

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203214Orig1s000**

**OFFICE DIRECTOR MEMO**

## Summary Basis for Regulatory Action

<b>Date</b>	November 6, 2012
<b>From</b>	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
<b>Subject</b>	Summary Review
<b>NDA/BLA #</b>	203214
<b>Supp #</b>	
<b>Applicant Name</b>	Pfizer
<b>Proprietary / Established (USAN) Names</b>	Xeljanz (tofacitinib)
<b>Dosage Forms / Strength</b>	5 and 10 mg tablets given twice a day
<b>Proposed Indication(s)</b>	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)
<b>Action:</b>	<i>Approval</i>

### 1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding tofacitinib. Please refer to the action package for other reviews containing more detailed discussion. Tofacitinib is a new molecular entity (NME) that inhibits Janus Associated Kinases (JAK) that is proposed for the treatment of adult patients with RA with inadequate response to one or more DMARDs. Tofacitinib is a small molecular entity and allows for oral dosing as opposed to that of biologic agents, which require injection, and is the first JAK inhibitor seeking approval for the treatment of RA.

Tofacitinib's inhibition action is promiscuous affecting multiple JAK family members (JAK1, JAK2, JAK3, TYK2). JAK signaling is involved in multiple pathways, such as colony-stimulating factor and growth hormone, and many cytokines. As such, JAK inhibitors are under development for a wide range of immune and hematopoietic disorders. Knockout mice and various recessive disorders have demonstrated the importance of JAKs in normal immune function. Due to their wide ranging effects on immune and hematopoietic systems, manipulation of JAK family members through inhibition has the potential to lead to adverse events associated with decreased function of the immune and hematopoietic systems.

Presently, there are many drugs approved for the treatment of RA as illustrated by the following tables from Dr. Chowdhury's review.

**Table 1. Non-biologic small molecule DMARDs approved for marketing in the United States**

Product Name (Trade Name) [Sponsor]	Mechanism of Action in RA	Year of First Approval for RA
Sulfasalazine (AZULFIDINE) [Pfizer]	Anti-inflammatory and antimicrobial	1950

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

**Table 2. Biologic large molecule DMARDs approved for marketing in the United States**

Product Name (Trade Name) [Sponsor] [year] *	Presentation and ROA †	Description and MOA ‡	Claims for adult RA §
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Vial 25 mg Prefilled syringe 25 or 50 mg/mL SureClick Autoinjector 50 mg/mL <i>SC injection</i>	Fusion protein consisting of TNF-R and human IgG1 Fc <i>TNF-<math>\alpha</math> inhibitor</i>	Clinical response Major clinical response Physical function response Radiographic response
Infliximab (REMICADE) [Centocor] {1999}	Vial 10 mg/mL <i>IV infusion</i>	Chimeric IgG1 k mAb <i>TNF-<math>\alpha</math> inhibitor</i>	Clinical response Major clinical response Physical function response Radiographic response
Anakinra (KINERET) [Amgen] {2001}	Prefilled syringe 100 mg <i>SC injection</i>	Recombinant polypeptide <i>IL-1 receptor antagonist</i>	Clinical response Physical function response Radiographic response
Adalimumab (HUMIRA) [Abbott] {2002}	Prefilled syringe 40 mg/0.8 mL Prefilled syringe 20 mg/0.4 mL Humira Pen 40 mg/0.8 mL <i>SC injection</i>	Human IgG1 k mAb <i>TNF-<math>\alpha</math> inhibitor</i>	Clinical response Major clinical response Physical function response Radiographic response
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Lyophilized powder 250 mg/vial <i>IV infusion</i>	Fusion protein consisting of CTLA-4 and human IgG1 Fc <i>T cell activation inhibitor through B7-1 and B7-2</i>	Clinical response Major clinical response Physical function response Radiographic response
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Vial 10 mg/mL <i>IV infusion</i>	Chimeric murine/human IgG1 k mAb <i>Anti CD20, B cell depletor</i>	Clinical response Physical function response Radiographic response
Golimumab (SIMPONI) [Centocor] {2009}	Prefilled syringe 50 mg/0.5 mL SmartJect Autoinjector 50 mg/0.5 mL <i>SC injection</i>	Humanized IgG1 k mAb <i>TNF-<math>\alpha</math> inhibitor</i>	Clinical response Physical function response
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder 200 mg/vial Prefilled syringe 200 mg/mL <i>SC injection</i>	Humanized Fab fragment <i>TNF-<math>\alpha</math> inhibitor</i>	Clinical response Major clinical response Radiographic response Physical function response
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Vial 20 mg/mL <i>IV infusion</i>	Humanized IgG1 k mAb <i>IL-6 receptor inhibitor</i>	Clinical response Major clinical response Radiographic response Physical function response

\* Year = Year of first approval for RA

† ROA = Route of administration

‡ MOA= Mechanism of action

§ Claims: Clinical response (or reducing signs and symptoms) assessed by ACR 20, 50, and 70 response over at least 3-6 month; Major clinical response defined as achieving ACR 70 response continuously over 6 months period; Physical function response (or improving physical function) assessed by health assessment questionnaire (HAQ) over at least 6 month period; Radiographic response (or inhibiting progression of structural damage) assessed radiographically by Total Sharp Score (TSS) and sometimes its components of erosion score (ES) or joint space narrowing (JSN) score over 6 or 12 months

This submission supports the approval of tofacitinib 5 mg twice a day for moderately to severely active RA as monotherapy for patients not tolerating methotrexate or in combination with methotrexate or other nonbiologic DMARDs. My summary of efficacy and safety and conclusions follows below.

### **Efficacy**

Efficacy for RA drugs traditionally have been evaluated on the basis of American College of Rheumatology (ACR) response<sup>1</sup>, Health Assessment Questionnaire-Disability Index (HAQ-DI)<sup>2</sup> assessment of physical functioning effect, Disease Activity Score (DAS)-28<sup>3</sup> and standardized radiographic scoring assessing effect on structural damage progression. Dose-ranging studies utilizing a range from 1 mg BID to 15 mg BID demonstrated a relatively flat dose-response for doses of 3 mg BID and above in subjects with inadequate response to background MTX therapy, with suggestions of dose-response for 5 mg BID and above as a monotherapy in patients with inadequate response to DMARDs . Based on this information, the sponsor chose to bring forth the 5 mg and 10 mg twice a day dosing for further development.

Five trials form the basis of efficacy and safety for tofacitinib as summarized in the table below from page 11 of Dr. Yim's review.

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<sup>1</sup> A compilation of 1) tender joint count (68 joints), 2) swollen joint count (66 joints) and 3 of 5 ACR core set measures (patient global VAS, physician global VAS, patient assessment of pain VAS, patient assessment of physical function, acute phase reactant ESR or CRP). This compilation is measured as 20% or 50% or 70% or greater improvement.

<sup>2</sup> 20 questions in 8 categories measuring fine movement of upper extremity, locomotor activities of lower extremities and activities of both. Activities include dressing, rising, eating, walking, etc. and are averaged based on a four-level difficulty scale from zero (no difficulty) to three (unable to do). Minimal clinical important difference for improvement is considered to be 0.22 units.

<sup>3</sup> Composite incorporating number of tender and swollen joints (out of 28), a patient global assessment VAS and ESR. Assess level of disease at a given timepoint. High activity DAS28 score >5.1, low activity <3.2.

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

\*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

Dr. Yim has summarized the primary endpoints for each study (From page 15, italics below).

*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.*

## ACR

The primary endpoint results are summarized in the table below from Dr. Yim's review (page 17).

**Table 3: 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
<b>Study A3921032 (3 months)</b>					
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%	-	-
<b>Study A3921044 (6 months)</b>					
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%	-	-
<b>Study A3921045 (3 months)</b>					
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%	-	-
<b>Study A3921046 (6 months)</b>					
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%	-	-
<b>Study A3921064 (6 months)</b>					
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%	-	-

This shows that tofacitinib demonstrated efficacy for both the 5 mg and 10 mg BID dosage on ACR20 compared to placebo with a trend of numerical improvement for the 10 mg BID dosage compared to the 5 mg BID dosage. ACR50 and ACR70 results demonstrate that the tofacitinib groups had greater improvement compared to placebo control groups with slightly higher numerical response rates in the 10 mg BID compared to the 5 mg BID dosed groups.

## HAQ-DI

HAQ-DI results are presented in the table below from page 18 of Dr. Yim's review.

**Table 4: HAQ-DI Endpoint Results**

HAQ-DI	FAS, N	LS Mean	LS Mean Difference	Difference vs. PBO (95% CI)	p value
<b>Study A3921032 (3 months)</b>					
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	-	-	-
<b>Study A3921044 (3 months)</b>					
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	-	-	-
<b>Study A3921045 (3 months)</b>					
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	-	-	-
<b>Study A3921046 (3 months)</b>					
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	-	-	-
<b>Study A3921064 (3 months)</b>					
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

HAQ-DI results are similar to those of the ACR, again with slightly higher response rates in higher dosage groups.

### **Radiographic outcomes**

The primary radiographic endpoint of Van der Heijde modified Sharp Score<sup>4</sup> for Study 1044 is presented below from page 20 of Dr. Yim’s review.

<sup>4</sup> Measures joint space narrowing (JSN) and erosions at 16 locations in each hand and wrist and 12 locations in each foot using a 6-point scale from 0 to 5 for a maximum total erosion score of 280. JSN based on 15 locations in each hand and wrist and 6 locations in each foot using a 5-point scale from 0 to 4 for a maximal score of 168. Theoretical maximum score of erosions + JSN is 448.

**Table 5: 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
<b>Pfizer Primary Analyses</b>			
<b>Month 6 (Primary Endpoint)</b>	n = 140*	n = 278*	n = 290*
mTSS LS means	0.47	0.12	0.06
p-value vs. placebo	-	0.0792	0.0376
<b>Analyses Based on Ranks</b>			
<b>Month 6 (Primary Endpoint)</b>			
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

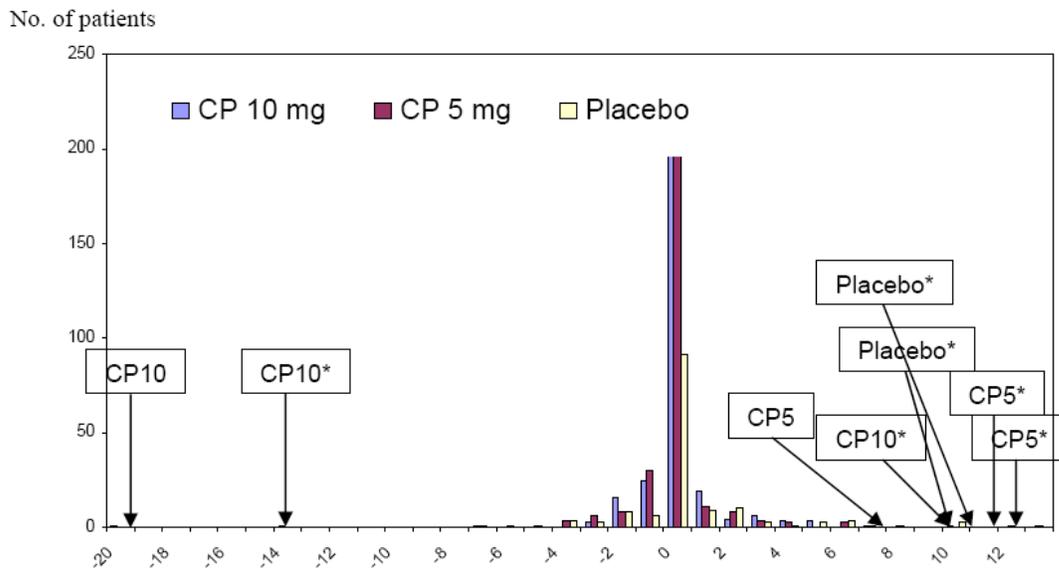
Sources: Summary of Clinical Efficacy Table 27; Study A3921044 CSR, Tables 11 and 14.2.15.1.6

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

The clinical and statistical reviewers question whether the results above are robust. The following graph from page 21 of Dr. Yim’s review illustrates their concern.

**Figure 1: Frequency Distribution of Change from Baseline in mTSS at Month 6**



\*Extrapolated data

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

Dr. Yim notes that the results for the 10 mg dose are driven mainly by two outliers, one of which is from extrapolated data. The review team concludes that there is uncertainty in the radiographic outcome and lack of robustness of the primary endpoint to sensitivity analysis

because there was a low amount of progression in the placebo group and small overall magnitude to the treatment effect.

I would note that radiographic trials in the current environment are very challenging. The total possible score for a mTSS is 448, yet the scale above demonstrates that trials are attempting to measure very small changes in score. The potential difference in scores between treatment groups is further reduced because of the ethical necessity to minimize the use of placebo, even as add-on treatment, and the need to limit the duration of inadequate control of disease activity. For this trial, the primary time point was at month 6, but many patients were advanced from one treatment group to another at Month 3 (49% of placebo patients and 26% of tofacitinib 5 mg patients) for non-response. This may account for the low amount of progression in the placebo group. This type of study design requires imputation methods to account for a large amount of missing data. The table below from Dr. Chowdhury’s review demonstrates the effect different imputation methods have upon the results.

**Table 7. mTSS score shown as change from baseline to month 6, study 1044, Study IV, or “Scan” \***

Treatment †	N	LS mean change from baseline	LS Mean	Difference vs placebo 95% CI	p-value
Primary analysis, Parametric, Linear extrapolation method					
Tof 5 mg + methotrexate	278	0.12	-0.34	-0.73, 0.04	0.079
Tof 10 mg + methotrexate	290	0.06	-0.40	-0.79, -0.02	0.038
Placebo + methotrexate	140	0.47			
Alternate pre-specified analysis, Non-parametric ‡					
Tof 5 mg + methotrexate	278	334	-41	-77, -6	0.024
Tof 10 mg + methotrexate	290	352	-23	-59, 12	0.198
Placebo + methotrexate	140	376			
Alternate sensitivity analysis, excluding one patients from Tof 10 mg group with change of over 20 units					
Tof 5 mg + methotrexate	278	0.11	-0.34	-0.69, 0.01	0.056
Tof 10 mg + methotrexate	289	0.12	-0.33	-0.68, 0.02	0.061
Placebo + methotrexate	140	0.45			
* Study ID shown as Pfizer’s study number, and as referred in tofacitinib product label, and as Pfizer “identified” at the May 9, 2012, AAC meeting					
† Tof = Tofacitinib oral tablets					
‡ LS means from non-parametric analysis were based on the rank-transformed radiograph data					

Because of the earlier use of DMARDs in general, and the use of methotrexate as background therapy in this trial, it is not surprising that radiographic progression in this cohort of RA patients is not as pronounced as in historical RA patient cohorts. However, this illustrates the increasing challenge of demonstrating treatment effect on structural damage outcomes. The improvement we have attained in therapy over the years have made such studies difficult and will require further thought (b) (4). In any event, Study 1044, while suggestive of a beneficial effect on radiographic progression, (b) (4)

### DAS-28 < 2.6

The DAS-28 results for those achieving a score less than 2.6 are listed below in a table from page 22 of Dr. Yim’s review.

**Table 6: Proportion of Patients with DAS28<2.6 Response**

Proportion with DAS28<2.6	FAS, N	Responder, n	Response rate (%)	Difference vs. PBO	p value
<b>Study A3921032 (3 months)</b>					
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%	-	-
<b>Study A3921044 (6 months)</b>					
Tofacitinib 5 mg BID	265	19	7%	5%	*
Tofacitinib 10 mg BID	257	47	18%	16%	*
Placebo (PBO)	129	2	2%	-	-
<b>Study A3921045 (3 months)</b>					
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%	-	-
<b>Study A3921046 (6 months)</b>					
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%	-	-
<b>Study A3921064 (6 months)</b>					
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

FDA did a slightly different analysis using ITT population and nonresponder imputation for missing data. With that analysis, Studies 1032 and 1064 fail to reach statistical significance.

## Overall efficacy

Tofacitinib doses of 5 mg and 10 mg BID demonstrated efficacy for signs and symptoms of RA as measured by ACR responses, DAS28 and HAQ-DI. For most outcomes, 10 mg BID provided a greater numerical response compared to the 5 mg BID dose.

Tofacitinib probably has not demonstrated an effect on structural outcomes, although that may be more due to limitations of the trial design than activity of the drug.

## Safety

As Dr. Chowdhury discusses, additional safety analyses of clinical data were requested from the sponsor during the review. This was because the sponsor had originally performed various pooling which limited quantification of safety events. These changes and their ramifications are thoroughly discussed in Dr. Chowdhury's review. As a result, events of interest including death, lymphoma, solid organ tumor, opportunistic infection, tuberculosis, SAE infections, herpes zoster, MACE events, hemoglobin level, lipid profile, neutrophil counts, liver function test and common adverse events were re-analyzed at time intervals of 0-3 months, 0-6 months, 0-12 months with appropriate treatment group assignment for patients switching from one treatment group to another. The re-analyzed safety is based on the five definitive efficacy and safety studies and two dose ranging studies (1025 and 1035). Results were also compared to adalimumab in those studies containing it as an active control. The tables below from Dr. Chowdhury's review demonstrate the results.

**Table 7. Summary of adverse event of interest in 0-12 months of treatment from seven studies \***

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

\* Two dose ranging efficacy and safety studies 1025 and 1035, and five definitive efficacy and safety studies 1045, 1046, 1064, 1044, and 1032 (ID as Pfizer's study number)

† Tof = Tofacitinib oral tablets

‡ Patients as treated are those who were randomized to the group plus placebo patients who were switched from placebo to tofacitinib treatment by study design or because of lack of response. Number of patients in the tofacitinib as treated group is larger than as randomized group because some patients from the placebo group advanced to tofacitinib groups at month 3 or month 6 by study design, and these patients are counted under both placebo group and tofacitinib group for the as treated group.

§ Excludes non-melanoma skin cancer NMSC)

**Table 8. Adverse event of interest from studies 1035 and 1064 for patients as treated \***

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

Treatment group †	Study 1035, 0-3 months ‡		Study 1064, 0-12 months	
	Adalimumab 40 mg	Tof, pooled 5 mg and 10 mg	Adalimumab 40 mg	Tof, pooled 5 mg and 10 mg
Patients with ≥ 1 , n	-	-	5	20 ¶
Incidence rate, per 100 PY	0	0	2.57	4.52
Malignancy, solid organ //				
Patients with ≥ 1 malignancy, n	1	-	1	3
Incidence rate, per 100 PY	8.94	0	0.51	0.68
Malignancy, lymphoma				
Patients with ≥ 1 lymphoma, n	0	0	0	0
Incidence rate, per 100 PY	-	-	-	-
MACE				
Patients with ≥ 1 MACE, n	-	-	3	2
Incidence rate, per 100 PY	0	-	1.54	0.45

\* Two studies that included adalimumab as a comparator (1035 was a dose ranging efficacy and safety study and 1064 was a definitive efficacy and safety study). Patients as treated are those who were randomized to the group plus placebo patients who were switched from placebo to tofacitinib treatment by study design or because of lack of response.

† Tof = Tofacitinib oral tablets

‡ Comparison between adalimumab and tofacitinib were done for 0-3 months because at month 3 all adalimumab patients and non-responders from placebo and tofacitinib 1 mg and 3 mg dose groups were advanced to tofacitinib 5 mg

§ 8 in tofacitinib 5 mg and 9 in tofacitinib 10 mg group based on patients as treated

¶ 7 in tofacitinib 5 mg and 13 in tofacitinib 10 mg group based on patients as treated

// Excludes non-melanoma skin cancer NMSC)

An examination of Table 10 reveals that tuberculosis and malignancy rates appear slightly increased when examining groups dosed with 5 mg BID compared to groups dosed with 10 mg BID. There were too few events in Table 11 to examine for dose-ordering except perhaps for serious infection rates (8 in the 5 mg group and 9 in the 10 mg group) and herpes zoster (7 in the 5 mg group and 13 in the 10 mg group) where there were no clear trends.

Lymphoproliferative disorders including lymphoma are always a concern with any drug that exerts its effects through the immune system. Only one case was noted in the 12-month data and this was in the 10 mg twice a day group. However, as noted in Dr. Chowdhury's review, overall lymphoma was reported in seven patients, all in the tofacitinib group (without dose-ordering). Tofacitinib is also being developed for allograft rejection, and at doses of 15 mg BID, 5 cases were noted in 218 treated patients (most EBV-positive). It was also noted in animal studies that in the high dose cynomolgus monkeys, 5 of 8 animals had lymphoma. (b) (4)

Laboratory tests of interest included lymphocyte and neutrophil counts, lipid parameters and liver enzyme tests. Lymphocyte count decrease below 500 cells/cmm occurred in 0.04% of patients in both the 5 and 10 mg twice-daily tofacitinib treatment groups during the first 3 months of treatment. Neutrophil count decrease below 1000 cells/cmm occurred in 0.07% of patients in both groups during the first 3 months of treatment.

Total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride elevations occurred in a dose-related manner in patients treated with tofacitinib. During the first 3 months of exposure,

LDL cholesterol increased by 15% and 19% in tofacitinib 5 mg and 10 mg groups respectively. There were too few cardiovascular events to evaluate if the changes in lipid profile translated into adverse events.

There was one case of probable drug-induced liver injury (DILI) reported in a patient treated with tofacitinib 10 mg twice daily. There did not appear to be transaminitis shifts associated with tofacitinib use, which some may feel is necessary to categorize this case specifically as a 'Hy's Law' case. It is an important distinction to make as any extrapolation of potential population effects may be limited to those cases of DILI that fulfill the strict definition of 'Hy's Law'. This is not to say that tofacitinib may not have the potential to cause DILI, only that our usual estimate of DILI as occurring at 1/10 the rate of Hy's Law cases based upon exposure (1/50,000 exposures in this case) may not be accurate.

In summary, tofacitinib use resulted in some safety concerns that occur with immunosuppressant drugs. These would include various infections and malignancy. There may be dose-ordering for some of these signals (tuberculosis, herpes zoster infection and malignancy). Laboratory tests demonstrated decreased lymphocyte and neutrophil counts comparing tofacitinib to placebo. Adverse lipid parameter changes were also noted with tofacitinib. It is also important to note that the events above were evaluated on a limited duration of 12 months of exposure which may not fully capture time-dependent events such as malignancy, lymphoma and others. Finally a case of probable DILI has been identified, which considering the size of the database may indicate rates of 1/50,000 (if Hy's Law), or less (if not).

DPARP plans on making a post marketing required study a condition of approval. This study will explore potential cardiovascular risks as well as others including further elucidation of malignancy and infectious risks. A REMS will also be required including a medication guide and communication plan outline the potential risks of therapy. I agree with this course of action.

### **Advisory Committee Meeting**

This NDA was discussed at the May 9, 2012 Arthritis Advisory Committee meeting. Discussion of the members are summarized nicely in Dr. Yim and Chowdhury's reviews. Overall, regarding whether there the efficacy and safety data provide substantial evidence to support approval for the treatment of moderately to severely active rheumatoid arthritis in patients who have had inadequate response to one or more DMARDs, the panel voted yes=8 and no=2.

### **Conclusions and Recommendations**

Tofacitinib 5 and 10 mg twice a day doses have both demonstrated efficacy. The 10 mg dose provided greater numeric response than the 5 mg dose for the primary and many secondary efficacy parameters. (b) (4)

DPARPs position is that the 5 mg twice a day dose is the optimum dose for patients. This is perhaps true for the majority of patients. However, there are probably some patients for which the 10 mg twice a day dose would provide greater relief and who would be willing to tolerate greater risk to achieve this goal. (b) (4)



As it stands at present, I agree that the 5 mg twice a day dose should be approved for treatment of adult patients with moderately to severely active RA as monotherapy for patients who cannot tolerate methotrexate, and as a combination with methotrexate or other non-biologic DMARDs and that a PMR study should be conducted as outlined above. A REMS communicating the risks of therapy and appropriate monitoring is also appropriate.

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/s/  
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CURTIS J ROSEBRAUGH  
11/06/2012