CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	November 6, 2012
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	203214
Applicant Name:	Pfizer Labs
Date of Submission:	October 21, 2011
PDUFA Goal Date:	November 21, 2012 (Original date was August 21, 2012)
Proprietary Name:	Xeljanz
Established Name:	Tofacitinib
Dosage form:	Tablets
Strength:	5 mg and 10 mg
Proposed Indications:	Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs), to be used as monotherapy or in combination with methotrexate or other non-biologic DMARDs.
Action:	Approval (5 mg Tablets) (b) (4)

1. Introduction

Pfizer submitted this NDA for tofacitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs) to be used as monotherapy or in combination with methotrexate or other non-biologic DMARDs. Pfizer proposed a recommended starting dose of 5 mg twice-daily, with a qualifier that some patients may benefit with an increased dose to 10 mg twice-daily based on clinical response. During review of the NDA, the Agency asked Pfizer for additional safety analyses for selected events of interest. Pfizer submitted these additional safety analyses on August 1 and 10, 2012. These analyses were submitted within the last 3 months of the review period and resulted in extension of the PDUFA goal date.

The submitted data support the approval of tofacitinib at a dose of 5 mg twice-daily for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to the non-biologic DMARD methotrexate. Tofacitinib can be used either as a monotherapy or in and in combination with methotrexate or other non-biologic DMARDs. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

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 as well as 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 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

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	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF-α inhibitor*	Clinical response Major clinical response Physical function 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 §**
	SC injection		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 *T cell activation inhibitor through B7-1 and B7-2*	Clinical response Major clinical response Physical function response Radiographic response
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Vial 10 mg/mL *IV infusion*	Chimeric murine/human IgG1 k mAb *Anti CD20, B cell depletor*	Clinical response Physical function response Radiographic response
Golimumab (SIMPONI) [Centocor] {2009}	Prefiled syringe 50 mg/0.5 mL SmartJect Autoinjector 50 mg/0.5 mL *SC injection*	Humanized IgG1 k mAb *TNF-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

About tofacitinib:

All biologic DMARDs approved for the treatment for RA are injectable agents that primarily target extracellular cytokines (Table 2). Tofacitinib is an oral, small molecule inhibitor of the intracellular tyrosine kinase called Janus kinase (JAK). JAK is critical for cytokine receptor binding-triggered signal transduction through STAT to the nuclei of cells. The JAK family consists of four members: JAK1, JAK2, JAK3, and TyK2. On cytokine binding to its receptor on cell membrane, JAKs are activated, which in turn phosphorylate cytokine receptors, creating docking sites for signaling molecules, especially for members of the STAT family. The STAT proteins form homo- or hetero-dimers and translocate to the nucleus where they induce transcription of target genes. Various JAK and STAT proteins are known to be involved in tissues affected in RA, therefore, inhibiting the JAK-STAT pathway seems a reasonable target for RA treatment.[2]

[2] Yamaoka K, Kubo S, Sonomoto K, Maeshima K, and Tanaka Y. JAK inhibitor: tofacitinib, a new disease modifying anti-rheumatic drug. Inflam and Reg 2011; 31:349-353.

In kinase assays, tofacitinib inhibits JAK1 and JAK3 and, to a lesser extent, JAK2 and TyK2. In the immune system, JAK1, JAK2, and TyK2 are ubiquitously expressed, whereas JAK3 expression is restricted to hematopoietic cells. JAK1 knockout mice display perinatal lethality (thought to be related to neuroapoptosis due to lack of gp130 signaling), and JAK1 inhibition would be expected to enhance susceptibility to infections related to defective signaling by class II cytokine receptors and receptors that use the gp130 subunit. JAK3 pairs with JAK1 to mediate signal transduction activity through the common gamma chain family of cytokines, including IL-2, -4, -7, -9, -15, and -21, which are integral to lymphocyte activation, proliferation, and function (Figure 1). JAK3 knockout mice display T and B cell lymphopenia without effects on myeloid lineage cells. Autosomal recessive JAK3 deficiency in humans results in a form of severe combined immunodeficiency disease (SCID) that is characterized by a lack of circulating T cells and NK cells, but a normal number of B cells.[3] JAK2 has a pivotal role in the signal transduction required in definitive erythropoiesis and JAK2 knockout mice are embryonically lethal due to a lack of erythropoiesis. TyK2 knockout mice are viable with no overt abnormalities, but do show reduced CD4+ cell differentiation to Th1 cells.

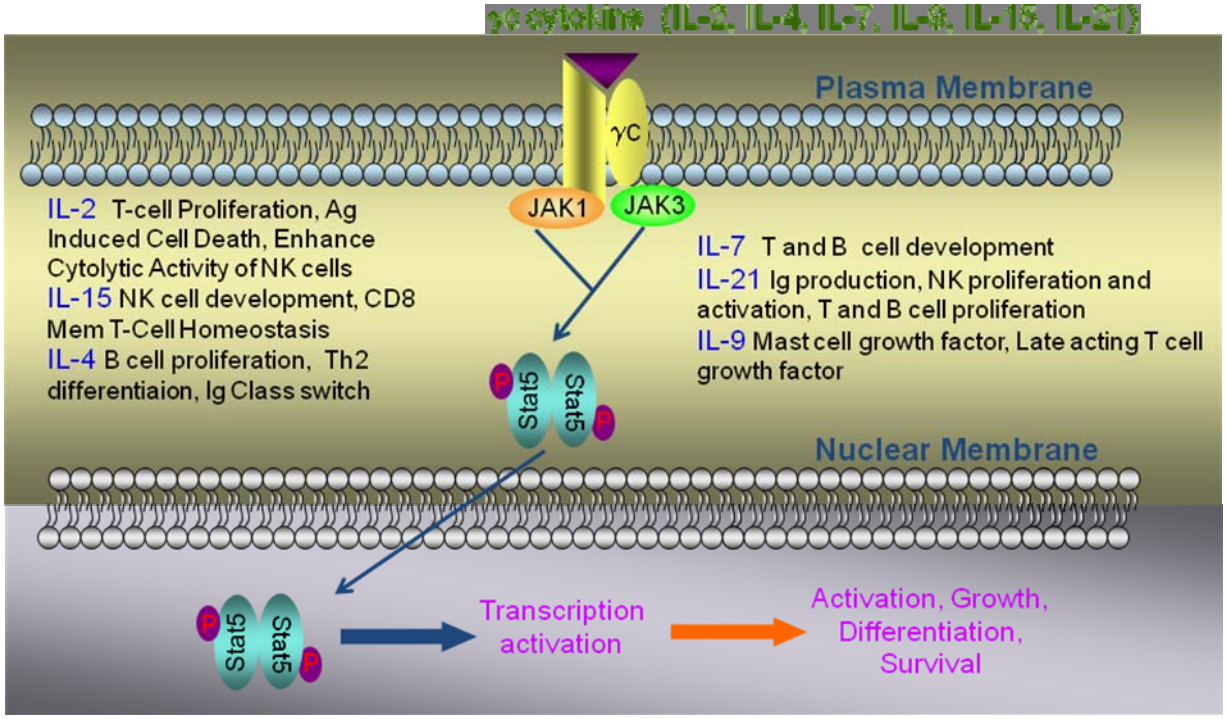

Figure 1. Schematic of JAK1/3-Stat5 signaling pathway

[3] Vijayakrishnan L, Venkataramanan R, and Gulati P. Treating inflammation with the Janus Kinase inhibitor CP-690,550. Trends Pharmacol Sci 2011; 32:25-34.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product, Xeljanz tablets, contains 5 mg and 10 mg tofacitinib (equivalent to 8 mg and 16 mg tofacitinib citrate, respectively) and standard compendial excipients. The drug product will be packaged as bottles containing 60 tablets and 180 tablets. The drug substance tofacitinib citrate is (b) (4) The drug substance is highly soluble, but has low permeability (BCS class 3). Pfizer followed Quality by Design (QbD) principles in their development of the manufacturing process for the drug substance and the drug product. The drug product of immediate-release tablets is manufactured with a (b) (4) The drug substance is manufactured by Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland. The drug product is manufactured and packaged in Frieburg, Germany, and is also being packaged in Puerto Rico. All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate or do not require review due to adequate information in the NDA. An expiry of 24 months is proposed and supported by submitted data.

4. Nonclinical Pharmacology and Toxicology

Pfizer conducted a complete and adequate toxicology program that included general toxicology studies in rodent and non-rodent species, reproductive and embryofetal development studies, and carcinogenicity studies. The target organs of toxicity in rats included: lymph nodes (lymphocyte depletion and atrophy), thymus (lymphocyte depletion and atrophy), spleen (lymphocyte depletion and atrophy), bone marrow (cellular decrease), changes in hematology (decreased white blood cells and red blood cells), adrenal gland (cortical vacuolation), gastrointestinal tract (stomach, duodenum, jejunum), liver (increased liver enzymes and hypertrophy), and lung (histiocytosis thought to be a result of immunosuppression). In general, the longer the duration of the toxicity study in rats, the more severe the toxicities were (e.g., shorter term studies showed lymphoid depletion, but the chronic study resulted in atrophy of the lymph organs). The toxicities in monkeys included severe immunosuppression resulting in infections and a decrease in immunosurveillance, resulting in lymphomas from lymphocryptovirus infection, and hematological changes similar to those described for rats. The target organs of toxicity in monkeys consisted of the spleen (viral inclusions and lymphocyte hyperplasia), thymus (lymphocyte hyperplasia), lymph nodes (lymphocyte hyperplasia), bone marrow (erythroid hyperplasia), and stomach (viral inclusions, inflammation-secondary infections). Shorter duration studies in the monkey resulted in general lymphocyte depletion of the lymph organs, whereas longer duration of treatment resulted in lymphocyte hyperplasia in these organs. The proposed human doses were covered by the NOAELs (no observed adverse effect levels) from animal studies; the limiting toxicities were thought to be monitorable in a clinical setting. Tofacitinib had no effects on fertility in male rats; however, fertility was reduced in female rats due to decreased corpora lutea and implantation sites and increased early resorptions and pre- and post-implantation losses. Tofacitinib was teratogenic (visceral and skeletal abnormalities) in rats and rabbits; maternal toxicity was evident in rats but not rabbits.

There were no effects on peri- and post-natal development in rats. The submitted data support pregnancy category C classification for tofacitinib. The carcinogenicity study showed no increased incidence of tumors in a 6-month transgenic mouse study. In a 2-year rat study, the findings were sex-specific and included interstitial cell adenomas in testis in males, benign thymomas in females, and malignant hibernomas in females.

5. Clinical Pharmacology and Biopharmaceutics

Pfizer submitted a complete and adequate clinical pharmacology program for tofacitinib. The absolute oral bioavailability of tofacitinib is 74%. Following oral administration of tofacitinib, peak plasma concentration is reached within 30 to 60 minutes with elimination half-life of about 3 hours. Clearance mechanisms of tofacitinib include hepatic metabolism (about 70%) and renal excretion of the parent molecule (about 30%). The metabolism of tofacitinib is primarily mediated by CYP3A4 with a minor contribution from CYP2C19. The plasma concentration of tofacitinib is affected in patients with hepatic impairment and renal impairment, and when given together with drugs that inhibit or induce CYP3A4. The recommended dose of tofacitinib is 5 mg QD for the following intrinsic and extrinsic factors: moderate or severe renal impairment; moderate hepatic impairment; co-administration with strong CYP3A4 inhibitors (e.g., ketoconazole); and co-administration with moderate CYP3A4 and strong CYP2C19 inhibitors (e.g., fluconazole). Tofacitinib is not recommended in patients with severe hepatic impairment or in combination with cyclosporine because of the risk of increased immunosuppression. Co-administration with strong CYP3A4 inducers (e.g., rifampin) reduces tofacitinib levels to inefficacious levels. Inhibitors of p-glycoprotein are not likely to substantially alter tofacitinib exposure. There is no substantial impact of food, age, weight, and gender on tofacitinib exposure. A thorough QT study was conducted for tofacitinib and reviewed by the QT study interdisciplinary review team. No significant QTc prolongation effect of tofacitinib at the doses tested was detected.

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 the review and regulatory decision for this application are shown in Table 3. The design and conduct of these studies are briefly described below, followed by efficacy 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 % ¶**
Dose Ranging Efficacy and Safety					
1025 2007-2008 Dose-ranging Study 2	-Over 18 years -Inadequate response to methotrexate -Methotrexate background -6 months	Tof 1 mg BID Tof 3 mg BID Tof 5 mg BID Tof 10 mg BID Tof 15 mg BID Tof 20 mg QD Placebo	71 68 71 75 75 80 69	ACR20 at wk 12	US (24%) EU (44%) L Am (32%) ROW (0%)
1035 2007-2009 Dose-ranging Study 1	-Over18 years -Inadequate response to a biologic or a non biologic DMARD -No background treatment -6 months	Tof 1 mg BID Tof 3 mg BID Tof 5 mg BID Tof 10 mg BID Tof 15 mg BID Ada 40 mg Placebo	54 52 50 61 57 53 59	ACR20 at wk 12	US (22%) EU (48%) L Am (22%) ROW (8%)
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 Study II "Sync" 2009-2011	-Over 18 years -Inadequate response to a non-biologic DMARD -Non-biologic DMARD background -12 months	Tof 5 mg BID Tof 10 mg BID Placebo 5 mg Placebo 10 mg	318 318 79 80	ACR20 at mo 6 HAQ-DI at mo 3 DAS28<2.6 at mo 6	US (17%) 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%)
Open Label Long Term Extension (LTE) Safety					
1024	"Roll-over" from studies 1045, 1046, 1064, 1044, and 1032 above	Tof 5 mg BID Tof 10 mg BID			
1041	"Roll-over" from Japanese Phase 2 study and study 1044 (Japanese only)	Tof 5 mg BID Tof 10 mg BID			

* 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

Study ID and Year *	Study Characteristics -Patient age -Response to past treatment -Concurrent background treatment -Study duration	Treatment groups †	N ‡	Primary efficacy variables §	Region % ¶
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 (studies 1035 and 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 placebo non-responder patients (studies 1025 and 1035) were advanced to tofacitinib 5 mg, and 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 (studies 1046, 1064, and 1044), 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.

The efficacy variables relevant to this submission were ACR response criteria, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the van der Heijde modified Total Sharp Score (mTSS), and the Disease Activity Score 28 (DAS-28). These are described below. An understanding of these endpoints will help the interpretation of the study results described in the subsequent section.

<u>The American College of Rheumatology (ACR) response</u> is a composite endpoint with seven components that are used to calculate the proportion of patients achieving a target percentage of improvement from baseline.[4,5] The ACR criteria have been used extensively in clinical trials in RA as a measure of efficacy of a therapeutic agent. The 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

[4] DT Felson, Anderson JJ, Boers M, et al. ACR preliminary definition of improvement in Rheumatoid Arthritis. Arthritis & Rheum 1995; 38:727-735.
[5] Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid Arthritis classification criteria. Arthritis & Rheum 2010; 62:2569-2581.

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). The ACR 50 and ACR 70 are similarly calculated using the higher 50% and 70% levels of improvement, respectively. The Agency has accepted ACR 20 response as an acceptable demonstration of efficacy of a therapeutic agent supporting a "clinical response" claim, and ACR 70 response lasting for 6 months as supportive of a claim of a "major clinical response."

Stanford Health Assessment Questionnaire-Disability Index (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). The HAQ-DI has been validated for use in RA, with a minimal clinically important difference (MCID) of 0.25 units (for a given patient) or 0.22 units (based on group means).[6] The Agency has accepted a "physical function response" claim based on HAQ-DI.

The van der Heijde modified Total Sharp Score (mTSS) is an accepted radiographic scoring system for RA joint damage.[7] X-rays of the hands and feet are graded based on joint space narrowing (Grades 0 to 4, 15 joints per hand, 6 joints per foot) and erosions (Grades 0 to 5, 16 joints per hand, 6 joints per foot). For the hands, joint space narrowing scores and erosion scores are summed separately, and the joint space narrowing score ranges from 0 to 168 and the erosion score ranges from 0 to 280 and their sum, the total radiographic score, ranges from 0 to 448. Although the theoretical maximum score is 448, the actual scores seen in RA clinical trials are much smaller because a given patient has only a fraction of joints affected by structural damage, as assessed by radiographic criteria. The smallest detectable difference on a per-individual basis has been identified for the van der Heijde modification of the Sharp score as approximately 5 units.[8] The Agency has accepted a "radiographic response" claim based on the mTSS.

Disease Activity Score 28 (DAS-28) is a composite index of RA disease activity which incorporates the number of tender and swollen joints (out of 28 possible), a patient global assessment of disease activity (0-100 mm visual analog scale), and ESR.[9] An alternative

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[6] B Bruce and JF Fries. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 2005; 23 (Suppl 39):S14-S18

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

[8] K Bruynesteyn et al., Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference.Arthritis & Rheum 2002; 46:913-920

[9] J Fransen and PLCM van Riel. The Disease Activity Score and the EULAR Response Criteria. Clin Exp Rheumatol 2005; 23 (Suppl 39): S93-S99

equation is available for use with CRP. These variables are summed and weighted mathematically into a single numerical value ranging from 0 to 10. The ACR response criteria and DAS-28 are conceptually similar, but differ with number of joints counted (e.g. DAS-28 does not include the joints of the feet), and physician global assessment, patient pain, and health assessment score, which are incorporated into the ACR response criteria but not in DAS-28. Another difference is that the DAS-28 measures disease activity at a given time point, whereas the ACR response criteria are calculated as improvement in the variables over a set period of time. A DAS-28 score >5.1 is indicative of high disease activity, and <3.2 of low disease activity. A score of <2.6 has been accepted by the Agency to describe an even lower threshold of disease activity.

c. Efficacy findings and conclusions

The submitted data show efficacy for tofacitinib for clinical response and improvement in physical function at the proposed doses of 5 mg and 10 mg twice-daily. Balancing efficacy and safety (safety discussed in section 8 below), 5 mg twice-daily is recommended as the optimum dose with no recommendation for dose escalation.

In the following sections, dose selection and dosing regimen for tofacitinib are discussed first, followed by a discussion of the efficacy data for the proposed claims of clinical response, physical function response, radiographic response, and closing with summary comments on efficacy.

<u>Dose selection and dose ranging:</u>

Pfizer conducted 5 dose-finding studies: 1025, 1035, 1039, 1040, and 1019. Dose selection was primarily based on study 1025, which assessed probability of achieving an efficacy target effect based on ACR response at week 12, and a safety surrogate of hemoglobin threshold for >2 g/dL decrease from baseline or an absolute level of <8 g/dL set at placebo-adjusted incidence of no more than 5% through week 24 of exposure. Pfizer carried 5 mg and 10 mg twice-daily doses to phase 3 studies based on results of study 1025 and supportive data from study 1035 (Figure 2 and Table 4). This decision is reasonable, but has some shortcomings as noted below.

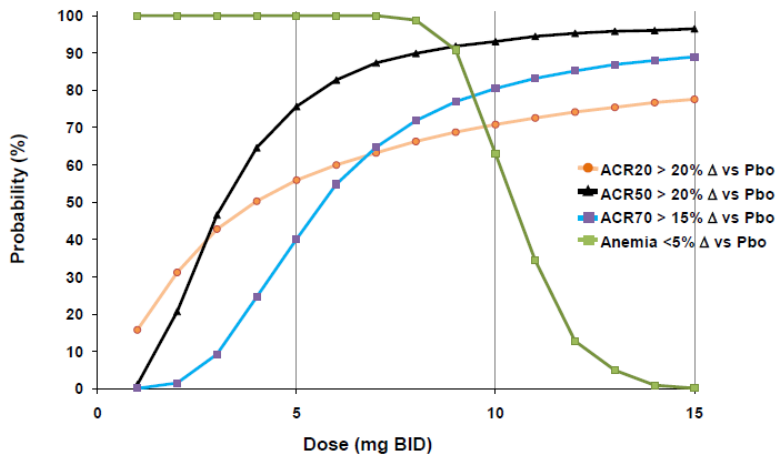

Figure 2. ACR response and anemia in study 1025

Table 4. ACR response rates (% patients with ACR response) at primary analysis time point

Study *	Time	Treatment †	ACR 20 %	ACR 50 %	ACR 70 %	P vs placebo ACR 20
1025	Week 12	Tof 1 mg BID	47	23	4	0.219
		Tof 3 mg BID	56	29	21	0.021
		Tof 5 mg BID	56	37	18	0.017
		Tof 10 mg BID	58	28	12	0.011
		Tof 15 mg BID	56	44	24	0.018
		Tof 20 mg QD	56	36	24	0.015
		Placebo	36	17	6	
1035	Week 12	Tof 1 mg BID	31	11	6	0.356
		Tof 3 mg BID	45	25	12	0.022
		Tof 5 mg BID	61	39	14	<0.001
		Tof 10 mg BID	72	46	25	<0.001
		Tof 15 mg BID	72	51	26	<0.001
		Ada 40 mg	39	21	4	0.070
		Placebo	24	10	3	

* Study ID shown as Pfizer's study number
† Tof = Tofacitinib oral tablets; Ada = adalimumab sc injection

From an efficacy standpoint, more emphasis was placed on the ACR 70 results as the dose response curve was steeper for the target effect with 10 mg twice daily being approximately double that of the 5 mg twice-daily dose (80% vs 40%). However, ACR 20 results show that the 5 mg twice-daily dose provided approximately 60% response, which is within range of the response seen with biological DMARDs. The 3 mg twice-daily dose also provided acceptable ACR responses (Table 4). There was little consideration given to other dose-related adverse events besides hemoglobin decrease. In particular, total lymphocyte subset count or function or adverse events related to lymphocytes were not considered in this model. Tofacitinib binds with higher affinity to JAK1 and JAK3, which affects lymphocytes. JAK2, which effects erythropoiesis, has lesser binding affinity for tofacitinib. From a dose frequency standpoint, the only dose frequency tested was twice-daily, except one dose of 20 mg once-daily in study 1025, with rationale of patient convenience and limited data suggesting prolonged pharmacodynamic effect of tofacitinib on CRP. Although tofacitinib has a pharmacokinetic half-life of about 3 hours, which would suggest a more frequent dosing regimen than twice-daily, Pfizer's decision to pursue twice-daily dosing regimen is reasonable from a patient convenience standpoint. Also, the overall data (including phase 3 data) did provide an acceptable risk-benefit for the recommended dose, and the data also show that increasing the nominal dose to achieve a twice-daily dosing frequency did not compromise patient safety.

The Clinical Pharmacology team conducted analyses with data from dose ranging studies for a possible dose-related effects of tofacitinib on counts of lymphocytes, T cells, T cell subsets, NK cells, and immunoglobulin levels. Other than NK cells, which showed a dose-related decrease in count, and B cells, which showed a dose-related increase, others cell counts did not show dose-related effect (data not shown in this review). This

analysis supports the notion that the effect of tofacitinib on lymphocytes is related to functional suppression rather than a lytic effect.[10]

Clinical response:
Tofacitinib treatment was associated with a higher proportion of patients with ACR 20 response in all 5 definitive studies at both 5 mg and 10 mg twice-daily doses and the differences between tofacitinib treatment arms and placebo treatment arms were statistically significant (Table 5). The 10 mg twice-daily dose was associated with a slightly higher proportion of patients with ACR 20 response compared to the 5 mg twice-daily dose in these studies. Results of ACR 50 and ACR 70 responses were consistent with the ACR 20 response (Table 5). Results of DAS-28 results (Table 6) were generally similar to the results of ACR response. None of the studies were designed to assess patients achieving incremental benefit in clinical response when escalating from an initial dose of 5 mg twice-daily to a dose of 10 mg twice-daily.

Table 5. ACR response rates (%with response) at primary analysis time point (ITT) *

Study †	Time	Treatment ‡	ACR 20 %	ACR 50 %	ACR 70 %	P vs placebo ACR 20
1045, Study I "Solo"	Month 3	Tof 5 mg BID	59	31	15	<0.001
		Tof 10 mg BID	65	37	20	<0.001
		Placebo	26	13	6	
1046, Study II "Sync"	Month 6	Tof 5 mg BID	52	34	13	<0.001
		Tof 10 mg BID	57	37	16	<0.001
		Placebo	31	13	3	
1064, Study III "Standard"	Month 6	Tof 5 mg BID	50	37	20	<0.001
		Tof 10 mg BID	51	35	22	<0.001
		Ada 40 mg	46	28	9	
		Placebo	28	12	2	
1044, Study IV "Scan"	Month 6	Tof 5 mg BID	50	32	15	<0.001
		Tof 10 mg BID	60	44	22	<0.001
		Placebo	24	8	1	
1032, Study V "Step"	Month 3	Tof 5 mg BID	41	26	14	0.003
		Tof 10 mg BID	48	28	11	<0.001
		Placebo	24	8	2	

* ITT = Intent-to-treat population defined as all randomized patients who took at least one dose of study drug
† Study ID shown as Pfizer's study number, and as referred to in the tofacitinib product label, and as identified by Pfizer at the May 9, 2012, AAC meeting
‡ Tof = Tofacitinib oral tablets; Ada = adalimumab sc injection

Table 6. DAS-28 <2.6 response rates (%with response) at primary analysis time point (ITT) *

Study †	Time	Treatment ‡	DAS-28 <2.6 %	P vs placebo DAS-28<2.6
1045, Study I "Solo"	Month 3	Tof 5 mg BID	6	0.603
		Tof 10 mg BID	8	0.145
		Placebo	4	
1046, Study II "Sync"	Month 6	Tof 5 mg BID	8	0.007
		Tof 10 mg BID	11	0.001
		Placebo	3	

[10] Maeshima K, Yamaoka K, Kubo S, et al. The JAK inhibitor tofacitinib regulates synovitis through inhibition of interferon-gamma and interleukin-17 production by human CD4+ T cells. Arthr Rheum 2012; 64:1790-98.

Study †	Time	Treatment ‡	DAS-28 <2.6 %	P vs placebo DAS-28<2.6
1064, Study III "Standard"	Month 6	Tof 5 mg BID	5	0.051
		Tof 10 mg BID	11	0.001
		Ada 40 mg	6	0.037
		Placebo	1	
1044, Study IV "Scan"	Month 6	Tof 5 mg BID	6	0.018
		Tof 10 mg BID	13	<0.001
		Placebo	1	
1032, Study V "Step"	Month 3	Tof 5 mg BID	6	0.055
		Tof 10 mg BID	8	0.011
		Placebo	2	

* ITT = Intent-to-treat population defined as all randomized patients who took at least one dose of study drug
† Study ID shown as Pfizer's study number, and as referred in tofacitinib product label, and as Pfizer "identified" at the May 9, 2012, AAC meeting
‡ Tof = Tofacitinib oral tablets; Ada = adalimumab sc injection

Physical function response:
Tofacitinib treatment was associated with an improvement in HAQ-DI scores in all 5 definitive studies at both 5 mg and 10 mg twice-daily doses, and the differences between tofacitinib treatment arms and placebo treatment arms were statistically significant (Table 7). The 10 mg twice-daily dose was associated with slightly higher response rates in the HAQ-DI compared to the 5 mg twice-daily dose in these studies. The benefit of tofacitinib over placebo for HAQ-DI in these studies ranged from 0.3 to 0.4 unites.

Table 7. HAQ-DI scores (mean change from baseline) at primary analysis time point (ITT) *

Study †	Time	Treatment ‡	HAQ-DI Δ from baseline	P vs placebo HAQ-DI
1045, Study I "Solo"	Month 3	Tof 5 mg BID	0.50	<0.001
		Tof 10 mg BID	0.60	<0.001
		Placebo	0.20	
1046, Study II "Sync"	Month 6	Tof 5 mg BID	0.44	<0.001
		Tof 10 mg BID	0.51	<0.001
		Placebo	0.20	
1064, Study III "Standard"	Month 6	Tof 5 mg BID	0.44	<0.001
		Tof 10 mg BID	0.53	<0.001
		Ada 40 mg	0.44	<0.001
		Placebo	0.22	
1044, Study IV "Scan"	Month 6	Tof 5 mg BID	0.36	<0.001
		Tof 10 mg BID	0.49	<0.001
		Placebo	0.15	
1032, Study V "Step"	Month 3	Tof 5 mg BID	0.46	<0.001
		Tof 10 mg BID	0.43	<0.001
		Placebo	0.23	

* ITT = Intent-to-treat population defined as all randomized patients who took at least one dose of study drug
† Study ID shown as Pfizer's study number, and as referred to in tofacitinib product label, and as identified by Pfizer at the May 9, 2012, AAC meeting
‡Tof = Tofacitinib oral tablets; Ada = adalimumab sc injection

Radiographic response:
Radiographic response was assessed in study 1044 using mTSS as the efficacy variable. The data as shown in Table 8 and Figure 3 are suggestive of a beneficial effect, but not

adequate to make a definitive conclusion. The reasons why a definitive conclusion cannot be made are elaborated on below.

Although the primary time point for analysis was at month 6, all placebo patients did not remain in their originally assigned group up to month 6. At month 3, placebo patients who did not achieve a predetermined improvement in signs and symptoms were advanced to tofacitinib 5 mg or 10 mg twice-daily treatment groups. At month 3, approximately 49% of patients from the placebo group were moved to a tofacitinib treatment group (24% patients to tofacitinib 5 mg twice-daily group and 25% patients to tofacitinib 10 mg twice-daily group). Large amounts of missing data at month 6 created problems with analysis, as an imputation method such as linear extrapolation or some alternate needed to be used. Table 8 shows varying results depending on the statistical method used.

Table 8. Effect of alternate analysis methods on mTSS score change from baseline to month 6, study 1044, Study IV, or "Scan" (rITT) *

Treatment †	N	LS mean change from baseline	Difference vs placebo LS Mean	95% CI	p-value
Primary analysis, Parametric, Linear extrapolation method					
Tof 5 mg + methotrexate	278	0.12	-0.34	-0.73, 0.04	0.079
Tof 10 mg + methotrexate	290	0.06	-0.40	-0.79, -0.02	0.038
Placebo + methotrexate	140	0.47			
Alternate pre-specified analysis, Non-parametric ‡					
Tof 5 mg + methotrexate	278	334	-41	-77, -6	0.024
Tof 10 mg + methotrexate	290	352	-23	-59, 12	0.198
Placebo + methotrexate	140	376			
Alternate sensitivity analysis, excluding one patient from Tof 10 mg group with change of over 20 units					
Tof 5 mg + methotrexate	278	0.11	-0.34	-0.69, 0.01	0.056
Tof 10 mg + methotrexate	289	0.12	-0.33	-0.68, 0.02	0.061
Placebo + methotrexate	140	0.45			

* rITT = Radiographic intent-to-treat population defined as all randomized patients who had valid baseline and month 3 radiographic data
† Tof = Tofacitinib oral tablets
‡ LS means from non-parametric analysis were based on the rank-transformed radiograph data

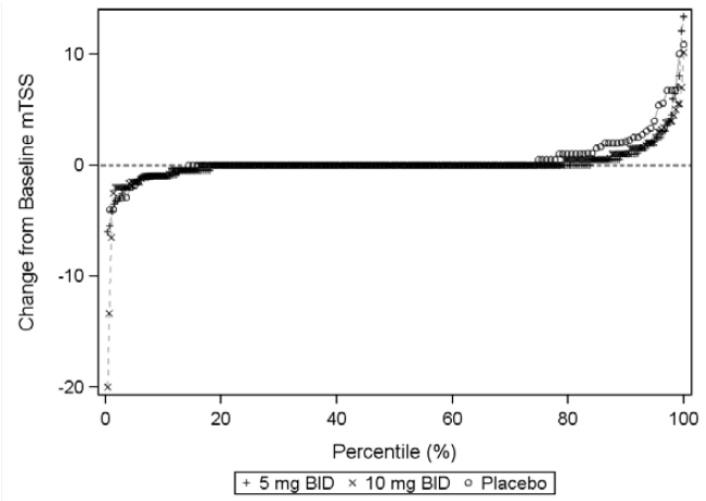

Figure 3. Cumulative probability plot of radiographic score change from baseline to month 6 (from Pfizer study report), study 1044, Study IV, or "Scan"

The proportion of study patients who had progression of structural damage during 6 months of the study was small, which created problems in analysis and interpretation of the data. The intent of this study was to show the effect of tofacitinib on progression of structural damage. The cumulative distribution of radiographic score change shows that only a fraction of patients (approximately 20%) experienced progression of structural damage in the 6-month time frame of the study (Figure 3, right side shows patients with progression). Patients on placebo appeared to have more progression of structural damage than patients on tofacitinib, but the analysis that included all patients (some with progression, some with no change, and some with improvement) makes it difficult to show an effect. The distribution of radiographic score change shows that some patients showed improvement of structural damage during the 6-month time frame of the study (Figure 3, left side shows patients with improvement), which is biologically implausible and is possibly an artifact of the measure. In this study, two patients on tofacitinib 10 mg twice-daily treatment had large improvements (shown with "x" in the left side of Figure 3). Removing one such patient changed the conclusion (Table 8).

Given the problems noted above, the single study 1044 is not adequate to support a prevention of radiographic progression claim. A second study providing corroborating data is not available.

Historically, the Agency has relied on 6-month or 12-month study results to support a prevention of radiographic progression claim for other DMARDs. Table 9 shows summary information for large molecule biological DMARDs from their product labels. Acknowledging the limitations of cross-study comparison,[11] it appears that the effect size of radiographic progression that occurred in the placebo/methotrexate arm in the tofacitinib study (Table 8) was smaller than those seen in past studies (Table 9). Whether this reflects an actual change in the natural history of radiographic progression in RA patients that is occurring recently compared to the past, or, an artifact attributable to certain aspects of study design and analysis (e.g., varying number of patients moving from the placebo to active treatment arms, various imputation methods used for missing data, various correction method used to express radiographic data, or different statistical methods) is not known. Nevertheless, because of ethical concerns regarding the long-term (such as longer than 12 weeks) use of placebo in patients with active RA, and the limitations of such studies as noted above, the design and conduct of studies to assess radiographic progression will need to change in the future.

Table 9. Large molecule biologic DMARDs mean radiographic changes (Total Sharp Score or modifications thereof) over 6 months and 12 months in clinical trials as described in product labels

Product Name (Trade Name)			Change from baseline	Methotrexate/Product (95% Confidence Interval)	P value
Etanercept (ENBREL)	6 months	Methotrexate	1.06	0.49 (0.06, 0.91)	0.001
		Enbrel 25 mg	0.57		
	12 months	Methotrexate	1.59	0.59 (-0.12, 1.30)	0.100

[11] Favalli EG, Pregnolato F, Biggioggero M, Merone L. The role of biologic agents in damage progression in rheumatoid arthritis: indirect comparison of data coming from randomized clinical trials. Ther Adv Musculoskel Dis 2012: 4:213-223.

Product Name (Trade Name)			Change from baseline	Methotrexate/Product (95% Confidence Interval)	P value
		Enbrel 25 mg	1.00 *		
Infliximab (REMICADE)	12 months Study 1	Methotrexate	6.9		<0.001
		Remi 3 mg/kg	1.3		
	12 months Study 2	Methotrexate	3.7		<0.001
		Remi 3 mg/kg	0.4 †		
Anakinra (KINERET)	12 months	Methotrexate	2.6	0.9 (0.3, 1.6)	<0.001
		Kin 100 mg/day	1.7		
Adalimumab (HUMIRA)	12 months	Methotrexate	2.7	2.6 (1.4, 3.8)	<0.001
		Humira 40 mg	0.1 †		
Abatacept (ORENCIA)	12 months	Methotrexate	2.43	1.36	<0.010
		Orencia 500-1000 mg	1.07 ‡		
Rituximab (RITUXAN)	12 months	Methotrexate	1.77	1.11 (0.47, 1.75)	
		Rituxan 1000 mg	0.66 ‡		
Certolizumab Pegol (CIMZIA)	6 months	Methotrexate	1.3	1.1	
		Cimzia	0.2		
	12 months	Methotrexate	2.8	2.4	
		Cimzia 400 mg	0.4 †		
Tocilizumab (ACTEMRA)	12 months	Methotrexate	1.17	0.83 (0.52, 1.13)	
		Actemra 4 mg/kg	0.33 ‡		
Modifications used: * Sharp; † van der Heijde-modified Sharp; ‡ Genant modified Sharp					

Summary comment on efficacy:
The submitted data show efficacy of tofacitinib 5 mg and 10 mg twice-daily as a monotherapy and as a combination therapy in patients with active RA for clinical response as measured by ACR criteria, and for improvement in physical function as measured by HAQ-DI. Efficacy of tofacitinib as a monotherapy (such as in patients who cannot tolerate non-biologic DMARDs, such as methotrexate) for clinical response and improvement in physical function is supported by data from study 1045.[12] Efficacy of tofacitinib as a combination therapy (such as a combination with methotrexate or other non-biologic DMARDs) for clinical response and improvement in physical function is supported by data from studies 1046, 1064, 1044, and 1032. Results of study 1064 show that in patients receiving background methotrexate, efficacy of tofacitinib for clinical response and improvement in physical function was numerically similar to adalimumab.[13]

The submitted data are not adequate to make definitive conclusions on the efficacy of tofacitinib on structural damage progression as measured by radiographic response. Results of study 1044 are suggestive of a beneficial effect. A definitive radiographic study to show benefit is not necessary to make a risk-benefit assessment for approval of a DMARD, such as tofacitinib. Improvements in clinical response and in physical function are adequate to support approval from an efficacy standpoint.

Of the various doses of tofacitinib tested in the clinical studies, 5 mg twice-daily appears to be the optimum dose. In the 5 definitive studies where tofacitinib 5 mg twice-daily

[12] Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Eng J Med 2012; 367:495-507.
[13] VanVollenhoven RF, Fleishmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Eng J Med 2012; 367:508-519.

and 10 mg twice-daily doses were studied, the 10 mg twice-daily dose provided a numerically higher response compared to the 5 mg twice-daily dose, but both the 5 mg twice-daily dose and the 10 mg twice-daily doses were consistently statistically superior to placebo for clinical response and improving physical function, and the 5 mg twice-daily dose provided responses that were within the range of the responses observed for biologic DMARDs. Balancing the possible efficacy advantage of the 10 mg twice-daily dose over the 5 mg twice-daily dose, and the safety risk of the 10 mg twice-daily dose over the 5 mg twice-daily dose (safety discussed in section 8 below), the 5 mg twice-daily dose appears to be the optimum dose for tofacitinib.

8. Safety

a. Safety database

During review of the NDA, the Agency asked Pfizer for additional safety analyses of clinical data for selected events of interest. In the sections below, the reasons and implications of the additional analyses and the dataset that was ultimately used by the Agency for safety analyses are discussed first, followed by a discussion of safety findings grouped under events or organ system of interest, summary comments on safety, and the rationale for a post-marketing safety study.

Pfizer's original safety analyses that were submitted to the NDA and discussed at the May 9, 2012, Arthritis Advisory Committee (discussed in section 9 below) were based on pooled safety data from five definitive efficacy and safety studies (1045, 1046, 1064, 1044, and 1032), five earlier studies (two dose-ranging studies 1025 and 1035, and additional studies 1039, 1019, and 1040), and two ongoing long-term extension studies 1024 and 1041 (some of these studies are listed in Table 3). There were various limitations in the datasets and methods of analysis that limited precise quantification of the safety risks of tofacitinib. First, the study designs allowed for early escape from placebo to tofacitinib treatment either by response or by study design (discussed in section 7b above) that resulted in unequal distribution of patients across treatment arms as the studies progressed and imprecise classification of patients to a treatment group. Second, some of the data sets analyzed were based on patients as originally randomized and not as ultimately treated, which is problematic because patients originally randomized to placebo ended up being treated with tofacitinib for a large part of the duration of treatment. Third, the primary safety data pool included the five definitive efficacy and safety studies (1045, 1046, 1064, 1044, and 1032) but not the two dose ranging efficacy and safety studies (1025 and 1035), which were reasonably large and had design and conduct elements essentially similar to the five definitive efficacy and safety studies. Fourth, the long-term extension study 1041 included in the safety database included patients who completed Japanese studies that were not included in the pooled short-term safety database. Fifth, the rules for capturing and reporting deaths, serious adverse events, and other adverse events of interest were not consistent and uniform.

The issues listed above with Pfizer's original analysis make it difficult to quantify and interpret the safety findings. Further, Pfizer reported results based on crude rates, and

often made comparisons to historical data from other studies. Based on the complexity of the study design and conduct, the Agency's statistical review team concluded that a model-based analysis was more appropriate. Also, the Agency deemed the comparator analyses within the tofacitinib program (such as tofacitinib to placebo, tofacitinib 5 mg to 10 mg twice-daily doses, tofacitinib to adalimumab) to be of primary importance, as opposed to external historical controls.

The Agency discussed with Pfizer these issues and limitations through many teleconferences, written communications dated May 22, June 4, and June 22, 2012, and at a face-to-face meeting on July 10, 2012. Through these interactions it was concluded that Pfizer would conduct further focused safety analyses pooling results from seven studies (two dose-ranging efficacy and safety studies 1025 and 1035, and five definitive efficacy and safety studies 1045, 1046, 1064, 1044, and 1032, listed in Table 3). The events of interest would include death, lymphoma, solid organ tumor, opportunistic infection, tuberculosis, SAE infection, herpes zoster, MACE events, hemoglobin level, lipid profile, neutrophil counts, liver function test, and common adverse events. The time intervals of interest would be 0-3 months, 0-6 months, 0-12 months, with appropriate treatment group assignments for patients switching from one treatment group to another treatment group. The rules for capturing events of interest would be uniform across events, i.e., events would count if they occurred within a 28-day window of stopping treatment or decreasing dose of tofacitinib, but a 28-day window would not apply to patients switching from placebo to tofacitinib or increasing tofacitinib dose. Following the above understanding and agreement, Pfizer conducted additional safety analyses and submitted these results to the NDA on August 1 and 10, 2012. Submission of these new analyses were considered as a major amendment and resulted in extension of the PDUFA time clock by 3 months. The Agency also conducted additional analyses to further evaluate the safety findings.

The dataset for the primary safety analysis is based on seven studies - two dose ranging efficacy and safety studies (1025 and 1035) and five definitive efficacy and safety studies (1045, 1046, 1064, 1044, and 1032) shown in Table 3. The numbers of patients randomized to different treatment groups in these studies were 292 to tofacitinib 5 mg twice-daily as monotherapy, 306 to tofacitinib 10 mg twice-daily as monotherapy, 1044 to tofacitinib 5 mg twice-daily in combination with DMARDs including methotrexate, 1043 to tofacitinib 10 mg twice-daily in combination with DMARDs including methotrexate, and 809 to placebo. In addition, safety analysis was done on a long-term population that included patients who participated in the seven studies mentioned above and earlier developmental studies. In the sections below, safety findings grouped under events or organ system of interest are described. Findings described below are primarily based on Pfizer's new analysis submitted on August 1 and 10, 2012, and not based on Pfizer's original analyses submitted to the NDA and discussed at the May 9, 2012, Arthritis Advisory Committee meeting. Two sets of analyses are presented, one based on patients as randomized and another based on as patients as treated. Patients as treated are defined as patients randomized to placebo or active treatment groups, plus patients initially randomized to placebo, that were later advanced to tofacitinib by either study design or because of lack of response. The two sets of analyses provide similar findings

qualitatively. The new analyses did not identify any new safety findings that were not identified with the original analysis, but provided data to refine the quantitative assessment of safety risk of tofacitinib to placebo, adalimumab, and between the two tofacitinib doses.

b. Safety findings and conclusion

Summary analysis of data comparing the two tofacitinib doses and placebo for events of interest from seven studies are shown in Table 10, and comparing tofacitinib and adalimumab from two studies that included adalimumab as active comparator are shown in Table 11. The safety data from the tofacitinib RA clinical program identified risks typical of a potent immunosuppressant such as infections, including opportunistic infections, tuberculosis, herpes zoster infection, malignancy, and some laboratory parameter changes (b) (4) Balancing efficacy (discussed in section 7 above) and safety data, tofacitinib 5 mg twice-daily appears to be the optimum dose for tofacitinib with no recommendation for dose escalation.

Table 10. Summary of adverse event of interest in 0-12 months of treatment from seven studies *

Treatment group †	Patients as randomized			Patients as treated ‡		
	Placebo	Tof 5mg BID	(b) (4)	Placebo	Tof 5mg BID	(b) (4)
Number of patients	809	1336		809	1689	
Exposure, patient-years	240	1056		240	1241	
Deaths						
Number of deaths, n	1	5		1	5	
Incidence rate, per 100 PY	0.42	0.47		0.42	0.40	
Serious infection events						
Patients with ≥ 1 SIE, n (%)	3	31 (2)		3 (<1)	34 (2)	
Incidence rate, per 100 PY	1.3	2.94		1.3	2.74	
Opportunistic infections						
Patients with ≥ 1, n	-	3		-	4	
Incidence rate, per 100 PY	0	0.28		0	0.32	
Tuberculosis						
Patients with ≥ 1 TB, n (%)	-	-		-	-	
Incidence rate, per 100 PY	0	0		0	0	
Herpes zoster infections						
Patients with ≥ 1 , n (%)	5 (<1)	42 (2)		5 (<1)	47 (3)	
Incidence rate, per 100 PY	2.1	3.98		2.1	3.79	
Malignancy, solid organ §						
Patients with ≥ 1 malignancy, n	-	5		0	5	
Incidence rate, per 100 PY	0	0.47		0	0.40	
Malignancy, lymphoma						
Patients with ≥ 1 lymphoma, n	-	-		-	-	
Incidence rate, per 100 PY	0	0		0	0	
MACE						
Patients with ≥ 1 MACE, n	2	4		2	6	
Incidence rate, per 100 PY	0.83	0.38		0.83	0.48	

* Two dose ranging efficacy and safety studies 1025 and 1035, and five definitive efficacy and safety studies 1045, 1046, 1064, 1044, and 1032 (ID as Pfizer's study number)
† Tof = Tofacitinib oral tablets
‡ Patients as treated are those who were randomized to the group plus placebo patients who were switched from placebo to tofacitinib treatment by study design or because of lack of response. Number of patients in the tofacitinib as treated group is larger than as randomized group because some patients from the placebo group advanced to tofacitinib

Treatment group †	Patients as randomized			Patients as treated ‡		
	Placebo	Tof 5mg BID	(b) (4)	Placebo	Tof 5mg BID	(b) (4)

groups at month 3 or month 6 by study design, and these patients are counted under both placebo group and tofacitinib group for the as treated group.
§ Excludes non-melanoma skin cancer (NMSC)

Table 11. Adverse event of interest from studies 1035 and 1064 for patients as treated *

Treatment group †	Study 1035, 0-3 months ‡		Study 1064, 0-12 months	
	Adalimumab 40 mg	Tof, pooled 5 mg and 10 mg	Adalimumab 40 mg	Tof, pooled 5 mg and 10 mg
Number of patients	53	110	204	500
Deaths				
Number of death, n	0	0	0	1
Serious infection events				
Patients with ≥ 1 SIE, n	-	-	3	17 §
Incidence rate, per 100 PY	0	0	1.54	3.84
Opportunistic infections				
Patients with ≥ 1, n	-	-	-	-
Tuberculosis				
Patients with ≥ 1 TB, n	-	-	-	2
Incidence rate, per 100 PY	0	0	0	0.45
Herpes zoster infections				
Patients with ≥ 1 , n	-	-	5	20 ¶
Incidence rate, per 100 PY	0	0	2.57	4.52
Malignancy, solid organ //				
Patients with ≥ 1 malignancy, n	1	-	1	3
Incidence rate, per 100 PY	8.94	0	0.51	0.68
Malignancy, lymphoma				
Patients with ≥ 1 lymphoma, n	0	0	0	0
Incidence rate, per 100 PY	-	-	-	-
MACE				
Patients with ≥ 1 MACE, n	-	-	3	2
Incidence rate, per 100 PY	0	-	1.54	0.45

* Two studies that included adalimumab as a comparator (1035 was a dose ranging efficacy and safety study and 1064 was a definitive efficacy and safety study). Patients as treated are those who were randomized to the group plus placebo patients who were switched from placebo to tofacitinib treatment by study design or because of lack of response.
† Tof = Tofacitinib oral tablets
‡ Comparison between adalimumab and tofacitinib was done for 0-3 months because at month 3 all adalimumab patients and non-responders from placebo and tofacitinib 1 mg and 3 mg dose groups were advanced to tofacitinib 5 mg
§ 8 in tofacitinib 5 mg and 9 in tofacitinib 10 mg group based on patients as treated
¶ 7 in tofacitinib 5 mg and 13 in tofacitinib 10 mg group based on patients as treated
// Excludes non-melanoma skin cancer (NMSC)

Death:
The number and frequency of deaths across the treatment groups were balanced (Table 10 and Table 11). The number and frequency of deaths on the long-term population did not show differences between treatment groups. The causes of death across treatment groups were consistent and typical of RA patients, with infections, malignancy, and cardiovascular disorders being common.

Infections including opportunistic infections, tuberculosis, and herpes zoster:
Infections including opportunistic infections and tuberculosis were associated with tofacitinib treatment, and the occurrence of tuberculosis was related to tofacitinib dose.

Infections leading to death occurred in 15 patients as of the data cut-off date of September 29, 2011. Of these deaths, 12 were due to pneumonia. All these deaths occurred in tofacitinib-treated patients with comparable frequency between the doses, except one death due to pyelonephritis in a placebo-treated patient.

Infection reported as a serious adverse event occurred more in tofacitinib-treated patients compared to other treatment groups with no dose ordering between the tofacitinib doses (Table 10, Table 11).

Opportunistic infection occurred only in tofacitinib treatment groups, with none occurring in placebo or adalimumab treatment groups (Table 10, Table 11). There was no dose ordering between the tofacitinib doses. There were a total of 8 opportunistic infections in as treated patients in the seven studies. Opportunistic infections also occurred in the long-term studies. These infections included esophageal candidiasis, Cytomegalovirus infection, Pneumocystis carinii pneumonia, Cryptococcus meningitis, Cryptococcus pneumonia, atypical mycobacterial infections, multi-dermatomal herpes zoster, and BK encephalitis.

Tuberculosis (b) (4) none occurring in tofacitinib 5 mg twice-daily, or placebo, or adalimumab treatment groups (Table 10, Table 11). (b) (4)

Herpes zoster infections occurred more in the tofacitinib groups compared to other treatment groups with a dose-ordering trend between the tofacitinib doses (Table 10, Table 11).

Malignancy:
Solid organ malignancy (excluding non-melanoma skin cancer) was associated with tofacitinib treatment, and its occurrence appeared to be related to tofacitinib dose (Table 10, Table 11). There were a total of 12 malignancies (solid organ and lymphoma) reported in tofacitinib-treated patients and 1 malignancy (solid organ) in an adalimumab treated patient in the RA program in the first 12 months (Table 10, Table 11). The types of malignancies were typical of that expected in RA patients, such as lung cancer, breast cancer, and gastric cancer, with the exception of one report each of liposarcoma and synovial sarcoma.

Lymphoproliferative disorders including lymphoma (such as B-cell lymphoma, Burkitt-like lymphoma, lymphomas in CNS and abdominal lymph nodes) were reported in 7 patients, one of which occurred during the 0-12 months of treatment period (Table 10), and the rest beyond 12 months of treatment. All 7 patients were in the tofacitinib treatment groups, approximately equally in the 5 mg twice-daily and 10 mg twice-daily

groups. All cases occurred late in the course of treatment with tofacitinib with a median of one year (range 149 to 807 days). In a tofacitinib development program for renal allograft rejection, there were 5 cases of lymphoproliferative disorders reported out of 218 treated patients (cumulative incidence of 2.3%). The cases occurred at 9 months or later in the course of tofacitinib treatment and most were in the setting of EBV-positive status. The dose of tofacitinib used in that program was 15 mg twice daily for 3 or 6 months and then 10 mg twice-daily. These findings are suggestive of a dose- and duration-dependent lymphoma risk with tofacitinib, particularly in immunocompromized patients. This is further supported by the observation in a 39-week cynomolgus monkey study where 3 out of 8 monkeys in the high-dose group had lymphoma, and multiple monkeys in lower dose groups had lymphocyte hyperplasia in lymphoid tissues.

Major adverse cardiovascular (MACE) analysis:
MACE analysis to assess cardiovascular safety was of interest because of known lipid profile alteration in patients with RA and the effect of tofacitinib on lipid profile (mentioned later). MACE analysis did not indicate a safety signal for cardiovascular mortality or morbidity in patients treated with tofacitinib (Table 10, Table 11).

Laboratory test parameters of interest:
Lymphocyte count decrease below 500 cells/cmm occurred in 0.04% patients in both the tofacitinib 5 mg and 10 mg twice-daily treatment groups during the first 3 months of treatment. These patients often developed infections that required treatment.

Neutrophil count decrease below 1000 cells/cmm occurred in in 0.07% patients in both the tofacitinib 5 mg and 10 mg twice-daily treatment groups during the first 3 months of treatment. There was no report of neutrophil count below 500 cells/cmm. There was no clear relationship between decrease in neutrophil count and infection.

Lipid parameter (total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride) elevations occurred in a dose-related manner in tofacitinib-treated patients at one month of exposure and remained stable thereafter. During the first 3 months of exposure LDL cholesterol increased by 15% and 19% in tofacitinib 5 mg twice-daily and 10 mg twice-daily treatment groups, respectively.

Liver enzyme test abnormality (enzymes greater than 3 times the upper limit of normal) was not common and not clearly dose- or treatment-related. However, there was one case of drug-induced liver injury reported in a patient treated with tofacitinib 10 mg twice-daily that occurred approximately 2.5 months into treatment.

Serum creatinine increased in a dose-related manner in tofacitinib-treated patients, which appeared to increase with time. In the long-term extension studies, up to 2% of patients were discontinued from tofacitinib due to protocol-specified discontinuation criteria for an increase in creatinine by more than 50% of baseline.

Common adverse reactions:
Common adverse reactions that occurred in 2% or more patients on tofacitinib and at least 1% greater than in placebo treated patients during the first 3 months included diarrhea, nasopharyngitis, upper respiratory tract infection, headache, and hypertension. These events did not have a clear dose ordering for tofacitinib.

Summary comment on safety:
The submitted data show that tofacitinib treatment in patients with RA carries the safety risks of serious infections, opportunistic infections, tuberculosis, herpes zoster infection, and malignancy, with all of these occurring at frequencies higher than in the placebo treatment group and most occurring at frequencies higher than in the adalimumab treatment group (Table 10, Table 11). These safety risks are consistent with the mechanism of action of tofacitinib as a potent immunosuppressant that primarily inhibits the JAK1 and JAK3 pathway. As discussed in section 2 above, JAK1 and JAK3 inhibition would be expected to enhance susceptibility to infections as this would suppress the function of T- and B-lymphocytes. (b) (4) Laboratory tests showed a higher frequency of lymphocyte count decrease and neutrophil count decrease with tofacitinib compared to placebo. These cellular count changes may partly explain the clinical safety findings described above. Although the cell count decrease was not dose related, it is possible that functional alterations of these cells may well be dose related. It is thought that the effect of tofacitinib on lymphocytes is related to functional suppression rather than a lytic effect.[14] In addition to these immune function alterations, tofacitinib treatment was also associated with adverse lipid parameter changes that were dose-related and an increase in serum creatinine that appeared to be dependant on duration of treatment. Considering these safety data, tofacitinib 5 mg twice-daily appears to be the optimum dose for the treatment of adult patients with moderately to severely active RA. Tofacitinib should not be used in combination with currently available biologic DMARDs because of safety concerns with the use of two potent immunosuppressive agents together.

Post-marketing required safety study:
There are residual uncertainties regarding cardiovascular safety given the lipid profile alterations seen with tofacitinib, and the long-term consequence of tofacitinib treatment on malignancy. Pfizer will conduct a long-term safety study in patients with RA to address these safety uncertainties. The study will include two doses of tofacitinib and an active comparator. The study will be of sufficient size and duration to evaluate these safety concerns. Such a study will also provide useful long-term data that will help further understand safety findings that are already identified as discussed above.

[14] Maeshima K, Yamaoka K, Kubo S, et al. The JAK inhibitor tofacitinib regulates synovitis through inhibition of interferon-gamma and interleukin-17 production by human CD4+ T cells. Arthr Rheum 2012; 64:1790-98.

c. REMS/RiskMAP

Pfizer submitted a Risk Evaluation and Mitigation Strategy (REMS) for tofacitinib consisting of a medication guide and communication plan. The review team and Office of Surveillance and Epidemiology (OSE) consultants agree that a medication guide and REMS consisting of a communication plan are warranted based on the safety profile of tofacitinib. The REMS will address serious risks associated with tofacitinib, including serious infections, including opportunistic infections, tuberculosis, malignancy, and changes in laboratory parameters such as blood count, which will require monitoring.

9. Advisory Committee Meeting

This application was discussed at an Arthritis Advisory Committee (AAC) meeting held on May 9, 2012. The major issues for discussion at the AAC meeting were: a) impact of the radiographic outcome data on the overall assessment of efficacy of tofacitinib for the treatment of RA, b) overall safety of tofacitinib and the relative safety of the 5 mg twice-daily dose compared to the 10 mg twice-daily dose, and c) whether the dose and dose frequency selected were adequately supported by PK profile and dose exploration. The Committee discussed these issues and concluded that radiographic data were limited and not conclusive. The Committee concluded that the efficacy parameters assessing clinical response and physical functioning were persuasive enough for approval from an efficacy standpoint, noting the absence of conclusive radiographic outcome data. The Committee discussed the safety profile and concluded that there were safety concerns with infection, malignancy, and laboratory parameter changes, and that the safety data were more favorable for the 5 mg twice-daily dose. The committee concluded that the dose exploration was adequate, and the 5 mg twice-daily was a reasonable dose. On voting questions, the Committee concluded that radiographic outcome data was not substantial (votes were 2 yes and 8 no), that overall data provided substantial evidence of efficacy of tofacitinib (votes were 10 yes and 0 no), that overall data demonstrated substantial safety for tofacitinib for approval (votes were 7 yes and 2 no with 1 abstention), and that the overall efficacy and safety data provided substantial evidence to support approval of tofacitinib for treatment of moderately to severely active RA (votes were 8 yes, and 2 no). The voting questions were for tofacitinib as the active moiety, and not specific to the 5 mg twice-daily or 10 mg twice-daily dose. During discussion most of the Committee members were favorable towards the 5 mg twice-daily dose, noting safety concerns with the 10 mg twice-daily dose.

10. Pediatric

Pfizer submitted plans for studying tofacitinib for polyarticular juvenile idiopathic arthritis (PJIA) with a request for deferral of studies in patients 2 to <17 years of age with PJIA, and a waiver for studies in patients less than 2 years of age as the disease is rare in this age group. The Pediatric Review Committee (PeRC) reviewed the tofacitinib pediatric program at a meeting held on July 11, 2012, and agreed with the requested deferral and waiver.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit was requested 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 the 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

Pfizer submitted Xeljanz as the proposed proprietary name, which DMEPA deemed acceptable.

b. Physician Labeling

Pfizer submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, and OPDP. Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to health care providers. The label contains efficacy and safety data from 2 dose-ranging efficacy and safety studies and 5 definitive efficacy and safety studies (Table 1), including data from tofacitinib 3 mg twice-daily dose and 10 mg twice-daily dose so that the relative efficacy differences and safety risks of different doses are presented that support the recommended 5 mg twice-daily dose. Safety risks of infection and malignancy are described as a Boxed Warning. The Division and Pfizer have agreed on the final labeling language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

A Medication Guide was required as discussed in section 8c above.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Pfizer has submitted adequate data to support approval of tofacitinib at a dose of 5 mg twice-daily for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to the non-biologic DMARD methotrexate. Tofacitinib can be used either as a monotherapy or in combination with methotrexate or other non-biologic DMARDs. The recommended regulatory action for this application is Approval.

(b) (4)

(b) (4)

b. Risk Benefit Assessment

The overall risk-benefit assessment supports approval of tofacitinib with a recommended dose of 5 mg twice-daily for treatment of moderately to severely active RA who have had an inadequate response or intolerance to the non-biologic DMARD methotrexate. Tofacitinib can be used either as a monotherapy or in combination with methotrexate or other non-biologic DMARDs. (b) (4)

The safety risks of tofacitinib are serious infections, including opportunistic infections, tuberculosis, herpes zoster, and malignancy. Laboratory findings of safety concern are lymphocyte count decrease, neutrophil count decrease, adverse lipid parameter change, and increased serum creatinine. (b) (4) The efficacy benefits of tofacitinib are beneficial clinical response and improvement in physical function when used as a monotherapy or as a combination therapy in patients with moderately to severely active RA. The tofacitinib 10 mg twice-daily dose provided a numerically higher response compared to the 5 mg twice-daily

dose, but both the 5 mg twice-daily dose and the 10 mg twice-daily dose were consistently statistically superior to placebo, and the 5 mg twice-daily dose provided a response that was within the range of the responses observed for biologic DMARDs. Balancing the dose-related safety risks and efficacy benefits, the tofacitinib 5 mg twice-daily dose is recommended as the optimum dose for use in RA.

All biologic DMARDs currently approved for RA are injectable products. Of the small molecule DMARDs that are oral, methotrexate is commonly used as a first-line treatment of RA, either alone or in combination with biologic DMARDs. Hydroxychloroquine, sulfasalazine, and leflunomide are also often used as a DMARD for the treatment of RA. Tofacitinib will provide a choice of a DMARD in a convenient oral dosage form.

c. Post-marketing Risk Management Activities

Post-marketing risk management activities will include a medication guide and a REMS consisting of a medication guide and communication plan. The risks to be addressed will include serious infections, including opportunistic infections, tuberculosis, malignancy, and changes in laboratory parameters such as blood count that will require monitoring.

d. Post-marketing Study Commitments

There will be a clinical post-marketing requirement (PMR) study as described towards the end of Section 8 above.

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/s/

BADRUL A CHOWDHURY
11/06/2012