CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 20, 2012
From	Sarah Yim, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 203214
Applicant	Pfizer
Date of Submission	October 21, 2011
PDUFA Goal Date	August 21, 2012
Proprietary Name / Established (USAN) names	Xeljanz/Tofacitinib
Dosage forms / Strength	5 and 10 mg immediate-release tablets
Proposed Indication(s)	1. Treatment of Adult Patients with Moderately to Severely Active Rheumatoid Arthritis (RA) and Inadequate Response to One or More Disease-Modifying-Anti-Rheumatic Drugs (DMARDs)
Recommended:	*Approval, with Revisions to Proposed Label*

1. Introduction

New Drug Application (NDA) 203214 from Pfizer for the new molecular entity (NME) tofacitinib (also known as CP-690,550), an oral small molecule inhibitor of the Janus associated kinases (JAK) being proposed for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). The product is being proposed as immediate-release tablets for oral administration in 5 and 10 mg dosage strengths. Pfizer proposes the recommended starting dose as 5 mg twice a day, with an added qualifier that some patients may benefit from an increase to 10 mg twice a day based on clinical response.

In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3 and, to a lesser extent, 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 by viruses and bacteria related to defective signaling by class II cytokine receptors and receptors that use the gp130 subunit. 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 erythropoesis. TyK2 knockout mice are viable with no overt abnormalities, but do show reduced CD4+ cell differentiation to Th1 cells. 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 lack of circulating T cells and NK cells, but a normal number of B-cells.[1]

If approved, tofacitinib would be the first JAK inhibitor for rheumatoid arthritis (RA), and the first orally administered agent approved since leflunomide's approval in 1998. However, one other JAK inhibitor, ruxolitinib, has been approved since November 2011 for myelofibrosis indications. The NDA for tofacitinib posed a number of review issues which will be the focus of this memorandum. These issues include:

- Whether the submitted data are adequate to conclude that tofacitinib is a disease-modifying agent for RA and if the conclusion applies to both proposed doses (5 and 10 mg BID)
- What the most pressing safety concerns are for tofacitinib, and whether there is a dose or exposure related increase in risk for these concerns.

These issues, and the overall benefit-risk profile of tofacitinib, were discussed at a meeting of the Arthritis Advisory Committee on May 9, 2012. Highlights of this discussion are summarized in Section 9, below.

2. Background

Rheumatoid Arthritis (RA) has been the prototypical autoimmune disease for drug development; especially since the late 1990s with the success of the targeted biologic therapies. It is a chronic, inflammatory polyarthritis affecting approximately 1% of adults worldwide, approximately 75% of whom are women. The majority of patients would have persistent, progressive disease which would result in increasing disability, if untreated.[2] Fortunately, many effective treatments have been developed and approved for RA, as summarized in Table 1 below.

[1] L Vijayakrishnan, R Venkataramanan, and P Gulati, "Treating inflammation with the Janus Kinase inhibitor CP-690,550." Trends Pharmacol Sci 2011 Jan; 32(1):25-34.
[2] SL Scott and S Steer, "The course of established rheumatoid arthritis," Best Practice & Research Clinical Rheumatology 2007, 21(5):943-967

Table 1 FDA Approved Drugs and Biologics for RA

FDA-Approved Drugs and Biologics for RA	
Small molecules	**Biologics**
Various NSAIDs	**TNF inhibitors**
Corticosteroids	Enbrel (etanercept)
Sulfasalazine	Remicade (infliximab)
Auranofin	Humira (adalimumab)
Methotrexate	Simponi (golimumab)
Azathioprine	Cimzia (certolizumab)
Penicillamine	**IL-1 inhibitors**
Cyclosporine	Kineret (anakinra)
Arava (leflunomide)	**T-cell Costimulatory Modulators**
	Orencia (abatacept)
	Anti-CD20
	Rituxan (rituximab)
	IL-6 inhibitors
	Actemra (tocilizumab)

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

One conundrum associated with the assessment of efficacy in RA is the possible dissociation between clinical and radiographic outcomes. Radiographic progression may occur in people who have very low apparent disease activity and patients with clinical disease activity may have no evidence of radiographic progression.[3] Thus, documentation of a benefit of treatment on structural damage progression has been an important goal of clinical development programs for new products proposed for RA, particularly if the product has a novel target. This has become an increasingly important aspect of the risk-benefit assessment for new RA treatments in light of the many approved treatments that have documented beneficial effects in inhibiting structural damage progression.

Relevant Regulatory History for Tofacitinib in RA

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

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

proceeding with the study, despite the lack of nonclinical support for all of the proposed doses, which would typically be required.

In January 2007, the Agency provided written feedback regarding the proposed design of Study A3921025 and an extension study. Study A3921025 included proposed doses of 1, 3, 5, 10, 15 mg BID and 20 mg QD, to be given with stable background methotrexate (MTX) for a duration of 6 months. The design of the study was considered generally acceptable, although it was noted that the nonclinical data appeared to only support chronic dosing in patients up to 5 mg BID. The review team at that time determined that previous clinical experience appeared to support the ability to proceed with the proposed study.

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

- Pure placebo control should be limited to 3 months, even if patients had apparent symptomatic improvement (i.e., ACR20).
- 5 mg BID and 10 mg BID doses appear reasonable; 3 mg BID should be considered. QD regimens may warrant further study.
- The safety database proposal appeared to be adequate (1500 patients on the to-be-marketed dose for a year or more).
- Concern regarding effects on lipids and the implications for cardiovascular safety, and the need for this to be comprehensively evaluated for NDA.

At the Pre-NDA meeting for this application in February 2011, general agreement was reached on the proposed format and content of NDA, and the adequacy (to support review of the application) of the nonclinical program and clinical safety database. (b) (4)

3. CMC/Device

CMC Reviewers: Craig Bertha, Ph.D.; Donghao Lu, Ph.D., Ying Wang, Ph.D., Bogdan Kurtyka, Ph.D.; Supervisory: Eric Duffy, Ph.D.

- **General product quality considerations**

The drug substance tofacitinib citrate (CP-690,550-10) is a white to off-white (b) (4) that is (b) (4) Tofacitinib citrate is highly soluble as per the Biopharmaceutics Classification System and the applicant indicates that it has low permeability (BCS class 3). The structure of tofacitinib citrate includes an arylamine function, which is a structural alert for mutagenicity. The drug substance is not photosensitive and the

stability data provided supports both the proposed retest period of (b) (4), as well as the post-approval stability protocol proposed. The drug substance is manufactured at Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland. It is packaged in (b) (4) (b) (4) and retest period of (b) (4) is supported.

The drug product immediate release tofacitinib tablets are formulated as film-coated round tablet. Two strengths, 5 mg and 10 mg, are proposed for commercialization. The strengths of the drug products are based on the equivalent amount of tofacitinib. The 5 mg tablets are white to off-white, film-coated, round tablets debossed with "Pfizer" on one side and "JKI5" on the other side. (b) (4) The tablets are manufactured with a (b) (4) (b) (4) The drug product is packed in high-density polyethylene (HDPE) bottles with desiccant and closures with induction seal liners. The drug product is manufactured and packaged in Frieburg, Germany and is also being packaged in Puerto Rico. The submitted drug product stability data include 12 months at long term storage condition of 25°C/60%RH and 6 month accelerated storage condition of 40°C/75%RH for 3 batches of each strength. The stability data supports the proposed 24 month shelf life for the drug product when stored at the proposed 20°C to 25°C (68°F to 77°F). (b) (4)

- **Facilities review/inspection**

At the time of this review, the Establishment Evaluation Request (EER) is still pending.

- **Other notable issues (resolved or outstanding)**

From a Chemistry, Manufacturing, and Controls (CMC) perspective, the application is recommended for approval pending an acceptable recommendation from the Office of Compliance regarding the facilities' inspections. No CMC Phase 4 commitments are recommended.

4. Nonclinical Pharmacology/Toxicology

Pharm-Tox Reviewer: Lawrence S. Leshin, D.V.M., Ph.D.; Supervisor: Molly Shea, Ph.D.

- **General nonclinical pharmacology/toxicology considerations**

Pivotal nonclinical toxicology studies were conducted in rats (6-month, doses of 0, 1, 10, 100 mg/kg/day) and cynomolgus monkeys (9-month, doses of 0, 0.5, 2, 10 mg/kg/day, 4 monkeys per sex per group). No-Observed-Adverse-Effect-Levels (NOAELs) could not be determined as adverse effects were noted in each of the lowest doses tested. Toxicities were associated

with suppression of the immune and hematopoietic systems, to include suppression of myeloid and erythroid bone marrow production, reductions in circulating red and white blood cells, increased bacterial infections, and reduced or atrophied lymphoid organs. Reversibility of these findings was not evaluated in the chronic toxicity studies. However shorter duration repeat-dose toxicity studies in rats and monkeys demonstrated that these findings were at least partially reversible.

In the nonclinical program, including shorter (i.e. 1 to 1.5 month) studies, adverse effects resulting in mortality included:

- in rats, bacterial infections of the kidney, lung alveolar histiocytosis and interstitial inflammation
- in monkeys, lymphomas, and bacterial and viral infections

In the 9-month (39-week) chronic toxicology study in cynomolgus monkeys, three monkeys in the high dose group (10 mg/kg/day) developed lymphomas. Pfizer concluded that these lymphomas were consistent with gamma herpes-virus induced lymphoproliferative disorder associated with immunosuppression. Additional details are discussed in the context of the human lymphoma findings in the RA and renal transplant settings in the safety section of this memorandum.

- **Carcinogenicity**

Tofacitinib was not mutagenic or genotoxic based on in vitro and in vivo tests for gene mutations, chromosomal damage, and DNA damage. Carcinogenicity was assessed in a 6-month mouse study and a 2-year rat study. The mouse study did not suggest oncogenic potential related to tofacitinib. The rat study neoplastic findings included interstitial cell adenomas of the testes, and benign thymomas and malignant hibernomas in females.

- **Reproductive toxicology**

In reproductive toxicology studies, tofacitinib did not appear to affect the fertility of male rats, but decreased pregnancy rate, numbers of corpora lutea, implantation sites, and viable fetuses in female rats, with an increase in early resorptions, pre-implantation loss and post-implantation loss. Tofacitinib was teratogenic (visceral and skeletal abnormalities) in rats and rabbits.

- **Other notable issues (resolved or outstanding)**

The Pharmacology/Toxicology team believes the information in this application is adequate to support approval. However they also recommend that the male fertility study and the juvenile rat study be performed again using a revised design:

1. In the male fertility study, males were administered tofacitinib for at least 63 days, but matings occurred after 1 month of treatment, an insufficient duration of drug exposure for a complete spermatogenic cycle. Therefore, at least the study in adult males should be repeated and conducted in accordance with ICH5(R2).

2. In the juvenile rat study, both males and females were administered CP-690550 from weaning on day 21 until near or at puberty in the female, and in the male through expected puberty for an appropriate duration of exposures in both sexes. However, they were not mated until a few weeks after drug dosing stopped, allowing for recovery of any potentially adverse effects on fertility. The study in juvenile animals was not required, but if done correctly, could be incorporated into labeling to provide safety for treatment of pediatric patients with regards to reproductive maturation and fertility. These differ from classic segment 3 postnatal studies in that in the segment 3 studies the juvenile animals are not dosed with drug, only the dams are dosed, and the juvenile are followed to see if there are generational effects of the drug. The study in juvenile rats incorporates drug administration directly to the juvenile animals. This is an optional study, but if conducted, should also be designed and evaluated as recommended in ICH5(R2).

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology reviewer: Lokesh Jain, Ph.D.; Supervisor: Suresh Doddapaneni, Ph.D.
Pharmacometrics reviewer: Lokesh Jain, Ph.D. and Atul Bhattaram, Ph.D.; Supervisor: Atul Bhattaram, Ph.D.
Pharmacogenomics reviewer: Jeffrey Kraft, Ph.D.; Supervisor: Michael Paconowski, Pharm.D., M.P.H.

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

The absolute bioavailability of tofacitinib at the 10 mg dose was 74%. The systemic exposure ($AUC_{0-\infty}$) and peak plasma concentration (C_{max}) increased in proportion to dose in the dose range of 1 to 100 mg. T_{max} was reached by approximately 0.5-1 hours following oral administration. Coadministration with food had no significant effect on the extent of absorption ($AUC_{0-\infty}$) but rate of absorption (C_{max}) was reduced by 32%. Upon multiple dosing, steady-state was reached by 24-48 hours with negligible accumulation. Tofacitinib is a substrate of P-gp transporter.

Tofacitinib has a total plasma protein binding of approximately 39%. Tofacitinib binds moderately to albumin and does not bind to alpha-1 acid glycoprotein. Steady-state volume of distribution (Vdss) for tofacitinib following intravenous infusion administration was 87 L, suggesting distribution into tissues.

Tofacitinib was extensively metabolized by the liver; primarily by CYP3A4 enzyme with minor contribution from CYP2C19. All metabolites comprise less than <8% of total drug exposure and their potency was reported to be ≤10% of the potency of tofacitinib for JAK1/3 inhibition. Based on in vitro studies, tofacitinib is not a substrate of BCRP transporter. Based on in vitro studies, at therapeutic concentrations, tofacitinib has low potential for induction or

inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 metabolic enzymes and low potential of inhibition for P-gp, OCT2, OATP1B1, OATP1B3.

Of the 94% drug recovered following oral administration in a mass balance study, approximately 29% and 51% was recovered in urine as parent drug and metabolites, respectively. In feces, proportion of parent and metabolites recovered was approximately 1% and 13%. The terminal elimination half-life of tofacitinib was approximately 3 hours after single- or multiple-dose administration.

- **Drug-drug interactions**

Tofacitinib coadministration with a strong CYP3A inhibitor, ketoconazole, increased the mean tofacitinib AUC (90%CI) by 103% (91%, 116%) and Cmax by 16% (5%, 29%).
When coadministration with a strong CYP3A4 inhibitor is necessary, the clinical pharmacology team recommends a dose reduction as follows:

- If 10 mg BID is an approved dose, then the dose with concomitant administration should not exceed 5 mg BID.
- If 5 mg BID is the limit, then a reduced dose of 5 mg QD is recommended.

Coadministration with a moderate CYP3A4 and strong CYP2C19 inhibitor, fluconazole, increased mean tofacitinib AUC (90%CI) by 79% (64%, 96%) and Cmax by 27% (12%, 44%). Thus the same dose reduction recommendation applies for moderate CYP3A4 and strong CYP2C19 inhibitors.

Tofacitinib coadministration with a strong CYP3A inducer, rifampin, resulted in substantial decreases in mean tofacitinib AUC (90%CI) by -84% (-86%, -82%) and in Cmax by -74% (-77%, -69%). Coadministration with rifampin is not recommended because that may result in ineffective concentrations of tofacitinib.

Coadministration with tacrolimus, a CYP3A substrate with narrow therapeutic index, increased mean (90%CI) tofacitinib AUC (90%CI) by 21% (13%, 30%) and decreased Cmax by -9% (-17%, -1%). Coadministration with cyclosporine, a CYP3A substrate with narrow therapeutic index and also an inhibitor of P-gp increased mean (90%CI) tofacitinib AUC (90%CI) by 73% (62%, 85%) and decreased C_{max} by -17% (-29%, -3%). The clinical pharmacology team raised concerns regarding a possible pharmacodynamic interaction with the tofacitinib and either tacrolimus or cyclosporine and recommended the two drugs not be coadministered. However, immunosuppressive drugs are not uncommonly combined based on the clinical judgment of the healthcare professional for the particular clinical scenario, and I would not recommend labeling specifically prohibiting coadministration on the basis of a concern for pharmacodynamic interaction alone.

Coadministration with methotrexate, had no significant effect on tofacitinib exposure and no dose adjustment is needed for tofacitinib when coadministered with methotrexate. Tofacitinib had no substantial effects on the plasma levels of oral contraceptives (ethinylestradiol and levonorgestrel), midazolam (CYP3A substrates), or methotrexate, thus no dose adjustment is needed for these drugs when coadministered with tofacitinib.

- **Intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment**

There was no substantial impact of age, weight, and gender on PK parameters, after accounting for differences in renal function (i.e., creatinine clearance).

For subjects with mild, moderate and severe renal impairment, mean percentage change in AUC (90%CI), compared to subjects with normal renal function were respectively: 41% (-5%, 109%), 71% (14%, 157%), and 156% (69%, 287%). Mean percentage changes in Cmax (90% CI) for these cases were respectively: 1% (-31%, 49%), 2% (-31%, 52%), and 21% (-19%, 81%). Based on these data, the clinical pharmacology team recommends dose reduction (as described above) of tofacitinib in patients with moderate and severe renal impairment.

For subjects with mild and moderate hepatic impairment, mean percentage change in AUC (90%CI), compared to subjects with normal hepatic function were respectively: 3% (-22%, 36%) and 65% (25%, 117%). Mean percentage change in Cmax (90% CI) for these cases were respectively: -1% (-25%, 32%) and 49% (12%, 97%). Based on these data, the clinical pharmacology team recommends dose reduction of tofacitinib for these patients. Tofacitinib was not evaluated in patients with severe hepatic impairment, but as tofacitinib is extensively hepatically metabolized, there is reason to believe that increased exposure, and risk, would occur in this population, and therefore use of tofacitinib in this population is not recommended.

- **Demographic interactions/special populations**

Based on available data are no major differences were seen in tofacitinib AUC and C_{max} between White, Black and Asian patients, after accounting for differences in renal function (i.e., creatinine clearance). However, population PK analysis in RA patients showed 43% lower apparent clearance in RA patients relative to a healthy adult.

- **Thorough QT study**

QT effect was evaluated in a randomized, blinded, crossover, single-dose study, in which 60 healthy subjects received a supra-therapeutic tofacitinib dose of 100 mg, placebo, and moxifloxacin 400 mg. The washout duration between treatment periods was 7 days. No significant QT prolongation effect was detected at the tested 100 mg tofacitinib dose. The largest upper bounds of the 2-sided 90% CI for the mean difference between CP-690,550 100 mg and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

- **Other notable issues (resolved or outstanding)**

The Office of Clinical Pharmacology has determined the information in NDA 203214 acceptable. No outstanding issues have been identified or Phase 4 commitments recommended.

6. Clinical Microbiology—N/A

7. Clinical/Statistical- Efficacy

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

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 "A32," 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.

(b) (4)

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

Brief Description of Efficacy Endpoints

- *ACR Response Rates*

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

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

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

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

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

The Agency has historically recognized a distinct claim in RA for "improvement in physical function" based on outcome measures such as the HAQ-DI.[5] This instrument assesses a patient's level of functional ability and includes questions pertaining to fine movements of the upper extremity, locomotor activities of the lower extremities, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent a comprehensive set of functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients respond on a four-level difficulty scale ranging from zero (no difficulty) to three (unable to do). The 8 category scores are averaged into an overall HAQ-DI score on a scale from zero (no disability) to 3 (completely disabled). The most widely accepted figure on the minimal clinically important difference in the HAQ-DI score is an improvement (decrease) of at least 0.22 units.

- *Disease Activity Score (DAS)-28*

The DAS28 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 erythrocyte sedimentation rate (ESR) results.[6] An alternative equation is available for use with c-reactive protein (CRP) results. These variables are summed and weighted mathematically into a single numerical value ranging from 0 to 10. Comparing the DAS28 and the ACR response criteria, beyond the differences in number of maximum tender or swollen joints counted (e.g. DAS28 does not include the joints of the feet), additional variables of physician global assessment, patient pain, and HAQ score are incorporated into the ACR response criteria. The DAS28 has additional utility in measuring the level of disease activity at a given timepoint, whereas the ACR response criteria are calculated as improvement in the variables over a set period of time. A DAS28 score >5.1 is indicative of high disease activity, and <3.2 of low disease activity. A score of <2.6 has been used to describe an even lower threshold of disease activity.

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

The Van der Heijde-modified Sharp radiographic scoring method grades the presence of erosions in the joints of the hands and feet, and the presence of joint space narrowing (JSN) in the hands, wrists, and feet.[7] The scores for each feature for the individual joints are summed. Erosions are assessed at 16 locations in each hand and wrists and 12 locations in each foot, using a 6-point scale from 0 to 5. Scores are derived based on the number and size of discrete erosions in each location, but are summed to a maximum of 5. Thus the maximum erosion score for the hands/wrists is 160, and the maximum erosion score for the feet is 120, for a maximum total erosion score of 280. JSN scores are based on 15 locations in each hand and

[5] B Bruce and JF Fries, "The Health Assessment Questionnaire (HAQ)." Clin Exp Rheumatol 2005; 23 (Suppl 39):S14-S18
[6] J Fransen and PLCM van Riel, "The Disease Activity Score and the EULAR Response Criteria." Clin Exp Rheumatol 2005; 23 (Suppl 39): S93-S99
[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

wrist and 6 locations in each foot, scored using a 5-point scale from 0 to 4: 0 = normal; 1 = focal or minimal and generalized narrowing; 2 = generalized narrowing <50%; 3 = generalized narrowing >50% or subluxation; and 4 = ankylosis or complete dislocation. The maximum total JSN for the hands/wrists is 120, and the maximum total JSN for the feet is 48, for a maximum total JSN score of 168. Therefore the theoretical maximum modified total Sharp Score (mTSS) is 448, although the actual clinical range in RA drug development trials is typically much lower because a given individual typically only has a fraction of his or her joints affected by radiographically evident damage.

Dose selection

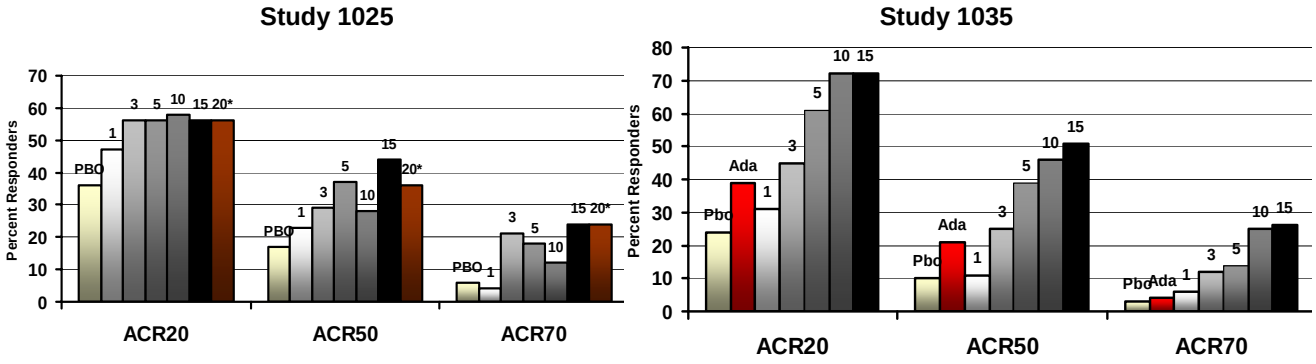
The proposed recommended starting dose is 5 mg twice a day, with an added qualifier that some patients may benefit from an increase to 10 mg twice a day based on clinical response. Pfizer selected 5 and 10 mg BID doses of tofacitinib based on dose-response modeling of safety and efficacy data from Study 1025, with supportive data from Study 1019 and Study 1035. The key design features of these studies and efficacy results for the American College of Rheumatology (ACR) Responses are summarized in Table 3 and Figure 1 below. On background methotrexate (MTX) in Study 1025, the dose response was very flat across the range of doses from 3 mg BID to 20 mg QD. There was some suggestion in Study 1035 (a monotherapy evaluation) that 10 mg BID might result in additional responders over 5 mg BID.

Table 3: Summary of Dose-Ranging Studies A3921025, A3921035, and A3921019

Summary of Dose-Ranging Studies A3921025, A3921035, and A3921019						
Study A3921025						
MTX-inadequate responder (IR)	Background MTX 6 month duration Endpt eval @ Escape option at 3 mos to 5 mg BID for the placebo, 1 mg and 30 mg BID, and 20 mg QD dose grps	CP-690,550	**Discontinued, n (%)**	**ACR20, n (%)[a]**	**ACR50, n (%)[a]**	**ACR70, n (%)[a]**
		1 mg BID (n=71)	9 (13)	33 (47)	16 (23)	3 (4)
		3 mg BID (n=68)	11 (16)	38 (56)	20 (29)	14 (21)
		5 mg BID (n=71)	15 (21)	40 (56)	26 (37)	13 (18)
		10 mg BID (n=75)	8 (11)	43 (58)	21 (28)	9 (12)
		15 mg BID (n=75)	15 (20)	42 (56)	33 (44)	18 (24)
		20 mg QD (n=80)	14 (17.5)	45 (56)	29 (36)	19 (24)
		Placebo (n=69)	15 (22)	25 (36)	12 (17)	4 (6)
Study A3921035						
DMARD-IR	Monotherapy 6 month duration Endpt eval @ Wk 12 Escape option at Wk 12 to 5 mg BID for pbo, 1 and 3 mg groups Adalimumab switch to 5 mg BID @ Wk 12	CP-690,550	**Discontinued, n (%)**	**ACR20, n (%)[b]**	**ACR50, n (%)[b]**	**ACR70, n (%)[b]**
		1 mg BID (n=54)	14 (26)	17 (31)	6 (11)	3 (6)
		3 mg BID (n=52)	8 (15)	23 (45)	13 (25)	6 (12)
		5 mg BID (n=50)	6 (12)	30 (61)	19 (39)	7 (14)
		10 mg BID (n=61)	6 (10)	44 (72)	28 (46)	15 (25)
		15 mg BID (n=57)	5 (9)	41 (72)	29 (51)	15 (26)
		Adalimumab 40 mg qow to 5 mg BID (n=53)	16 (30)	21 (39)	11 (21)	2 (4)
		Placebo (n = 59)	16 (27)	14 (24)	6 (10)	2 (3)
Study A3921019						
DMARD-IR	Monotherapy 6 weeks duration	CP-690,550	**Discontinued, n (%)**	**ACR20, n (%)[c]**	**ACR50, n (%)[c]**	**ACR70, n (%)[c]**
		5 mg BID (n=61)	3 (5)	43 (70)	20 (33)	8 (13)
		15 mg BID (n=69)	9 (13)	56 (81)	37 (54)	15 (22)
		30 mg BID (n=69)	17 (25)	53 (77)	35 (51)	19 (28)
		Placebo (n=65)	17 (74)	19 (29)	4 (6)	2 (3)

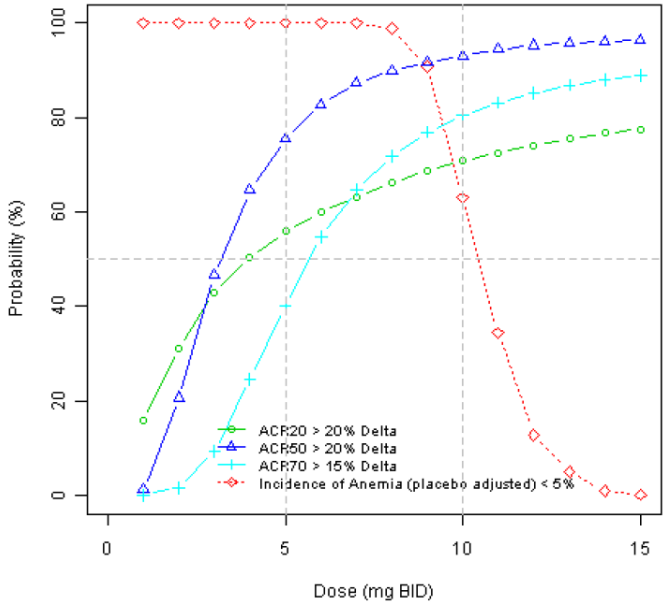
Source: a) Tables 7, 17, 22, and 24, A3921025 CSR, full analysis set, BOCF for missing data
b) Tables 7, 20, 23, and 25, A3921035 CSR, full analysis set, BOCF for missing data
c) Tables 5, 11, 12, and 13, A3921019 CSR, full analysis set, LOCF for missing data

Figure 1: Bar Graphs of Dose-Ranging Study Results for ACR Responses in Study 1025 and Study 1035



Pfizer selected the doses of 5 mg BID and 10 mg BID for further study in Phase 3. The key drivers of their dose selection were ACR responses for efficacy and effect on hemoglobin (and associated anemia incidence) as a safety variable. Hemoglobin and LDL were initially chosen as safety variables because, "effects on other endpoints were either clinically insignificant or the incidence of events were insufficient to model."[8] Since the management of LDL requires patient-specific considerations, it was not ultimately utilized for dose-selection. As shown in Figure 2 below, doses between 5 and 10 mg BID would be anticipated to be where the likelihood of ACR responses is close to maximal, and the risk of anemia is at the beginning of a steep increase, thus 5 to 10 mg BID was determined by Pfizer as being the desirable dose range. As noted in the regulatory history section above, at EOP2 the Agency review team agreed that the selection of the 5 mg BID and 10 mg BID dose regimens appeared to be adequately justified, although 3 mg BID or QD regimens were also thought to warrant further consideration.

Figure 2: Dose-Response Curves for ACR Responses vs. Decrease in Hemoglobin



[8] Module 2.7.3 Summary of Clinical Efficacy, Section 2.7.3.4.2.1, Page 150

Additional dose-ranging studies were performed in Japan (A3921039, A3921040), but as these studies were not unique in design or results they will not be covered in detail in this memorandum.

Study conduct

Treatment groups in the studies were generally balanced with respect to demographics and baseline characteristics. Overall completion rates were in the 75 to 85% range for active and control groups in the studies utilizing background DMARDs and somewhat higher in monotherapy Study 1045. Dropout rates due to adverse events were higher in the tofacitinib treatment groups (6-12%) compared to the placebo control groups (3-7%), with the exception of monotherapy Study 1045, where they were roughly equal. Conversely, dropout rates due to lack of efficacy were somewhat higher in the placebo groups of the studies (1-4% with tofacitinib, 3-8% with placebo). This pattern and amount of missing data is consistent with other RA clinical development programs.

Pfizer's primary analysis population definition differed from the intent-to-treat (ITT) population in that the primary analysis was done on the "Full Analysis Set" (FAS), which included all patients who were randomized, and received at least one dose of study drug, AND who had at least one post-baseline measurement. Thus the FAS population denominator changed depending on the outcome measure being analyzed. Where the FAS population differed most from the ITT population was in the analysis of the radiographic endpoints. Missing data and their impact on the analyses of the respective study endpoints will be discussed in the sections below pertaining to those endpoints.

All five studies are designed to establish superiority of the two doses of tofacitinib (5 mg and 10 mg BID) to placebo for all the primary endpoints.

Studies 1032, 1045, 1046, and 1064 had three primary endpoints, in sequence, as follows:

1. Proportion of patients with ACR20 improvement
    a. At Month 3 for Studies 1032 and 1045
    b. At Month 6 for Studies 1046 and 1064
2. Mean change from baseline to Month 3 in HAQ-DI
3. Proportion of patients with DAS28<2.6
    a. At Month 3 for Studies 1032 and 1045
    b. At Month 6 for Studies 1046 and 1064

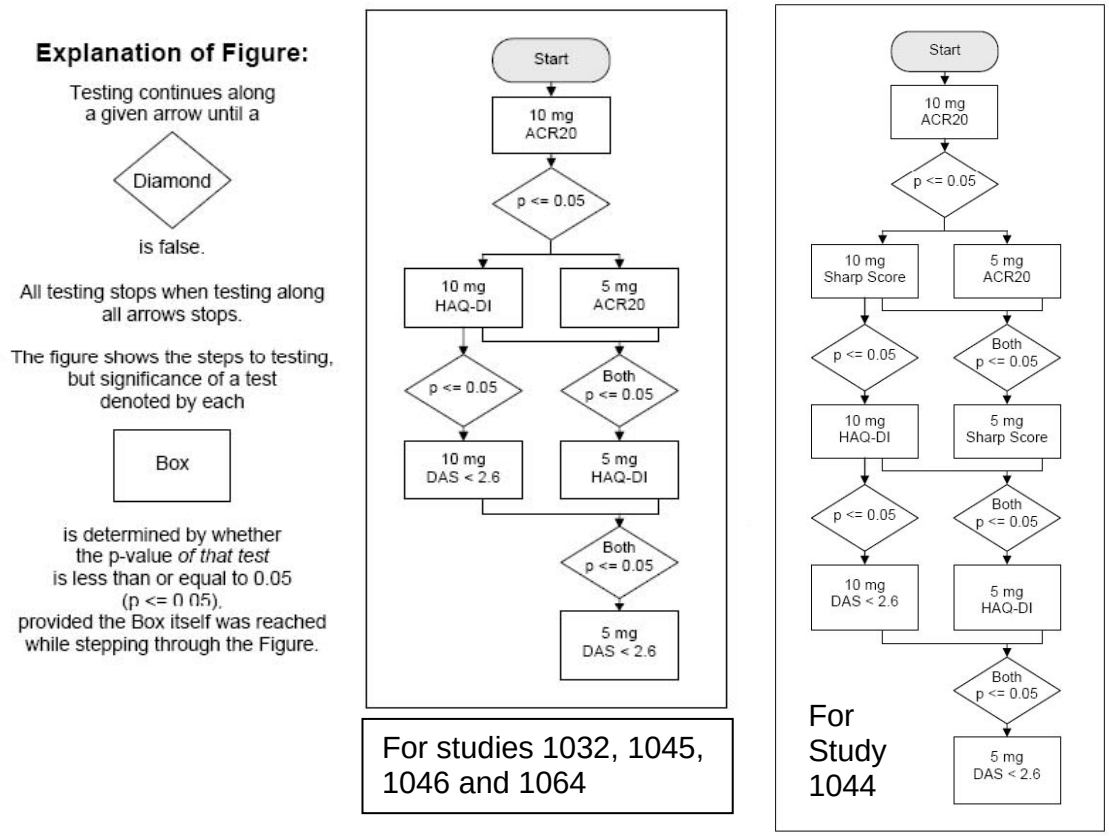
Study 1044 had four primary efficacy endpoints, in sequence, as follows:

1. Proportion of patients with ACR20 improvement at Month 6
2. Mean change from baseline to Month 6 in modified Total Sharp Score (mTSS)
3. Mean change from baseline to Month 3 in HAQ-DI
4. Proportion of patients with DAS28<2.6 at Month 6.

In order to control the probability of type 1 error, Pfizer assessed each endpoint sequentially using a gatekeeping/step-down approach where statistical significance can be claimed for the

next endpoint in the sequence only if the prior endpoints have met the requirements for significance. Additionally, as there are two doses within each endpoint, the gate-keeping/step-down approach was to be applied with respect to dose as well, i.e., the high dose (10 mg BID) at a given endpoint could achieve significance only if the high dose at the prior endpoint is significant. For each endpoint, and for each dose group, the comparison with placebo was to be conducted using a significance level (alpha) set at 0.05 (2-sided) or equivalently 0.025 (1--sided). The step down procedure is explained diagrammatically as follows:

Figure 3: Primary Analysis Stepdown Procedure in the 5 Phase 3 RA Studies



Efficacy findings

- *ACR Response Rates*

The primary endpoint for all 5 Phase 3 trials was the proportion of patients experiencing an ACR20 response at Month 3 (Studies 1032, 1044, and 1045) or at Month 6 (Studies 1045 and 1064). As shown in Table 4 below, tofacitinib treatment was associated with a higher proportion of ACR20 responders in all 5 trials at both 5 mg and 10 mg doses, and the differences were statistically significant compared to the placebo control groups. Because missing data were conservatively imputed as equating to non-response, Pfizer's primary analysis using the FAS population and FDA's analysis using the ITT population produced essentially the same results (data not shown). Although the 10 mg dose was associated with a

slightly higher proportion of responders in 4 of 5 studies, the proportion of responders in the 5 mg dose group was similar. The studies were not designed to assess whether patients who began with 5 mg BID would experience a benefit from increasing their dose to 10 mg BID.

Table 4: Summary of ACR20 Response Rates (Primary Endpoint) in Phase 3 RA Studies

ACR20 Responses	FAS, N	Responder, n	Response rate (%)	Difference vs. PBO	p value
Study A3921032 (3 months)					
Tofacitinib 5 mg BID	**132**	**55**	**42%**	**17%**	0.0025
Tofacitinib 10 mg BID	**133**	**64**	**48%**	**23%**	<0.0001
Placebo (PBO)	131	32	25%	-	-
Study A3921044 (6 months)					
Tofacitinib 5 mg BID	**309**	**159**	**52%**	**26%**	<0.0001
Tofacitinib 10 mg BID	**309**	**191**	**62%**	**36%**	<0.0001
Placebo (PBO)	154	39	26%	-	-
Study A3921045 (3 months)					
Tofacitinib 5 mg BID	**241**	**144**	**60%**	**33%**	<0.0001
Tofacitinib 10 mg BID	**242**	**159**	**66%**	**39%**	<0.0001
Placebo (PBO)	120	32	27%	-	-
Study A3921046 (6 months)					
Tofacitinib 5 mg BID	**311**	**164**	**53%**	**22%**	<0.0001
Tofacitinib 10 mg BID	**309**	**180**	**58%**	**27%**	<0.0001
Placebo (PBO)	157	49	31%	-	-
Study A3921064 (6 months)					
Tofacitinib 5 mg BID	**196**	**101**	**52%**	**24%**	<0.0001
Tofacitinib 10 mg BID	**196**	**103**	**53%**	**25%**	<0.0001
Adalimumab 40 mg	199	94	47%	19%	0.0008
Placebo (PBO)	106	30	28%	-	-

Consistent with the primary endpoint results, the proportion of patients experiencing ACR50 and ACR70 levels of improvement was higher in the tofacitinib groups compared to the placebo control group, with the proportions being similar but slightly higher in the 10 mg group than the 5 mg group. Differences compared to the placebo control group were statistically significant.

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

All Phase 3 trials also assessed the treatment effect of tofacitinib on HAQ-DI. The change in HAQ-DI score was assessed from baseline to Month 3 in all five studies. Tofacitinib treatment was associated with a statistically significant improvement (decrease) in HAQ-DI (mean change from baseline), with the tofacitinib treatment groups experiencing a 0.3 to 0.4 unit improvement over placebo in the studies. In four of the five Phase 3 studies the 10 mg dose group appeared to be associated with slightly greater improvement in HAQ-DI. As mentioned previously, the studies were not designed to assess whether increasing from the 5 mg to the 10 mg dose would be associated with an increased likelihood or greater degree of benefit.

For this continuous endpoint, Pfizer's analysis assumed a missing-at-random mechanism for missing data regardless of reason and used a mixed-effect repeated-measure model. FDA reanalyzed the data by applying a baseline-observation-carried-forward imputation for missing data and produced similar results. Analysis of HAQ-DI results in Study 1044 fell lower in the statistical hierarchy than the analyses of the radiographic endpoint for the corresponding tofacitinib dose. Thus, the statistical significance of the HAQ-DI results in Study 1044 is

dependent on the statistical significance of the radiographic results, which are in question (and described in further detail below).

Table 5: HAQ-DI Endpoint Results

HAQ-DI	FAS, N	LS Mean	LS Mean Difference	Difference vs. PBO (95% CI)	p value
Study A3921032 (3 months)					
Tofacitinib 5 mg BID	**117**	**-0.5**	**-0.3**	**(-0.4, -0.1)**	0.0002
Tofacitinib 10 mg BID	**125**	**-0.5**	**-0.3**	**(-0.4, -0.1)**	<0.0001
Placebo (PBO)	118	-0.2	-	-	-
Study A3921044 (3 months)					
Tofacitinib 5 mg BID	**294**	**-0.4**	**-0.3**	**(-0.4, -0.2)**	*
Tofacitinib 10 mg BID	**300**	**-0.6**	**-0.4**	**(-0.5, -0.3)**	<0.0001
Placebo (PBO)	146	-0.2	-	-	
Study A3921045 (3 months)					
Tofacitinib 5 mg BID	**237**	**-0.5**	**-0.3**	**(-0.4, -0.2)**	<0.0001
Tofacitinib 10 mg BID	**227**	**-0.6**	**-0.4**	**(-0.5, -0.2)**	<0.0001
Placebo (PBO)	109	-0.2	-	-	-
Study A3921046 (3 months)					
Tofacitinib 5 mg BID	**292**	**-0.5**	**-0.3**	**(-0.4, -0.2)**	<0.0001
Tofacitinib 10 mg BID	**292**	**-0.6**	**-0.4**	**(-0.5, -0.3)**	<0.0001
Placebo (PBO)	147	-0.2	-	-	-
Study A3921064 (3 months)					
Tofacitinib 5 mg BID	**188**	**-0.6**	**-0.3**	**(-0.4, -0.2)**	<0.0001
Tofacitinib 10 mg BID	**185**	**-0.7**	**-0.4**	**(-0.5, -0.3)**	<0.0001
Adalimumab 40 mg	190	-0.5	-0.2	(-0.4, -0.1)	<0.0001
Placebo (PBO)	98	-0.3	-	-	-

*p value significant, but HAQ-DI endpoint falls below radiographic endpoint in the hierarchy for Study 1044 and should not be tested

- *Radiographic Outcomes: Van der Heijde Modified Total Sharp Score*

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

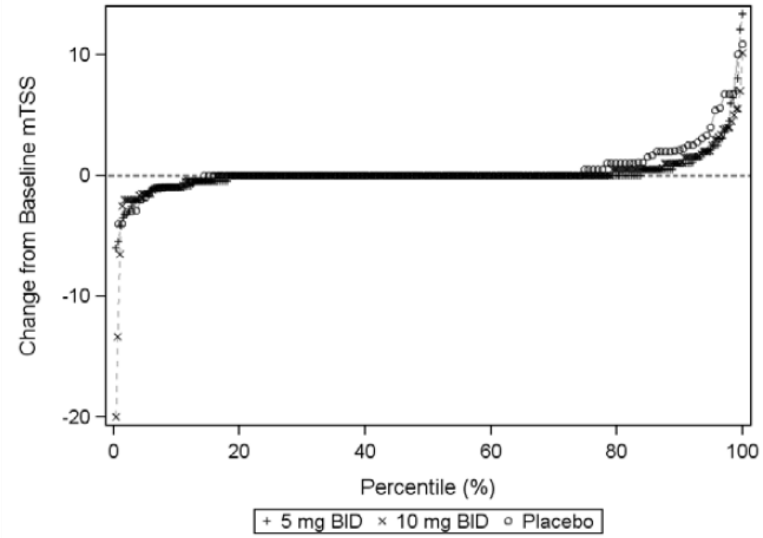
Patients with missing data at Month 6 or Month 12 had their data imputed using linear extrapolation from baseline to their last radiographs prior to exiting their assigned treatment group. This imputation method has been used historically in other RA development programs assessing structural damage,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

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

however given the small treatment effect size and the distribution of the data (see below), it is difficult to rule out a major impact of the missing data on overall results.

As illustrated in Figure 4 below, which contains Study 1044 results and is consistent with the distribution observed in other RA programs, only a fraction (approximately 20%) of patients experience progression in the time frame of the study. Placebo patients (designated by circles in Figure 4) did appear to have more worsening in mTSS scores than did tofacitinib-treated patients.

Figure 4: Cumulative Probability Plot of Radiograph Score Changes from Baseline to Month 6



Source: Figure 23 of the A3921044 Clinical Study Report

As shown in Table 6 below, in the primary analysis, only the change from baseline in mTSS for the tofacitinib 10 mg group achieved statistical significance compared to the placebo group. The statistical significance of the findings changes when non-parametric analyses were used—only the tofacitinib 5 mg group results achieved statistical significance.

Table 6: Analyses of Change from Baseline in Modified Total Sharp Scores, Study A3921044

Analyses of Radiographic Outcomes: Change from Baseline in Modified Total Sharp Scores (mTSS) in Study A3921044			
	PBO + MTX	CP 5 mg BID + MTX	CP 10 mg BID + MTX
Assigned to study treatment (tx)	n = 160	n = 321	n = 319
Received at least 1 dose of study tx	n = 160	n = 321	n = 316
"Full Analysis Set"	n = 156	n = 316	n = 309
Pfizer Primary Analyses			
Month 6 (Primary Endpoint)	n = 140*	n = 278*	n = 290*
mTSS LS means	0.47	0.12	0.06
p-value vs. placebo	-	0.0792	0.0376
Analyses Based on Ranks			
Month 6 (Primary Endpoint)			
ANCOVA with ranked data p-value	-	0.0237	0.1979
Wilcoxon test p-value	-	0.0216	0.1751
Van der Waerden test p-value	-	0.0283	0.1410
Van Elteren test p-value	-	0.0245	0.1710

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

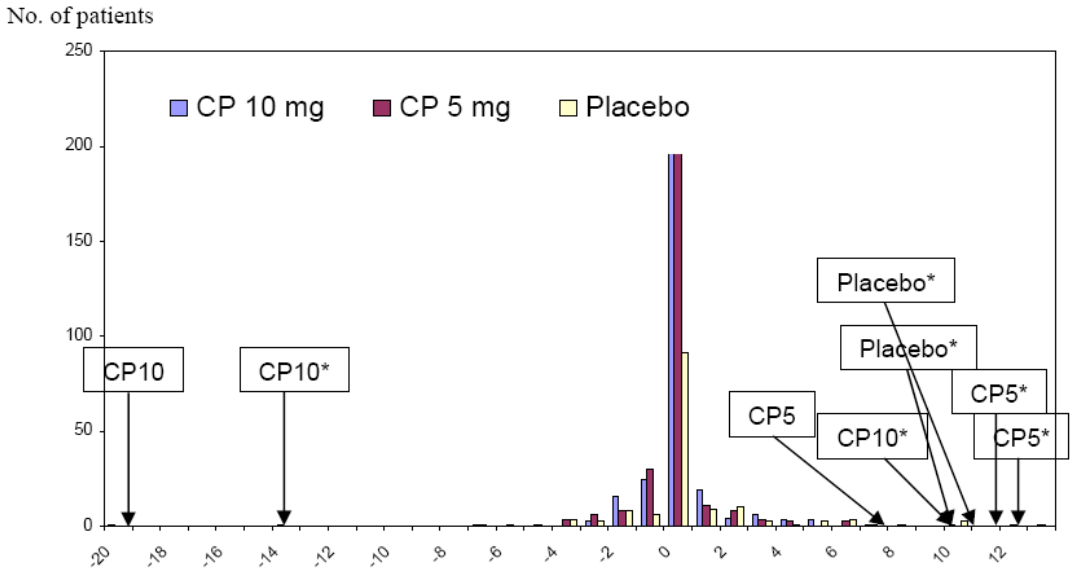
Results in Table 7 below show that fewer patients progressed in the tofacitinib 5 mg group, suggesting that the greater mean change in mTSS observed in the 10 mg group is due to an outlier or very few outliers. This conclusion is also supported by other exploratory analyses performed by FDA statisticians, including the outlier analyses shown in Figure 5 below. Further illustrating the lack of conclusiveness of the radiographic data, a change in the definition of "no progression" from a change in mTSS of ≤0.5 units to 0 units results in a loss in statistical significance for the tofacitinib 10 mg dose group, as shown in Table 7 below.

Table 7: Rates of "No Progression" Based on Change from Baseline to Month 6 in mTSS

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

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

Figure 5: Frequency Distribution of Change from Baseline in mTSS at Month 6



*Extrapolated data

Source: Figure 3 of the statistical review by Dr. Yongman Kim

Figure 5 also illustrates how much of the outlier data is extrapolated (annotated by asterisks), which again raises questions about the conclusiveness of the apparent overall radiographic results. Also, when the single subject who had an improvement of 20 units was excluded from the analysis, the tofacitinib 10 mg group results lose statistical significance.

In summary, there is uncertainty in the radiographic outcome results for tofacitinib due to a number of factors:

- A low amount of progression was observed in the placebo control group, limiting the treatment effect size that could be demonstrated
- The small apparent treatment effect size is susceptible to change depending on analytical approach, missing data, and missing data imputation method, and in this case appears to be driven by few extreme observations
- The data are not consistent with respect to dose
- Corroborating data (i.e., from another study) are not available to help resolve residual uncertainty

Therefore, although data are suggestive of a possible benefit, it is not possible to make definitive conclusions about the treatment effect of tofacitinib on structural damage progression. This is particularly important in determining the overall benefit-risk profile of tofacitinib, which is associated with serious safety concerns, as will be discussed in the safety sections of this memorandum.

- *Disease Activity Score (DAS)-28 <2.6*

The proportion of patients achieving a DAS28 less than 2.6 was the final endpoint in the sequence of primary endpoints in the statistical hierarchy of the Phase 3 RA trials. This was

assessed at Month 3 in Studies 1045 and 1032 and at Month 6 in Studies 1044, 1046, and 1064. A low proportion of patients in each group achieved this low level of disease activity, although the proportion of responders was higher in the tofacitinib groups by 2 to 12% compared to placebo. There was a trend toward a higher proportion of responders in the 10 mg group compared to the 5 mg group in each of the studies, but the proportion of responders was numerically similar between groups.

Table 8: Proportion of Patients with DAS28<2.6 Response

Proportion with DAS28<2.6	FAS, N	Responder, n	Response rate (%)	Difference vs. PBO	p value
Study A3921032 (3 months)					
Tofacitinib 5 mg BID	119	8	7%	5%	0.0497
Tofacitinib 10 mg BID	125	11	9%	7%	0.0105
Placebo (PBO)	120	2	2%	-	-
Study A3921044 (6 months)					
Tofacitinib 5 mg BID	265	19	7%	5%	*
Tofacitinib 10 mg BID	257	47	18%	16%	*
Placebo (PBO)	129	2	2%	-	-
Study A3921045 (3 months)					
Tofacitinib 5 mg BID	232	13	6%	2%	0.6179
Tofacitinib 10 mg BID	229	20	9%	5%	0.1042
Placebo (PBO)	114	5	4%	-	-
Study A3921046 (6 months)					
Tofacitinib 5 mg BID	263	24	9%	6%	0.0038
Tofacitinib 10 mg BID	270	36	13%	10%	<0.0001
Placebo (PBO)	148	4	3%	-	-
Study A3921064 (6 months)					
Tofacitinib 5 mg BID	177	11	6%	5%	0.0151
Tofacitinib 10 mg BID	176	22	13%	12%	<0.0001
Adalimumab 40 mg	178	12	7%	6%	0.0091
Placebo (PBO)	92	1	1%	-	-

*p value significant, but DAS28 endpoint falls below radiographic endpoint in the hierarchy for Study 1044 and should not be tested

In the primary analysis of the FAS population, using a nonresponder imputation for missing data, the difference between each tofacitinib dose group and the placebo group was statistically significant, with the exception of monotherapy Study 1045, where neither the 5 mg nor the 10 mg dose group was associated with a statistically significant difference. In FDA's analysis using the ITT population and nonresponder imputation for missing data, the 5 mg dose groups in Studies 1032 and 1064 do not reach statistical significance. Therefore only results from Studies 1046 and 1044 would support the efficacy of the 5 mg dose for this endpoint. Using either the FAS or ITT population, the efficacy of the 10 mg dose is supported by all studies except monotherapy Study 1045.

- **Discussion of statistical and clinical efficacy reviews with explanation for CDTL's conclusions and ways that any disagreements were addressed.**

The clinical and statistical review teams are in agreement that tofacitinib at both 5 and 10 mg doses is efficacious for signs and symptoms (ACR Responses, DAS28) as well as for physical function (HAQ-DI). Regarding the effect of tofacitinib on structural outcomes, as assessed via radiographic outcomes, although the data submitted are suggestive of a treatment effect, it is not possible to draw definitive conclusions. Although on occasion (depending on study and efficacy outcome) the 10 mg dose appeared to be associated with a small amount of additional benefit over the 5 mg dose, this was not a consistent finding across all studies and endpoints.

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

As discussed above, the primary unresolved efficacy issue is the question of tofacitinib's effect on radiographic/structural outcomes. Another radiographic outcomes study will likely be needed to support the currently submitted data. (b) (4)

8. Safety

Studies contributing to integrated safety analyses, and Pfizer's pooling and attribution strategies

A summary of the studies contributing to the primary integrated safety analyses may be found in Table 9 below. These included 5 Phase 3 studies—1032, 1044, 1046, 1064, and 1045—and 5 Phase 2 studies—1025, 1035, 1019, and Japanese studies 1039 and 1040. Most of the submitted integrated safety analyses focused on the Phase 3 study data. However, for exposure-adjusted incidence of Adverse Events of Special Interest (AESI) and incidence rates per 6-month intervals for AESI, Pfizer included the Phase 2 study data, as Phase 2 patients were rolled over into Long-Term Extensions (LTE) where they continued to receive tofacitinib. These Phase 2 study patients comprised the subgroup with the longest duration of exposure. The LTE safety data therefore included patients from Phase 2 and Phase 3 studies, as described in Table 9, below. Of note, the LTEs were originally designed (since 2006) such that all patients entering, irrespective of previous study treatment, received tofacitinib 5 mg BID. LTE Study 1024 was amended in January 2009 to initiate open-label dosing of tofacitinib at 10 mg BID, with the exception of patients in China, who continue to receive 5 mg BID upon entering the LTE. In LTE Study 1041, created specifically for patients from Japan, patients continue to receive 5 mg BID upon entering the LTE.

As noted in Table 9 and Figure 6 below, placebo-controlled periods were limited to 3 to 6 months. For studies 1032 and 1045, which were 6 months in duration, all placebo-group patients were transitioned to tofacitinib at Month 3. For Studies 1044, 1046 and 1064, which were longer in duration, placebo-group non-responders were "escaped" to tofacitinib treatment early, at Month 3; and all of the remaining placebo-group patients were transitioned to tofacitinib treatment at Month 6. In Phase 2 study 1025, which was 6 months in duration, nonresponders in the tofacitinib 1 or 3 mg BID group, or the 20 mg QD group, or the placebo control group were escaped to tofacitinib 5 mg BID at Month 3. In Phase 2 study 1035, which was 6 months in duration, nonresponders in the tofacitinib 1 or 3 mg BID group were escaped to tofacitinib 5 mg BID at Month 3, but all patients in the placebo or adalimumab groups were transitioned to tofacitinib 5 mg BID at Month 3 irrespective of responder status. Nonresponders were defined as patients who did not have at least a 20% improvement from baseline levels in both tender/painful and swollen joint counts at the Month 3 visit.

The aforementioned design features of the Phase 2 and Phase 3 studies complicate the comparison of tofacitinib to control groups. For comparisons of incidence per time period

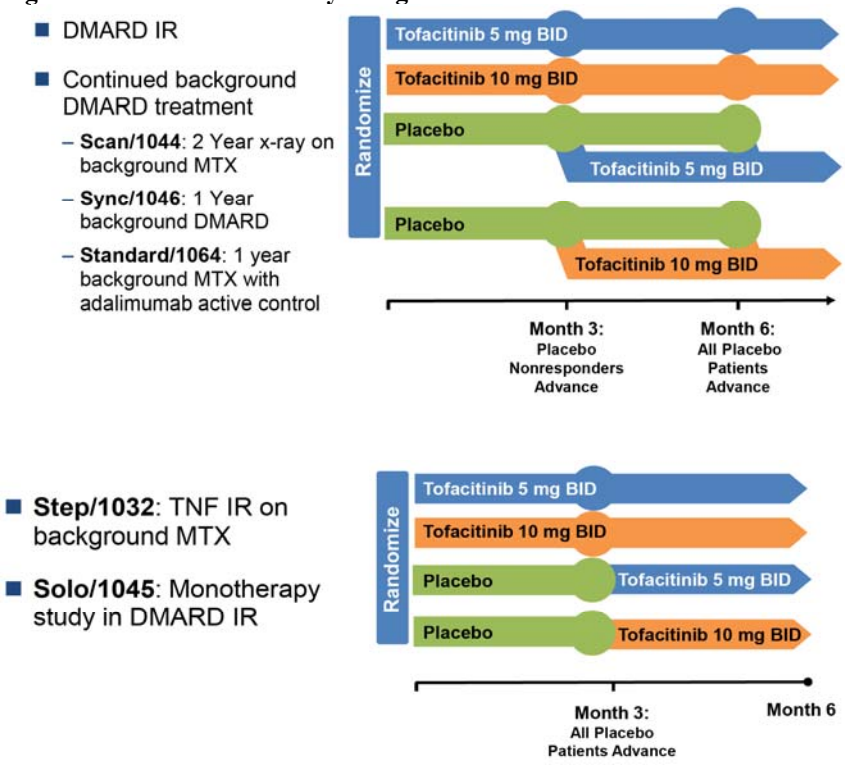
during the controlled period analyses (up to 12 months), attribution to treatment was as follows:

- Months 0 to 3: patients were on randomized treatment. Adverse events were counted towards the assigned treatment
- Months 3 to 6: patients may have remained on randomized treatment, escaped due to lack of response, or transitioned to tofacitinib by design. Adverse events were counted towards the treatment a given patient was receiving at the time of the adverse event.
- Greater than 6 months: patients randomized to tofacitinib 5 or 10 mg, or to adalimumab in Study 1064 remained on originally assigned treatment; all other patients were either escaped or transitioned to tofacitinib by design. Adverse events were counted towards the treatment a given patient was receiving at the time of the adverse event.

Table 9: Summary of Phase 2 and Phase 3 Studies with Associated Long-Term Extension

Protocol Duration	Patient Population	Treatment Arms	Number per arm	Associated LTE
Phase 3 Studies				
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	LTE 1024
A3921044 2 years, but 1 yr data submitted for NDA	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)** ***(All are on tofacitinib after Week 24)***	321 316 81 79	LTE 1024 except in Japan patients to LTE 1041
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)** ***(All are on tofacitinib after Week 24)***	315 318 79 80	LTE 1024
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 ***(After Week 24,all PBO/MTX pts are on tofacitinib; adalimumab patients stay on adalimumab through end of study)***	204 201 56 52 204	LTE 1024
A3921045 6 months	Moderate to severe RA DMARD-IR Monotherapy 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	LTE 1024
Phase 2 Studies				
A3921025 6 months	RA Dose-Ranging MTX-IR Stable background MTX Total n = 507	Tofacitinib 1 mg BID + MTX **(to tofacitinib 5 mg BID@ Mo.3 if NR)** Tofacitinib 3 mg BID + MTX **(to tofacitinib 5 mg BID@ Mo.3 if NR)** Tofacitinib 5 mg BID + MTX Tofacitinib 10 mg BID + MTX Tofacitinib 15 mg BID + MTX Tofacitinib 20 mg QD + MTX **(to tofacitinib 5 mg BID@ Mo. 3 if NR)** PBO + MTX **(to tofacitinib 5 mg BID@ Mo. 3 if NR)**	70 68 71 74 75 80 69	LTE 1024
A3921039 12 wks Japan	Japanese RA Dose-ranging MTX-IR Stable background MTX Total n = 136	Tofacitinib 1 mg BID + MTX Tofacitinib 3 mg BID + MTX Tofacitinib 5 mg BID + MTX Tofacitinib 10 mg BID + MTX PBO + MTX	28 27 27 26 28	LTE 1041
A3921019 6 wks	RA Dose-Ranging Monotherapy MTX-IR or TNF-IR Total n = 264	Tofacitinib 5 mg BID Tofacitinib 15 mg BID Tofacitinib 30 mg BID PBO	61 69 69 65	LTE 1024
A3921035 6 months	RA Dose-Ranging Monotherapy MTX-IR Total n = 384	Tofacitinib 1 mg BID **(to tofacitinib 5 mg BID@ Mo. 3 if NR)** Tofacitinib 3 mg BID **(to tofacitinib 5 mg BID@ Mo. 3 if NR)** Tofacitinib 5 mg BID Tofacitinib 10 mg BID Tofacitinib 15 mg BID PBO **to tofacitinib 5 mg BID@ Mo. 3** Adalimumab 40 mg SC every 2 wks **to tofacitinib 5 mg BID@ Mo.3**	54 51 49 61 57 59 53	LTE 1024
A3921040 12 wks Japan	Japanese RA Dose-ranging Monotherapy Total n = 317	Tofacitinib 1 mg BID Tofacitinib 3 mg BID Tofacitinib 5 mg BID Tofacitinib 10 mg BID Tofacitinib 15 mg BID PBO	53 53 52 53 54 52	LTE 1041

Figure 6: Basic Phase 3 Study Design Schemata



For the LTE, because dose adjustments were permitted during the long-term studies, a definition was created for assigning a patient to a dose group for the pooled data: patients were included in a dose group based on the highest dose (CP5 or CP10) that they received in the first 3 months of participation in the long-term study. Where applicable, baseline values for each patient in the LTE studies were determined by the length of time between completion of the index study and enrollment in the LTE studies. Baseline values for patients who entered the LTE studies within 14 days of completing the index study were the baseline values from the index study (which includes a large majority of the patients). For the other patients, baseline values were derived from the last pre-drug visit on entry into the LTE studies.

For Adverse Events of Special Interest (AESI), which included serious infections, herpes zoster, overall malignancies excluding non-melanoma skin cancer (NMSC), lung cancer, breast cancer, and NMSC, Pfizer provided analyses of incidence rates broken down into 6-month intervals. For these analyses, the zero time point occurred when patients were first started on tofacitinib, regardless of whether this occurred at baseline (for patients originally randomized to tofacitinib) or at Months 3 or 6 (for patients advancing to tofacitinib from placebo). Patients in these analyses could be from any of the Phase 2, Phase 3, or long-term extension studies in RA. A similar approach was taken for exposure-adjusted incidence analyses.

For patients discontinuing from the studies, serious adverse events (SAE) were reported starting from the time the patient provided informed consent (prior to receiving investigational product) through and including 28 calendar days after the last administration of the

investigational product. Twenty eight calendar days is not unreasonable, given the very short half-life (~3 hours) but somewhat more extended pharmacodynamic effect (~2 wks) of tofacitinib. SAE occurring after this time period were reported if a causal relationship to study drug was suspected.

- **Adequacy of the database, major findings/signals, special studies**

As of the original submission data cut-off (March 29, 2011), the extent of the safety database comprised of the RA Phase 2, Phase 3 and LTE studies included a total of 4816 patients and 5716 patient-years of exposure to all doses of tofacitinib. The exposure to tofacitinib, by dose and duration (≥6 months), in the RA clinical development program is summarized in Table 10 below. Exposure to placebo and adalimumab controls is significantly lower in the RA safety database due to intentional design features of the controlled trials (e.g., unequal randomization, limited duration of the placebo controlled period). Notably, the majority of patients with longer durations of exposure (i.e., greater than 24 months) were those who received tofacitinib 5 mg BID, because these were patients who entered the LTE from the Phase 2 studies; whereas patients entering from the Phase 3 studies began with tofacitinib 10 mg BID, following a protocol amendment in January 2009.

Table 10: Exposure to Tofacitinib by Dose and Duration in Phase 2, Phase 3 and LTE Studies in RA

Duration of exposure	5 mg BID (n=1677)	10 mg BID (n=1755)	5 mg/10 mg BID* (n=1178)
≥ 6 months	1366	1321	1135
≥ 12 months	1107	939	905
≥ 24 months	580	8	105

Source: Table 12, Integrated Summary of Safety (clinical data cut-off March 29, 2011);
*Subjects in 5 mg/10 mg BID group represent those who received different doses between the index study and the extension study.

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

Death

As of the 120-day safety update (data cut-off September 29, 2011), a total of 49 deaths were reported in the RA clinical development program. Of these, 45 have occurred in tofacitinib-treated patients, one in a placebo-treated patient and 3 in adalimumab-treated patients. The majority of deaths occurred in the Phase 3 studies or LTE. Two deaths occurred during the Phase 2 studies—a single patient in Study 1025 on tofacitinib 3 mg BID who died of pneumonia after receiving tofacitinib for 36 days (event occurred 14 days after last study treatment) and a single patient from Study 1035 who died of a hemorrhagic cerebrovascular accident after receiving tofacitinib for 140 days (46 days after last study treatment). There were no deaths in the Phase 1 studies.

For the Phase 3 studies 12-month pooled safety population (which includes the controlled period of up to 12 months in Study 1064 for the adalimumab control group), deaths from all causes irrespective of timing of occurrence, were as follows:

- one patient died in the placebo treatment group (0.1%, exposure-adjusted incidence of 0.5/100 patient-years)
    - a patient in Study 1044 who died of pyelonephritis/sepsis
- three deaths occurred in the adalimumab treatment group (1.5%, exposure-adjusted incidence of 1.7/100 patient-years)
    - one patient with cardiac arrest, one patient with non-small cell lung cancer, and one patient with bone marrow hypoplasia
- Eight deaths occurred in the tofacitinib 5 mg bid group (0.7%, 0.9/100 patient-years) and four deaths occurred in the tofacitinib 10 mg BID group (0.3%, 0.4/100 patient-years).

Thus, mortality rates did not appear to be consistently elevated in the tofacitinib treatment groups compared to the control groups and there did not appear to be an increased risk of death with the higher dose during the 12-month pooled safety period.

In the LTE, there were 17 deaths in patients receiving tofacitinib 5 mg BID (1.3%, exposure-adjusted incidence of 0.8/100 patient-years) and 3 deaths in patients receiving tofacitinib 10 mg BID (0.2%, 0.3/100 patient-years). Thus the exposure-adjusted incidence of death did not appear to be increased with longer duration of exposure in the long-term extension and the relative incidence between the doses remained consistent. The causes of death in tofacitinib-treated patients were consistent with the profile of an immunosuppressant and also with the underlying patient population, with infections, malignancy and cardiovascular disorders being most common.

Nonfatal Serious Adverse Events (SAE)

The proportion of patients experiencing SAE and the exposure-adjusted incidence of SAE during the controlled period of the Phase 3 RA trials and during the LTE is summarized in Table 11 below. The proportion of patients treated with tofacitinib and experiencing SAE in a given interval appears to be roughly similar to the proportion of patients experiencing SAE in the corresponding control groups. The same can be said for the exposure-adjusted incidence of SAE by treatment group. However, when broken down by System-Organ-Class (SOC), tofacitinib treatment appears to be associated with an increased risk of infections. In the LTE, the rate of neoplasms and malignancies appeared to increase. These particular SAE will be discussed in detail in sections to follow. Although there did not appear to be an increased risk of SAE for the 10 mg BID dose over the 5 mg BID dose in the controlled period of the studies, the exposure-adjusted incidence of SAE was increased for the 10 mg BID dose in the LTE. As noted above, exposure to tofacitinib in the LTE data for this submission is predominantly with the 5 mg BID dose regimen.

Table 11: Summary of SAE in Phase 3 RA Trials (by Time Intervals) and LTE

Summary of Serious Adverse Events (SAE) in Phase 3 RA Trials and LTE									
	12-Month Pooled Safety					Long-Term Extension (LTE)***			
	PBO	ADA	CP 5 mg BID	CP 10 mg BID	CP all doses*	CP 5 mg BID	CP 10 mg BID	LTE, all doses data cut-off 29-Mar-11	Updated LTE data cut-off 29-Sep-11
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
0 to 12 Month Summary									
Total number of SAEs	31	20	122	108	230	363	181	544	711
Total patients with ≥1 SAE, n (%)	30 (4.4)	19 (9.3)	104 (8.6)	87 (7.2)	211 (7.0)	217 (16.4)	120 (6.3)	337 (10.4)	446 (12.7)
Exposure for event, patient-years	200	175	873	890	2044	2110	860	2971	4172
Incidence of SAEs, event per 100 patient-years	15.0	10.9	11.9	9.8	10.3	10.3	14.0	11.3	10.7
0 to 3 Month Interval									
Number of patients in group	681	204	1216	1214	2430				
Total patients with ≥1 SAE, n (%)	24 (3.5)	5 (2.5)	38 (3.1)	33 (2.7)	71 (2.9)				
3 to 6 Month Interval									
Number of patients in group	221	204	1451	1439	2890				
Total patients with >1 SAE, n (%)	7 (3.2)	2 (1.0)	40 (2.8)	34 (2.4)	74 (2.6)				
>6 Months Interval**									
Number of patients in group	-	204	1056	1046	2102				
Total patients with >1 SAE, n (%)	-	12 (5.9)	42 (4.0)	35 (3.3)	77 (3.7)				

Source: Summary of Clinical Safety (data cut-off March 29, 2011), adapted from Tables 62-69 and 120-Day Safety Update, adapted from tables 18-19 Integrated Summary of Safety (ISS), Tables 76 to 80
CP=CP-690,550, also known as tofacitinib
*CP All Doses group represents data for patients as treated and includes patients originally assigned to tofacitinib 5 or 10 mg BID as well as patients escaped to or transitioned by design to tofacitinib 5 mg or 10 mg BID
**This interval applicable only to Studies 1044, 1046 and 1064
***LTE includes patients from Phase 2 studies as well

Discontinuations due to Adverse Events (DAE)

The proportion of patients discontinuing due to an adverse event in any given interval was slightly higher in the tofacitinib treatment groups compared to the control groups, as shown in Table 12 below. Infections were the most common reason for discontinuation (approximately 2.5% in the tofacitinib groups compared to 0.3% in the placebo group). However, investigations were also a common reason (up to 2% in the tofacitinib 10 mg group), and there were certain laboratory abnormalities that were pre-specified to trigger discontinuation. Adverse events of infections and laboratory abnormalities are discussed in further detail in separate sections below.

Table 12: Patient Disposition due to AE in Phase 3 RA Trials (by Time Intervals)

	PBO	ADA	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All doses
Phase 3 studies (0-3 months), n (%)					
Enrolled, n	681	204	1216	1214	2430
Subjects discontinued due to AE	22 (3)	10 (5)	52 (4)	49 (4)	101 (4)
Subjects with dose reduced/interrupted due to AE	38 (6)	15 (7)	103 (9)	99 (8)	202 (8)
Phase 3 studies (3-6 months), n (%)					
Total number in group, n	221	204	1451	1439	2890
Subjects discontinued due to AE	4 (2)	9 (4)	36 (3)	45 (3)	81 (3)
Subjects with dose reduced/interrupted due to AE	4 (2)	10 (5)	96 (7)	90 (6)	186 (6)
Phase 3 studies (>6 months), n (%)					
Total number in group, n	-	204	1056	1046	2102
Subjects discontinued due to AE	-	4 (2)	18 (2)	24 (2)	42 (2)
Subjects with dose reduced/interrupted due to AE	-	6 (3)	69 (7)	85 (8)	154 (7)

Source: Integrated Summary of Safety, adapted form Tables P3ALL 4.1.1, 4.1.2, 4.1.3

Common AE

Adverse events in the Infections and Infestations SOC were the most common adverse events in the RA Phase 3 studies. In the first 3 months of the Phase 3 studies, approximately 20 to 21% of patients in the tofacitinib groups experienced an infectious event, compared to 18% of patients in the placebo group and 16% of patients in the adalimumab group. The most common infections were bronchitis, nasopharyngitis, upper respiratory tract infection, and urinary tract infection. Gastrointestinal (GI) disorders were next most common, occurring in 16 to 17% of the tofacitinib-treated patients compared to 14% of patients in the placebo group and 10% of patients in the adalimumab group. The most common GI disorders were diarrhea, dyspepsia, and nausea. Infections remained the most common adverse event over time, with increasing exposure, in the Phase 3 studies, as well as in the LTE.

Table 13: Summary of Common Adverse Events in Phase 3 RA Trials and LTE

Summary of Common Adverse Events in Phase 3 RA Trials (by Time Intervals) and LTE									
	12-Month Pooled Safety					Long-Term Extension (LTE)***			
	PBO	ADA	CP 5 mg BID	CP 10 mg BID	CP all doses*	CP 5 mg BID	CP 10 mg BID	LTE, all doses data cut-off 29-Mar-11	Updated LTE data cut-off 29-Sep-11
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
0 to 12 Month Summary									
Total number of AEs	787	302	3265	3416	6681	4899	2848	7747	n.r.
Total patients with ≥1 AE, n (%)	337 (55)	149 (73)	874 (72)	878 (72)	2057 (68)	1047 (79)	1088 (57)	2135 (66)	n.r.
Exposure for event, patient-years	128	86	394	388	783	766	473	1239	n.r.
Incidence of AEs, event per 100 patient-years	295.7	173.6	201.6	206.1	203.8	136.7	230.1	172.4	n.r.
Most Common SOC									
Infections and Infestations	*145 (21)*	*97 (48)*	*685 (56)*	*739 (61)*	*1424 (47)*	*698 (53)*	*583 (31)*	*1281 (40)*	*n.r.*
Gastrointestinal Disorders	*97 (14)*	*21 (10)*	*204 (17)*	*189 (16)*	*393 (13)*	*388 (29)*	*220 (12)*	*608 (19)*	*n.r.*
Musculoskeletal Disorders	*78 (11)*	*25 (12)*	*170 (14)*	*157 (13)*	*327 (11)*	*308 (23)*	*205 (11)*	*513 (16)*	*n.r.*
0 to 3 Month Interval									
Number of patients in group	681	204	1216	1214	2430				
Total patients with ≥1 AE, n (%)	363 (53)	105 (51.5)	624 (51)	653 (54)	1277 (53)				
Most Common SOC									
Infections and Infestations	*125 (18)*	*33 (16)*	*243 (20)*	*257 (21)*	*500 (21)*	*Top infections: bronchitis, nasopharyngitis, URI, UTI*			
Gastrointestinal Disorders	*97 (14)*	*21 (10)*	*204 (17)*	*189 (16)*	*393 (16)*	*Top preferred terms: diarrhea, dyspepsia, nausea*			
Investigations	*34 (5)*	*11 (5)*	*71 (6)*	*101 (8)*	*172 (7)*	*Top preferred term: CPK increased*			
3 to 6 Month Interval									
Number of patients in group	221	204	1451	1439	2890				
Total patients with >1 AE, n (%)	58 (26)	68 (33)	579 (40)	556 (39)	1135 (39)				
Most Common SOC									
Infections and Infestations	*20 (9)*	*28 (14)*	*249 (17)*	*244 (17)*	*493 (17)*	*Top infections: nasopharygitis, pharyngitis, URI, UTI*			
Musculoskeletal Disorders	*8 (4)*	*13 (6)*	*81 (6)*	*84 (6)*	*165 (6)*	*Top preferred term: back pain*			
>6 Months Interval**									
Number of patients in group	-	204	1056	1046	2102				
Total patients with >1 AE, n (%)	-	83 (41)	445 (42)	478 (46)	923 (44)				
Most Common SOC									
Infections and Infestations	-	*36 (18)*	*193 (18)*	*238 (23)*	*431 (20.5)*	*Top infections: bronchitis, nasopharygitis, URI, UTI, H. Zoster*			

Source: Summary of Clinical Safety (data cut-off March 29, 2011), adapted from Tables 62-69 and 120-Day Safety Update, adapted from tables 18-19 Integrated Summary of Safety (ISS), Tables 34-36, 40-41, 47-49
CP=CP-690,550, also known as tofacitinib; n.r. = not reported; SOC = System-Organ-Class
*CP All Doses group represents data for patients as treated and includes patients originally assigned to tofacitinib 5 or 10 mg BID as well as patients escaped to or transitioned by design to tofacitinib 5 mg or 10 mg BID
**This interval applicable only to Studies 1044, 1046 and 1064
***LTE includes patients from Phase 2 studies as well

Laboratory Abnormalities

Tofacitinib treatment was associated with changes in certain hematologic, hepatobiliary, serum chemistry (creatinine and creatine phosphokinase) and lipid parameters. The Phase 3 protocols

incorporated pre-specified criteria for increased monitoring or discontinuation due to laboratory abnormalities. Discontinuation criteria were as follows:

- Absolute Neutrophil Count (ANC) <500/mm^3
- Hemoglobin (Hb) ≤8 g/dL or decreased by ≥30%
- Platelets <75,000/mm^3
- Elevated AST or ALT > 3 x Upper Limit of Normal (ULN) with
  - Total bilirubin > 2 x ULN or
  - Increased INR (coagulopathy)
- Elevated AST or ALT >5 x ULN
- Elevated creatinine >50% of baseline or ≥30% at end of study

Anemia, defined as hemoglobin <8 g/dL or a drop of 2 mg/dL or more, and liver enzyme elevations, defined as AST or ALT greater than 3 times ULN, were the most common criteria triggering further monitoring in the Phase 3 studies and LTE. These appeared to be generally balanced between the treatment groups during the controlled periods of the studies. Increases in serum creatinine were the most common laboratory abnormality triggering discontinuation criteria, and the proportion of patients meeting these criteria was higher with tofacitinib treatment. The proportion of patients meeting anemia and serum creatinine criteria increased with increasing duration of exposure. Further details regarding laboratory abnormalities are described below.

Hematologic abnormalities

Figure 7: Hematologic trends, 0-12 months, in the Phase 3 RA studies

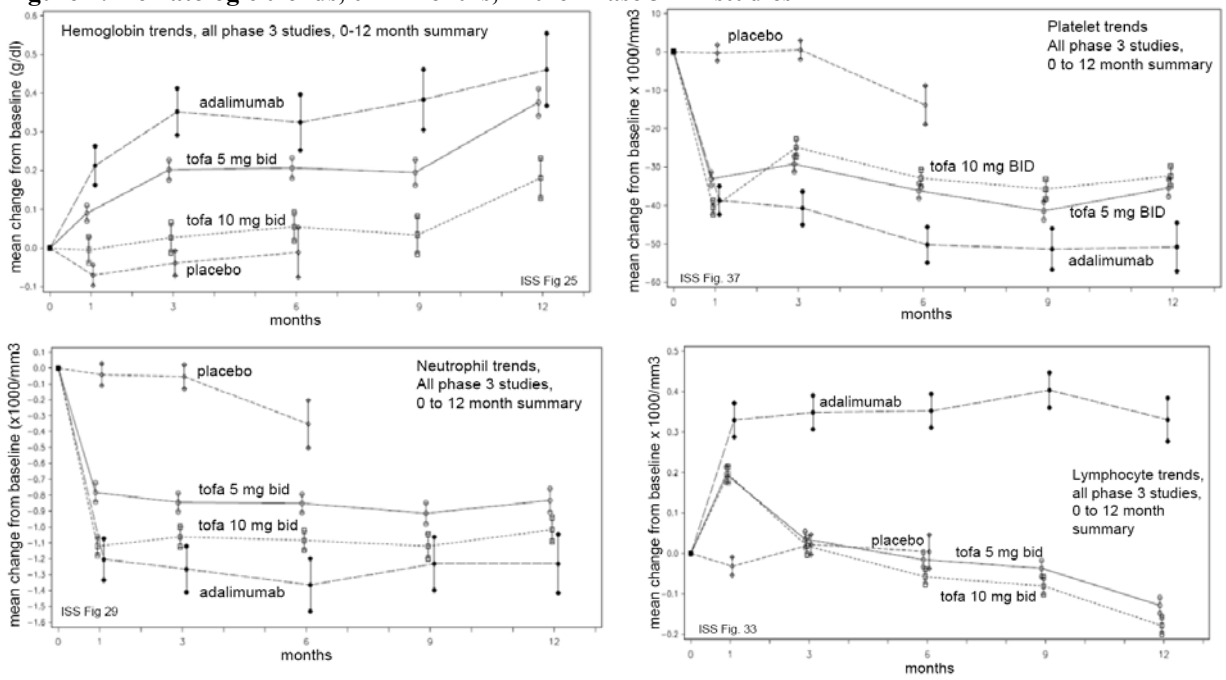


Figure 7 above summarizes the mean changes in hematologic parameters over 12-months in the Phase 3 RA studies. The first 3 months are the true placebo controlled period and months 3 to 6 include patients who are crossing over from placebo to tofacitinib treatment. The

adalimumab control group was present for the entire 12 month period. Changes in platelets, neutrophils and lymphocytes were present by month 1, then plateaued. Changes in hemoglobin occurred through month 3 then plateaued. Although the mean changes are numerically small, these graphs are helpful to demonstrate the time period during which treatment-related changes are occurring. Hemoglobin increasing and platelets decreasing are likely related to control of inflammation. The increased JAK2 inhibition of tofacitinib 10 mg BID compared to the 5 mg BID dose is notable in that hemoglobin did not increase very much over placebo in the 10 mg group, despite control of inflammation.

The proportion of patients experiencing a drop in hemoglobin of 1 to 2 g/dL was approximately 10% in the 12-month pooled safety population. Approximately 2% of patients on tofacitinib 10 mg BID experienced a drop in hemoglobin of 2 to 3 g/dL. Few patients experienced anemia of worse severity. The proportion of patients experiencing neutropenia was approximately 2 to 3% in each group. No patients experienced absolute neutrophil counts of less than 500/mm^3. A high proportion of patients experienced moderate to severe levels of lymphopenia (between 500 to 1500/mm^3). In the 12-month pooled safety period, the proportion of patients in this category was close to 40%, compared to 21% of adalimumab-treated patients. This proportion increased in the LTE up to 59% of patients receiving tofacitinib 5 mg BID.

There did not appear to be an association between neutropenia at an absolute neutrophil count (ANC) of 500/mm^3 or greater and an increased risk of infection. No patients reached ANCs of <500/mm^3. In contrast, when tofacitinib-associated lymphopenia reached absolute lymphocyte counts less than 500/mm^3, there was a clearly increased risk of infection. Eight of 10 patients experiencing this level of lymphopenia in the long-term extension developed infections, including 4 serious infections (3 events of herpes zoster—one of these patients also later developed disseminated TB) and 1 case each of pyelonephritis, urinary tract infection, pneumonia, and erysipelas.

Platelets decreased in the first month of treatment in the adalimumab and tofacitinib treatment groups and stabilized thereafter. Platelets also decreased in the placebo control group after these patients were switched to active treatment, in a similar pattern. Tofacitinib treatment did not appear to increase the risk of thrombocytopenia.

Hepatic enzyme abnormalities

Liver test abnormalities were relatively common in the RA clinical development program, but were mostly mild (1 x ULN, approximately 20% of patients). Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. Tofacitinib administration was associated with small (<10 IU/L) elevations of mean ALT and AST. Small elevations in total bilirubin (~0.05 mg/dL) were also observed, which were comparable to the changes with adalimumab (0.08 mg/dL). In monotherapy study 1045, there were no clinically significant changes in the mean values of ALT, AST and total bilirubin (data not shown), which is consistent with data from Phase 2 monotherapy studies (1019, 1035, and 1040). In LTE studies, similar small increases were documented in ALT, AST (both <5 IU/L) and total

bilirubin (~0.05 mg/dL). Significant liver test abnormalities were uncommon; 6 patients met laboratory criteria for Hy's law.

Hy's law is used during clinical development to assess a drug's potential of inducing fulminant hepatic failure with larger/longer exposure, which is a rare and usually fatal event. Approximately 10% of Hy's law cases develop acute liver failure. The components of Hy's law are:

- Evidence of hepatocellular injury by any elevated aminotransferase of >3xULN,
- Evidence of liver dysfunction by increase in bilirubin ≥2xULN and without evidence of cholestasis by ALP <2xULN
- No other cause such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Six patients, all in the LTE studies, met the laboratory criteria for Hy's law (subjects with), but five of these cases did not meet the third criterion due to the presence of significant confounding factors. The sixth case was a 32 year old woman on tofacitinib at 10 mg BID and MTX who experienced asymptomatic transaminitis while on study, had both MTX and tofacitinib discontinued, and 3 months later developed jaundice and increased transaminase levels that responded to prednisolone and azathioprine, which was suggestive of possible autoimmune hepatitis, although the patient did not have autoantibodies typically associated with autoimmune hepatitis, such as anti-smooth muscle antibodies or anti-liver/kidney microsomal antibody. Because of the lack of autoantibodies and temporal relationship to the addition of tofacitinib to this patient's regimen, Agency hepatologist Dr. John Senior concluded this case was suggestive of drug induced liver injury, and was a case meeting Hy's Law criteria.

Serum creatinine/renal function

Tofacitinib treatment was associated with a small (<0.1 mg/dL) dose- and length of exposure-dependent elevations of serum creatinine. This effect appeared to be plateauing by Month 12. To explore the effects of tofacitinib on renal function, Pfizer conducted a 14-day repeat dose study (Study 1033) of 15 mg BID in healthy volunteers and did not observe effects on renal function (measured glomerular filtration rate using iohexol serum clearance), renal plasma flow, or 24-hour urinary creatinine clearance. However, it important to note that the observed dose- and length of exposure-dependent increases in mean serum creatinine levels were associated with an increasing incidence of patients meeting the protocol criteria for discontinuation due to creatinine increases, particularly in the long-term extensions, where approximately 2% of patients were discontinued due to confirmed creatinine increases of more than 50% of baseline. There did not otherwise appear to be an increase in the proportion of patients experiencing serious adverse events of renal failure.

Lipid abnormalities

Tofacitinib treatment was associated with dose-dependent increases in total, LDL, and HDL cholesterol within one month of treatment and then generally plateaued. Mean triglycerides,

LDL levels, and HDL levels increased by approximately 15%. The overall LDL/HDL ratios did not appear to change. Internal consultation from the Division of Metabolic and Endocrine Products (DMEP) was obtained regarding the implications of these lipid parameter changes. DMEP consultants were of the opinion that the net effect of tofacitinib on cardiovascular risk in patients with RA is difficult to predict, and that a cardiovascular outcomes study would be the only way to accurately define tofacitinib's risk profile in this regard.

Serum creatine phosphokinase (CPK)

Tofacitinib treatment was associated with limited dose-dependent increases in CPK of approximately 40 to 60 IU/L over the first 6 months of therapy and plateauing thereafter. These changes did not appear to be associated with an increased risk of myopathic adverse events.

- **Immunogenicity**

As an orally administered small molecule, tofacitinib is not expected to be associated with immunogenicity.

- **Special safety concerns**

Malignancy

Table 14 below contains a summary of malignancies during the controlled period of the Phase 3 studies, and in the long term extensions. This includes a break-down of malignancies by time-interval during the controlled period of the Phase 3 studies. Note that there are small discrepancies (1-2 cases) between the 0 to 12 month summary provided by the applicant and the accounting of cases during the interval periods; therefore the numbers in the interval periods and the 0-12 month summary do not exactly match. During the controlled period, the crude incidence of malignancy was low in each treatment arm but the incidence was slightly higher in the tofacitinib 10 mg group. The exposure-adjusted incidence of malignancies was 0.6/100 patient-years in the adalimumab and tofacitinib 5 mg BID groups, but higher (0.9/100 patient-years) in the tofacitinib 10 mg group.

The rate of malignancies numerically increased in the LTE and will be further described in additional analyses below. The exposure-adjusted incidence rate in the 10 mg tofacitinib group remained higher than in the 5 mg tofacitinib group in the LTE. Overall, the types of malignancies observed followed the pattern of malignancies that would generally be expected in the underlying patient population, with certain exceptions, such as liposarcoma and synovial sarcoma. Non-melanoma skin cancer (NMSC) and solid tumors (e.g., lung and breast) occurred most commonly.

Table 14: Malignancy Summary, Phase 3 Controlled Period by Time Intervals, and LTE

Summary of Serious Adverse Events of Malignancy in Phase 3 RA Trials (by Time Intervals) and LTE									
	12-Month Pooled Safety					Long-Term Extension (LTE)***			
	PBO	ADA	CP 5 mg BID	CP 10 mg BID	CP all doses*	CP 5 mg BID	CP 10 mg BID	LTE, all doses data cut-off 29-Mar-11	Updated LTE data cut-off 29-Sep-11
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
0 to 12 Month Summary									
Total exposure, patient-years	203	178	904	910	2098	2235	881	3116	4407
Number of patients with ≥1 malignancy exc. NMSC, n (%)	0	1 (0.5)	5 (0.4)	8 (0.7)	13 (0.4)	23 (1.7)	12 (0.6)	35 (1.1)	50 (1.4)
Rate per 100 patient-years	0	0.6	0.6	0.9	0.7	1.0	1.4	1.1	1.1
Malignancy Type, n (rate per 100 patient-years)									
Solid Tumors	-	1 (0.6)	5 (0.6)	7 (0.8)	12 (0.6)	21 (1.0)	12 (1.4)	33 (1.1)	48 (1.1)
Top 3: Lung cancer	-	*1 (0.6)*	*2 (0.2)*	*1 (0.1)*	*3 (0.1)*	*3 (0.1)*	*5 (0.6)*	*8 (0.3)*	*12 (0.3)*
Breast cancer	-	-	-	*3 (0.3)*	*3 (0.1)*	*5 (0.2)*	*1 (0.1)*	*6 (0.2)*	*8 (0.2)*
Gastric cancer	-	-	*1 (0.1)*	-	*1 (<0.1)*	*2 (0.1)*	-	*2 (0.1)*	*4 (0.1)*
Hematologic	-	-	-	1 (0.1)	1 (<0.1)	2 (<0.1)	-	2 (<0.1)	2 (<0.1)
NMSC	2 (1.0)	2 (1.1)	3 (0.3)	5 (0.6)	8 (0.4)	7 (0.3)	6 (0.7)	13 (0.4)	23 (0.5)
0 to 3 Month Interval									
Number of patients in group	681	204	1216	1214	2430				
Total patients with ≥1 malig., n (%)	0	0	4 (0.3)	4 (0.3)	8 (0.3)				
Malignancy Type, n									
Solid Tumors	-	-	*3*	*4*	*7*				
Hematologic	-	-	-	-	-				
NMSC	-	-	*1*	-	*1*				
3 to 6 Month Interval									
Number of patients in group	221	204	1451	1439	2890				
Total patients with ≥1 malig., n (%)	2 (0.9)	0	2 (0.1)	3 (0.2)	5 (0.2)				
Malignancy Type, n									
Solid Tumors	*1*	-	*2*	*3*	*5*				
Hematologic	-	-	-	-	-				
NMSC	*1*	-	-	-	-				
>6 Months Interval**									
Number of patients in group	-	204	1056	1046	2102				
Total patients with ≥1 malig., n (%)	-	1 (0.5)	2 (0.2)	2 (0.2)	4 (0.2)				
Malignancy Type, n									
Solid Tumors	-	*1*	*2*	*1*	*3*				
Hematologic	-	-	-	*1*	*1*				
NMSC	-	-	-	-	-				

Sources: Summary of Clinical Safety (data cut-off March 29, 2011), Tables 110-112 and 120-Day Safety Update, adapted from tables 34-47 Integrated Safety Analysis on Malignancy, Tables 12 to 18, and 40
CP=CP-690,550, also known as tofacitinib; n.r. = not reported; SOC = System-Organ-Class
*CP All Doses group represents data for patients as treated and includes patients originally assigned to tofacitinib 5 or 10 mg BID as well as patients escaped to or transitioned by design to tofacitinib 5 mg or 10 mg BID
**This interval applicable only to Studies 1044, 1046 and 1064
***LTE includes patients from Phase 2 studies as well

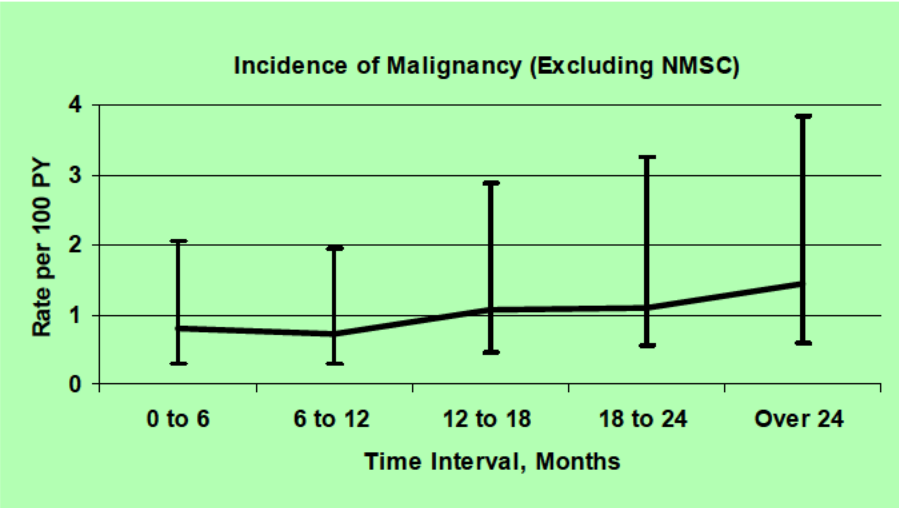
A breakdown of malignancies by 6-month time interval in the RA clinical development program may be found in Table 15 and Figure 8 below. These data include the Phase 2 RA studies. A concerning finding is the numerical increase in malignancy incidence when comparing the first 12 months versus the second 12 months and the third 12 month period. Although confidence intervals overlap, this would not be unexpected given that the studies were not powered to detect a difference in malignancies, and the Agency does not typically expect a statistical difference in safety outcomes to be shown in studies designed to demonstrate efficacy. This pattern is consistent with a scenario where increasing exposure to tofacitinib increases the risk of malignancies. At the March 9, 2012 Advisory Committee meeting, Pfizer presented data for Month 24 to Month 36 and Month 36 to Month 48 instead of the grouping of "≥24 months" presented below. In those analyses, the malignancy rate appeared to steeply drop. However, as there are few patients in the time intervals beyond 24 months (and the patients in those intervals are predominantly with the 5 mg dose), those data do not reassure that the trend of increasing risk is not present, particularly with the 10 mg BID dose.

Table 15: Incidence Rates of Malignancies over Time in Phase 2, Phase 3, and LTE RA Studies, Excluding Non-melanoma Skin Cancer

	0 to 6 Months	6 to 12 Months	12 to 18 Months	18 to 24 Months	>24 Months
Total no. patients	4791	4012	3126	2054	941
No. (%) patients with events	17 (0.35)	13 (0.32)	13 (0.42)	8 (0.39)	14 (1.49)
Exposure for event (pt-yr)	2166.0	1811.0	1229.1	736.7	976.1
Incidence rate, in events per 100 pt-yr (95% CI)	0.785 (0.488, 1.263)	0.718 (0.417, 1.236)	1.058 (0.614, 1.821)	1.086 (0.543, 2.171)	1.434 (0.850, 2.422)

CI=confidence interval; pt-yr=patient-years.
Cases based on safety database.
Patients' exposure time is counted from first dose of CP in the index study through last known dose in the extension study.
Some events may have occurred after the end of treatment; these events were counted in the numerator and patients' full CP treatment exposure was included in denominator.
Includes Protocols A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044(1 year), A3921045, A3921046, A3921064 and A3921109.
Source: Sponsor's Table 36 in the 120-day safety update; data-cutoff date 29 Sep 2011

Figure 8: Graphical Representation of Malignancies per 6-month Time Interval



Source data are from Table 36 of the 120-day safety update

A final malignancy-related concern pertains to whether tofacitinib might increase the risk of lymphoproliferative disorders specifically. This concern was raised by the recurrent presence of lymphoma cases in the development program, including the nonclinical program and clinical development in other indications, as will be described in further detail below.

Nonclinical lymphoma findings

A 39-week chronic toxicology study in cynomolgus monkeys was performed, which evaluated CP-690,550 at doses of 0, 0.5, 2, or 10 mg/kg/day (4 monkeys per sex per group). Three of eight monkeys in the high dose group (10 mg/kg/day) developed lymphomas. Two of the 3 lymphomas were B cell lymphomas and positive for lymphocryptovirus by

immunohistochemical positive for Epstein-Barr Virus (EBV)-encoded small RNA (EBNA-2) and in situ hybridization for the EBER-1 gene staining. One of 3 monkeys had a lymphoma in the peri-thymic fat that was determined to be a T-cell lymphoma based on immunohistochemical staining. Pfizer's conclusion was that "effects of exaggerated pharmacology were observed at a dose of 10 mg/kg/day and the target tissues were red blood cells, peripheral blood lymphocytes, and lymphoid tissues. The lymphoproliferative changes observed in this study, including the development of malignant lymphomas, are consistent with gamma herpesvirus-induced lymphoproliferative disorder observed in immunosuppressed monkeys."[9]

Lymphoma in the Post-Transplant Setting

Five cases of post-transplant lymphoproliferative disorder (PTLD) were reported in 218 tofacitinib-treated patients in a renal allograft Phase 2b study, for a cumulative incidence of 2.3%. In that study, patients were randomized 1:1:1 to one of two CP-690,550 (tofacitinib) regimens or to a cyclosporine control regimen. One tofacitinib arm was dosed at 15 mg BID for the first 6 months, then reduced to 10 mg BID, and the other arm received 15 mg BID for the first 3 months, then reduced to 10 mg BID. A summary of these cases is as follows:

- A 62 year old male who developed a lymphoproliferative disorder involving the brain, stomach, colon, and pericardium (EBV positive) after ~9 months of exposure
- A 39 year old male who developed a Non-Hodgkin's Lymphoma (NHL) of the brain (EBV positive) after ~10 months of exposure
- A 53 year old male who developed post-transplant Hodgkin's Lymphoma of the lungs (EBV positive) after ~10 months of exposure
- A 71 year old male who developed NHL of the brain (EBV positive) after ~19 months of exposure
- A 46 year old male who developed large B-cell lymphoma of the brain (EBV positive) after ~29 months of exposure

No patients randomized to the cyclosporine control regimen in the study were reported with a PTLD during the same time period.

Per recent reviews, the incidence of PTLD in renal transplant recipients would be expected to be up to 1 to 2%[10], and CNS PTLD comprises approximately 10 to 20% of cases.[11] Thus, the findings in the aforementioned study appear to suggest increased risk with tofacitinib.

[9] Study Report for Study 2003-0301, pg. 6
[10] Sampaio et al., "Impact of Epstein Barr virus donor and recipient serostatus on the incidence of post-transplant lymphoproliferative disorder in kidney transplant recipients." Nephrol Dial Transplant 2012, Jan 24 [Epub ahead of print]
[11] Jagadeesh et al., "Post transplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations." Current Treatment Options in Oncology 2012, 13:122-136

Lymphoma in RA

A total of 7 cases of lymphoproliferative disorder had been reported as of the writing of this document—5 cases as of the 120-day safety update (data cut-off date September 29, 2011) and 2 cases reported since that update:

- A 78 year old female on CP-690,550 at 5 mg BID + MTX developed Primary CNS diffuse B-cell lymphoma (EBV negative) after 818 days of exposure
- A 51 year old female on CP-690,550 at 5 mg BID developed a lymphoproliferative disorder involving the abdominal lymph nodes (EBV positive) after 227 days of exposure
- A 61 year old female on CP-690,550 at 5 mg BID developed mantle cell lymphoma (blastoid variant) after approximately 9 months of exposure
- A 47 year old female on CP-690,550 at 10 mg BID + MTX developed lymphoma of the thymus after 220 days of exposure
- A 69 year old female on CP-690,550 at 10 mg BID + MTX developed diffuse large B-cell lymphoma of the breast after 642 days of exposure
- A 65 year old male on CP-690,550 at 10 mg BID developed Non-Hodgkin's lymphoma (high grade B-cell Burkitt-like lymphoma) after 149 days of exposure
- A 63 year old male whose therapy has not yet been unblinded developed "lymphoproliferation" after 449 days of exposure.

No cases have yet been identified as occurring in the placebo controlled treatment groups of the studies, acknowledging that exposure in the placebo control groups is much less than the exposure to tofacitinib in these studies.

There is general agreement that the underlying risk of lymphoma is increased in RA patients, so whether the observed cases in the tofacitinib RA clinical development program represent an additional risk is difficult to determine. However, the presence of atypical lymphomas such as CNS lymphoma and breast lymphoma, the findings of lymphoma in the nonclinical program, and the likelihood of increased risk in the post-renal transplant setting are suggestive of a consistent safety signal of increased risk.

Infections

Infections leading to death

In the RA clinical development program for tofacitinib, through the 120-day safety update (data cut-off September 29, 2011), a total of 15 patients died as a consequence of infection—12 patients died of pneumonia, one from pyelonephritis, one from appendicitis, and one from septic arthritis. All cases occurred in tofacitinib-treated patients except the one case of pyelonephritis occurring in a placebo-treated patient. The pattern of serious infections and deaths related to serious infection is consistent with a conclusion that tofacitinib is associated with significant immunosuppression.

Serious nonfatal infections

During the 12-month pooled safety period, the proportion of patients experiencing a serious infection was increased in the tofacitinib groups (3 to 3.2/100 patient-years) compared to the placebo control group (1.5/100 patient-years) and the adalimumab control group (1.7/100 patient-years). In the LTE, the proportion of patients experiencing a serious infection was similar in the tofacitinib 5 mg group (2.3/100 patient-years), but was increased in the tofacitinib 10 mg group (4.9/100 patient-years). The most common serious infection by far was pneumonia. Cellulitis, abscesses, and herpes zoster events were also common serious infections. In general, the rates of serious infection and types of serious infection observed are consistent with other immunosuppressive products approved for the treatment of RA, although variability in the data makes it difficult to be definitive.[12]

Table 16: Serious Infectious Events (SIE) in Phase 3 RA Trials (by Time Intervals) and LTE

Summary of Serious Adverse Events of Infection in Phase 3 RA Trials (by Time Intervals) and LTE									
	12-Month Pooled Safety					Long-Term Extension (LTE)***			
	PBO	ADA	CP 5 mg BID	CP 10 mg BID	CP all doses*	CP 5 mg BID	CP 10 mg BID	LTE, all doses data cut-off 29-Mar-11	Updated LTE data cut-off 29-Sep-11
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
0 to 12 Month Summary									
Total exposure, patient-years	203	179	901	909	2094	2222	879	3101	4378
Total number of SIEs	6	4	33	30	63	76	58	134	172
Patients with ≥1 SIE, n (%)	3 (0.4)	3 (1.5)	29 (2.4)	27 (2.2)	61 (2.0)	50 (3.8)	43 (2.3)	93 (2.9)	131 (3.7)
Incidence of SIE events per 100 patient-years	3.0	2.2	3.7	3.3	3.0	3.4	6.6	4.3	3.9
Incidence of affected patients per 100 patient-years	1.5	1.7	3.2	3.0	2.9	2.3	4.9	3.0	3.0
Most common preferred terms, n (rate per 100 patient-years)									
Pneumonia	-	-	*11 (1.2)*	*6 (0.7)*	*17 (0.8)*	*17 (0.8)*	*13 (1.5)*	*30 (1.0)*	*40 (0.9)*
Cellulitis	-	*2 (1.1)*	*6 (0.7)*	*1 (0.1)*	*7 (0.3)*	*3 (0.1)*	*4 (0.5)*	*7 (0.2)*	*9 (0.2)*
Herpes zoster	-	-	*4 (0.4)*	*1 (0.1)*	*5 (0.2)*	*7 (0.3)*	*1 (0.1)*	*9 (0.3)*	*10 (0.2)*
Abscess	-	*1 (0.6)*	*3 (0.3)*	*1 (0.1)*	*4 (0.2)*	*3 (0.1)*	*8 (1.0)*	*11 (0.4)*	*11 (0.3)*
Gastroenteritis	*1 (0.5)*	-	*1 (0.1)*	*1 (0.1)*	*2 (0.1)*	*3 (0.1)*	*3 (0.3)*	*6 (0.2)*	*11 (0.3)*
0 to 3 Month Interval									
Number of patients in group	681	204	1216	1214	2430				
Total patients with ≥1 SIE, n (%)	2 (0.3)	0	11 (0.9)	12 (1.0)	n.r.				
3 to 6 Month Interval									
Number of patients in group	221	204	1451	1439	2890				
Total patients with ≥1 SIE, n (%)	3 (1.4)	2 (1.0)	10 (0.7)	8 (0.6)	n.r.				
>6 Months Interval**									
Number of patients in group	-	204	1056	1046	2102				
Total patients with ≥1 SIE, n (%)	-	2 (1.0)	12 (1.1)	13 (1.2)	n.r.				

Sources: Summary of Clinical Safety (data cut-off March 29, 2011), Tables 68 and 93; and 120-Day Safety Update, adapted from tables 18, 23
Integrated Safety Analysis on Infection, Tables 18
CP=CP-690,550, also known as tofacitinib; n.r. = not reported
*CP All Doses group represents data for patients as treated and includes patients originally assigned to tofacitinib 5 or 10 mg BID as well as patients escaped to or transitioned by design to tofacitinib 5 mg or 10 mg BID
**This interval applicable only to Studies 1044, 1046 and 1064
***LTE includes patients from Phase 2 studies as well

Opportunistic Infections and Tuberculosis

No cases of OI or TB were noted in the placebo or adalimumab control groups of the Phase 3 RA Trials. However there were 3 patients (0.2%) in the tofacitinib 5 mg BID group and 10 patients (0.8%) in the tofacitinib 10 mg BID group who experienced opportunistic infections during the 12-month pooled safety period. Six patients (0.5%) in the tofacitinib 10 mg BID

[12] DE Furst, "The risk of infections with biologic therapies for rheumatoid arthritis." Semin Arthritis Rheum 2010, 39:327-346

group and no patients in the tofacitinib 5 mg BID group experienced infection with TB during the 12-month pooled safety period. Proportions of patients experiencing OI or TB events in the LTE were similar or lower.

In the RA development program as a whole (not limited to the Phase 3 trials and LTE), a total of 34 opportunistic infections, including TB, have been reported; all of which have occurred in tofacitinib-treated patients. These include 14 patients who developed TB, 7 patients with esophageal candidiasis, 4 patients with cytomegalovirus (CMV) infection, 3 patients with Pneumocystis pneumonia, 2 patients with cryptococcal infection (1 pneumonia, 1 meningitis), 2 patients with atypical mycobacterial infection, 1 patient with BK virus encephalitis, and 1 patient with disseminated Herpes zoster.

The number and pattern of opportunistic infections observed with tofacitinib treatment suggests significant immunosuppression that is apparent with both doses, although somewhat higher with the 10 mg BID dose.

Herpes Zoster

Herpes zoster events were common in the tofacitinib Phase 3 RA trials and LTE, and occurred more frequently in the tofacitinib groups compared to the control groups. Approximately 3% of tofacitinib-treated patients experienced a herpes zoster event during the 12-month pooled safety period compared to 0.4% of placebo-treated patients. In the LTE, 7% of patients receiving tofacitinib 5 mg BID and 2% of patients receiving 10 mg BID experienced a herpes zoster event. Serious herpes zoster events were relatively infrequent, and only occurred with tofacitinib treatment.

Cardiovascular Adverse Events

Cardiovascular disorders were identified as events of interest for monitoring and analyses because of tofacitinib-induced change in lipid parameters (an approximate 15% increase in triglycerides, LDL, and HDL). Thus pre-specified monitoring and adjudication of cardiovascular events were incorporated into the RA Phase 3 program. The adjudication of CV events was performed in a blind fashion by an external Cardiovascular Safety Endpoint Adjudication Committee (CV-SEAC) consisting of three cardiologists and governed by a Charter.

The endpoint of major adverse cardiovascular events (MACE) was defined as the composite of the following:

- CV death: coronary, cerebrovascular, cardiac (e.g., sudden cardiac death), and non-cardiac vascular (e.g., pulmonary embolism)
- Non-fatal CV events: myocardial infarction, cerebrovascular events

The overall baseline cardiovascular risk profile was low and comparable among the treatment arms in the Phase 3 program. The proportion of patients with 2 or more coronary risk factors was around 22% and only 10-13% of the Phase 3 population had a 10-year Framingham risk of over 10%.

The few MACE events that were observed during the trials occurred at similar rates in tofacitinib treatment groups (0.4/100 patient-years in the 5 mg group, 0.7/100 patient-years in the 10 mg group) compared to the placebo group (1/100 patient-years). Importantly, the exposure-adjusted rates from the LTE studies remained consistent with the rates observed during the controlled periods of the Phase 3 studies.

- **Discussion of primary reviewer's comments and conclusions**
- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**

Dr. Nikolov and I are in agreement that the currently submitted safety data and analyses are adequate to inform the decision regarding the benefit-risk profile of the product. The safety data submitted for tofacitinib suggests it is associated with significant immunosuppression, as manifested by increased risks of serious infection and malignancy, as well as important laboratory abnormalities such as lymphopenia and cholesterol elevation. Some of these risks appeared to have a dose- and exposure- dependent increase, such as serious infections, malignancy, and mechanism-of-action-related laboratory abnormalities such as lymphopenia and anemia.

Safety concerns such as these are not uncommon with the immunosuppressive agents utilized to treat rheumatoid arthritis, and are therefore not issues that necessarily preclude approval. However, increasing risk of malignancy over time with longer exposure would be a concerning finding that has not been observed with other approved RA treatments. Because of this concern, the higher exposure-adjusted incidence of malignancy with the 10 mg BID dose regimen compared to the 5 mg BID dose regimen, and the small incremental increase in efficacy, Dr. Nikolov and I agree that the benefit-risk of 10 mg BID is not favorable based on the currently available data.

To further address dose and exposure dependent safety concerns, as well as potential cardiovascular risks associated with treatment-related lipid changes, we recommend a long-term active-controlled safety study to be done as a postmarketing requirement.

- **Discussion of notable safety issues (resolved or outstanding)**.

1) Pfizer's safety pooling and integration strategy
Pfizer's pooling and integration strategy (described above at the beginning of Section 8) was consistent with other historical programs in RA and thus was not flagged as a concern at the pre-NDA meeting for this application. However, on further evaluation, members of the review team determined that additional safety analyses were warranted as follows:

- Phase 2 dose-ranging studies 1025 and 1035 were of sufficiently similar design and patient population that they should be included in all integrated safety analyses (they were only included in analyses of the adverse events of interest in the original submission)
- Studies done only in Japan should be excluded from the analyses due to differences in patient population such as background medication use. This would affect the integrated

analyses of adverse events of interest and of the long-term extension, since all Phase 2 RA studies were included in the original submission analyses.

- To assess the safety profile of 5 mg BID relative to 10 mg BID for the 0 to 6 and 6 to 12 month periods of the 7 studies (the 5 submitted Phase 3 studies along with Study 1025 and Study 1035), for adverse events of interest, integrated analyses stratified by study, using Poisson regression with an offset term to account for differing exposure times and study, to account for differing patient populations and/or study designs, as follows:
    - Only patients originally randomized to tofacitinib 5 mg BID and 10 mg BID
    - Patients originally randomized to tofacitinib 5 and 10 mg BID plus patients who transitioned to tofacitinib 5 and 10 mg BID by study design (Month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064)
    - Patients originally randomized to tofacitinib 5 and 10 mg BID plus patients who transitioned to tofacitinib 5 and 10 mg BID by study design plus patient who escaped to tofacitinib 5 and 10 mg BID due to active disease.
- Sensitivity analyses of the integrated analyses by time intervals where patients are accounted for by treatment and duration of treatment. For example, in the 0 to 3 month analyses, if a placebo patient escaped to tofacitinib due to uncontrolled disease activity or transitioned to tofacitinib by design and had an adverse event at Month 4, that placebo patient would be counted twice—once in the placebo group (no adverse event, but counted in the denominator), and once in a tofacitinib group (counted as having the adverse event, and also counting in the denominator), as they will be in the first 3 months of treatment with tofacitinib.
- Kaplan-Meier Plots from 0 to 12 months for each adverse event of interest. This will be done by pooling the 7 studies and using the randomized sequence (i.e., 5 mg BID, 10 mg BID, placebo to 5 mg BID, and placebo to 10 mg BID).

The bulk of these analyses will be submitted July 30, 2012. The sensitivity analyses require new datasets and will take longer.

2) The following Postmarketing Requirement is warranted:

A controlled clinical trial to evaluate the long term safety of tofacitinib in patients with rheumatoid arthritis—the trial should include two doses of tofacitinib and an active comparator. The trial should be of sufficient size and duration to evaluate safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy.

9. Advisory Committee Meeting

This NDA was discussed at the May 9, 2012 Arthritis Advisory Committee meeting. The following is a brief summary of the questions to the committee and surrounding discussions. The reader is also referred to the full transcript of the meeting that will be available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm286552.htm

1) **DISCUSSION:** Discuss the radiographic outcomes data for the 5 mg and 10 mg doses of tofacitinib and the impact of these data on the overall assessment of efficacy of tofacitinib for the treatment of rheumatoid arthritis.

Committee Discussion: *The committee agreed that the radiographic outcomes data for the 5 mg and 10 mg doses of tofacitinib was limited given the missing data and methods used for imputation. However, the committee agreed that radiographic studies are a difficult standard to meet in order to demonstrate efficacy, and noted that the sponsor's studies were especially challenging given the limited placebo exposure in the trial design. The committee agreed that there was a positive response in both drug groups although not definitive. When assessing the overall efficacy of tofacitinib for the treatment of rheumatoid arthritis, the committee agreed that they would also consider the other measured clinical parameters (ACR20 ACR50, ACR70, DAS28-4(ESR), etc.). If this drug product were approved, the committee stated that they would like to see more long term data demonstrating radiographic improvement.*

2) **DISCUSSION:** Discuss the safety data for tofacitinib

   a. Address the following safety issues:

      (1) Malignancy overall, and lymphoma in particular
      (2) Serious infections
      (3) Abnormal hematologic parameters
      (4) Lipid parameter changes
      (5) Cardiovascular safety profile

Committee Discussion: *The committee agreed that there are concerns with this drug for the following safety issues: malignancy, lymphoma, infections, abnormal hematologic parameters, lipid parameter changes, and cardiovascular disease. The committee stated that the rheumatoid arthritis patient population is already at risk for these issues, and that the data suggests that tofacitinib might increase their risk over time, especially for malignancy and infections. Due to limited long term safety data, the committee expressed concern for the unknown risks to patients if given chronically. Therefore, the committee suggested that more long term safety data, either pre-marketing or post-marketing, be collected in order to fully understand the risks to this patient population.*

   b. Include a discussion of the overall safety profile of the 5 mg dose and the 10 mg dose, and whether the data are more favorable for one dose versus the other.

Committee Discussion: *Given the overall safety profile of the 5 mg and 10 mg dose, the committee agreed that the safety data are more favorable for the 5 mg dose. The committee agreed that there was a concern for over-immunosuppression and malignancy with the 10 mg dose, especially if given with other immunosuppressives. However, the committee agreed that the 10mg dose might be a viable option for refractory patients who are willing to accept the risk of treatment.*

3) **DISCUSSION:** Discuss whether the dose and dosing frequency selected are adequately supported by the existing dose exploration data and the pharmacokinetic profile of tofacitinib.

Committee Discussion: *The committee agreed that the starting dose of tofacitinib 5 mg twice a day was supported by the existing dose exploration data and the pharmacokinetic profile of tofacitinib. However, the committee stated that there was a concern for the use of the 10 mg dose. The committee also noted that the 3 mg dose of tofacitinib displayed similar efficacy to a comparator, adalimumab, and they suggested that further studies into lower doses might be warranted. The committee stated that these lower doses of tofacitinib would offer the option of individualized dosing for at-risk patients given the safety profile of this drug.*

4) **VOTE:** Do the data provide substantial evidence of the efficacy of tofacitinib for radiographic outcomes?

Vote: Yes= 2 No = 8 Abstain = 0

Committee Discussion: *The majority of the committee did not agree that the data provided substantial evidence for the efficacy of tofacitinib for radiographic outcomes. However, the committee agreed that the radiographic data was encouraging. The committee stated that the data was lacking in quality and did not meet the FDA standards for substantial evidence.*

a. If not, what further data should be obtained?

Committee Discussion: *The committee agreed that a second study demonstrating positive results would make the evidence more substantial.*

Please see the transcript for details of the committee discussion.

5) **VOTE:** Overall, do the data provide substantial evidence of the efficacy of tofacitinib for the treatment of moderately to severely active rheumatoid arthritis in patients who have had inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs)?

Vote: Yes= 10 No = 0 Abstain = 0

Committee Discussion: *The committee unanimously agreed that the data provide substantial evidence of the efficacy of tofacitinib for the treatment of moderately to severely active rheumatoid arthritis in patients who have had inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). The committee agreed that the efficacy of tofacitinib was compelling across all five studies and was demonstrated to be at least as good as the comparators.*

a. If not, what further data should be obtained?

Committee Discussion: *Since the vote for question #5 was unanimously "Yes", there was no discussion about what further data should be obtained.*

Please see the transcript for details of the committee discussion.

6) **VOTE:** Is the safety profile of tofacitinib adequate to support approval of tofacitinib for the treatment of moderately to severely active rheumatoid arthritis in patients who have had inadequate response to one or more DMARDs?

Vote: Yes= 7 No = 2 Abstain = 1

Committee Discussion: *The majority of the committee agreed that the safety profile of tofacitinib is adequate to support approval of tofacitinib for the treatment of moderately to severely active rheumatoid arthritis in patients who have had inadequate response to one of more DMARDs. The committee members further specified that this drug should be started at a 5 mg dose and be titrated up as needed. The committee members who voted "No" stated that there were other agents for this indication with which the safety profile is better understood and that the proposed indication is too broad. Based on its current safety profile, these committee members stated that tofacitinib should be reserved for patients who have tried these other agents and are willing to take on unknown risks.*

a. If not, what further data should be obtained?

Committee Discussion: *The committee agreed that stringent post-marketing studies, such as large registries and systematic patient-centered pharmacovigilance, are warranted in order to elucidate long-term safety data.*

Please see the transcript for details of the committee discussion.

7) **VOTE:** Do the efficacy and safety data provide substantial evidence to support approval of tofacitinib for the treatment of moderately to severely active rheumatoid arthritis in patients who have had inadequate response to one or more DMARDs?

Vote: Yes= 8 No = 2 Abstain = 0

Committee Discussion: *The majority of the committee agreed that the efficacy and safety data provide substantial evidence to support the approval of tofacitinib for the treatment of moderately to severely active rheumatoid arthritis in patients who have had inadequate response to one or more DMARDs. However, the committee stated that tofacitinib should only be considered after attempting treatment with another biologic agent given that the currently available biologics have more efficacy and safety data. They further stated that tofacitinib should be initiated at a dose of 5 mg twice daily and escalated as needed.*

a. If not, what further data should be obtained?

Committee Discussion: *The committee members who voted "No" reiterated that the proposed indication targets too broad patient population and long-term safety data should be collected in order to fully understand the risks to this patient population.*

10. Pediatrics

- **Peds exclusivity board review - PPSR/WR**

Pfizer submitted a Proposed Pediatric Study Request (PPSR) on October 31, 2011, 10 days after submitting NDA 203214. Because the due date for a decision regarding the PPSR was early in the review cycle (February 28, 2012), before an adequate assessment of the benefit-risk profile of the product could be made, the PPSR was denied as premature.

- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment**

Polyarticular juvenile idiopathic arthritis (PJIA) has been considered the juvenile equivalent of adult rheumatoid arthritis, and thus a study in PJIA patients would be required by the Pediatric Research Equity Act (PREA) if this NDA in RA patients is approved. With this NDA, Pfizer submitted a request for a partial waiver for children under 2 years of age, because studies in this age group are impossible or highly impractical due to the rarity of PJIA in children under 2 years of age. A deferral was requested for children ages 2 to <17 years of age because studies in adults are complete and ready for approval.

(b) (4)

(b) (4)

The tofacitinib pediatric program was discussed at the Pediatric Review Committee (PeRC) meeting on July 11, 2012. The PeRC agreed with the requested waiver and deferral. Regarding the PPSR, should it be resubmitted, PeRC mentioned that any written request would need to include all the pediatric populations that would potentially benefit from tofacitinib. Due to its mechanism of action, it is likely that this would include other inflammatory disease populations (such as pediatric inflammatory bowel disease) and possibly pediatric oncology patients.

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**

Three clinical sites covering study protocols for 1044, 1045, 1046, and 1064 were selected for inspection—one in the United States, one in Brazil, and one in Poland. In addition, Pfizer's site in Groton, CT was also inspected. In each case, inspection findings supported the acceptability of the clinical data submitted.

- **Other discipline consults**—Not applicable
- **Any other outstanding regulatory issues**—Not applicable

12. Labeling

- **Proprietary name**

The proposed proprietary name for tofacitinib is Xeljanz. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of

Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing and Advertising) and was found to be acceptable.

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

At the time of this review, the Office of Medication Error Prevention and Risk Management has provided interim comments on the proposed Risk Evaluation and Mitigation Strategy (REMS) originally submitted by Pfizer. These comments have been relayed to Pfizer and are anticipated with the revised REMS that has been requested based on the risks identified during the course of this review, including serious infection, malignancy, and laboratory abnormalities.

- **Physician labeling**

Major issues with the currently proposed labeling (version submitted 2-8-12 or earlier):

(b) (4)

1 Page Of Draft Labeling Has Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

- [redacted] (b) (4)

As of the time of this review, the review team is waiting on submission of revised labeling and REMS in order to finalize necessary revisions.

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

As discussed above.

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

Requested revisions from DMEPA have been relayed and revised carton and container labels are pending.

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

Review by the Office of Medication Error Prevention and Risk Management has not been completed pending submission of a revised Medication Guide.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of the 5 mg BID dose regimen of tofacitinib for the treatment of adult patients with rheumatoid arthritis who have had inadequate response to or are intolerant of methotrexate.

- **Risk Benefit Assessment**

1) Analysis of condition
Rheumatoid Arthritis (RA) is a serious inflammatory disease that results in premature morbidity and mortality and disability if left untreated. Before the current era of highly effective treatments, the natural history of RA generally followed 3 typical courses—progressive disease, which occurred in 70% of patients and was characterized by an invariable trend towards progressive joint destruction; intermittent disease, which occurred in 25% of patients where flares of arthritis were followed by intermissions for variable periods; and "malignant" RA, which was uncommon but included severe extra-articular disease (including

vasculitis) which was often fatal.[14] Early, aggressive treatment with Disease Modifying Anti-Rheumatic Drugs (DMARDs) appears to have altered the course of RA, although the details of this are difficult to characterize over the long-term. Because of the severity of the untreated disease, potent immunosuppressives have been commonly used in the treatment RA, with their incumbent risks, such as an increased susceptibility to serious infection.

2) Unmet medical need

As noted in Section 2 of this memorandum, there are 9 targeted biologic DMARDs currently approved for RA, but these are all injectable products for either subcutaneous or intravenous administration. Of the 8 oral small molecules approved for RA (not including nonsteroidal anti-inflammatory drugs, which are used for adjunctive analgesia), methotrexate is the predominant and typically foundational DMARD that is used, although sulfasalazine and leflunomide are also used. Hydroxychloroquine and chloroquine are also used in combination with other DMARDs for possible additive effects, although they are not approved specifically for RA. Gold (auranofin), cyclosporine, and penicillamine have some beneficial effects, but their use is limited by significant toxicities. The last orally administered DMARD approved is leflunomide (1998). Thus, there are a limited number of orally administered DMARD options that are commonly used, and a new orally administered DMARD would be a welcome addition to the therapeutic armamentarium for RA.

3) Benefits

- As described in Section 7 above, all five submitted Phase 3 studies provided corroborating evidence of the efficacy of tofacitinib for reducing the signs and symptoms of RA, based on the proportion of patients experiencing improvement in the ACR response criteria and reduction in DAS28 to less than 2.6. The proportion of patients experiencing improvement in the tofacitinib 5 mg BID and 10 mg BID treatment groups was similar, albeit slightly higher with the 10 mg BID regimen.
- Four of the five Phase 3 studies provided corroborating evidence of the efficacy of tofacitinib for improving physical function, as measured by HAQ-DI. Similar results were observed in the fifth study (Study 1044) but due to the hierarchical ordering of endpoints, statistical testing could not formally be done for both doses. The level of improvement, based on mean change from baseline, was similar for both dose regimens.
- The effect of tofacitinib on structural damage progression, as assessed by radiographs, was evaluated in a single study (Study 1044). These results were suggestive of a possible benefit, but it was not possible to make definitive conclusions about the treatment effect of tofacitinib on structural damage progression. The small treatment effect size was susceptible to change depending on analytical approach, missing data, and missing data imputation method, and the primary analysis results were driven by few extreme observations that were often derived (i.e. extrapolated) data.

4) Risks

- The risks associated with tofacitinib are consistent with significant immunosuppression. Tofacitinib treatment was associated with an increased risk of serious infections, including

[14] DL Scott and S Steer, "The course of established rheumatoid arthritis," Best Practice & Research Clinical Rheumatology 2007, 21(5):943-967.

tuberculosis and opportunistic infections. Infections, and especially tuberculosis infection, appeared to be dose and exposure-related.

- Tofacitinib treatment was associated with an increased risk of malignancy that appeared to be dose-dependent but also length of exposure-related (i.e., possible increasing risk over time). The latter potential risk was not well characterized in the submitted data, as the vast majority of data from greater than 24 months' exposure was only with the 5 mg BID dose regimen. Therefore further evaluation is warranted in the postmarketing period, if tofacitinib is approved. There also appeared to be a specific increased risk for lymphoma.
- Tofacitinib treatment was also associated with laboratory abnormalities in hematologic parameters, lipid parameters, liver enzyme elevations, and serum creatinine elevations. This included dose-dependent neutropenia, and progressive lymphopenia, which was also associated with increased risk of infection. Dose-dependent elevations occurred in total cholesterol, LDL, and HDL, but these were not associated with an increase in cardiovascular events during the timeframe of the clinical trials. Liver enzyme elevations were mostly mild, but one case meeting Hy's law criteria was identified in which drug-induced liver injury could not be excluded. Small elevations in serum creatinine were also noted, but did not otherwise appear to be associated with an increased risk of renal injury or impairment.

5) Benefit-Risk Overview

Based on the data in this submission, the seriousness of RA, and the need for additional orally administered therapies, the benefit-risk profile of tofacitinib in RA is adequately favorable to support approval in the 5 mg BID dose regimen. (b) (4)

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

A Risk Evaluation and Mitigation Strategy (REMS) is warranted that should include a communication plan and medication guide. The communication plan and medication guide should include discussion of the risks of serious infection and malignancy, as well as the laboratory abnormalities and recommended monitoring.

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

1. Nonclinical Male Fertility Study in rats

2. Controlled clinical trial to evaluate the long term safety of tofacitinib in patients with rheumatoid arthritis. The trial should include two doses of tofacitinib and an active comparator. The trial should be of sufficient size and duration to evaluate safety events

of interest, including cardiovascular adverse events, opportunistic infections, and malignancy.

3. Assessment of pharmacokinetic parameters and dosing, efficacy, and safety of tofacitinib in the pediatric population ≥2 years to <17 years with polyarticular JIA (to address PREA)

- **Recommended Comments to Applicant**

None.

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

/s/

SARAH K YIM
07/20/2012