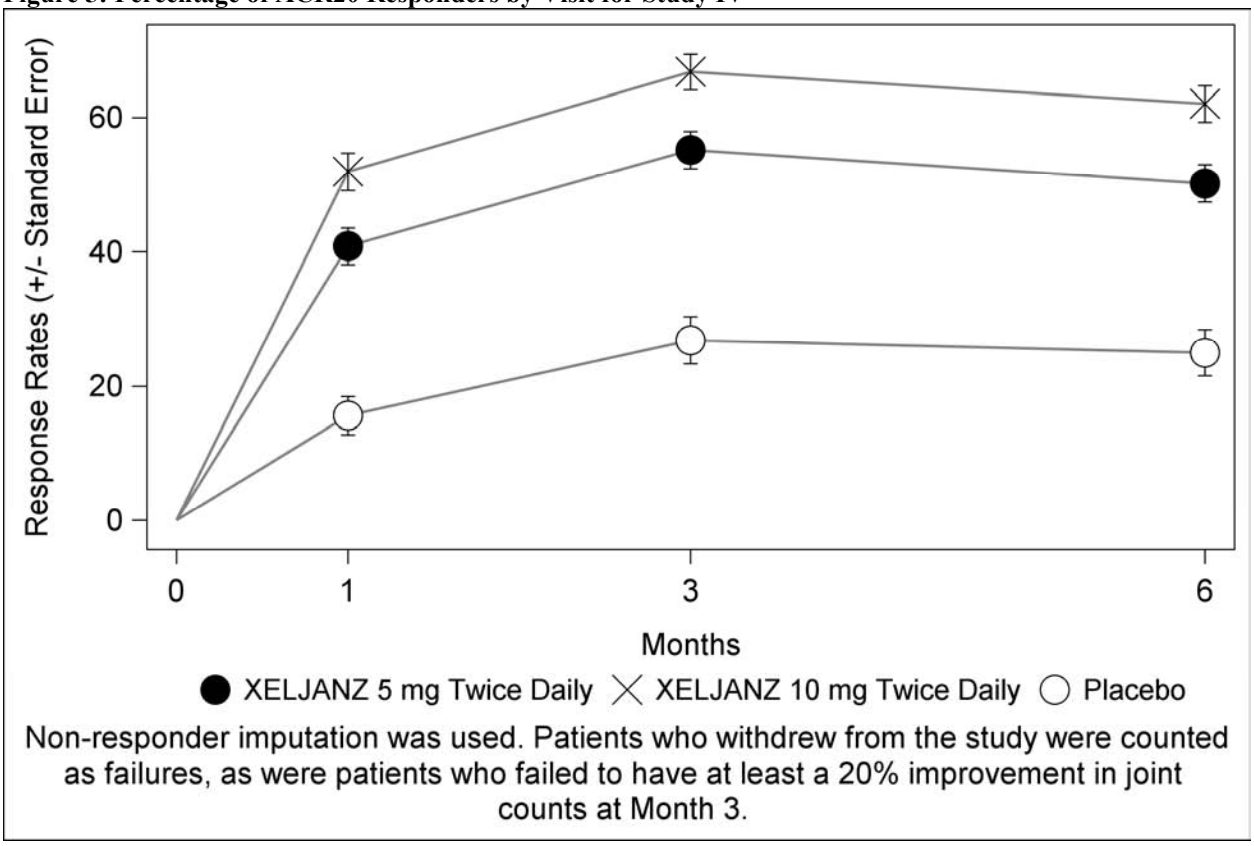
	Study IV					
	XELJANZ 5 mg Twice Daily + MTX N=321		**XELJANZ 10 mg Twice Daily + MTX N=316**		**Placebo + MTX N=160**	
Component (mean) [a]	Baseline	Month 3[a]	Baseline	Month 3[a]	Baseline	Month 3[a]
Number of tender joints (0-68)	24 (14)	13 (14)	23 (15)	10 (12)	23 (13)	18 (14)
Number of swollen joints (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.

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

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



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).

Inform patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking XELJANZ. Instruct patients to take XELJANZ only as prescribed.

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

LAB-0445-3.0

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:

NDA 20-3214/S002

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	November 18, 2013
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	203214, Supplement 002
Applicant Name:	Pfizer Labs (ownership transferred to PF Prism CV)
Date of Submission:	January 18, 2013
PDUFA Goal Date:	November 18, 2013
Proprietary Name:	Xeljanz
Established Name:	Tofacitinib
Dosage form:	Tablets
Strength:	5 mg
Proposed Indications:	Inclusion of SF-36 improvement data in the Clinical Studies section of the product labeling. Tofacitinib is approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response (b) (4) be used as monotherapy or in combination with methotrexate or other non-biologic DMARDs.
Action:	Approval

1. Introduction

Pfizer submitted this NDA supplement (b) (4) for inclusion of SF-36 findings in the Clinical Studies section of the product label for tofacitinib based on data submitted (b) (4). The original NDA was approved in November 2012, (b) (4). This summary review will provide an overview of the application, and reasoning and rationale for inclusion of SF-36 results in the Clinical Studies section of the product label. On July 11, 2013, Pfizer submitted a letter informing the Agency that the responsibility of tofacitinib NDA has been transferred to a new sponsor called PR Prism CV.

2. Background

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 and slow disease progression or produce a disease-modifying effect on joint damage. Approved DMARDs and some of their features are listed in Table 1 and Table 2. Methotrexate is

Reference ID: 3414515

the most commonly used DMARD because of its proven efficacy and well-understood long-term effects. Tumor necrosis factor (TNF)-blockers are commonly used DMARDs because of their proven efficacy and safety profile and relatively long-term use experience (Table 2). Treatment of RA is typically initiated with NSAIDs or low-dose corticosteroids, with introduction of non-biologic DMARDs early in the course of the disease to prevent joint damage and bony erosions. Methotrexate is often the initial DMARD used as a single agent in patients with low disease activity or without features of poor prognosis, and then combined with other DMARDs, commonly biologics such as TNF blockers, in patients with high disease activity or with features of poor prognosis.[1]

Table 1. Non-biologic 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 large molecule 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-α 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-α inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Anakinra (KINERET) [Amgen] {2001}	Prefilled syringe 100 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 Prefilled syringe 20 mg/0.4 mL Humira Pen 40 mg/0.8 mL *SC injection*	Human IgG1 k mAb *TNF-α 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	Clinical response Major clinical response

[1] Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, 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 and Res 2012; 64:625-39.

Product Name (Trade Name) [Sponsor] {year} *	**Presentation and *ROA*** †	**Description and *MOA*** ‡	**Claims for adult RA** §
		T cell activation inhibitor through B7-1 and B7-2	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-α inhibitor*	Clinical response Physical function response
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder 200 mg/vial Prefilled syringe 200 mg/mL *SC injection*	Humanized Fab fragment *TNF-α 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 Major 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 assessed by ACR 20, 50, and 70 response over at least 3-6 month; Major clinical response defined as achieving ACR 70 response continuously over 6-month period; Physical function response (or improving physical function) assessed by health assessment questionnaire (HAQ) over at least 6-month period; Radiographic response (or inhibiting 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 6 or 12 months

Efficacy finding descriptions in RA product labeling:

For marketing approval of product for the treatment of RA, sponsors are required to demonstrate evidence of efficacy in two key RA domains – "clinical response" by American College of Rheumatology (ACR) criteria using ACR-20 threshold,[2] and "physical function response" by Health Assessment Questionnaire-Disability Index (HAQ-DI).[3] Demonstration of efficacy in other domains that are important to patients health are often assessed, and these include prevention of structural damage progression, clinical remission, and other aspects of RA. The Clinical Studies section of product label describes the efficacy findings from the key RA domains, and some other secondary and other efficacy findings. The Agency's prior precedence for inclusion or exclusion of some secondary and other efficacy findings for some products approved for RA is shown in Appendix 1.

The SF-36 information in the RA product labeling has not been consistent. The SF-36 results were described in some older product labeling, but not in recent product labeling

[2] ACR 20 response is calculated as at least 20% reduction in tender joint count of 68 joints, and at least 20% reduction in swollen joint count of 66 joints, and at least a 20% reduction in at least 3 of the following 5 measures: patient global assessment of arthritis on a visual analog scale, physician global assessment of arthritis on a visual analog scale, patient assessment of pain on a visual analog scale, patient assessment of physical functioning (e.g., health assessment questionnaire), and acute phase reactant (ESR or CRP).

[3] HAQ-DI assesses a patient's level of functional ability and includes questions regarding fine movements of the upper extremities, locomotor activities of the lower extremities, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning intended to represent a comprehensive set of functional activities, including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients are asked to grade their status on a scale from 0 (no difficulty) to 3 (unable to do) for each question. The 8 category scores are averaged into an overall HAQ-DI score on a scale from 0 (no disability) to 3 (completely disabled).

(Appendix 1). In the following section the SF-36 instrument is briefly described, followed by the background that resulted in the inconsistency in describing SF-36 findings in RA product labels.

Short Form (SF-36) instrument:

The SF-36 is a multi-purpose, short-form health survey. It was originally developed in 1980s and 90s to satisfy minimum psychometric standards for group comparisons, and has been used in health planning and policy, and health services evaluation in an era of cost containment, and has subsequently been validated in many diseases, including RA and other rheumatic conditions. The developers of SF-36 states that it is the most widely used health status questionnaire in the world, translated in over 130 languages, and that it has been validated across countries and cultures. The developers of SF-36 also state that it has content, concurrent, criterion, construct, and predictive evidence of validity.[4]

The SF-36 consists of questions grouped into eight domains: four for physical health and four for mental health. The eight domains are reported as two psychometrically-based summary measures: physical component summary (PCS) and mental component summary (MCS). The PCS and MCS are reported based on normative-based scoring. The conceptual model to derive the two summary scores is presented in Figure 1, where the solid lines identify a major positive contribution to the summary score and the dashed lines indicate a negative contribution.

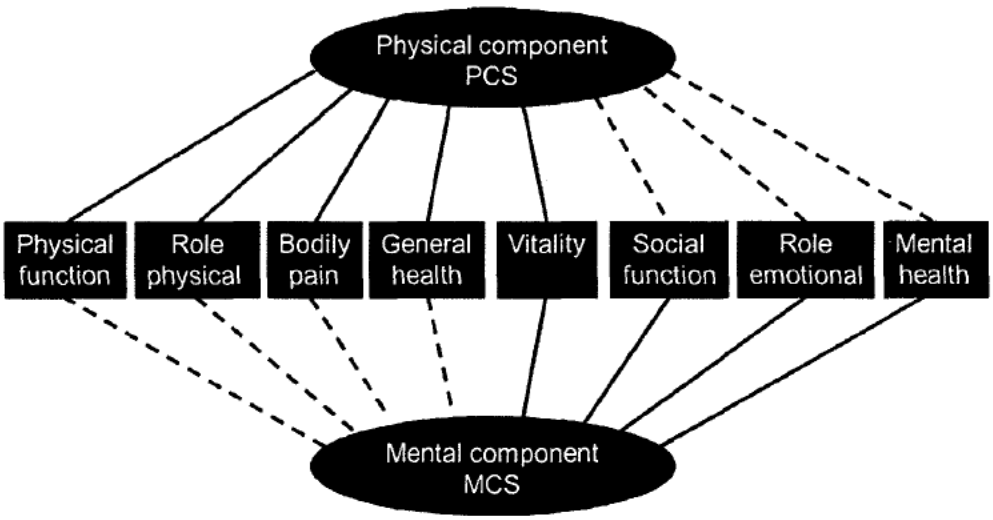


Figure 1. Conceptual model for deriving the PCS and the MCS from individual domains

Status of SF-36 in RA product labeling:

The use of SF-36 in RA drug development and the description of SF-36 findings in the RA product labels have evolved over time. In the past, SF-36, and more specifically the

[4] SF-36 Health Survey Update, John E, Ware; at http://www.sf-36.org/tools/sf36.shtml

Physical Component Summary (PCS), has been used as supportive evidence of efficacy for the "prevention of disability" claim assessed by HAQ-DI. The 1999 RA Guidance, which has been removed and updated with draft RA guidance published in 2013, mentioned use of SF-36 as a support of "prevention of disability" claim assessed by HAQ-DI. The intent at that time was to obtain data from long-term trials, such as 2 or 5 years, in RA. With approval of effective products for RA, it is no longer ethical to conduct long-term trials to assess "prevention of disability." The claim has morphed into "physical function response" that is assessed by HAQ-DI in short-term trials, such as 12 or 24 weeks.

In 2007-2008, the Study Endpoints and Labeling Development (SEALD) staff in the immediate Office of the New Drugs (OND) raised concerns and asked that SF-36 not be included in RA product labeling. The major concerns of the SEALD staff were that the SF-36 is a generic health survey that has not been shown to represent a health related quality of life in RA, and that PCS and MCS are composite measures of weighted scores from 8 sub-concepts or domains that are not independent and do not measure pure physical or mental functioning and therefore cannot be described in a way that is meaningful. Multiple internal discussions between the SEALD team and the then review division (Division of Anesthesia, Analgesia, and Rheumatology Products, DAARP) occurred. Ultimately, due to the level of concern expressed by SEALD, DAARP reevaluated the need for SF-36 and determined that SF-36 was not needed to support the improvement in physical function response claim because of the extensive accrued experience with HAQ-DI, and the observation that SF-36 results in RA studies were consistent with HAQ-DI results. As a result, SF-36 information from later products approved for RA did not mention SF-36 in the product labeling (Appendix 1). (b) (4)

This decision to discontinue inclusion of SF-36 in RA product labels has not been uniformly accepted by industry, academia, and research community. (b) (4) As a result of the community's concerns, and because of this submission from Pfizer, the SEALD staff and DPARP have had multiple additional discussions about SF-36 to consider the best approach for moving forward. To address the community's concerns, and to be consistent with the way SF-36 has been used as a general health status instrument in RA trials, the Division tentatively decided to re-implement inclusion of SF-36 findings in RA product labeling as a measure of general health status rather than its previous use as a supportive measure for improvement in "prevention of disability" or "physical function response." To mitigate the risk of inappropriate conclusions and potential loss of information, and to be in line with the recommendations by the SF-36 researchers, the Division tentatively decided that results of PCS and MCS along with the relevant 8 domains will be described in the labeling in qualitative general language. The Division discussed this tentative decision, and as it would apply to this tofacitinib submission, at a Center level Regulatory briefing held on September 20, 2013. At the Regulatory Briefing, the science behind development of SF-

36, data and applicability of SF-36 in RA clinical studies, the Agency's internal regulatory history of SF-36, the tofacitinib SF-36 data, and the Division's tentative decision to re-implement inclusion of SF-36 findings in RA product labeling were presented by DPARP and Office of Biostatistics review teams, and discussed by senior level management participants. The SEALD staff expressed dissenting views at the Regulatory Briefing. The Division's tentative decision to re-implement including SF-36 results in RA product labeling was supported for implementation by CDER senior management.

3. Chemistry, Manufacturing, and Controls

Tofacitinib is an approved and marketed product and there are no CMC issues.

4. Nonclinical Pharmacology and Toxicology

No new non-clinical toxicology studies were required or performed for this application. The pharmacology and toxicology data were reviewed with the original application.

5. Clinical Pharmacology and Biopharmaceutics

No new clinical pharmacology studies were required or performed for this application. The clinical pharmacology data were reviewed with the original application.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the studies that form the basis of review and regulatory decision for this application are shown in Table 3. The design and conduct of the studies are briefly described below, followed by SF-36 findings and conclusions. Safety findings are discussed in the following section.

Table 3. Relevant clinical studies

Study ID and Year *	**Study Characteristics -Patient age -Response to past treatment -Concurrent background treatment -Study duration**	**Treatment groups †**	**N ‡**	**Primary efficacy variables §**	**Region % ¶**
Definitive Efficacy and Safety – Monotherapy					
1045 Study I "Solo" 2009-2010	-Over 18 years -Inadequate response to a biologic or a non-biologic DMARD -No background treatment -6 months	Tof 5 mg BID Tof 10 mg BID Placebo 5 mg Placebo 10 mg	244 245 61 61	ACR20 at mo 3 HAQ-DI at mo 3 DAS28<2.6 at mo 3	US (25%) EU (34%) L Am (27%) ROW (14%)
Definitive Efficacy and Safety – Background DMARD					
1046	-Over 18 years	Tof 5 mg BID	318	ACR20 at mo 6	US (17%)

Study ID and Year *	Study Characteristics -Patient age -Response to past treatment -Concurrent background treatment -Study duration	Treatment groups †	N ‡	Primary efficacy variables §	Region % ¶
Study II "Sync" 2009-2011	-Inadequate response to a non-biologic DMARD -Non-biologic DMARD background -12 months	Tof 10 mg BID Placebo 5 mg Placebo 10 mg	318 79 80	HAQ-DI at mo 3 DAS28<2.6 at mo 6	EU (25%) L Am (14%) ROW (44%)
1064 Study III "Standard" 2009-2011	-Over 18 years -Inadequate response to methotrexate -Methotrexate background -12 months	Tof 5 mg BID Tof 10 mg BID Placebo 5 mg Placebo 10 mg Ada 40 mg	204 201 56 52 204	ACR20 at mo 6 HAQ-DI at mo 3 DAS28<2.6 at mo 6	US (15%) EU (56%) L Am (12%) ROW (18%)
1044 Study IV "Scan" 2009-open	-Over 18 years -Inadequate response to methotrexate -Methotrexate background -24 months (12 month interim)	Tof 5 mg BID Tof 10 mg BID Placebo 5 mg Placebo 10 mg	321 319 81 79	ACR20 at mo 6 mTSS at mo 6 HAQ-DI at mo 3 DAS28<2.6 at mo 6	US (17%) EU (24%) L Am (14%) ROW (45%)
Definitive Efficacy and Safety – Background DMARD – Inadequate TNF responder					
1032 Study V "Step" 2009-2011	-Over 18 years -Inadequate response to a TNF inhibitor -Methotrexate background -6 months	Tof 5 mg BID Tof 10 mg BID Placebo 5 mg Placebo 10 mg	133 134 66 66	ACR20 at mo 3 HAQ-DI at mo 3 DAS28<2.6 at mo 3	US (42%) EU (46%) L Am (5%) ROW (7%)

* Study ID shown (from top to bottom) as Pfizer's study number, as referred to in the tofacitinib product label, and as identified by Pfizer at the May 9, 2012, AAC meeting. Year shows when study subject enrollment started – completed.
† Tof = Tofacitinib oral tablets; Ada = adalimumab sc injection
‡ Number randomized
§ ACR20 = Proportion of patients achieving 20% improvement from baseline in American College of Rheumatology defined criteria; HAQ-DI = Change from baseline in Health Assessment Questionnaire Disability Index; DAS28<2.6 = Percentage achieving Disease Activity Score for 28-joint counts in patients with ESR less than 2.6; mTSS = Change from baseline in van der Heijde modified Total Sharp Score;
¶ % As randomized; US: United States; EU = European continent for dose ranging studies, European continent and Canada for pivotal studies; L Am = Latin America - Americas excluding US and Canada; ROW = Rest of the world

b. Design and conduct of the studies

All studies were randomized, double-blinded, placebo-controlled (study 1064 also had active treatment arms), and conducted in patients 18 years of age and older with moderate to severe active RA diagnosed according to the American College of Rheumatology (ACR) criteria. Tofacitinib at various doses was given either as monotherapy or in combination with methotrexate in patients with various histories of response to previous treatments as shown in Table 3. In all studies, placebo treatment duration was less than active treatment duration. In studies 6 months in duration, at month 3 all placebo-treated patients (studies 1045 and 1032) were advanced to tofacitinib 5 mg or 10 mg in a blinded fashion. In studies 12 months or longer in duration (stud y 1064), at month 3 placebo non- responder patients and at month 6 all placebo-treated patients were advanced to tofacitinib 5 mg or 10 mg in a blinded fashion. The primary efficacy variables in the various studies are listed in Table 3. In the definitive studies (studies 1045, 1046, 1064, 1044, and 1032), primary efficacy variables were evaluated in a step-down order as follows: ACR20 response rate, change in mTSS (study 1044 only), change from baseline in HAQ-DI, and percentage achieving DAS-28<2.6. Statistical significance was tested for the 10 mg dose followed by the 5 mg dose. Safety assessment in all studies included recording of adverse events, vital signs, physical examination, and clinical laboratory

measures.

SF-36 was one of the many endpoints assessed in these studies. Missing data for an SF-36 item on completed questionnaires was imputed as suggested by the developers of the SF-36 instrument, using the mean from the all other items within the same domain, provided at least 50% of the items in that domain were completed. Otherwise, missing values were not imputed, and only observed values were used in the analyses. Statistical tests were conducted at the two sided 0.05 level of significance, and confidence intervals were calculated as two sided at the 95% level of confidence. The SF-36 analyses were not included in the statistical hierarchy and therefore the statistical tests for SF-36 are only nominal and do not control for overall type 1 error.

c. Efficacy findings and conclusions

The submitted data showed efficacy for tofacitinib for clinical response and improvement in physical function in RA. These findings formed the basis of approval of tofacitinib for RA in November 2012. These data are not described any further in this review. In subsequent sections of this review only SF-36 data are discussed.

The submitted data show consistent benefit on SF-36 across various studies with tofacitinib, and are adequate to support inclusion of SF-36 findings in the Clinical Studies section of the product labeling.

At Month 3, all five studies showed nominally significant differences between tofacitinib 5 and 10 mg twice-daily over placebo for changes from baseline in SF-36 PCS score, and all but study 1064 showed nominally significant differences between tofacitinib 5 and 10 mg twice-daily over placebo for changes from baseline in SF-36 MCS score (Figure 2). Further, all five studies showed consistent improvements in tofacitinib 5 and 10 mg twice-daily over placebo for changes from baseline in the individual SF-36 domains, and reaching nominal significance for studies 1032, 1044, and 1045 for all 8 domains (Figure 3). All responses suggested a small incremental dose-response between tofacitinib 5 and 10 mg twice-daily regimens. The SF-36 results were consistent with the overall treatment benefit observed in the primary efficacy endpoints, as discussed in the original NDA review.

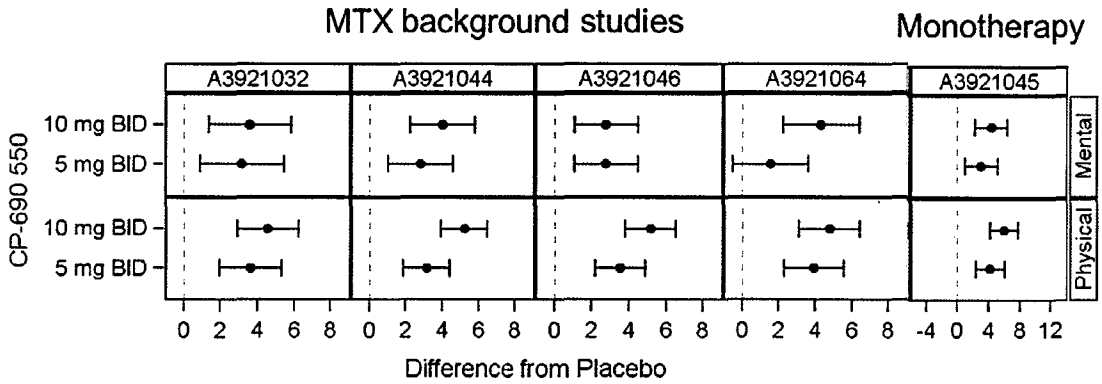


Figure 2. Summary of SF-36 PCS and MCS from tofacitinib studies in RA at month 3.

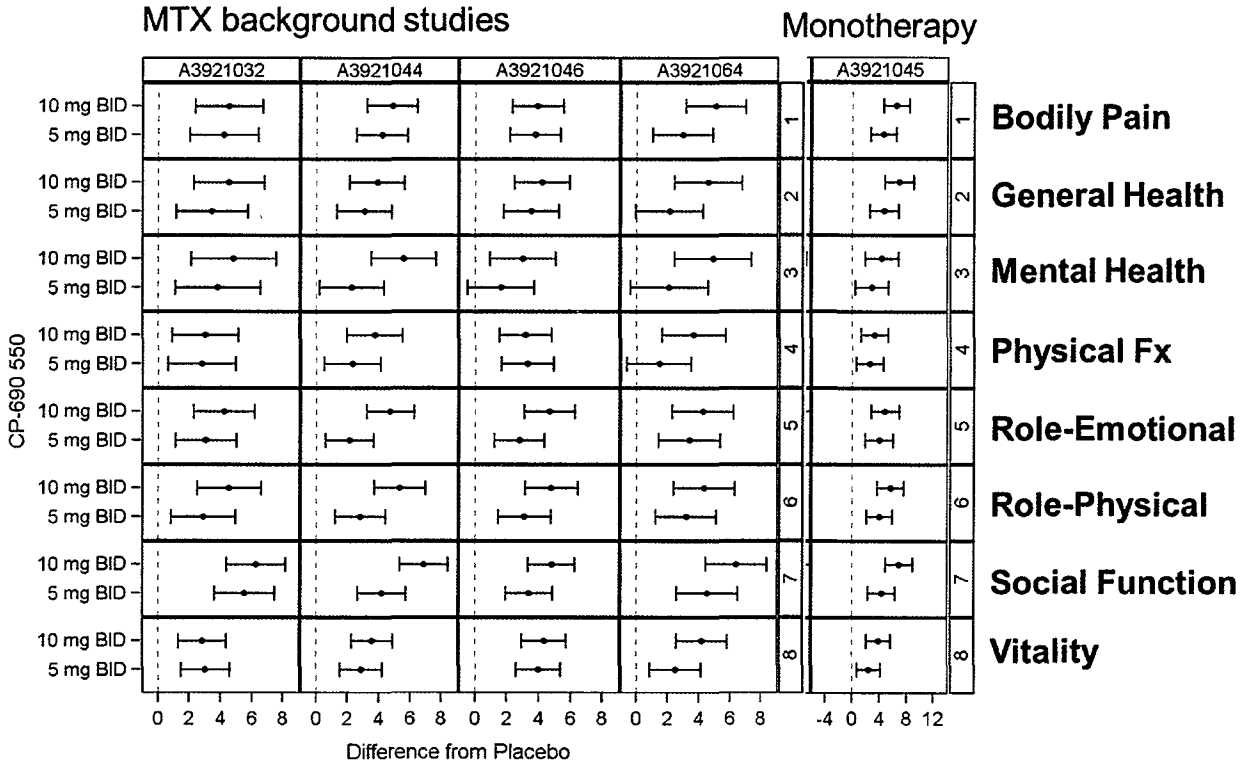


Figure 3. Summary of SF-36 domains data from tofacitinib studies in RA at month 3

8. Safety

a. Safety database

No new safety information was submitted with this application.

b. Safety findings and conclusion

The safety analysis of tofacitinib was conducted during review of the original NDA. The submitted data showed that tofacitinib treatment in patients with RA is associated with safety risks of serious infections, opportunistic infections, tuberculosis, herpes zoster infection, and malignancy.

c. REMS/RiskMAP

Tofacitinib has REMS that address risks associated with tofacitinib, including serious infections such as opportunistic infections, tuberculosis, malignancy, and changes in laboratory parameters such as blood count, which require monitoring. The REMS will remain unchanged as no new safety information was submitted with this application.

9. Advisory Committee Meeting

This original tofacitinib application was discussed at an Arthritis Advisory Committee (AAC) meeting held on May 9, 2012. This supplement is for an ancillary claim for the already approved RA indication; thus no AAC meeting was warranted. This submission and the regulatory history of SF-36 for RA was discussed at an internal Center level Regulatory Briefing on September 20, 2013, as discussed in section 2 above.

10. Pediatric

The pediatric issues for tofacitinib were discussed at a Pediatric Review Committee (PeRC) meeting held on July 11, 2012. This applicant does not involve PREA requirements. There are no new pediatric issues with this application.

11. Other Relevant Regulatory Issues

a. DSI Audits

During review of the original tofacitinib application DSI audit was conducted for 3 clinical study sites based on high enrollment. Final reports of the DSI inspections revealed adherence to Good Clinical Practices. Minor deficiencies were noted, but these were isolated and deemed unlikely to impact data integrity and patient safety. During review of this submission, no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No potentially conflicting financial interests were identified.

c. Others

There are no outstanding issues with consults received from Office of Prescription Drug Promotion (OPDP), Division of Medication Error, Prevention, and Analysis (DMEPA), or from other groups in CDER.

12. Labeling

a. Proprietary Name

There is no issue with the proposed proprietary name as the name Xeljanz was previously reviewed and found to be acceptable.

b. Physician Labeling

The labeling of tofacitinib was reviewed previously with the original approval in November 2012. With this application the existing label will be updated to include new information regarding SF-36 in the Clinical Studies section. The SF-36 findings will be described under a separate subsection titled "Other Health Related Outcomes" to reflect the intended use of SF-36 as a general health status instrument, and not as supportive

evidence of improvement of "physical function response." The findings will be described in qualitative terms stating improvement in PCS, MCS, and all 8 domains.

With this labeling review, the description of the dose-ranging studies will be modified to mitigate concerns regarding possible comparative effectiveness against a TNF blocker.

c. Carton and Immediate Container Labels

Tofacitinib is a marketed product and there were no changed to the carton and immediate container labels with this application.

d. Patient Labeling and Medication Guide

Tofacitinib has a Medication Guide that will remain unchanged.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Pfizer has submitted adequate data to support inclusion of SF-36 findings in the Clinical Studies section of the product labeling. The regulatory action for this application is Approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment of tofacitinib remains favorable, as determined at the time of the original approval in November 2012. The current submission does not alter risk-benefit assessment of tofacitinib for use in patients with RA.

c. Post-marketing Risk Management Activities

There are no new post-marketing risk management activities that will be required on the basis of this submission.

d. Post-marketing Study Commitments

There are no new post-marketing requirements or commitments based on review of this submission.

Appendix 4. Secondary and other claims for recently approved biologic DMARDs in their respective product labels

Proposed to be included in the Rayos product label	Etanercept (**ENBREL**) {1998} * †	Infliximab (**REMICADE**) {1999}	Anakinra (**KINERET**) {2001}	Adalimumab (**HUMIRA**) {2002}	Abatacept (**ORENCIA**) {2005}	Rituximab (**RITUXAN**) {2006}	Golimumab (**SIMPONI**) {2009}	Certolizumab (**CIMZIA**) {2009}	Tocilizumab (**ACTEMRA**) {2010}
ACR 50	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ACR 70	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ACR components	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12 wk ACR 20 response figure	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Morning stiffness ‡	Yes – 2 trials	No	No	No	Yes – 1 trial	No	No	No	No
DAS 28	No	No	No	No	Yes – 1 trial	No	No	No	Yes – 1 trial
[redacted] (b) (4)									

* Year = Year of first approval for RA

† Of the small molecule DMARDs, **Arava** (leflumide), approved for RA in 1998, has the following secondary and other claims: ACR 50, ACR 70, ACR components, 12 wk ACR 20 response figure, morning stiffness (based on 3 trials), Health related QOL (based on 1 trial), and SF 36 health survey (based on 1 trial). **Arava** does not have DAS 28 and Fatigue claims.

Of the NSAIDs approved for signs and symptoms of RA, **EC-Naprosyn** and **Naprosyn** have the following secondary and other claims: reduction in joint swelling, reduction in duration of morning stiffness, reduction in disease activity, and increased mobility. **Indocin** has the following secondary and other claims: reduction in joint swelling, average number of joints involved, and morning stiffness; increased mobility, and improved functional capability.

‡ Label languages: "**Enbrel** was significantly better than placebo in all components of ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness. " "**Orencia** treated patients experienced greater improvement than placebo treated patients in morning stiffness." "**Arava** was significantly superior to placebo in improving morning stiffness, a measure of RA disease activity, not included in the ACR response criteria." **EC-Naprosyn** and **Naprosyn**: "Improvement in patients treated for rheumatoid arthritis was demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time." "Improvement in patients treated with **Indocin** for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength."

[redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

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/s/

BADRUL A CHOWDHURY
11/18/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-3214/S002

OFFICER/EMPLOYEE LIST

Officer/Employee List

Application: NDA 203214/S-002

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

1. Abugov, Robert
2. Bowen, Philantha
3. Buenconsejo, Joan
4. Chowdhury, Badrul
5. Jafari, Ladan
6. Komo, Scott
7. Nikolov, Nikolay
8. Permutt, Thomas
9. Yim, Sarah

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-3214/S002

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 28, 2013
From	Nikolay P. Nikolov, M.D.
Subject	Cross-Discipline Team Leader Review
NDA # **Supplement#**	203,214 Supplement 002
Applicant	Pfizer
Date of Submission	January 18, 2013
PDUFA Goal Date	November 18, 2013
Proprietary Name / Established (USAN) names	Xeljanz/tofacitinib
Dosage forms / Strength	5 mg oral immediate-release tablets
Proposed Claim	(b) (4) [redacted]
Recommended:	*Approval, with Revisions to Proposed Label*

1. Introduction

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 (b) (4) [redacted]. The product is an immediate-release tablet for oral administration in 5 mg dosage strength.

This submission is a request (b) (4) [redacted] for inclusion of SF-36 data in the product labeling (b) (4) [redacted]. It is being reviewed as a labeling supplement with clinical data (NDA 203,214/002) and Pfizer proposes the following labeling changes in the Physical Function Response section of Section 14:

(b) (4) [redacted]

Historically, SF-36 has been included in the labeling for RA products, as supportive data for the Health Assessment Questionnaire Disability Index (HAQ-DI) for the claim of

improvement in physical function. The Division has denied proposed labeling for SF-36 since 2008 due to concerns raised by the Study Endpoints and Labeling Development (SEALD) staff about the SF-36 instrument and in particular the use of the SF-36 physical component summary (PCS) score and mental component summary (MCS) score in RA product labels. Continued pushback from the rheumatology academic community has provided the impetus for DPARP to reassess the SF-36 for re-implementation in RA product labels. The relevant regulatory history of SF-36 use in RA drug development and labeling, and the implications to the tofacitinib labeling were discussed at an internal Regulatory Briefing on September 20, 2013 as summarized in Section 2. Background below.

The overall development program was discussed in detail in the review of the original NDA. This document will focus on:

- Regulatory history of SF-36 in RA product labeling
- General discussion on SF-36 instrument
- Analyses on the SF-36 data from the tofacitinib clinical development
- Updated labeling recommendations to include SF-36 results as a measure of general health status.

The overall clinical efficacy and risk-benefit analysis of tofacitinib remain consistent with the original NDA. Further, the Agency's analyses of the SF-36 data are in general agreement with the sponsor's analyses. Thus the SF-36 data submitted are adequate to support inclusion in product labeling.

2. Background

Rheumatoid arthritis (RA) is a chronic symmetric inflammatory polyarthritis, affecting approximately 1% of the adult population worldwide. Sustained RA activity results in irreversible joint destruction, functional impairment and increased morbidity and mortality, and significantly impacts society and the health care system.[i] Thanks to the advances in our understanding of the disease and the established drug development pathway, many effective treatments have been developed and approved for RA. The approval of most of these products was supported by establishing efficacy in the key domains of the disease, namely clinical response and physical function based on internationally agreed upon endpoints. The clinical response has been assessed by ACR response rates[1] and measures of low disease activity, such as DAS28[2] less than 2.6, have been used as supportive evidence of efficacy in this domain. For physical function, HAQ-DI[3] is usually used to demonstrate an improvement in physical

1 ACR20 (50, 70) response criteria — American College of Rheumatology response criteria is a dichotomous composite endpoint indicating the proportion of patients with at least 20 (50, 70) percent improvement in the number of tender and swollen joints, and in three out of the remaining five ACR core-set measures: patient pain, patient global assessment of disease, physician global assessment of disease, physical functioning assessment (Health Assessment Questionnaire-Disability Index (HAQ-DI)), and acute phase reactants.
2 DAS28 — Disease Activity Score 28 is a mathematically calculated, continuous, composite endpoint with differential weighting given to each of the following components: tender joint count (28 joints), swollen joint count (28 joints), acute phase reactant, and patient global assessment of arthritis.
3 HAQ-DI assesses the degree of difficulty a patient has experienced during the past week in eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

function, and the SF-36, and more specifically the Physical Component Summary (PCS) has been historically used as supportive evidence of efficacy in this domain. Other outcomes that have important implications for patients and health care providers, such as radiographic endpoints, have been used to provide further characterization of the efficacy of a drug product and its utility in clinical practice.

However, there has been a recent emphasis on studying the effects of treatments on aspects of the disease that are important to patients and are not captured by other outcomes.[ii] These measures include patient-reported outcomes (PROs) such as the generic SF-36 health survey, the subject of this supplemental application.

Relevant Regulatory History of SF-36 in Tofacitinib RA Development

The SF-36 was not specifically discussed with the sponsor during tofacitinib development interactions. However, SF-36 was collected as a patient-reported outcome of interest in the protocols of all Phase 3 confirmatory clinical studies and submitted in the original NDA on November 21, 2011 (b) (4).

(b) (4)

his rationale is further discussed in the section Regulatory History of SF-36 in RA Drug Development below.

Regulatory History of SF-36 in RA Drug Development

The purpose of this section is to discuss the regulatory history of Short Form 36 (SF-36) Health Survey in rheumatoid arthritis (RA) drug development and the Division of Pulmonary, Allergy, and Rheumatology Products' (DPARP) justification for re-implementing SF-36 in RA product labeling as stand-alone results reflecting general health status. The history, development, use, and imitations of the SF-36 instrument are described in further detail in Section Clinical/Statistical - Efficacy below.

In the 1999 RA Guidance, the SF-36 was mentioned as a validated general health status measure that should be collected in trials intended to support a "prevention of disability" claim, and that patients should not worsen on this measure over the duration of the trial. The primary measures mentioned for the claim included the Health Assessment Questionnaire (HAQ) and the Arthritis Impact Measure Scales (AIMS). This claim was intended to encourage long-term trials (i.e. 2 to 5 years) in RA. Over time, the language of the claim and data required morphed. The claim became "improvement in physical function," the primary measure used throughout development programs became the HAQ-DI, and shorter trials were accepted, as significant improvement could be observed within 12 to 24 weeks, and it became difficult to justify long-term placebo-controlled trials with the approval of highly effective therapies.

Implementation of SF-36 in RA product labels was fairly consistent. Between 1998 and 2005, six disease modifying antirheumatic drugs (DMARDs) were approved for the treatment of

patients with RA in this context as shown in Table 1. In most of these labels, mention of SF-36 is limited to a descriptive statement that improvements in SF-36 PCS and MCS were also observed. The last approved label with SF-36 (Orencia, 2005) contains the statement, "Health-related quality of life was assessed by the SF-36 questionnaire…improvement was observed in the Orencia group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS)." In 2006, rituximab (Rituxan) was approved for RA (b) (4)

Table 1. Efficacy Claims in Approved Labels of Recent (>1998) DMARDs for RA

Efficacy Claims in Currently Approved Labels of Recent (>1998) Disease Modifying Anti-Rheumatic Drugs (DMARDs) for RA											
	Arava	Remicade	Enbrel	Kineret	Humira	Orencia	Rituxan	Cimzia	Simponi	Actemra	Xeljanz
ACR 20/50/70 Response	x	x	x	x	x	x	x	x	x	x	x
ACR components	x	x	x	x	x	x	x	x	x	x	x
Time course of response	x	x	x		x	x	x	x	x	x	x
Open-label maintenance	x	x	x		x	x					
Major Clinical Response		x	x		x	x		x		x	
Radiographic response	x	x	x	x	x	x	x	x		x	
Proportion of non-progressors		x	x		x	x	x			x	
Open-label maintenance			x		x						
Physical Function											
HAQ-DI	x	x	x	x	x	x	x	x	x	x	x
SF-36	x	x	x	x	x	x					
Open-label maintenance	x	x	x		x	x	x				
DAS28 <2.6											
Proportion of responders						x				x	x
Residual active joints						x				x	x
Morning stiffness	x		x			x					

In 2007-2008, the SEALD staff raised major concerns with the use of SF-36 in RA products labeling. These included (1) SF-36 is a generic health survey that has not been shown to represent a health related quality of life (HRQoL) in RA and (2) PCS, MCS are composite measures of weighted scores from all 8 subconcepts/domains, are not independent and do not measure pure physical or mental functioning and cannot be described in a way that is meaningful. Multiple internal discussions between the SEALD staff and the review division (at the time, the Division of Anesthesia, Analgesia, and Rheumatology Products, DAARP) occurred.

Ultimately, due to the level of concern expressed by SEALD staff, DAARP reevaluated the need for SF-36 and determined that SF-36 was not needed to support the "improvement in physical function" claim. As a result, SF-36 information from four RA products, golimumab/Simponi, certolizumab/Cimzia, tocilizumab/Actemra, and most recently tofacitinib/Xeljanz, was not included in the product labeling.

In addition to expected pushback from sponsors, who felt that this created an unlevel playing field, the decision to no longer include SF-36 in RA product labeling has been questioned by the RA academic and research community.

The community's rationale for the importance of SF-36 includes: (1) SF-36 is a legacy instrument with well-known limitations and implications that is widely used by the RA research community throughout the world; (2) SF-36 provides additional important information on the impact of the disease on the patient that is not captured by other outcome measures used in RA trials; (3) SF-36 is utilized throughout the world for health care policy and decision-making. The SF-36 has been extensively studied in the context of RA and other rheumatic diseases with a wealth of data across countries and cultures. The question about the content validity of the SF-36 in RA or other related rheumatic conditions, that the instrument does not measure what it is purported to measure, does not appear to be supported by the wealth of published literature on SF-36. It is ubiquitous in rheumatology and by far the most commonly used generic health status outcome in RA reported in over 150 articles[iii]. It was used in 80% of the published clinical studies in RA reporting PROs[iv] indicating that the community understands what SF-36, including the 8 domains and the summary scores, measure. Studies to date have yielded evidence of content, construct, and predictive validity of SF-36. Further, a systematic review of the literature on the measurement properties of physical function scales for use in patients with RA, has identified the SF-36 as relevant generic questionnaire with respect to content validity for measuring physical functioning[v], supported by the fact that in RA SF-36 PCS is well correlated with HAQ-DI.

Based on the accumulated clinical data and the evidence of construct validity, responsiveness, and reliability in RA, SF-36 has been shown to:

- Assess disease aspects important to patients
- Provide a multidimensional view of the impact of RA and improvements associated with effective treatment[vi]
- Be a sensitive instrument to demonstrate treatment-associated changes in RA across populations with different demographic and disease characteristics
- Offer comparison with age- and gender matched norms and with other disease states and co-morbidities[vii]
- Be non-redundant with other endpoints[viii], [ix]
- Reflects impact of early and later disease[x], [xi]
- Have generally accepted Minimal Clinically Important Difference (MCID) values for improvement as well as deterioration[xii], [xiii]

As a result of the rheumatology community's concerns, SEALD staff and DPARP have had multiple additional discussions about the SF-36, to consider the best approaches for moving forward. To address the above concerns, and to be consistent with the way this instrument has been used in the community as a general health status instrument, the Division has tentatively decided to implement SF-36 in RA product labeling as a measure of general health status rather than its previous use as a supportive measure for improvement in physical function. To mitigate the risk of inappropriate conclusions and potential loss of information, and to be in line with the recommendations by the SF-36 researchers to interpret the results of PCS and MCS along with the 8 domains, the Division plans to use labeling consistent with the abatacept (Orencia) label.

The Division discussed the internal regulatory history of SF-36 and associated scientific and regulatory issues and implication at an internal Center level Regulatory Briefing on September 20, 2013. The concerns raised by the SEALD staff were also addressed at the Regulatory Briefing and the Division's tentative decision to re-implement SF-36 in RA product labeling was supported by CDER senior management.

3. CMC/Device

No new CMC information was submitted with this supplement. . Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original NDA.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original NDA.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original NDA.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Overview of the Clinical Program

Five randomized placebo-controlled trials have been submitted as the primary evidence of efficacy and safety of tofacitinib, as summarized in Table 2 below. As study numbers all begin with "A392," they will at times be abbreviated by the last four digits of the study number. A single trial (1044) evaluated radiographic outcomes, a single trial (1064) included a control arm with the TNF inhibitor adalimumab, and a single trial (1045) evaluated tofacitinib monotherapy.

Patients completing the Phase 3 trials had the option to enroll in open-label long-term extension (LTE) studies. Study 1041 is an LTE for patients completing clinical development studies in Japan (Phase 2 studies 1039 and 1049, and Japanese participants in global Study 1044). Study 1024 is the LTE for all other patients in the clinical development program. These studies allowed for 5 or 10 mg BID doses, to be adjusted as needed for either efficacy or safety reasons. Prior to amendment 3 (January 2009), all patients were initiated on 5 mg BID upon entry in the LTE. Subsequent to this, all patients (with exceptions in certain countries) have been initiated on 10 mg BID.

Table 2: Summary of the Phase 3 Studies in RA Submitted for the NDA

Protocol Duration	Patient Population	Treatment Arms	Number per arm	Primary Endpoints	Timepoint Assessed
Patients with incomplete response to prior TNF inhibitor					
A3921032 6 months	Moderate to severe RA TNF-IR Stable background MTX Total n = 399	Tofacitinib 5 mg BID + MTX Tofacitinib 10 mg BID + MTX PBO + MTX (to tofacitinib 5 mg BID@Mo.3) PBO + MTX (to tofacitinib 10 mg BID@Mo.3)	133 134 66 66	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
Patients with incomplete response to prior MTX or other DMARDs					
A3921044 2 years*	Moderate to severe RA MTX-IR Stable background MTX Total n = 797	Tofacitinib 5 mg BID + MTX Tofacitinib 10 mg BID + MTX PBO + MTX (to tofacitinib 5 mg BID@Mo.6 or Mo.3 if NR) PBO + MTX (to tofacitinib 10 mg BID@Mo.6 or Mo.3 if NR)	321 316 81 79	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6
A3921046 1 year	Moderate to severe RA DMARD-IR Stable background DMARDs Total n = 792	Tofacitinib 5 mg BID + DMARD Tofacitinib 10 mg BID + DMARD PBO + DMARD (to tofacitinib 5 mg BID@Mo.6 or Mo.3 if NR) PBO + DMARD (to tofacitinib 10 mg BID@Mo.6 or Mo.3 if NR)	315 318 79 80	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
A3921064 1 year	Moderate to severe RA MTX-IR Stable background MTX Total n = 717	Tofacitinib 5 mg BID + MTX Tofacitinib 10 mg BID + MTX PBO + MTX (to tofacitinib 5 mg BID@Mo.6 or Mo.3 if NR) PBO + MTX (to tofacitinib 10 mg BID@Mo.6 or Mo.3 if NR) PBO + adalimumab + MTX	204 201 56 52 204	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
A3921045 6 months	Moderate to severe RA DMARD-IR No background to Month 3 Total n = 610	Tofacitinib 5 mg BID + MTX Tofacitinib 10 mg BID + MTX PBO (to tofacitinib 5 mg BID@Mo.3) PBO (to tofacitinib 10 mg BID@Mo.3)	243 245 61 61	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3

*One year efficacy data submitted for Study 1044
Legend: BID=two times daily; DMARD=Disease-modifying anti-rheumatic drug; IR=incomplete response; MTX=methotrexate; NR=nonresponder
mTSS=Modified Total Sharp Score; PBO=placebo

Phase 3 Confirmatory Studies

Background DMARD Studies in RA

Study A3921032 (Phase 3) was a 6-month study in which 399 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to at least one approved TNF-inhibitor biologic agent received CP-690,550 5 or 10 mg BID 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 CP-690,550 5 or 10 mg BID. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in HAQ-DI and proportion with DAS28-4(ESR) less than 2.6. The last primary efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock. The SF-36 was not included in the statistical hierarchy of endpoints; however SF-36 was systematically collected per protocol at baseline, Week 2, Months 1, 3 and 6 (or at early termination).

Study A3921044 (Phase 3) is an ongoing 2-year study 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 CP-690,550 5 or 10 mg BID or placebo added to background MTX. At the Month 3 visit, non-responding placebo patients were advanced in a blinded fashion to a second predetermined treatment of CP-690,550 5 or 10 mg BID. 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, change from baseline in mean modified Total Sharp Scores at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6. The last primary efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock. The SF-36 was not included in the statistical hierarchy of endpoints; however SF-36 was systematically collected per protocol at baseline, Months 1, 3, 6, 9, 12, 15, 18, 21 and 24 (or at early termination).

Study A3921046 (Phase 3) was a 12-month study in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a nonbiologic DMARD received CP- 690,550 5 or 10 mg BID or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). Placebo patients were advanced as in Study A3921044. 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. The last primary efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock. The SF-36 was not included in the statistical hierarchy of endpoints; however SF-36 was systematically collected per protocol at baseline, Months 1, 3, 6, 9, and 12 (or at early termination).

Study A3921064 (Phase 3) was a 12-month study in which 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received CP-690,550 5 or 10 mg BID, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. Placebo patients were advanced as in Study A3921044. 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. The last primary efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock. The SF-36 was not included in the statistical hierarchy of endpoints; however SF-36 was systematically collected per protocol at baseline, Months 1, 3, 6, 9, and 12 (or at early termination).

Monotherapy Study in RA

Study A3921045 (Phase 3) was a 6-month monotherapy study in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic or biologic) received CP-690,550 5 or 10 mg BID 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 CP-690,550 5 or 10 mg BID. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in HAQ-DI, and rates of DAS28-4(ESR) <2.6. The last primary efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock. The SF-36 was not included in the statistical hierarchy of endpoints; however SF-36 was systematically collected per protocol at baseline, Months 3 and 6 (or at early termination).

Key eligibility criteria

Key eligibility criteria for enrollment in Phase 3 studies were:

- Men and women 18 years of age or greater who had been diagnosed as having rheumatoid arthritis (RA) and who had evidence of active RA as manifested by .6 out of 66 swollen and ≥6 out of 68 tender/painful joints and an elevated acute phase reactant test (CRP>7 mg/dL and/or ESR> 28 mm/h). For Study A3921046 the minimum swollen and tender/painful joint count is ≥4. Aside from RA, autoimmune rheumatic diseases other than Sjögren's Syndrome were exclusionary.
- Previous DMARD therapy and response eligibility criteria:
    - For 1035, 1045, and 1046 the patients must have had an inadequate therapeutic response to at least one traditional or biologic DMARD.
    - For 1025, 1044 and 1064 the patients must have had an inadequate therapeutic response to MTX.
    - For 1032 the patients must have had an inadequate response to at least one TNF inhibitor and must have had active disease despite stably dosed MTX.
- Appropriate contraceptive measures were required for men (when background traditional DMARD therapy was protocol mandated) and women of childbearing potential (all studies). Pregnant and nursing women were excluded. Other exclusions were: serious, chronic or current infections, including tuberculosis, herpes zoster, hepatitis B or C, HIV; recent receipt of a live virus vaccine; a first degree relative with a hereditary immunodeficiency; evidence or history of a lymphoproliferative disorder; past treatment with lymphocyte depleting therapies other than B cell selective therapies (the latter was allowed with evidence of adequate B cell recovery); uncontrolled medical conditions; baseline clinically significant abnormalities in safety laboratory tests including hemoglobin, leukocyte, neutrophil and platelet counts, hepatic transaminases, serum creatinine; use of prohibited CYP3A inhibitors or inducers; recent history of alcohol or drug abuse.

Endpoints in Phase 3 RA Development Program

The protocol-specified endpoints in the tofacitinib RA development program are based on the model summarized in Table 3.

The sponsor's choice of SF-36 as an endpoint in their Phase 3 studies has been driven by the results of qualitative studies from structured RA patient interviews that have identified global concepts, such as overall well-being as highly relevant to RA patients, along with pain, which is already captured as one of the ACR response criteria core components.

The development, measurement and psychometric properties, evidence of validity and reliability, limitations, and use of SF-36 as a measure of general health status are described in the next section "Brief Description of Short Form 36 (SF-36) Instrument".

Table 3. Efficacy Endpoint Model for the Phase 3 Confirmatory Studies in Tofacitinib RA Development Program

Concept/Outcome	Measurement Tool	Sample Endpoint
Signs and symptoms	ACR20, 50, 70	Proportion of subjects achieving >=20, 50, or 70% improvement in ACR responder criteria
Disease-specific Physical functioning	HAQ-DI	Change from baseline
Functional health status	SF-36v2 Health Survey	Change from baseline in all 8 SF-36 domains and the 2 summary measures (PCS and MCS)
Fatigue	FACIT-Fatigue	Change from baseline in FACIT-Fatigue scores
Sleep	MOS-Sleep Scale	Change from baseline in Overall Sleep and Sleep Problem Summary scales
Work participation	WLQ	Change from baseline in WLQ subscale scores

ACR20 = American College of Rheumatology >=20% improvement criteria[16]; HAQ-DI= Health Assessment Questionnaire – Disability Index; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; WLQ = Work Limitations Questionnaire; MOS-Sleep = Medical Outcomes Study–Sleep; SF-36 = SF-36v2 Health Survey.

Source: Patient Reported Outcome Evidence Dossier, Table 1.1

Detailed protocol design, study conduct and results of endpoints such as ACR responses and HAQ-DI for individual studies are discussed in the original NDA and will not be discussed in this review.

Brief Description of Short Form 36 (SF-36) Instrument

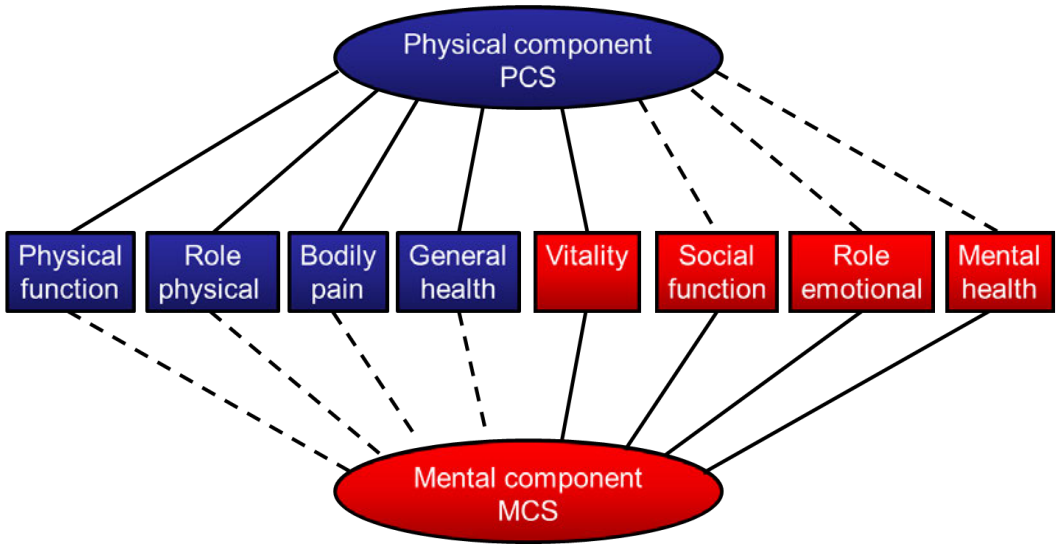
The SF-36 is a multi-purpose, short-form health survey. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index.

It was originally developed to satisfy minimum psychometric standards for group comparisons in 1980s and 90s and has been used in health planning and policy, and health services evaluation in an era of cost containment, and has subsequently been validated in many diseases, including RA and other rheumatic conditions. This is the most widely used health status questionnaire in the world, translated in over 130 languages and validated across countries and cultures, and reported in over 4000 publications.[xiv]

The SF-36 consists of 36 questions relating to either physical or mental health. One question asks respondents to rate the amount of change experienced in their health in general and the remaining 35 questions are divided into eight domains: four for physical health (physical health, bodily pain, physical functioning and physical role limitations) and four for mental health (mental health, vitality, social functioning and emotional role limitation). The eight domains are age, and gender adjusted and scored 0 (severe impairment) – 100 (no impairment).

Subsequently, two psychometrically-based summary measures, physical component summary (PCS) and mental component summary (MCS), were developed to simplify the analysis and interpretation of the SF-36. PCS measures how decrements in physical function affect day to day activities and MCS measures the impact of mental affect and symptoms of pain on quality of life. The PCS and MCS are reported based on normative-based scoring. The conceptual model to derive the two summary scores is presented in Figure 1, where the solid lines identify a major positive contribution to the summary score and the dashed lines indicate a negative contribution.

Figure 1. Conceptual Model for Deriving PCS and MCS from the Individual Domains



Several issues with the component scores have been raised by the SF-36 scientific community:

- Interpretation: There are issues with the interpretation of the summary scores (PCS and MCS) because both summary scores are calculated as a weighted sum of all eight subscale scores rather than the weighted sum of the four scales hypothesized in the measurement model (i.e., PCS consisting of PF, RP, BP, and GH; MCS consisting of VT, SF, RE, and MH).
- Many articles by measurement experts have voiced concern that the component scores do not adequately summarize the eight subscale scores.[xv, xvi]
- Multiple cases have been published where the change in component scores and the change in subscale scores have been inconsistent. Usually the inconsistencies occur in cases where there is a large effect in a domain subscale with a substantial negative factor coefficient.
- The method used by the developers forced the PCS and MCS to be uncorrelated. Several authors have stated that is unrealistic and is one of the causes for the negative factor scores coefficients. They proposed an alternative method that allows the PCS and MCS to be correlated. However, the developers respond that the alternative method is more difficult to interpret and there are still some negative

factor score coefficients although they are smaller in absolute value than the case that assumes the PCS and MCS are uncorrelated.[xvii]

- Several authors have shown for several different populations that the best fitting model is one that computes the component scores using only the four subscales they were hypothesized to include.

Table 4. Factor Score Coefficients for Calculating the SF-36 Summary Scores

Factor Score Coefficients for Calculating the SF-36 Summary Scores		
SF-36 Scale	**PCS**	**MCS**
Physical Functioning (PF)	0.42402	-0.22999
Role Physical (RP)	0.35119	-0.12329
Bodily Pain (BP)	0.31754	-0.09731
General Health (GH)	0.24954	-0.01571
Vitality (VT)	0.02877	0.23534
Social Functioning (SF)	-0.00753	0.26876
Role Emotional (RE)	-0.19206	0.43407
Mental Health (MH)	-0.22069	0.48581

- Acceptability of the factor score coefficients
  Because the factor score coefficients were derived from a sample of the U.S. general population, it is imperative to assess whether this sample has the same factor structure for the eight domain subscales as the RA patient population. Several authors have provided evidence that the factor structure was similar between the U.S. general population and the RA patient population.

Importantly, based on the above considerations and because of the potential loss of information and the risk of inappropriate conclusions with using only the eight domains or the summary scores, the SF-36 researchers have consistently emphasized the need to interpret the results of the domains, and PCS and MCS in parallel.

SF-36 in Tofacitinib Development Program
Statistical Reviewer: Robert Abugov, Ph.D.
Statistical Team Leader: Joan Buenconsejo, Ph.D.
This section is largely excerpted/adapted from Dr. Abugov's review.

Summary: Dr. Abugov's review did not identify issues that would prevent approval of this application.

Statistical Analysis of SF-36 Data

Change from baseline SF-36 components and domains were analyzed as continuous variables using mixed effect repeated measures models, including fixed effects of treatment, non-

baseline visit, treatment by non-baseline visit interaction, baseline measurement, and geographic region, and with random effect patient using compound symmetric covariance matrices. The timing of post-baseline SF36 assessments are described in Section "Overview of the Clinical Program" above.

Confidence intervals for the proportion of responders for each SF-36 component and domain were also calculated, using normal approximations to the binomial.

Statistical tests were conducted at the two sided 0.05 level of significance, and confidence intervals were calculated as two sided at the 95% level of confidence. However, because the endpoints were exploratory and examined without control of overall type 1 error, any statistically significant results claimed by the sponsor should be considered only as nominal, with calculated p-values underestimating true type 1 error probabilities.

Data used for statistical tests included all patients who received one dose of the study drug to which they were randomized.

Importantly, the SF-36 analyses were not included in the statistical hierarchy and therefore, the significance testing or associated control of type 1 error in the face of multiple hypothesis tests were not formally evaluated. Thus, the statistical tests for SF-36 are only nominal.

Handling of SF-36 Missing Data

Missing data for an SF-36 item on completed questionnaires was imputed as suggested by the producer of the SF-36 instrument, using the mean from the all other items within the same domain, provided at least 50% of the items in that domain were completed. Otherwise, missing values were not imputed, and only observed values, including data collected after patient escape or withdrawal from randomized treatment, were used in the analyses.

Patient Disposition

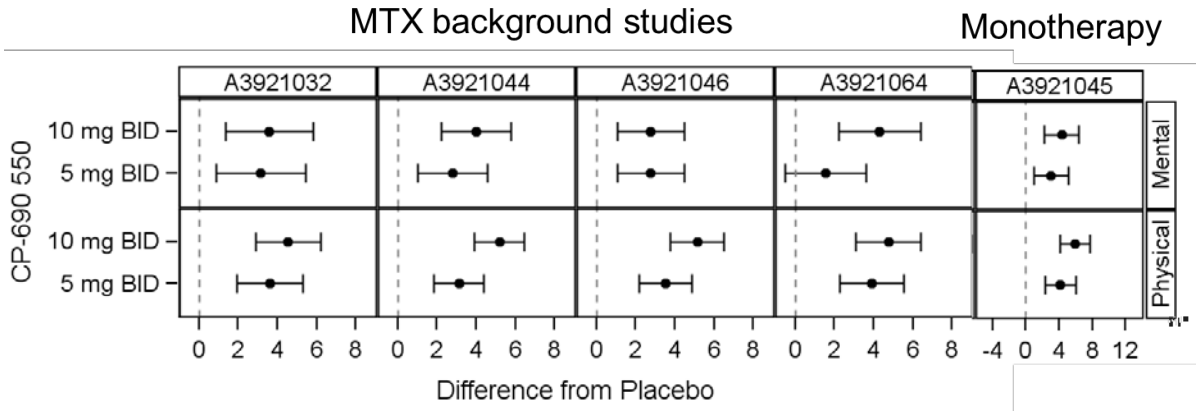
The population in the tofacitinib RA development program consisted of adult patients with long-standing, moderate-to-severely active RA who had inadequate response to one or more DMARDs or, in Study 1032, one or more TNF inhibitors. For further discussion on the patients' disease and demographic characteristics and disposition the reader is referred to the review of the original NDA.

The overall proportion of missing SF-36 questionnaires was low across all five studies (less than 15% at Months 3 and 6) and balanced among the treatment groups, consistent with the patients' disposition described in the original NDA. From the available SF-36 questionnaires, less than 0.5% of the items were missing, without a clear pattern to suggest a systematic bias in reporting.

Results of SF-36 Data

At Month 3, all five studies showed nominally significant differences between tofacitinib (5 and 10 mg BID dosing) and placebo for changes from baseline in SF-36 physical component score (PCS) score, and all but study 1064 showed nominally significant differences between tofacitinib (5 and 10 mg BID dosing) and placebo for changes from baseline in SF-36 mental component score (MCS) score as shown in Figure 2 below. The change in MCS in study 1064 was however in the same direction as the rest of the studies. The PCS and MCS responses suggested a small incremental dose-response between tofacitinib 5 and 10 mg BID regimens, consistent with the overall treatment benefit observed in the primary efficacy endpoints, as discussed in the original NDA.

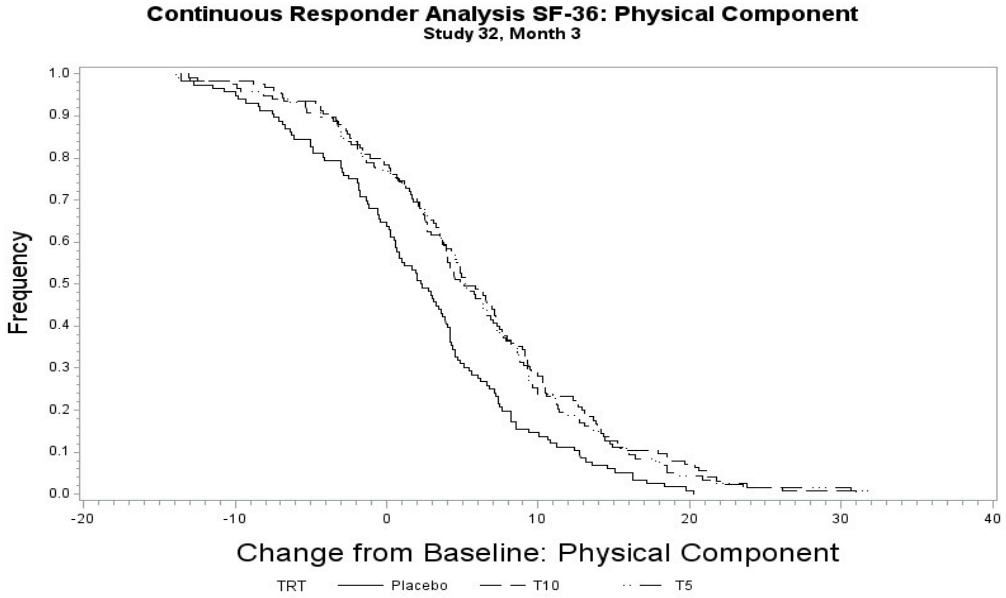
Figure 2. Summary of SF-36 PCS and MCS Data from Tofacitinib Confirmatory Studies in RA, by Study and By Dose at Month 3



Source: Patient Reported Outcome Evidence Dossier, Figures 3.2 and 3.4

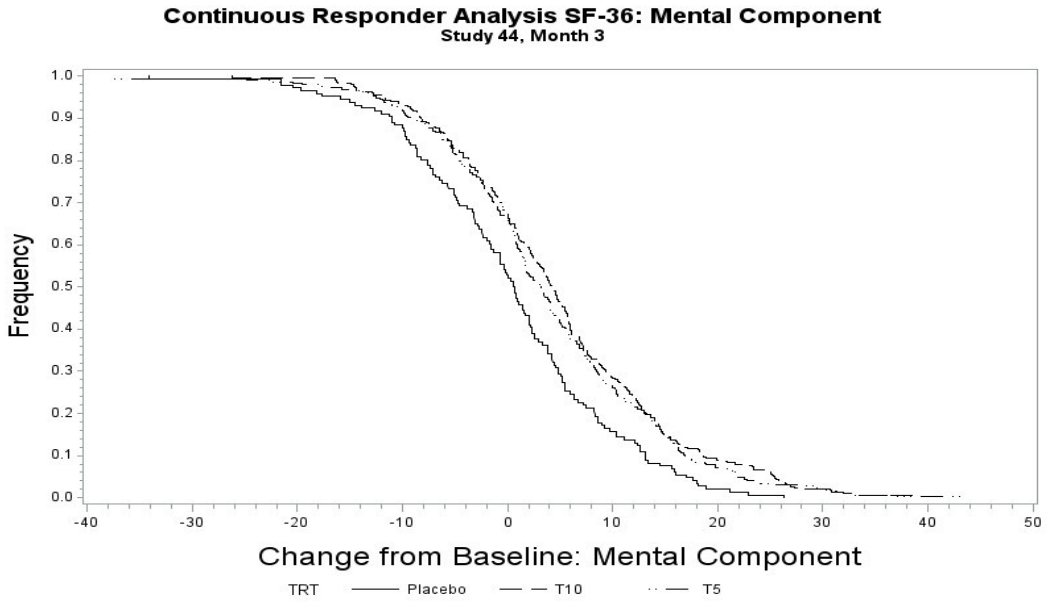
Sensitivity analysis, conducted by the FDA statistical reviewer, Dr. Robert Abugov examined the continuous responder functions between placebo and treatment showing consistent results with the analyses of the mean change from baseline with clear separation between the tofacitinib and placebo groups, as shown in Figure 3 as representative of SF-36 PCS data from study 1032 and in Figure 4 as representative of SF-36 MCS data from study 1044.

Figure 3. Change from Baseline SF-36 Physical Component Score, Month 3, Study 1032, Continuous Responder Analysis



Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.0037
Source: Dr. Abugov's statistical team review

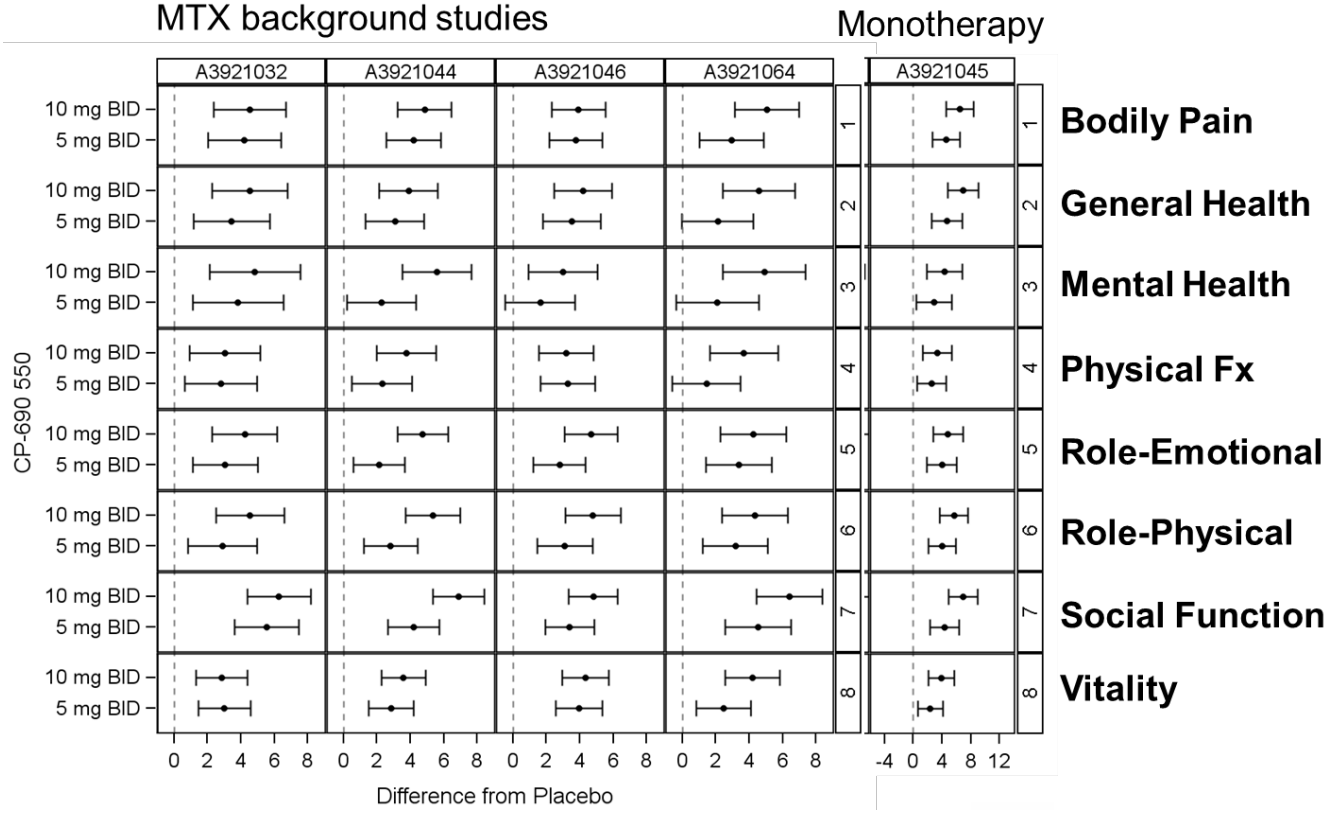
Figure 4. Change from Baseline SF-36 Mental Component Score, Month 3, Study 1044, Continuous Responder Analysis



Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.0260
Source: Dr. Abugov's statistical team review

Further, all five studies showed consistent improvements in tofacitinib (5 and 10 mg BID dosing) as compared with placebo for changes from baseline in the individual SF-36 domains as shown in Figure 5 reaching nominal significance for studies 1032, 1044, and 1045 for all 8 domains. For studies 1046 and 1064, the results were also nominally significant for most of the domains with consistent trends in the rest of the domains.

Figure 5. Summary of SF-36 Domains Data from Tofacitinib Confirmatory Studies in RA, by Study and By Dose



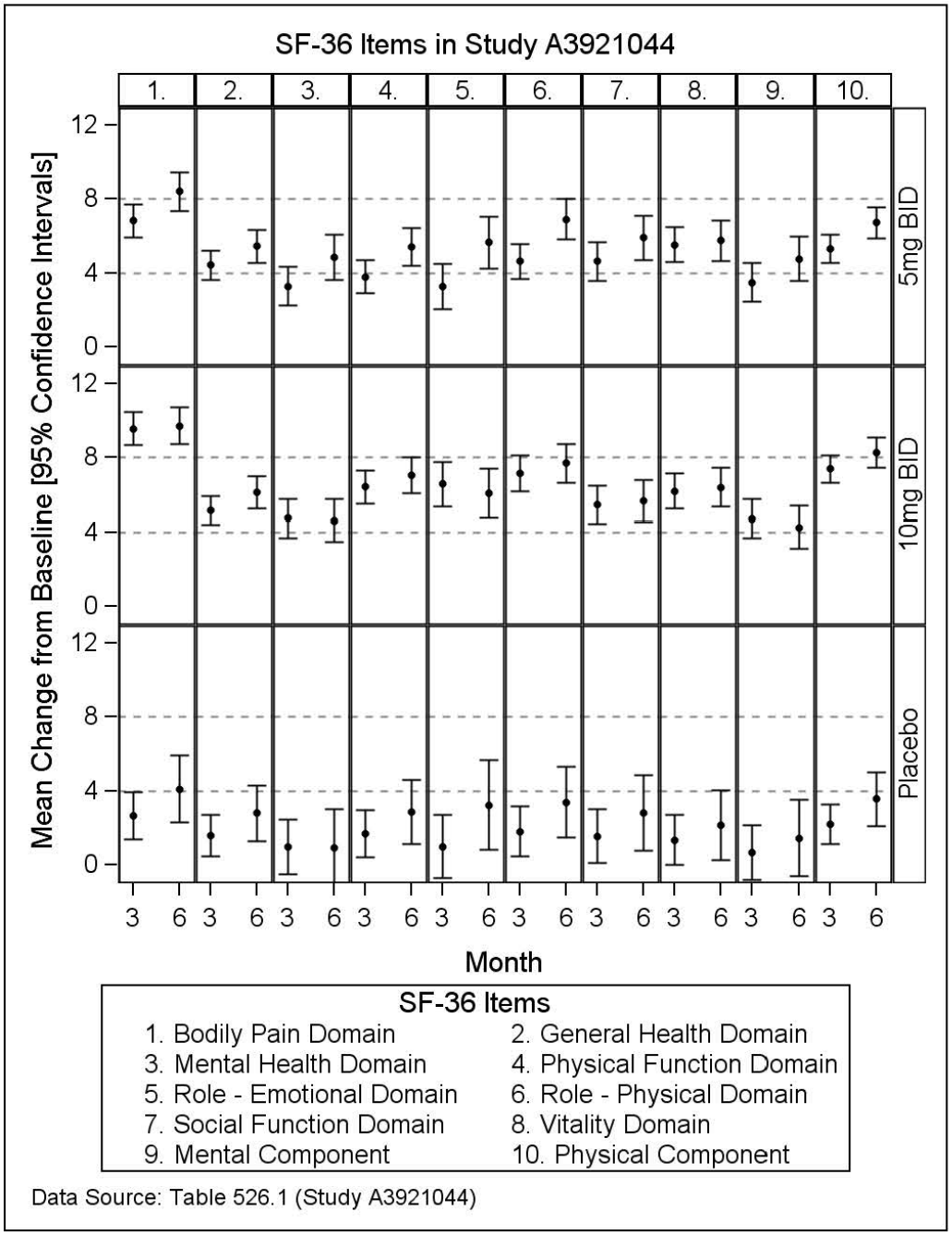
Source: Patient Reported Outcome Evidence Dossier, Figures 3.1 and 3.3

Timing of SF-36 assessment

The sponsor proposed to include Month 3 SF-36 data in the product labeling with the rationale that all five Phase 3 studies contributed placebo-controlled data for 3 months as opposed to only 3 studies (1044, 1046, and 1064) which had Month 6 placebo-controlled period. Further, the Month 6 data were confounded by the early escape and transition to active treatment before Month 6 as allowed by the protocols. Therefore, the Month 3 data were more robust to support the labeling claim. To further support the tofacitinib efficacy on SF-36, the sponsor has presented mean change from baseline in each of the SF-36 domains for both Month 3 and Month 6 which shows consistent efficacy across the year-long studies 1044, 1046, and 1064 represented in Figure 6 for study 1044 and Figure 7 for study 1065. Clinically significant improvements, i.e. exceeding the generally accepted minimally clinically important

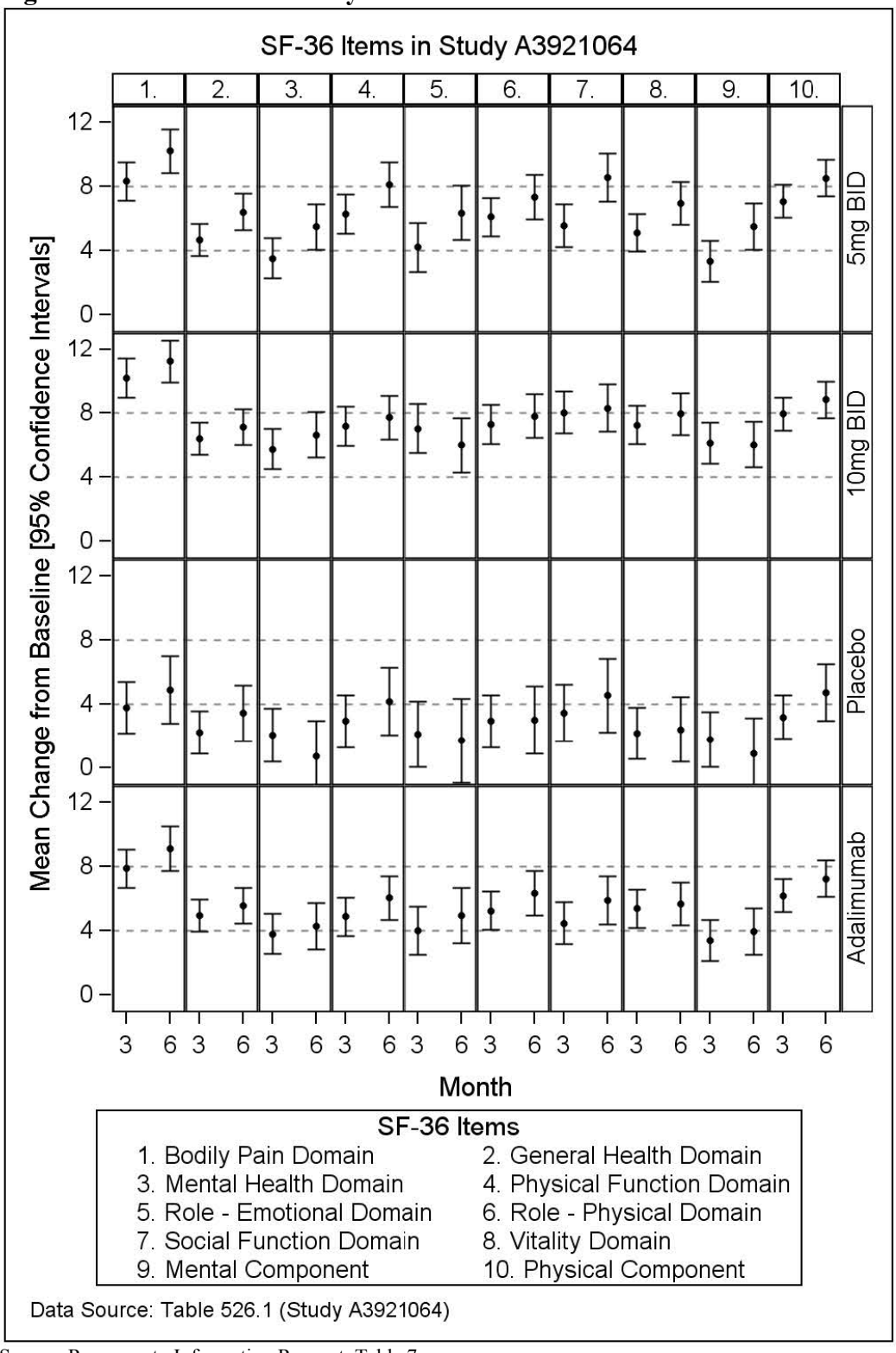
differences[xviii],[xix], were seen in tofacitinib-treated patients compared with placebo-treated patients at Month 3 supported by consistent results at Month 6 with changes from baseline.

Figure 6. SF-36 Items in Study 1044



Source: Response to Information Request, Table 6

Figure 7. SF-36 Items in Study 1064



Source: Response to Information Request, Table 7

The FDA analyses, conducted by the statistical review team, were in general agreement with the analyses presented by the sponsor.

Of note, these SF-36 results are consistent with the treatment effects observed in other RA products, as described in the published literature.[xx, xxi, xxii, xxiii, xxiv]

- **Includes discussion of both the statistical reviewer review and the clinical efficacy review with explanation for CDTL's conclusions and ways that any disagreements were addressed.**

None.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

For completeness for SF-36 interpretation as a general health status instrument, description of PCS and MCS scores along with the individual SF-36 domains is warranted. This recommendation is consistent with standard practice in reporting SF-36 results because of the potential loss of information and the risk of inappropriate conclusions with using only the eight domains or the summary scores. Further, this approach is consistent with the analysis and reporting of composite endpoints, in this case PCS and MCS, where the analyses and reporting of the individual components, in this case the SF-36 domains, are descriptive without requiring statistical significance, i.e. adjusting for multiplicity.

Because assessments of SF-36 were not included in the statistical hierarchy of testing and not controlled for type 1 error for multiple endpoints, true statistical significance and p-values could not be calculated. Collectively however, the SF-36 data from the Phase 3 clinical studies in this submission indicate that compared to placebo, tofacitinib 5 mg BID and 10 mg BID improves all eight SF-36 domains as well as PCS and MCS in patients with active RA supporting the proposed labeling language of:

(b) (4)

8. Safety

No new safety information was submitted with this supplement. The safety information from tofacitinib development 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.

Overall, the safety data from 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 (excluding non-melanoma skin cancer, NMSC) 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.

9. Advisory Committee Meeting

This supplemental application is for an ancillary claim for an already approved indication; thus no Advisory Committee meeting was warranted. An advisory committee meeting was held for the original NDA on May 9, 2012.

10. Pediatrics

The pediatric issues were discussed in the reviews of the original NDA.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues
- **Financial disclosures**—No issues
- **Other GCP issues**—No issues
- **DSI audits –** The OSI audits were conducted as part of the original NDA
- **Other discipline consults**—Not applicable

- **Any other outstanding regulatory issues**—Not applicable

12. Labeling

- **Proprietary name**

The trade name for tofacitinib, Xeljanz, has already been reviewed and approved.

- **Address important issues raised by brief discussion of DDMAC and OSE Division comments.**

None.

- **Physician labeling**

I recommend the following major revisions (all to Section 14, Clinical Studies):

1) Proposed SF-36 labeling language:

- Describe SF-36 data under a separate subsection "Other Health Related Outcomes" to reflect the intended use of SF-36 as a general health status instrument and not only as supportive evidence of improvement in physical function.
- For completeness for SF-36 interpretation, include a description of physical component summary (PCS) and mental component summary (MCS) scores. This recommendation is consistent with standard practice in reporting SF-36 results because of the potential loss of information and the risk of inappropriate conclusions with using only the eight domains or the summary scores. Further, this approach is consistent with the analysis and reporting of composite endpoints, where the analyses and reporting of the individual components are descriptive without requiring statistical significance, i.e. adjusting for multiplicity.
- (b) (4)

  Proposed labeling revisions (new language in *red* and deletions are in ~~*strikethrough*~~):

  "Other Health Related Outcomes
  (b) (4) *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* (b) (4) *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."*

2) (b) (4)

(b) (4)

Proposed labeling revisions (new language in *red* and deletions are in ~~*strikethrough*~~):

> *"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.* ~~*Furthermore, there was a smaller proportion of patients who responded to adalimumab monotherapy compared to those treated with XELJANZ doses 3 mg twice daily and greater*~~*. 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. ... "*
>
> (b) (4)
> *Study 1was a dose-ranging monotherapy trial not designed to provide comparative effectiveness data and should not be interpreted as evidence of superiority to adalimumab."*

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.**

None.

- **Carton and immediate container labels (if problems are noted)**

Carton and container labels are already approved, and no changes are proposed or warranted.

- **Patient labeling/Medication guide (if considered or required)**

The Patient labeling/Medication guide is a part of REMS and was approved as with the original NDA. No changes are proposed to the Patient labeling/Medication guide with this submission.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this supplement with revisions to the labeling as discussed in Section 12. Labeling.

- **Risk Benefit Assessment**

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 SF-36 results in Section 14 of the prescribing information. 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, and general health status.

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

This supplement does not warrant new or modification of the already approved postmarketing risk evaluation and management strategies (REMS).

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

This supplement does not warrant new postmarketing requirements or commitments.

- **Recommended Comments to Applicant**

None.

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/s/

NIKOLAY P NIKOLOV
10/27/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-3214/S002

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	203,214/0002
Priority or Standard	Standard
Submit Date	January 18, 2013
Received Date	January 18, 2013
PDUFA Goal Date	November 18, 2013
Division / Office	DPARP/OND
Reviewer Name	Nikolay P. Nikolov, M.D.
Review Completion Date	October 11, 2013
Established Name	Tofacitinib (CP-690,550)
Trade Name	Xeljanz
Therapeutic Class	Janus kinase (JAK) inhibitor
Applicant	Pfizer
Formulation(s)	Tablets
Dosing Regimen	5 or 10 mg BID
Indication	Rheumatoid Arthritis (RA), SF-36 claim
Intended Population	Moderate-to-Severe RA

Template Version: March 6, 2009

1. Introduction

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 2012 for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had inadequate response (b) (4) . The product is an immediate-release tablet for oral administration in 5 mg dosage strength.

This submission is a request for (b) (4) inclusion of SF-36 data in the product labeling (b) (4) . It is being reviewed as a labeling supplement with clinical data (NDA 203,214/002) and Pfizer proposes the following labeling changes in the Physical Function Response section of Section 14:

(b) (4)

Historically, SF-36 has been included in the labeling for RA products, as supportive data for the Health Assessment Questionnaire Disability Index (HAQ-DI) for the claim of improvement in physical function. The Division has denied proposed labeling for SF-36 since 2008 due to concerns raised by the Study Endpoints and Labeling Development (SEALD) team about the SF-36 instrument and in particular the use of the SF-36 physical component summary (PCS) score and mental component summary (MCS) score in RA product labels. Continued pushback from the rheumatology academic community has provided the impetus for DPARP and SEALD to reassess the SF-36 for re-implementation in RA product labels. The relevant regulatory history of SF-36 use in RA drug development and labeling, and the implications to the tofacitinib labeling were discussed at an internal Regulatory Briefing on September 20, 2013 as summarized in Section 2. Background below.

The overall development program was discussed in detail in the primary review of the original NDA dated, June 26, 2012. This document will focus on:

- Regulatory history of SF-36 in RA product labeling
- General discussion on SF-36 instrument
- Analyses on the SF-36 data from the tofacitinib clinical development
- Updated labeling recommendations to include SF-36 results as a measure of general health status.

The overall clinical efficacy and risk-benefit analysis of tofacitinib remain consistent with the original NDA application. Further, the Agency's analyses of the SF-36 data are in general agreement with the sponsor's analyses. Thus the SF-36 data submitted are adequate to support inclusion in product labeling.

2. Background

Rheumatoid arthritis (RA) is a chronic symmetric inflammatory polyarthritis, affecting approximately 1% of the adult population worldwide. Sustained RA activity results in irreversible joint destruction, functional impairment and increased morbidity and mortality, and significantly impacts society and the health care system.[i] Thanks to the advances in our understanding of the disease and the established drug development pathway, many effective treatments have been developed and approved for RA. The approval of most of these products was supported by establishing efficacy in the key domains of the disease, namely clinical response and physical function based on internationally agreed upon endpoints. The clinical response has been assessed by ACR response rates[1] and measures of low disease activity, such as DAS28[2] less than 2.6, have been used as supportive evidence of efficacy in this domain. For physical function, HAQ-DI[3] is usually used to demonstrate an improvement in physical function, and the SF-36, and more specifically the Physical Component Summary (PCS) has been historically used as supportive evidence of efficacy in this domain. Other outcomes that have important implications for patients and health care providers, such as radiographic endpoints, have been used to provide further characterization of the efficacy of a drug product and its utility in clinical practice.

However, there has been a recent emphasis on studying the effects of treatments on aspects of the disease that are important to patients and are not captured by other outcomes.[ii] These measures include patient-reported outcomes (PROs) such as the generic SF-36 health survey, the subject of this supplemental application.

Relevant Regulatory History of SF-36 in Tofacitinib RA Development

The SF-36 was not specifically discussed with the sponsor during tofacitinib development interactions. However, SF-36 was collected as a patient-reported outcome of interest in the protocols of all Phase 3 confirmatory clinical studies and submitted in the original NDA on November 21, 2011 to support a labeling claim of improvement in physical functioning.

(b) (4)

This rationale is further discussed in the section Regulatory History of SF-36 in RA Drug Development below.

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1 ACR20 (50, 70) response criteria — American College of Rheumatology response criteria is a dichotomous composite endpoint indicating the proportion of patients with at least 20 (50, 70) percent improvement in the number of tender and swollen joints, and in three out of the remaining five ACR core-set measures: patient pain, patient global assessment of disease, physician global assessment of disease, physical functioning assessment (Health Assessment Questionnaire-Disability Index (HAQ-DI)), and acute phase reactants.
2 DAS28 — Disease Activity Score 28 is a mathematically calculated, continuous, composite endpoint with differential weighting given to each of the following components: tender joint count (28 joints), swollen joint count (28 joints), acute phase reactant, and patient global assessment of arthritis.
3 HAQ-DI assesses the degree of difficulty a patient has experienced during the past week in eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

Regulatory History of SF-36 in RA Drug Development

The purpose of this section is to discuss the regulatory history of Short Form 36 (SF-36) Health Survey in rheumatoid arthritis (RA) drug development and the Division of Pulmonary, Allergy, and Rheumatology Products' (DPARP) justification for re-implementing SF-36 in RA product labeling as stand-alone results reflecting general health status. The history, development, use, and imitations of the SF-36 instrument are described in further detail in Section Clinical/Statistical - Efficacy below.

In the 1999 RA Guidance, the SF-36 was mentioned as a validated general health status measure that should be collected in trials intended to support a "prevention of disability" claim, and that patients should not worsen on this measure over the duration of the trial. The primary measures mentioned for the claim included the Health Assessment Questionnaire (HAQ) and the Arthritis Impact Measure Scales (AIMS). This claim was intended to encourage long-term trials (i.e. 2 to 5 years) in RA. Over time, the language of the claim and data required morphed. The claim became "improvement in physical function," the primary measure used throughout development programs became the HAQ-DI, and shorter trials were accepted, as significant improvement could be observed within 12 to 24 weeks, and it became difficult to justify long-term placebo-controlled trials with the approval of highly effective therapies.

Implementation of SF-36 in RA product labels was fairly consistent. Between 1998 and 2005, six disease modifying antirheumatic drugs (DMARDs) were approved for the treatment of patients with RA in this context as shown in Table 1. In most of these labels, mention of SF-36 is limited to a descriptive statement that improvements in SF-36 PCS and MCS were also observed. The last approved label with SF-36 (Orencia, 2005) contains the statement, "Health-related quality of life was assessed by the SF-36 questionnaire…improvement was observed in the Orencia group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS)." In 2006, rituximab (Rituxan) was approved for RA but was not given labeling for SF-36 because 2-year data were not submitted.

Table 1. Efficacy Claims in Approved Labels of Recent (>1998) DMARDs for RA

Efficacy Claims in Currently Approved Labels of Recent (>1998) Disease Modifying Anti-Rheumatic Drugs (DMARDs) for RA											
	Arava	Remicade	Enbrel	Kineret	Humira	Orencia	Rituxan	Cimzia	Simponi	Actemra	Xeljanz
ACR 20/50/70 Response	x	x	x	x	x	x	x	x	x	x	x
ACR components	x	x	x	x	x	x	x	x	x	x	x
Time course of response	x	x	x		x	x	x	x	x	x	x
Open-label maintenance	x	x	x		x	x					
Major Clinical Response		x	x		x	x		x		x	
Radiographic response	x	x	x	x	x	x	x	x		x	
Proportion of non-progressors		x	x		x	x	x			x	
Open-label maintenance			x		x						
Physical Function											
HAQ-DI	x	x	x	x	x	x	x	x	x	x	x
SF-36	x	x	x	x	x	x					
Open-label maintenance	x	x	x		x	x	x				
DAS28 <2.6											
Proportion of responders						x				x	x
Residual active joints						x				x	x
Morning stiffness	x		x			x					

In 2007-2008, the SEALD team raised major concerns with the use of SF-36 in RA products labeling. These included (1) SF-36 is a generic health survey that has not been shown to represent a health related quality of life (HRQoL) in RA and (2) PCS, MCS are composite measures of weighted scores from all 8 subconcepts/domains, are not independent and do not measure pure physical or mental functioning and cannot be described in a way that is meaningful. Multiple internal discussions between the SEALD team and the review division (at the time, the Division of Anesthesia, Analgesia, and Rheumatology Products, DAARP) occurred.

Ultimately, due to the level of concern expressed by SEALD, DAARP reevaluated the need for SF-36 and determined that SF-36 was not needed to support the improvement in physical function claim. (b) (4)

In addition to expected pushback from sponsors, who felt that this created an unlevel playing field, the decision to no longer include SF-36 in RA product labeling has been questioned by the RA academic and research community.

The community's rationale for the importance of SF-36 includes: (1) SF-36 is a legacy instrument with well-known limitations and implications that is widely used by the RA research community throughout the world; (2) SF-36 provides additional important information on the impact of the disease on the patient that is not captured by other outcome measures used in RA trials; (3) SF-36 is utilized throughout the world for health care policy and decision-making. The SF-36 has been extensively studied in the context of RA and other rheumatic diseases with a wealth of data across countries and cultures. The question about the content validity of the SF-36 in RA or other related rheumatic conditions, that the instrument

does not measure what it is purported to measure, does not appear to be supported by the wealth of published literature on SF-36. It is ubiquitous in rheumatology and by far the most commonly used generic health status outcome in RA reported in over 150 articles[iii]. It was used in 80% of the published clinical studies in RA reporting PROs[iv] indicating that the community understands what SF-36, including the 8 domains and the summary scores, measure. Studies to date have yielded evidence of content, construct, and predictive validity of SF-36. Further, a systematic review of the literature on the measurement properties of physical function scales for use in patients with RA, has identified the SF-36 as relevant generic questionnaire with respect to content validity for measuring physical functioning[v], supported by the fact that in RA SF-36 PCS is well correlated with HAQ-DI.

Based on the accumulated clinical data and the evidence of construct validity, responsiveness, and reliability in RA, SF-36 has been shown to:

- Assess disease aspects important to patients
- Provide a multidimensional view of the impact of RA and improvements associated with effective treatment[vi]
- Be a sensitive instrument to demonstrate treatment-associated changes in RA across populations with different demographic and disease characteristics
- Offer comparison with age- and gender matched norms and with other disease states and co-morbidities[vii]
- Be non-redundant with other endpoints[viii], [ix]
- Reflects impact of early and later disease[x],[xi]
- Have generally accepted Minimal Clinically Important Difference (MCID) values for improvement as well as deterioration[xii],[xiii]

As a result of the rheumatology community's concerns, SEALD and DPARP have had multiple additional discussions about the SF-36, to consider the best approaches for moving forward. To address the above concerns, and to be consistent with the way this instrument has been used in the community as a general health status instrument, the Division has decided to implement SF-36 in RA product labeling as a measure of general health status rather than its previous use as a supportive measure for improvement in physical function. To mitigate the risk of inappropriate conclusions and potential loss of information, and to be in line with the recommendations by the SF-36 researchers to interpret the results of PCS and MCS along with the 8 domains, the Division plans to use labeling consistent with the abatacept (Orencia) label.

The regulatory history of SF-36 was extensively discussed at an internal Regulatory Briefing on September 20, 2013 and the Division's decision to re-implement SF-36 in RA product labeling was supported by CDER senior management.

3. CMC/Device

No new CMC information was submitted with this supplement. . Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original NDA application.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original NDA application.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was submitted with this supplement. Such information is not required for the regulatory decision on this supplement. The relevant information was previously reviewed in the original NDA application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Overview of the Clinical Program

Five randomized placebo-controlled trials have been submitted as the primary evidence of efficacy and safety of tofacitinib, as summarized in Table 2 below. As study numbers all begin with "A392," they will at times be abbreviated by the last four digits of the study number. A single trial (1044) evaluated radiographic outcomes, a single trial (1064) included a control arm with the TNF inhibitor adalimumab, and a single trial (1045) evaluated tofacitinib monotherapy.

Patients completing the Phase 3 trials had the option to enroll in open-label long-term extension (LTE) studies. Study 1041 is an LTE for patients completing clinical development studies in Japan (Phase 2 studies 1039 and 1049, and Japanese participants in global Study 1044). Study 1024 is the LTE for all other patients in the clinical development program. These studies allowed for 5 or 10 mg BID doses, to be adjusted as needed for either efficacy or safety reasons. Prior to amendment 3 (January 2009), all patients were initiated on 5 mg BID upon entry in the LTE. Subsequent to this, all patients (with exceptions in certain countries) have been initiated on 10 mg BID.

Table 2: Summary of the Phase 3 Studies in RA Submitted for the NDA

Protocol Duration	Patient Population	Treatment Arms	Number per arm	Primary Endpoints	Timepoint Assessed
Patients with incomplete response to prior TNF inhibitor					
A3921032 6 months	Moderate to severe RA TNF-IR Stable background MTX Total n = 399	Tofacitinib 5 mg BID + MTX Tofacitinib 10 mg BID + MTX PBO + MTX (to tofacitinib 5 mg BID@Mo.3) PBO + MTX (to tofacitinib 10 mg BID@Mo.3)	133 134 66 66	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
Patients with incomplete response to prior MTX or other DMARDs					
A3921044 2 years*	Moderate to severe RA MTX-IR Stable background MTX Total n = 797	Tofacitinib 5 mg BID + MTX Tofacitinib 10 mg BID + MTX PBO + MTX (to tofacitinib 5 mg BID@Mo.6 or Mo.3 if NR) PBO + MTX (to tofacitinib 10 mg BID@Mo.6 or Mo.3 if NR)	321 316 81 79	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6
A3921046 1 year	Moderate to severe RA DMARD-IR Stable background DMARDs Total n = 792	Tofacitinib 5 mg BID + DMARD Tofacitinib 10 mg BID + DMARD PBO + DMARD (to tofacitinib 5 mg BID@Mo.6 or Mo.3 if NR) PBO + DMARD (to tofacitinib 10 mg BID@Mo.6 or Mo.3 if NR)	315 318 79 80	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
A3921064 1 year	Moderate to severe RA MTX-IR Stable background MTX Total n = 717	Tofacitinib 5 mg BID + MTX Tofacitinib 10 mg BID + MTX PBO + MTX (to tofacitinib 5 mg BID@Mo.6 or Mo.3 if NR) PBO + MTX (to tofacitinib 10 mg BID@Mo.6 or Mo.3 if NR) PBO + adalimumab + MTX	204 201 56 52 204	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
A3921045 6 months	Moderate to severe RA DMARD-IR No background to Month 3 Total n = 610	Tofacitinib 5 mg BID + MTX Tofacitinib 10 mg BID + MTX PBO (to tofacitinib 5 mg BID@Mo.3) PBO (to tofacitinib 10 mg BID@Mo.3)	243 245 61 61	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3

*One year efficacy data submitted for Study 1044
Legend: BID=two times daily; DMARD=Disease-modifying anti-rheumatic drug; IR=incomplete response; MTX=methotrexate; NR=nonresponder
mTSS=Modified Total Sharp Score; PBO=placebo

Phase 3 Confirmatory Studies

Background DMARD Studies in RA

Study A3921032 (Phase 3) was a 6-month study in which 399 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to at least one approved TNF-inhibitor biologic agent received CP-690,550 5 or 10 mg BID 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 CP-690,550 5 or 10 mg BID. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in HAQ-DI and proportion with DAS28-4(ESR) less than 2.6. The last primary efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock. The SF-36 was not included in the statistical hierarchy of endpoints; however SF-36 was systematically collected per protocol at baseline, Week 2, Months 1, 3 and 6 (or at early termination).

Study A3921044 (Phase 3) is an ongoing 2-year study 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 CP-690,550 5 or 10 mg BID or placebo added to background MTX. At the Month 3 visit, non-responding placebo patients were advanced in a blinded fashion to a second predetermined treatment of CP-690,550 5 or 10 mg BID. 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, change from baseline in mean modified Total Sharp Scores at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6. The last primary efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock. The SF-36 was not included in the statistical hierarchy of endpoints; however SF-36 was systematically collected per protocol at baseline, Months 1, 3, 6, 9, 12, 15, 18, 21 and 24 (or at early termination).

Study A3921046 (Phase 3) was a 12-month study in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a nonbiologic DMARD received CP- 690,550 5 or 10 mg BID or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). Placebo patients were advanced as in Study A3921044. 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. The last primary efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock. The SF-36 was not included in the statistical hierarchy of endpoints; however SF-36 was systematically collected per protocol at baseline, Months 1, 3, 6, 9, and 12 (or at early termination).

Study A3921064 (Phase 3) was a 12-month study in which 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received CP-690,550 5 or 10 mg BID, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. Placebo patients were advanced as in Study A3921044. 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. The last primary efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock. The SF-36 was not included in the statistical hierarchy of endpoints; however SF-36 was systematically collected per protocol at baseline, Months 1, 3, 6, 9, and 12 (or at early termination).

Monotherapy Study in RA

Study A3921045 (Phase 3) was a 6-month monotherapy study in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic or biologic) received CP-690,550 5 or 10 mg BID 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 CP-690,550 5 or 10 mg BID. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in HAQ-DI, and rates of DAS28-4(ESR) <2.6. The last primary efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock. The SF-36 was not included in the statistical hierarchy of endpoints; however SF-36 was systematically collected per protocol at baseline, Months 3 and 6 (or at early termination).

Key eligibility criteria

Key eligibility criteria for enrollment in Phase 3 studies were:

- Men and women 18 years of age or greater who had been diagnosed as having rheumatoid arthritis (RA) and who had evidence of active RA as manifested by .6 out of 66 swollen and ≥6 out of 68 tender/painful joints and an elevated acute phase reactant test (CRP>7 mg/dL and/or ESR> 28 mm/h). For Study A3921046 the minimum swollen and tender/painful joint count is ≥4. Aside from RA, autoimmune rheumatic diseases other than Sjögren's Syndrome were exclusionary.
- Previous DMARD therapy and response eligibility criteria:
    - For 1035, 1045, and 1046 the patients must have had an inadequate therapeutic response to at least one traditional or biologic DMARD.
    - For 1025, 1044 and 1064 the patients must have had an inadequate therapeutic response to MTX.
    - For 1032 the patients must have had an inadequate response to at least one TNF inhibitor and must have had active disease despite stably dosed MTX.
- Appropriate contraceptive measures were required for men (when background traditional DMARD therapy was protocol mandated) and women of childbearing potential (all studies). Pregnant and nursing women were excluded. Other exclusions were: serious, chronic or current infections, including tuberculosis, herpes zoster, hepatitis B or C, HIV; recent receipt of a live virus vaccine; a first degree relative with a hereditary immunodeficiency; evidence or history of a lymphoproliferative disorder; past treatment with lymphocyte depleting therapies other than B cell selective therapies (the latter was allowed with evidence of adequate B cell recovery); uncontrolled medical conditions; baseline clinically significant abnormalities in safety laboratory tests including hemoglobin, leukocyte, neutrophil and platelet counts, hepatic transaminases, serum creatinine; use of prohibited CYP3A inhibitors or inducers; recent history of alcohol or drug abuse.

Endpoints in Phase 3 RA Development Program

The protocol-specified endpoints in the tofacitinib RA development program are based on the model summarized in Table 3.

The sponsor's choice of SF-36 as an endpoint in their Phase 3 studies has been driven by the results of qualitative studies from structured RA patient interviews that have identified global concepts, such as overall well-being as highly relevant to RA patients, along with pain, which is already captured as one of the ACR response criteria core components.

The development, measurement and psychometric properties, evidence of validity and reliability, limitations, and use of SF-36 as a measure of general health status are described in the next section "Brief Description of Short Form 36 (SF-36) Instrument".

Table 3. Efficacy Endpoint Model for the Phase 3 Confirmatory Studies in Tofacitinib RA Development Program

Concept/Outcome	Measurement Tool	Sample Endpoint
Signs and symptoms	ACR20, 50, 70	Proportion of subjects achieving >=20, 50, or 70% improvement in ACR responder criteria
Disease-specific Physical functioning	HAQ-DI	Change from baseline
Functional health status	SF-36v2 Health Survey	Change from baseline in all 8 SF-36 domains and the 2 summary measures (PCS and MCS)
Fatigue	FACIT-Fatigue	Change from baseline in FACIT-Fatigue scores
Sleep	MOS-Sleep Scale	Change from baseline in Overall Sleep and Sleep Problem Summary scales
Work participation	WLQ	Change from baseline in WLQ subscale scores

ACR20 = American College of Rheumatology >=20% improvement criteria[16]; HAQ-DI= Health Assessment Questionnaire – Disability Index; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; WLQ = Work Limitations Questionnaire; MOS-Sleep = Medical Outcomes Study–Sleep; SF-36 = SF-36v2 Health Survey.

Source: Patient Reported Outcome Evidence Dossier, Table 1.1

Detailed protocol design, study conduct and results of endpoints such as ACR responses and HAQ-DI for individual studies are discussed in the original NDA application and will not be discussed in this review.

Brief Description of Short Form 36 (SF-36) Instrument

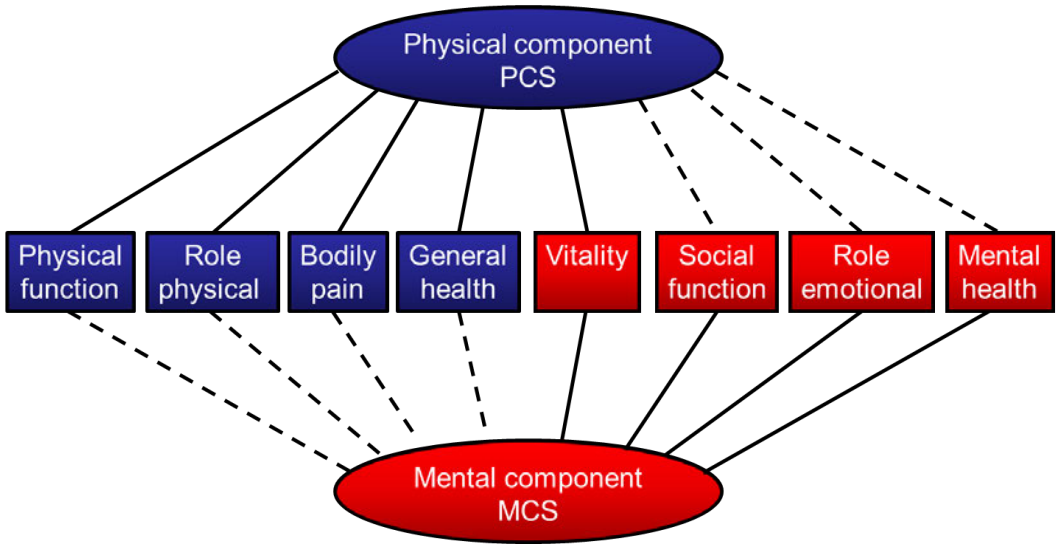
The SF-36 is a multi-purpose, short-form health survey. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index.

It was originally developed to satisfy minimum psychometric standards for group comparisons in 1980s and 90s and has been used in health planning and policy, and health services evaluation in an era of cost containment, and has subsequently been validated in many diseases, including RA and other rheumatic conditions. This is the most widely used health status questionnaire in the world, translated in over 130 languages and validated across countries and cultures, and reported in over 4000 publications.[xiv]

The SF-36 consists of 36 questions relating to either physical or mental health. One question asks respondents to rate the amount of change experienced in their health in general and the remaining 35 questions are divided into eight domains: four for physical health (physical health, bodily pain, physical functioning and physical role limitations) and four for mental health (mental health, vitality, social functioning and emotional role limitation). The eight domains are age, and gender adjusted and scored 0 (severe impairment) – 100 (no impairment).

Subsequently, two psychometrically-based summary measures, physical component summary (PCS) and mental component summary (MCS), were developed to simplify the analysis and interpretation of the SF-36. PCS measures how decrements in physical function affect day to day activities and MCS measures the impact of mental affect and symptoms of pain on quality of life. The PCS and MCS are reported based on normative-based scoring. The conceptual model to derive the two summary scores is presented in Figure 1, where the solid lines identify a major positive contribution to the summary score and the dashed lines indicate a negative contribution.

Figure 1. Conceptual Model for Deriving PCS and MCS from the Individual Domains



Several issues with the component scores have been raised by the SF-36 scientific community:

- Interpretation: There are issues with the interpretation of the summary scores (PCS and MCS) because both summary scores are calculated as a weighted sum of all eight subscale scores rather than the weighted sum of the four scales hypothesized in the measurement model (i.e., PCS consisting of PF, RP, BP, and GH; MCS consisting of VT, SF, RE, and MH).
- Many articles by measurement experts have voiced concern that the component scores do not adequately summarize the eight subscale scores.[xv, xvi]
- Multiple cases have been published where the change in component scores and the change in subscale scores have been inconsistent. Usually the inconsistencies occur in cases where there is a large effect in a domain subscale with a substantial negative factor coefficient.
- The method used by the developers forced the PCS and MCS to be uncorrelated. Several authors have stated that is unrealistic and is one of the causes for the negative factor scores coefficients. They proposed an alternative method that allows the PCS and MCS to be correlated. However, the developers respond that the alternative method is more difficult to interpret and there are still some negative

factor score coefficients although they are smaller in absolute value than the case that assumes the PCS and MCS are uncorrelated.[xvii]

- Several authors have shown for several different populations that the best fitting model is one that computes the component scores using only the four subscales they were hypothesized to include.

Table 4. Factor Score Coefficients for Calculating the SF-36 Summary Scores

Factor Score Coefficients for Calculating the SF-36 Summary Scores		
SF-36 Scale	**PCS**	**MCS**
Physical Functioning (PF)	0.42402	-0.22999
Role Physical (RP)	0.35119	-0.12329
Bodily Pain (BP)	0.31754	-0.09731
General Health (GH)	0.24954	-0.01571
Vitality (VT)	0.02877	0.23534
Social Functioning (SF)	-0.00753	0.26876
Role Emotional (RE)	-0.19206	0.43407
Mental Health (MH)	-0.22069	0.48581

- Acceptability of the factor score coefficients
  Because the factor score coefficients were derived from a sample of the U.S. general population, it is imperative to assess whether this sample has the same factor structure for the eight domain subscales as the RA patient population. Several authors have provided evidence that the factor structure was similar between the U.S. general population and the RA patient population.

Importantly, based on the above considerations and because of the potential loss of information and the risk of inappropriate conclusions with using only the eight domains or the summary scores, the SF-36 researchers have consistently emphasized the need to interpret the results of the domains, and PCS and MCS in parallel.

SF-36 in Tofacitinib Development Program

Statistical Analysis of SF-36 Data

Change from baseline SF-36 components and domains were analyzed as continuous variables using mixed effect repeated measures models, including fixed effects of treatment, non-baseline visit, treatment by non-baseline visit interaction, baseline measurement, and geographic region, and with random effect patient using compound symmetric covariance matrices. The timing of post-baseline SF36 assessments are described in Section "Overview of the Clinical Program" above.

Confidence intervals for the proportion of responders for each SF-36 component and domain were also calculated, using normal approximations to the binomial.

Statistical tests were conducted at the two sided 0.05 level of significance, and confidence intervals were calculated as two sided at the 95% level of confidence. However, because the endpoints were exploratory and examined without control of overall type 1 error, any statistically significant results claimed by the sponsor should be considered only as nominal, with calculated p-values underestimating true type 1 error probabilities.

Data used for statistical tests included all patients who received one dose of the study drug to which they were randomized.

Importantly, the SF-36 analyses were not included in the statistical hierarchy and therefore, the significance testing or associated control of type 1 error in the face of multiple hypothesis tests were not formally evaluated. Thus, the statistical tests for SF-36 are only nominal.

Handling of SF-36 Missing Data

Missing data for an SF-36 item on completed questionnaires was imputed as suggested by the producer of the SF-36 instrument, using the mean from the all other items within the same domain, provided at least 50% of the items in that domain were completed. Otherwise, missing values were not imputed, and only observed values, including data collected after patient escape or withdrawal from randomized treatment, were used in the analyses.

Patient Disposition

The population in the tofacitinib RA development program consisted of adult patients with long-standing, moderate-to-severely active RA who had inadequate response to one or more DMARDs or, in Study 1032, one or more TNF inhibitors. For further discussion on the patients' disease and demographic characteristics and disposition the reader is referred to the review of the original NDA application.

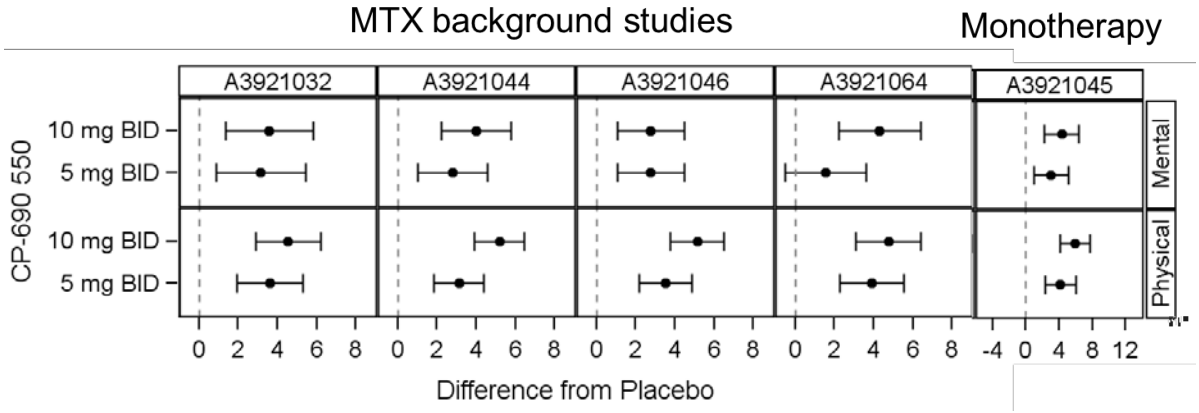
The overall proportion of missing SF-36 questionnaires was low across all five studies (less than 15% at Months 3 and 6) and balanced among the treatment groups, consistent with the patients' disposition described in the original NDA application. From the available SF-36 questionnaires, less than 0.5% of the items were missing, without a clear pattern to suggest a systematic bias in reporting.

Results of SF-36 Data

At Month 3, all five studies showed nominally significant differences between tofacitinib (5 and 10 mg BID dosing) and placebo for changes from baseline in SF-36 physical component score (PCS) score, and all but study 1064 showed nominally significant differences between tofacitinib (5 and 10 mg BID dosing) and placebo for changes from baseline in SF-36 mental component score (MCS) score as shown in Figure 2 below. The change in MCS in study 1064 was however in the same direction as the rest of the studies. The PCS and MCS responses

suggested a small incremental dose-response between tofacitinib 5 and 10 mg BID regimens, consistent with the overall treatment benefit observed in the primary efficacy endpoints, as discussed in the original NDA application.

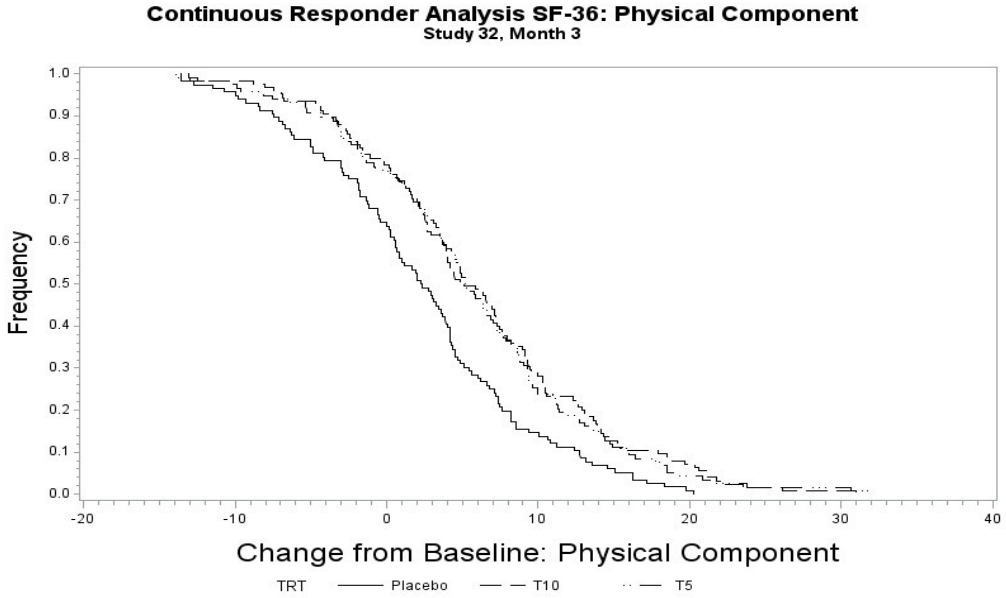
Figure 2. Summary of SF-36 PCS and MCS Data from Tofacitinib Confirmatory Studies in RA, by Study and By Dose at Month 3



Source: Patient Reported Outcome Evidence Dossier, Figures 3.2 and 3.4

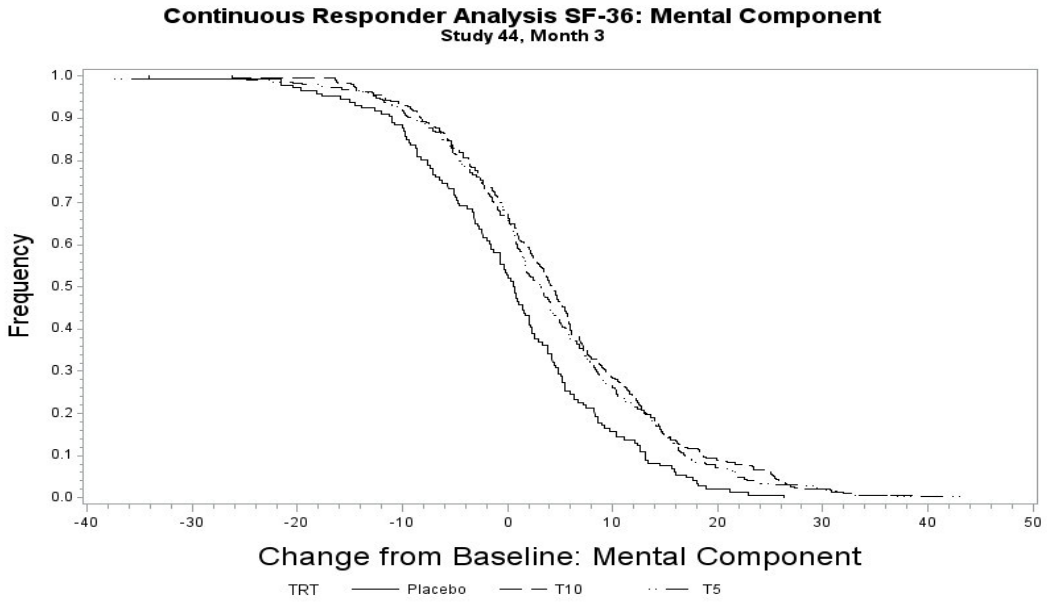
Sensitivity analysis, conducted by the FDA statistical reviewer, Dr. Robert Abugov examined the continuous responder functions between placebo and treatment showing consistent results with the analyses of the mean change from baseline with clear separation between the tofacitinib and placebo groups, as shown in Figure 3 as representative of SF-36 PCS data from study 1032 and in Figure 4 as representative of SF-36 MCS data from study 1044.

Figure 3. Change from Baseline SF-36 Physical Component Score, Month 3, Study 1032, Continuous Responder Analysis



Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.0037
Source: Dr. Abugov's statistical review

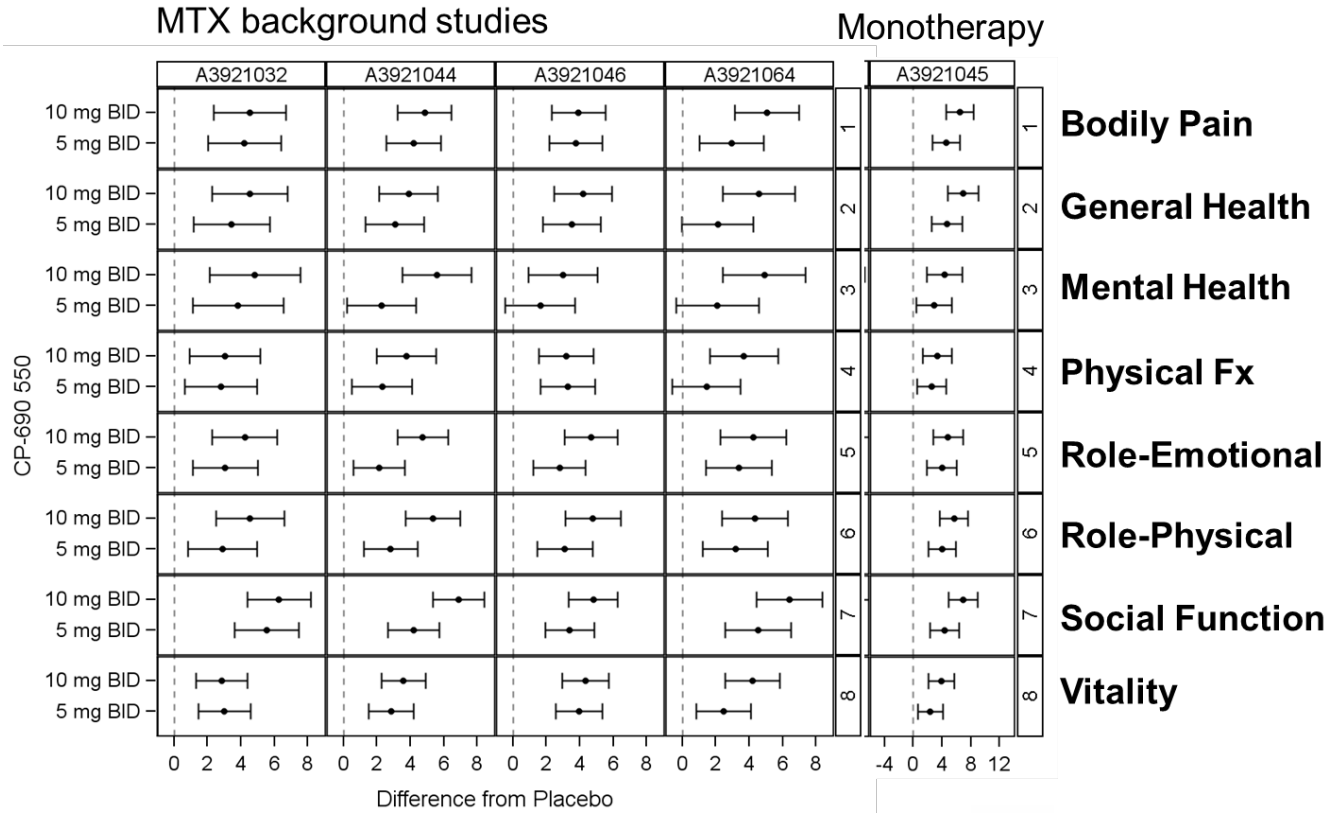
Figure 4. Change from Baseline SF-36 Mental Component Score, Month 3, Study 1044, Continuous Responder Analysis



Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.0260
Source: Dr. Abugov's statistical review

Further, all five studies showed consistent improvements in tofacitinib (5 and 10 mg BID dosing) as compared with placebo for changes from baseline in the individual SF-36 domains as shown in Figure 5 reaching nominal significance for studies 1032, 1044, and 1045 for all 8 domains. For studies 1046 and 1064, the results were also nominally significant for most of the domains with consistent trends in the rest of the domains.

Figure 5. Summary of SF-36 Domains Data from Tofacitinib Confirmatory Studies in RA, by Study and By Dose



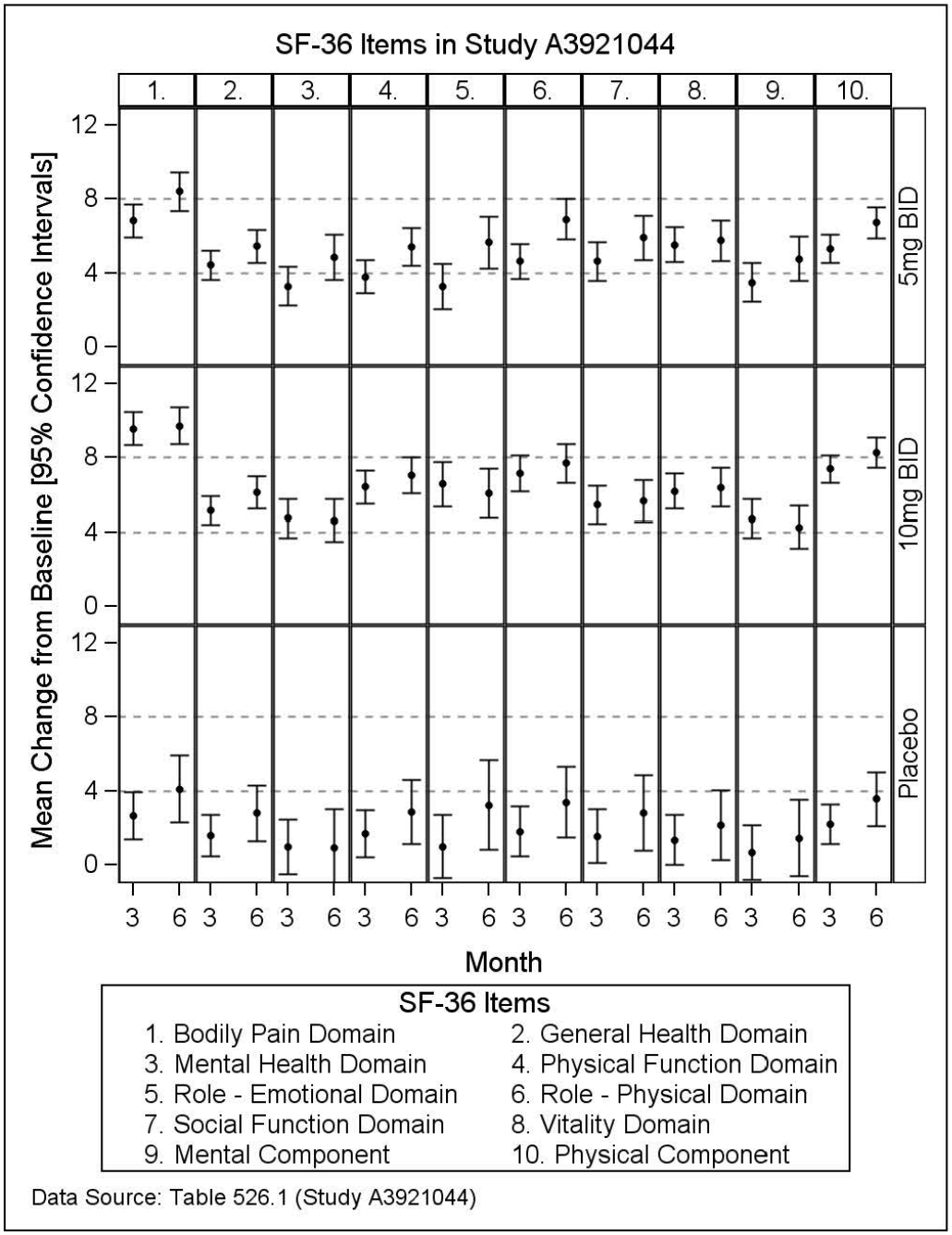
Source: Patient Reported Outcome Evidence Dossier, Figures 3.1 and 3.3

Timing of SF-36 assessment

The sponsor proposed to include Month 3 SF-36 data in the product labeling with the rationale that all five Phase 3 studies contributed placebo-controlled data for 3 months as opposed to only 3 studies (1044, 1046, and 1064) which had Month 6 placebo-controlled period. Further, the Month 6 data were confounded by the early escape and transition to active treatment before Month 6 as allowed by the protocols. Therefore, the Month 3 data were more robust to support the labeling claim. To further support the tofacitinib efficacy on SF-36, the sponsor has presented mean change from baseline in each of the SF-36 domains for both Month 3 and Month 6 which shows consistent efficacy across the year-long studies 1044, 1046, and 1064 represented in Figure 6 for study 1044 and Figure 7 for study 1065. Clinically significant improvements, i.e. exceeding the generally accepted minimally clinically important

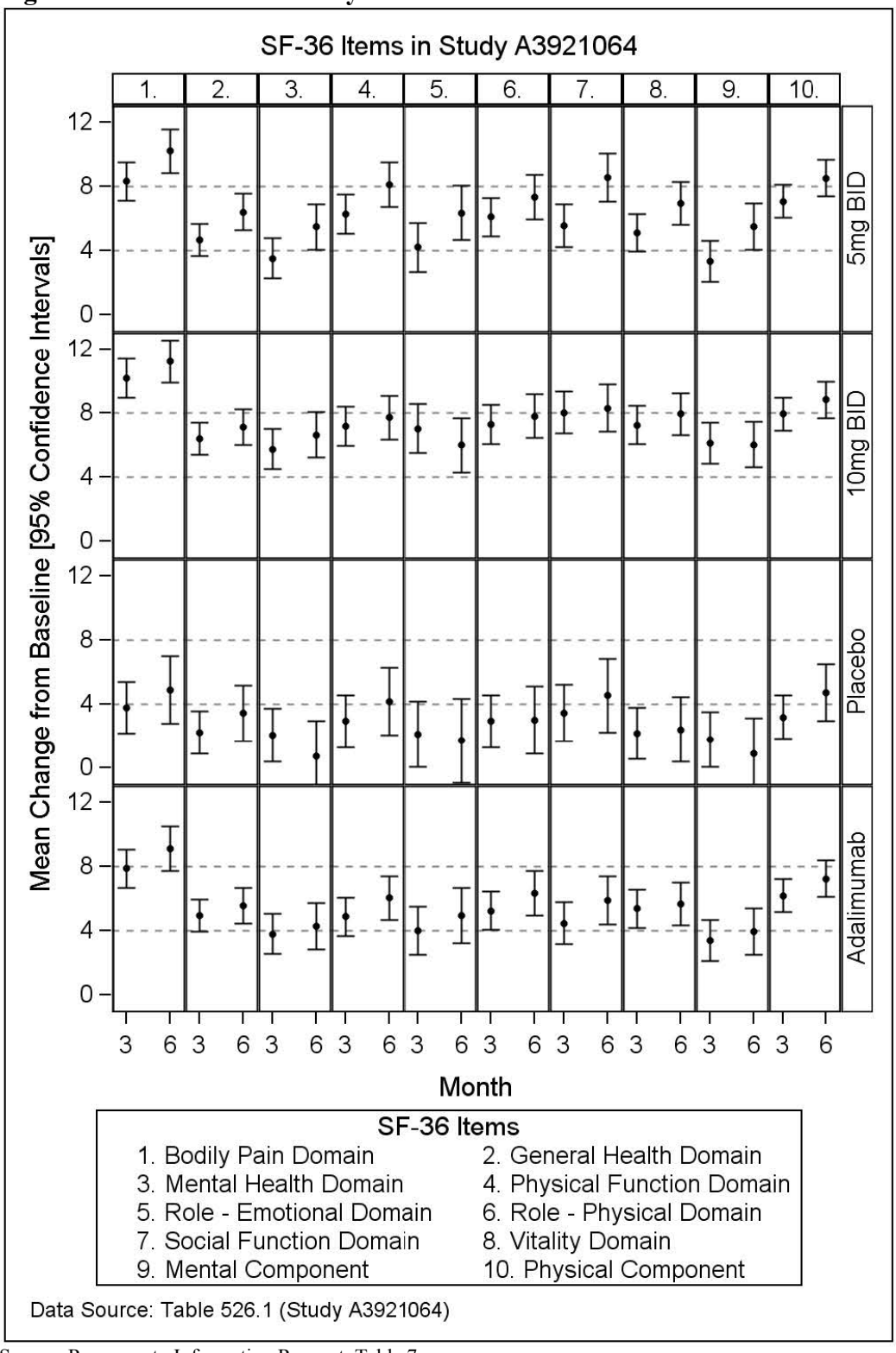
differences[xviii],[xix], were seen in tofacitinib-treated patients compared with placebo-treated patients at Month 3 supported by consistent results at Month 6 with changes from baseline.

Figure 6. SF-36 Items in Study 1044



Source: Response to Information Request, Table 6

Figure 7. SF-36 Items in Study 1064



Source: Response to Information Request, Table 7

The FDA analyses, conducted by the statistical review team, were in general agreement with the analyses presented by the sponsor.

Of note, these SF-36 results are consistent with the treatment effects observed in other RA products, as described in the published literature.[xx], [xxi], [xxii], [xxiii], [xxiv]

Because assessments of SF-36 were not included in the statistical hierarchy of testing and not controlled for type 1 error for multiple endpoints, true statistical significance and p-values could not be calculated. Collectively however, the SF-36 data from the Phase 3 clinical studies in this submission indicate that compared to placebo, tofacitinib 5 mg BID and 10 mg BID improves all eight SF-36 domains as well as PCS and MCS in patients with active RA supporting the proposed labeling language of:

(b) (4)

[redacted]

8. Safety

No new safety information was submitted with this supplement. The safety information from tofacitinib development 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.

Overall, the safety data from 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 (excluding non-melanoma skin cancer, NMSC) 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.

9. Advisory Committee Meeting

This supplemental application is for an ancillary claim for an already approved indication; thus no Advisory Committee meeting was warranted. An advisory committee meeting was held for the original NDA application on May 9, 2012.

10. Pediatrics

The pediatric issues were discussed in the reviews of the original NDA application.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues
- **Financial disclosures**—No issues
- **Other GCP issues**—No issues
- **DSI audits –** The OSI audits were conducted as part of the original NDA application
- **Other discipline consults**—Not applicable
- **Any other outstanding regulatory issues**—Not applicable

12. Labeling

- **Proprietary name**

The trade name for tofacitinib, Xeljanz, has already been reviewed and approved.

- **Address important issues raised by brief discussion of DDMAC and OSE Division comments.**

None.

- **Physician labeling**

I recommend the following major revisions (all to Section 14, Clinical Studies):

1) Proposed SF-36 labeling language:

- Describe SF-36 data under a separate subsection "Other Health Related Outcomes" to reflect the intended use of SF-36 as a general health status instrument and not only as supportive evidence of improvement in physical function.

- For completeness for SF-36 interpretation, include a description of physical component summary (PCS) and mental component summary (MCS) scores. This recommendation is consistent with standard practice in reporting SF-36 results because of the potential loss of information and the risk of inappropriate conclusions with using only the eight domains or the summary scores. Further, this approach is consistent with the analysis and reporting of composite endpoints, where the analyses and reporting of the individual components are descriptive without requiring statistical significance, i.e. adjusting for multiplicity.
- (b) (4)

Proposed labeling revisions (new language in *red* and deletions are in ~~*strikethrough*~~):

> ***"Other Health Related Outcomes***
> (b) (4) *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* (b) (4) *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."*

(b) (4)

Proposed labeling revisions (new language in *red* and deletions are in ~~*strikethrough*~~):

> *"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.* (b) (4) *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. ... "*
>
> (b) (4) *Study 1was a dose-ranging monotherapy trial not designed to provide comparative effectiveness data and should not be interpreted as evidence of superiority to adalimumab."*

- **Carton and immediate container labels (if problems are noted)**

Carton and container labels are already approved, and no changes are proposed or warranted.

- **Patient labeling/Medication guide (if considered or required)**

The Patient labeling/Medication guide is a part of REMS and was approved as with the original NDA application. No changes are proposed to the Patient labeling/Medication guide with this submission.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this supplement with revisions to the labeling as discussed in Section 12. Labeling.

- **Risk Benefit Assessment**

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 SF-36 results in Section 14 of the prescribing information. 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, and general health status..

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

This supplement does not warrant new or modification of the already approved postmarketing risk evaluation and management strategies (REMS).

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

This supplement does not warrant new postmarketing requirements or commitments.

- **Recommended Comments to Applicant**

None.

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/s/

NIKOLAY P NIKOLOV
10/11/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-3214/S002

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 #:	NDA 203,214 / SE-002
Supplement #:	
Drug Name:	Xeljans® (tofacitinib) tablets 5 or 10 mg BID
Indication(s):	Rheumatoid Arthritis (RA), SF-36 claim
Applicant:	Pfizer
Date(s):	1/18/2013 (submitted) 1/18/2013 (received) 11/18/2013 (PDUFA date)
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Scott Komo, Dr.P.H.
Concurring Reviewers:	Joan Buenconsejo, Ph.D.
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Nikolay Nikolov, M.D. (Medical Reviewer) Sarah Yim, M.D. (Supervisory Associate Director) Badrul A Chowdhury, M.D., Ph.D. (Medical Division Director)
Project Manager:	Philantha Bowen

Keywords: NDA review, labeling, factor analysis

Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

Table of Contents

1 EXECUTIVE SUMMARY

The Applicant submitted an NDA efficacy supplement for tofacitnib (NDA 203,214 SE-2) on 1/14/2013. They proposed to add the results for the 36-item short-form survey (SF-36) from their rheumatoid arthritis (RA) clinical trials to the current label for tofacitinib (XELJANZ). Currently, tofacitinib is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. The Applicant proposes to add the following language to the label:

The SF-36 was designed for use in the Medical Outcomes Study (MOS) as a measure of general health. The instrument covers eight health concepts or domains. It consists of three levels: (1) items; (2) eight domain scales that aggregate 2-10 items each; and, (3) two summary measures that aggregate scales. All but one of the thirty-six items (self-reported health transition) are used in the scoring of the eight scales. Also, each item is used in scoring only one scale.

Each of the eight domain scale scores is computed as the unweighted sum of the individual items included in the scale. The two summary scores, the physical component score (PCS) and the mental component score (MCS), were derived using a factor analytic method that consisted of a principal components analysis that selected two factors followed by an orthogonal (varimax) rotation. This analysis was conducted in subjects from a 1990 survey in the US general population.

Based on the submission and a review of the literature, I find there is evidence that the eight domain scales are reliable and have both cross-sectional and longitudinal construct validity in the RA patient population. However, there have been issues raised in the literature for the summary scores (PCS and MCS) on their interpretation, inconsistencies between changes in the domain scale and summary scores, and their adequacy as a summarization of the scale scores. Because of these potential issues, the developers (Ware et al., 2001) as well as other authors (Hann et al., 2008; Taft et al., 2007) recommend that interpretation of the summary scores should not be performed in isolation but instead be based on both the summary and domain scale scores.

Content validity, the extent to which the instrument measures the construct it purports to measure, was not evaluated in this review. Because of this fact, the following labeling recommendations are contingent on a finding that the instrument has adequate content validity. Based on the evidence reviewed, it is acceptable to report the results for the domain scale scores review. In addition, if reporting of the summary measures (PCS and MCS) is deemed to be informative, then I recommend that both the summary measures and the domain scale scores should be reported.

2 INTRODUCTION

This review evaluates the 36-item short form survey (SF-36) literature, including a description of the instrument, a discussion of its use in RA patients, and a discussion of the appropriateness of its inclusion in product labeling for RA products. It is important to note that a discussion of the content validity of this instrument will not be presented in this review. Also, the SF-36 results in the tofacitnib trials will not be discussed here; Dr. Robert Abugov, the statistical reviewer, will discuss the SF-36 results in his review.

An NDA efficacy supplement for tofacitnib (NDA 203,214 SE-2) was submitted on 1/14/2013. The Applicant proposed to add the SF-36 results from their rheumatoid arthritis (RA) clinical trials to the current label for tofacitinib (XELJANZ). Currently, tofacitinib is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. The Applicant proposes to add the following language to the label:

3 STATISTICAL EVALUATION

3.1 History of the SF-36

The 36-item short-form survey (SF-36) was designed for use in the Medical Outcomes Study (MOS) as a measure of general health. It was designed for use in clinical practice and research, health policy evaluations, and general population studies. It has an eight-scale profile of scores as well as physical and mental health summary measures. The instrument was first available in standard form in 1990 (Ware et al., 1990). The 36 items were chosen from 245 items included in the MOS. The items included in the SF-36 are presented in Appendix Table A-1.

There are two forms of the SF-36. The first is the acute form where item responses are based on a 1-week recall. The second form is the standard version where item responses are based on a 4-week recall.

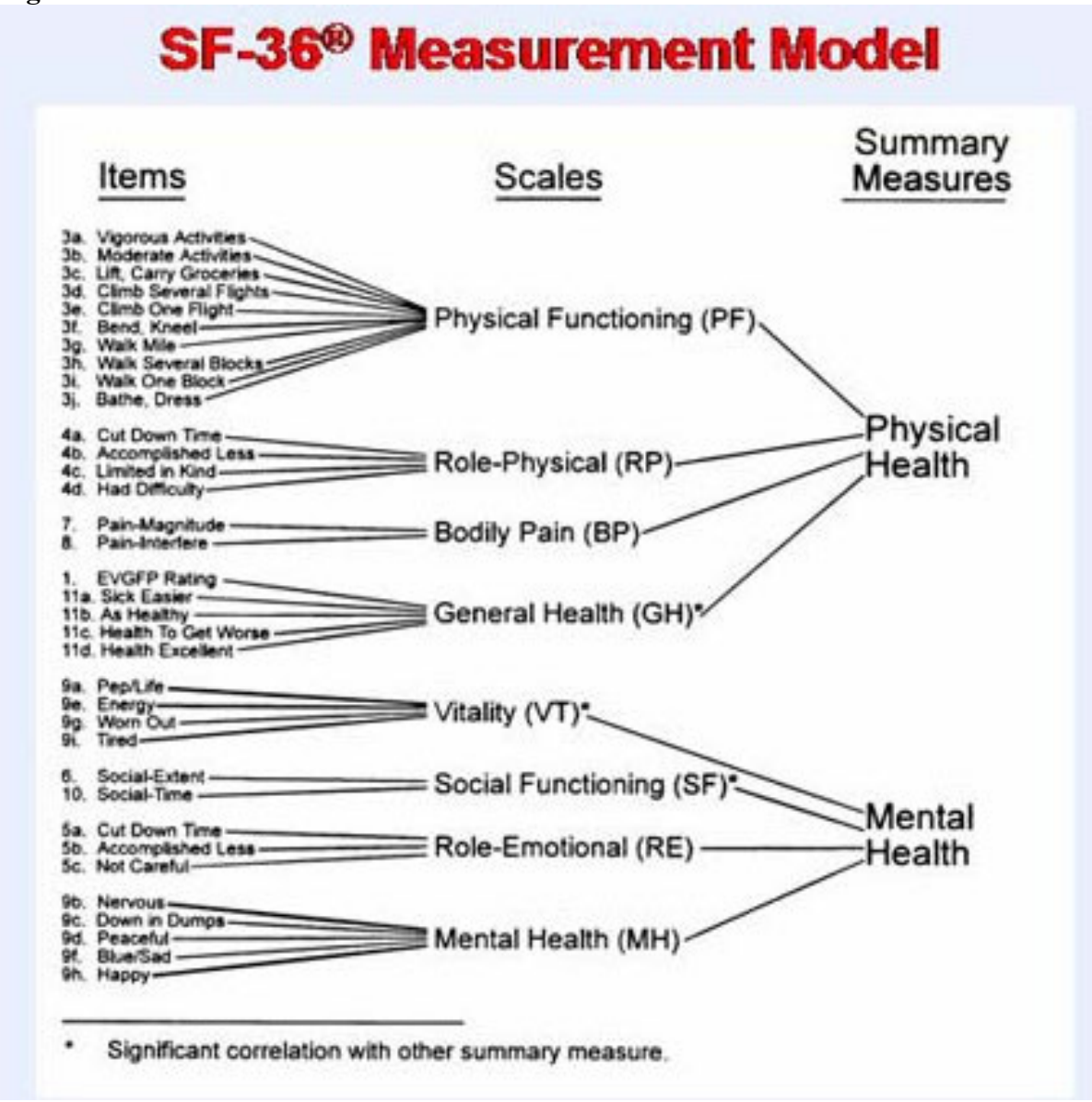
The developers included eight health concepts (out of the forty included in the MOS) that were most frequently included in widely used health surveys (physical functioning, role physical, social functioning, role emotional, mental health, and general health perceptions) as well as two additional concepts strongly supported by empirical work (bodily pain and vitality) (Ware et al., 1992).

The instrument has three levels: (1) items; (2) eight scales that aggregate 2-10 items each; and, (3) two summary measures that aggregate scales. All but one of the thirty-six items (self-reported

health transition) are used in the scoring of the eight scales. Also, each item is used in scoring only one scale.

Figure 1 depicts the conceptual model for the SF-36:

Figure 1: SF-36 measurement model



Source: Ware et al., (2000)

Summary Scores

The eight scales were hypothesized to form two distinct factors due to the physical and mental health variance they have in common. The developers used a factor analytic method that consisted of a principal components analysis that selected two factors followed by an orthogonal (varimax) rotation, which forced the two components to be uncorrelated. Principal components

analysis is a dimension reduction technique that attempts to form a small number of linear combinations (components) of the variables (scale scores) that capture most of the information contained in the variables (scale scores). The motivation for the subsequent rotation was to make the results more interpretable by rotating the factors to find a pattern of factor loadings where items load most strongly on one factor, and much more weakly on the other factor. In this case, the factor loadings are the correlations of the summary scores with the eight scale scores. Based on the correlation pattern of the summary scores with the eight scale scores, the summary scores have been interpreted as the physical and mental components of health status.

Using this procedure, several studies showed that the physical and mental health factors accounted for 80-85% of the variance in the eight scales for the U.S. general population (Ware et al., 1994) and among MOS patients (McHorney et al., 1993; Ware et al., 1994). The discovery that most of the reliable variance in the eight SF-36 scales could be captured in two components led to construction of the physical and mental health summary measures. The developers hoped that the use of summary measures would make it possible to reduce the number of statistical comparisons involved in analyzing the SF-36, from eight to two, without a substantial loss of information.

It is important to note that the summary scores were not constructed based on a conceptual model depicted in Figure 1 (i.e., each summary score composed of 4 scales) but were instead derived empirically from analyses of subjects from a 1990 survey in the US general population using a principal components analysis. This analytic approach resulted in a situation where each summary score (component) is constructed as a weighted sum of ALL eight scale scores. In addition, these summary scores (components) are uncorrelated with each other with the weights chosen to maximize the scale score variance explained among the fewest number of components.

3.2 Scoring of the Instrument

For items, scales, and component scores, the SF-36 is scored such that a higher score indicates a better health state. Details of the scoring algorithm used to compute scale and component scores can be found in Ware et al. (2000); a summary is presented below.

Each of the eight scale scores is computed using the Likert method of summated scoring for items within each scale, i.e. an unweighted sum of the individual items. These scale scores are called the raw scale scores. The Likert summative method of scoring assumes that the item mean and variance for items within the same scale are roughly equal.

The raw scale scores are linearly transformed to a 0 - 100 scale. These scores are called the transformed scale scores and for each scale, they are computed as follows:

$$\text{Transformed scale score} = \frac{\text{Raw scale score} - \text{Smallest possible raw score}}{\text{Largest possible range for raw scale scores}} \times 100$$

Standardized scale scores are computed using the transformed scale scores. The scores are standardized using the norms from a 1998 survey of the U.S. general population (Norms are

available for standard form: Appendix Table A-2 and acute form: Appendix Table A-3). For each scale, the standardized scale score is computed as follows:

$$\text{Standardized scale score} = \frac{\text{Transformed scale score} - \text{norm mean}}{\text{norm standard deviation}}$$

To allow comparison across both scale scores and the summary measures described below, the developers created norm-based scores. They used data from a 1998 general U.S. population survey as the norms. Linear transformations were performed to transform scores to a 0 – 100 scale such that the general U.S. population would have a mean of 50 and a standard deviations of 10. This transformation achieves the same mean and standard deviation for all eight scales. Each scale score is computed using the standardized scale scores as computed above. For each scale, the norm-based scale scores are computed below:

$$\text{Norm-based scale score} = (\text{Standardized scale score} \times 10) + 50$$

The two summary measures, the physical component score (PCS) and the mental component score (MCS), are calculated using the standardized scores calculated above and the factor score coefficients derived from a factor analysis of the standardized scale scores in a 1990 survey of the U.S. general population. Aggregate component scores are first calculated as the sum of the products of the standardized scale score and the factor score. Norm-based component scores are then calculated by multiplying the aggregate component scores by 10 and adding 50 to each quantity.

To handle missing data for any of the items, the developers recommended an algorithm that substitutes a person-specific mean of the completed items in the same scale for any missing item when the respondent answered at least 50 percent of the items in a scale. If more than 50% of the items in a scale are missing then the scale score will be considered missing. In addition, if any of the scale scores are missing, then the summary scores will also be considered missing.

3.3 Psychometric properties of the SF-36 as a generic instrument of health

The psychometric properties of the SF-36 in the general U.S. population have been extensively studied (Ware et al., 2000). A brief summary of the psychometric findings for the general U.S. population is presented below.

In order demonstrate content validity of the instrument in the general population, the developers pointed out that the SF-36 includes eight of the most frequently measured health concepts measured in most of the widely available generic health surveys. In addition, the SF-36 scales correlate substantially ($r \geq 0.40$) with most of the general health concepts omitted from this instrument but included in the MOS and also with the frequency and severity of many symptoms and problems.

To assess the content validity of the summary scores, the developers examined the factor loadings of the scale scores for the two summary scores. They found that the scales loaded highest on the component they were hypothesized to belong to. In addition, mental health, role emotional, and social functioning scales and the mental component score (MCS) summary

measure have been shown to be the most valid of the SF-36 scales as mental health measures. This pattern of results has been replicated in both cross-cultural and longitudinal tests using the method of known-groups validity. The physical functioning, role physical, and bodily pain scales and the physical component score (PCS) summary were shown to be the most valid SF-36 scales for measuring physical health

To assess criterion validity, the developers compared the SF-36 scales to the longer scales included in the MOS. Relative to the longer MOS measures they were constructed to reproduce, the SF-36 scales captured approximately 80-90% of the information in the longer MOS scales (McHorney et al., 1993).

Ware et al. (1992) confirmed the acceptability of the method of summated ratings and standardized SF-36 scoring algorithms. They showed that the items can be aggregated without score standardization or item weighing. The developers did not feel the need for standardization of items within a scale because the items had roughly equivalent means and standard deviations. They also did not feel there was a need to weight items because the items were felt to be equally representative (i.e., items with roughly equivalent relationships to the underlying scale dimension).

The correlation between each item and its hypothesized scale was used to assess item-internal consistency. An item was deemed to be internally consistent if the correlation was greater than or equal to 0.40. Because of the small number of items in some of the scales, the internal consistency correlation estimates were corrected to account for the overlap between that item and the scale score. The correction amounted to estimating the correlation between the item and the sum of all other items in the same scale (Howard and Forehand, 1962). All items have been shown to correlate substantially ($r \geq 0.40$, corrected for overlap) with their hypothesized scales with rare exceptions (McHorney et al., 1993; Ware et al., 1993).

Item discriminant validity was assessed to determine whether each item correlates higher with its hypothesized scale than with the other scales. When the correlation between an SF-36 item and its hypothesized scale (concept) was significantly higher than the correlations with other SF-36 scales, its inclusion in that hypothesized item grouping was supported. A success was counted whenever an item correlated significantly higher (two standard errors or more) with its hypothesized scale compared to another SF-36 scale. The item discriminant validity success rate was computed by dividing the total number of successes by the total number of tests performed. Ware et al. (2000) found that the SF-36 consistently demonstrated strong item discriminant validity.

3.4 SF-36 in Rheumatoid Arthritis Patients

As discussed above, the developers provided psychometric evidence for the use of the SF-36 as a generic health instrument in the general population. However, we cannot assume that the psychometric evidence provided by the developers for the US general population can be extrapolated to RA patients. Thus, evidence needs to be provided that the SF-36 is a valid and reliable instrument in the RA population. A discussion of the psychometric evidence follows, along with a discussion on its interpretation in this setting.

The SF-36 has been shown to be reliable in sample of patients from four clinical trials of patients with osteoarthritis and RA (Kosinski et al., 1999). Reliability was demonstrated using an intraclass correlation coefficient (ICC). The intraclass correlation coefficient (ICC) was highest for scales primarily associated with physical health (PF, RP, BP), vitality (VT) and general health (GH) while scales primarily associated with mental health (SF, RE, and MH) had lower ICC value (see Table 1).

Kosinski et al., 1999) also found the SF-36 scales to have high internal-consistency, as measured by Cronbach's alpha ($\alpha \geq 0.7$), across four clinical trials of patients with osteoarthritis and RA (see Table 1).

Table 1: Reliability of the SF-36 in osteoarthritis and RA patients

Table 2.3 – Reliability of the SF-36 scales in RA patients[50]

Reliability	PF	RP	BP	GH	VT	SF	RE	MH
Test-retest								
ICC*	0.88	0.83	0.90	0.82	0.91	0.52	0.66	0.55
Cronbach's Alpha								
Range across 4 clinical trial	0.88	0.86	0.75	0.76	0.81	0.80	0.84	0.79
samples of OA and RA	-	-	-	-	-	-	-	-
	0.91	0.87	0.85	0.79	0.87	0.87	0.88	0.84
RA patients from MIRA Trial	0.94	0.88	0.87	0.81	0.87	0.83	0.82	0.82

PF = Physical Functioning; RP = Role Physical; BP = Bodily Pain; GH = General Health; VT = Vitality; SF = Social Functioning; RE = Role Emotional; MH = Mental Health; OA = Osteoarthritis; RA = Rheumatoid Arthritis; MIRA = Minocycline In Rheumatoid Arthritis; ICC = Intraclass Correlation Coefficient

**150 RA patients recruited from an outpatient clinic who reported no change after 2 weeks.*

Source: Kosinski et al. 1999

The Applicant provided evidence of convergent validity of the SF-36 in RA patients by showing that the SF-36 scale scores correlated well ($r \geq 0.40$) with the efficacy endpoints used in the tofacitinib trials. Specifically, the SF-36 scales correlated well with the joint tenderness scores and both the physician and patient global assessment scores in the five tofacitnib clinical trials.

In the tofacitinib trials, the Applicant also assessed construct validity by evaluating how well the SF-36 scale scores were able to distinguish between RA patients known to differ in key criterion variables. The magnitude of change was generally consistent with groups based on Disease Activity Score- 28 (DAS28) and arthritis activity severity. In particular, the physical functioning, bodily pain, and role emotional scales were able to discriminate across all three (low/moderate/high) DAS28-based RA patient groups, while the bodily pain, vitality, and mental health scales were able to differentiate groups based on self-reported arthritis activity (low/moderate/high).

In addition, Tuttleman et al. (1997) also demonstrated the convergent validity of the SF-36 in RA patients. As can be seen from Table 2, the BP scale correlated well (all correlations ≥ 0.40) with the joint tenderness, joint swelling, physician global, and patient global measures, with estimates similar to those observed for pain measured using a visual analog scale (VAS). The PF, RP and

SF scales correlated well with joint tenderness scores and physician and patient global scores, but not with joint swelling scores. The RE and MH scales tended to have lower correlations with the four measures of disease activity.

Table 2: Spearman correlations of SF-36 scales with outcome measures using in RA trials

Outcome measure	PF	RP	BP	GH	VT	SF	RE	MH	M-HAQ	Pain VAS
MIRA trial (n=207)										
Tenderness[(1)]	-0.47	-0.44	-0.59	-0.44	-0.51	-0.49	-0.27	-0.36	0.57	0.60
Swelling[(1)]	-0.29	-0.30	-0.44	-0.26	-0.27	-0.31	-0.13	-0.24	0.33	0.44
Physician Global[(1)]	-0.42	-0.43	-0.56	-0.32	-0.38	-0.41	-0.27	-0.28	0.55	0.59
Patient Global[(1)]	-0.41	-0.43	-0.64	-0.39	-0.44	-0.42	-0.23	-0.27	0.59	0.66

PF = Physical Functioning; RP = Role Physical; BP = Bodily Pain; GH = General Health; VT = Vitality; SF = Social Functioning; RE = Role Emotional; MH = Mental Health; OA = Osteoarthritis; RA = Rheumatoid Arthritis;

Source: Tuttleman et al. (1997)

Because the summary measures are computed using the factor loadings from U.S. general population, it is essential that the factor structure is similar for the general population and RA patients. Hann and Reeves (2008) found that the factor structure (factor score loadings) can vary considerably by disease. Kosinski et al (1999) found a similar factor structure for subjects in the U.S. general population and subjects in four clinical trials of osteoarthritis and rheumatoid arthritis. They assessed similarity in factor structure examining the correlations of the eight scales with the summary measures. As can be seen in Table 3, the correlations between the scale scores and the summary scores are similar for the arthritis trials and the U.S. general population.

Table 3: Correlations of scale and summary scores for the US General Population and Arthritis Patients

SF-36 Scales	Hypothesized Factor Content (P/M)*	Arthritis Trials		U.S. Population†	
		PCS	MCS	PCS	MCS
PF	P	.81	.23	.85	.12
RP	P	.75	.36	.81	.27
BP	P	.74	.37	.76	.28
GH	P/M	.55	.47	.69	.37
VT	M/P	.48	.60	.47	.64
SF	M	.55	.68	.42	.67
RE	M	.16	.83	.17	.78
MH	M	.11	.85	.17	.87

* P, physical factor content; M, mental factor content.

† Reprinted with permission from Ware et al. SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.

PF, Physical Functioning; RP, Role Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental Health.

Source: Kosinksi et al. (1999)

Tugwell et al. (2007) provided evidence of the responsiveness of the SF-36 summary measures from seven clinical trials of patients with osteoarthritis and RA. The standardized response mean

across the seven trials was 0.42 for PCS and 0.21 for MCS, suggesting a moderate effect size for PCS and a small effect size for MCS.

3.5 Interpretation of results for the SF-36

A critical piece of information required to interpret SF-36 analyses in a clinical trial is the minimum clinically important difference (MCID). The MCID is defined as the minimum change (improvement) for a -patient considered to be clinically meaningful. This information is critical to ensure that the observed treatment effect is clinically meaningful to RA patients. Strand et al. (2007) noted that changes of five to ten points in domain scores and 2.5 to 5.0 points in PCS and MCS are have been found to represent an MID in clinical trials of arthritis patients.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

Missing Data

The endpoint of interest in the clinical trials using the SF-36 is generally either the domain scores (e.g. tofacitinib) or the summary scores. Because items are generally not the endpoint of interest, Sponsors often do not explicitly state in either the protocol or statistical analysis plan how they handle missing items but rather state they followed the instrument developer's scoring algorithms.

It is important that the proportion of missing items be reported by individual item. The amount of missing item data may be not be readily apparent because, as stated previously, missing item data are usually imputed using the person-specific mean of the non-missing items in the same scale as long as the respondent answered at least 50 percent of the items in a scale. The magnitude of item missingness is needed in order to assess data quality. In addition, the use of the developer recommended imputation method has the potential for bias because in some of the scales, e.g. physical functioning, items ask about activities of varying difficulty (see Appendix Table A-1). Thus, if the more difficult items were missing and their response imputed by the average of the easier items, this could potentially bias the scale score estimate.

It was determined for the tofacitinib submission that missing data were not a large concern because very few items were missing.

Issues with the Summary Scores

There has been debate on the use of the SF-36 summary scores. The issues with the summary scores focus on their interpretation, the inconsistencies between changes in the scale and summary scores, and their adequacy as a summarization of the scale scores. I will discuss the individual issues below.

Questions have arisen on the interpretation of the summary scores because they are a weighted sum of all eight scales. As discussed earlier, this is due to the developer's use of a factor analysis to compute the summary scores. The ensuing discussion will provide greater details on the

developer's method of summary score calculation and point out potential issues in the methods used.

As discussed previously, the summary scores were developed using a principal components analysis (PCA) in order to capture most of the scale score information followed by an orthogonal rotation, performed to increase the interpretability of the factors. A major criticism of the rotations used in factor analysis is that there is no unique pattern of factor loadings, i.e. there are an infinite number of patterns of factor loadings that fit the data equally well, and researchers can pick the rotation that results in a pattern of factor loadings that most closely fits their hypothesized model.

When looking at the pattern of factor loadings from which the developers posited that the two components represented the physical and mental aspects of health, it can be seen that some of the domains load substantially on both components (see Table 4). The developers point out that the middle four scales (BP, GH, VT and SF) are the most complicated with respect to factor content. They state, "This should not be surprising; SF items, for example, ask about both physical and mental health status." They point out substantial confounding is introduced because each of these scales adds information about more than one component of health.

Table 4: Factor Loadings

Domain	*PCS*	*MCS*
PF	0.88	0.04
RP	0.78	0.30
BP	0.77	0.24
MH	0.12	0.90
RE	0.19	0.81
SF	0.44	0.71
VT	0.59	0.57
GH	0.68	0.32

Source: Ware et al. (2001)

The factor score coefficients used in the summary score calculations are presented in Table 5. Some authors expressed concern with the factor coefficients and their effect on the summary scores. Authors have pointed out several potential issues with the summary scores and found that the factor coefficients are the likely problem. When examining the factor scores coefficients, it is important to note that the scales not hypothesized to belong to the summary measures based on the conceptual model (i.e., PCS: VT, SF, RE, and MH; MCS: PF, RP, BP, and GH) have negative coefficients. In addition, the absolute value of some of these negative coefficients is substantial (PCS: RE and MH; MCS: PF).

Table 5: Factor Score Coefficients

SF-36 Scale	PCS	MCS
PF	0.42402	-0.22999
RP	0.35119	-0.12329
BP	0.31754	-0.09731
GH	0.24954	-0.01571
VT	0.02877	0.23534
SF	-0.00753	0.26876
RE	-0.19206	0.43407
MH	-0.22069	0.48581

Source: Ware et al., 2000

Multiple published cases (Simon et al., 1998; Thombs et al., 2008) warn of inconsistent results between changes in scale and summary scores. Simon et al. (1998) provided an example of this inconsistency in a study of 536 patients taking antidepressant treatment. At baseline, patients had modest impairment in the PF, RP, BP, and GH scales (0.10 to 0.68 standard deviations below national norms) but showed no impairment on the PCS (mean=51). At month 3, all four scales (PF, RP, BP, and GH) showed statistically significant improvement but the PCS was unchanged (mean=50). The authors warn these inconsistencies are more likely to occur in cases where there is a large treatment effect in a scale with a substantial negative factor coefficient. For PCS, this would be either the RE or MH scale and for the MCS, this would be either the PF, RP, or BP scale.

Taft (2001) questioned whether summary scores adequately represent the scale scores. Nortvedt et al. (2000) reported that MCS scores considerably underestimated the mental health problems of multiple sclerosis patients. They found that the MCS was closer to the norm than expected given that the scores for the four scales most related to mental health (SF, RE, MH, and VT) were considerably below the norm and there was a high prevalence of depression. Farivar (2007) also found inconsistencies in a random sample of patients who received medical care. They found that the PCS underestimated physical health status relative to the norm and that the MCS was more similar to the norm than warranted in their study where the physical scale scores were well below the norm and mental scale scores were somewhat below the norm.

Ware et al. (2001) responded that potential inconsistencies cited by Taft (2001) were hypothetical and not a real life issue. The results for the scale and summary scores were consistent in their review of approximately 250 treatment trials. They also reported on a 52-week treatment trial of approximately 400 RA patients that found consistent results between scale and summary scores.

Multiple authors (Farivar et al. 2007, Hann et al. 2008) questioned the algorithm that used an orthogonal rotation that forced the PCS and MCS to be uncorrelated. The cited issue is that it is not realistic to assume physical and mental health are uncorrelated. The authors think this is the main reason for the substantial negative factor score coefficients and their potential problems cited above.

Farivar et al. (2007) and Hann et al. (2008) proposed an alternative method that uses an oblique rotation that allows the summary scores to be correlated. This rotation resulted in very few negative factor score coefficients and even those few were close to zero. They also found that there was substantial correlation between PCS and MCS (0.4 - 0.7) when the factors are allowed to be correlated.

However, the developers (Ware et al., 2001) stated, "Orthogonal (uncorrelated) scores for the two principal health components best discriminate between physical and mental health outcomes." In the same article, they also state, "These components would not be as valid as the best scale, particularly when differences are concentrated in one scale." They encouraged that interpretation of the summary scores should be done in concert with a profile of the scale scores.

They cautioned that the summary scores should be interpreted carefully when the condition of treatment has strong effect on a scale with a substantial negative component. Use of the oblique rotation also decreased the extent to which scales loaded positively to one component and negatively to the other.

4.2 Conclusions and Recommendations

As discussed in the previous section, there is evidence that the eight domain scales are reliable and have both cross-sectional and longitudinal construct validity in the RA patient population. However, there have been issues raised in the literature for the summary scores (PCS and MCS) on their interpretation, inconsistencies between changes in the domain scale and summary scores, and their adequacy as a summarization of the scale scores. Because of these potential issues, the developers (Ware et al., 2001) as well as other authors (Hann et al., 2008; Taft et al., 2007) recommend that interpretation of the summary scores should not be performed in isolation but instead be based on both the summary and domain scale scores.

Content validity, the extent to which the instrument measures the construct it purports to measure, was not evaluated in this review. Because of this fact, the following labeling recommendations are contingent on a finding that the instrument has adequate content validity. Based on the evidence reviewed, it is acceptable to report the results for the domain scale scores review. In addition, if reporting of the summary measures (PCS and MCS) is deemed to be informative, then I recommend that both the summary measures and the domain scale scores should be reported.

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APPENDICES

Table A-1: Items in SF-36 (version 2) by Scale

Scale	Item	Item Content
Physical Functioning (PF)	3a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
	3b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
	3c	Lifting or carrying groceries
	3d	Climbing several flights of stairs
	3e	Climbing one flight of stairs
	3f	Bending, kneeling, or stooping
	3g	Walking more than one mile
	3h	Walking several hundred yards
	3i	Bathing or dr4essing yourself
Role Physical (RP)	4a	Cut down the amount of time you spent on work or other activities
	4b	Accomplished less than you would like
	4c	Were limited in the kind of work or other activities
	4d	Had difficulty performing the work or other activities (for example, it took extra effort)
Bodily Pain (BP)	7	Intensity of bodily pain
	8	Extent pain interfered with normal work
General Health (GH)	1	Is your health: excellent, very good, good, fair, poor
	11a	I seem to get sick a little easier than other people
	11b	I am as healthy as anybody I know
	11c	I expect my health to get worse
	11d	My health is excellent
Vitality (VT)	9a	Feel full of life
	9e	Have a lot of energy
	9g	Feel worn out
	9i	Feel tired
Social Functioning (SF)	6	Extent health problems interfered with normal social activities
	10	Frequency health problems interfered with social activities
Role Emotional (RE)	5a	Cut down the amount of time spent on work or other activities
	5b	Accomplished less than you would like
	5c	Did work or other activities less carefully than usual
Mental Health (MH)	9b	Been very nervous
	9c	Felt so down in the dumps that nothing could cheer you up
	9d	Felt calm and peaceful
	9f	Felt downhearted and depressed
	9h	Been happy
Reported Health Transition (HT)	2	Rating of health now compared to one year ago

Source: Ware et al., 2000

Table A-2: 1998 General U.S. Population Means and Standard Deviations (Standard form)

SF-36 Scale	Mean	Standard Deviation
PF	83.29094	23.75883
RP	82.50964	25.52028
BP	71.32527	23.66224
GH	70.84570	20.97821
VT	58.31411	20.01923
SF	84.30250	22.91921
RE	87.39733	21.43778
MH	74.98685	17.75604

Source: Ware et al. (2000)

Table A-3: 1998 General U.S. Population Means and Standard Deviations (Acute form)

SF-36 Scale	Mean	SD
PF	82.62455	24.43176
RP	82.65109	26.19282
BP	73.86999	24.00884
GH	70.78372	21.28902
VT	58.41968	20.87823
SF	85.11568	23.24464
RE	87.50009	22.01216
MH	75.76034	18.04746

Source: Ware et al. (2000)

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/s/

SCOTT S KOMO
11/06/2013

JOAN K BUENCONSEJO
11/07/2013
I concur

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

Statistical Review

CLINICAL STUDY

NDA / Sequence Number:	sNDA 203214 / Seq 0060
Drug Name:	Xeljans® (tofacitinib)
Proposed Claim:	SF-36 Domains
Current Indication:	Rheumatoid arthritis
Applicant:	Pfizer
Date(s):	Received: 01-18-2013 PDUFA Due Date: 11-18-2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II/Office of Biostatistics
Statistical Reviewer:	Robert Abugov, Ph.D.
Concurring Reviewer:	Joan Buenconsejo, Ph.D.
Statistics Supervisor:	Thomas Permutt, Ph.D. (Division Director)
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
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Project Manager:	Colette Jackson

Keywords: NDA review, Clinical Studies

Contents

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1 EXECUTIVE SUMMARY

Pfizer has proposed inclusion of additional endpoints, all eight domains of Short Form 36 (SF-36), on the clinical study section of the product label for Xeljanz (tofacitinib) administered twice daily (bid) in 5 mg or 10 mg tablets for the treatment of patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate.

This submission strongly suggests that, compared to placebo, tofacitinib 5 mg or 10 mg bid improves all eight SF-36 domains in patients with active RA. Determination of true statistical confidence was not possible because, in the exploratory analyses provided by the sponsor, type 1 error was not controlled for multiple endpoints. Nevertheless, the difference between tofacitinib and placebo was numerically positive in all five studies for all eight SF-36 domains, suggesting that the observed improvements were not spurious.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Pfizer proposes inclusion of additional endpoints, all eight domains of SF-36, on the clinical study section of the product label for tofactinib, a Janus kinase inhibitor already approved for the treatment of patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate.

2.1.2 History of Drug Development

The original biometrics review of tofacitinib for the treatment of RA was submitted to DARRTS by Dr. Yongman Kim on June 25, 2012, with approval granted November 6, 2012. Dr. Kim's review provided an extensive account of the drug development history; highlights are summarized below.

The development program for tofacitinib was first introduced to the Agency in 2004 under IND 070903, with the EOP2 meeting conducted in December 2008. A teleconference was held with the sponsor in January 2010 to discuss submitted phase 3 protocols, with statistical discussions focusing on control of type 1 error and handling of missing data. At the subsequent pre-NDA meeting held in February 2011, the Agency informally agreed to the proposed format for the submission, with tofacitinib 10mg bid (T10) and 5mg bid (T5) dose regimens to be tested for safety and efficacy. In May 2012, an Arthritis Advisory Committee voted 10 to 0 that efficacy had been demonstrated for signs and symptoms as well as quality of life in patients with rheumatoid arthritis, and recommended approval of the 5mg bid dose regimen. Approval for the 5mg bid dose was granted by the Agency on November 6, 1012.

Dr. Kim's review noted several problems in the submission, lack of control of type 1 error for some endpoints and use of modified intent to treat (patients administered at least one dose of randomized study medication) rather intent to treat populations for evaluation of efficacy.

Although the proposed label supplement for SF-36 claims positive results from three studies, the current review will address all five phase 3 studies in the original RA submission (Table 1).

Table 1. Randomized Phase 3 Efficacy Studies for RA

Study	Design	Population	SF-36 Label Claims
A3921032 (Study V)	P bid + MTX T5 bid + MTX T10 bid + MTX Parallel arm DB P to W12	Adults Active RA Inadequate resp to TNF N=399 1:1:1	All domains, W12
A3921044 (Study IV)	P bid + MTX T5 bid + MTX T10 bid + MTX Parallel arm DB EE W12 P to W24	Adults Active RA Inadequate resp to MTX N=797 1:2:2	All domains, W12
A3921064 (Study III)	P bid + MTX T5 bid + MTX T10 bid + MTX A40 q2W + MTX Parallel arm DB EE W12 P to W24	Adults Active RA Inadequate resp to MTX N=717 1:2:2:2	Not claimed
A3921046 (Study II)	P bid + DMARD T5 bid + DMARD T10 bid + DMARD Parallel arm DB EE W12 P to W24	Adults Active RA Inadequate resp to DMARDs N=792 1:2:2	Not claimed

Table 1 (continued)

Study	Design	Population	SF-36 Label Claims
A3921045 (Study I)	P bid T5 bid T10 bid Parallel arm DB P to W12	Adults Active RA Inadequate resp to DMARD N=610 1:2:2	All domains, W12

Study numbers in parentheses cross reference to label.
P placebo, DB double blind, EE early escape, MTX methotrexate, A40 adalimumab injection 40 mg, q2W every two weeks DMARD disease modifying anti-rheumatic drug, TNF tumor necrosis factor

2.2 Data Sources

This NDA submission references sequence 0000 data, currently located at:

\\Cdsesub1\evsprod\NDA203214\0000\m5\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of data and analyses provided in this submission was adequate.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Five phase 3, randomized, parallel arm, double blinded, international trials enrolled adults with active RA to receive placebo, tofacitinib 5 mg bid, or tofacitinib 10 mg bid (Table 1). Trial 44 (all trials henceforth will be referred to by the last two digits) additionally randomized patients to subcutaneous injection with adalimumab 40 mg q2W. Trial 32 enrolled patients whose RA was refractory to treatment with TNF inhibitors, trials 44 and 45 enrolled patients with RA refractory to treatment with methotrexate (MTX), and trials 46 and 64 enrolled patients with RA refractory to treatment with disease modifying anti-rheumatic drugs (DMARDs). Tofacitinib was provided as an add-on therapy to MTX in studies 32, 44, and 64, as an add-on therapy to DMARDs in study 46, and as an add-on therapy to antimalarials in study 45. All studies were placebo controlled at least until week 12. Studies 32 and 45 terminated placebo at week 12, and studies 44, 46 and 64 provided early escape at week 12, with non-escape placebo control continuing until week 24.

Early escape patients were those without an improvement of at least 20% in both the tender and swollen joint counts. Those originally assigned to placebo were rerandomized 1:1 or 1:1:1 (in the case of study 64) to active treatment for the remainder of the study, and those originally assigned to active treatment remained on active treatment.

Collection of data continued for up to one week following patient withdrawals from study.

3.2.2 Statistical Methodologies

Change from baseline SF-36 components and domains were analyzed as continuous variables using mixed effect repeated measures models, including fixed effects of treatment, non-baseline visit, treatment by non-baseline visit interaction, baseline measurement, and geographic region, and with random effect patient using compound symmetric covariance matrices. Non-baseline visits included months 0.5, 1, and 3 for study 32, months 0.5, 1, 2, and 3 for studies 45 and 46, and months 1 and 3 for studies 44 and 64.

Confidence intervals for the proportion of responders for each SF-36 component and domain were also calculated, using normal approximations to the binomial.

Statistical tests were conducted at the two-sided 0.05 level of significance, and confidence intervals were calculated as two sided at the 95% level of confidence. However, because the endpoints were exploratory and examined without control of overall type 1 error, any statistically significant results claimed by the sponsor should be considered only as nominal, with calculated p-values underestimating true type 1 error probabilities.

Data used for statistical tests included all patients who received one dose of the study drug to which they were randomized.

Missing data for an SF-36 item on completed questionnaires was imputed as suggested by the producer of the SF-36 instrument, using the mean from the all other items within the same domain, provided at least 50% of the items in that domain were completed. Otherwise, missing values were not imputed, and only observed values, including data collected after patient escape or withdrawal from randomized treatment, were used in the analyses.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient demographics in the original submission for all five phase 3 studies were reviewed by Dr. Yongmen Kim, who found "no noticeable imbalances of the demographics and baseline characteristics between treatment groups."

In all studies, more than 85% of the patients completed the SF-36 questionnaire at final placebo controlled visit (Table 2). Patterns of early escape were consistent with efficacy; for each study with a provision for early escape therapy, the percentage of patients meeting early escape criteria was numerically higher in the placebo control than in the two tofacitinib treatments.

Table 2. Available SF-36 Questionnaire Data, Observed.

Study	Timepoint	N (%)		
		P	T5	T10
32	Full Analysis Set	132	133	134
	Baseline	132 (100)	133 (100)	134 (100)
	Month 3	117 (88.6)	118 (88.7)	125 (93.3)
44	Full Analysis Set	156	316	309
	Baseline	156 (100)	315 (99.7)	309 (100)
	Month 3	149 (95.5)	298 (94.3)	306 (99)
	Early Escape	45 (30.2)	29 (9.7)	22 (7.2)
	Month 6	140 (89.7)	286 (90.5)	290 (93.9)
45	Full Analysis Set	122	241	243
	Baseline	122 (100)	239 (99.2)	243 (100)
	Month 3	108 (88.5)	235 (97.5)	225 (92.6)
46	Full Analysis Set	158	312	315
	Baseline	158 (100)	312 (100)	315 (100)
	Month 3	148 (93.7)	297 (95.2)	295 (93.7)
	Early Escape	38 (25.5)	27 (9.1)	24 (8.1)
	Month 6	145 (91.8)	282 (90.4)	283 (89.8)
64	Full Analysis Set	107	201	199
	Baseline	106 (99.1)	201 (100)	199 (100)
	Month 3	100 (93.5)	191 (95)	187 (94)
	Early Escape	29 (29)	21 (11)	21 (11.2)
	Month 6	95 (88.8)	176 (87.6)	183 (92)

source: n 2013 06 03.sas

Consistent with efficacy of tofacitinib, discontinuations of treatment because of insufficient clinical response occurred numerically more often among placebo than among tofacitinib treated patients (Table 3 through Table 5), .

Table 3. Patient Disposition, Three Month Studies 32 and 45

Study	Time	Final State	N (%)		
			P	T5	T10
32	Month 0	FAS	132	133	134
	Month 3	Total Discontinued	21 (15.9)	18 (13.5)	16 (12.1)
		INSUFFICIENT RESPONSE	9 (6.8)	2 (1.5)	2 (1.5)
		ADVERSE EVENT	6 (4.5)	7 (5.3)	6 (4.5)
		PROTOCOL VIOLATION	2 (1.5)	0 (0)	1 (0.8)
		LOST TO FOLLOW-UP	1 (0.8)	1 (0.8)	1 (0.8)
		OTHER	2 (1.5)	1 (0.8)	1 (0.8)
		DOESN'T MEET ENTRANCE CRITERIA	0 (0)	0 (0)	2 (1.5)
		NO LONGER WILLING	1 (0.8)	7 (5.3)	3 (2.3)
45	Month 0	FAS	122	241	243
	Month 3	Total Discontinued	15 (12.3)	5 (2)	17 (6.9)
		INSUFFICIENT RESPONSE	6 (4.9)	0 (0)	1 (0.4)
		ADVERSE EVENT	5 (4.1)	2 (0.8)	5 (2)
		SUBJECT DIED	0 (0)	0 (0)	1 (0.4)
		PROTOCOL VIOLATION	1 (0.8)	2 (0.8)	6 (2.4)
		OTHER	1 (0.8)	0 (0)	1 (0.4)
		NO LONGER WILLING	2 (1.6)	1 (0.4)	3 (1.2)

source: Disposition 2014 06 04.sas

Table 4. Patient Disposition, Six Month Study 44

Study	Time	Final State	N (%)		
			P	T5	T10
44	Month 0	FAS Population	156	316	309
	Month 3	Total Discontinued	11 (7.1)	24 (7.6)	13 (4.2)
		ADVERSE EVENT	4 (2.6)	12 (3.8)	7 (2.3)
		INSUFFICIENT RESPONSE	1 (0.6)	0 (0)	0 (0)
		LOST TO FOLLOW-UP	1 (0.6)	1 (0.3)	0 (0)
		NO LONGER WILLING	1 (0.6)	4 (1.3)	3 (1)
		OTHER	1 (0.6)	3 (0.9)	1 (0.3)
		PROTOCOL VIOLATION	2 (1.3)	3 (0.9)	2 (0.6)
		STUDY TERMINATED BY SPONSOR	1 (0.6)	1 (0.3)	0 (0)
	Month 6	Total Discontinued	20 (12.8)	38 (12)	31 (10)
		ADVERSE EVENT	8 (5.1)	20 (6.3)	16 (5.2)
		INSUFFICIENT RESPONSE	2 (1.3)	3 (0.9)	1 (0.3)
		LOST TO FOLLOW-UP	1 (0.6)	2 (0.6)	0 (0)
		NO LONGER WILLING	3 (1.9)	4 (1.3)	5 (1.6)
		OTHER	1 (0.6)	4 (1.3)	2 (0.6)
		OTHER UNRECORDED	0 (0)	0 (0)	1 (0.3)
		PROTOCOL VIOLATION	2 (1.3)	3 (0.9)	5 (1.6)
		STUDY TERMINATED BY SPONSOR	3 (1.9)	1 (0.3)	0 (0)
		SUBJECT DIED	0 (0)	0 (0)	1 (0.3)
		WITHDRAWN DUE TO PREGNANCY	0 (0)	1 (0.3)	0 (0)

source: Disposition 2014 06 04.sas

Table 5. Patient Disposition, Six Month Studies 46 and 64

Study	Time	Final State	N (%)		
			P	T5	T10
46	Month 0	FAS Population	158	312	315
	Month 3	Total Discontinued	8 (5.1)	21 (6.7)	21 (6.7)
		ADVERSE EVENT	2 (1.3)	7 (2.2)	10 (3.2)
		INSUFFICIENT RESPONSE	2 (1.3)	3 (1)	1 (0.3)
		NO LONGER WILLING	0 (0)	9 (2.9)	2 (0.6)
		OTHER	0 (0)	1 (0.3)	2 (0.6)
		PROTOCOL VIOLATION	4 (2.5)	1 (0.3)	6 (1.9)
	Month 6	Total Discontinued	12 (7.6)	37 (11.9)	38 (12.1)
		ADVERSE EVENT	3 (1.9)	14 (4.5)	18 (5.7)
		INSUFFICIENT RESPONSE	4 (2.5)	10 (3.2)	6 (1.9)
		NO LONGER WILLING	0 (0)	10 (3.2)	4 (1.3)
		OTHER	0 (0)	1 (0.3)	3 (1)
		PROTOCOL VIOLATION	5 (3.2)	2 (0.6)	6 (1.9)
64	Month 0	FAS Population	107	201	199
	Month 3	Total Discontinued	11 (10.3)	11 (5.5)	14 (7)
		ADVERSE EVENT	4 (3.7)	8 (4)	8 (4)
		INSUFFICIENT RESPONSE	3 (2.8)	1 (0.5)	2 (1)
		NO LONGER WILLING	1 (0.9)	0 (0)	1 (0.5)
		OTHER	1 (0.9)	1 (0.5)	0 (0)
		PROTOCOL VIOLATION	2 (1.9)	1 (0.5)	3 (1.5)
	Month 6	Total Discontinued	15 (14)	34 (16.9)	26 (13.1)
		ADVERSE EVENT	4 (3.7)	16 (8)	16 (8)
		INSUFFICIENT RESPONSE	5 (4.7)	6 (3)	4 (2)
		LOST TO FOLLOW-UP	0 (0)	1 (0.5)	0 (0)
		NO LONGER WILLING	1 (0.9)	3 (1.5)	2 (1)
		OTHER	2 (1.9)	5 (2.5)	1 (0.5)
		PROTOCOL VIOLATION	3 (2.8)	3 (1.5)	3 (1.5)

source: Disposition 2014 06 04.sas

That item completion rate was greater than 99% among all SF-36 questionnaires filled out at baseline (Table 12), month 3 (Table 13), and month 6 (Table 14), alleviated concerns regarding the effect of missing items on calculated scores.

3.2.4 Results and Conclusions

3.2.4.1 Efficacy and SF-36, Month 3

Product label revisions proposed by the sponsor contain claims for all eight domains of SF-36 at month 3. As mentioned earlier in this review, the two SF-36 components and the four domains comprising each component were included in the study protocols only as exploratory variables, without plans for significance testing or associated control of type 1 error in the face of multiple hypothesis tests. Consequently, the statistical tests provided by the sponsor for SF-36 are only nominal, with p-values underestimating true type 1 error.

To partially control further increases in type 1 error, tests of exploratory endpoints were arranged in a hierarchy for this review. In particular, I will consider the four domains of the physical component of SF-36 as potentially of nominal significance in a particular study only if the physical component of SF-36 itself is significant, and I will consider the four domains of the mental component of SF-36 as potentially of nominal significance only if the mental component of SF-36 is significant. Further, assuming that, for RA, improvement of the mental component depends on improvement of the physical component, the mental component was considered as potentially of nominal significance only if the physical component proves nominally significant.

All five studies showed nominally significant differences between T5 and P for changes from baseline SF-36 physical component score (Figure 1, underlying Table 15) and its four underlying domains: physical function (Figure 3, underlying Table 17), role-physical (Figure 4, underlying Table 18), bodily pain (Figure 5, underlying Table 19), and general health (Figure 6, underlying Table 20).

Studies 32, 45, 55, and 46, but not 64, showed nominally significant differences between T5 and P for changes from baseline SF-36 mental component score (Figure 2, underlying Table 16). All four studies significant for mental component score showed nominally significant differences between T5 and P in three underlying domains: vitality (Figure 7, underlying Table 21), social function (Figure 8, underlying Table 22), and mental health (Figure 10, underlying Table 24). One study 46, failed nominal significance between T5 and P for fourth underlying domain, role-emotional (Figure 9, underlying Table 23). Because study 64 failed for differences between T5 and P for the mental component score, it was not considered for nominal significance in any of the four underlying mental component domains. Nevertheless, numerical differences consistently indicated superiority of T5 over P even when nominal significance was not achieved.

Responses among patients randomized to T10 numerically exceeded those among patients randomized to T5 (Table 15 to Table 24); further analyses demonstrated nominally significant differences between T10 and P for all components and domains in all five studies.

In summary, nominal significance was achieved in all eight domains of SF-36 in three of five studies, providing some support for the sponsor's proposed claim that (b) (4)

Figure 1. Change from Baseline SF-36 Physical Component Score, Month 3

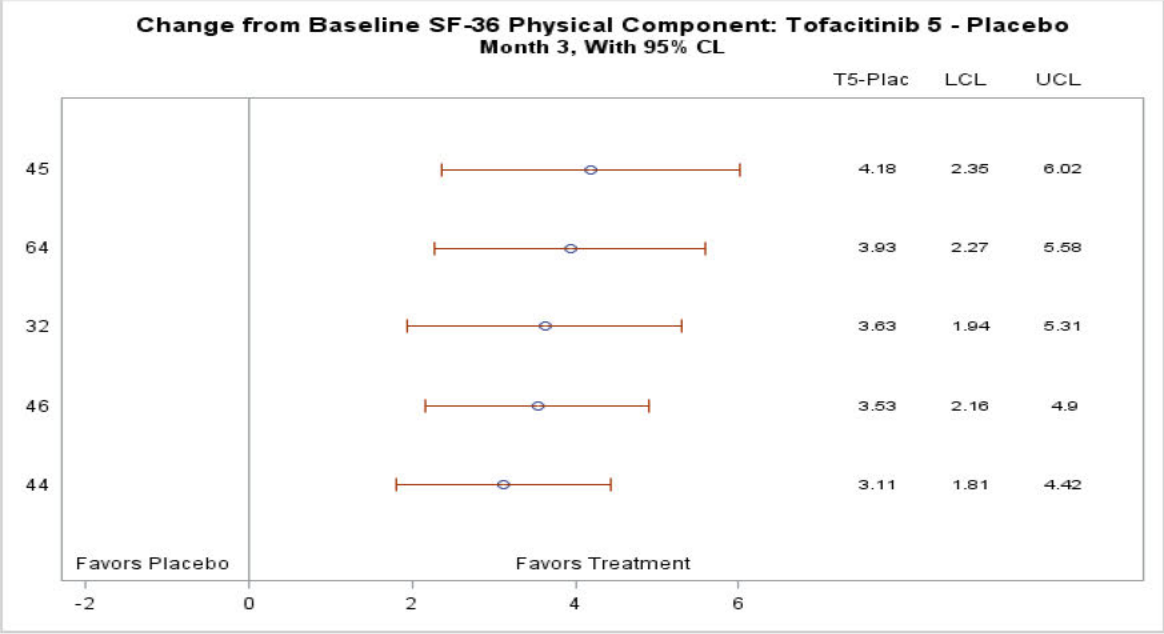


Figure 2. Change from Baseline SF-36 Mental Component Score, Month 3

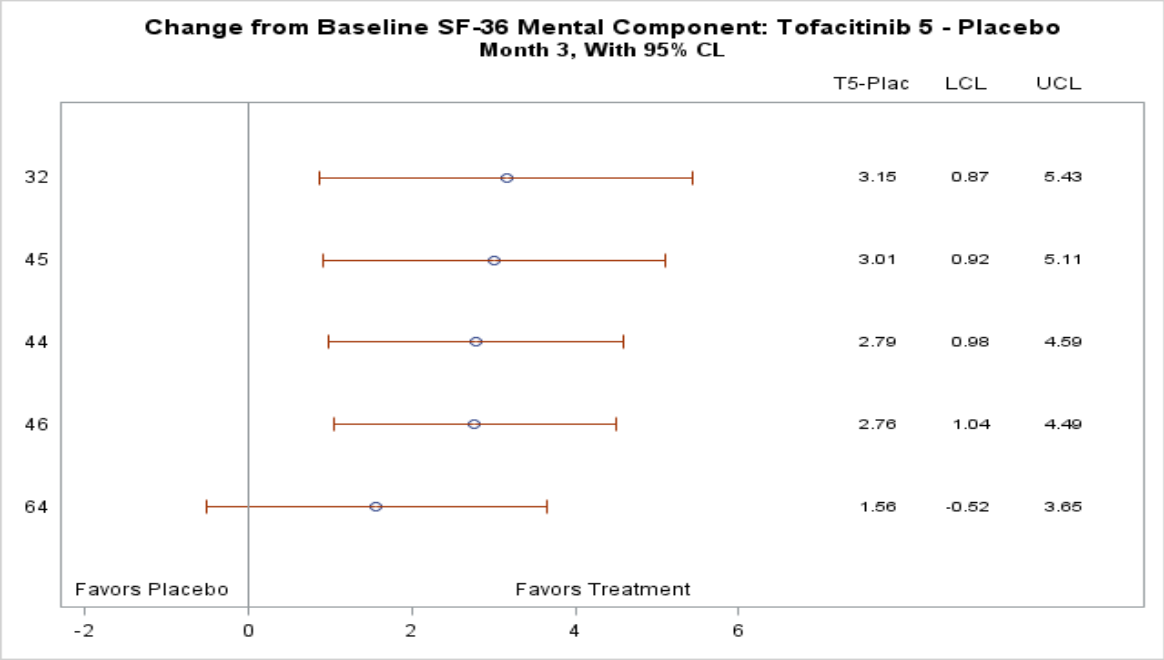


Figure 3. Change from Baseline SF-36 Physical Function Domain, Month 3

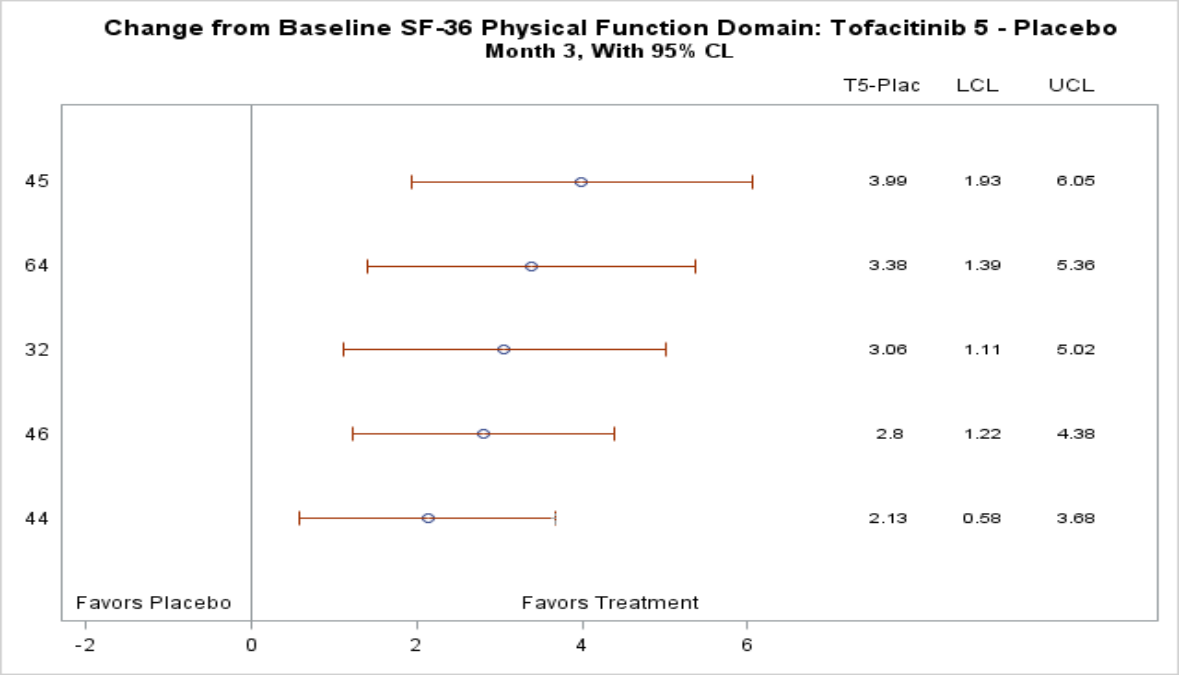


Figure 4. Change from Baseline SF-36 Role Physical Domain, Month 3

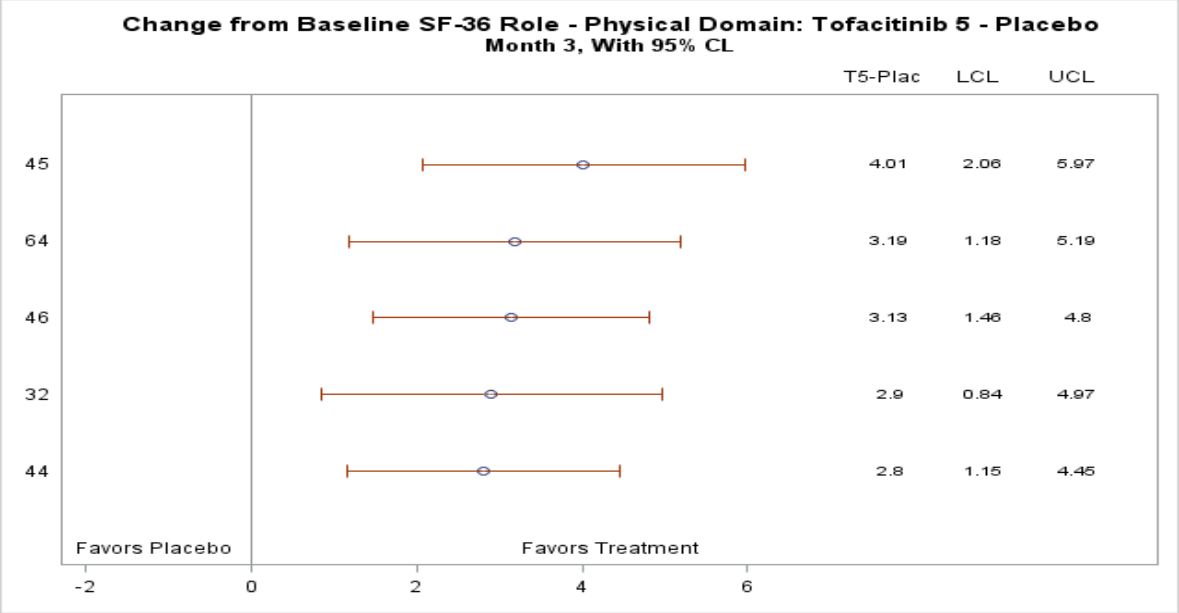


Figure 5. Change from Baseline SF-36 Bodily Pain Domain, Month 3

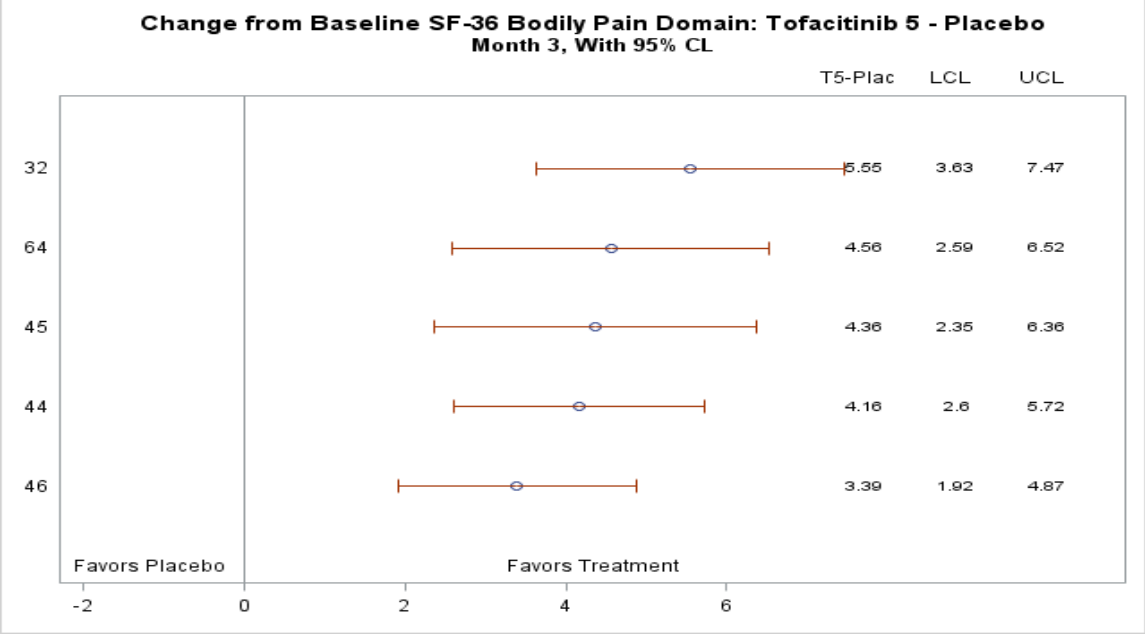


Figure 6. Change from Baseline SF-36 General Health Domain, Month 3

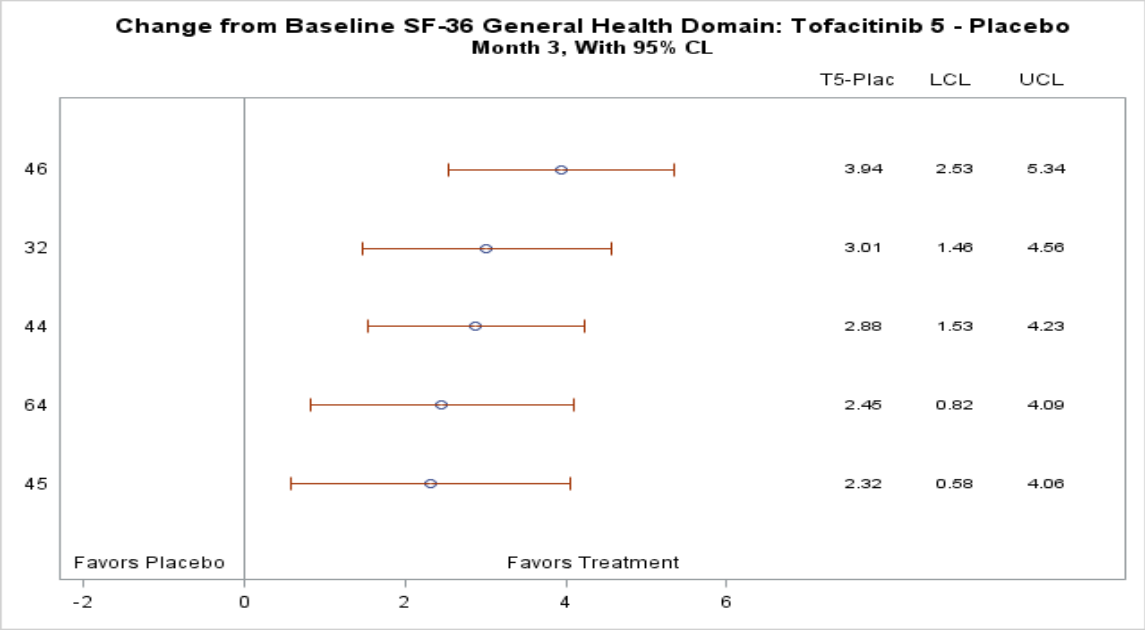


Figure 7. Change from Baseline SF-36 Vitality Domain, Month 3

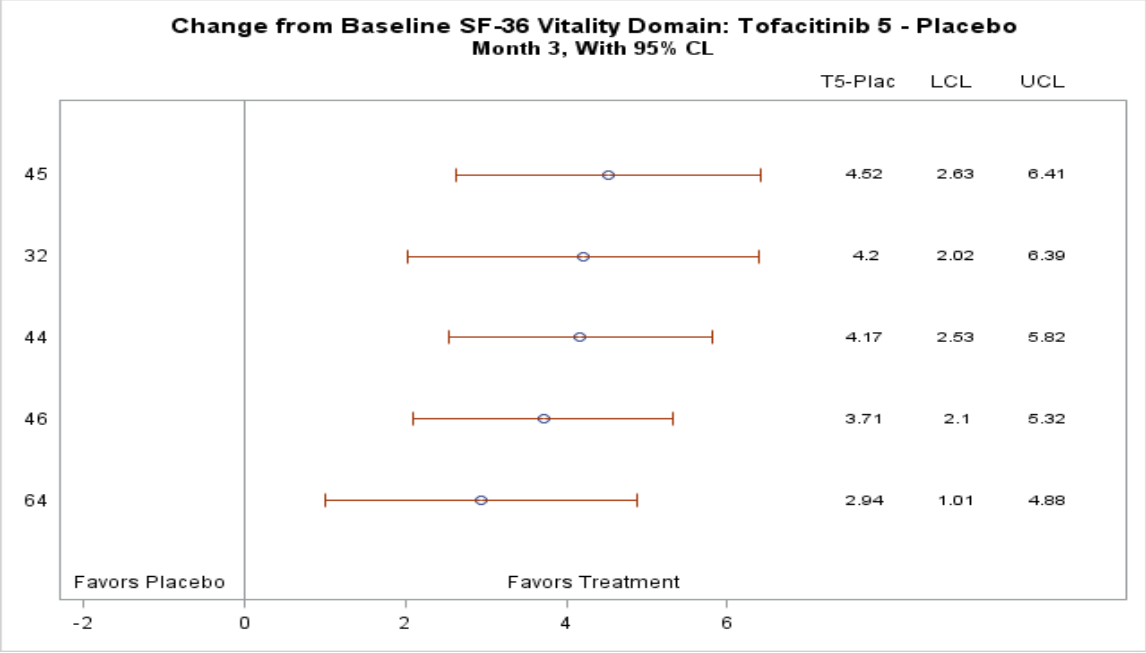


Figure 8. Change from Baseline SF-36 Social Function Domain, Month 3

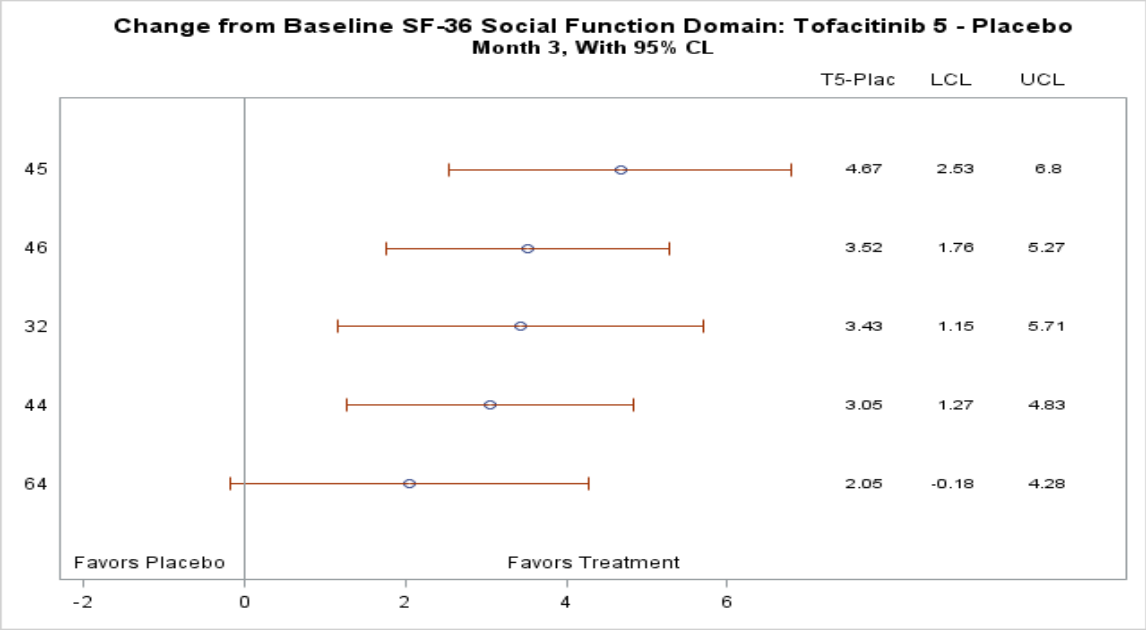


Figure 9. Change from Baseline SF-36 Role-Emotional Domain, Month 3

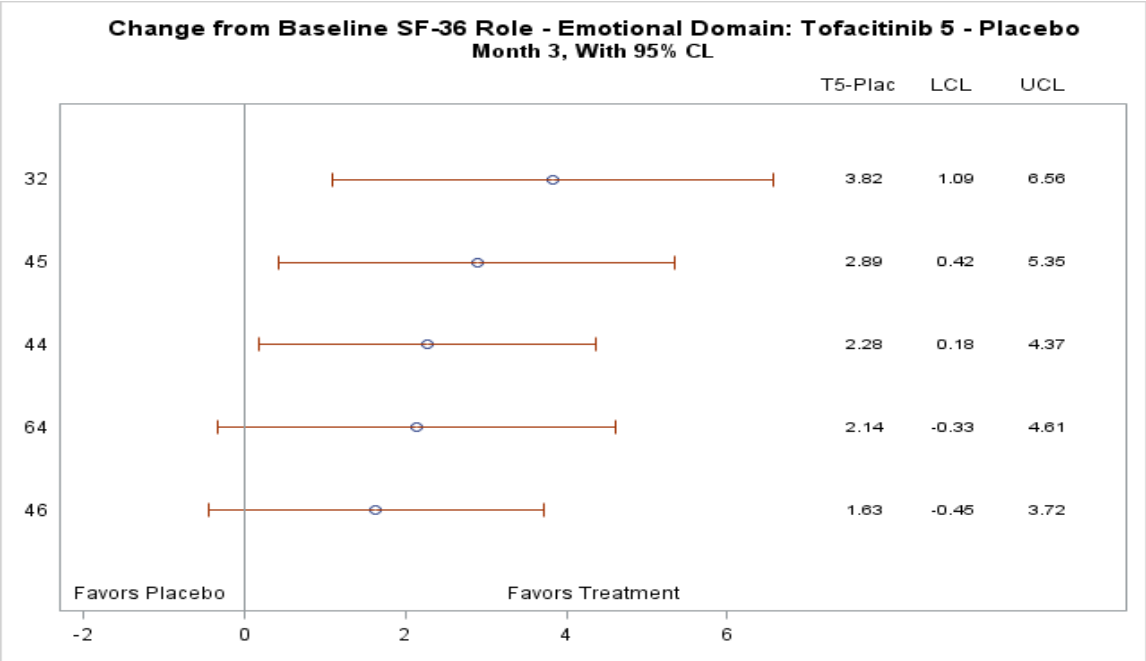
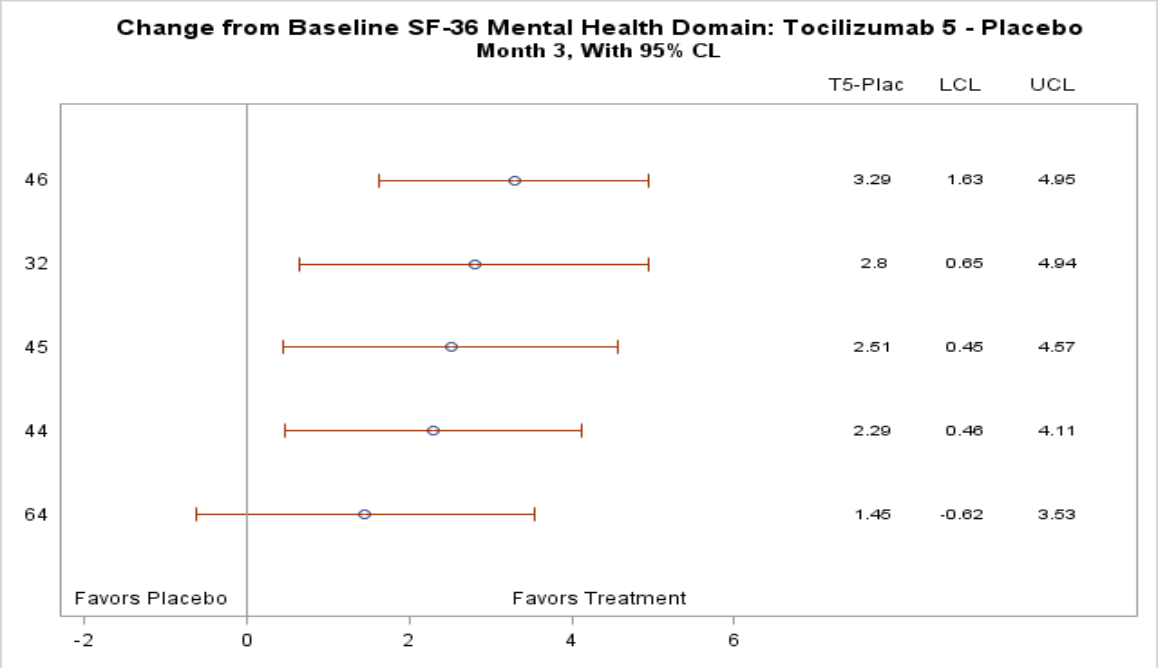


Figure 10. Change from Baseline SF-36 Mental Health Domain, Month 3



source: forest plots.sas sf36lsmean 2013 05 07.sas

3.2.4.2 Means and Extremes of Efficacy, Month 3

The analyses of Section 3.2.4.1 measure efficacy as a change of the mean. Change of mean may be driven by a combination of treatment effects on: (i) change experienced by a large percentage of patients, (ii) decrease in the the percentage of patients who experience extremes of deteriorations, or (iii) increase in the percentage of patients who experience extremes of improvements. Such changes may be examined graphically using the cumulative distribution function (cdf) or, synonymously, the continuous responder function (crf), which is (1 – the cdf),

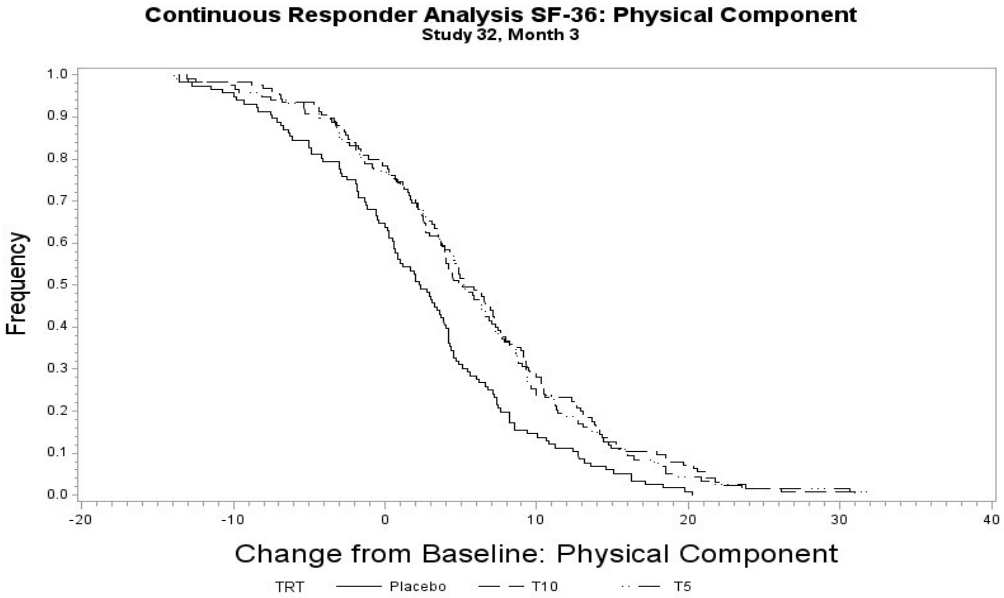
For typical distributions, treatment effects experienced by a large percentage of patients are indicated by continuous responder functions with differences in between placebo and treatment which increase with change from baseline and then decrease at higher values of change from baseline (e.g. Figure 11) . Treatment effects which reduce the percentage of patients experiencing extreme deteriorations are indicated by differences between treatment and placebo at the extreme upper left of the continuous responder function (e.g. Figure 12), and treatment effects which increases the percentage of patients experiencing extreme improvements are indicated by differences at the extreme lower right of the continuous responder function (e.g. Figure 13).

For Figure 11, study 32 was chosen as a representative continuous responder analysis for physical function because it was the third of five studies ranked by mean difference between placebo and treatment (Figure 1). Similarly representative examples for the mental component score and the physical function, role-physical, bodily pain, general health, vitality, social function, and role-emotional domains suggest that the effects of tofacitinib are experienced by a large percentage of patients for all SF-36 components and domains (Figure 14, Figure 15, Figure 16, Figure 17, Figure 18, Figure 19, Figure 20, and Figure 21 respectively), that tofacitinib increases the percentage of patients with extreme benefits for the physical and mental component component scores and the physical function, role physical, bodily pain, and vitality domains, and that tofacitinib decreases the percent of patients experiencing extreme deteriorations for the general health domain.

It is important, however, to note that studies chosen as 'representative' were not necessarily 'typical,' especially for analyses of extremes, where sample size in any given study was, by definition, small, and conclusions consequently fragile. For example, three of the five phase 3 studies (studies 44, 46, and 64) showed tofacitinib decreasing the percentage of patients with extreme deteriorations of the physical component, and two of five studies (studies 32 and 64) showed tofacitinib decreasing the percentage of patients with extreme deteriorations of the mental component.

Kolmogorov-Smirnov tests for overall differences between the curves for placebo and T5 are provided on the lower left hand of each continuous responder analysis. Use of the Kolmogorov-Smirnov test for differences between two continuous responder functions is justified because, for each value on the x-axis the value of the crf = (1 – cdf), and therefore the figure of merit in the Kolmogorov-Smirnov test, maximum absolute difference between cdf curves, will be equal to the maximum absolute difference between the crf curves. Another, similarly justifiable statistical test, is the Kuiper two sample test, which is more sensitive to distributional differences at the extremes.

Figure 11. Change from Baseline SF-36 Physical Component Score, Month 3, Study 32, Continuous Responder Analysis



Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.0037

Figure 12. Change from Baseline SF-36 Physical Component Score, Month 3, Study 64, Upper Left Corner of Continuous Responder Analysis

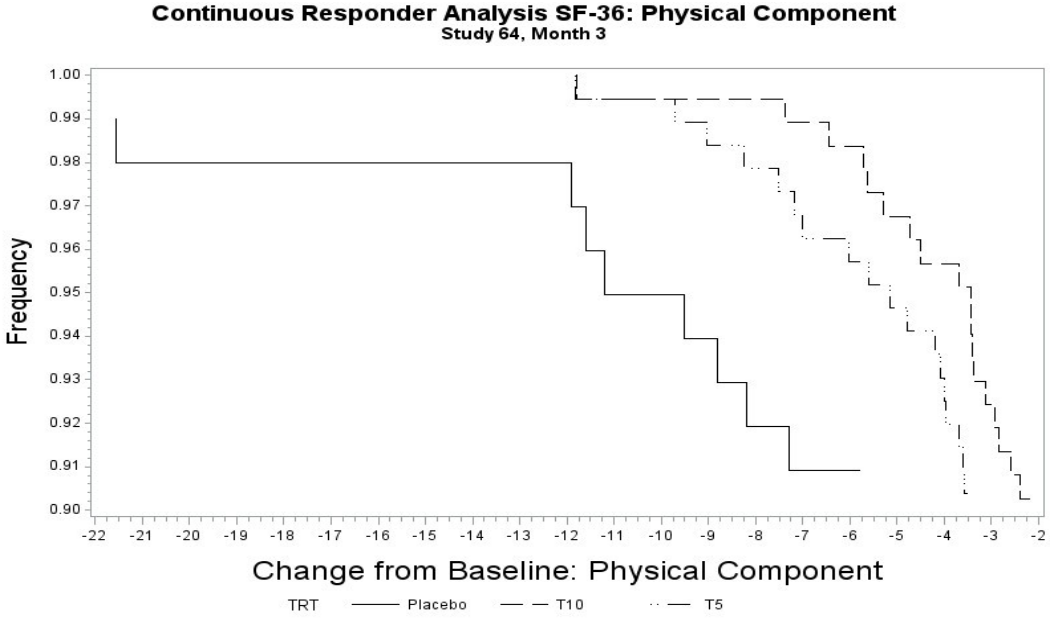


Figure 13. Change from Baseline SF-36 Physical Component Score, Month 3, Study 32, Lower Right Corner of Continuous Responder Analysis

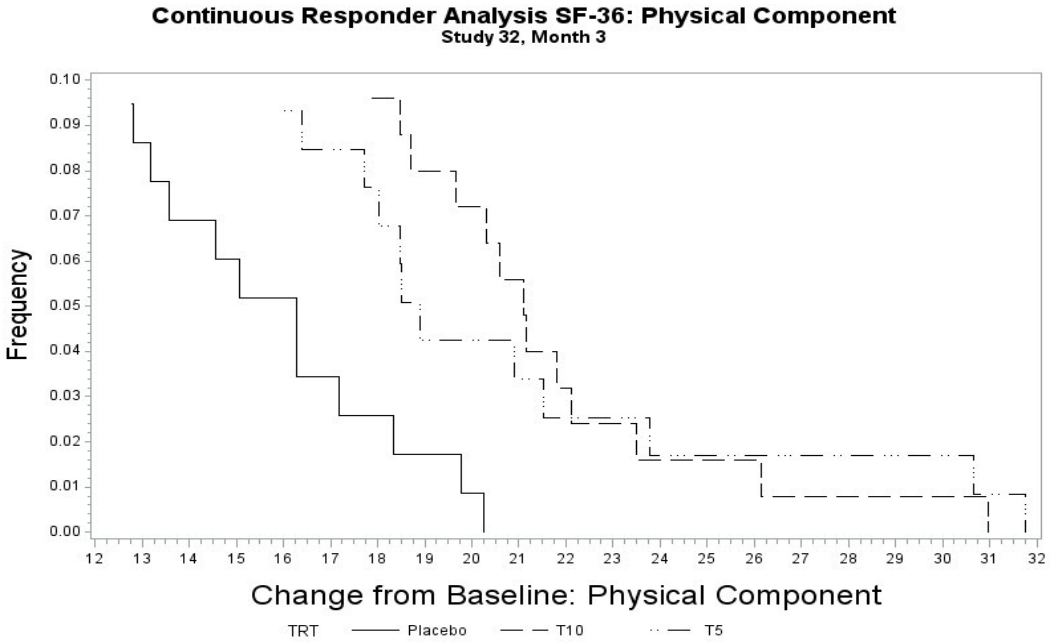
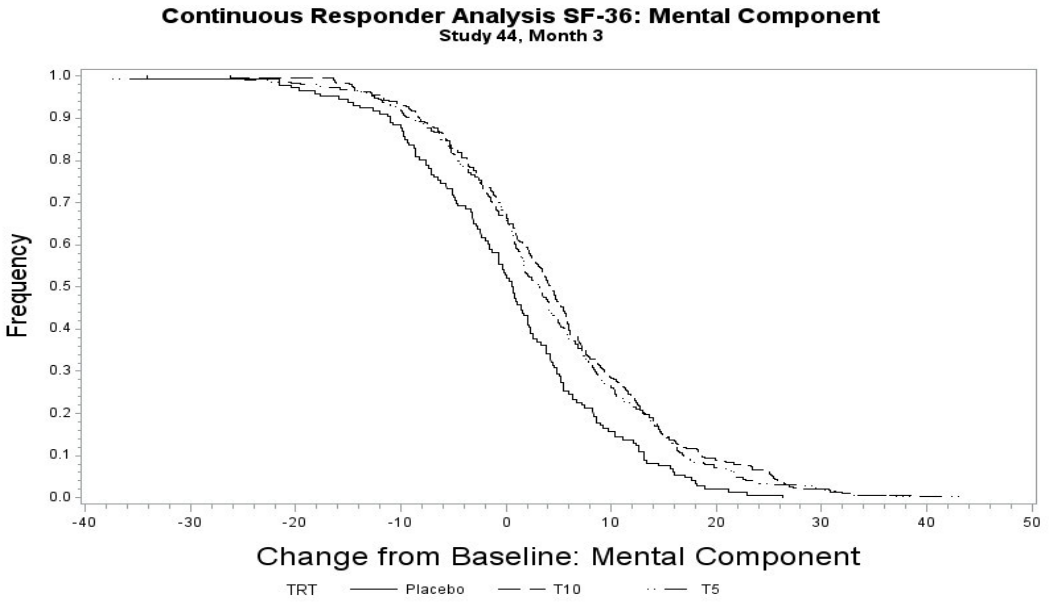
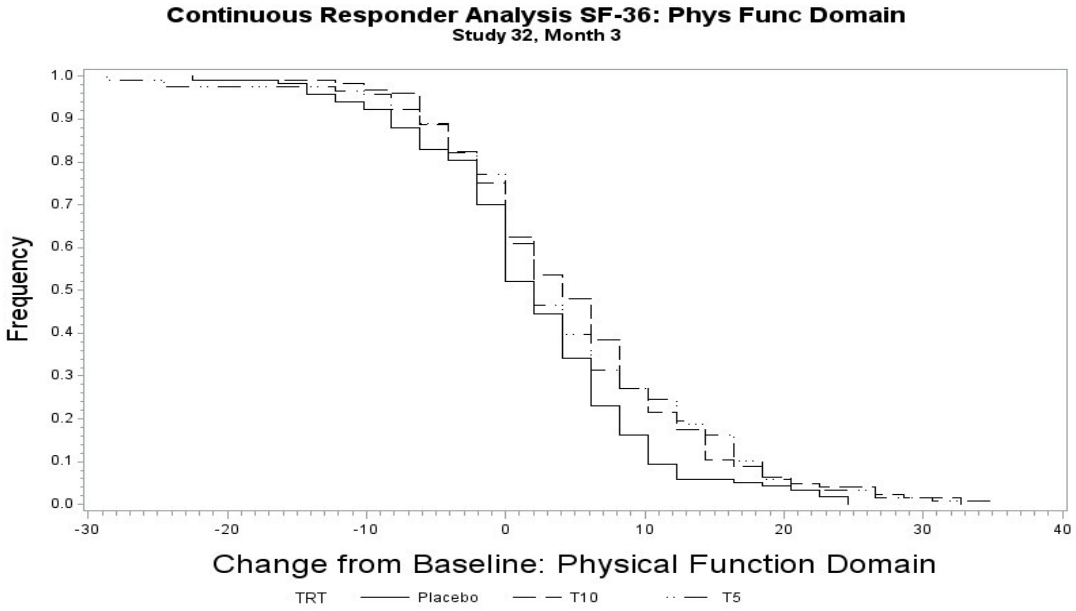


Figure 14. Change from Baseline SF-36 Mental Component Score, Month 3, Study 44, Continuous Responder Analysis



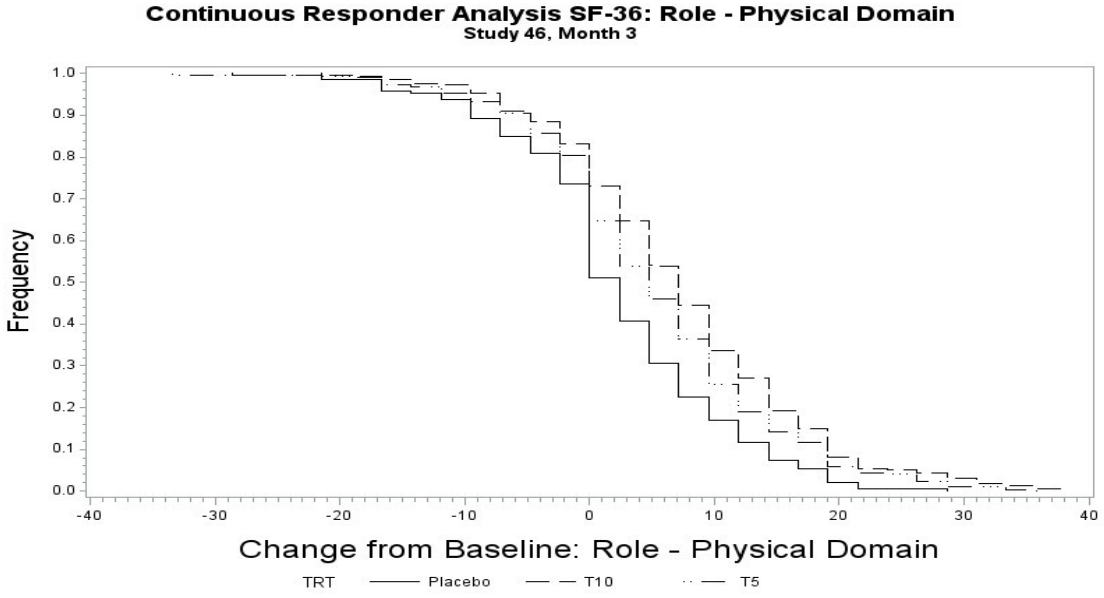
Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.0260

Figure 15. Change from Baseline SF-36 Physical Function Domain, Month 3, Study 32, Continuous Responder Analysis



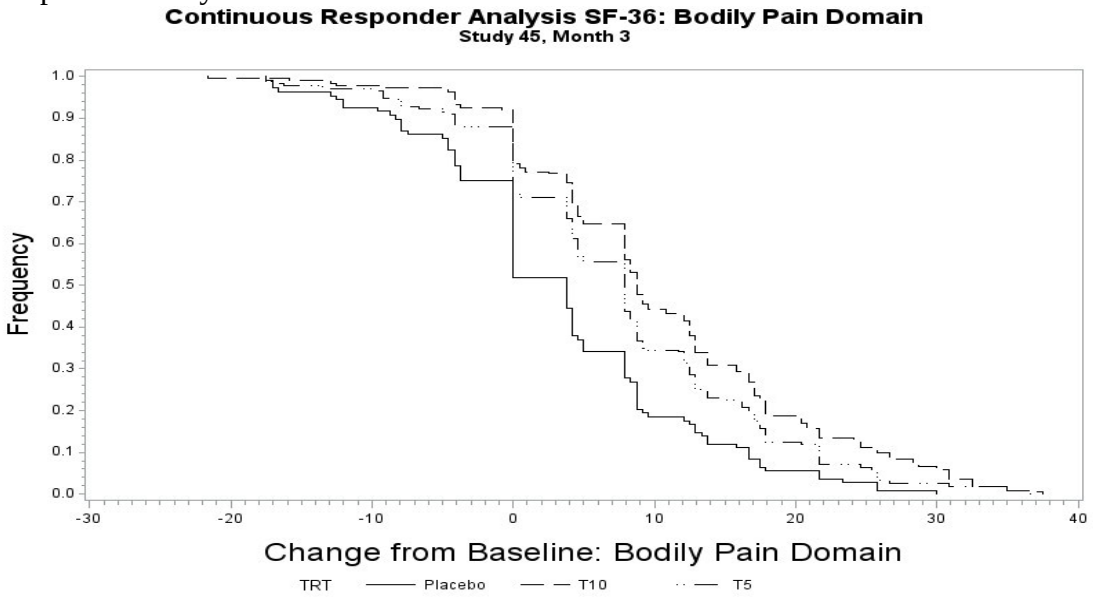
Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.1336

Figure 16. Change from Baseline SF-36 Role Physical Domain, Month 3, Study 46, Continuous Responder Analysis



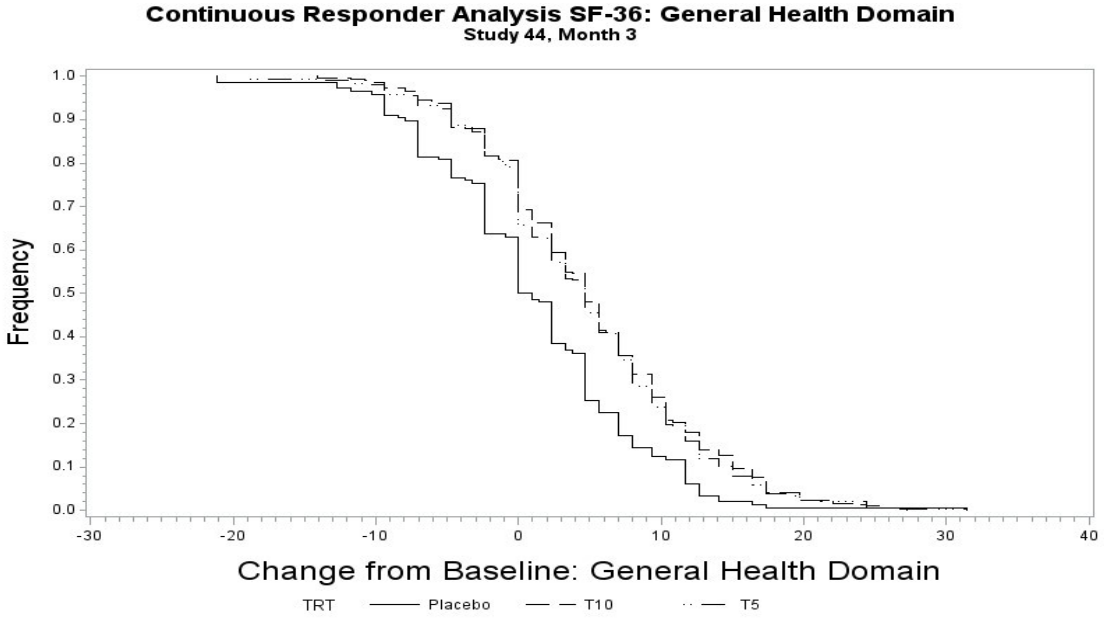
Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.0165

Figure 17. Change from Baseline SF-36 Bodily Pain Domain, Month 3, Study 45, Continuous Responder Analysis



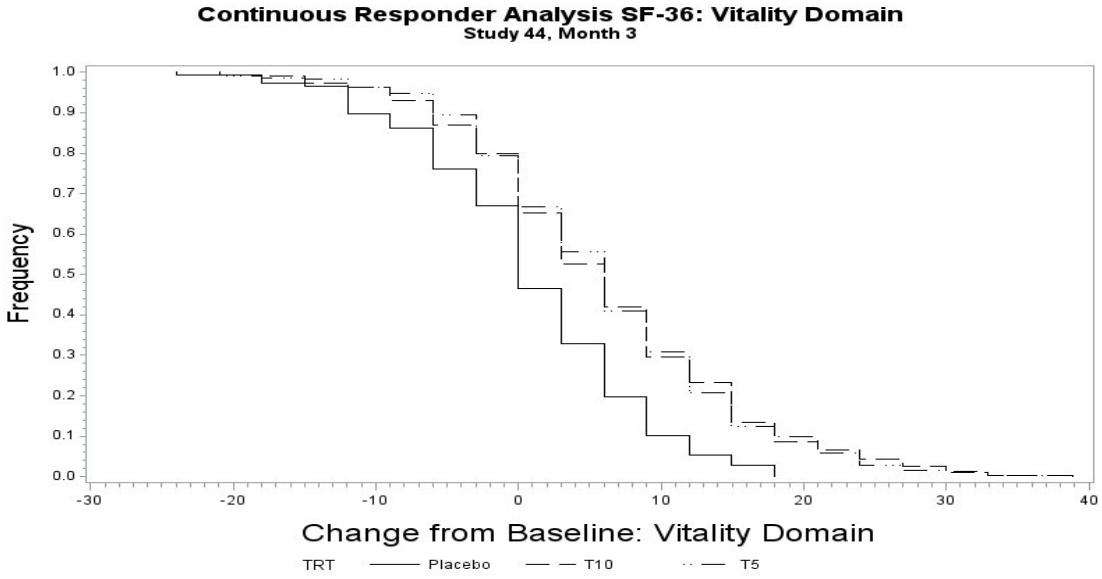
Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.0005

Figure 18. Change from Baseline SF-36 General Health Domain, Month 3, Study 44, Continuous Responder Analysis



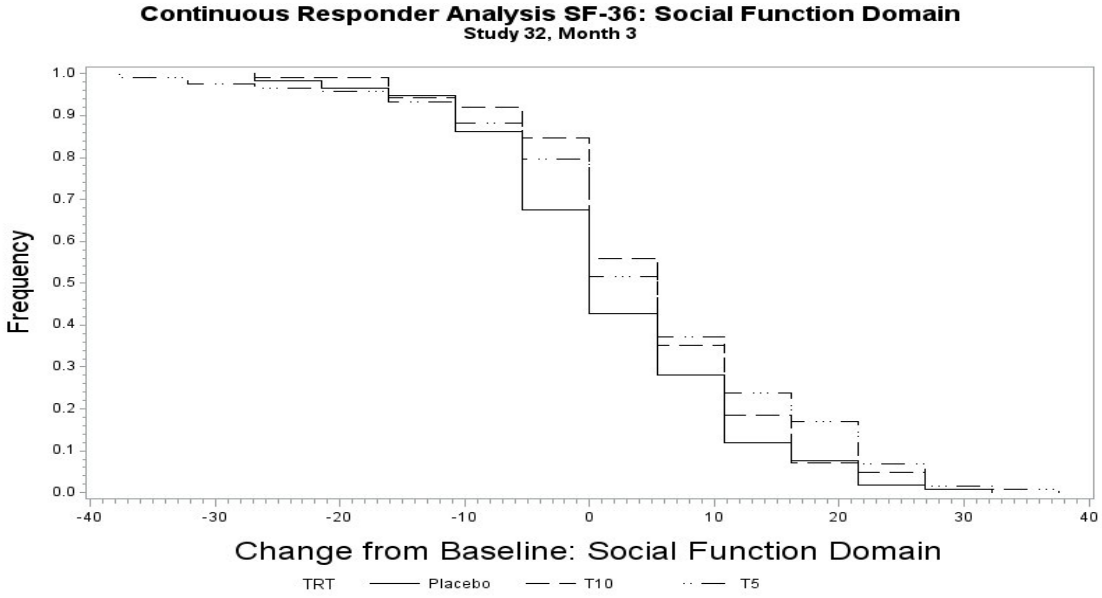
Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.0003

Figure 19. Change from Baseline SF-36 Vitality Domain, Month 3, Study 44, Continuous Responder Analysis



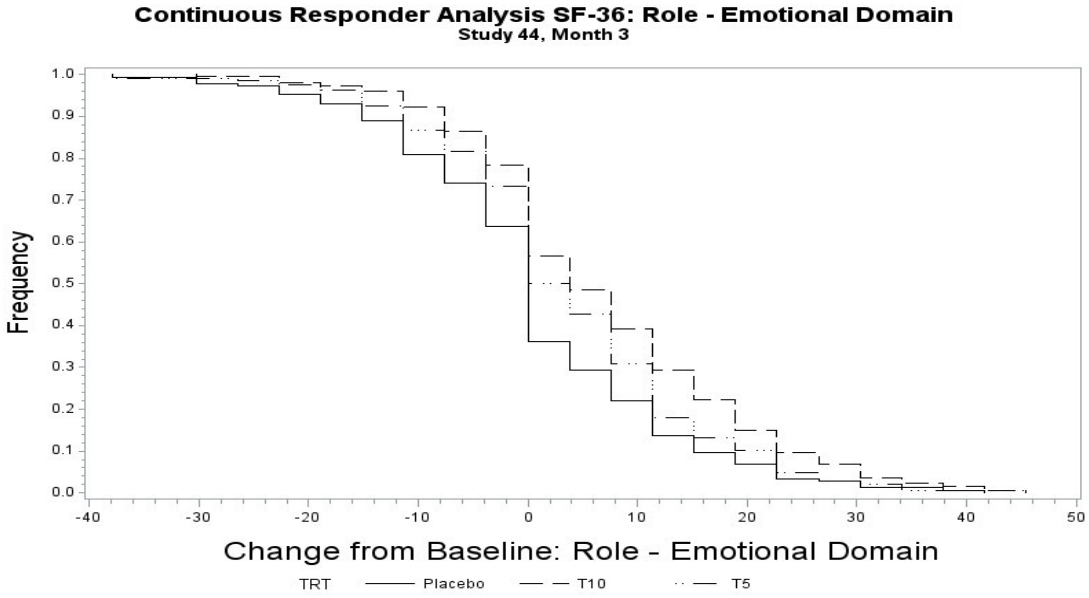
Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = <.0001

Figure 20. Change from Baseline SF-36 Social Function Domain, Month 3, Study 32, Continuous Responder Analysis



Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.3520

Figure 21. Change from Baseline SF-36 Role Emotional Domain, Month 3, Study 44, Continuous Responder Analysis.



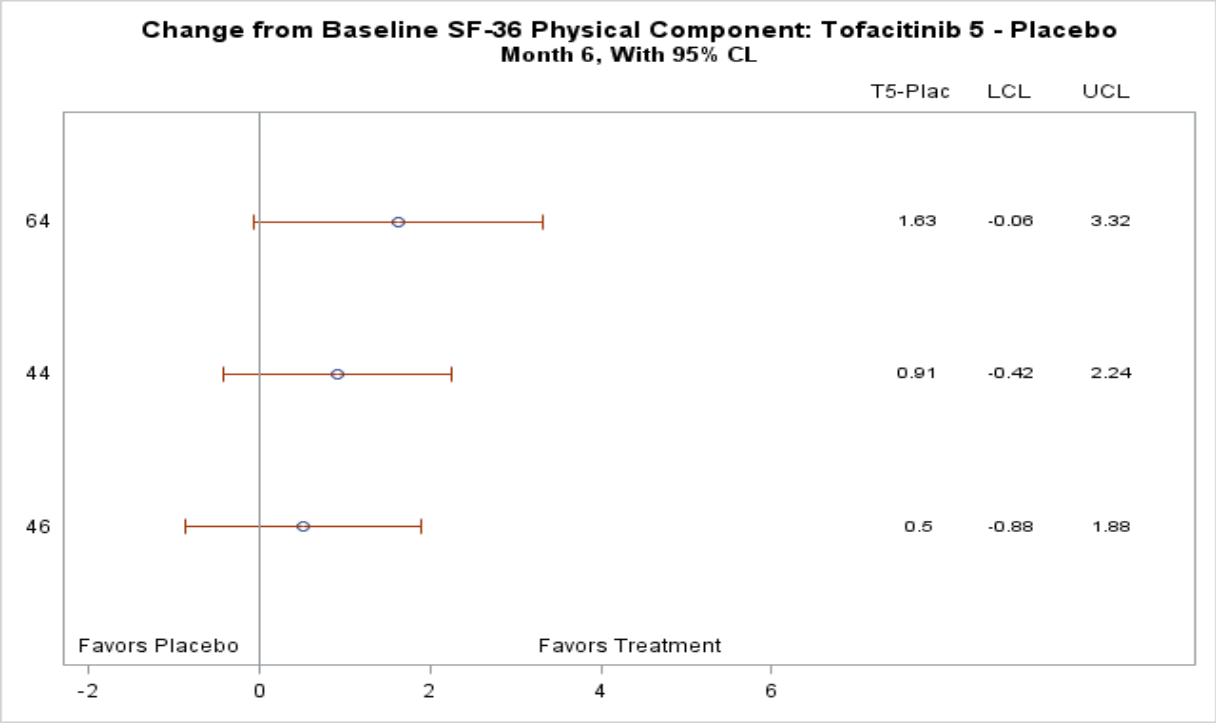
Kolmogorov-Smirnov Test Tofacitinib 5 mg vs Placebo: P-Value = 0.0428
source: SF36 CRA T5 vs P 2013 05 24.sas

3.2.4.3 Efficacy and SF-36, Month 6

The proposed label revisions do not include claims for SF-36 improvements at month 6. Nevertheless, efficacy with regard to SF-36 at month 6 is examined below to explore potential attenuation of treatment effects with time.

Initial evaluations of observed data appeared to be problematic for improvement by tofacitinib of the SF-36 physical component at month 6, with none of the three studies with placebo controls at month 6 showing statistically significant differences between T5 and placebo (Figure 22, underlying Table 25) .

Figure 22. Change from Baseline SF-36 Physical Component Score, Month 6



source: forest plots.sas sf36lsmean 2013 05 07.sas

The reduction in difference between T5 and placebo between months 3 (Figure 1) and 6 (Figure 22) necessarily implies that difference from baseline increased from month 3 to month 6 more among patients randomized to placebo than among patients randomized to T5 (compare Table 15 to Table 25). The cause of increased response among patients initially randomized to placebo appears to be rerandomization of placebo treated patients to escape therapy at the month 3 visit. At month 3, 25% to 30% of patients initially randomized to placebo were rerandomized to receive escape therapy T5 or T10 (Table 2). Compared to placebo patients not provided escape therapy, change from baseline SF-36 physical component for patients provided escape therapy was numerically lower at month 3 (Table 6), and numerically higher at month 6 (Table 7). This implies that placebo patients who entered early escape at month 3 experienced a numerically larger increase from month 3 to month 6 for physical component SF-36 than those who did not enter early escape.

Table 6. Change from Baseline SF-36 Physical Component Score, by Early Escape Therapy, Month 3

Study	Physical Component				EE – No EE			
	EE	P No EE	T5	T10	Mean	P-Value	UCL	LCL
44	0.02 (77)	4.99 (62)	5.39 (282)	7.47 (283)	-4.97	<.0001	-7.18	-2.76
46	1.48 (74)	3.43 (67)	6.14 (278)	7.68 (276)	-1.95	0.093	-4.23	0.33
64	1.99 (48)	4.9 (46)	7.38 (172)	8.12 (180)	-2.91	0.0414	-5.71	-0.11

source: sf36lsmean M6 EE 2013 06 10.sas
EE placebo early escape

There are at least four hypotheses to explain larger increases in the SF-36 physical component from month 3 to month 6 among early escape placebo patients. First, such increases may have been driven by regression to the mean, i.e. at the month 3 visit, patients assigned to early escape were randomly experiencing poor outcomes relative to their average outcomes and might have improved to levels seen among placebo patients without escape therapy. Second, early escape placebo treated patients may have improved because they initiated treatment at month 3 with tofacitinib. Third, in the natural history of RA, it may be that patients experiencing exacerbations of RA are typically followed by larger improvements in patient condition, either by having a larger probability of improvement or by having a larger magnitude of improvement among patients who do improve.

Table 7. Change From Baseline SF-36 Physical Component Score by Early Escape Therapy Among Placebo Patients, Month 6

Study	Physical Component				EE – No EE			
	EE	P No EE	T5	T10	Mean	P-Value	UCL	LCL
44	5.86 (77)	4.74 (62)	6.23 (282)	8.01 (284)	1.12	0.3212	-1.09	3.33
46	7.13 (76)	6.19 (68)	7.3 (279)	8.18 (279)	0.93	0.4191	-1.33	3.2
64	7.38 (48)	5.71 (46)	8.16 (173)	8.71 (180)	1.67	0.2418	-1.13	4.47

source: sf36lsmean M6 EE 2013 05 02.sas

Regarding the third hypothesis, discussions with the medical reviewer for this submission, Nikolay Nikolov M.D., concerning the natural history of RA suggest that, among patients with low SF-36 scores, patients experiencing deteriorations are not more likely to improve, but those who do improve may experience larger improvements, but only because there may more room on the SF-36 scale for improvement. At baseline, there are no large differences between placebo patients who enter early escape and those who do not enter early escape (Table 8), and so there is no difference in potential for improvement from baseline to month 6. Therefore, we can distinguish the first two hypotheses while preserving randomization and the lack of difference in baseline SF-36 score between placebo patients who don't escape and those who do escape by examining change from baseline at month 6. In particular, if, among patients randomized to placebo, those entering early escape showed greater improvement from baseline than those not entering early escape, regression to mean is rejected in favor of positive response to administration of tofacitinib.

Table 8. Baseline Physical Component Score Among Placebo Patients, by Early Escape

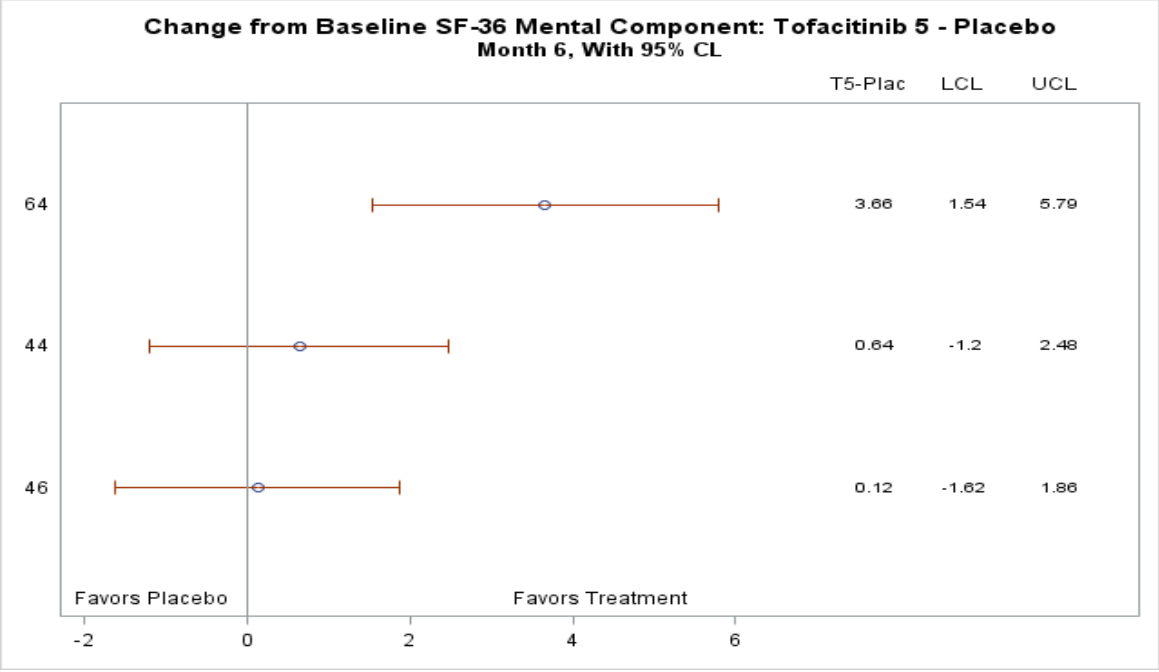
Study	Early Escape		No EE - Yes EE	
	No	Yes	Difference	P-Value
44	34.78 (62)	34.6 (77)	0.18	0.90
46	33.67 (68)	32.3 (76)	1.37	0.29
64	33.42 (46)	33.03 (47)	0.39	0.76

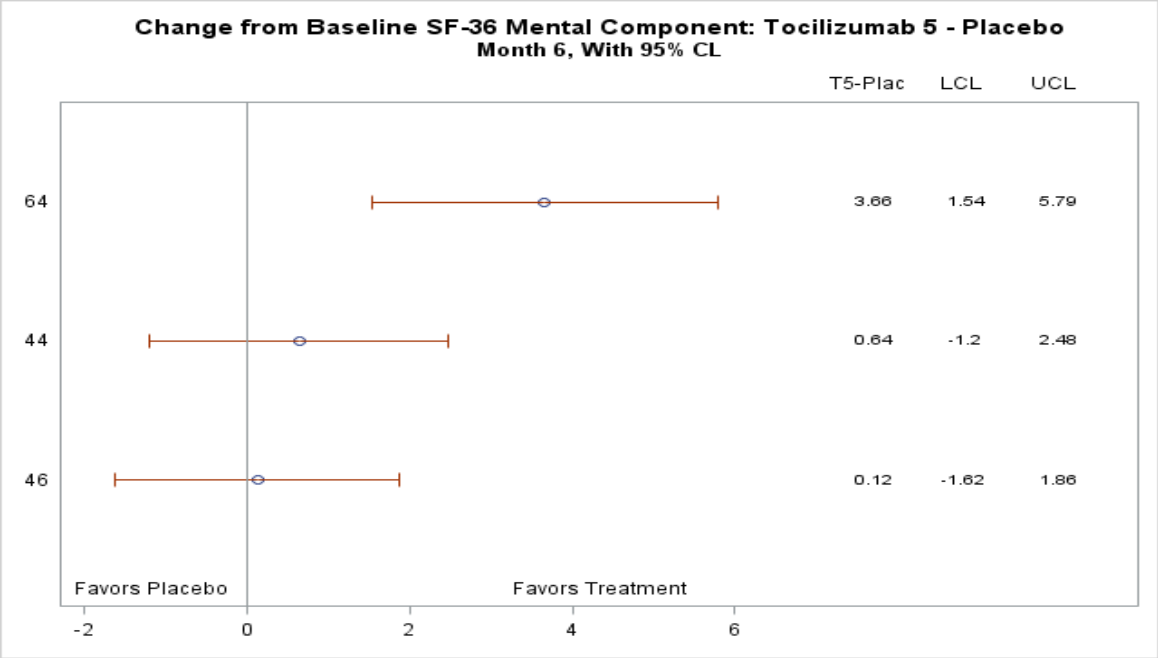
source: sf36lsmean M6 EEBase 2013 06 04.sas

There was some indication that escape therapy with tofacitinib was efficacious and caused the apparent reduction of the difference between P and T5 at month 6 compared to month 3. In particular, among patients initially randomized to placebo, the change from baseline SF-36 physical component score was numerically higher among patients who were reassigned at month 3 to early escape therapy (Table 16). However, perhaps due to small sample size, differences between early escape placebo patients and non-early escape placebo to month 6 were not statistically significant, and so regression to the mean by early escape patients as a cause of reduced treatment effect at month 6 could not be conclusively rejected.

Results for the mental component at month 6 were similar to those for the physical component. Two of three studies showed no statistically significant difference at month 6 between placebo and T5 in change from baseline SF-36 mental component (Figure 23). Patients randomized to placebo who were selected for early escape had numerically lower changes from baseline SF-36 mental component patients at month 3 than those who did not enter early escape (Table 9). Differences in baseline values of mental component score did not differ according to early escape status among patients randomized to placebo (Table 10). Similar to the physical component, there was a numerical, but not statistically significant indication that the loss of efficacy at month 6 was attributable to early escape therapy rather than attenuation of tofacitinib's effect (Table 11).

Figure 23. Change from Baseline SF-36 Mental Component Score, Month 6





source: forest plots.sas sf36lsmean 2013 05 07.sas

Table 9. Change From Baseline SF-36 Mental Component Score by Early Escape Therapy, Month 3

Study	Mental Component				EE – Placebo No EE			
	EE	P no EE	T5	T10	Mean	P-Value	UCL	LCL
44	-0.96 (77)	3.22 (62)	3.64 (282)	4.72 (283)	-4.18	0.0074	-7.23	-1.12
46	-0.06 (74)	3.46 (67)	4.53 (278)	4.24 (276)	-3.52	0.0165	-6.39	-0.64
64	1.28 (48)	2.79 (46)	3.52 (172)	6.06 (180)	-1.51	0.3939	-4.97	1.96

source: sf36lsmean M6 EE 2013 06 10.sas

Table 10. Baseline Mental Component Score Among Placebo Patients, by Early Escape Therapy

Study	Early Escape		No EE – Yes EE	
	No	Yes	Difference	P-Value
44	34.78 (62)	34.6 (77)	0.18	0.90
46	33.67 (68)	32.3 (76)	1.37	0.29
64	33.42 (46)	33.03 (47)	0.39	0.76

source: sf36lsmean M6 EEBase 2013 06 04.sas

Table 11. Change From Baseline SF-36 Mental Component Score by Early Escape Therapy Among Placebo Patients, Month 6

Study	Mental Component				EE – Placebo No EE			
	EE	P no EE	T5	T10	Mean	P-Value	UCL	LCL
44	3.62 (77)	2.59 (62)	3.82 (282)	4.56 (284)	1.03	0.5092	-2.03	4.08
46	4.54 (76)	3.28 (68)	4.11 (279)	4.75 (279)	1.26	0.3861	-1.59	4.12
64	1.92 (48)	1.2 (46)	5.03 (173)	5.72 (180)	0.73	0.6807	-2.74	4.19

source: sf36lsmean M6 EE 2013 05 02.sas

3.3 Evaluation of Safety

Safety reviews of tofacitinib were conducted for the original submission by the medical reviewer, Nikolay Nikolov, M.D. and the statistical reviewer, Youngman Kim, Ph.D.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses of major efficacy endpoints were reviewed by the statistical reviewer for the original submission, Youngman Kim, Ph.D.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical issues

Because assessments of SF-36 were exploratory, without control of type 1 error for multiple endpoints, true statistical significance and confidence intervals could not be calculated.

5.2 Collective evidence

This submission provides suggestive evidence that tofacitinib 5 mg improves all eight domains of SF-36. Because SF-36 was an exploratory endpoint, statistical significance was only nominal; however the numerical consistency of the improvements suggests they are not spurious.

5.3 Conclusions and Recommendations

This submission strongly suggests that, compared to placebo, tofacitinib 5 mg bid improves all eight SF-36 domains in patients with active RA. Determination of true statistical confidence was not possible because type 1 error was not controlled among multiple endpoints; nevertheless the numerical consistency of improvements suggests they are not spurious.

5.4 Labeling Recommendations

The sponsor proposes adding the following statement to the product label:

6 Appendix

6.1 Missing Item Rates from Filled Out Questionnaires

Table 12. Missing Item Rates from Questionnaires Filled Out at Baseline Visit

Item	Item Characteristics	Nmissing	Ntotal	PropMissing
1	IN GENERAL HEALTH IS	2	399	0.005
2	RATE HEALTH IN GENERAL NOW	1	399	0.003
3	HEALTH LIMIT VIGOROUS ACTIVITIES	2	1492	0.001
7	HEALTH LIMIT CLIMBING ONE FLIGHT	1	707	0.001
9	HEALTH LIMIT WALKING MORE THAN A MILE	1	399	0.003
10	HEALTH LIMIT WALK SEVERAL HUNDRED YARDS	1	604	0.002
11	HEALTH LIMIT WALKING ONE HUNDRED YARDS	1	707	0.001
12	HEALTH LIMIT BATHING OR DRESSING	1	785	0.001
21	BODILY PAIN	1	604	0.002
27	HAD A LOT OF ENERGY	1	707	0.001
29	FEEL WORN OUT	1	399	0.003
30	BEEN A HAPPY PERSON	1	707	0.001
32	TIME HEALTH/EMOTION INTERFERED	1	780	0.001
34	AS HEALTHY AS ANYBODY	1	604	0.002
35	EXPECT HEALTH TO GET WORSE	1	785	0.001
36	HEALTH IS EXCELLENT	1	604	0.002

source: items completed 2013 056 04.sas

Table 13. Missing Item Rates from Questionnaires Filled Out at Month 3

Item	Item Characteristics	Nmissing	Ntotal	PropMissing
1	IN GENERAL HEALTH IS	1	741	0.001
3	HEALTH LIMIT VIGOROUS ACTIVITIES	1	662	0.002
4	HEALTH LIMIT MODERATE ACTIVITIES	2	1395	0.001
5	HEALTH LIMIT LIFTING OR CARRYING	2	1229	0.002
6	HEALTH LIMIT CLIMBING SEVERAL FLIGHTS	2	1395	0.001
7	HEALTH LIMIT CLIMBING ONE FLIGHT	3	1755	0.002
8	HEALTH LIMIT BENDING, KNEELING, STOOPING	3	1962	0.002
9	HEALTH LIMIT WALKING MORE THAN A MILE	3	1962	0.002
10	HEALTH LIMIT WALK SEVERAL HUNDRED YARDS	2	1395	0.001
11	HEALTH LIMIT WALKING ONE HUNDRED YARDS	4	1962	0.002
12	HEALTH LIMIT BATHING OR DRESSING	2	1395	0.001
13	PHYSICAL HEALTH CUT DOWN TIME WORK	4	1300	0.003
14	PHYSICAL HEALTH ACCOMPLISHED LESS	3	567	0.005
15	PHYSICAL HEALTH LIMITED IN WORK	5	1962	0.003
16	PHYSICAL HEALTH DIFFICULTY PERFORM WORK	3	567	0.005
17	EMOTIONAL PROBLEM CUT DOWN TIME WORK	6	1300	0.005
18	EMOTIONAL PROBLEM ACCOMPLISHED LESS	7	1660	0.004
19	EMOTIONAL PROBLEM NOT WORK AS CAREFULLY	6	1660	0.004

source: items completed 2013 056 04.sas

Table 13 (continued)

Item	Item Characteristics	Nmissing	Ntotal	PropMissing
20	EXTENT HEALTH/EMOTION INTERFERED	1	662	0.002
21	BODILY PAIN	1	662	0.002
22	PAIN INTERFERE NORMAL WORK	3	1962	0.002
26	FELT CALM AND PEACEFUL	1	733	0.001
27	HAD A LOT OF ENERGY	2	1395	0.001
28	FELT DOWNHEARTED DEPRESSED	1	662	0.002
29	FEEL WORN OUT	3	1755	0.002
31	FEEL TIRED	1	741	0.001
32	TIME HEALTH/EMOTION INTERFERED	4	1395	0.003
33	GET SICK A LITTLE EASIER	3	2136	0.001
34	AS HEALTHY AS ANYBODY	3	2136	0.001
35	EXPECT HEALTH TO GET WORSE	4	2496	0.002
36	HEALTH IS EXCELLENT	3	2136	0.001

source: items completed 2013 056 04.sas

Table 14. Missing Item Rates from Questionnaires Filled Out at Month 6

Item	Item Characteristics	Nmissing	Ntotal	PropMissing
1	IN GENERAL HEALTH IS	1	628	0.002
2	RATE HEALTH IN GENERAL NOW	1	628	0.002
3	HEALTH LIMIT VIGOROUS ACTIVITIES	3	2038	0.001
4	HEALTH LIMIT MODERATE ACTIVITIES	3	2038	0.001
5	HEALTH LIMIT LIFTING OR CARRYING	2	1335	0.001
6	HEALTH LIMIT CLIMBING SEVERAL FLIGHTS	3	1335	0.002
7	HEALTH LIMIT CLIMBING ONE FLIGHT	3	1335	0.002
8	HEALTH LIMIT BENDING, KNEELING, STOOPING	2	1335	0.001
9	HEALTH LIMIT WALKING MORE THAN A MILE	2	1335	0.001
10	HEALTH LIMIT WALK SEVERAL HUNDRED YARDS	2	1335	0.001
11	HEALTH LIMIT WALKING ONE HUNDRED YARDS	2	1335	0.001
12	HEALTH LIMIT BATHING OR DRESSING	2	1335	0.001
13	PHYSICAL HEALTH CUT DOWN TIME WORK	8	2894	0.003
14	PHYSICAL HEALTH ACCOMPLISHED LESS	7	2894	0.002
15	PHYSICAL HEALTH LIMITED IN WORK	7	2894	0.002
16	PHYSICAL HEALTH DIFFICULTY PERFORM WORK	7	2894	0.002
17	EMOTIONAL PROBLEM CUT DOWN TIME WORK	8	2894	0.003
18	EMOTIONAL PROBLEM ACCOMPLISHED LESS	8	2894	0.003
19	EMOTIONAL PROBLEM NOT WORK AS CAREFULLY	7	2894	0.002

source: items completed 2013 056 04.sas

Table 14 (continued)

Item	Item Characteristics	Nmissing	Ntotal	PropMissing
22	PAIN INTERFERE NORMAL WORK	1	703	0.001
29	FEEL WORN OUT	1	707	0.001
32	TIME HEALTH/EMOTION INTERFERED	5	2587	0.002
33	GET SICK A LITTLE EASIER	2	1177	0.002
34	AS HEALTHY AS ANYBODY	2	1177	0.002
35	EXPECT HEALTH TO GET WORSE	2	1177	0.002
36	HEALTH IS EXCELLENT	3	1880	0.002

source: items completed 2013 056 04.sas

6.2 Supplemental Tables: SF-36 Components and Domains

Table 15. Change from Baseline SF-36 Physical Component Score, Month 3

Study	Physical Component			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
32	2.03 (116)	5.65 (118)	6.57 (125)	3.63	<.0001	1.94	5.31
44	2.2 (146)	5.32 (294)	7.38 (300)	3.11	<.0001	1.81	4.42
45	2.61 (107)	6.79 (233)	8.55 (224)	4.18	<.0001	2.35	6.02
46	2.41 (146)	5.95 (293)	7.54 (290)	3.53	<.0001	2.16	4.9
64	3.28 (99)	7.21 (187)	8.07 (185)	3.93	<.0001	2.27	5.58

source: SF36lsmean 2013 05 08.sas

Table 16. Change from Baseline SF-36 Mental Component Score, Month 3

Study	Mental Component			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
32	0.37 (116)	3.52 (118)	3.96 (125)	3.15	0.0068	0.87	5.43
44	0.71 (146)	3.5 (294)	4.73 (300)	2.79	0.0026	0.98	4.59
45	1.12 (107)	4.13 (233)	5.41 (224)	3.01	0.0049	0.92	5.11
46	1.6 (146)	4.36 (293)	4.35 (290)	2.76	0.0017	1.04	4.49
64	1.78 (99)	3.34 (187)	6.13 (185)	1.56	0.1408	-0.52	3.65

source: SF36lsmean 2013 05 08.sas

Table 17. Change from Baseline SF-36 Physical Function Domain, Month 3

Study	Physical Function			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
32	1.55	4.61	5.77	3.06	0.0021	1.11	5.02
	(117)	(118)	(125)				
44	1.7	3.83	6.44	2.13	0.0069	0.58	3.68
	(146)	(295)	(300)				
45	2.14	6.13	6.95	3.99	0.0002	1.93	6.05
	(108)	(235)	(224)				
46	1.7	4.5	6.36	2.80	0.0005	1.22	4.38
	(147)	(294)	(291)				
64	3.01	6.39	7.29	3.38	0.0009	1.39	5.36
	(99)	(187)	(185)				

source: SF36lsmean 2013 05 08.sas

Table 18. Change from Baseline SF-36 Role-Physical Domain, Month 3

Study	Role - Physical			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
32	1.7	4.6	6.24	2.9	0.0059	0.84	4.97
	(117)	(118)	(125)				
44	1.8	4.61	7.11	2.8	0.0009	1.15	4.45
	(146)	(295)	(300)				
45	1.89	5.9	7.54	4.01	<.0001	2.06	5.97
	(107)	(233)	(224)				
46	2.59	5.71	7.37	3.13	0.0002	1.46	4.8
	(147)	(294)	(292)				
64	3.26	6.45	7.62	3.19	0.0019	1.18	5.19
	(99)	(188)	(185)				

source: SF36lsmean 2013 05 08.sas

Table 19. Change from Baseline SF-36 Bodily Pain Domain, Month 3

Study	Bodily Pain			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
32	2.49 (117)	8.05 (118)	8.77 (125)	5.55	<.0001	3.63	7.47
44	2.68 (146)	6.85 (295)	9.57 (300)	4.16	<.0001	2.6	5.72
45	3.92 (108)	8.27 (235)	10.85 (224)	4.36	<.0001	2.35	6.36
46	3.89 (147)	7.28 (294)	8.68 (292)	3.39	<.0001	1.92	4.87
64	3.84 (99)	8.4 (187)	10.29 (185)	4.56	<.0001	2.59	6.52

source: SF36lsmean 2013 05 08.sas

Table 20. Change from Baseline SF-36 General Health Domain, Month 3

Study	General Health			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
32	0.66 (117)	3.68 (118)	3.52 (125)	3.01	0.0001	1.46	4.56
44	1.56 (146)	4.44 (294)	5.14 (300)	2.88	<.0001	1.53	4.23
45	2.47 (108)	4.79 (235)	6.36 (224)	2.32	0.0091	0.58	4.06
46	1.32 (147)	5.25 (294)	5.6 (291)	3.94	<.0001	2.53	5.34
64	2.22 (99)	4.67 (188)	6.4 (185)	2.45	0.0033	0.82	4.09

source: SF36lsmean 2013 05 08.sas

Table 21. Change from Baseline SF-36 Vitality Domain, Month 3

Study	Vitality			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
32	2.20 (117)	6.4 (118)	6.71 (125)	4.2	0.0002	2.02	6.39
44	1.39 (146)	5.56 (295)	6.22 (300)	4.17	<.0001	2.53	5.82
45	2.07 (108)	6.59 (235)	8.52 (224)	4.52	<.0001	2.63	6.41
46	2.62 (147)	6.33 (294)	6.48 (292)	3.71	<.0001	2.1	5.32
64	1.98 (99)	4.93 (188)	7.07 (185)	2.94	0.003	1.01	4.88

source: SF36lsmean 2013 05 08.sas

Table 22. Change from Baseline SF-36 Social Function Domain, Month 3

Study	Social Function			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
32	0.76 (117)	4.2 (118)	5.27 (125)	3.43	0.0032	1.15	5.71
44	1.61 (146)	4.66 (295)	5.51 (300)	3.05	0.0008	1.27	4.83
45	0.63 (108)	5.29 (235)	7.51 (224)	4.67	<.0001	2.53	6.8
46	1.68 (147)	5.2 (294)	5.85 (292)	3.52	<.0001	1.76	5.27
64	3.49 (99)	5.54 (188)	8.01 (185)	2.05	0.0717	-0.18	4.28

source: SF36lsmean 2013 05 08.sas

Table 23. Change from Baseline SF-36 Role-Emotional Domain, Month 3

Study	Role - Emotional			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
32	-0.82	3	4.02	3.82	0.0062	1.09	6.56
	(116)	(118)	(125)				
44	0.99	3.26	6.58	2.28	0.0332	0.18	4.37
	(146)	(295)	(300)				
45	1.21	4.1	5.52	2.89	0.0216	0.42	5.35
	(107)	(233)	(224)				
46	2.21	3.85	5.2	1.63	0.1248	-0.45	3.72
	(146)	(293)	(291)				
64	2.33	4.47	7.29	2.14	0.089	-0.33	4.61
	(99)	(188)	(185)				

source: SF36lsmean 2013 05 08.sas

Table 24. Change from Baseline SF-36 Mental Health Domain, Month 3

Study	Mental Health			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
32	1.43	4.22	4.47	2.8	0.0106	0.65	4.94
	(117)	(118)	(125)				
44	1.03	3.32	4.77	2.29	0.0141	0.46	4.11
	(146)	(295)	(300)				
45	2.22	4.73	5.52	2.51	0.0169	0.45	4.57
	(108)	(235)	(224)				
46	1.44	4.73	4.64	3.29	0.0001	1.63	4.95
	(147)	(294)	(292)				
64	2.15	3.6	5.86	1.45	0.1704	-0.62	3.53
	(99)	(188)	(185)				

source: SF36lsmean 2013 05 08.sas

Table 25. Change from Baseline SF-36 Physical Component Score, Month 6

Study	Physical Component			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
44	5.31	6.22	8	0.91	0.1783	-0.42	2.24
	(139)	(282)	(284)				
46	6.62	7.12	8.07	0.5	0.4787	-0.88	1.88
	(144)	(279)	(279)				
64	6.45	8.07	8.58	1.63	0.0594	-0.06	3.32
	(94)	(173)	(180)				

source: SF36lsmean 2013 05 08.sas

Table 26. Change from Baseline SF-36 Mental Component Score, Month 6

Study	Physical Component			T5 - Placebo			
	P	T5	T10	Mean	P-Value	UCL	LCL
44	3.08	3.73	4.56	0.64	0.493	-1.2	2.48
	(139)	(282)	(284)				
46	3.93	4.05	4.81	0.12	0.8926	-1.62	1.86
	(144)	(279)	(279)				
64	1.4	5.06	5.75	3.66	0.0007	1.54	5.79
	(94)	(173)	(180)				

source: SF36lsmean 2013 05 08.sas

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

/s/

ROBERT ABUGOV
09/24/2013

JOAN K BUENCONSEJO
09/27/2013
I concur.

STATISTICS FILING CHECKLIST

sNDA Number: 203214 **Applicant: Pfizer** **Stamp Date: 01/18/2013**

Drug Name: Tofacitinib **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index sufficient to locate necessary reports, tables, data, etc.	**x**			
2	Original protocols, statistical analysis plans, and subsequent amendments available.	**x**			
3	Safety and efficacy for gender, racial, and geriatric subgroups investigated (if applicable).	**x**			
4	Data sets in EDR available and conform to applicable guidance.	**x**			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Y

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

/s/

ROBERT ABUGOV
03/11/2013

JOAN K BUENCONSEJO
03/12/2013
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-3214/S002

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 administration**
Applicant	PF Prism C.V.
Application/Supplement Number	NDA 203214/S-002
Type of Application	Efficacy Supplement
Indication(s)	Treatment of rheumatoid arthritis
Office/Division	ODEII/DPARP
Division Project Manager	Philantha Bowen
Date FDA Received Application	January 18, 2013
Goal Date	November 18, 2013
Date PI Received by SEALD	November 4, 2013
SEALD Review Date	November 6, 2013
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: *Without Boxed Warning, HL meets 1/2 page limit.*

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: *Insert horizontal line separating TOC from FPI.*

NO 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: *Center "Dosage Forms and Strengths" heading in between the horizontal lines and extend horizontal line on the left side of the heading to extend the entire column width.*

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 line of white space in between the product title and the Initial U.S. Approval.*

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: *I&U, first bulleted item, insert reference at end of statement (i.e., "(1.1)"). Drug Interactions, add cross references to respective subsections of section 7 at end of each bulleted statement (i.e., first bulleted item "(2.1, 7.1)", second item "(2.1, 7.2)", and third item "(2.2, 7.3)".*

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

Selected Requirements of Prescribing Information

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:

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:

NO 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: *Remove white space in between the BW heading and statement referring to the full prescribing information, center the see full prescribing information statemen, and italicize and use all lower case letters for the entire statement (i.e., the words "full prescribing information" should be in italics and "boxed warning" should be all lower case letters).*

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

N/A 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:

N/A 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:

N/A 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

NO

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: *Reword I&U statement to follow statement above (i.e., remove commas and move "is" to immediately after product name, "XELJANZ is an inhibitor of Janus kinases (JAKs) indicated for…").*

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:

Selected Requirements of Prescribing Information

N/A 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*

*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
11/06/2013

ERIC R BRODSKY
11/06/2013
I agree. Eric Brodsky, labeling team leader, signing for Sandy Kweder, Acting SEALD Director.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 05, 2013

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-002 - XELJANZ® (tofacitinib) tablets for oral administration (Xeljanz)

Reference is made to DPARP's consult request dated October 23, 2013, requesting review of the proposed Package Insert (PI) for Xeljanz. The PI has been updated to include language regarding functional health status.

OPDP has reviewed the proposed PI entitled, "NDA 203214 (S-002) – FDA Label (10-21-13).doc" that was sent via e-mail from DPARP to OPDP on October 24, 2013. OPDP's comments on the PI are provided directly on the attached marked-up copy of the labeling (see below).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

20 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page


(b) (4)

12 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ADEWALE A ADELEYE
11/05/2013

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:

NDA 20-3214/S002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **203214** SUPPL # **002** HFD # **570**

Trade Name: Xeljanz

Generic Name: tofacitinib

Applicant Name: P.F. Prism CV

Approval Date, If Known: November 18, 2013

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 improvement in general health status, assessed by the Short Form health survey (SF-36).

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: A3921032
Study #2: A3921044
Study #3: A3921046
Study #4: A3921064
Study #5: A3921045

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:

All of the following investigations were relied upon in NDA 203214/0

Study #1: A3921032
Study #2: A3921044
Study #3: A3921046
Study #4: A3921064
Study #5: A3921045

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: 11/18/13

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

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
11/21/2013

BADRUL A CHOWDHURY
11/21/2013

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Regulatory Briefing
Meeting Date and Time:	September 20, 2013; 11:00 a.m. – 1:00 p.m.
Meeting Topic:	The SF-36 in Rheumatoid Arthritis: A Fresh Look at an Old Instrument
Application Number:	sNDA 203214/S-002
Product Name:	Xeljanz (tofacitinib) Tablets
Meeting Chair:	RADM (Retired) Sandra L. Kweder, M.D., USPHS
Meeting Recorder:	Philantha Bowen, MPH, RN Sr. Regulatory Project Management Officer Division of Pulmonary, Allergy, and Rheumatology Products

PRESENTERS

Nikolay P. Nikolov, M.D.
Acting Clinical Team Leader, DPARP, OND, CDER, FDA

Scott Komo, Dr.P.H.
Statistical Reviewer, DB IV, OB, CDER, FDA

Sarah K. Yim, M.D.
Associate Director, DPARP, OND, CDER, FD**A**

FDA ATTENDEES

Refer to the attached attendance sheet for attendees. Note that this list may not be inclusive.

1.0 BACKGROUND

The purpose of the regulatory briefing discussion is to discuss the best approach to address the use of the Short Form 36 (SF-36) results in rheumatoid arthritis (RA) product labels, with the primary focus on sNDA 203214/002, an efficacy supplement submitted by Pfizer seeking inclusion of SF-36 results in the label for Xeljanz® (tofacitinib) tablets.

SF-36 has historically been included in the labeling for RA products, as supportive data for the Health Assessment Questionnaire Disability Index (HAQ-DI) for the claim of improvement in physical function. The Division has denied proposed labeling for SF-36 since 2008 due to concerns raised by the Study Endpoints and Labeling Development (SEALD) team about the SF-36 instrument and in particular the use of the SF-36 physical component summary score and mental component summary score in RA product labels. Continued pushback from the rheumatology academic community has provided the impetus for DPARP and SEALD to reassess the SF-36 for re-implementation in RA product labels.

In the past, implementation of SF-36 in RA product labels was fairly consistent. Between 1998 and 2005, six disease modifying antirheumatic drugs (DMARDs) were approved for the treatment of patients with RA within this context as shown in Table 1. In most of these labels, mention of SF-36 is limited to a descriptive statement that improvements in SF-36 physical component score (PCS) and mental component score (MCS) were also observed. In 2007-2008, the SEALD team raised major concerns with the use of SF-36 in RA products labeling which included: 1) SF-36 is a generic health survey that has not been shown to represent a health related quality of life (HRQoL) in RA; and 2) PCS, MCS are composite measures of weighted scores from all 8 subconcepts/domains (see Figure 1), are not independent and do not measure pure physical or mental functioning and cannot be described in a way that is meaningful. Multiple internal discussions between the SEALD team and the review division (then the Division of Anesthesia, Analgesia, and Rheumatology Products, DAARP) occurred.

Ultimately, due to the level of concern expressed by SEALD, DAARP reevaluated the need for SF-36 and determined that SF-36 was not needed to support the improvement in physical function claim. (b) (4)

Table 1. Efficacy Claims in Approved Labels of Recent (>1998) DMARDS for RA

Efficacy Claims in Currently Approved Labels of Recent (>1998) Disease Modifying Anti-Rheumatic Drugs (DMARDs) for RA											
	Arava	Remicade	Enbrel	Kineret	Humira	Orencia	Rituxan	Cimzia	Simponi	Actemra	Xeljanz
ACR 20/50/70 Response	x	x	x	x	x	x	x	x	x	x	x
ACR components	x	x	x	x	x	x	x	x	x	x	x
Time course of response	x	x	x		x	x	x	x	x	x	x
Open-label maintenance	x	x	x		x	x					
Major Clinical Response		x	x		x	x		x		x	
Radiographic response	x	x	x	x	x	x	x	x		x	
Proportion of non-progressors		x	x		x	x	x			x	
Open-label maintenance			x		x						
Physical Function											
HAQ-DI	x	x	x	x	x	x	x	x	x	x	x
SF-36	x	x	x	x	x	x					
Open-label maintenance	x	x	x		x	x	x				
DAS28 <2.6											
Proportion of responders						x				x	x
Residual active joints						x				x	x
Morning stiffness	x		x			x					

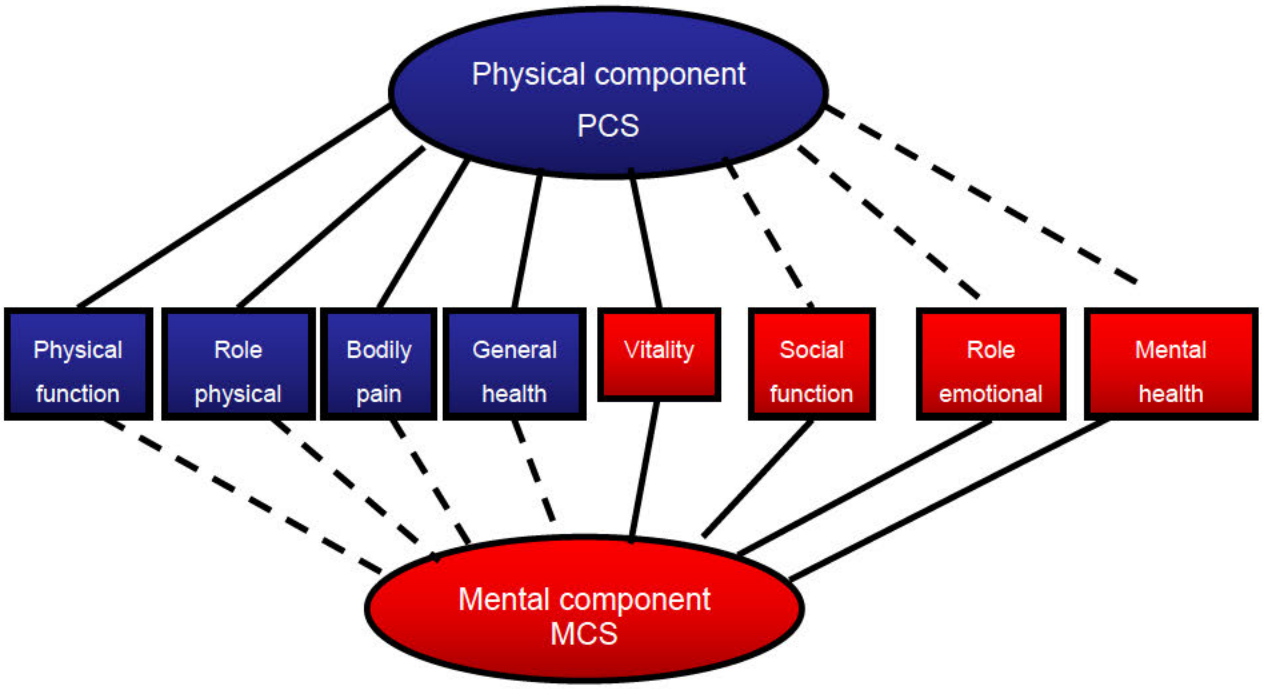
The community's rationale for the importance of SF-36 includes: (1) SF-36 is a legacy instrument with well known limitations and implications that is widely used by the RA research community throughout the world; (2) SF-36 provides additional important information on the impact of the disease on the patient that is not captured by other outcome measures used in RA trials; and (3) SF-36 is utilized throughout the world for health care policy and decision-making.

Based on the accumulated clinical data and the evidence of validity and reliability in RA, SF-36 has been shown to:

- Assess disease aspects important to patients
- Provide a multidimensional view of the impact of RA and improvements associated with effective treatment
- Be a sensitive instrument to demonstrate treatment-associated changes in RA across populations with different demographic and disease characteristics
- Offer comparison with age- and gender matched norms and with other disease states and co-morbidities
- Be non-redundant with other endpoints
- Reflects impact of early and later disease
- Have accepted MCID values for improvement as well as deterioration

DPARP and SEALD have had additional discussions regarding the SF-36 to consider the best approaches for moving forward. The Division plans to implement SF-36 in RA product labeling as an instrument for a claim of improvement in general health status rather than its previous use as a supportive measure of improvement in physical function. Rather than using PCS and MCS alone, mention of results for the 8 domains (Figure 1) will be included to facilitate interpretation. Since RA patients may or may not have significant decrement in mental health domains at baseline, this raises questions on how to handle labeling if results are not consistent across PCS, MCS and the 8 domains.

Figure 1: SF-36- Model Used to Derive PCS, MCS



Language proposed for use in RA product labeling is consistent with the language used in abatacept (Orencia) labeling:

(b) (4)

2.0 DISCUSSION

History of SF-36/Regulatory History

Dr. Nikolov presented an overview and background information on the history of SF-36 in RA drug development, highlighting the primary objectives of RA development in relation to domains that are key to patients (i.e. clinical response, physical function, and structural outcomes). Moreover, the presentation noted elements of the SF-36 survey, including but not limited to, the use, purpose, and correlation with disease specific instruments. According to the 1999 RA Guidance, the SF-36 should be used to support HAQ-DI for the improvement in physical function claim. As such, labeling referenced the survey. Between 1998 and 2007 six DMARDS therapies were approved with descriptive SF-36 language in the labeling. This language reflects summary information along with PCS and MCS data. (b) (4)

During 2007-2008, the Division and the SEALD team engaged in several discussions

regarding the usefulness of the SF-36. SEALD staff's concerns have been that the SF-36 was a generic tool, did not represent HRQoL, the PCS and MCS were not independent elements, but rather a reflection of weighted scores from all 8 domains within the survey, and the tool does not definitively measure physical and mental functioning in a manner that would be clinically meaningful. Based on the concerns expressed by SEALD staff and the fact that sufficient experience with HAQ-DI has accumulated to allow for its independent use as evidence for the improvement in physical function claim, the review Division (then the Division of Anesthesia, Analgesia, and Rheumatology Products) agreed to stop including SF-36 in product labeling. This decision was met with a significant criticism not only by sponsors due to the uneven playing field, but also by the rheumatology academic community who has used this instrument and was familiar with its limitations, utility, and interpretation, including the summary scores. Prompted by a specific application in house (tofacitinib for the treatment of patients with RA) discussed later in the presentation, DPARP is now seeking to re-implement the SF-36 in RA product labeling as a separate health status efficacy claim, not a supportive claim for physical functioning, understanding the limitations of the SF-36 health survey.

SF-36 Conceptual Model

Dr. Komo followed with a presentation describing the SF-36 conceptual model as a 36 item instrument consisting of questions that address each of the 8 domains (refer to Figure 1 above). These domains are then categorized into 2 primary summary scores: the physical and mental component scores. Moreover, Dr. Komo explained the SF-36 and the associated summary scores in terms of scoring, derivation, calculation, and interpretation of the summary scores (PCS and MCS) with respect to the scale scores (8 domains). With respect to the interpretation of the scores, Dr. Komo clarified that the data reflects a 100 point scale, therefore a score of 5 out of 100 is statistically significant. Recognizing the limitations of the SF-36, Dr. Komo discussed adequacy of the survey scores, as well as highlighted cases of inconsistencies between the scale and summary scores. In order to reduce the potential for negative coefficients and effect size, the literature recommends that the summary scores be interpreted in conjunction with the scales scores. As such, the summary and scales scores of the SF-36 is an invaluable tool in the RA population based upon the literature and rationale provided for the need of an instrument that is specific to RA. Lastly, Dr. Komo summarized the current evidence supporting the use of SF-36 in the RA population. In re-implementing the SF-36 into labeling for DMARDS therapies, the Division agrees with the survey developers and researchers pertaining to interpreting summary scores in conjunction with scale scores.

Tofacitinib Development

Dr. Nikolov provided an overview and summary of the tofacitinib development program, noting that the safety and efficacy data were derived from five randomized, placebo-controlled phase 3 trials. Additionally, Dr. Nikolov summarized the SF-36 data for the PCS, MCS, and the 8 domains, pointing the consistency in: 1) the 8 domains and the summary scores; 2) the observed treatment effects for DMARDS approved with and without the SF-36 claim in the labeling; and 3) the treatment effects of clinical trials cited

in published literature. Lastly, Dr. Nikolov described the value of the SF-36 in RA drug development and highlighted the premise of 2013 RA Guidance which allows industry to include additional RA endpoints. In conclusion, Dr. Nikolov conveyed the Division's position to re-implement the SF-36 into labeling for improvement in general health status and proposed language consistent with the Orencia product label.

The panel verbalized understanding of the Guidance to require that benefit on clinical response and physical function must be demonstrated before the SF-36 claim is accepted/granted. The Division agreed and clarified that the SF-36 would be an ancillary claim. Efficacy in RA would be established based upon signs and symptoms, clinical response, and physical functioning. If efficacy is not established in these primary areas, then the SF-36 claim would not be accepted.

SF-36 Discussion

Dr. Yim began the discussion and acknowledged SEALD's continued concerns about the SF-36 instrument and its lack of content validity. Prior to presenting the questions, the Division asked the regulatory panel whether the SF-36, in general, should be considered for in labeling in light of SEALD staff's concerns.

Laurie Burke representing the SEALD staff, commented that policy makers and the non-health care professionals need to have an understanding of what the tool measures and its relation to their health status. The basis for the disagreement with the use of SF-36 in the labeling is based upon the lack of a definitive way to describe the PCS and MCS in order to know and delineate the elements they are intended to measure. Laurie Burke reiterated its prior recommendation to use the 8 domains or the PF-10 for physical functioning in labeling, pointing out that the domain names, for example, "*role physical*", should not be used. The domain names are unclear. Laurie Burke recommends using what the domains actually measure. Moreover, she stated that including the needs and desires of health care policy-makers and academia in the way we evaluate a label may create a path in labeling that leads to an approach that would be different from the standard way we review labeling. The regulatory panel stated that rheumatologists or the RA community will not be confused by the SF-36 scores and the scale has been used extensively.

The panel questioned the Division's approach if the SF-36 did not win or if only 1 summary score won, for inclusion in the labeling. The Division commented that if the summary scores were not concordant, it is possible that the SF-36 would still be accepted with the PCS score as statistically significant to demonstrate a treatment difference, because MCS is not consistently impaired/reduced in RA patient populations. All other scores (i.e. scales or domains) would be included as supportive information. In turn, the panel asked if there are cases whereby the individual domain scores lack support, but the summary scores are supportive in RA. The Division stated that this outcome has not been seen in RA.

In terms of content validity, the Division sought clarification on previous comments regarding the lack of content validity, despite literature support for content validity of the SF-36. Laurie Burke explained content validity as having evidence and knowledge of the

item to be measured and one is able to identify what is being measured. She acknowledged that RA physicians use the SF-36 and it is meaningful to the RA community, however, the instrument lacks content validity because it is a weighted score, inclusive of all 8 domains. As such, the PCS does not measure the physical health and MCS does not measure the mental health. The panel sought SEALD's position on the use of the individual scores for the 8 domains. SEALD stated that the individual scores (8 domains) of the SF-36 would be valuable in RA, but combining these values for the PCS and MCS (summary score) is not acceptable based upon SEALD's previous comments.

Dr. Lisa Lavange, Director of the Office of Biostatistics, explained the principles, component analysis, and summarized the historic rationale and derivation of the PCS and MCS, as well noting that the research is reproducible and the summary scores are derived from a validated algorhythm, thus are not arbitrary. The panel concluded that there appeared to be sufficient evidence to support using the summary scores in the manner in which these scores were constructed. SEALD agreed but also stated that the summary scores do not represent what they measure.

The regulatory panel stated that the SF-36 is used globally and has been referenced in numerous NIH studies. Moreover, this tool is well-documented in literature. If interpretation of the scores is a concern, a member of the panel recommended the use of the 8 domains in conjunction with the PCS and MCS.

Referring to tofacitinib and slide 42 entitled, *SF-36 Data: 8 Domains,* the panel asked the Division to clarify the minimal clinically important difference (MCID). The Division stated that the MCID can be defined and interpreted using the mean accepted values. Slide 42 provides a summary of MCID of individual patients. The panel questioned the Division's threshold/criteria regarding this data for inclusion in a drug label. The Division stated that a global statement would be included in labeling. The MCID has not been used for labeling, but is available for the SF-36, suggesting it can be interpreted in a clinically meaningful way.

3.0 QUESTIONS

1. Comment on whether SF-36 data from a single study may be sufficient for inclusion in labeling

The Division stated that SF-36 would be an ancillary claim in the label. Guidance is sought as to whether two studies are required to support labeling. The panel commented two studies are expected, however if only a single study was conducted/submitted to support the claim, then it would be acceptable.

The Division commented on the consistency of data in the literature and the lack of discordance seen among the endpoints. In response, SEALD commented that the wealth of literature supporting the SF-36 is driven by its target audience, as well as by academia and others who desire the SF-36 claim. Additionally, SEALD stated that perhaps consideration should be given to the need to integrate health assessors into labeling discussions/decisions similar to current European practice. If the PCS and MCS is incorporated back into labeling, questions may arise regarding the Agency's

policy on the inclusion of general health measures, such as QoL and health status, which has not been accepted previously.

Due to political standards in this country, the regulatory panel stated that the Agency is unable to pursue a similar path like the Europeans regarding the integration of stakeholders into regulatory policy decision making. In turn, the Agency has taken in account the patients requests expressing the need to know more about the effects of treatment on their health status. This request has led to the incorporation of additional endpoints in clinical trials.

2. Comment on whether the claim can be granted if the results are discordant:
   - Among the 8 domains
   - Between the PCS and MCS
   - Between the summary score (PCS, MCS) and the 8 domains

The Division commented that discordance has not been observed among the data. Generally, a statistically significant difference may or may not be evident with MCS. However, a treatment difference is consistently observed with the PCS. For completeness, the PCS, as well as MCS would be included in the labeling. The panel asked whether more descriptive information would be necessary in the label, since there appears to be a dose-response. Referring to the Orencia label, the Division clarified that the data results would be reported in the clinical studies section, not a claim in the indication.

The Division stated that the labeling for Orencia outlines improvement in health status. SEALD asked whether it would be acceptable to present the summary scores without the 8 domains. The regulatory panel recommended the inclusion of the 8 domains in conjunction with the PCS and MCS scores for presentation in the label.

3. Comment on whether the size of treatment effect should be described in labeling

The regulatory panel commented that broad statements are not informative, whereas numerical summaries provide more information. However, the panel also questioned whether the inclusion of scales, graphs, and numerical information would expand the label and noted that such information which may focus more attention on the SF-36, which is a supportive claim (not primary or secondary) instead of the primary endpoints in the label .

The Division proposes to include the summary scores since they provide the basis for the statistical evaluation of the instrument's results in trials and asked if the panel recommended the use of only the 8 domains. The panel acknowledged previous comments regarding the history and derivation of the summary scores, as well as SEALD's comment pertaining to the lack of content validity for the summary scores. The regulatory panel recognizes that the naming of the summary scores can be

misleading and result in misinterpretation since PCS and MCS represent a combination of attributes, not simply physical and mental as indicated by their names. However, due their extensive use and support in the literature and in the RA community, the panel stated it would be difficult to object to the use of the SF-36 and the summary scores.

5.0 ATTACHMENTS AND HANDOUTS

Attachment 1

Slide Presentation

Attachment 2

List of meeting attendees

The SF-36 in Rheumatoid Arthritis: A Fresh Look at an Old Instrument

With attention to Tofacitinib's SF-36 supplement

Regulatory Briefing
September 20, 2013

Division of Pulmonary, Allergy, and Rheumatology Products

Outline

- History of SF-36 in RA Drug Development
  Nikolay P. Nikolov, M.D.
  Acting Clinical Team Leader, DPARP, OND, CDER, FDA
- Overview of SF-36 Instrument
  Scott Komo, Dr.P.H.
  Statistical Reviewer, DB IV, OB, CDER, FDA
- Overview of Tofacitinib SF-36 Data and Closing Remarks
  Nikolay P. Nikolov, M.D.
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- Questions and Discussion
  Sarah K. Yim, M.D.
  Associate Director, DPARP, OND, CDER, FDA

RA Drug Development

- Objectives of RA drug development are to assess efficacy in key domains important to patients:
  - Clinical response/Signs and symptoms of disease:
    - ACR response criteria
    - DAS28, as supportive
  - Physical function:
    - HAQ-DI
    - SF-36, as supportive
  - Structural outcomes:
    - Radiographic outcomes
  - Other aspects of RA

Short Form-36 Health Survey

- Multi-purpose, generic health survey
- Originally developed to satisfy minimum psychometric standards for group comparisons in 1980s and 90s:
  - Used in health planning and policy, health services evaluation in era of cost containment
  - Subsequently validated in many disease, including RA
- Most widely used health status questionnaire in the world (used in ~ 4000 publications)

SF-36 Health Survey in RA

- Reflects the decrease in overall health status for this population
- Correlates with disease specific instruments such as:
  - HAQ-DI, MHAQ,
  - DAS28, CDAI, SDAI
- Sensitive to treatment-related changes in clinical outcomes in RCTs of multiple DMARDs

SF-36 in RA Drug Development

- In the 1999 RA guidance, SF-36 was recommended as a measure to:
  - Support HAQ-DI for the "Prevention of Disability/ Improvement in Physical Function" claim and
  - Incentivize the conduct of long-term clinical trials
- In this context, SF-36 was used in labeling:
  - PCS has been primarily used to support the HAQ-DI data for "Improvement in Physical Function" claim
  - MCS has been reported for completeness even if unchanged (RA patients may not have significant baseline decrements in mental components)

SF-36 in RA Drug Development

- 6 DMARDs approved for RA between 1998 and 2007 with descriptive SF-36 claim:
  - All are summaries (No effect size is given)
  - All give PCS results
  - All except Arava give MCS results
  - Orencia labeling also identifies “all 8 domains”
  - “Health-related quality of life was assessed by the SF-36 questionnaire ...improvement was observed in the ORENCIA group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS)”
- Rituxan (2006) did not receive SF-36 labeling because 2-year data were not submitted as requested

SF-36 in RA Product Labeling

Efficacy Claims in Currently Approved Labels of Recent (>1998) Disease Modifying Anti-Rheumatic Drugs (DMARDs) for RA

	Arava	Remicade	Enbrel	Kineret	Humira	Orencia	Rituxan	Cimzia	Simponi	Actemra	Xeljanz
ACR 20/50/70 Response	x	x	x	x	x	x	x	x	x	x	x
ACR components	x	x	x	x	x	x	x	x	x	x	x
Time course of response	x	x	x		x	x	x	x	x	x	x
Open-label maintenance	x	x	x		x	x					
Major Clinical Response		x	x		x	x		x		x	
Radiographic response	x	x	x	x	x	x	x	x		x	
Proportion of non-progressors		x	x		x	x	x			x	
Open-label maintenance			x		x						
Physical Function											
HAQ-DI	x	x	x	x	x	x	x	x	x	x	x
SF-36	x	x	x	x	x	x					
Open-label maintenance	x	x	x		x	x	x				
DAS28 <2.6											
Proportion of responders						x				x	x
Residual active joints						x				x	x
Morning stiffness	x		x			x					

SF-36 in RA Drug Development

- In 2007-8 SEALD expressed strong concerns about the use of SF-36 in RA product labeling:
  - SF-36 is a generic health survey that has not been shown to represent a HRQoL in RA
  - PCS, MCS are composite measures of weighted scores from all 8 subconcepts/domains, are not independent and
  - Do not measure pure physical or mental functioning and cannot be described in a way that is meaningful
- The Division (DAARP) agreed to stop using SF-36 because it was no longer considered necessary to support HAQ-DI for the physical function claim

SF-36 in RA Drug Development

- 5 DMARDs were approved for RA between 2008 and the present with no SF-36 claim:
  - (b) (4)
  - Pharmaceutical companies and academic researchers continued to have great interest in SF-36 and published results to disseminate them
  - Consistent push-back from the academic community as well as from pharmaceutical companies

SF-36 in RA Drug Development

- Community's rationale for continued use:
  1. SF-36 is a legacy instrument with well known limitations and implications that is widely used by the RA research community throughout the world
  2. SF-36 provides additional important information on the impact of disease on the patient that is not captured by other outcome measures used in RA trials
  3. SF-36 is utilized throughout the world for health care policy and decision-making

SF-36 in RA Drug Development

- As a result, SEALD and DPARP have had multiple additional discussions about the SF-36 to consider best approaches for moving forward
- The Division now plans to re-implement SF-36 in RA product labeling as a separate health status claim
- The question: how best to portray SF-36 results in labeling, keeping in mind the limitations of the instrument

Outline

- History of SF-36 in RA Drug Development
  Nikolay P. Nikolov, M.D.
  Acting Clinical Team Leader, DPARP, OND, CDER, FDA
- Overview of SF-36 Instrument
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- Questions and Discussion
  Sarah K. Yim, M.D.
  Associate Director, DPARP, OND, CDER, FDA

SF-36 Instrument: Outline

- Overview of the SF-36
  - Development
  - Scoring
- Issues with the SF-36 summary scores
- Evidence for use of the SF-36 in a RA population
  - Reliability
  - Construct validity
  - Responsiveness
  - Interpretation
- Summary

SF-36: Conceptual Model

- 36 items
- 8 health concepts or domains
- 2 summary measures
  - Physical component score (PCS)
    - Physical functioning (PF)
    - Role physical (RP)
    - Bodily pain (BP)
    - General health (GH)
  - Mental component score (MCS)
    - Social functioning (SF)
    - Role emotional (RE)
    - Mental health (MH)
    - Vitality (VT)

SF-36 Scoring

- Higher score indicates a better health state
- Each item contributes to only one scale except for single item on reported health transition
- Raw scale scores:

  Sum of individual items
- Transformed scale scores:

  Raw scale scores transformed to a 0 – 100 scale
- Standardized scale scores

  Computed comparing the transformed scale scores with the norms from 1998 survey of US general population

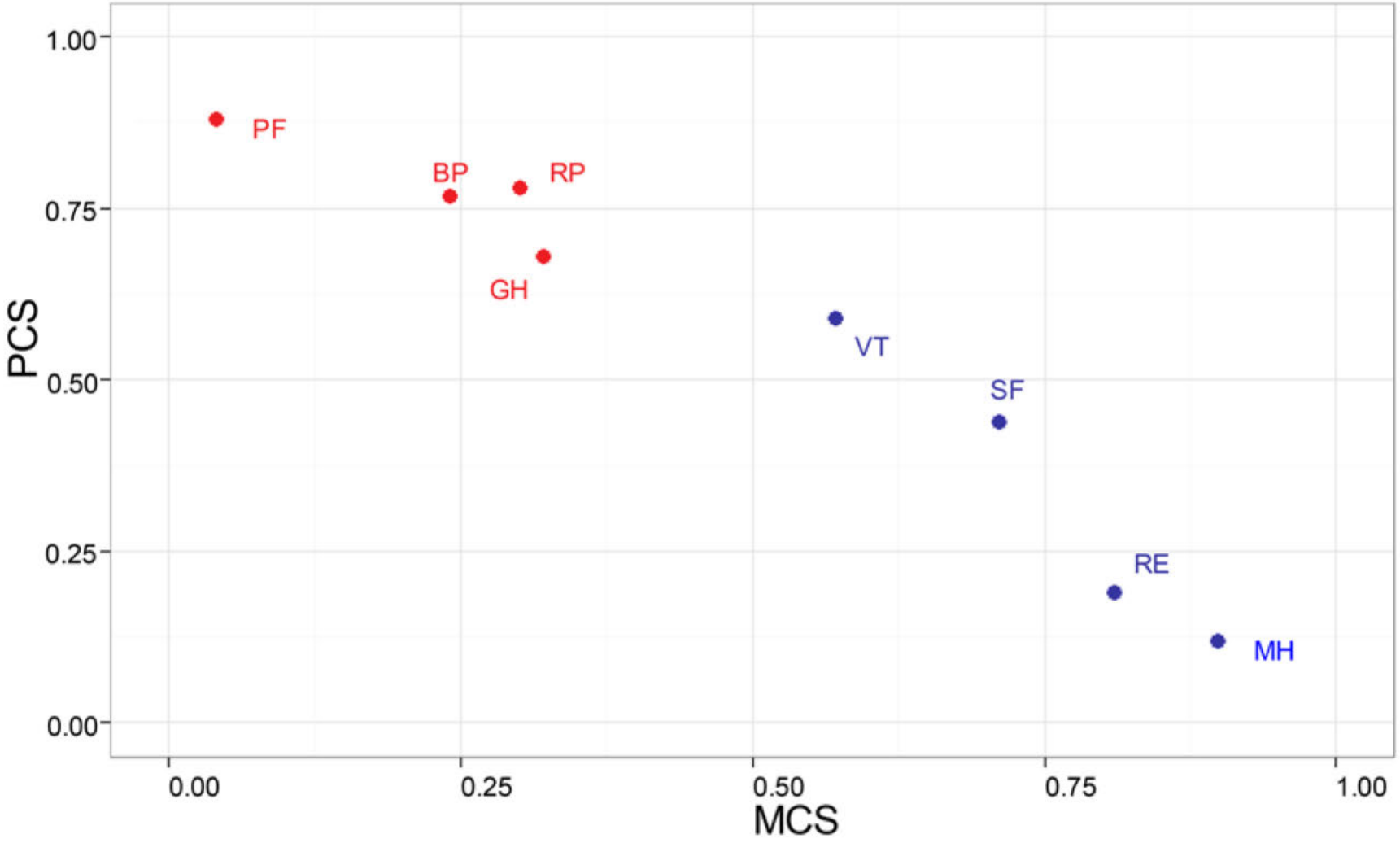
Summary Scores (PCS and MCS)

- Developed to reduce the number of statistical comparisons from eight to two without substantial loss of information
- Not constructed based on a conceptual model (i.e., each summary score composed of 4 scales)
- Derived empirically from analyses of subjects from a 1990 survey in the US general population

SF-36: Summary Scores Derivation

- Used a principal components analysis that summarized the 8 scale scores into smaller number of components
- Each component constructed as weighted sum of ALL 8 scale scores
  - Components are uncorrelated with each other
  - Weights chosen to maximize the scale score variance explained among the fewest number of components
- 2 components were extracted from the 8 scales
- Based on the correlation pattern of summary scores with the 8 scales, the summary scores have been interpreted as physical and mental components of health status

Correlation of Scale and Component Scores



Summary Score Calculation (PCS and MCS)

Summary Scores are calculated as the sum of the products of

- Standardized scale scores
- Factor score coefficients

SF-36 Scale	PCS	MCS
Physical Functioning	0.42	-0.23
Role Physical	0.35	-0.12
Bodily Pain	0.32	-0.10
General Health	0.25	-0.02
Vitality	0.03	0.24
Social Functioning	-0.01	0.27
Role Emotional	-0.19	0.43
Mental Health	-0.22	0.49

Interpretation of Summary Scores

PCS and MCS calculated as weighted sum of all 8 scale scores, not as the combination of the four scales hypothesized in the conceptual model

Inconsistencies between Changes in Scale and Summary scores

- Multiple cases published warning of inconsistent results between summary score change and scale score change
- Authors warn of potential inconsistencies in cases where there is large treatment effect in scales with substantial negative factor coefficients
  - PCS: RE and MH
  - MCS: PF, RP, and BP

Adequacy of Summary Scores

- Questions have arisen whether summary scores adequately represent the scale scores.
- Several examples published for different chronic diseases where MCS was closer to the norm then expected given
  - Scores for the 4 scales most related to mental health were considerably below the norm
  - High prevalence of depression

Developer's Response to Inconsistency Criticism

- Hypothetical inconsistency, not a real life issue
- Scale and summary scores were consistent for the most part in their review of approximately 250 treatment trials
- They cited a 52-week treatment trial of approximately 400 RA patients that found:
  - Consistent results between scale and summary scores
  - Large improvement in PCS that did not cancel out the improvement in MCS

Correlation of PCS and MCS

- Multiple authors questioned the algorithm that forced the PCS and MCS to be uncorrelated
  - Unrealistic assumption that physical and mental health are uncorrelated
  - Main reason for the substantial negative factor score coefficients
  - Proposed alternative method that allows summary scores to be correlated that resulted in
    - Very few negative factor score coefficients
    - Substantial correlation (0.4 - 0.7) between summary scores
- For several different populations, publications have shown the best fitting model is one that includes only the 4 hypothesized scales for each summary measure

Recommended Interpretation of Summary Scores

Developers as well as multiple authors have recommended that summary scores be interpreted in conjunction with scale scores

SF-36: Why psychometric evidence is needed for patients with arthritis

- Cannot assume that the psychometric evidence provided by the developers for the US general population can be extrapolated to RA patients
- Factor structure (i.e., relationship between the scale and summary scores) can vary considerably by disease

Reliability in arthritis patients

Multiple publications have demonstrated the reliability of the SF-36 in RA patients based on

- Test-retest reliability in stable patients
- Internal consistency

  Measures the correlation of items within a scale

Construct Validity in RA patients

Multiple publications have demonstrated the construct validity of the SF-36 in RA patients based on

- Cross-sectional analyses of correlations of various RA measures with PCS and the scales most related to physical health
- PCS changes as well as changes for scales most related to physical health are consistent with severity groupings based on several RA measures
- Cross-sectional analyses of PCS and the scales most related to physical health are able to discriminate across severity groupings based on several RA measures

Summary scores: Similarity of factor structure

- Summary scores calculated using factor score coefficients from US general population
- Important to assess similarity of factor structure (i.e., relationship between the scale and summary scores) between US general population and RA patient population
- Several authors have provided evidence that factor structure is similar between the US general population and RA patient population

Responsiveness in RA patients

- Tugwell (2007) provided evidence of responsiveness of the summary measures in 7 OA and RA trials
- Moderate effect size for PCS

Standardized PCS response mean was 0.42

- Small effect size for MCS

Standardized MCS response mean was 0.21

Interpretation in RA patients

- Strand et al. (2007) noted that multiple authors have found the following minimally clinically important differences (MCID) for RA patients
  - 5 points for scale scores
  - 2.5 for the summary scores

Summary

- Issues with summary scores (PCS and MCS)
  - Interpretation

    Summary scores are weighted average of all 8 scale scores
  - Potential inconsistencies of change between scale and summary scores
  - Cases where summary scores may not adequately estimate health status
  - Developers claim scores for the most part are consistent

Summary - 2

- Issues with summary scores (PCS and MCS)
  - Questionable assumption that physical and mental health status are uncorrelated

    Thought to be responsible for negative factor coefficients and inconsistent results between scale and factor scores

Summary - 3

- Evidence of reliability and construct validity for the SF-36 in RA patients
- Evidence of similarity of factor structure between RA patients and general population
- Evidence of responsiveness for RA patients
- Evidence for MCID in RA patients for scale and summary scores

Summary - 4

- We agree with the recommendation from the developers as well as multiple authors that summary scores be interpreted in conjunction with scale scores

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  Associate Director, DPARP, OND, CDER, FDA

Tofacitinib Development

- Product: tofacitinib, Xeljanz (JAK inhibitor),
- Dosage: 5 mg BID, IR tablets
- Approved for the treatment of adults with moderate-to-severe active RA (November 2012):
  - Signs and symptoms of RA, based on:
    - ACR20, 50, and 70 response rates and DAS28-4(ESR)<2.6
  - Physical function, based on change from baseline in HAQ-DI
- Efficacy data on SF-36 from the original NDA
- Proposed labeling:
  - [redacted] (b) (4)

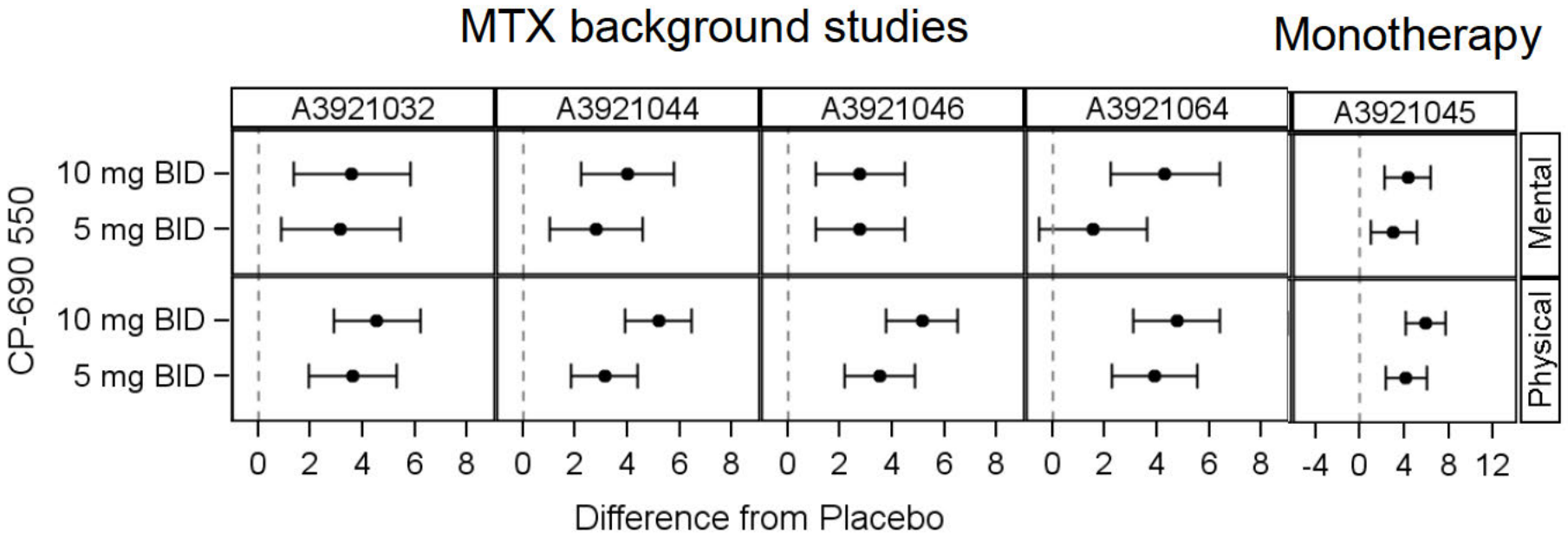
Tofacitinib Development

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

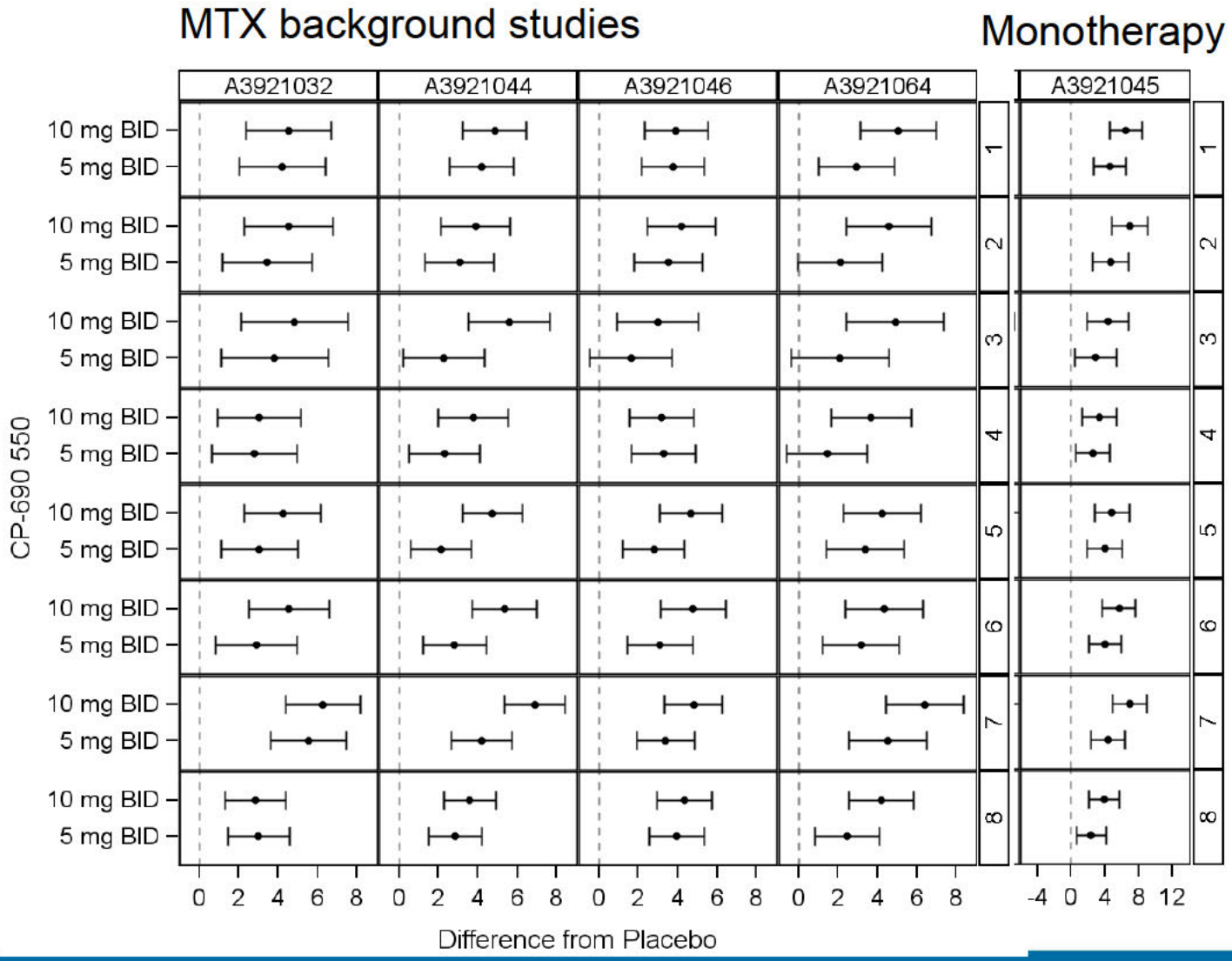
EP = endpoint

SF-36 Data: PCS, MCS

- Summary data at Month 3



SF-36 Data: 8 Domains



Bodily Pain

General Health

Mental Health

Physical Fx

Role-Emotional

Role-Physical

Social Function

Vitality

Value of SF-36 in RA Drug Development

- Multidimensional view of the impact of RA and improvements associated with effective treatment
- A sensitive instrument to demonstrate treatment-associated changes in RA across populations with different demographic and disease characteristics
- Offers comparison with age- and gender matched norms and with other disease states and co-morbidities

Value of SF-36 in RA Drug Development

- Non-redundant with other endpoints
- Reflects impact of early and later disease
- Accepted MCID values for improvement as well as deterioration
- Well documented evidence of validity and reliability in RA clinical trials with a wealth of data across countries and cultures

Value of SF-36 in RA Drug Development

- 2013 RA Draft Guidance allows for inclusion of endpoints that address other aspects of RA important to patients asking the sponsors to provide a justification which should include importance, clinical relevance, and non-redundancy with other measures

SF-36 in RA: Division's Position

- Objectives of RA drug development are to assess efficacy in key domains important to patients:
  - Clinical response/Signs and symptoms of disease:
    - ACR response criteria
  - Physical function:
    - HAQ-DI
  - Structural outcomes:
    - Radiographic outcomes
  - Other aspects of RA:
    - Health status as measured by SF-36

SF-36 RA Labeling Possibility

Section 14, Clinical Studies:

- "Health status was assessed by the Short Form Health Survey (SF-36). Patients receiving TRADE demonstrated greater improvement from baseline compared to placebo in PCS, MCS and in all 8 domains of the SF-36 at Month X."

- Consistent with Orencia labeling

Outline

- History of SF-36 in RA Drug Development
  Nikolay P. Nikolov, M.D.
  Acting Clinical Team Leader, DPARP, OND, CDER, FDA
- Overview of SF-36 Instrument
  Scott Komo, Ph.D.
  Statistical Reviewer, DB IV, OB, CDER, FDA
- Overview of Tofacitinib SF-36 Data and Closing Remarks
  Nikolay P. Nikolov, M.D.
  Acting Clinical Team Leader, DPARP, OND, CDER, FDA
- Questions and Discussion
  Sarah K. Yim, M.D.
  Associate Director, DPARP, OND, CDER, FDA

Topics for Discussion

1. Comment on whether SF-36 data from a single study may be sufficient for inclusion in labeling
2. Comment on whether the claim can be granted if the results are discordant:
   - Among the 8 domains
   - Between the PCS and MCS
   - Between the summary score (PCS, MCS) and the 8 domains
3. Comment on whether the size of treatment effect should be described in labeling

Thank you!

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/s/

PHILANTHA M BOWEN
11/21/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: November 8, 2013

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-002 (Xeljanz) – Request for Label Revisions (#2)

# of Pages including cover: 37

Thank you.

NDA 203214/S-002
Tofacitinib Tablets
PF Prism C.V.

Dr. Nickie Kilgore:

Your submission dated October 28, 2013, to sNDA 203214/S-002 containing revised labeling is currently under review. In enclosed label the FDA-proposed insertions are underlined and deletions are in strike-out. Additionally, we have outlined additional recommendations/revisions below regarding the package insert. Be advised that these comments are not all-inclusive and we may have additional recommendations as we continue our review of the label.

Highlights (HL) Section:

1. Throughout HL remove extra white space, i.e., remove all white space below the major headings in HL (i.e., text should be presented immediately beneath the heading) and remove extra white space above the major headings (i.e., retain one line of white space above each major heading).

2. Insert horizontal line separating table of contents (TOC) from full prescribing information (FPI).

3. Center "Dosage Forms and Strengths" heading in between the horizontal lines and extend horizontal line on the left side of the heading to extend the entire column width.

4. Remove line of white space in between the product title and the Initial U.S. Approval.

5. *Indications and Usage:*:

    - In the first bulleted item, insert reference at end of statement (i.e., "(1.1)"). Drug Interactions, add cross references to respective subsections of section 7 at end of each bulleted statement (i.e., first bulleted item "(2.1, 7.1)", second item "(2.1, 7.2)", and third item "(2.2, 7.3)"

    - Reword this statement to follow statement above (i.e., remove commas and move "is" to immediately after product name, "XELJANZ is an inhibitor of Janus kinases (JAKs) indicated for…").

6. *Box Warning:*

    - Remove white space in between the BW heading and statement referring to the full prescribing information, center the see full prescribing information statemen, and italicize and use all lower case letters for the entire statement (i.e., the words "full prescribing information" should be in italics and "boxed warning" should be all lower case letters)

NDA 203214/S-002
Tofacitinib Tablets
PF Prism C.V.

Submit a clean copy and a tracked-change version of the label incorporating the recommendations in the attached package insert by Tuesday, November 12, 2013, 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-002
Tofacitinib Tablets
PF Prism C.V.

Drafted: Bowen/11-8-13
Clearance: Jafari/11-8-13
Finalized: Bowen/11-8-13

33 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PHILANTHA M BOWEN
11/08/2013

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)
October 23, 2013		203214/S-002	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Xeljanz (tofacitinib)			November 6, 2013

NAME OF FIRM:	
PF Prism C.V.	PDUFA Date: November 21, 2013

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: Original submission dated January 18, 2013; Recent labeling submission dated May 30, 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 functional health status. 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: November 18, 2013

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
10/24/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: October 21, 2013

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-002 (Xeljanz) – Request for Label Revisions

# of Pages including cover: 37

Thank you.

NDA 203214/S-002
Tofacitinib Tablets
PF Prism C.V.

Dr. Nickie Kilgore:

Your labeling submission dated May 30, 2013, to sNDA 203214/S-002 is currently under review. The enclosed label contains clarification FDA comments pertaining to the changes made 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 Monday, October 28, 2013, 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-002
Tofacitinib Tablets
PF Prism C.V.

Drafted: Bowen/10-21-12

Clearance: Jafari/10-21-13
Nikolay/10-21-13
Yim/10-21-13

Finalized: Bowen/10-2-13

34 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PHILANTHA M BOWEN
10/21/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 17, 2013

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	**From:** Philantha Bowen, MPH Sr. Program Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 860-686-7545	**Fax number:** 301-796-9728
Phone number: 860-441-5030	**Phone number:** 301-796-2466

Subject: NDA 203214/S-002 – Statistical Information Request

Total no. of pages including cover: 3

Comments: **TIME-SENSITIVE - Please Acknowledge Receipt**

Document to be mailed: YES ☑ NO

NDA 203214/S-002
Tofacitinib
Pfizer, Inc.

Dr. Kilgore:

Reference is made to supplemental NDA (sNDA) dated January 18, 2013, to NDA 203214/S-002 to support the inclusion of Short Form-36v2 Health Survey data in the tofacitinib labeling and the FDA information request dated May 20, 2013. Your response dated May 28, 2013, to our request is currently under review.

We have the following comment and request for information:

> In the response, you did not provide all of the requested references that were cited in the Patient-Reported Outcome Evidence Dossier: Short Form-36v2 Health Survey (SF-36). The following are examples of the missing references and does not represent a complete listing of all of the missing references. Ensure that all of the cited references are submitted.
>
> *Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, Phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006; 54:2793-2806*
>
> *Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000; 343(22):1594-*1602

We request that you submit the requested information to the sNDA by Monday, June 24, 2013.

If you have any questions, contact me at 301-796-2466.

{See appended electronic signature page}

_____

Philantha Montgomery Bowen, MPH, RN
Sr. Program Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 203214/S-002
Tofacitinib
Pfizer, Inc.

Drafted: Bowen/6-17-13

Clearance: Barnes/6-17-13

Finalized: Bowen/6-17-13

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/s/

PHILANTHA M BOWEN
06/17/2013

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
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 20, 2013

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	**From:** Philantha Bowen, MPH Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 860-686-7545	**Fax number:** 301-796-9728
Phone number: 860-441-5030	**Phone number:** 301-796-2466

Subject: NDA 203214/S-002 – Information Request

Total no. of pages including cover: 3

Comments: **TIME-SENSITIVE - Please Acknowledge Receipt**

Document to be mailed: YES ☑ NO

NDA 203214/S-002
Tofacitinib
Pfizer, Inc.

Dr. Kilgore:

Your supplemental NDA (sNDA) dated January 18, 2013, to support the inclusion of Short Form-36v2 Health Survey in the tofacitinib labeling is currently under review. We have the following request for information:

- Submit copies of the references cited in the Patient-Reported Outcome Evidence Dossier: Short Form-36v2 Health Survey (SF-36).

We request that you submit the requested information to the sNDA by May 28, 2013.

If you have any questions, contact me at 301-796-2466.

{See appended electronic signature page}

_____

Philantha Montgomery Bowen, MPH, RN
Sr. Progam Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 203214/S-002
Tofacitinib
Pfizer, Inc.

Drafted: Bowen/5-20-13

Clearance: Jafari/5-20-13
Buenconsejo/5-20-13

Finalized: Bowen/5-20-13

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/s/

PHILANTHA M BOWEN
05/20/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: April 9, 2013

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	**From:** Philantha Bowen, MPH Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 860-686-7545	**Fax number:** 301-796-9728
Phone number: 860-441-5030	**Phone number:** 301-796-2466

Subject: NDA 203214/S-002 – Clinical Information Request

Total no. of pages including cover: 4

Comments: **TIME-SENSITIVE - Please Acknowledge Receipt**

Document to be mailed: YES ☑ NO

NDA 203214/S-002
Tofacitinib
Pfizer, Inc.

Dr. Kilgore:

Your supplemental NDA (sNDA) dated January 18, 2013, to support the inclusion of Short Form-36v2 Health Survey in the tofacitinib labeling is currently under review. We are re-evaluating the utility of SF-36 and how the SF-36 endpoint would be best implemented in labeling, including Physical and Mental Component Scores (PCS and MCS) and the SF-36 individual domains. We have the following request for information:

1. Provide evidence of external validation for each component, PCS and MCS, and each domain of SF-36 in the context of rheumatoid arthritis (RA), and explain why each component and domain of SF-36 should be included on a product label for RA.

2. For each component, PCS and MCS, and each domain of SF-36, provide the value of the clinical important difference between treatments and the value of the minimum important change within subjects. Explain how each value was developed, and how these values should be used to interpret the results.

3. Provide references documenting the scientific basis for each of your answers to questions 1 and 2 above. Include a copy of each cited paper in an appendix.

4. Provide the scoring manual used to calculate domains and components of SF-36. Also include details on how missing items are handled by the scoring algorithm.

5. Where SF-36 items were reported missing, carefully detail the rules you used to impute missing SF-36 data, including, and differentiating between:
    a. rules suggested by the producer of the instrument
    b. additional rules used in the data analysis

6. For each study, provide the following information:

    a. A dataset flagging items missing for calculation of SF36 for each patient, by item and visit.
    b. A lookup table in dataset format to translate the value of coded variable EFQUESN in the SF36 analysis datasets of each study to its associated SF-36 item, component, or domain.
    c. The program used in each study to compile SF-36 items into components and domains of SF-36.
    d. The program used in each study for the analysis of the components and domains of SF-36.
    e. Report on the amount of missing data for the SF-36 in terms of the following:

        i. percent of patients not completing the instrument at each assessment timepoint
        ii. percent of missing by item for each assessment timepoint

7. Provide a justification for the proposed timing of SF-36 assessment at Month 3 and how this compares with controlled Month 6 data.

We request that you submit the requested information to the sNDA by May 3, 2013, or you may propose a timeline for submitting the requested information.

If you have any questions, contact me at 301-796-2466.

{See appended electronic signature page}

_____

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 203214/S-002
Tofacitinib
Pfizer, Inc.

Drafted: Bowen/3-9-13

Clearance: Jafari/3-9-13

Finalized: Bowen/3-9-13

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/s/

PHILANTHA M BOWEN
04/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203214/S-002

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: 002

PRODUCT NAME: XELJANZ (Tofacitinib) Tablets, 5 mg

DATE OF SUBMISSION: January 18, 2013

DATE OF RECEIPT: January 18, 2013

This supplemental application proposes the following change: the inclusion of language in the package insert regarding the improvement in functional health status.

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 March 19, 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

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/s/

PHILANTHA M BOWEN
01/31/2013