CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES (ADDENDUM)

NDA/BLA #:	NDA 203,214
Drug Name:	Xeljanz (tofacitinib) 5 mg and 10 mg tablets
Indication(s):	Treatment of Rheumatoid Arthritis
Applicant:	Pfizer Inc.
Date(s):	Submitted: October 21, 2011; PDUFA: August 21, 2012
	Extension: November 21, 2012
Review Priority:	Standard
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Keywords: NDA review, clinical studies, safety

This is an addendum for NDA 203214 to reflect changes in Tables 12, 13, 20 and 22 from the safety statistical review dated October 1, 2012. I also would like to clarify that the comparison between tofacitinib and adalimumab was based on 12 month data, and not during the first 3 months as stated in the Executive Summary. Specifically, we wrote in the original review

"Based on comprehensive analyses of the major safety events of interest, there is a suggestion that tofacitinib might be associated with a higher risk of serious infections, and herpes infections compared to placebo, as well as to adalimumab, during the first 3 months of use."

The revised text is

"Based on comprehensive analyses of the major safety events of interest, there is a suggestion that tofacitinib might be associated with a higher risk of serious infections, and herpes infections compared to placebo during the first 3 months of use, as well as to adalimumab, during the first 12 months of use."

In section 3.3.1 of the review, zero death was reported in the combined tofacitinib 5 mg and 10 mg group (Table 12). Our clinical team noted that there is one reported death in Study 1064 in the tofacitinib group. After checking the applicant's report, we concluded that one patient receiving tofacitinib died in 29 days after the first 12 months of exposure and no deaths were reported in the adalimumab group. The revised tables with corrected results are presented in Tables 12 and 13.

In Table 20 in the review, the reported number of patients treated with tofacitinib 10 mg in trials 1045, 1046 and 1064 were incorrect. These counts have been updated to 297, 391 and 245 respectively. Also in Table 20, number of patients treated with tofacitinib 10 mg who experienced a serious infection in trials 1046 and 1064 were incorrectly reported as 8 and 8 respectively. The counts have been updated to reflect the correct counts: 7 and 9.

Table 1. Events of interest among subjects randomized to tofacitinib 5 mg, 10 mg, and adalimumab in trials A3921035 and 1064

		Tofacitinib 5 mg, 10 mg and adalimumab								
Trial	N	Death	MACE	lymphoma	solid organ tumors	malignancy excluding NMSC	opportunistic infections	tuberculosis	serious infections	herpes zoster
						Adalimumab				
A3921035[1]	53	0	0	0	1	1	0	0	0	0
A3921064[2]	204	0	3	0	1	1	0	0	3	5
						tofacitinib 5 mg and 10 mg				
A3921035[1]	110	0	0	0	0	0	0	0	0	0
A3921064[2]	405	1	2	0	3	3	0	2	15	19

[1]Months 0-3 only
[2]Months 0-12

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Table 2. Incidence ratio of events of interest, comparing tofacitinib (5 mg and 10 mg) vs. adalimumab during months 0 – 12 + 28 days based on randomized treatment assignment in trial A3921064

	Incidence ratio (95% CI)	Mantel-Haenszel RR (95% CI)	Risk Difference[3] (95% CI) per 100 py	Adalimumab[1] events/100 py	Tofacitinib[2] events/100 py
death	ND	ND	0.25 (-0.24, 0.73)	0	0.26
MACE	0.39 (0.07, 2.35)	0.34 (0.06, 1.99)	-1.01 (-2.89, 0.87)	1.54	0.53
lymphoma	ND	ND	-	0	0
Solid organ tumors	1.77 (0.18,16.99)	1.51 (0.16, 14.43)	0.28 (-1.07, 1.63)	0.51	0.80
malignancy excluding NMSC	1.77 (0.18,16.99)	1.51 (0.16, 14.43)	0.28 (-1.07, 1.63)	0.51	0.80
opportunistic infections	ND	ND	-	0	0
tuberculosis	ND	ND	0.53 (-0.20, 1.26)	0	0.53
serious infections	2.59 (0.75, 8.94)	2.52 (0.74, 8.60)	2.43 (-0.19, 5.06)	1.54	3.98
herpes zoster	1.98 (0.74, 5.31)	1.91 (0.73, 5.05)	2.47 (-0.67, 5.60)	2.57	5.04

ND = not defined. Reference level is adalimumab
[1]A total of 194.5 years of exposure were observed among patients on adalimumab
[2]A total of 377.1 years of exposure were observed among patients on tofacitinib
[3]Events in Tofacitinib per 100 py – Events in Adalimumab per 100py

Table 3. Events of interest during months 0-12 + 28 days among subjects randomized to tofacitinib 5mg or 10mg + patients who transitioned from placebo to tofacitinib at either month3 or month 6 (by design or by response).

Tofacitinib 5mg and 10mg, Months 0-12 + all patients who transitioned from placebo to tofacitinib

Trial	N	death	MACE	lymphoma	solid organ tumors	malignancy excluding NMSC	opportunistic infections	tuberculosis	serious infections	herpes zoster
						tofacitinib 5mg				
A3921025	89	0	0	0	1	1	0	0	1	1
A3921032	191	0	3	0	0	0	0	0	4	1
A3921035	74	0	0	0	0	0	0	0	0	1
A3921044	394	3	0	0	2	2	3	0	16	20
A3921045	298	0	0	0	0	0	0	0	2	2
A3921046	388	1	2	0	0	0	1	0	3	15
A3921064	255	1	1	0	2	2	0	0	8	7
** Total **	1689	5	6	0	5	5	4	0	34	47
						tofacitinib 10mg				
A3921025	74	0	0	0	0	0	0	0	1	2
A3921032	187	1	0	0	0	0	0	0	3	2
A3921035	61	0	0	0	0	0	0	0	0	0
A3921044	384	1	2	1	2	3	3	1	9	21
A3921045	297	1	2	0	1	1	0	1	4	5

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A3921046	391	2	1	0	2	2	1	2	7	7
A3921064	245	0	1	0	1	1	0	2	9	13
** Total **	1639	5	6	1	6	7	4	6	33	50

In section 4 of the review, results from the analyses of selected safety endpoints were presented in Table 22. The analyses were based on the as treated population defined as all randomized patients plus patients who transitioned from placebo to tofacitinib by study design. In consultation with the clinical review team, we decided to include, in addition to the definition above, all placebo patients who advanced to tofacitinib by response in the analyses. The change is on the footnote. The numbers are the same except in malignancy where the upper bound is now 0.7% instead of 0.8%.

Table 4: Integrated Analyses of Efficacy and Safety (Updated)

	Tofacitinib 5 mg versus placebo	**Tofacitinib 10 mg versus placebo**	**Tofacitinib versus placebo**	**Tofacitinib 10 mg versus 5 mg**
Efficacy Endpoints †				
ACR20 at Week 12 (difference in proportions)	28% (24%, 32%)	34% (30%, 38%)	31% (27%, 35%)	6% (3%, 10%)
HAQ-DI at Week 12 (mean difference)	-0.23 (-0.28, -0.18)	-0.32 (-0.36, -0.27)	-0.27 (-0.32, -0.23)	-0.08 (-0.13, -0.04)
Selected Safety Endpoints ‡ (difference in rates)				
Serious Infection (0 – 3 months)			1.3% (-0.2%, 2.8%)	
Herpes Infection (0 – 3 months)			1.9% (-0.3% 4.2%)	
Tuberculosis Infection (0 – 12 months)				0.5% (0.1%, 0.9%)
Malignancy (0 – 12 months)				0.2% (-0.4%, 0.7%)

† includes all randomized patients. Nonresponder imputation was applied to missing binary outcome data and baseline observation was carried forward to missing HAQ-DI score at week 12.
‡ includes all randomized patients plus patients who transitioned from placebo to tofacitinib by study design and by response

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/s/

YONGMAN KIM
10/09/2012

JOAN K BUENCONSEJO
10/09/2012
I concur with the review amendment.

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CLINICAL STUDIES

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Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Joan Buenconsejo, Ph.D.
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Concurring Reviewers:	Mat Soukup, Ph.D.
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Clinical Team:	Nikolay Nikolov, M.D.
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1 EXECUTIVE SUMMARY

Pfizer proposes tofacitinib (CP-690,550) 5 mg and 10 mg orally administered twice a day (BID) for the treatment of rheumatoid arthritis (RA). To support this marketing application, the applicant submitted data from 21 Phase 1 studies, six Phase 2 studies, and five Phase 3 studies. The focus of the statistical review was on the five Phase 3 studies 1032, 1044, 1045, 1046, and 1064. Please refer to the statistical review by Yongman Kim dated on June 23, 2012 for a detailed review of the efficacy data. That review concluded that there is substantial evidence of efficacy of tofacitinib 5 mg or 10 mg for the treatment of rheumatoid arthritis. This is based on consistent findings in the domains of reducing signs and symptoms of RA (as measured by ACR20) and improving physical function (as measured by HAQ-DI).

The focus of the safety statistical review was on the controlled portion of the two Phase 2 studies 1025 and 1035, and the five Phase 3 studies 1032, 1044, 1045, 1046, and 1064. Based on comprehensive analyses of the major safety events of interest, there is a suggestion that tofacitinib might be associated with a higher risk of serious infections, and herpes infections compared to placebo, as well as to adalimumab, during the first 3 months of use (b) (4) [redacted] Therefore, the direction of the difference in risk, if any, is not known with much confidence. The analyses conducted in this review indicate no evidence of a difference in the risk of death, MACE, lymphoma, solid organ tumors, opportunistic infections excluding tuberculosis, serious infections and herpes zoster infections between patients treated with tofacitinib 5 mg or 10 mg.

Overall, the clinical benefit of tofacitinib 5 mg and 10 mg twice a day was generally comparable. Numerical differences were observed in ACR20 response rates and change in HAQ-DI between the two doses; however these were not consistent across the randomized controlled studies and any differences were small. (b) (4) [redacted] Clinical assessment of the balance of the risk and benefit of the 10 mg dose is needed as the differences in the efficacy between tofacitinib 10 mg and 5 mg for symptomatic treatment of RA may not justify the potential risk of serious diseases like malignancy and serious infections. The risk-benefit profile as it currently stands may favor the tofacitinib 5 mg group.

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2 INTRODUCTION

This document is a joint statistical safety review representing the work of Joan Buenconsejo, Yongman Kim, and Eugenio Andraca-Carrera. The application under consideration is NDA 203,214 from Pfizer for the new molecular entity tofacitinib (also known as CP-690,550) for the treatment of patients with moderately to severely active rheumatoid arthritis (RA)

This review will focus only on the results from the analyses of major safety events of interest including death, lymphoma, solid organ tumor, opportunistic infection, tuberculosis, serious infection, herpes zoster, and cardiovascular (MACE) events. While tofacitinib therapy was shown to be associated with changes in some laboratory values, as well as increase in other adverse events by the applicant, we will not be presenting these results. The objectives of this review are to highlight some of the issues identified during the review of safety data including the steps we have taken, to discuss the outcome from the re-analyses of the safety data, and to provide comments on how adverse events should be reported in the label. For additional review of the safety data including laboratory values, and other AEs, please refer to the clinical review of Dr. Nikolay Nikolov.

The NDA was submitted on October 21, 2011 by Pfizer. Pfizer proposes tofacitinib (CP-690,550) 5 mg and 10 mg orally administered twice a day (BID) for the treatment of rheumatoid arthritis (RA). To support this marketing application, the applicant submitted data from 21 Phase 1 studies, six Phase 2 studies, and five Phase 3 studies. The focus of the statistical review was on the five Phase 3 studies A3921032, A3921044, A3921045, A3921046, and A3921064. Please refer to the statistical review by Yongman Kim dated on June 23, 2012 for a detailed review of the efficacy data. That review concluded that there is substantial evidence of efficacy of tofacitinib 5 mg or 10 mg for the treatment of rheumatoid arthritis. This is based on consistent findings in the domains of reducing signs and symptoms of RA (as measured by ACR20) and improving physical function (as measured by HAQ-DI). (b) (4)

The applicant's safety evaluation was based on the integrated safety data from five key double-blind phase 3 studies in RA (A3921032, A3921044, A3921045, A3921046, and A3921064). These data were supported by integrated data from five completed phase 2 studies (A3921025, A3921039, A3921019, A3921035, and A3921040) and integrated data from two ongoing long-term extension (LTE) studies (A3921024 and A3921041), see Table 2.

Dr. Kim, in his review, expressed our concern that the safety summaries the applicant provided may not be adequate to make regulatory decision regarding the safety of tofacitinib 5 mg or 10 mg doses. Specifically, we were concerned with the number of studies included in the main integrated safety analyses, on how the results were summarized based on pooled data without controlling for differential study designs and patient populations, and the inability to properly account for those placebo patients who advanced to tofacitinib. These issues made it difficult for us to interpret the findings. The applicant reported the results primarily based on crude rates. Given the complexity of the study design, we believed that a model-based approach is more

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appropriate to summarize the safety data. The clinical team was also concerned about the entry criteria, the inclusion of the Japanese studies, and the dose adjustments provisions in the long-term extension studies (see Section 3.1). Because of the potential limitations of the safety data presentation and analyses in the original application, the Division asked the applicant to provide alternative approaches to analyze the safety data, particularly those major events of interest. The Division sent information requests on May 22, June 4, and June 22 requesting safety datasets with selected variables from existing database and additional analyses accounting for differences in length of exposure and the cross-over nature of the design. Teleconferences were held between the Division and the applicant to clarify some issues regarding the requests. A Type A meeting between the Division and the applicant was held on July 10, 2012 to discuss the potential for alternative safety analyses to address the Agency's questions, and the potential impact of the submission timing on the review of the NDA, particularly in light of the August 21, 2012 action date. Since multiple information requests were sent to the applicant, the Division clarified at the meeting that the analyses requested from the June 20, 2012 letter supersedes the June 4, 2012 request, and that the applicant should submit all requested analyses from the June 20 letter prior to the PDUFA action date. Furthermore, the Division acknowledged the receipt of the requested datasets (from the May 22 and June 4 letters) and informed them that we will be conducting additional analyses to the safety data. The applicant provided two timelines for submission presented in Table 1.

Table 1: Applicant's timelines for submission of FDA safety request

Table 1. Revised proposal for FDA Safety Request

Analysis	Scope	Timeline
Special safety events	**Consistent with 20 June IR[a]**	**Week of July 30th**
K-M plots for special safety events	**By randomized sequence (0-12 M) for the 7 studies**	**Week of July 30th**
Common AEs and Labs for labeling, Part 1	**0-3 M presentation as originally randomized[b]**	**Week of July 30th**
Common AEs and Labs for labeling, Part 2	**Sensitivity Analysis for as-treated patients[b]**	~~**Week of September 17th**~~ August 19, 2012*

[a] Incidence rates for requested intervals and population
[b] As proposed in response to FDA comments regarding July 10th meeting

* Date corrected during the July 20, 2012 meeting

In response to the Information Request dated June 20, 2012, the applicant submitted the following on August 1, 2012 (serial number 34).

1. Exposure Estimates and Incidence Rates Tables (As Treated)
2. Kaplan-Meier Plots and Survival Function Tables (As Randomized)
3. Treatment-emergent AE Tables (As Randomized)
4. Laboratory Data As Randomized Tables

On August 10, 2012 (serial number 37), they submitted the following:

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1. Treatment-emergent AE Tables (As Treated)
2. Laboratory Data As Treated Tables

These two submissions fulfilled the requested analyses from the June 20, 2012 information request.

Table 2: List of all studies included in analysis

Protocol	Patient Population	Design *Duration*	Enrolled *Randomization*	Treatment Arms
Patients with incomplete response to prior TNF inhibitor				
A3921025	Moderate-to-severe RA MTX-IR, Stable background MTX	R,DB, PC *Dose-ranging* *6 months*	507 *1:1:1:1:1:1:1*	CP 1 mg BID (→CP 5 mg BID @ Mo3 if NR)+ MTX CP 3 mg BID (→CP 5 mg BID @ Mo3 if NR)+ MTX CP 5 mg BID + MTX CP 10 mg BID + MTX CP 15 mg BID + MTX CP 20 mg QD (→CP 5 mg BID @ Mo3 if NR)+ MTX Placebo (→CP 5 mg BID @ Mo3 if NR)+ MTX
A3921032	Moderate-to-severe RA TNF-IR, Stable background MTX	R, DB, PC *6 months*	399 *2:2:1:1*	CP 5 mg BID + MTX CP 10 mg BID + MTX Placebo (→CP 5 mg BID @ Mo3)+ MTX Placebo (→CP 10 mg BID @ Mo3)+ MTX
Patients with incomplete response to MTX or other DMARDs				
A3921035	Moderate-to-severe RA DMARD-IR, No background MTX	R,DB, AC *Dose-ranging* *6 months*	797 *1:1:1:1:1:1:1*	CP 1 mg BID (→CP 5 mg BID @ Mo3 if NR) CP 3 mg BID (→CP 5 mg BID @ Mo3 if NR) CP 5 mg BID CP 10 mg BID CP 15 mg BID Adalimumab (→CP 5 mg BID @ Mo3) Placebo (→CP 5 mg BID @ Mo3 if NR)
A3921044	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC *Two years**	797 *4:4:1:1*	CP 5 mg BID + MTX CP 10 mg BID + MTX PBO (→CP 5 mg BID @ Mo 6 or Mo3 if NR)+ MTX PBO (→CP 10 mg BID @ Mo 6 or Mo3 if NR)+ MTX
A3921046	Moderate-to-severe RA DMARD-IR, Stable background DMARDs#	R, DB, PC *One-year*	792 *4:4:1:1*	CP 5 mg BID + DMARD CP 10 mg BID + DMARD PBO (→CP 5 mg BID @ Mo 6 or Mo3 if NR) + DMARD PBO (→CP 10 mg BID @ Mo 6 or Mo3 if NR) + DMARD
A3921064	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, AC *One year*	717 *4:4:1:1:4*	CP 5 mg BID + PBO SC+ MTX CP 10 mg BID + PBO SC + MTX PBO (→CP 5 mg BID @ Mo 6 or Mo3 if NR) + PBO SC + MTX PBO (→CP 10 mg BID @ Mo 6 or Mo3 if NR) + PBO SC + MTX PBO + adalimumab + MTX
A3921045	Moderate-to-severe RA DMARD-IR, No background to Month 3	R, DB, PC *6 months*	610 *4:4:1:1*	CP-690,550 5 mg BID CP-690,550 10 mg BID PBO → CP 5 mg BID @ Mo 3 PBO → CP 10 mg BID @ Mo 3

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3 STATISTICAL EVALUATION

3.1 Review of the Applicant's Original Safety Evaluation

The applicant focused on two main safety populations in their report. This includes patients in the Phase 3 RA studies (pooled) and patients in the two LTE studies (pooled).

For simplicity, the last four digits will be used to denote the study number. For example, study 1025 refers to study A3921025.

Phase 2 and Phase 3 RA Studies

The Phase 3 studies group includes data from the five Phase 3 RA studies which were pooled (1032, 1045, 1046, 1064, and 1044). Four of these studies were designed to administer tofacitinib along with a background DMARD (typically MTX), and one study administered tofacitinib as monotherapy.

Studies 1032, 1044, 1045, 1046, and 1064 were of similar design, except for the population studied, the study duration, and treatment arms. They were all phase 3, randomized, double-blind, placebo-controlled studies and are presented to allow for comparison of tofacitinib to placebo over 3 – 6 months and, in one study, to the active control adalimumab over 12 months. In four of these studies, patients were randomized to CP5, CP10, placebo (→CP5 at month 3 or 6), placebo (→CP10 at month 3 or 6) in a 4:4:1:1 ratio, and in study 1032 in a 2:2:1:1 ratio. Patients originally randomized to placebo were advanced to either tofacitinib 5 mg or 10 mg at 3 or 6 months, per protocol design, resulting in 3 treatment periods: 0 to 3 months (placebo-controlled portion of the studies), 3 to 6 months (some patients remained on placebo; some advanced to tofacitinib treatment), and >6 months (no placebo group; all patients advanced to tofacitinib treatment). In other words, there are two ways for placebo patients to advance to tofacitinib:

1. cross-over by response: placebo patients who did not meet response criteria at a specified timepoint will advance to tofacitinib

2. cross-over by design: (all remaining) placebo patients at specified timepoint will advance to tofacitinib.

In general, the applicant presented the Phase 3 safety data by the overall 0 to 12 months duration, except for adverse events, serious adverse events, and discontinuations due to adverse events where data were also presented by treatment period. Incidence rates adjusted for patient-years of exposure and the corresponding 95% confidence intervals were calculated based on the number of patients with events. The applicant reported the rates by treatment group in two ways: (1) based on their original randomized treatment arms (i.e. as randomized), and (2) based on combining CP5 and CP10 groups and adding those placebo patients who advanced to tofacitinib

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(i.e. as treated). During the first 3 months, safety data are summarized based on as randomized population (Table 3). At month 3, 460 out of 681 patients treated with placebo were advanced to either tofacitinib 5 mg or 10 mg at month 3, by either protocol design or by response. Even when these patients started tofacitinib therapy, they were counted in the 3 to 6 month group. Similarly, those patients who advanced to either tofacitinib 5 mg or 10 mg at month 6 were counted in the > 6 month group even though they had just started tofacitinib therapy at that point.

Table 3: Safety Analysis Population in Phase 3 Rheumatoid Arthritis Studies, as randomized and treated (Applicant's)

Studies	Placebo	CP5 mg	CP10 mg	All Doses*	Adalimumab
0 – 3 months	681	1216	1214	2430	204
3 – 6 months	221	1451	1439	2890	204
> 6 months		1056	1046	2102	204

As noted earlier, we were concerned that the safety summaries the applicant provided may not be adequate to support regulatory decision regarding the safety of tofacitinib 5 mg or 10 mg doses. Together with the clinical team, we agreed that the two dose-ranging studies (studies 1025 and 1035) are sufficiently similar in design and patient population to the Phase 3 studies to be included in the key integrated analyses. We also agreed that data from these studies should not be simply pooled for analysis but instead should be adjusted by study given the differing study designs and patient populations. Furthermore, the analyses should take into account placebo patients who advanced to tofacitinib and to take advantage of this unique design by applying modeling approaches to analyze the data, instead of relying on crude rates described by time point of measurement. As an example, suppose a patient who was initially treated with placebo but who advanced to tofacitinib 5 mg at month 3 experienced an adverse event at month 5, the applicant reported the event in the tofacitinib 3 – 6 months when in actuality this patient had been receiving tofacitanib for only 2 months.

In summary, we identified three sets of comparison for safety evaluation:

1. tofacitinib versus placebo (at 0 to 3 months), discussed in Section 3.3.1.
2. tofacitinib versus adalimumab (at 0 to 12 months), discussed in Section 3.3.2.
3. tofacitinib 5 mg versus tofacitinib 10 mg (at 0 to 12 months), discussed in Section 3.3.3.

The risk of events was assessed through a Poisson regression model stratified by study with an offset term given by the logarithm of time until first event or censoring to the following safety data:

1. Only patients originally randomized to tofacitinib 5 and 10 mg BID.
2. Patients originally randomized to tofacitinib 5 and 10 mg BID + 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).
3. Patients originally randomized to tofacitinib 5 and 10 mg BID + patients who transitioned to tofacitinib 5 and 10 mg BID by study design (month 3 for studies

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1032 and 1045, and Month 6 for studies 1044, 1046, and 1064) + patients who escaped to tofacitinib 5 and 10 mg BID due to active disease.

Poisson regression was chosen since it models count data. It can also model count data per unit time to account for different length of exposure through an offset term (a variable that is forced to have a regression coefficient of 1). The offset term (i.e. (natural) log of the time of exposure) is added to the fitted equation. This model also allows us to account for differing study designs and patient populations by adjusting for study.

Long-Term Extension Studies

The applicant also provided the results from the long-term extension (LTE) studies. The LTE group included pooled data from the two ongoing LTE studies (1024 and 1041) in which patients from Phase 2 or Phase 3 studies continued participation and received CP5 or CP10 mg BID. Patients were allowed to continue on background RA therapy, including approved DMARDs and glucocorticoids. In the LTE studies, patients were followed longer than in the Phase 3 studies, currently up to 3 years. Of note, only patients from studies 1039 and 1040 (Phase 2 Japan studies) and from study 1044 were eligible for study 1041, whereas all other patients were eligible for study 1024. Dose adjustments (including increases to CP10, or decreases from CP10 to CP5) and temporary discontinuations were allowed in both LTE studies based on the investigator's evaluation of individual patient needs. The following are enrollment criteria for patients in study 1024:

1. Patients from a Phase 2 qualifying study received either CP5 or CP10 if enrolled after Protocol Amendment 3
2. Patients enrolling from a Phase 3 index study received CP10, except patients from China who received CP5 (Protocol Amendment 8)

According to the applicant's report, because dose adjustment 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) they received in the first 3 months of participation in the long-term study. Furthermore, patients in the CP5 mg group had a longer exposure time (in total patient years of drug exposure) compared to the CP10 mg group. Therefore, the applicant warned that direct comparison of percentages for AEs, SAEs, and discontinuations due to AEs between the CP5 and CP10 mg groups needs to be interpreted with caution as the percentages do not take into account the longer exposure time in the CP5 mg group. Event rates, adjusted for patient years of observation, are provided for events of special interest, which take into account the time patients are exposed to drug.

We are concerned about the safety summaries generated from the LTE studies. One concern is the inclusion of the Japanese studies since patients from these studies are generally different and their background medication use may also be different. The entry criteria and the dose adjustments provisions in the LTE studies are problematic. Like the applicant, we are wary about making any direct comparisons between CP5 and CP10 mg groups since it is difficult to discriminate who and when patients are taking CP5 or CP10. The applicant attempted to take into account the longer exposure time in the CP5 mg group by calculating event rates adjusted

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for patient-years of exposure for the events of special interest. While this approach is generally reasonable, there is an underlying assumption that events occur at a constant rate over time which may not be necessarily true in most cases. Furthermore, this does not address the problem that many patients received both 5 mg and 10 mg BID during the long-term extension. Attributing an adverse event to a particular dose is problematic.

In summary, we recommend excluding the results from the LTE studies in the label for the following reasons:

1. Inability to compare CP5 and CP10 mg groups due to the dose adjustment provisions and different inclusion criteria
2. Lack of control arm(s) to compare the safety profile of tofacitinib

3.2 Review of the Applicant's New Safety Evaluation and Label

On August 1, 2012 and August 10, 2012, the applicant submitted the results from the re-analyses of the safety data. These include:

1. Exposure Estimates and Incidence Rates Tables (As Treated)
2. Kaplan-Meier Plots and Survival Function Tables (As Randomized)
3. Treatment-emergent AE Tables (As Randomized)
4. Laboratory Data As Randomized Tables
5. Treatment-emergent AE Tables (As Treated)
6. Laboratory Data As Treated Tables

On August 13, 2012 (serial number 36), the applicant submitted a revised draft labeling text. Included in the Adverse Reactions section (Section 6) of the label is information from the seven double-blind, randomized, controlled, multi-center clinical trials. They reported the results from both the controlled portion and the long-term extension of the studies. They specifically reported the infection rates, laboratory tests values, and common adverse reactions.

In the label, the applicant reported that infection is the most common adverse event during the first 3 months of exposure. The results from the applicant's analyses (submitted on August 1 and August 10) are presented in Table 4. Of note, the analyses were conducted based two sets of population: (1) on all randomized patients (i.e. as-randomized), (2) all randomized patients plus all placebo patients who advanced to tofacitinib either at month 3 or month 6 (i.e. as-treated). Slightly more patients reported adverse events in the as-treated population compared to the randomized population; however, the proportions are the same between the two populations. Slightly more patients experienced infections in the tofacitinib group compared to placebo.

A summary of major events of interest taken from applicant's report (submitted on August 1 and August 10) is presented in Table 5. For most of the events, crude incidences were provided because of convergence issue (according to the applicant). The problem using crude incidence is discussed in detail in Section 3.1. Nonetheless, there appears to be a greater incidence of serious infections (including tuberculosis, opportunistic infection, and herpes zoster) in the tofacitinib group compared to the placebo group. This difference also appears to be dose-dependent (based

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on as treated population). There is also a slight dose-dependent increase in the incidence of solid organ tumor.

As noted in Section 3.1, to confirm the applicant's results and to further describe events, additional analyses were conducted by Dr. Kim and Dr. Andraca-Carrera and the results are described in Section 3.3.

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Table 4: Selected Common Adverse Events

	As Randomized (0 – 3 months)					As Treated (0 – 3 months)				
	5 mg BID		(b) (4)	Placebo		5 mg BID		(b) (4)	Placebo	
	N	%		N	%	N	%		N	%
Total N	1336			809		1476			809	
Infections	277	21%		147	18%	296	20%		147	18%
Upper respiratory	60	5%		27	3%	66	5%		27	3%
Nasopharyngitis	51	4%		23	3%	52	4%		23	3%
UTI	34	3%		15	2%	37	3%		15	2%

Table 5: Applicant's Analyses of Major Events of Interest

	As Randomized (0 – 12 months)					As Treated (0 – 12months)				
	5 mg BID		(b) (4)	Placebo		5 mg BID		(b) (4)	Placebo	
	N	Rate /py		N	Rate /py	N	Rate /py		N	Rate /py
Total N	1336			809		1814			809	
Death	5	0.5		1	0.4	5	0.4		1	0.4
Lymphoma	0	0		0	0	0	0		0	0
Solid Organ	5	0.5		0	0	5	0.4		0	0
Serious Infection	30	3.2		3	1.2	32	2.8		3	1.2
Tuberculosis	0	0		0	0	0	0		0	0
Opportunistic Infections	3	0.3		0	0	4	0.4		0	0
Herpes Zoster	41	3.4*		5	1.8*	47	3.5*		5	1.8*
CV MACE†	4	0.5*		2	1.0	6	0.6		2	1.0

* Adjusted rate is from Poisson regression with independent variables for treatment group and protocol
† CV MACE events were only adjudicated for the phase 3 studies (N=1526 for CP 5 mg, N=1504 for CP10, and N=681 for PBO)

3.3 Review of the Safety Data

This section evaluates the association between the use of tofacitinib and major safety events of interest including death, lymphoma, solid organ tumor, opportunistic infection excluding tuberculosis, tuberculosis, serious infection, herpes zoster, and cardiovascular (MACE) events. These events are assessed in seven Phase 2 and Phase 3 clinical trials for tofacitinib: A3921025, 1032, 1035, 1044, 1045, 1046 and 1064. The population of interest comprises of all subjects randomized to tofacitinib 5 mg BID, 10 mg BID, adalimumab or placebo in these trials. Subjects reported to have "withdrawn after screening/randomization but prior to treatment" are excluded from all analyses. In all analyses in this document subjects are censored at the time of their first recorded event. All subjects' time and events after their first recorded event are excluded from all analyses.

As mentioned in the previous section, we identified three sets of comparisons for safety evaluation: tofacitinib vs. placebo, tofacitinib vs. adalimumab and tofacitinib 5 mg vs. tofacitinib 10 mg. These three sets of comparisons are discussed in Sections 3.3.1, 3.3.2, and 3.3.3 respectively.

The risk of events is assessed through a Poisson regression model stratified by study with an offset term given by the logarithm of time until first event or censoring. The parameter estimated by the Poisson model after anti-logarithmic transformation is the Incidence Ratio (IR). The Mantel-Haenszel Risk Ratio is also shown in tables as a secondary analysis method. For rare events such as the ones evaluated in this review, both measures of risk are expected to produce similar results. Note that the MH Risk Ratio does not take into account the subject-specific time of exposure, only the number of subjects in each treatment arm. Also shown in tables is the observed pooled event rate per 100 patient years of exposure for each event of interest and treatment arm. The Mantel-Haenszel Risk Difference per 100 patient-years of exposure is shown to compare the risk of events adjusted for differences between trials.

3.3.1 Tofacitinib vs. placebo

This subsection compares the risk of major safety events of interest among patients randomized to tofacitinib 5 mg or 10 mg, to patients randomized to placebo in the seven trials of interest.

Patients randomized to placebo in trials 1032 and 1045 switched treatment to either tofacitinib 5 mg or tofacitinib 10 mg at month 3 by trial design. Patients randomized to placebo in the other five trials of interest (1025, 1035, 1044, 1046 and 1064) switched treatment to tofacitinib at month 3 if they were considered non-responders with regards to an efficacy endpoint at month 3, and switched treatment to tofacitinib at month 6 otherwise. Because of the design of these trials, we considered that the primary comparison between placebo and tofacitinib should be performed using only the first 3 months after randomization in all trials.

For the purpose of this analysis the last day of the 0 – 3 month period for all patients was defined as follows:

1. If a patient switched treatment from placebo to tofacitinib before 100 days, then the

last recorded date on placebo was considered to be the subject's last date.

2. If a patient did not switch treatment before 100 days, then the last date on randomized treatment was the randomization date + 90 days.

Table 6, Table 7 and Table 8 show the number of observed major events of interest by trial among patients randomized to placebo (N=809), tofacitinib 5 mg (N=1336) and tofacitinib 10 mg (N=1349) during the first 3 months after randomizations in the seven trials. These tables show that there were few major safety events observed during this time. An imbalance was observed among serious infections (1 event / 839 patients on placebo and 11/2685 on tofacitinib) and herpes zoster infections (3/839 on placebo and 23/2685 on tofacitinib). Table 9 shows the corresponding estimated incidence ratio (IR), Mantel-Haenszel risk ratio, Mantel-Haenszel risk difference, and pooled incidence by treatment arm.. The pooled incidence is presented in this review in order to be consistent with tables produced by the sponsor. The formal comparison of the risk of events between tofacitinib and placebo should be based on the incidence ratio, Mantel-Haenszel risk ratio and Mantel Haenszel risk difference, which account for differences across trials. The estimated IR and 95% CI for serious infections associated with tofacitinib was 2.89 (0.34, 24.15), with p-value=0.31, and with herpes zoster infections was 2.11 (0.63, 7.06), with p-value=0.22. The observed imbalance of serious infections and herpes zoster infections show a possible increased risk associated with tofacitinib compared to placebo, but this effect did not reach statistical significance. Due to the small number of events, it is possible that important differences may not have been detected (in either direction) and could not be expected to reliably produce statistical significance.

Table 6. Events of interest during months 0 – 3 among subjects randomized to placebo

		Placebo								
Trial	N	death	MACE	lymphoma	solid organ tumors	malignancy excluding NMSC	opportunistic infections	tuberculosis	serious infections	herpes zoster
A3921025	69	0	0	0	0	0	0	0	0	1
A3921032	132	0	0	0	0	0	0	0	0	0
A3921035	59	0	0	0	0	0	0	0	0	0
A3921044	160	0	0	0	0	0	0	0	0	0
A3921045	122	0	1	0	0	0	0	0	0	0
A3921046	159	0	0	0	0	0	0	0	0	2
A3921064	108	0	0	0	0	0	0	0	1	0
** Total	**809**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**3**

Table 7. Events of interest during months 0 – 3 among subjects randomized to tofacitinib 5 mg

		Tofacitinib 5 mg								
Trial	N	death	MACE	lymphoma	solid organ tumors	Malignancy excluding NMSC	opportunistic infections	tuberculosis	serious infections	herpes zoster
A3921025	71	0	0	0	0	0	0	0	0	0
A3921032	133	0	1	0	0	0	0	0	0	0
A3921035	49	0	0	0	0	0	0	0	0	0

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A3921044	321	1	0	0	0	0	0	0	3	3
A3921045	243	0	0	0	0	0	0	0	0	0
A3921046	315	0	1	0	0	0	0	0	1	2
A3921064	204	0	0	0	1	1	0	0	1	1
** Total **	**1336**	**1**	**2**	**0**	**1**	**1**	**0**	**0**	**5**	**6**

(b) (4)

Table 9. Incidence ratio of events of interest, comparing tofacitinib vs. placebo during months 0 – 3 based on randomized treatment assignment

	Incidence ratio (95% CI)	Mantel-Haenszel RR (95% CI)	Mantel-Haenszel Risk Difference³ (95% CI)	Placebo¹ events/100 py	Tofacitinib² events/100 py
death	ND	ND	0.14 (-0.13, 0.41)	0	0.15
MACE	0.60 (0.01, 6.84)	0.66 (0.07, 6.07)	-0.21 (-1.43, 1.01)	0.54	0.31
lymphoma	ND	ND	-	0	0
solid organ tumors	ND	ND	0.28 (-0.11, 0.67)	0	0.31
malignancy excluding NMSC	ND	ND	0.28 (-0.11, 0.67)	0	0.31
opportunistic infections	ND	ND	-	0	0
tuberculosis	ND	ND	-	0	0
serious infections	2.89 (0.34, 24.15)	2.99 (0.39, 22.78)	1.05 (-0.40, 2.49)	0.54	1.70
herpes zoster	2.11 (0.63, 7.06)	2.22 (0.66, 7.48)	1.83 (-0.44, 4.10)	1.63	3.55

ND = not defined. Reference level is placebo
¹A total of 183.9 patient years of exposure were observed among patients on placebo
²A total of 648.1 patient years of exposure were observed among patients on tofacitinib
³Events in Tofacitinib per 100 py – Events in Placebo per 100py, with MH study weights

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3.3.1.1 Tofacitinib vs. placebo, sensitivity analysis

An alternative analysis was conducted comparing tofacitinib vs. placebo using the first 3 months after randomization, as in the previous analysis, with the addition of months 3 – 6 after randomization of patients who switched treatment from placebo to tofacitinib by study design at month 3 in trials A3921032 and 1045. The events among the additional patients included in this analysis are shown in Table 10. There was 1 additional death, 2 additional MACE, 2 additional serious infections and 2 additional herpes zoster infections reported among 218 additional patients who switched treatment to tofacitinib at month 3. The updated estimates of the corresponding pooled incidences and incidence ratios are shown in Table 11

These analyses suggest that tofacitinib might be associated with a higher risk of serious infections and herpes infections than placebo during the first 3 months of use. However, the estimated incidence ratio were not significantly different from 1 at the α=0.05 level, possibly due to the small number of events observed in these trials.

Table 10. Events of interest during months 3 – 6 among subjects who switched from placebo to tofacitinib by design at month3 in trials A3921032 and 1045

	Tofacitinib 5 mg and 10 mg, Months 3-6									
Trial	N	death	MACE	lymphoma	solid organ tumors	malignancy excluding NMSC	opportunistic infections	tuberculosis	serious infections	herpes zoster
						tofacitinib 5 mg				
A3921032	58	0	2	0	0	0	0	0	1	0
A3921045	55	0	0	0	0	0	0	0	1	0
** Total **	**113**	**0**	**2**	**0**	**0**	**0**	**0**	**0**	**2**	**0**
						tofacitinib 10 mg				
A3921032	53	1	0	0	0	0	0	0	0	0
A3921045	52	0	0	0	0	0	0	0	0	2
** Total **	**105**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**

Table 11. Incidence ratio of events of interest, comparing tofacitinib vs. placebo during months 0 – 3 based on randomized treatment assignment + months 3 – 6 of patients who switched treatment by design from placebo to tofacitinib at month 3

	Incidence ratio (95% CI)	Mantel-Haenszel RR (95% CI)	Mantel-Haenszel Risk Difference³ (95% CI)	Placebo¹ events/100 py	Tofacitinib² events/100 py
death	ND	ND	0.31 (-0.12, 0.73)	0	0.29
MACE	1.13 (0.13, 10.16)	1.18 (0.15, 9.04)	0.07 (-1.22, 1.36)	0.54	0.57
lymphoma	ND	ND	-	0	0
solid organ tumors	ND	ND	0.28 (-0.11, 0.66)	0	0.29
malignancy excluding NMSC	ND	ND	0.28 (-0.11, 0.66)	0	0.29
opportunistic infections	ND	ND	-	0	0
tuberculosis	ND	ND	-	0	0

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serious infections	3.36 (0.44, 25.80)	3.49 (0.46, 26.39)	1.29 (-0.17, 2.76)	0.54	1.86
herpes zoster	2.18 (0.66, 7.26)	2.31 (0.68, 7.82)	1.93 (-0.29 4.16)	1.63	3.58

ND = not defined. Reference level is placebo
[1]A total of 183.9 years of exposure were observed among patients on placebo
[2]A total of 698.8 years of exposure were observed among patients on tofacitinib
[3]Events in Tofacitinib per 100 py – Events in Placebo per 100py, with MH study weights

3.3.2 Tofacitinib vs. adalimumab

Two trials, A3921035 and 1064, randomized patients to an adalimumab treatment arm. This subsection compares the risk of major safety events of interest among patients randomized to tofacitinib 5 mg or 10 mg to patients randomized to adalimumab in these two trials.

Trial 1035 had duration of 6 months. Fifty-three patients were randomized to adalimumab and 110 patients were randomized to tofacitinib 5 mg or 10 mg. Patients were also randomized to tofacitinib 1mg, 3mg and 15 mg; but these patients are not included in the analyses discussed in this document. Table 12 shows that only one major safety event of interest, a solid organ tumor, was reported among patients randomized to adalimumab. There were no events reported among subjects randomized to tofacitinib. Due to the small sample size and lack of reported events, it is not possible to make a meaningful comparison between the risk of events in adalimumab and tofacitinib in trial 1035.

Trial 1064 had duration of 12 months. Two hundred four patients were randomized to adalimumab and 405 patients were randomized to tofacitinib 5 mg or 10 mg. Table 12 shows that there were more malignancy (excluding NMSC), tuberculosis, herpes zoster and serious infections reported among patients on tofacitinib than patients on adalimumab. [1]Months 0-3 **only**
[2]Months 0-12
Table 13 shows that the estimated incidence ratio for malignancy (excluding NMSC), 1.77 (0.18,16.99), serious infections, 2.59 95% CI (0.75, 8.94), and herpes zoster infections, 1.98 (0.74, 5.31), suggest a possibly higher risk of malignancy and infections associated with the use of tofacitinib. However, the estimated incidence ratios were not significantly different from 1 at the α=0.05 level, due to the small sample size and number of reported events.

Table 12. Events of interest among subjects randomized to tofacitinib 5 mg, 10 mg, and adalimumab in trials A3921035 and 1064

		Tofacitinib 5 mg, 10 mg and adalimumab								
Trial	N	Death	MACE	lymphoma	solid organ tumors	malignancy excluding NMSC	opportunistic infections	tuberculosis	serious infections	herpes zoster
					adalimumab					
A3921035[1]	53	0	0	0	1	1	0	0	0	0
A3921064[2]	204	0	3	0	1	1	0	0	3	5
					tofacitinib 5 mg and 10 mg					
A3921035[1]	110	0	0	0	0	0	0	0	0	0
A3921064[2]	405	0	2	0	3	3	0	2	15	19

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[1]Months 0-3 only
[2]Months 0-12

Table 13. Incidence ratio of events of interest, comparing tofacitinib (5 mg and 10 mg) vs. adalimumab during months 0 – 12 + 28 days based on randomized treatment assignment in trial A3921064

	Incidence ratio (95% CI)	Mantel-Haenszel RR (95% CI)	Risk Difference[3] (95% CI) per 100 py	Adalimumab[1] events/100 py	Tofacitinib[2] events/100 py
death	ND	ND	-	0	0
MACE	0.39 (0.07, 2.35)	0.34 (0.06, 1.99)	-1.01 (-2.89, 0.87)	1.54	0.53
lymphoma	ND	ND	-	0	0
solid organ tumors	1.77 (0.18,16.99)	1.51 (0.16, 14.43)	0.28 (-1.07, 1.63)	0.51	0.80
malignancy excluding NMSC	1.77 (0.18,16.99)	1.51 (0.16, 14.43)	0.28 (-1.07, 1.63)	0.51	0.80
opportunistic infections	ND	ND	-	0	0
tuberculosis	ND	ND	0.53 (-0.20, 1.26)	0	0.53
serious infections	2.59 (0.75, 8.94)	2.52 (0.74, 8.60)	2.43 (-0.19, 5.06)	1.54	3.98
herpes zoster	1.98 (0.74, 5.31)	1.91 (0.73, 5.05)	2.47 (-0.67, 5.60)	2.57	5.04

ND = not defined. Reference level is adalimumab
[1]A total of 194.5 years of exposure were observed among patients on adalimumab
[2]A total of 377.1 years of exposure were observed among patients on tofacitinib
[3]Events in Tofacitinib per 100 py – Events in Adalimumab per 100py

3.3.3 Tofacitinib 5 mg vs. tofacitinib 10 mg

This subsection compares the risk of major safety events of interest among patients randomized to tofacitinib 5 mg and patients randomized to tofacitinib 10 mg in the seven trials of interest. As described in Section 3.1 three analyses were conducted to compare the safety of tofacitinib 5 mg and tofacitinib 10 mg:

1) Only patients originally randomized to tofacitinib 5 and 10 mg BID at baseline.
2) Patients originally randomized to tofacitinib 5 and 10 mg BID + patients who advanced 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).
3) Patients originally randomized to tofacitinib 5 and 10 mg BID + patients who advanced 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 who escaped to tofacitinib 5 and 10 mg BID due to active disease.

In these analyses patients are censored at the first of the following times: patient's first recorded event, patient's last tofacitinib dose + 28 days window, or 12 months after randomization + 28 days window.

Analysis 1 is discussed in section 3.3.3.1. Analyses 2 and 3 are discussed in section 3.3.3.2.

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3.3.3.1 Tofacitinib 5 mg vs. 10 mg during months 0 – 12 based on randomized treatment assignment

Comparable numbers of deaths were observed between the 5 mg group and the 10 mg group (5 vs. 4); (b) (4) The number of solid organ tumors, serious infections and herpes zoster infections were comparable between the tofacitinib doses.

Table 15 shows the estimated incidence ratio for these events. Due to the small number of events, the confidence intervals associated with the IRs of malignancy (excluding NMSC), death and MACE were large and preclude meaningful conclusions. (b) (4) (b) (4)

Table 14. Events of interest during months 0 – 12 + 28 days among subjects randomized to tofacitinib 5 mg or 10 mg

		Tofacitinib 5 mg and 10 mg, Months 0-12								
Trial	N	death	MACE	lymphoma	Solid organ tumors	malignancy excluding NMSC	opportunistic infections	tuberculosis	Serious infections	herpes zoster
						tofacitinib 5 mg				
A3921025	71	0	0	0	1	1	0	0	1	1
A3921032	133	0	1	0	0	0	0	0	3	1
A3921035	49	0	0	0	0	0	0	0	0	1
A3921044	321	3	0	0	2	2	2	0	16	16
A3921045	243	0	0	0	0	0	0	0	1	2
A3921046	315	1	2	0	0	0	1	0	3	14
A3921064	204	1	1	0	2	2	0	0	7	7
** Total **	**1336**	**5**	**4**	**0**	**5**	**5**	**3**	**0**	**31**	**42**

(b) (4)

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Table 15. Incidence ratio of events of interest, comparing tofacitinib 10 mg vs. tofacitinib 5 mg during months 0 – 12 + 28 days based on randomized treatment assignment

(b) (4)

	Incidence ratio (95% CI)	Mantel-Haenszel RR (95% CI)	Mantel-Haenszel Risk Difference[3] (95% CI)	Tofacitinib 5 mg[1] events / 100 py
Death	0.80 (0.21, 2.95)	0.80 (0.22, 3.00)	-0.10 (-0.65, 0.46)	0.47
MACE	1.49 (0.42, 5.30)	1.50 (0.42, 5.30)	0.19 (-0.39, 0.77)	0.38
Lymphoma	ND	ND	0.09 (-0.09, 0.28)	0
solid organ tumors	1.18 (0.36, 3.87)	1.20 (0.37, 3.94)	0.09 (-0.53, 0.70)	0.47
Malignancy excluding NMSC	1.38 (0.44, 4.35)	1.41 (0.45, 4.42)	0.18 (-0.46, 0.82)	0.47
opportunistic infections	1.31 (0.29, 5.87)	1.34 (0.30, 5.97)	0.09 (-0.40, 0.57)	0.28
Tuberculosis	ND	ND	0.56 (0.11, 1.01)	0
serious infections	0.95 (0.58, 1.57)	0.98 (0.59, 1.60)	-0.13 (-1.55, 1.28)	2.94
herpes zoster	0.98 (0.64, 1.51)	1.00 (0.66, 1.52)	-0.06 (-1.71, 1.59)	3.98

ND = not defined. Reference level is tofacitinib 5 mg

[1]A total of 1055.5 years of exposure were observed among patients on tofacitinib 5 mg

(b) (4)

3.3.3.2 Tofacitinib 5 mg vs. 10 mg during months 0 – 12 based on randomized treatment assignment + subjects who switched treatment from placebo to tofacitinib

Analyses 2 and 3 described in Section 3.3.3.1 include patients who switched treatment from placebo to tofacitinib at months 3 and 6. Table 16 and Table 17 show the number of special safety events of interest observed among these subjects. These tables show that few additional events were observed among patients who switched from placebo to tofacitinib. Among patients who switched to tofacitinib 5 mg there were 2 additional MACE, 1 opportunistic infection, 3 serious infections and 5 herpes infections.

(b) (4)

Table 16. Events of interest during months 3 – 12 + 28 days among subjects who switched from placebo to tofacitinib by at month 3

		Events during months 3 – 12 among switchers from placebo to tofacitinib at month 3								
Trial	N	death	MACE	lymphoma	Solid organ tumors	malignancy excluding NMSC	opportunistic infections	tuberculosis	serious infections	herpes zoster
					switch from placebo to tofacitinib 5 mg					
A3921025[1]	18	0	0	0	0	0	0	0	0	0
A3921032	58	0	2	0	0	0	0	0	1	0
A3921035	25	0	0	0	0	0	0	0	0	0
A3921044	42	0	0	0	0	0	0	0	0	2
A3921045	55	0	0	0	0	0	0	0	1	0
A3921046	37	0	0	0	0	0	0	0	0	0
A3921064	28	0	0	0	0	0	0	0	0	0
** Total **	**263**	**0**	**2**	**0**	**0**	**0**	**0**	**0**	**2**	**2**

(b) (4)

[redacted]

Table 17. Events of interest during months 6 – 12 + 28 days among subjects who switched from placebo to tofacitinib by at month 6

		Events during months 6 – 12 among switchers from placebo to tofacitinib at month 6								
Trial	N	death	MACE	lymphoma	solid organ tumors	malignancy excluding NMSC	opportunistic infections	tuberculosis	serious infections	herpes zoster
					Switch from placebo to tofacitinib 5 mg					
A3921044	31	0	0	0	0	0	1	0	0	2
A3921046	36	0	0	0	0	0	0	0	0	1
A3921064	23	0	0	0	0	0	0	0	1	0
** Total **	**90**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**1**	**3**

(b) (4)

[redacted]

Analysis 2 includes all patients randomized to tofacitinib 5 mg or 10 mg at baseline plus patients who switched treatment from placebo to tofacitinib (by design) at month 3 in trials 1032 and 1045, plus patients who switched treatment from placebo to tofacitinib at month 6 in trials 1044, 1046 and 1064. Note that patients who switched treatment at month 6 in these last 3 trials were considered "responders" based on an efficacy outcome at month 3; therefore they may be different from patients originally randomized to tofacitinib or from those who switched treatment by design at month 3 in trials 1032 and 1045. The patients and counts of events used in Analysis 2 are shown in

Table 18. The updated incidence ratios based on Analysis 2 are shown in Table 19. Due to the small number of additional events among switchers, the results of Analysis 2 are similar to those of Analysis 1 shown in Table 15, except for the estimated IR of MACE which went from 1.49 (0.42, 5.30) in Analysis 1 to 1.00 (0.32, 3.10) in Analysis 2 due to the additional 2 MACE events observed among subjects who switched treatment to tofacitinib 5 mg.

Reference ID: 3197461

Table 18. Events of interest during months 0 – 12 + 28 days among subjects randomized to tofacitinib 5 mg or 10 mg + patients who transitioned from placebo to tofacitinib by study design (month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064).

Tofacitinib 5 mg and 10 mg, Months 0 – 12 + patients who transitioned from placebo to tofacitinib by study design										
Trial	N	death	MACE	lymphoma	solid organ tumors	malignancy excluding NMSC	opportunistic infections	tuberculosis	serious infections	herpes zoster
						tofacitinib 5 mg				
A3921025	71	0	0	0	1	1	0	0	1	1
A3921032	191	0	3	0	0	0	0	0	4	1
A3921035	49	0	0	0	0	0	0	0	0	1
A3921044	352	3	0	0	2	2	3	0	16	18
A3921045	298	0	0	0	0	0	0	0	2	2
A3921046	351	1	2	0	0	0	1	0	3	15
A3921064	227	1	1	0	2	2	0	0	8	7
** Total **	**1539**	**5**	**6**	**0**	**5**	**5**	**4**	**0**	**34**	**45**

(b) (4)

Table 19. Incidence ratio of events of interest, comparing tofacitinib 10 mg vs. tofacitinib 5 mg during months 0 – 12 + 28 days based on randomized treatment assignment + patients who transitioned from placebo to tofacitinib by study design (month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064).

(b) (4)

	Incidence ratio (95% CI)	Mantel-Haenszel RR (95% CI)	Mantel-Haenszel Risk Difference³ (95% CI)	Tofacitinib 5 mg¹ events / 100 py
Death	0.80 (0.21, 2.96)	0.81 (0.22, 3.00)	0.00 (-0.54, 0.54)	0.44
MACE	1.00 (0.32, 3.10)	1.01 (0.33, 3.13)	0.00 (-0.59, 0.59)	0.53
Lymphoma	ND	ND	0.09 (-0.08, 0.25)	0
solid organ tumors	1.18 (0.36, 3.88)	1.20 (0.37, 3.93)	0.08 (-0.49, 0.65)	0.44
Malignancy excluding NMSC	1.38 (0.44, 4.35)	1.41 (0.45, 4.41)	0.17 (-0.42, 0.76)	0.44
opportunistic infections	0.99 (0.25, 3.94)	1.01 (0.25, 4.01)	-0.01 (-0.49, 0.48)	0.35
tuberculosis	ND	ND	0.52 (0.11, 0.94)	0
serious infections	0.93 (0.57, 1.51)	0.95 (0.59, 1.53)	-0.20 (-1.56, 1.17)	2.98
herpes zoster	0.99 (0.65, 1.49)	1.00 (0.67, 1.50)	-0.04 (-1.64, 1.54)	3.94

ND = not defined. Reference level is tofacitinib 5 mg
¹A total of 1142.7 years of exposure were observed among patients on tofacitinib 5 mg

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(b) (4)

Analysis 3 includes all patients in Tables 10 – 12, including patients considered "non-responders" based on an efficacy outcome at month 3 who switched treatment from placebo to tofacitinib. The patients and counts of events used in Analysis 3 are shown in Table 20. The updated incidence ratios based on Analysis 3 are shown in Table 21. The results are similar to those of Analysis 2 shown in Table 19.

Table 20 and Table 21 show that few additional events were observed among patients who switched from placebo to tofacitinib, with the exception of herpes zoster infections, in which 2 new events were observed among switchers to tofacitinib 5 mg (b) (4) Three additional herpes infections were observed among switchers to tofacitinib 5 mg at month 6, (b) (4)

Table 20. Events of interest during months 0 – 12 + 28 days among subjects randomized to tofacitinib 5 mg or 10 mg + patients who transitioned from placebo to tofacitinib at either month3 or month 6 (by design or by response).

Tofacitinib 5 mg and 10 mg, Months 0-12 + all patients who transitioned from placebo to tofacitinib

Trial	N	death	MACE	lymphoma	solid organ tumors	malignancy excluding NMSC	opportunistic infections	tuberculosis	serious infections	herpes zoster
						tofacitinib 5 mg				
A3921025	89	0	0	0	1	1	0	0	1	1
A3921032	191	0	3	0	0	0	0	0	4	1
A3921035	74	0	0	0	0	0	0	0	0	1
A3921044	394	3	0	0	2	2	3	0	16	20
A3921045	298	0	0	0	0	0	0	0	2	2
A3921046	388	1	2	0	0	0	1	0	3	15
A3921064	255	1	1	0	2	2	0	0	8	7
** Total **	1689	5	6	0	5	5	4	0	34	47

(b) (4)

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Table 21. Incidence ratio of events of interest, comparing tofacitinib 10 mg vs. tofacitinib 5 mg during months 0 – 12 + 28 days based on randomized treatment assignment + patients who transitioned from placebo to tofacitinib at either month3 or month 6 (by design or by response).

	Incidence ratio (95% CI)	Mantel-Haenszel RR (95% CI)	Mantel-Haenszel Risk Difference (95% CI)	Tofacitinib 5 mg[1] events / 100 py
Death	0.80 (0.22, 2.99)	0.80 (0.22, 3.00)	0.00 (-0.50, 0.50)	0.40
MACE	1.01 (0.33, 3.12)	1.02 (0.33, 3.15)	0.00 (-0.54, 0.55)	0.48
Lymphoma	ND	ND	0.08 (-0.08, 0.24)	0
solid organ tumors	1.21 (0.37, 3.97)	1.25 (0.38, 4.13)	0.09 (-0.44, 0.61)	0.40
Malignancy excluding NMSC	1.42 (0.45, 4.45)	1.45 (0.46, 4.63)	0.17 (-0.38 0.71)	0.40
opportunistic infections	0.99 (0.25, 3.98)	1.02 (0.26, 4.05)	0.00 (-0.45, 0.45)	0.32
tuberculosis	ND	ND	0.49 (0.10, 0.88)	0
serious infections	0.97 (0.60, 1.57)	1.00 (0.62, 1.60)	-0.06 (-1.34, 1.22)	2.74
herpes zoster	1.07 (0.72, 1.59)	1.09 (0.74, 1.61)	0.27 (-1.26, 1.80)	3.79

(b) (4)

ND = not defined. Reference level is tofacitinib 5 mg
[1]A total of 1240.1 years of exposure were observed among patients on tofacitinib 5 mg

(b) (4)

The three analyses comparing tofacitinib 5 mg to 10 mg show no evidence of a difference in the risk of death, MACE, lymphoma, solid organ tumors, opportunistic infection excluding tuberculosis, serious infections or herpes zoster infections between patients treated with tofacitinib 5 mg and 10 mg. It is possible that no difference in risk was found between both treatment arms because of the small sample size and observed number of events. It is possible that a larger sample size with correspondingly larger number of observed events could show a difference in the risk of one or more of these events between tofacitinib 5 mg and 10 mg. (b) (4)

There were no new tuberculosis infections among switchers to tofacitinib. (b) (4)

3.3.4 Summary of results

In Section 3.3.1, we compared the risk of major safety events of interest among patients randomized to tofacitinib 5 mg and 10 mg, and patients randomized to placebo during months 0 – 3 of the clinical trials. This analysis suggests that tofacitinib might be associated with a higher risk of serious infections, IR 2.89 (0.34, 24.15), and herpes infections, IR 2.11 (0.63,

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7.06), than placebo during the first 3 months of use. However, the estimated incidence ratios were not significantly different from 1, possibly due to the small number of observed events during months 0-3. Therefore, the direction of the difference in risk, if any, is not known with much confidence.

Section 3.3.2 compared the risk of major safety events of interest among patients randomized to tofacitinib and patients randomized to adalimumab in trials 1035 and 1064. Trial 1035 had only one major safety event of interest, a solid organ tumor, reported among patients randomized to adalimumab and no events reported among subjects randomized to tofacitinib. Due to the lack of reported events in trial 1035, it was not possible to compare the risk of events between the two treatments. In trial 1064, tofacitinib had a higher rate of serious infections than adalimumab, IR 2.59 (0.75, 8.94), and herpes zoster infections, IR 1.98 (0.74, 5.31). These estimated incidence ratios were not significantly different from 1 at the α=0.05 level, due to the small sample size and number of reported events.

Section 3.3.3 compared the risk of major safety events of interest among patients receiving tofacitinib 5 mg or tofacitinib 10 mg. The analyses conducted in this review found no evidence of a difference in the risk of death, MACE, lymphoma, solid organ tumors, opportunistic infections excluding tuberculosis, serious infections and herpes zoster infections between patients treated with tofacitinib 5 mg or 10 mg. (b) (4) It is possible that a larger sample size could show a statistically significant difference in the risk of one or more of these events between tofacitinib 5 mg and 10 mg.

4 SUMMARY AND CONCLUSIONS

Pfizer proposes tofacitinib (CP-690,550) 5 mg and 10 mg orally administered twice a day (BID) for the treatment of rheumatoid arthritis (RA). To support this marketing application, the applicant submitted data from 21 Phase 1 studies, six Phase 2 studies, and five Phase 3 studies. The focus of the efficacy statistical review was on the five Phase 3 studies 1032, 1044, 1045, 1046, and 1064. Please refer to the statistical review by Dr. Kim dated on June 23, 2012 for a detailed review of the efficacy data. Dr. Kim concluded that there is substantial evidence of efficacy of tofacitinib 5 mg or 10 mg for the treatment of rheumatoid arthritis. This is based on consistent findings in the domains of reducing signs and symptoms of RA as measured by ACR20, and improving physical function as measured by HAQ-DI.

The focus of this statistical review was on the controlled portion of the two Phase 2 studies 1025 and 1035, and the five Phase 3 studies 1032, 1044, 1045, 1046, and 1064. Based on comprehensive analyses of the major safety events of interest, there is suggestion that tofacitinib might be associated with a higher risk of serious infections, and herpes infections compared to placebo, as well as to adalimumab during the first 3 months of use. Furthermore, there is some

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(b) (4)

Therefore, the direction of the difference in risk, if any, is not known with much confidence. The analyses conducted in this review found no evidence of a difference in the risk of death, MACE, lymphoma, solid organ tumors, opportunistic infections excluding tuberculosis, serious infections and herpes zoster infections between patients treated with tofacitinib 5 mg or 10 mg.

To quantify the risk-benefit profile of tofacitinib 5 mg and 10 mg, an integrated analysis of the seven randomized-controlled studies was conducted for the primary endpoints, ACR20 and HAQ-DI at week 12, as well as DAS28 responders at week 12. For binary outcomes, difference in proportions (or rates for the safety endpoints) was calculated using Mantel-Haesnzel statistics controlled by study. For continuous outcome (i.e. HAQ-DI), mean difference was calculated using analysis of covariance adjusting for study, site, and baseline score.

Overall, there is a 6% difference in the proportion of patients achieving an ACR20 response in the tofacitinib 10 mg group compared tofacitinib 5 mg group, and the mean difference in HAQ-DI scores between tofacitinib 10 mg and 5 mg is about 0.08 (Table 22). (b) (4)

Clinical assessment of the balance of risk and benefit of the 10 mg dose is needed as the differences in the efficacy between tofacitinib 10 mg and 5 mg for symptomatic treatment of RA may not justify the potential risk (b) (4)

The risk-benefit profile as it currently stands may favor the tofacitinib 5 mg group.

Table 22: Integrated Analyses of Efficacy and Safety

	Tofacitinib 5 mg versus placebo	**Tofacitinib 10 mg versus placebo**	**Tofacitinib versus placebo**	**Tofacitinib 10 mg versus 5 mg**
Efficacy Endpoints †				
ACR20 at Week 12 (difference in proportions)	28% (24%, 32%)	34% (30%, 38%)	31% (27%, 35%)	6% (3%, 10%)
HAQ-DI at Week 12 (mean difference)	-0.23 (-0.28, -0.18)	-0.32 (-0.36, -0.27)	-0.27 (-0.32, -0.23)	-0.08 (-0.13, -0.04)
Selected Safety Endpoints ‡ (difference in rates)				
Serious Infection (0 – 3 months)			1.3% (-0.2%, 2.8%)	

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Herpes Infection (0 – 3 months)		1.9% (-0.3% 4.2%)	
Tuberculosis Infection (0 – 12 months)			0.5% (0.1%, 0.9%)
Malignancy (0 – 12 months)			0.2% (-0.4%, 0.8%)

† includes all randomized patients. Nonresponder imputation was applied to missing binary outcome data and baseline observation was carried forward to missing HAQ-DI score at week 12.
‡ includes all randomized patients plus patients who transitioned from placebo to tofacitinib by study design

The following are our labeling recommendations

1. Include all seven randomized-controlled studies (1025, 1035, 1032, 1044, 1045, 1046, and 1064) in the Adverse Reactions and Clinical Trials sections.
2. In the Adverse Reactions section, report the number of events and adjusted incidence ratios with confidence intervals for the major events of interest. (b) (4)
3. In the Clinical Trials section, include the results from the analyses of ACR20, HAQ-DI, and DAS28 in the label. (b) (4)

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Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 203214
Drug name:	tofacitinib
Indication(s):	Rheumatoid arthritis
Applicant:	Pfizer
Documents Reviewed:	Electronic submission Electronically submitted dataset Dated: 2011-10-21
Review Priority:	Normal
Biometrics Division:	Division of Biometrics 6
Statistical Reviewer:	Matthew Jackson, PhD
Concurring Reviewer:	Karl Lin, PhD
Medical Division:	DPARP
Reviewing Pharmacologist:	Lawrence Leshin, Ph.D.
Keywords:	Animal Mouse Rat Carcinogenicity

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Background

In this submission the sponsor included reports of two animal carcinogenicity studies, in mice and rats, to assess the carcinogenic potential of tofacitinib when administered by gavage, once daily at appropriate drug levels for about 26 weeks (in the mouse study) or 104 weeks (in the rat study). Results of this review have been discussed with the reviewing pharmacologist, Lawrence Leshin, Ph.D..

In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

Chapter 1

Mouse Study

1.1 Experimental design

The study comprised one hundred and fifteen CB6F1/Jic-TgrasH2 Tac mice of each sex. The mice were separated by sex, so that two separate experiments were conducted. In both the male and female mice experiments, these mice were randomly assigned to five groups, a control group (twenty five animals), a low dose group (twenty five animals), a mid dose group (twenty five animals), a high dose group (twenty five animals), and a positive control group (fifteen animals).

In both experiments, the low dose group reveived a daily dose of tofacitinib of 25 mg per kilogram of bodyweight. The mid dose received a daily dose of 75 mg/kg, and the high dose goup received a dose of 200mg/kg. The vehicle for tofacitinib was 0.5% methylcellulose (w/v), which was administered to all animals, including those in the control group, but not those in the positive control group, by gavage, for a daily dose volume of 10 mL per kilogram of bodyweight. The positive control animals received a single dose of 75 mg/kg of N-nitroso-N-methylurea (MNU). The vehicle for the positive control animals was acidified saline, administered in a single intreperitneal dose of 10 mL/kg on day 1 of the study.

Animals were examined for mortality, abnormality, and signs of distress twice a day. Detailed observations, including palpation exams, were conducted weekly. Complete necroscopies were performed on all animals, except for the positive control animals, after sacrifice, euthanasia, or after being found dead. In the case of the positive control animals, only those organs expected to show signs of tumorigenicity related to the positive control agent were analyzed.

1.2 Sponsor's analysis

1.2.1 Survival analysis

The two-tailed Tarone trend test using the control and tofacitinib groups was performed at the 0.05 level of significance. If the initial test showed a significant trend, then one-tailed Tarone tests in the same direction of that trend were to be performed at the 0.05 level in a sequential, step-down manner (i.e., from highest dose to lowest dose).

No significant results have been reported execpt that, as expected, the animals in the positive control group had considerably reduced survival relative to the negative control.

1.2.2 Tumor analysis

For each tumor type, a dose response relationship was tested using the Cochran-Armitage trend test at the 5% level. In the event of a positive finding, the test would be repeated with the highest dose group excluded.

The only noteworthy findings were increased incidence of a number of neoplasms in the positive control group compared with the negative control.

1.3 Data analysis

1.3.1 Survival analysis

The Kaplan-Meier survival plots are shown as figures 1.1 and 1.2. The numbers and proportions of animals surviving to various times are presented in table 1.1. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table 1.2, and the results of log-rank survival tests comparing the treated groups with the control group are presented in table 1.3.

Figure 1.1: Survival curves for female mice

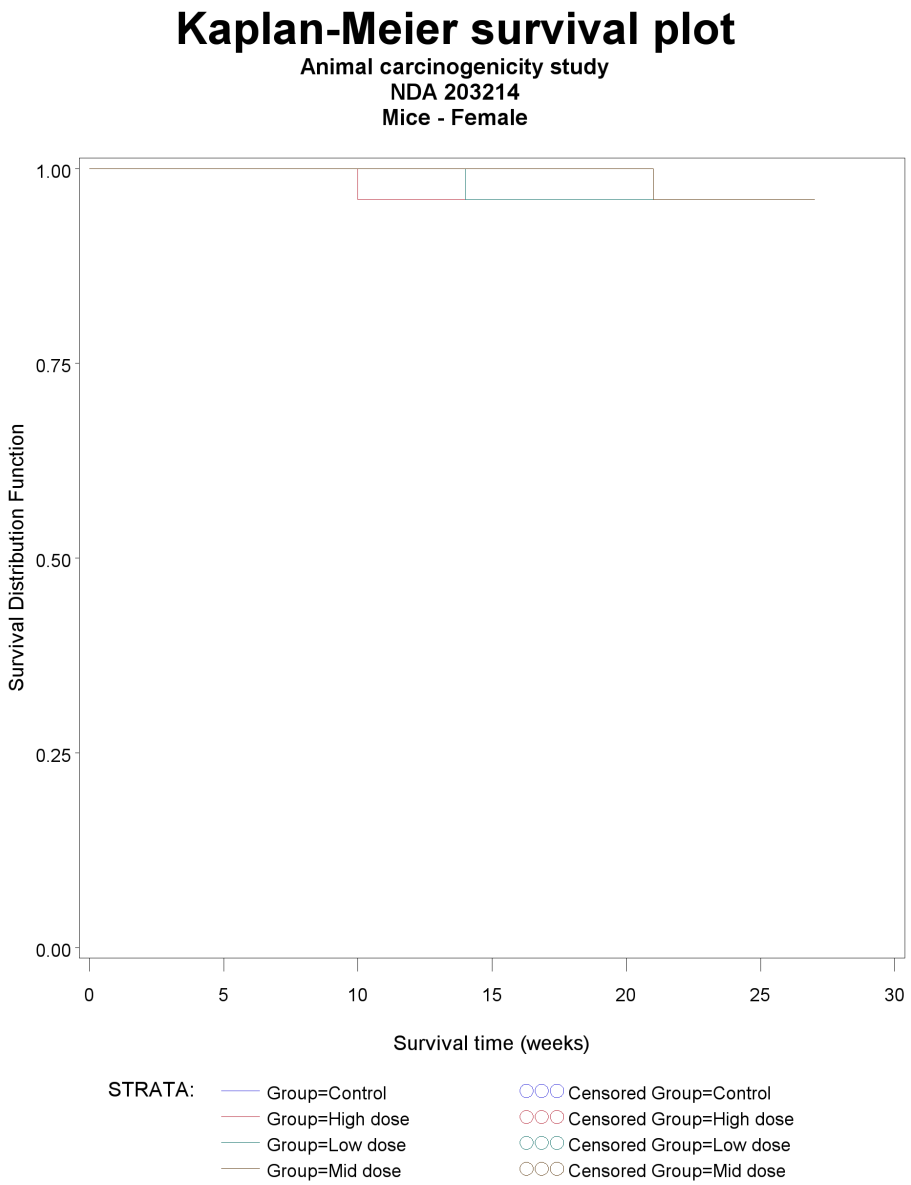

Figure 1.2: Survival curves for male mice

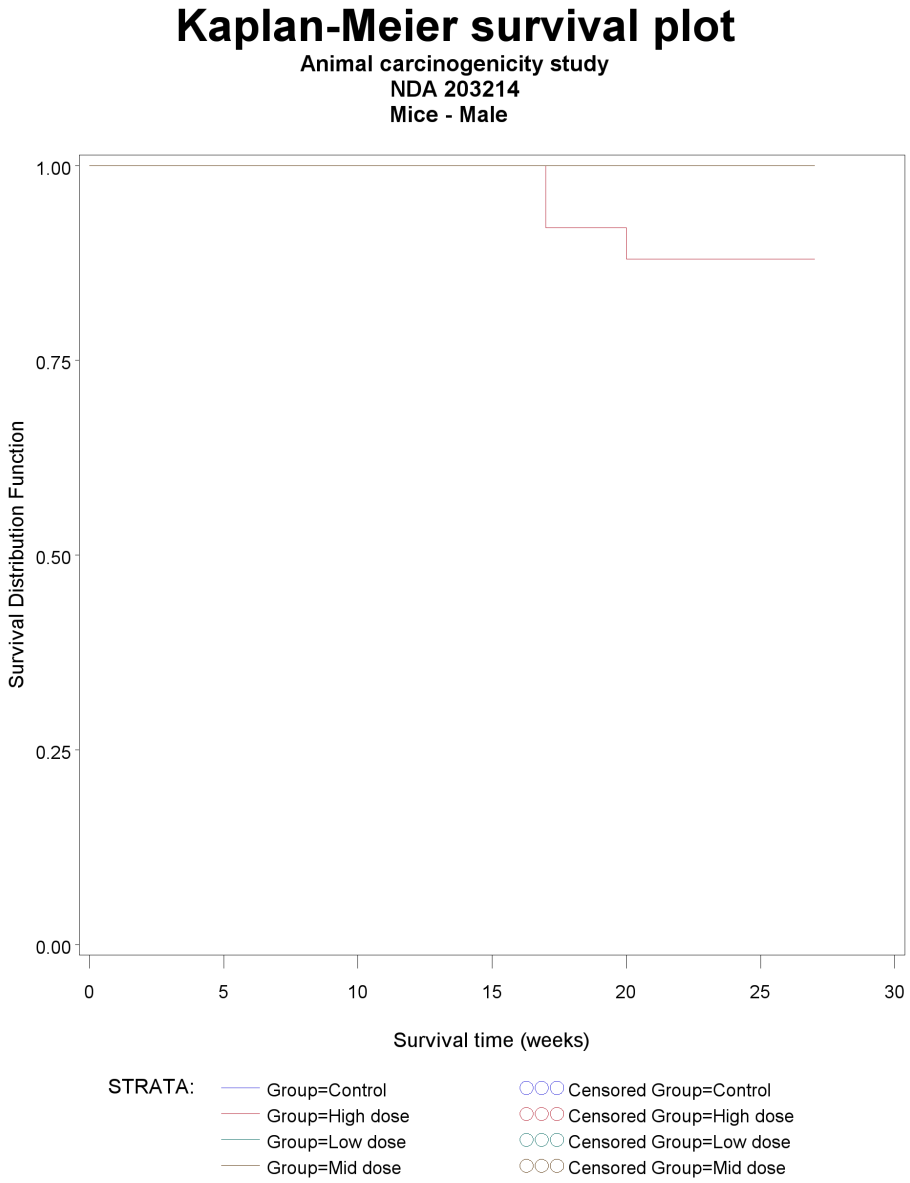

Table 1.1

Survival rates at key times
NDA 203214
Animal carcinogenicity study
Mice

Species and Sex	*Dose Group*	*Dose (mg per kg)*	*Number at start*	*Number alive after 12 weeks*	*Percentage alive after 12 weeks*	*Number alive after 19 weeks*	*Percentage alive after 19 weeks*	*Number alive after 22 weeks*	*Percentage alive after 22 weeks*	*Number sacrificed*	*Percentage sacrificed*	*maxtime*
Mice - Female	Control	0	25	25	100%	24	96%	24	96%	.	.	.
	Low dose	25	25	25	100%	24	96%	24	96%	.	.	.
	Mid dose	75	25	25	100%	25	100%	24	96%	.	.	.
	High dose	200	25	24	96%	24	96%	24	96%	.	.	.
Mice - Male	Control	0	25	25	100%	25	100%	25	100%	.	.	.
	Low dose	25	25	25	100%	25	100%	25	100%	.	.	.
	Mid dose	75	25	25	100%	25	100%	25	100%	.	.	.
	High dose	200	25	25	100%	23	92%	22	88%	.	.	.

Commentry In the case of the female mice, the numbers of premature deaths is too small to draw any statistical conclusions about toxic effects. Among male mice, however, all three of the premature deaths occured in the high dose group. This is sufficient to conclude the existence of a dose related trend in mortality ($p = 0.0022$). The comparison between the high dose group and the control is also significant: ($p = 0.0130$).

1.3.2 Tumor analysis

Endpoints

Analyses have been conducted using the sponsor's submitted dataset, and the sponsor's chosen nomenclature. In this dataset, organs or tissue types are described as being either tumorous, examined but found unusable due to autolysis, or unexamined. An organ that has been examined but was not found to be tumorous is not mentioned in the dataset.

From these data, we can infer the numbers of animals for which each organ or tissue type was examined, but only in those cases where at least one anomalous finding (i.e., a tumor was found, or a sample that was planned to be analyzed could not be, either because no sample was taken or becasue the sample was unusable due to autolosys) was reported. Organs which can thus be deduced to have been successfully analyzed in the majority of animals are, for the purposes of this review, considered *primary*. The lists of primary organs in the experiments on female and male mice respectively are presented in tables 1.4 and 1.5.

Organ or tissue types which were examined in only a few animals are considered *secondary*.

In the mouse study, there are no secondary organs.

Each tumor type found in a primary organ of at least one animal is considered a co-primary endpoint. In addition, in consultation with Lawrence Leshin, Ph.D., a list of combination endpoints has been drawn up. This list is presented in table 1.6.

Table 1.2: Results of log-rank tests of survival across all groups

Log-rank tests of survival
NDA 203214
Animal carcinogenicity study
Mice

Sex	*Test of homogeneity: chi squared statistic*	*Test of homogeneity: degrees of freedom*	*Number of groups*	*Test of homogeneity: p-value*	*Test of trend (two tailed): p-value*	*Test of trend (one tailed): p-value*
Female	0.0005	3	4	1.0000	0.9868	0.4934
Male	9.3162	3	4	0.0254	0.0043	0.0022

Table 1.3

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 203214
Animal carcinogenicity study
Mice

Species and Sex	*Quantity*	*Low dose*	*Mid dose*	*High dose*
Mice - Female	Chi squared test statistic	0.0000	0.0001	0.0002
	p-value of comparison with control	1.0000	0.9942	0.9885
Mice - Male	Chi squared test statistic	0.0000	0.0000	6.1671
	p-value of comparison with control	1.0000	1.0000	0.0130

Table 1.4

Primary organs in study of female mice
NDA 203214
Animal carcinogenicity study

Organ or tissue name
Body, Whole/Cav
Gallbladder
GI, Harderian
GI, Mandib Saliv
LN, Inguinal
LN, Mesenteric
Lung
Mammary, Female
Nerve, Optic
Ovary
Oviduct
Parathyroid
Peyer's Patch
Skin/Subcutis
Stomach, Nongl
Teeth, Other
Thymus
Thyroid
Ureter
Urinary Bladder

Reference ID: 3155338

Table 1.5

Primary organs in study of male mice
NDA 203214
Animal carcinogenicity study

Organ or tissue name
Body, Whole/Cav
Bone, Sternum
Gallbladder
GI, Harderian
LN, Inguinal
LN, Mesenteric
Lung
Marrow, Sternum
Nerve, Optic
Nerve, Sciatic
Parathyroid
Peyer's Patch
Pituitary
Skin/Subcutis
Stomach, GI
Stomach, Nongl
Thymus
Thyroid
Trachea
Ureter

Reference ID: 3155338

Table 1.6

Customized and combination endpoints analyzed
NDA 203214
Animal carcinogenicity study

Composite endpoint
Acinar cell tumors
All Thymomas
Angiomas, hemangiomas, and hemangiosarcomas
Basal cell adenomas and carcinomas
Bronchiolar-alveolar tumors
C-cell tumors
Fibromas and fibrosarcomas of the skin and subcutis
Follicular cell tumors
Glial brain tumors
Islet cell tumors
Kidney and urinary transitional cell tumors
Kidney carcinomas
Leukemias
Lipomas
Lipomas and hibernomas
Meningeal tumors
Ovarian granulosa, theca and luteal tumors
Pheochromocytomas
Schwannomas
Sebaceous cell tumors
Squamous cell carcinoma or papilloma
Squamous cell tumors of the skin and subcutis
Uterine, vaginal, and cervical adenomas
Uterine, vaginal, and cervical polyps
Uterine, vaginal, and cervical tumors

Reference ID: 3155338

Statistical procedure

The tumor data were analyzed for dose response relationships and pairwise comparisons of tumor incidence in each of the treated groups versus the vehicle control group. Both the dose response relationship tests and pairwise comparisons were performed using the poly-k method described in the paper of Bailer and Portier[1] and developed in the paper of Bieler and Williams[2]. In this method, given a tumor type T, an animal h that lives the full study period (w_m) or dies before the terminal sacrifice with at least one tumor of type T gets a score of $s_h = 1$. An animal that dies at week w_h before the end of the study without such a tumor gets a score of

$$s_h = \left(\frac{w_h}{w_m}\right)^k < 1.$$

The adjusted group size is defined as $\sum_h s_h$. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops at least one tumor of type T, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. The test is repeated for each tumor type T.

One critical point to consider in the application of the poly-k test is the choice of the appropriate value of k, which depends on the relationship between tumor onset time and increased dose. There is no consensus for the correct value to use for studies of transgenic mice. In the absence of such a consensus, this review uses the value $k = 1$, a value which is consistent with the assumption of constant hazard over the twenty six week period of the study. In any event, when there is little premature mortality (as is typically the case with transgenic mouse studies — see section 1.3.1), the analyses are not very sensitive to variations in the value of k.

For the calculation of p-values, the exact permutation method was used.

Under normal circumstances, since so many end points are being tested, it is appropriate to make some sort of multiplicity adjustment in order to control type I error. However, in the case of transgenic mice there is no guidance specifying how this should be done. Furthermore, in light of the fact that exact tests tend to be very conservative when considering rare events, the fact that there are only twenty five animals in each group, and the fact that tumorigenesis is very rare over the twenty six weeks that transgenic mouse studies typically run, it seems reasonable to consider each test as having yielded positive findings whenever the p-value is below 0.05.

Noteworthy results

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables 1.7 (female mice) and 1.8 (male mice). The results of analyses of customized endpoints (see table 1.6) are presented in tables 1.9 and 1.10.

No statistical tests were conducted in either sex for which the reported p-value was below 0.05.

1.3.3 Analysis of unexamined and autolytic organs

Unexamined animals

No animals have been reported as completely unexamined.

Organs reported autolytic

The numbers of organs found in female mice to be autolytic to the extent that analysis of collected tiussue was not possible are presented in table 1.11. The numbers of such organs found in male mice are presented in table 1.12.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables 1.13 and 1.14.

1.3.4 Tables of results

Table 1.7

Table of reported tumors in Mouse Study
NDA 203214
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 25*	*Low dose Size = 25*	*Mid dose Size = 25*	*High dose Size = 25*
Body, Whole/Cav	Hemangiosarcoma	P-value of test of trend or comparison	.9988	.9059	1	1
		Number of animals reported with tumor	4	2	0	0
GI, Harderian	Adenoma	P-value of test of trend or comparison	.4176	.2447	.5000	.5000
		Number of animals reported with tumor	0	2	1	1
Lung	Adenoma, Bronchiolar-Alveo	P-value of test of trend or comparison	.8565	.5000	.5000	1
		Number of animals reported with tumor	1	2	2	0
	Carcinoma, Bronchiolar-Alv	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Skin/Subcutis	Carcinoma, Squamous Cell	P-value of test of trend or comparison	.4947		.4894	
		Number of animals reported with tumor	0	0	1	0
Thymus	Malignant Thymoma	P-value of test of trend or comparison	.6065	.5000	.4889	
		Number of animals reported with tumor	0	1	1	0

Reference ID: 3155338

Table 1.8

Table of reported tumors in Mouse Study
NDA 203214
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 25*	*Low dose Size = 25*	*Mid dose Size = 25*	*High dose Size = 25*
Body, Whole/Cav	Hemangioma	P-value of test of trend or comparison	.4898		.5000	
		Number of animals reported with tumor	0	0	1	0
	Hemangiosarcoma	P-value of test of trend or comparison	.8244	.5000	1	.8670
		Number of animals reported with tumor	2	3	0	1
GI, Harderian	Adenoma	P-value of test of trend or comparison	.7423	1	.7551	1
		Number of animals reported with tumor	1	0	1	0
Lung	Adenoma, Bronchiolar-Alveo	P-value of test of trend or comparison	.3708	1	.7551	.7340
		Number of animals reported with tumor	1	0	1	1
	Carcinoma, Bronchiolar-Alv	P-value of test of trend or comparison	.4898		.5000	
		Number of animals reported with tumor	0	0	1	0
Skin/Subcutis	Carcinoma, Squamous Cell	P-value of test of trend or comparison	.7423	.5000		
		Number of animals reported with tumor	0	1	0	0

Reference ID: 3155338

Table 1.9

Table of reported tumors in Mouse Study
NDA 203214
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 25*	*Low dose Size = 25*	*Mid dose Size = 25*	*High dose Size = 25*
All Thymomas	P-value of test of trend or comparison	.6065	.5000	.4889	
	Number of animals reported with tumor	0	1	1	0
Angiomas, hemangiomas, and hemangiosarcomas	P-value of test of trend or comparison	.9988	.9059	1	1
	Number of animals reported with tumor	4	2	0	0
Bronchiolar-alveolar tumors	P-value of test of trend or comparison	.9259	.6957	.6957	1
	Number of animals reported with tumor	2	2	2	0
Squamous cell carcinoma or papilloma	P-value of test of trend or comparison	.5000		.5000	
	Number of animals reported with tumor	0	0	1	0
Squamous cell tumors of the skin and subcutis	P-value of test of trend or comparison	.4947		.4894	
	Number of animals reported with tumor	0	0	1	0

Reference ID: 3155338

Table 1.10

Table of reported tumors in Mouse Study
NDA 203214
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 25*	*Low dose Size = 25*	*Mid dose Size = 25*	*High dose Size = 25*
Angiomas, hemangiomas, and hemangiosarcomas	P-value of test of trend or comparison	.8007	.5000	.8827	.8670
	Number of animals reported with tumor	2	3	1	1
Bronchiolar-alveolar tumors	P-value of test of trend or comparison	.3437	1	.5000	.7340
	Number of animals reported with tumor	1	0	2	1
Squamous cell carcinoma or papilloma	P-value of test of trend or comparison	.7449	.5000		
	Number of animals reported with tumor	0	1	0	0
Squamous cell tumors of the skin and subcutis	P-value of test of trend or comparison	.7423	.5000		
	Number of animals reported with tumor	0	1	0	0

Reference ID: 3155338

Table 1.11

Organs reported as autolytic
NDA 203214
Animal carcinogenicity study
Female Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
Gallbladder	.	.	.	.	.	.	1	4.0%	1	1.0%
Mammary, Female	1	4.0%	2	8.0%	.	.	1	4.0%	4	4.0%
Parathyroid	10	40%	14	56%	10	40%	8	32%	42	42%
Peyer's Patch	3	12%	1	4.0%	1	4.0%	.	.	5	5.0%
Thymus	1	4.0%	1	4.0%	2	8.0%	3	12%	7	7.0%

Table 1.12

Organs reported as autolytic
NDA 203214
Animal carcinogenicity study
Male Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
Gallbladder	.	.	.	.	.	.	2	8.0%	2	2.0%
Parathyroid	8	32%	12	48%	14	56%	9	36%	43	43%
Peyer's Patch	.	.	1	4.0%	.	.	5	20%	6	6.0%

Table 1.13

Organs reported as unexamined
NDA 203214
Animal carcinogenicity study
Female Mice

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
Gallbladder	.	.	.	.	.	.	2	8.0%	2	2.0%
LN, Inguinal	2	8.0%	1	4.0%	4	16%	4	16%	11	11%
LN, Mesenteric	.	.	1	4.0%	2	8.0%	1	4.0%	4	4.0%
Nerve, Optic	1	4.0%	.	.	.	.	.	.	1	1.0%
Ovary	.	.	.	.	1	4.0%	.	.	1	1.0%
Oviduct	.	.	.	.	1	4.0%	.	.	1	1.0%
Parathyroid	.	.	1	4.0%	1	4.0%	1	4.0%	3	3.0%
Skin/Subcutis	.	.	.	.	1	4.0%	.	.	1	1.0%
Thyroid	.	.	1	4.0%	1	4.0%	1	4.0%	3	3.0%
Ureter	1	4.0%	1	4.0%	1	4.0%	1	4.0%	4	4.0%
Urinary Bladder	.	.	1	4.0%	.	.	.	.	1	1.0%

Reference ID: 3155338

Table 1.14

Organs reported as unexamined
NDA 203214
Animal carcinogenicity study
Male Mice

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
Bone, Sternum	.	.	.	.	.	.	1	4.0%	1	1.0%
Gallbladder	2	8.0%	2	8.0%	2	8.0%	3	12%	9	9.0%
LN, Inguinal	.	.	.	.	1	4.0%	4	16%	5	5.0%
LN, Mesenteric	1	4.0%	.	.	.	.	.	.	1	1.0%
Marrow, Sternum	.	.	.	.	.	.	1	4.0%	1	1.0%
Nerve, Optic	3	12%	2	8.0%	3	12%	.	.	8	8.0%
Nerve, Sciatic	.	.	.	.	1	4.0%	.	.	1	1.0%
Parathyroid	.	.	1	4.0%	.	.	1	4.0%	2	2.0%
Pituitary	2	8.0%	.	.	.	.	.	.	2	2.0%
Skin/Subcutis	.	.	.	.	1	4.0%	.	.	1	1.0%
Thymus	.	.	.	.	.	.	1	4.0%	1	1.0%
Thyroid	.	.	1	4.0%	.	.	1	4.0%	2	2.0%
Trachea	.	.	.	.	.	.	1	4.0%	1	1.0%
Ureter	.	.	1	4.0%	.	.	2	8.0%	3	3.0%

Reference ID: 3155338

1.4 Positive control study

1.4.1 Survival analysis

The Kaplan-Meier survival plots of negative and positive controls are shown as figures 1.3 and 1.4. The numbers and proportions of animals surviving to various times are presented in table 1.15. The results of the log-rank test of survival are presented in table 1.16.

Figure 1.3: Survival curves for female mice (positive control study)

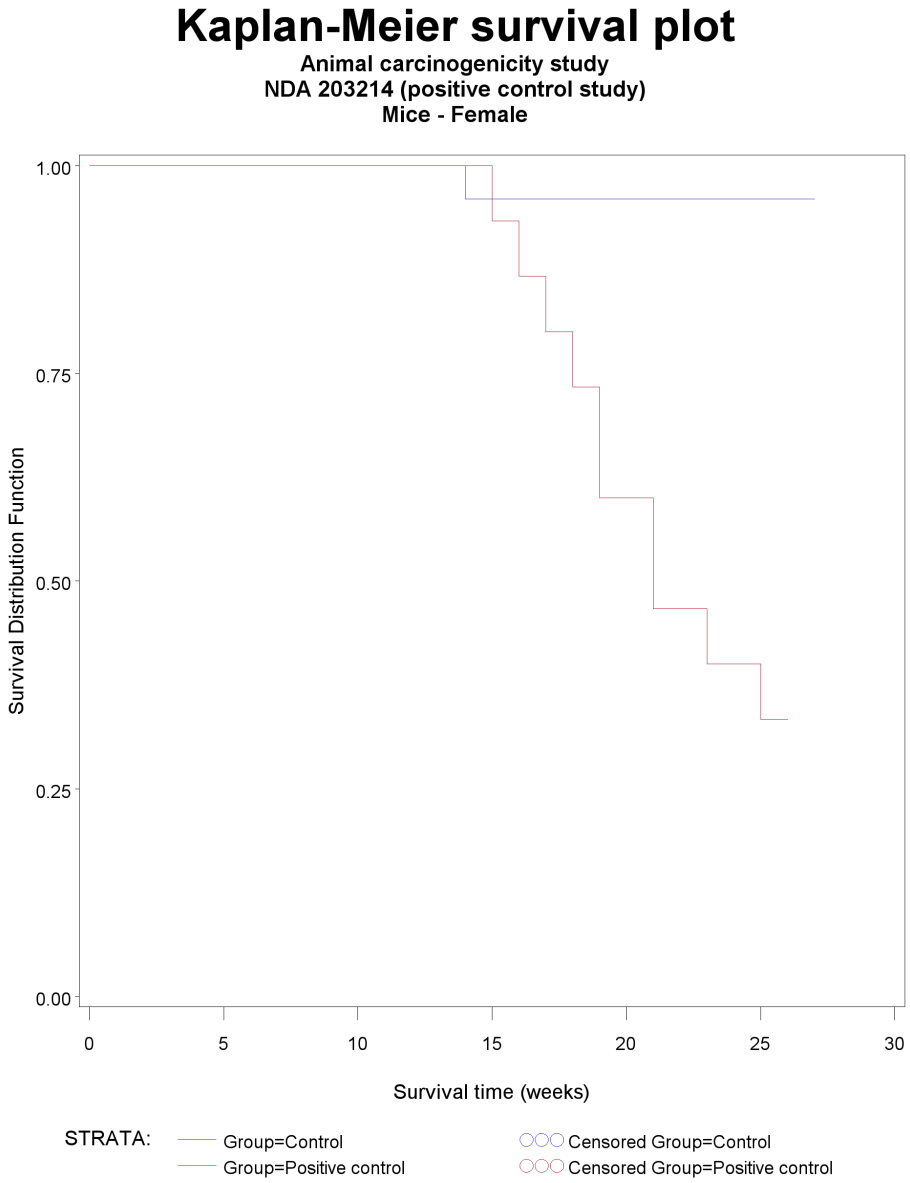

Figure 1.4: Survival curves for male mice (positive control study)

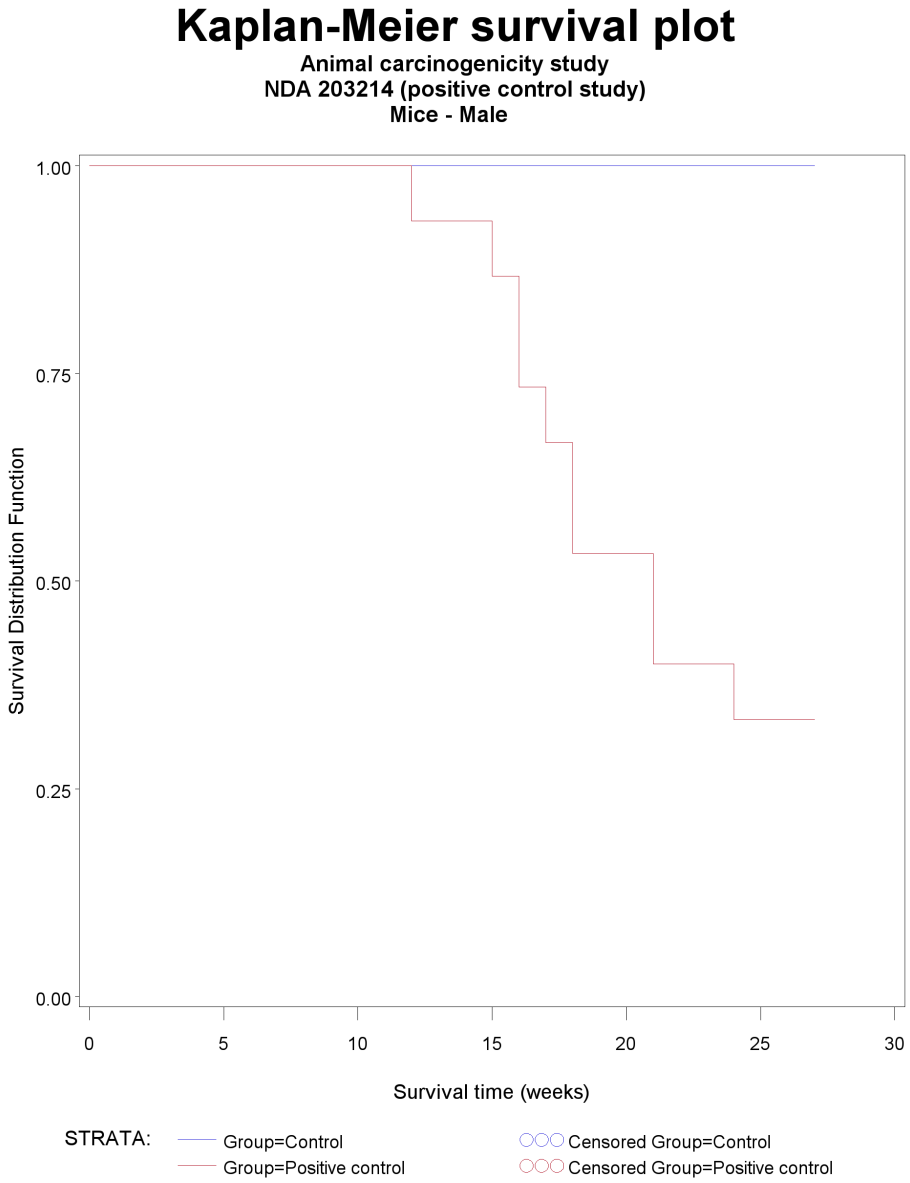

Table 1.1

Survival rates at key times
NDA 203214 (positive control study)
Animal carcinogenicity study
Mice

Species and Sex	*Dose Group*	*Dose (mg per kg)*	*Number at start*	*Number alive after 12 weeks*	*Proportion alive after 12 weeks*	*Number alive after 19 weeks*	*Proportion alive after 19 weeks*	*Number alive after 22 weeks*	*Proportion alive after 22 weeks*	*Number alive at termination*	*Proportion alive at termination*
Mice - Female	Control	0	25	25	100%	24	96%	24	96%	24	96%
	Positive control	1	15	15	100%	11	73%	7	47%	5	33%
Mice - Male	Control	0	25	25	100%	25	100%	25	100%	25	100%
	Positive control	1	15	15	100%	8	53%	6	40%	5	33%

Commentry The animals in the positive control group experienced sharply increased levels of mortality. The p-values of the log rank test were below 0.0001 for both female and male animals. We may safely conclude that the positive control agent was indeed highly toxic.

1.4.2 Tumor analysis

Endpoints

As for the main carcinogenicity study, analyses have been conducted using the sponsor's submitted dataset, and the sponsor's chosen nomenclature. The lists of primary organs considered in the positive control study are presented in tables 1.17 and 1.18. No combination endpoints have been considered.

Table 1.16

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 203214 (positive control study)
Animal carcinogenicity study
Mice

Species and Sex	*Quantity*	*Positive control*
Mice - Female	Chi squared test statistic	22.5893
	p-value of comparison with control	<0.0001
Mice - Male	Chi squared test statistic	24.4080
	p-value of comparison with control	<0.0001

Table 1.17

Primary organs in study of female mice
NDA 203214 (positive control study)
Animal carcinogenicity study

Organ or tissue name
Body, Whole/Cav
Gl, Mandib Saliv
LN, Inguinal
Lung
Mammary, Female
Nerve, Optic
Parathyroid
Peyer's Patch
Skin/Subcutis
Stomach, Nongl
Teeth, Other
Thymus
Ureter

Reference ID: 3155338

Table 1.18

Primary organs in study of male mice
NDA 203214 (positive control study)
Animal carcinogenicity study

Organ or tissue name
Body, Whole/Cav
Gallbladder
GI, Harderian
LN, Mesenteric
Lung
Nerve, Optic
Parathyroid
Pituitary
Skin/Subcutis
Stomach, GI
Stomach, Nongl

Reference ID: 3155338

Statistical procedure

Pairwise tests of tumor incidence between the control and positive control groups have been conducted for all tumor types reported in the primary organs, using the same procedure as described in section 1.3.2. Separate trend tests have not been conducted, since a trend test across two groups (treated and control) simply reduces to the pairwise test, and so adds no additional information.

Noteworthy results

The results of the statistical analyses of tumor incidence are presented in tables 1.19 (female mice) and 1.20 (male mice).

Lymphosarcomas The positive control was associated with elevated incidence rates of lymphosarcoma in both female and male animals. No control animals of either sex developed such cancers, but seven female and eight male positive control animals did. The p-values of the test of comparison were, in each case, less than or equal to 0.0001.

Squamous cell tumors of the stomach The positive control was associated with sharply elevated levels of squamous cell papillomas of the stomach; twelve female and eleven male animals developed such tumors, all in the positive control groups. In both sexes, the p-values of the comparisons were below 0.0001. The female positive control mice also experienced an elevated incidence of squamous cell carcinomas of the stomach. This result was less striking than for papillomas ($p = 0.0201$), but is still noteworthy.

Keratoacanthomas in female mice Among female mice, the positive control group experienced a sharp increase in keratoacanthomas (seven animal, compared with none in the control group). The p-value of the test of comparison is 0.0001. There is no corresponding result for male mice.

1.4.3 Tables of results

Table 1.19

Table of reported tumors in Mouse Study
NDA 203214 (positive control study)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Positive control*
Body, Whole/Cav	Hemangiosarcoma	P-value of test of comparison		.8209
		Number of animals reported with tumor	4	1
		Poly-3 adjusted incidence rate	17%	10%
		95% CI for poly-3 adjusted incidence rate (%)	(4.54,37.4)	(0.25,48.2)
		Poly-3 adjusted number of animals at risk	24.2	9.9
	Lymphosarcoma	P-value of test of comparison		.0001
		Number of animals reported with tumor	0	7
		Poly-3 adjusted incidence rate	0.0%	54%
		95% CI for poly-3 adjusted incidence rate (%)	(0,14.2)	(25.1,84.8)
		Poly-3 adjusted number of animals at risk	24.2	12.9
Lung	Adenoma, Bronchiolar-Alveo	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	4.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.1,21.1)	(0,33.6)
		Poly-3 adjusted number of animals at risk	24.2	9.5
	Carcinoma, Bronchiolar-Alv	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	4.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.1,21.1)	(0,33.6)
		Poly-3 adjusted number of animals at risk	24.2	9.5
Skin/Subcutis	Carcinoma, Squamous Cell	P-value of test of comparison		.2727
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	11%
		95% CI for poly-3 adjusted incidence rate (%)	(0,14.2)	(0.25,48.2)
		Poly-3 adjusted number of animals at risk	24.2	9.5
	Keratoacanthoma	P-value of test of comparison		.0001
		Number of animals reported with tumor	0	7

Reference ID: 3155338

Table 1.19

Table of reported tumors in Mouse Study
NDA 203214 (positive control study)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Positive control*
		Poly-3 adjusted incidence rate	0.0%	55%
		95% CI for poly-3 adjusted incidence rate (%)	(0,14.2)	(25.1,84.8)
		Poly-3 adjusted number of animals at risk	24.2	12.7
	Papilloma, Squamous Cell	P-value of test of comparison		.0682
		Number of animals reported with tumor	0	2
		Poly-3 adjusted incidence rate	0.0%	21%
		95% CI for poly-3 adjusted incidence rate (%)	(0,14.2)	(2.52,60.0)
		Poly-3 adjusted number of animals at risk	24.2	9.5
Stomach, Nongl	Carcinoma, Squamous Cell	P-value of test of comparison		.0201
		Number of animals reported with tumor	0	3
		Poly-3 adjusted incidence rate	0.0%	28%
		95% CI for poly-3 adjusted incidence rate (%)	(0,14.2)	(6.02,65.2)
		Poly-3 adjusted number of animals at risk	24.2	10.5
	Papilloma, Squamous Cell	P-value of test of comparison		<0.0001
		Number of animals reported with tumor	0	12
		Poly-3 adjusted incidence rate	0.0%	90%
		95% CI for poly-3 adjusted incidence rate (%)	(0,14.2)	(57.2,99.8)
		Poly-3 adjusted number of animals at risk	24.2	13.3
Teeth, Other	Malignant Odontoma	P-value of test of comparison		.2727
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	10%
		95% CI for poly-3 adjusted incidence rate (%)	(0,14.2)	(0.25,48.2)
		Poly-3 adjusted number of animals at risk	24.2	9.9

Reference ID: 3155338

Table 1.20

Table of reported tumors in Mouse Study
NDA 203214 (positive control study)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Positive control*
Body, Whole/Cav	Hemangiosarcoma	P-value of test of comparison		.2809
		Number of animals reported with tumor	2	2
		Poly-3 adjusted incidence rate	8.0%	22%
		95% CI for poly-3 adjusted incidence rate (%)	(0.98,26.0)	(2.52,60.0)
		Poly-3 adjusted number of animals at risk	25.0	9.0
	Lymphosarcoma	P-value of test of comparison		<0.0001
		Number of animals reported with tumor	0	8
		Poly-3 adjusted incidence rate	0.0%	62%
		95% CI for poly-3 adjusted incidence rate (%)	(0,13.7)	(31.6,90.1)
		Poly-3 adjusted number of animals at risk	25.0	13.0
GI, Harderian	Adenoma	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	4.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.1,20.4)	(0,36.9)
		Poly-3 adjusted number of animals at risk	25.0	8.5
Lung	Adenoma, Bronchiolar-Alveo	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	4.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.1,20.4)	(0,36.9)
		Poly-3 adjusted number of animals at risk	25.0	8.5
Skin/Subcutis	Keratoacanthoma	P-value of test of comparison		.2647
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	11%
		95% CI for poly-3 adjusted incidence rate (%)	(0,13.7)	(0.25,48.2)
		Poly-3 adjusted number of animals at risk	25.0	9.2
	Papilloma, Squamous Cell	P-value of test of comparison		.2424
		Number of animals reported with tumor	0	1

Reference ID: 3155338

Table 1.20

Table of reported tumors in Mouse Study
NDA 203214 (positive control study)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Positive control*
		Poly-3 adjusted incidence rate	0.0%	12%
		95% CI for poly-3 adjusted incidence rate (%)	(0,13.7)	(0.28,52.7)
		Poly-3 adjusted number of animals at risk	25.0	8.5
Stomach, Nongl	Carcinoma, Squamous Cell	P-value of test of comparison		.2424
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	11%
		95% CI for poly-3 adjusted incidence rate (%)	(0,13.7)	(0.28,52.7)
		Poly-3 adjusted number of animals at risk	25.0	8.8
	Papilloma, Squamous Cell	P-value of test of comparison		<0.0001
		Number of animals reported with tumor	0	13
		Poly-3 adjusted incidence rate	0.0%	92%
		95% CI for poly-3 adjusted incidence rate (%)	(0,13.7)	(59.5,99.8)
		Poly-3 adjusted number of animals at risk	25.0	14.1

Reference ID: 3155338

Chapter 2

Rat Study

2.1 Experimental design

The study comprised two hundred and sixty Crl:CD(SD) rats of each sex. The rats were separated by sex, so that two separate experiments were conducted. In both the male and female rat experiments, these animals were randomly assigned to four groups, a control group (seventy animals), a low dose group (sixty animals), a mid dose group (sixty animals) and a high dose group (seventy animals).

In both experiments, the low dose group reveived a daily dose of tofacitinib of 10 mg per kilogram of bodyweight. The mid dose received a daily dose of 30 mg/kg, and the high dose goup received a dose of 75mg/kg (male animals, or female animals after day 133) or 100 mg/kg (female animals up to day 132). The vehicle for tofacitinib was 0.5% methylcellulose (w/v), which was administered to all animals, including those in the control group, by gavage, for a daily dose volume of 10 mL per kilogram of bodyweight.

As noted above, the dose level for the high dose female rats changed after day 133, from 100 mg/kg to 75 mg/kg.

Animals were examined for mortality, abnormality, and signs of distress twice a day. Detailed observations, including palpation exams, were conducted weekly. Complete necroscopies were performed on all animals after sacrifice, euthanasia, or after being found dead.

2.2 Sponsor's analysis

2.2.1 Survival analysis

The two-tailed Tarone trend test using the control and tofacitinib groups was performed at the 0.05 level of significance. If the initial test showed a significant trend, then one-tailed Tarone tests in the same direction of that trend were to be performed at the 0.05 level in a sequential, step-down manner (i.e., from highest dose to lowest dose).

Significant increases in mortality were observed in the mid and high dose groups in the male rat experiment. No significant results were reported from the female rat experiment.

2.2.2 Tumor analysis

Group incidences of each observed neoplastic lesion or combination were analyzed using a one-sided Peto trend test and pairwise tests (treated versus control groups only) for evidence of a positive relationship between neoplasm incidence and dose.

Analysis of tumors found in non-protocol tissues presumed that all animals not examined for that tissue did not have that tumor.

After making an adjustment for multiple testing, the sponsor provided a list of statistically significant findings. These are presented in table 2.1.

The sponsor notes that the result for hibernomas is contingent on these being considered rare tumors, but that recent evidence suggests that they have been becoming more common, in which case this would fail to be a significant finding.

The sponsor also claims that the cervix and uterus are essentially the same organ, and that it is more appropriate way to analyze these data using the cervix/uterus combination rather than individual organs. The trend test for the uterus/cervix combination for benign endometrial stromal polyps did not yield a statistically significant result.

2.3 Data analysis

2.3.1 Survival analysis

The Kaplan-Meier survival plots are shown as figures 2.1 and 2.2. The numbers and proportions of animals surviving to various times are presented in table 2.2. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table 2.3, and the results of log-rank survival tests comparing the treated groups with the control group are presented in table 2.4.

Figure 2.1

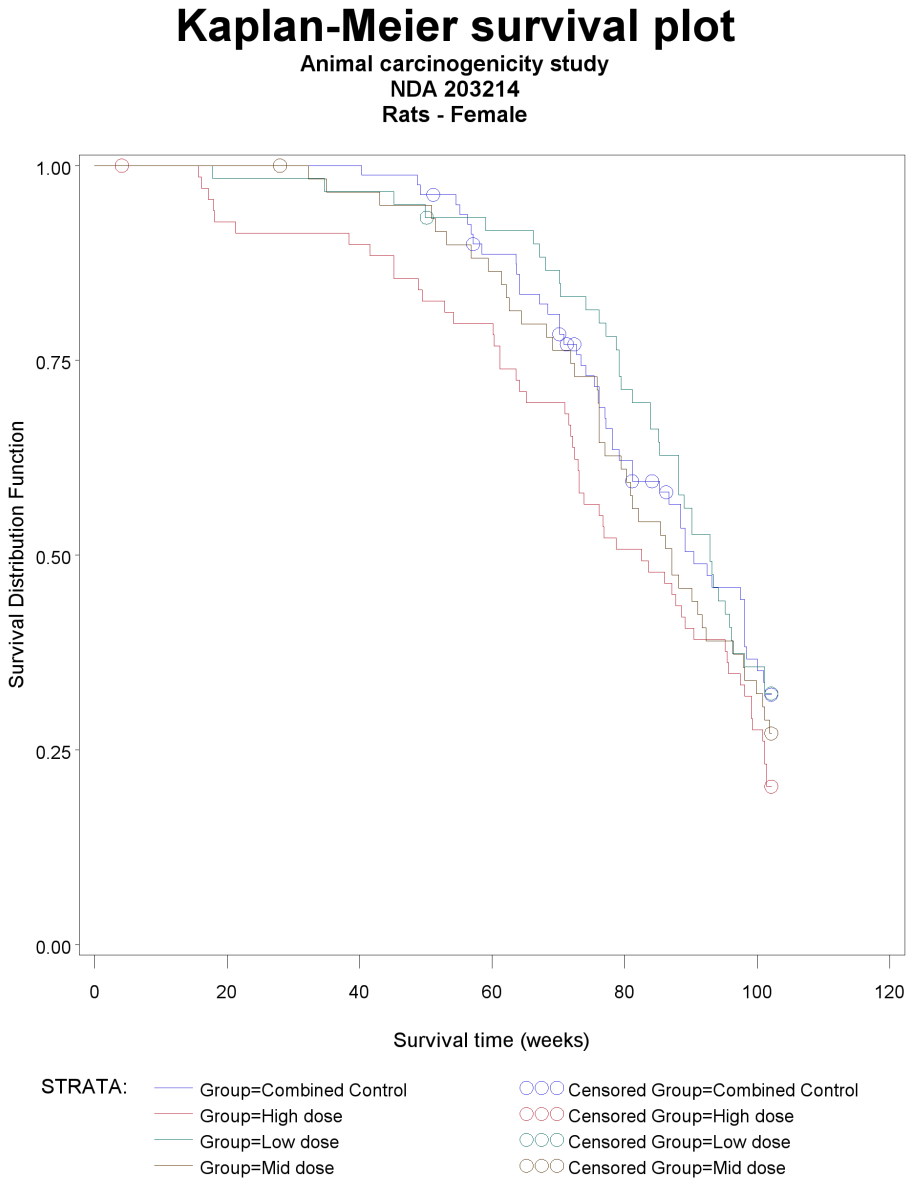
Kaplan-Meier survival plot
Animal carcinogenicity study
NDA 203214
Rats - Female
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
120
Survival time (weeks)
STRATA:
Group=Combined Control
Group=High dose
Group=Low dose
Group=Mid dose
Censored Group=Combined Control
Censored Group=High dose
Censored Group=Low dose
Censored Group=Mid dose

Figure 2.2

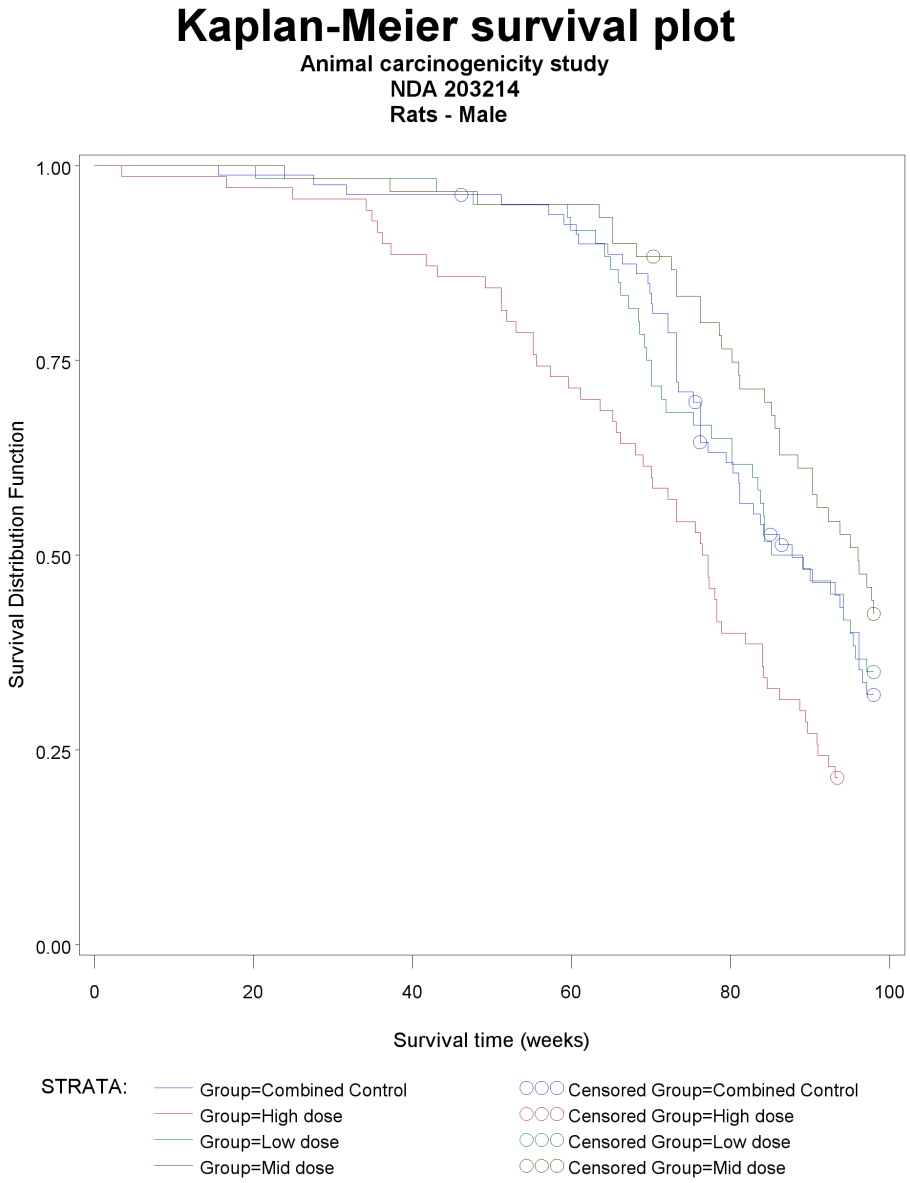
Kaplan-Meier survival plot
Animal carcinogenicity study
NDA 203214
Rats - Male
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
Survival time (weeks)
STRATA:
Group=Combined Control
Group=High dose
Group=Low dose
Group=Mid dose
Censored Group=Combined Control
Censored Group=High dose
Censored Group=Low dose
Censored Group=Mid dose

Table 2.1: Sponsor's significant results

Sex	Organ	Tumor or combination	Significant pairwise tests	Trend test
Male	Body, Whole/Cav	Angiomas	Low dose	Not significant
Male	Body, Whole/Cav	Angiomas and hemangiosarcomas	Low dose	Not significant
Male	Pituitary	Adenomas	High dose	Significant
Male	Skin/Subcutis	Benign lipomas	None	Significant
Male	Testis	Interstitial cell tumors	High dose	Significant
Female	Thymus	Benign and malignant thymomas	High dose	Significant
Female	Body, Whole/Cav	Hibernomas	Mid dose, High dose	Significant
Female	Cervix	Endometrial stromal polyps	None	Significant

Table 2.2

Survival rates at key times
NDA 203214
Animal carcinogenicity study
Rats

Species and Sex	*Dose Group*	*Dose (mg per kg)*	*Number at start*	*Number alive after 52 weeks*	*Percentage alive after 52 weeks*	*Number alive after 78 weeks*	*Percentage alive after 78 weeks*	*Number alive after 90 weeks*	*Percentage alive after 90 weeks*	*Number sacrificed*	*Percentage sacrificed*	*maxtime*
Rats - Female	Combined Control	0	80	76	95%	49	61%	33	41%	.	.	.
	Low dose	10	60	55	92%	46	77%	33	55%	.	.	.
	Mid dose	30	60	54	90%	37	62%	27	45%	.	.	.
	High dose	79.5	70	57	81%	36	51%	28	40%	.	.	.
Rats - Male	Combined Control	0	80	75	94%	48	60%	30	38%	.	.	.
	Low dose	10	60	57	95%	39	65%	29	48%	.	.	.
	Mid dose	30	60	57	95%	47	78%	36	60%	.	.	.
	High dose	75	70	56	80%	32	46%	19	27%	.	.	.

Commentry Visual inspection of figures 2.1 and 2.2 indicates that in both sexes, the high dose animals appear to have experienced higher mortality than their lower dose peers. These observations are confirmed by the statistical tests; in both sexes, a significant trend is observed ($p = 0.0274$ for female rats and $p = 0.0010$ for male rats). Furthermore, the direct comparison between the high dose male group with the combined control also yields a significant difference: $p = 0.0166$. None of the other pairwise comparisons yield significant results. Nonetheless, we may conclude that there is evidence of a dose related increase in mortality.

2.3.2 Tumor analysis

Endpoints

As in the mouse study, organs have been classed as either primary or secondary (see Section 1.3.2). The lists of organs adduced to be primary are presented in tables 2.5 and 2.6. In the rat study, there are no secondary organs.

The same customized endpoints have been analyzed as were considered in the mouse study (see table 1.6).

Table 2.3

Log-rank tests of survival
NDA 203214
Animal carcinogenicity study
Rats

Sex	*Test of homogeneity: chi squared statistic*	*Test of homogeneity: degrees of freedom*	*Number of groups*	*Test of homogeneity: p-value*	*Test of trend (two tailed): p-value*	*Test of trend (one tailed): p-value*
Female	5.0692	3	4	0.1668	0.0282	0.0141
Male	23.4798	3	4	<.0001	0.0004	0.0002

Table 2.4

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 203214
Animal carcinogenicity study
Rats

Species and Sex	*Quantity*	*Low dose*	*Mid dose*	*High dose*
Rats - Female	Chi squared test statistic	0.0111	0.5897	3.3068
	p-value of comparison with control	0.9160	0.4425	0.0690
Rats - Male	Chi squared test statistic	0.0003	1.4461	8.8637
	p-value of comparison with control	0.9861	0.2292	0.0029

Table 2.5

Primary organs in study of female rats
NDA 203214
Animal carcinogenicity study

Organ or tissue name
Adrenal, Cortex
Adrenal, Medulla
Body, Whole/Cav
Brain
Cavity, Abdomin
Cavity, Thoracic
Cecum
Cervix
Colon
Duodenum
Eye
Foot/Foot Pad
GI, Clitoral
GI, Zymbal's
Ileum
Kidney
LN, Inguinal
LN, Mesenteric
Liver
Mammary, Female
Ovary
Pancreas
Parathyroid
Peyer's Patch
Pituitary
Skin/Subcutis
Teeth, Other
Thymus
Thyroid
Ureter
Urinary Bladder
Uterus
Vagina

Reference ID: 3155338

Table 2.6

Primary organs in study of male rats
NDA 203214
Animal carcinogenicity study

Organ or tissue name
Adrenal, Cortex
Adrenal, Medulla
Body, Whole/Cav
Bone, Other
Brain
Cavity, Abdomin
Cavity, Oral
Foot/Foot Pad
GI, Zymbal's
Heart
Jejunum
Joint, Other
Kidney
LN, Inguinal
LN, Other
Liver
Lung
Mammary, Male
Nerve, Optic
Nerve, Sciatic
Pancreas
Parathyroid
Peyer's Patch
Pituitary
Seminal Vesicle
Skin/Subcutis
Spinal Cord
Stomach, Nongl
Testis
Thymus
Thyroid
Ureter
Urinary Bladder

Reference ID: 3155338

Statistical procedure

As with the mouse study (see Section 1.3.2), the tumor data were analyzed for dose response relationships and pairwise comparisons of tumor incidence in each of the treated groups versus the control group, using the poly-k method described in the paper of Bailer and Portier[1] and developed in the paper of Bieler and Williams[2].

Again, it is critical consider the choice of the appropriate value of k, which depends on the relationship between tumor onset time and increased dose. For long term 104 week standard rat and mouse studies, a value of $k = 3$ is suggested in the literature, and so has been used in this review. For the calculation of p-values, the exact permutation method was used.

For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of significance levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for a submission with two species, and a significance level $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for a submission with one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control, the FDA guidance suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors, for both submissions with one or two species, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman [3]. In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin [4] showed that this rule for multiple testing for dose response relationship is also suitable for poly-k tests.

Since this is a study involving two species, it follows that for the comparisons of tofacitinib with control, we use the thresholds for significance presented in table 2.7.

Noteworthy results

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables 2.8 (female rats) and 2.9 (male rats). The results of analyses of customized endpoints (see table 1.6) are presented in tables 2.10 and 2.11.

Individual tumor types in female rats for which tests yielding p-values below 0.05 were conducted are presented in table 2.12, which is excerpted from table 2.8. Combination tumor types for which tests yielding p-values below 0.05 were conducted are presented in table 2.14, which is excerpted from table 2.10. Individual tumor types in male rats for which tests yielding p-values below 0.05 were conducted are presented in table 2.13, which is excerpted from table 2.9. Combination tumor types for which tests yielding p-values below 0.05 were conducted are presented in table 2.15, which is excerpted from table 2.11.

This study has generated many results with p-values below 0.05, but most of these results (but not the result for interstitial cell tumors!) are either only slightly below 0.05, and thus do not remain significant after making an adjustment for multiple testing, or else are the result of comparisons between the control group and either the low or mid dose group, without a corresponding increase in observed incidence in the high dose group. The most noteworthy results are below.

Interstitial cell tumors There is strong evidence of an association between dosage and incidence of interstitial cell tumors. Just one control animal developed such a tumor, compared with two low dose animals, four mid dose animals, and fourteen high dose animals. Both the test of trend and the comparison between the combined control group and the high dose group yield p-values below 0.0001. This must be considered a positive finding.

Thymomas in female rats The sponsor considers thymomas to be rare tumors. However, seven female animals developed such tumors; four in the high dose group, two in the mid dose group, and one in the low and mid dose group. As a result, the test of trend is strongly significant, even after adjusting for multiplicity ($p = 0.0124$). The comparison between the high dose group and

Table 2.7: Critical p-values used to determine statistical significance

Type of test	Rare tumor	Common tumor
Trend	0.025	0.005
Pairwise test between placebo and high dose	0.05	0.01

the control group is also significant, although not strongly so ($p = 0.0382$). Since thymomas are considered rare tumors, this is considered a positive finding.

One of these seven animals, a mid dose animal, was found to have a malignant thymoma; the remaining six were found to have benign thymomas. When only the benign thymomas are considered, the results are much the same: the test of trend yields a p-value of 0.0094, and the result of the pairwise test between the high dose group and the control group remains the same ($p = 0.0382$).

There is no sign of a corresponding result among male rats.

Lipomas and hibernomas When all lipomas and hibernomas are combined, the resulting tests generate striking results in both male and female rats. As long as this endpoint is considered to be rare, then the findings should be considered positive in both sexes. Some of the consitiuent endpoints are also significant in and of themselves. Table 2.16 summarizes the results for the relavant endpoints.

Among female rats, no cases were reported in the control group, and the poly-3 survival adjusted incidence rates in the low, mid, and high dose groups were 5%, 15% and 15% respectively. The p-value of the test of trend is 0.0206, and the p-values of the comparisons of the mid and high dose groups yield p-values of 0.0209 and 0.0225 respectively.

The situation is similar for male rats. The incidence rates in the control, low, mid, and high dose groups are 5.1%, 0.0%, 5.1% and 22% respectively. The p-value of the test of trend is 0.0014, which is significant even if the tumor type is considered common. However, the comparison between the high dose group and the control group yields a weaker result: $p = 0.0394$.

The task of adjudicating the rarity of a combination tumor type is somewhat tricky. Using the observed data from the control group to estimate the underlying (survival unadjusted) incidence rates, we find that for female rats, our point estimate is 0.0%, and our confidence interval is $(0.0\%, 5.5\%)$. Conversely for male rats, our point estimate is 5.1%, and our confidence interval is $(0.3\%, 9.9\%)$. In other words, the female rat data suggest a rare tumor type, but are consistent with a common tumor type, and the male rat data suggest a common tumor type, but are consistent with a rare tumor type.

Considering the constituent parts of this composite endpoint brings us to the question of hibernomas. The sponsor claims that malignant hibernomas have been historically considered rare tumors, with an incidence rate below 1%, but that incidence rates have increased to about 3.5% over the past decade. In this study, the absence of any cases in the female control group certainly yields a point estimate for the underlying incidence of 0%, but the 95% confidence interval for the underlying rate again extends up to 5.1%, so the observed rate of 0% is consistent with the tumor type being either rare or common. Among males, the situation is reversed. The point estimate (for the unadjusted incidence rate) is 2.9%, but the 95% confidence interval extends down to 0.04%, so this observed rate is also consistent with the tumor type being considered either rare or common. However, in the *Statistical Methods* section of the sponsor's report, Table A chacterizes these tumors as rare, at least in the case of female rats.

The sponsor makes no corresponding determination for lipomas, except to conclude that lipomas of the skin/subcutis are considered rare in male rats.

In conclusion, it seems appropriate to consider this composite endpoint to be rare in female rats. Accordingly, this is considered a positive finding. Among male rats, the situation is less clear cut. However, given that the test of trend yields a strongly positive result, even when the tumor is considered common, that the evidence that the tumor type is common is weak, that the comparison between the control and high dose groups does yield a significant result when the tumor type is

considered rare, and given the corroboratory evidence from the female rat study, it is reasonable to consider this a positive finding too[1].

When malignant hibernomas are considered on their own, the results for the male rats become insignificant, and the results for the female rats become less significant. However, the poly-3 survival adjusted incidence rates for malignant hibernomas in female rats were 0%, 5%, 13%, and 10% in the combined control, low, mid and high dose groups respectively. Since the observed incidence rate is higher in the mid dose group than in the high dose group, the test of trend yields a result that is only slightly below 0.05; $p = 0.0493$. However, the comparisons of both the mid and high dose group with the control also yield p-values below 0.05; $p = 0.0209$ and $p = 0.0494$ respectively. After making an adjustment for multiplicity, the comparisons between the both the mid dose group and the high dose group with the control group remains significant, as long as hibernomas are considered rare, although the test of trend does not. In the absence of a significant result for the test of trend, this should most likely be considered a negative finding.

When white fat lipomas are considered independently of hibernomas, the results for the female rats become insignificant. Among male rats, the results both for lipomas of the kidneys and for lipomas of the skin/subcutis are individully suggestive of a tumorigenic effect, but neither is significant on its own. When combined however, the test of trend is strongly significant ($p = 0.0031$), even if these are considered common tumors. The comparison between the high dose group and the control group narrowly misses significance if these are considered rare tumors ($p = 0.0549$), but is nowhere near significant if we use the stricter standard associated with common tumors. The sponsor considers lipomas of the skin/cutis to be rare in male rats, but makes no comment about lipomas of the kidneys, although in this dataset at least, these seem to be more rare than skin/cutis lipomas. Consequently, it seems reasonable to consider this a rare tumor type, in which case the fact of the non-significance of the comparison between the control and high dose group seems a small factor compared to the strongly significant result of the test of trend. Accordingly, this should be considered a positive finding.

Endometrial stromal polyps Five female rats developed cervical endometrial stromal polyps; two in the mid dose group and three in the high dose group. The sponsor considers these to be rare tumors. It follows that the result of the test of trend remains significant ($p = 0.0186$), even after making an adjustment for multiplicity. On the other hand, when these tumors are combined with uterine and vaginal polyps, the result loses all significance; the p-value of the test of trend is 0.2726. After discussion with CDER toxicologists, it seems that it is inappropriate to consider cervical polyps in isolation, so this should be considered a negative finding.

2.3.3 Analysis of unexamined and autolytic organs

Unexamined animals

No animals have been reported as completely unexamined.

Organs reported autolytic

The numbers of organs found in female rats to be autolytic to the extent that analysis of collected tiussue was not possible are presented in table 2.17. The numbers of such organs found in male rats are presented in table 2.18.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables 2.19 and 2.20.

[1]It should be noted, however, that mitigating against the idea of using the results from the female rat study to buttress those of the male rat study, is the fact that the bulk of the tumors noted in the female rats were hibernomas (i.e., brown fat lipomas), whereas the bulk of the tumors found in the male rats were white fat lipomas.

2.3.4 Tables of results

Table 2.8

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
Adrenal, Cortex	Adenoma	P-value of test of trend or comparison	.4011	.2287		.4615
		Number of animals reported with tumor	0	2	0	1
	Carcinoma	P-value of test of trend or comparison	.7210	1	.7057	1
		Number of animals reported with tumor	1	0	1	0
Adrenal, Medulla	Malignant Pheochromocytoma	P-value of test of trend or comparison	.2883	.4750		.4615
		Number of animals reported with tumor	0	1	0	1
	Pheochromocytoma	P-value of test of trend or comparison	.1593	.1963	.0425	.1570
		Number of animals reported with tumor	2	5	7	5
Body, Whole/Cav	Angioma	P-value of test of trend or comparison	.2213	.2801	.6979	.2612
		Number of animals reported with tumor	1	3	1	3
	Hemangiosarcoma	P-value of test of trend or comparison	.6861	.6636	.6204	.8491
		Number of animals reported with tumor	2	2	2	1
	Histiocytic Sarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
	Lymphosarcoma	P-value of test of trend or comparison	.4730	.7343	.7057	.7133
		Number of animals reported with tumor	1	1	1	1
	Malignant Hibernoma	P-value of test of trend or comparison	.0493	.2287	.0209	.0494
		Number of animals reported with tumor	0	2	5	4
	Malignant Mesothelioma	P-value of test of trend or comparison	.7200	.4750		
		Number of animals reported with tumor	0	1	0	0
	Malignant Plasmacytoma	P-value of test of trend or comparison	.2400			.4615
		Number of animals reported with tumor	0	0	0	1
Brain	Malignant Astrocytoma	P-value of test of trend or comparison	.3588	1	.7057	.7133
		Number of animals reported with tumor	1	0	1	1
Cervix	Granular Cell Tumor	P-value of test of trend or comparison	.3575	1	.6979	.7133
		Number of animals reported with tumor	1	0	1	1
	Polyp, Endometrial Stromal	P-value of test of trend or comparison	.0186		.2033	.0939

Reference ID: 3155338

Table 2.8

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
		Number of animals reported with tumor	0	0	2	3
Duodenum	Leiomyosarcoma	P-value of test of trend or comparison	.4702		.4545	
		Number of animals reported with tumor	0	0	1	0
Eye	Squamous Cell Carcinoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
GI, Clitoral	Carcinoma	P-value of test of trend or comparison	.7878	.2405		
		Number of animals reported with tumor	0	2	0	0
	Carcinoma, Squamous Cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
GI, Zymbal's	Carcinoma	P-value of test of trend or comparison	.2915	.4875		.4675
		Number of animals reported with tumor	0	1	0	1
Kidney	Carcinoma, Tubule Cell	P-value of test of trend or comparison	.7219	.4815		
		Number of animals reported with tumor	0	1	0	0
	Lipoma	P-value of test of trend or comparison	.2400			.4615
		Number of animals reported with tumor	0	0	0	1
Liver	Carcinoma, Hepatocellular	P-value of test of trend or comparison	.4667		.4474	
		Number of animals reported with tumor	0	0	1	0
	Cholangioma	P-value of test of trend or comparison	.2877	.4815		.4615
		Number of animals reported with tumor	0	1	0	1
Mammary, Female	Carcinoma	P-value of test of trend or comparison	.8628	.4664	.5227	.8718
		Number of animals reported with tumor	18	19	16	11
	Fibroadenoma	P-value of test of trend or comparison	.9655	.9056	.9918	.9839
		Number of animals reported with tumor	25	17	11	12
Ovary	Granulosa/Theca Cell Tumor	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Luteoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0

Reference ID: 3155338

Table 2.8

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
	Malignant Granulosa/Theca	P-value of test of trend or comparison	.9781	.8554	1	1
		Number of animals reported with tumor	2	1	0	0
Pancreas	Adenoma, Islet Cell	P-value of test of trend or comparison	.1670	.2225		.2098
		Number of animals reported with tumor	0	2	0	2
	Carcinoma, Islet Cell	P-value of test of trend or comparison	.5912	.4750	.4545	
		Number of animals reported with tumor	0	1	1	0
Parathyroid	Adenoma	P-value of test of trend or comparison	.4095	1	1	.6964
		Number of animals reported with tumor	1	0	0	1
Pituitary	Adenoma	P-value of test of trend or comparison	.4573	.8092	.9369	.6314
		Number of animals reported with tumor	56	46	41	47
Skin/Subcutis	Carcinoma, Basal Cell	P-value of test of trend or comparison	.7181	.4750		
		Number of animals reported with tumor	0	1	0	0
	Fibroma	P-value of test of trend or comparison	.2455	1	1	.6204
		Number of animals reported with tumor	2	0	0	2
	Fibrosarcoma	P-value of test of trend or comparison	.4667		.4545	
		Number of animals reported with tumor	0	0	1	0
	Keratoacanthoma	P-value of test of trend or comparison	.7200	.4815		
		Number of animals reported with tumor	0	1	0	0
Teeth, Other	Ameloblastic Odontoma	P-value of test of trend or comparison	.4702		.4545	
		Number of animals reported with tumor	0	0	1	0
Thymus	Malignant Thymoma	P-value of test of trend or comparison	.4476		.4384	
		Number of animals reported with tumor	0	0	1	0
	Thymoma	P-value of test of trend or comparison	.0094	.4875	.4384	.0382
		Number of animals reported with tumor	0	1	1	4
Thyroid	Adenoma, C-cell	P-value of test of trend or comparison	.2656	.2359	.3445	.2568
		Number of animals reported with tumor	6	9	7	8
	Adenoma, Follicular Cell	P-value of test of trend or comparison	.2877	.4815		.4615

Reference ID: 3155338

Table 2.8

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
		Number of animals reported with tumor	0	1	0	1
	Carcinoma, C-cell	P-value of test of trend or comparison	.4702		.4545	
		Number of animals reported with tumor	0	0	1	0
	Carcinoma, Follicular Cell	P-value of test of trend or comparison	.1669		.4545	.4615
		Number of animals reported with tumor	0	0	1	1
Uterus	Adenoma	P-value of test of trend or comparison	.4702		.4545	
		Number of animals reported with tumor	0	0	1	0
	Polyp, Endometrial Stromal	P-value of test of trend or comparison	.9580	.9294	.9135	1
		Number of animals reported with tumor	3	1	1	0
Vagina	Adenoma, Basal Cell	P-value of test of trend or comparison	.7200	.4815		
		Number of animals reported with tumor	0	1	0	0
	Polyp	P-value of test of trend or comparison	.4631		.4474	
		Number of animals reported with tumor	0	0	1	0
	Stromal Sarcoma	P-value of test of trend or comparison	.2400			.4615
		Number of animals reported with tumor	0	0	0	1

Reference ID: 3155338

Table 2.9

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
Adrenal, Cortex	Adenoma	P-value of test of trend or comparison	.6051	.8586	.8800	.8156
		Number of animals reported with tumor	2	1	1	1
	Carcinoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Adrenal, Medulla	Malignant Pheochromocytoma	P-value of test of trend or comparison	.8467	.8586	.6926	1
		Number of animals reported with tumor	2	1	2	0
	Pheochromocytoma	P-value of test of trend or comparison	.5906	.3016	.9481	.5398
		Number of animals reported with tumor	7	9	3	6
Body, Whole/Cav	Angioma	P-value of test of trend or comparison	.3545	.0216	.1249	.1762
		Number of animals reported with tumor	0	5	3	2
	Hemangiosarcoma	P-value of test of trend or comparison	.6316	.8586	1	.8156
		Number of animals reported with tumor	2	1	0	1
	Histiocytic Sarcoma	P-value of test of trend or comparison	.9799	.8586	1	1
		Number of animals reported with tumor	2	1	0	0
	Leukemia, Granulocytic	P-value of test of trend or comparison	.2029			.4242
		Number of animals reported with tumor	0	0	0	1
	Lrg Granular Cell Leukemia	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Lymphosarcoma	P-value of test of trend or comparison	.3356	.2264	.5000	.4242
		Number of animals reported with tumor	0	2	1	1
	Malignant Hibernoma	P-value of test of trend or comparison	.1223	1	.7533	.3983
		Number of animals reported with tumor	1	0	1	2
	Malignant Mesothelioma	P-value of test of trend or comparison	.9920	.7946	1	1
		Number of animals reported with tumor	3	2	0	0
Bone, Other	Osteosarcoma	P-value of test of trend or comparison	.3682	1	1	.6723
		Number of animals reported with tumor	1	0	0	1
Brain	Granular Cell Tumor	P-value of test of trend or comparison	.7226	.4722		

Reference ID: 3155338

Table 2.9

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
		Number of animals reported with tumor	0	1	0	0
	Malignant Astrocytoma	P-value of test of trend or comparison	.7849	.2264		
		Number of animals reported with tumor	0	2	0	0
	Malignant Granular Cell Tu	P-value of test of trend or comparison	.4745		.5000	
		Number of animals reported with tumor	0	0	1	0
	Malignant Oligodendrogliom	P-value of test of trend or comparison	.4745		.5000	
		Number of animals reported with tumor	0	0	1	0
Cavity, Abdomin	Fibrosarcoma	P-value of test of trend or comparison	.7226	.4722		
		Number of animals reported with tumor	0	1	0	0
	Malignant Schwannoma	P-value of test of trend or comparison	.7226	.4722		
		Number of animals reported with tumor	0	1	0	0
	Osteosarcoma	P-value of test of trend or comparison	.7226	.4722		
		Number of animals reported with tumor	0	1	0	0
Cavity, Oral	Carcinoma, Squamous Cell	P-value of test of trend or comparison	.0400			.1762
		Number of animals reported with tumor	0	0	0	2
GI, Zymbal's	Carcinoma	P-value of test of trend or comparison	.2350	.4722	.5000	.4242
		Number of animals reported with tumor	0	1	1	1
Heart	Endocardial Schwannoma	P-value of test of trend or comparison	.4701	.7250	1	.6723
		Number of animals reported with tumor	1	1	0	1
Kidney	Carcinoma, Transitional Ce	P-value of test of trend or comparison	.2533	.4722		.4242
		Number of animals reported with tumor	0	1	0	1
	Carcinoma, Tubule Cell	P-value of test of trend or comparison	.3660	.2195		.4242
		Number of animals reported with tumor	0	2	0	1
	Lipoma	P-value of test of trend or comparison	.0400			.1762
		Number of animals reported with tumor	0	0	0	2
Liver	Adenoma, Hepatocellular	P-value of test of trend or comparison	.5623	.4722	.2467	
		Number of animals reported with tumor	0	1	2	0

Reference ID: 3155338

Table 2.9

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
	Carcinoma, Hepatocellular	P-value of test of trend or comparison	.1236	1	.1873	.3983
		Number of animals reported with tumor	1	0	4	2
Lung	Adenoma, Bronchiolar-Alveo	P-value of test of trend or comparison	.0400			.1762
		Number of animals reported with tumor	0	0	0	2
Mammary, Male	Carcinoma	P-value of test of trend or comparison	.4745		.5000	
		Number of animals reported with tumor	0	0	1	0
Nerve, Sciatic	Malignant Schwannoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Pancreas	Adenoma, Acinar Cell	P-value of test of trend or comparison	.2350	.4722	.5000	.4242
		Number of animals reported with tumor	0	1	1	1
	Adenoma, Islet Cell	P-value of test of trend or comparison	.4995	.8531	.3374	.8092
		Number of animals reported with tumor	2	1	4	1
	Carcinoma, Acinar Cell	P-value of test of trend or comparison	.4745		.5000	
		Number of animals reported with tumor	0	0	1	0
	Carcinoma, Islet Cell	P-value of test of trend or comparison	.7770	.1624	.1060	1
		Number of animals reported with tumor	1	4	5	0
Parathyroid	Adenoma	P-value of test of trend or comparison	.5845	.4853	.5070	
		Number of animals reported with tumor	0	1	1	0
Pituitary	Adenoma	P-value of test of trend or comparison	.0337	.7819	.2684	.1164
		Number of animals reported with tumor	29	24	33	33
Seminal Vesicle	Adenoma	P-value of test of trend or comparison	.7226	.4722		
		Number of animals reported with tumor	0	1	0	0
Skin/Subcutis	Adenoma, Basal Cell	P-value of test of trend or comparison	.2029			.4242
		Number of animals reported with tumor	0	0	0	1
	Adenoma, Sebaceous Cell	P-value of test of trend or comparison	.7226	.4722		
		Number of animals reported with tumor	0	1	0	0
	Amelanotic Melanoma	P-value of test of trend or comparison	.4745		.5000	

Reference ID: 3155338

Table 2.9

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
		Number of animals reported with tumor	0	0	1	0
	Carcinoma, Sebaceous Cell	P-value of test of trend or comparison	.4745		.5000	
		Number of animals reported with tumor	0	0	1	0
	Carcinoma, Squamous Cell	P-value of test of trend or comparison	.2029			.4242
		Number of animals reported with tumor	0	0	0	1
	Fibroma	P-value of test of trend or comparison	.1351	.2195	.5000	.1762
		Number of animals reported with tumor	0	2	1	2
	Fibrosarcoma	P-value of test of trend or comparison	.2337	.9244	.6626	.5125
		Number of animals reported with tumor	3	1	3	3
	Keratoacanthoma	P-value of test of trend or comparison	.8593	.5165	.9911	.8394
		Number of animals reported with tumor	8	8	2	4
	Lipoma	P-value of test of trend or comparison	.0380	1	.7533	.2121
		Number of animals reported with tumor	1	0	1	3
	Papilloma, Squamous Cell	P-value of test of trend or comparison	.9799	.8586	1	1
		Number of animals reported with tumor	2	1	0	0
Spinal Cord	Malignant Astrocytoma	P-value of test of trend or comparison	.2044			.4242
		Number of animals reported with tumor	0	0	0	1
Stomach, Nongl	Carcinoma, Squamous Cell	P-value of test of trend or comparison	.4745		.5000	
		Number of animals reported with tumor	0	0	1	0
Testis	Interstitial Cell Tumor	P-value of test of trend or comparison	<0.0001	.4578	.1790	<0.0001
		Number of animals reported with tumor	1	2	4	14
Thymus	Malignant Thymoma	P-value of test of trend or comparison	.4737		.5000	
		Number of animals reported with tumor	0	0	1	0
	Thymoma	P-value of test of trend or comparison	.3563	1	1	.6590
		Number of animals reported with tumor	1	0	0	1
Thyroid	Adenoma, C-cell	P-value of test of trend or comparison	.4281	.2825	.4798	.4307
		Number of animals reported with tumor	6	8	7	6

Reference ID: 3155338

Table 2.9

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
	Adenoma, Follicular Cell	P-value of test of trend or comparison	.0380	1	.7533	.2121
		Number of animals reported with tumor	1	0	1	3
	Carcinoma, C-cell	P-value of test of trend or comparison	.5706	.4722	.5000	
		Number of animals reported with tumor	0	1	1	0
	Carcinoma, Follicular Cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Urinary Bladder	Papilloma, Transitional Ce	P-value of test of trend or comparison	.4779		.5000	
		Number of animals reported with tumor	0	0	1	0

Reference ID: 3155338

Table 2.10

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
All Thymomas	P-value of test of trend or comparison	.0124	.4875	.1887	.0382
	Number of animals reported with tumor	0	1	2	4
Angiomas, hemangiomas, and hemangiosarcomas	P-value of test of trend or comparison	.4108	.3023	.5592	.4301
	Number of animals reported with tumor	3	5	3	4
Basal cell adenomas and carcinomas	P-value of test of trend or comparison	.7764	.2287		
	Number of animals reported with tumor	0	2	0	0
C-cell tumors	P-value of test of trend or comparison	.2620	.2359	.2568	.2568
	Number of animals reported with tumor	6	9	8	8
Fibromas and fibrosarcomas of the skin and subcutis	P-value of test of trend or comparison	.2605	1	.8431	.6204
	Number of animals reported with tumor	2	0	1	2
Follicular cell tumors	P-value of test of trend or comparison	.0993	.4815	.4545	.2098
	Number of animals reported with tumor	0	1	1	2
Glial brain tumors	P-value of test of trend or comparison	.3588	1	.7057	.7133
	Number of animals reported with tumor	1	0	1	1
Islet cell tumors	P-value of test of trend or comparison	.2646	.1027	.4545	.2098
	Number of animals reported with tumor	0	3	1	2
Kidney carcinomas	P-value of test of trend or comparison	.7219	.4815		
	Number of animals reported with tumor	0	1	0	0
Lipomas	P-value of test of trend or comparison	.2400			.4615
	Number of animals reported with tumor	0	0	0	1
Lipomas and hibernomas	P-value of test of trend or comparison	.0206	.2287	.0209	.0225
	Number of animals reported with tumor	0	2	5	5
Ovarian granulosa, theca and luteal tumors	P-value of test of trend or comparison	.9984	.9624	1	1
	Number of animals reported with tumor	4	1	0	0
Pheochromocytomas	P-value of test of trend or comparison	.1593	.1963	.0425	.1570
	Number of animals reported with tumor	2	5	7	5

Table 2.10

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
Squamous cell carcinoma or papilloma	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	2	0	0	0
Uterine, vaginal, and cervical adenomas	P-value of test of trend or comparison	.5896	.4815	.4545	
	Number of animals reported with tumor	0	1	1	0
Uterine, vaginal, and cervical polyps	P-value of test of trend or comparison	.2726	.9294	.4000	.5737
	Number of animals reported with tumor	3	1	4	3
Uterine, vaginal, and cervical tumors	P-value of test of trend or comparison	.1710	.8754	.2603	.4035
	Number of animals reported with tumor	4	2	6	5

Reference ID: 3155338

Table 2.11

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
Acinar cell tumors	P-value of test of trend or comparison	.2456	.4722	.2467	.4242
	Number of animals reported with tumor	0	1	2	1
All Thymomas	P-value of test of trend or comparison	.3184	1	.7534	.6590
	Number of animals reported with tumor	1	0	1	1
Angiomas, hemangiomas, and hemangiosarcomas	P-value of test of trend or comparison	.4672	.1056	.5125	.3717
	Number of animals reported with tumor	2	6	3	3
Basal cell adenomas and carcinomas	P-value of test of trend or comparison	.2029			.4242
	Number of animals reported with tumor	0	0	0	1
Bronchiolar-alveolar tumors	P-value of test of trend or comparison	.0400			.1762
	Number of animals reported with tumor	0	0	0	2
C-cell tumors	P-value of test of trend or comparison	.4602	.2105	.3848	.4307
	Number of animals reported with tumor	6	9	8	6
Fibromas and fibrosarcomas of the skin and subcutis	P-value of test of trend or comparison	.1133	.5948	.5144	.2186
	Number of animals reported with tumor	3	3	4	5
Follicular cell tumors	P-value of test of trend or comparison	.0867	1	.8800	.3717
	Number of animals reported with tumor	2	0	1	3
Glial brain tumors	P-value of test of trend or comparison	.3356	.2264	.5000	.4242
	Number of animals reported with tumor	0	2	1	1
Islet cell tumors	P-value of test of trend or comparison	.7306	.3109	.0629	.8927
	Number of animals reported with tumor	3	5	9	1
Kidney and urinary transitional cell tumors	P-value of test of trend or comparison	.2350	.4722	.5000	.4242
	Number of animals reported with tumor	0	1	1	1
Kidney carcinomas	P-value of test of trend or comparison	.4981	.1052		.4242
	Number of animals reported with tumor	0	3	0	1
Leukemias	P-value of test of trend or comparison	.3658	1	1	.6723
	Number of animals reported with tumor	1	0	0	1

Reference ID: 3155338

Table 2.11

Table of reported tumors in Rat Study
NDA 203214
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 80*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 70*
Lipomas	P-value of test of trend or comparison	.0031	1	.7533	.0549
	Number of animals reported with tumor	1	0	1	5
Lipomas and hibernomas	P-value of test of trend or comparison	.0014	1	.6925	.0394
	Number of animals reported with tumor	2	0	2	7
Meningeal tumors	P-value of test of trend or comparison	.5706	.4722	.5000	
	Number of animals reported with tumor	0	1	1	0
Pheochromocytomas	P-value of test of trend or comparison	.7534	.3948	.9233	.7286
	Number of animals reported with tumor	9	10	5	6
Schwannomas	P-value of test of trend or comparison	.7106	.6609	1	.8156
	Number of animals reported with tumor	2	2	0	1
Sebaceous cell tumors	P-value of test of trend or comparison	.5706	.4722	.5000	
	Number of animals reported with tumor	0	1	1	0
Squamous cell carcinoma or papilloma	P-value of test of trend or comparison	.1441	.8586	.8800	.3717
	Number of animals reported with tumor	2	1	1	3
Squamous cell tumors of the skin and subcutis	P-value of test of trend or comparison	.6316	.8586	1	.8156
	Number of animals reported with tumor	2	1	0	1

Table 2.12

Table of tumors reported significant (alpha < 0.05) in at least one arm - Rat Study
NDA 203214
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Adrenal, Medulla	Pheochromocytoma	P-value of test of trend or comparison	.1593	.1963	.0425	.1570
		Number of animals reported with tumor	2	5	7	5
		Poly-3 adjusted incidence rate	4.7%	12%	20%	14%
		95% CI for poly-3 adjusted incidence rate (%)	(0.57,16.2)	(4.08,26.8)	(8.19,36.9)	(4.54,29.5)
		Poly-3 adjusted number of animals at risk	42.6	40.3	35.6	36.8
Body, Whole/Cav	Malignant Hibernoma	P-value of test of trend or comparison	.0493	.2287	.0209	.0494
		Number of animals reported with tumor	0	2	5	4
		Poly-3 adjusted incidence rate	0.0%	5.0%	13%	10%
		95% CI for poly-3 adjusted incidence rate (%)	(0,8.4)	(0.61,17.3)	(4.3,28.1)	(2.79,24.2)
		Poly-3 adjusted number of animals at risk	42.3	39.9	38.7	39.2
Cervix	Polyp, Endometrial Stromal	P-value of test of trend or comparison	.0186		.2033	.0939
		Number of animals reported with tumor	0	0	2	3
		Poly-3 adjusted incidence rate	0.0%	0.0%	5.6%	8.1%
		95% CI for poly-3 adjusted incidence rate (%)	(0,8.4)	(0,9.3)	(0.68,19.2)	(1.7,22.5)
		Poly-3 adjusted number of animals at risk	42.3	38.7	35.4	36.9
Thymus	Thymoma	P-value of test of trend or comparison	.0094	.4875	.4384	.0382
		Number of animals reported with tumor	0	1	1	4
		Poly-3 adjusted incidence rate	0.0%	2.6%	3.1%	12%
		95% CI for poly-3 adjusted incidence rate (%)	(0,8.6)	(0.06,13.5)	(0.08,16.2)	(3.2,27.5)
		Poly-3 adjusted number of animals at risk	41.6	39.1	32.6	34.4

Reference ID: 3155338

Table 2.13

Table of tumors reported significant (alpha < 0.05) in at least one arm - Rat Study
NDA 203214
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Body, Whole/Cav	Angioma	P-value of test of trend or comparison	.3545	.0216	.1249	.1762
		Number of animals reported with tumor	0	5	3	2
		Poly-3 adjusted incidence rate	0.0%	14%	7.6%	6.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,9.3)	(4.67,30.3)	(1.57,20.9)	(0.85,23.5)
		Poly-3 adjusted number of animals at risk	38.0	35.2	39.3	28.8
Cavity, Oral	Carcinoma, Squamous Cell	P-value of test of trend or comparison	.0400			.1762
		Number of animals reported with tumor	0	0	0	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	6.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,9.3)	(0,10.3)	(0,9.3)	(0.85,23.5)
		Poly-3 adjusted number of animals at risk	38.0	34.0	38.1	29.0
Kidney	Lipoma	P-value of test of trend or comparison	.0400			.1762
		Number of animals reported with tumor	0	0	0	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	7.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,9.3)	(0,10.3)	(0,9.3)	(0.85,23.5)
		Poly-3 adjusted number of animals at risk	38.0	34.0	38.1	28.5
Lung	Adenoma, Bronchiolar-Alveo	P-value of test of trend or comparison	.0400			.1762
		Number of animals reported with tumor	0	0	0	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	7.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,9.3)	(0,10.3)	(0,9.3)	(0.85,23.5)
		Poly-3 adjusted number of animals at risk	38.0	34.0	38.1	28.6
Pituitary	Adenoma	P-value of test of trend or comparison	.0337	.7819	.2684	.1164
		Number of animals reported with tumor	29	24	33	33
		Poly-3 adjusted incidence rate	58%	52%	66%	71%
		95% CI for poly-3 adjusted incidence rate (%)	(42.2,71.8)	(36.1,67.1)	(50.1,78.8)	(55.1,84.0)
		Poly-3 adjusted number of animals at risk	50.1	46.6	50.2	46.6
Skin/Subcutis	Lipoma	P-value of test of trend or comparison	.0380	1	.7533	.2121
		Number of animals reported with tumor	1	0	1	3

Reference ID: 3155338

Table 2.13

Table of tumors reported significant (alpha < 0.05) in at least one arm - Rat Study
NDA 203214
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	2.6%	0.0%	2.6%	10%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,13.8)	(0,10.3)	(0.06,13.8)	(2.11,27.4)
		Poly-3 adjusted number of animals at risk	38.6	34.0	38.2	29.5
Testis	Interstitial Cell Tumor	P-value of test of trend or comparison	<0.0001	.4578	.1790	<0.0001
		Number of animals reported with tumor	1	2	4	14
		Poly-3 adjusted incidence rate	2.6%	5.8%	10%	41%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,13.8)	(0.7,19.7)	(2.87,24.8)	(24.6,60.8)
		Poly-3 adjusted number of animals at risk	38.7	34.3	39.0	33.8
Thyroid	Adenoma, Follicular Cell	P-value of test of trend or comparison	.0380	1	.7533	.2121
		Number of animals reported with tumor	1	0	1	3
		Poly-3 adjusted incidence rate	2.6%	0.0%	2.6%	10%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,13.8)	(0,10.3)	(0.06,13.8)	(2.11,27.4)
		Poly-3 adjusted number of animals at risk	38.2	34.0	38.3	29.3

Reference ID: 3155338

Table 2.14

Table of tumors reported significant (alpha < 0.05) in at least one arm - Rat Study
NDA 203214
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
All Thymomas	P-value of test of trend or comparison	.0124	.4875	.1887	.0382
	Number of animals reported with tumor	0	1	2	4
	Poly-3 adjusted incidence rate	0.0%	2.6%	6.1%	12%
	95% CI for poly-3 adjusted incidence rate (%)	(0,8.6)	(0.06,13.5)	(0.74,20.8)	(3.2,27.5)
	Poly-3 adjusted number of animals at risk	41.6	39.1	32.7	34.4
Lipomas and hibernomas	P-value of test of trend or comparison	.0206	.2287	.0209	.0225
	Number of animals reported with tumor	0	2	5	5
	Poly-3 adjusted incidence rate	0.0%	5.0%	13%	13%
	95% CI for poly-3 adjusted incidence rate (%)	(0,8.4)	(0.61,17.3)	(4.3,28.1)	(4.19,27.4)
	Poly-3 adjusted number of animals at risk	42.3	39.9	38.7	39.5
Pheochromocytomas	P-value of test of trend or comparison	.1593	.1963	.0425	.1570
	Number of animals reported with tumor	2	5	7	5
	Poly-3 adjusted incidence rate	4.7%	12%	20%	14%
	95% CI for poly-3 adjusted incidence rate (%)	(0.57,16.2)	(4.08,26.8)	(8.19,36.9)	(4.54,29.5)
	Poly-3 adjusted number of animals at risk	42.6	40.3	35.6	36.8

Reference ID: 3155338

Table 2.15

Table of tumors reported significant (alpha < 0.05) in at least one arm - Rat Study
NDA 203214
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Bronchiolar-alveolar tumors	P-value of test of trend or comparison	.0400			.1762
	Number of animals reported with tumor	0	0	0	2
	Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	7.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,9.3)	(0,10.3)	(0,9.3)	(0.85,23.5)
	Poly-3 adjusted number of animals at risk	38.0	34.0	38.1	28.6
Lipomas	P-value of test of trend or comparison	.0031	1	.7533	.0549
	Number of animals reported with tumor	1	0	1	5
	Poly-3 adjusted incidence rate	2.6%	0.0%	2.6%	16%
	95% CI for poly-3 adjusted incidence rate (%)	(0.06,13.8)	(0,10.3)	(0.06,13.8)	(5.45,34.7)
	Poly-3 adjusted number of animals at risk	38.6	34.0	38.3	30.5
Lipomas and hibernomas	P-value of test of trend or comparison	.0014	1	.6925	.0394
	Number of animals reported with tumor	2	0	2	7
	Poly-3 adjusted incidence rate	5.1%	0.0%	5.1%	22%
	95% CI for poly-3 adjusted incidence rate (%)	(0.61,17.3)	(0,10.3)	(0.61,17.3)	(8.98,40.0)
	Poly-3 adjusted number of animals at risk	39.5	34.0	39.0	32.4

Reference ID: 3155338

Table 2.16: Lipomas and hibernomas in rat study

Endpoint	Sex	p-value of trend test	Control	Low dose		Mid dose		High dose	
			Incidence	Incidence	p-value	Incidence	p-value	Incidence	p-value
All lipomas and hibernomas	Female	0.0206	0.0%	5.0%	0.2287	13%	0.0209	13%	0.0225
	Male	0.0014	5.1%	0.0%	1	5.1%	0.6925	22%	0.0394
All lipomas	Female	0.2400	0.0%	0.0%	·	0.0%	·	2.7%	0.4651
	Male	0.0031	2.6%	0.0%	1	2.6%	0.7533	16%	0.0549
Malignant hibernomas	Female	0.0493	0.0%	5.0%	0.2287	13%	0.0209	10%	0.0494
	Male	0.1223	2.6%	0.0%	1	2.6%	0.7533	6.7%	0.3983
Lipomas of skin/subcutis	Female	·	0.0%	0.0%	·	0.0%	·	0.0%	·
	Male	0.0380	2.6%	0.0%	1	2.6%	0.7533	10%	0.2121
Lipomas of kidneys	Female	0.2400	0.0%	0.0%	·	0.0%	·	2.7%	0.4615
	Male	0.0400	0.0%	0.0%	·	0.0%	·	7.0%	0.1762

Table 2.17

Organs reported as autolytic
NDA 203214
Animal carcinogenicity study
Female Rats

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
LN, Inguinal	5	7.1%	6	10%	6	10%	20	29%	37	15%
Mammary, Female	.	.	.	.	.	.	2	2.9%	2	0.8%
Parathyroid	2	2.9%	.	.	4	6.7%	3	4.3%	9	3.6%
Peyer's Patch	3	4.3%	.	.	4	6.7%	18	26%	25	10%
Thymus	3	4.3%	.	.	3	5.0%	6	8.6%	12	4.8%

Table 2.18

Organs reported as autolytic
NDA 203214
Animal carcinogenicity study
Male Rats

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
Jejunum	.	.	.	.	.	.	1	1.4%	1	0.4%
LN, Inguinal	4	5.7%	7	12%	13	22%	16	23%	40	16%
Parathyroid	4	5.7%	2	3.3%	2	3.3%	.	.	8	3.2%
Peyer's Patch	3	4.3%	2	3.3%	4	6.7%	10	14%	19	7.6%
Thymus	1	1.4%	1	1.7%	2	3.3%	3	4.3%	7	2.8%

Table 2.19

Organs reported as unexamined
NDA 203214
Animal carcinogenicity study
Female Rats

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
Adrenal, Medulla	.	.	.	.	.	.	1	1.4%	1	0.4%
Cavity, Abdomin	.	.	.	.	.	.	1	1.4%	1	0.4%
Cavity, Thoracic	.	.	.	.	1	1.7%	1	1.4%	2	0.8%
Cecum	1	1.4%	.	.	.	.	.	.	1	0.4%
Colon	1	1.4%	.	.	.	.	.	.	1	0.4%
Foot/Foot Pad	.	.	.	.	1	1.7%	.	.	1	0.4%
GI, Clitoral	2	2.9%	.	.	.	.	.	.	2	0.8%
GI, Zymbal's	1	1.4%	.	.	.	.	.	.	1	0.4%
Ileum	1	1.4%	.	.	.	.	.	.	1	0.4%
LN, Inguinal	.	.	.	.	1	1.7%	1	1.4%	2	0.8%
LN, Mesenteric	.	.	.	.	.	.	2	2.9%	2	0.8%
Skin/Subcutis	.	.	.	.	.	.	1	1.4%	1	0.4%
Thymus	.	.	.	.	.	.	1	1.4%	1	0.4%
Ureter	.	.	.	.	2	3.3%	4	5.7%	6	2.4%
Urinary Bladder	.	.	.	.	.	.	1	1.4%	1	0.4%
Vagina	.	.	.	.	.	.	1	1.4%	1	0.4%

Reference ID: 3155338

Table 2.20

Organs reported as unexamined
NDA 203214
Animal carcinogenicity study
Male Rats

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
Bone, Other	.	.	1	1.7%	.	.	.	.	1	0.4%
Foot/Foot Pad	.	.	.	.	.	.	1	1.4%	1	0.4%
Joint, Other	1	1.4%	.	.	.	.	.	.	1	0.4%
LN, Inguinal	3	4.3%	3	5.0%	3	5.0%	6	8.6%	15	6.0%
LN, Other	.	.	1	1.7%	.	.	.	.	1	0.4%
Nerve, Optic	1	1.4%	.	.	.	.	.	.	1	0.4%
Skin/Subcutis	.	.	.	.	1	1.7%	1	1.4%	2	0.8%
Spinal Cord	.	.	1	1.7%	.	.	.	.	1	0.4%
Thymus	.	.	.	.	.	.	1	1.4%	1	0.4%
Ureter	5	7.1%	2	3.3%	2	3.3%	4	5.7%	13	5.2%
Urinary Bladder	.	.	1	1.7%	.	.	.	.	1	0.4%

Reference ID: 3155338

Chapter 3

Conclusions

3.1 Mouse study

The main tumor study on transgenic mice was a negative study — no positive findings were reported in either the female or male experiments. However, the high levels of autolysis in the parathyroid, in both female and male mice, mean that the study should be considered inconclusive with respect to tumors of this organ.

The dose level in the high dose male animals was most likely close to the MTD, since an increase in mortality was noted in that group. No such evidence was found in the female mouse experiment.

The positive control study was positive, with the animals in the positive control group developing lymphosarcomas, squamous cell tumors of the stomach, and keratoacanthomas (female mice only) at considerably higher rates than the control group.

3.2 Rat study

Both the female and male rat studies were positive.

In male rats, tofacitinib was strongly associated with an increase in interstitial cell tumors (both the test of trend and the comparison between high dose and control yielded p-values below 0.0001). There was also evidence of an association between tofacitinib and hibernomas and lipomas. When white fat lipomas were consided independently of hibernomas, the test of trend was strongly significant $p = 0.0031$, although the comparison between the control and high dose group was not quite significant, even for rare tumors ($p = 0.0549$). However, when white and brown fat lipomas were combined, both the test of trend ($p = 0.0014$) and the comparison between the control and high dose group ($p = 0.0394$) are significant, as long as these are considered rare tumors.

(If they are considered common, then the test of trend remains significant.)

The combination of hibernomas and lipomas was also a positive finding in the female rat experiment. The test of trend, and the comparisons of both the mid dose and the high dose groups with the control group yielded p-values below 0.025 ($p = 0.0206$, $p = 0.0209$ and $p = 0.0225$ respectively). The fact of the significant result from the comparison between the mid dose group and the control group is especially noteworthy here. It should be stressed that these findings remain positive only as long as these are considered rare tumors, which is a point of some debate. On the other hand, the fact that the male and female rats both developed such tumors provides strong corroboratory evidence of a tumorigenic effect.

The female rat experiment is also positive for thymomas. These are considered by the sponsor to be rare tumors, so the results of the test of trend ($p = 0.0124$) and the comparison between the control and high dose groups ($p = 0.0382$) are considered statistically significant.

In addition to these positive findings, the number of male animals for which the inguinal lymph node has been left unexamined means that the study should be considered inconclusive with respect to tumors of this organ.

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 203,214

Drug Name: Xeljanz (tofacitinib) 5 mg and 10 mg tablets

Indication(s): Treatment of Rheumatoid Arthritis

Applicant: Pfizer Inc.

Date(s): Submitted: October 21, 2011
PDUFA: August 21, 2012

Review Priority: Standard

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

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APPENDICES 37

Reference ID: 3150054

1 EXECUTIVE SUMMARY

Pfizer Inc., proposes tofacitinib (CP-690,550) 5 mg and 10 mg orally administered twice a day (BID) for the treatment of rheumatoid arthritis. To support this marketing application, the applicant submitted data from 21 Phase 1 studies, six Phase 2 studies, and five Phase 3 studies. The focus of this statistical review is on the five Phase 3 studies A3921032, A3921044, A3921045, A3921046, and A3921064.

During the review of the clinical studies, several statistical issues that warrant further exploration of data and discussion in the review were identified. The applicant's primary analysis was conducted in the full analysis set (FAS) defined as all randomized patients with at least one post-baseline measurement. In general, the division adheres to the intent-to-treat (ITT) principle and includes all randomized patients regardless of whether or not they have post-baseline observations in the analysis. Re-analyses of the data using the ITT population and handling patients with missing post-baseline measurement as treatment failures produced similar results to the applicant's primary analyses using the FAS population. The impact of missing data was not prominent because missing binary endpoints such as the American College of Rheumatology's ACR20 or Disease Activity Score (DAS28) of less than 2.6 were treated conservatively using non-responder imputation, and missing radiographic data were imputed using a linear extrapolation method. The applicant assumed a missing-at-random (MAR) mechanism for missing data regardless of reason and used a mixed-effect repeated-measures (MMRM) model to analyze continuous endpoints such as HAQ-DI. Re-analysis of the data by applying baseline observation carried forward (BOCF) imputation for missing data gave similar results to the applicant's primary analysis. There was a multiplicity adjustment issue in the analyses of the secondary endpoints because their proposed sequential method does not rigorously control the family-wise type-1 error rate (refer to sections 3.2.2 and 0). There were also inconsistent findings from the applicant's pre-specified primary analysis using ANCOVA model and pre-specified sensitivity analysis using rank-based ANCOVA model when evaluating the radiographic endpoint in study 1044. Outliers were identified in each dose group and exploratory analyses were conducted. Refer to section 0 for more detail regarding these findings on radiographic endpoints.

The major efficacy findings are as follows:

1. In all five efficacy studies, A3921032, A3921044, A3921045, A3921046, and A3921064, a statistically significantly higher proportion of patients in the tofacitinib group (5 mg or 10 mg) achieved ACR20 response compared to placebo.

2. In studies A3921032, A3921045, A3921046, and A3921064, a statistically significant difference in HAQ-DI score was observed in patients treated with tofacitinib 5 mg or tofacitinib 10 mg compared to placebo.

3. For DAS28 response, while there is consistent evidence that a significantly higher proportion of patients in the tofacitinib 10 mg group achieved DAS28 response compared

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to placebo, only one study (study A3921046) showed a statistical significant difference between 5 mg and placebo.

4. There is evidence in study A3921044 that tofacitinib 10 mg and tofacitinib 5 mg may have some activity on radiographic progression. However, there is uncertainty associated with the results for the following reasons (section 0):
    a. There was less progression in the placebo control group than presumed when the applicant powered the study, therefore, the observed treatment effect size was smaller than anticipated;
    b. Less than 40% of patients had some change in mTSS from baseline and only 16% of patients' radiographic scores improved;
    c. Data are not consistent with respect to dose;
    d. The magnitude of effect in tofacitinib 10 mg group is sensitive to outliers;
    e. It is unclear how excluded data may affect the overall conclusion;
    f. The evidence for an effect in radiographic progression is from a single study.

There were no noticeable treatment differences in terms of ACR20 across gender and age subgroups.

In summary, there is substantial evidence of efficacy of tofacitinib 5 mg or 10 mg for the treatment of rheumatoid arthritis. This is based on consistent findings in the domains of reducing signs and symptoms of RA as measured by ACR20, and improving physical function as measured by HAQ-DI. (b) (4)

Because the safety of tofacinitib 5 mg and 10 mg dose groups are still under review, it is premature to discuss the risk-benefit profile of tofacitinib at this time.

Reference ID: 3150054

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Tofacitinib (CP-690,550) is being proposed as immediate-release tablets for oral administration in 5 mg and 10 mg dosage strengths for the treatment of rheumatoid arthritis.

2.1.2 History of Drug Development and Regulatory Interactions

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

In December 2008, the applicant had an EOP2 meeting with the division, where input was received regarding the proposed Phase 3 program. A teleconference was held on January 28, 2010 between the applicant and the division to discuss further the Phase 3 program. All Phase 3 protocols (A3921032, A3921045, A3921044, A3921046, A3921064, and (b) (4) were amended following the teleconference. Review of the statistical analysis plan (SAP) for protocol A3921045 (serial 128, dated May 7, 2010) was conducted and comments were provided to the applicant. The statistical comments pertained mostly to the handling of missing data (HAQ-DI and DAS-28) and multiplicity. The applicant submitted their response to the statistical comments for protocol A3921045 on December 23, 2010 (SN225) and presented their approach to handling missing HAQ-DI data. According to them, these changes apply to all their Phase 3 protocols (i.e. A3921032, A3921045, A3921044, A3921046, A3921064, and (b) (4)). A Pre-NDA meeting was held on February, 2011 and we informally agreed to the format and content of the new drug application (NDA). At the meeting we also reminded them that to support the primary radiographic endpoint, it would be important to show that the slope of structural damage over time does not increase from 6 to 12 months compared to 0 to 6 months, as advised during the EOP2 meeting.

On October 21, 2011, the NDA was submitted. On January 20, 2012, the applicant noticed that their DAS28-4(erythrocyte sedimentation rate or ESR) calculation was wrong since they used physician's global assessment instead of subject's global assessment in the formula for DAS. I confirmed their calculation error, and that the error was not propagated to the other efficacy parameters. They submitted revised study reports and datasets with re-calculated DAS parameters.

The Arthritis Advisory Committee convened on May 9, 2012 to discuss the efficacy and safety of tofacitinib 5 mg and 10 mg doses. The 10-member committee discussed the efficacy of treatment on signs and symptoms, quality of life, and radiographic structural damage

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progression, as well as potential safety signals including malignancy, serious infections and laboratory abnormalities. The committee voted 8 to 2 that that the available radiographic data were not adequate but voted 10 to 0 that efficacy has been demonstrated for signs and symptoms and quality of life in patients with rheumatoid arthritis. The committee voted 7 to 2 that the available data for safety (particularly in the 5 mg dose group) were adequate, but asked for long term postmarketing data. Overall, they voted 8 to 2 for approval (5 mg dose) with changes to the indication.

2.1.3 Specific Study Reviewed

My focus is on the five efficacy studies, A3921032, A3921045, A3921044, A3921046, and A3921064 (hereafter referred to as 1032, 1044, 1045, 1046, and 1064). Of note, study 1044 had radiographic data in addition to signs and symptoms data as in other studies.

2.1.4 Major Statistical Issues

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

1. Robustness of efficacy data – analysis sets (ITT vs. FAS excluding subjects without baseline or at least one post-baseline measurements), missing data (MMRM based on MAR assumption on HAQ-DI), statistical analysis models (parametric vs nonparametric analysis on mTSS from study 1044)

2. Multiplicity adjustment – proposed sequential test appears not to control family-wise type 1 error rate

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

2.2 Data Sources

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

\\CDSESUB5\EVSPROD\NDA203214\203214.enx

Reference ID: 3150054

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted efficacy data are acceptable in terms of quality and integrity. I was able to reproduce the primary and secondary efficacy endpoints analyses. No noticeable deviations between the case report forms and analysis datasets relevant to primary and secondary endpoints were identified. The applicant found errors in their calculation of the DAS parameter and revised the study reports and efficacy datasets including DAS parameter. I confirmed that the error was fixed and did not propagate to other parameters such as ACR20.

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

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies 1032, 1044, 1045, 1046, and 1064 were almost of similar design, except for the population studied, the study duration, and treatment arms. They were all phase 3, randomized, double-blind, placebo-controlled studies designed to demonstrate efficacy of tofacitinib (CP-690,550) 5 mg BID and 10 mg BID (hereafter referred to as CP5 and CP10) over placebo in the domains of reducing signs and symptoms of RA as measured by ACR20 response criteria, slowing the progression of structural damage, as measured by change from baseline in van der Heijde modified Sharp score, and improving physical function as measured by HAQ-DI. The applicant also planned to evaluate the disease activity by comparing the rate of achieving DAS28 (ESR) response.

A summary of the study design and endpoints is presented in Table 1. In the Phase 3 studies, patients originally randomized to placebo were advanced to either CP5 or CP10 at 3 or 6 months. In studies 1032 and 1045, all placebo patients received CP-690,550 at Month 3. In studies 1044, 1046, and 1064, placebo nonresponders were advanced at Month 3, and all remaining placebo patients were advanced at Month 6. Nonresponders were defined as those patients who did not have at least a 20% improvement from baseline levels in both the tender/painful and swollen joint counts at the Month 3 visit.

Reference ID: 3150054

Table 1: Summary of Study Design

Study ID	Study Design	Population, Sample Size Randomization	Primary & Secondary Endpoints
A3921032	A 6-month, placebo-controlled, 3-arm parallel study of CP-690550 5 or 10 mg BID or placebo added to background MTX At M3, all placebo patients are advanced to their second predetermined treatment.	Subjects with active RA who had an inadequate response to at least one TNF inhibitors 399 2:2:1:1	*M3 ACR20 response* *M3 Change from baseline in HAQ-DI* *M3 DAS28-4(ESR) < 2.6*
A3921045	A 6-month, placebo-controlled, 3-arm parallel study of CP-690550 5 or 10 mg BID or placebo At M3, all placebo patients are advanced to their second predetermined treatment.	Subjects with active RA who had an inadequate response to a DMARD 610 4:4:1:1	*M3 ACR20 response* *M3 Change from baseline in HAQ-DI* *M3 DAS28-4(ESR) < 2.6*
A3921064	A 12-month, placebo-controlled, 4-arm parallel study of CP-690550 5 or 10 mg BID, adalimumab 40 mg SC Q2W or placebo added to background MTX At M3, non-responding patients are advanced to a second pre-determined treatment of CP-690550 5 or 10 mg BID. At M6, all placebo patients are advanced to their second predetermined treatment.	Subjects with active RA who had an inadequate response to MTX 717 4:4:1:1:4	*M6 ACR20 response* *M3 Change from baseline in HAQ-DI* *M6 DAS28-4(ESR) < 2.6*
A3921046	A 12-month, placebo-controlled, 3-arm parallel study of CP-690550 5 or 10 mg BID or placebo added to background DMARD treatment Placebo patients are advanced as in Study A3921064.	Subjects with active RA who had an inadequate response to non-biologic DMARD 792 4:4:1:1	*M6 ACR20 response* *M3 Change from baseline in HAQ-DI* *M6 DAS28-4(ESR) < 2.6*

A3921044	A 2-year, placebo-controlled, 3-arm parallel study of CP-690550 5 or 10 mg BID or placebo added to background MTX Placebo patients are advanced as in Study A3921064.	Subjects with active RA who had an inadequate response to MTX 797 4:4:1:1	*M6 ACR20 response* ***M6 Change from baseline in Total Sharp Score*** *M3 Change from baseline in HAQ-DI* *M6 DAS28-4(ESR) < 2.6*

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Studies 1032, 1045, 1046, and 1064 have three primary efficacy endpoints (in sequence):

1. Signs and symptoms as measured by ACR20 at Month 3 (studies 1032 and 1045) or at Month 6 (studies 1046 and 1064);
2. Physical function as measured by the HAQ-DI change from baseline at Month 3;
3. Incidence of DAS <2.6 at Month 3 (Studies 1045 and 1032) or at Month 6 (Studies 1046 and 1064).

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

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

3.2.2 Statistical Methodologies

All five studies were designed to establish superiority of two doses (5 mg and 10 mg BID) of tofacitinib (CP-690,550) to placebo for all primary endpoints. In these comparisons, the placebo refers to the combined placebo data from sequence 3 and 4 for Month 3 and Month 6 analyses.

The following are the protocol-specified analytical approach for the primary endpoints:

- For the binary endpoints such as ACR20 and DAS28 at Month 3 or Month 6, the normal approximation for the difference in binomial proportions was used to compare treatment difference. Missing values due to a patient dropping from the study for any reason (e.g., lack of efficacy or adverse event), if the ACR value can not be determined (e.g. baseline data is missing), or if a patient advanced at Month 3 to the next dose in the sequence to which the patient was randomized (in studies 1044, 1046, and 1064), that patient's ACR20 or DAS28 will be set to nonresponsive (that is, baseline observation carried forward, BOCF) on or after Month 3 visit. This also goes by the name Non Responder Imputation (NRI).

- For HAQ-DI at Month 3 or at Month 6, the mixed-effect model with repeated measures including treatment, site (US, Europe/Canada, Latin America, Asia/Other), baseline value, visit, and treatment-by-visit interaction as fixed effects and patient as random effect was pre-specified to compare treatment difference. Compound symmetry was assumed (though the applicant proposed to check the robustness of the results by fitting other structured covariance matrices, e.g., autoregressive 1, and unstructured. as well). It was also pre-specified that no imputation will be applied to missing data. In one of the communications with the Division, the applicant maintained that the assumption of missing at random for missing data in the HAQ-DI analysis is reasonable, and they gave justifications when different reasons for dropout occur.

- For the change from baseline in the modified Sharp score at Month 6, the analysis of covariance (ANCOVA) with treatment, and site (US, Europe/Canada, Latin America, Asia/Other) as fixed effects and actual baseline value as a covariate was pre-specified as the primary analysis. Month 6 measurements for patients with missing values due to either patient advancement at Month 3 or due to patient dropout (before advancement, i.e. Month 3 or Month 6) were imputed using a linear extrapolation based on radiographs either at Month 3 or prior to withdrawal.

Several robustness or sensitivity analyses (e.g. per protocol analysis) for each of the primary endpoint (i.e. ACR20, DAS, HAQ-DI) were pre-specified in the protocol to support the interpretation of the primary analyses. Specifically, for the change from baseline in the modified Sharp score, ANCOVA model on the ranks with treatment as factor, and rank baseline modified Sharp score as covariate was pre-specified as a sensitivity analysis. Missing values were imputed by linear extrapolation like above, and the resulting imputed data were ranked. However, the protocol also stipulated that conclusions (statistical significance/superiority) for comparisons of all the primary endpoints between each dose of CP-690,550 and placebo group would be based on results of the primary analyses.

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

Figure 1).

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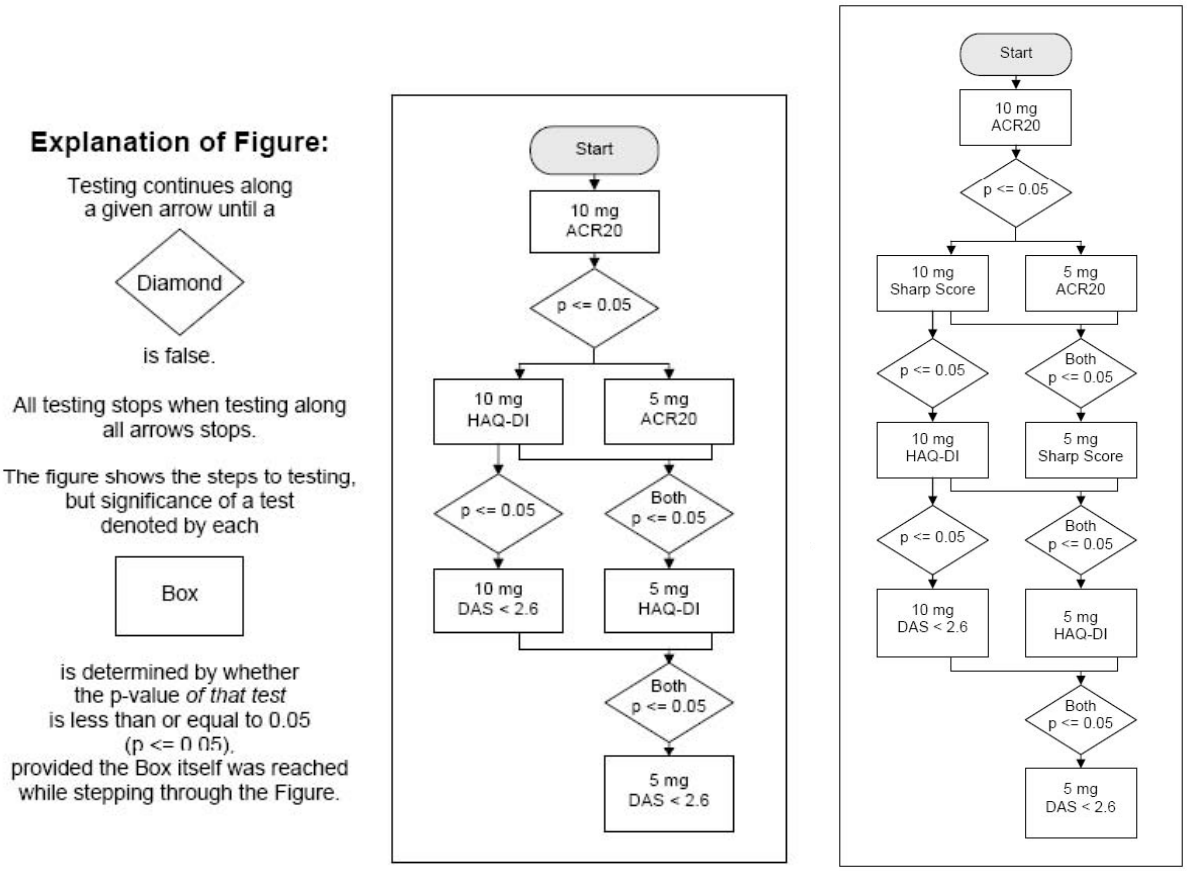
Figure 1: Primary Analysis Stepdown Procedure – Studies 1032, 1045, 1046, 1064 and 1044



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Studies 1032, 1045, 1046, and 1064	Study 1044

Except in study 1044, no interim analysis was planned. For study 1044, one interim analysis was planned. The interim analysis was performed at 100% accrual at the completion of Month 12, which included all the primary analyses. All the inferences were based on year 1 interim analyses. The year 2 analyses (that is, the final analyses) is considered supportive.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The patient disposition can be summarized as follows:

- Completion rates:
  - Background DMARD studies (1032, 1044, 1046, & 1064): 74-84% in active groups; 77-87% in placebo groups
  - Monotherapy study (1045): 92% in active group; 86% in placebo group
- Dropouts rates due to adverse events (AE):
  - Background DMARD studies: 6-12% in active groups; 3-7% in placebo groups
  - Monotherapy study: 3% in active group; 4% in placebo group
- Dropouts rates due to lack of efficacy (LOE):
  - Background DMARD studies: 2-4% in active groups; 3-8% in placebo groups
  - Monotherapy study: 1% in active group; 6% in placebo group

The detail of disposition by study can be found from Table 22 in the appendix.

There were no noticeable imbalances of the demographics and baseline characteristics between treatment groups as shown again Table 23 and Table 24 in the appendix.

The efficacy analysis was conducted on the Full Analysis Set (FAS) population. The applicant originally defined FAS to include all randomized participants who received at least one study drug. However, in their actual analyses, they excluded subjects among FAS who did not have baseline or at least one post baseline measurement. In my analyses of the primary and secondary efficacy endpoints, I included all randomized patients who took at least one dose of study medication regardless of status of measurements obtained (intent-to-treat population or ITT). In the analyses of radiographic data, patients who did not have the baseline data were excluded since baseline data is needed for linear extrapolation of missing 6 or 12 month data. Therefore, all patients who had valid baseline and Month 3 radiographic data were included in the analysis. I defined the analysis set as radiographic ITT (rITT) which agrees with applicant's FAS.

In addition, the applicant excluded patients from sites with data integrity or procedural issues. Specifically, 15 patients were randomized from Site 1048 and all had radiographic data in their

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database. Among them, 6 patients were included in their analysis and remaining 9 patients from the site were excluded even if they had 6 month data. Moreover, there were 9 patients randomized from Site 1155 and only one had radiographic data in their database and the patient's data were included in their analyses. Finally, there were 8 patients randomized from Site 1174. All patients from this site were excluded even if they had 6 month data in their database. I conducted additional analyses to assess the sensitivity of the results when including or excluding these patients in the analysis dataset.

For other efficacy endpoints, there was discrepancy in analysis sets between the applicant and me. Main reason for the discrepancy is that the applicant excluded subjects with no baseline or without at least one valid post-baseline measurement (Table 2).

Table 2: Analysis Populations for Analyses of Primary and Secondary Endpoints

	PBO	CP 5 mg	CP 10 mg
Study 1032			
FAS (by applicant)	132	133	134
ACR20	131	132	133
HAQ-DI	118	117	125
DAS28	120	119	125
ITT (by reviewer)	132	133	134
ACR20			
HAQ-DI			
DAS28			
Study 1044			
FAS (by applicant)	156	316	309
ACR20	154	309	309
HAQ-DI	146	294	300
DAS28	129	265	257
mTSS †	140 (139*)	278 (277*)	290
ITT (by reviewer)	160	321	316
ACR20			
HAQ-DI			
DAS28			
mTSS	140	278	290
Study 1045			
FAS (by applicant)	122	241	243
ACR20	120	241	242
HAQ-DI	109	237	227
DAS28	114	232	229

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ITT (by reviewer)	122	243	245
ACR20			
HAQ-DI			
DAS28			
Study 1046			
FAS (by applicant)	158	312	315
ACR20	157	311	309
HAQ-DI	147	292	292
DAS28	148	263	270
ITT (by reviewer)	159	315	318
ACR20			
HAQ-DI			
DAS28			

Study 1064

	PBO	CP 5 mg	CP 10 mg	Adalimumab
FAS (by applicant)	107	201	199	201
ACR20	106	196	196	199
HAQ-DI	98	188	185	190
DAS28	92	117	176	178
ITT (by reviewer)	108	204	201	204
ACR20				
HAQ-DI				
DAS28				

Note (*): In the study report of 1044, applicant reported one less patient from the tofacitinib 5 mg and placebo groups, respectively, although study database and their analysis included those two patients' radiographic data.
† Submitted radiographic data including all patients from Sites 1048 and 1174, N=144//282/296 (PBO/CP5/CP10)

3.2.4 Results and Conclusions

In this presentation of the results, the results from studies 1032, 1045, 1046, and 1064 regarding ACR20, HAQ-DI, and DAS28-4(ESR) less than 2.6 are summarized. This is followed by presentation of the results from study 1044 including mTSS. The reason for a separate presentation for the results from study 1044 is that only this study had radiographic data and there is an issue of multiplicity adjustment. Both the applicant's analyses and my analyses are presented.

3.2.4.1 Results from Studies 1032, 1045, 1046 and 1064

Results from the analyses of primary and some key secondary endpoints by the applicant for studies 1032, 1045, 1046, and 1064 are presented in Table 3, Table 4, and Table 5. Results from the applicant's analyses provided consistent evidence of improvement on signs and symptoms of

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RA. In all four studies, a statistically significantly higher proportion of patients in the tofacitinib group (CP5 or CP10) achieved ACR20 response compared to placebo.

All four studies also provided evidence of improvement in physical function as measured by HAQ-DI. In all four studies, a statistically significant difference in HAQ-DI score was observed in patients treated with tofacitinib 5 mg or tofacitinib 10 mg compared to placebo. In the applicant's analyses, three of the four studies showed a significantly higher proportion of patients in the tofacitinib group (CP5 or CP10) achieved DAS28 response compared to placebo.

Table 3: Applicant's Analysis on ACR20 (FAS)

Treatment	N	N	Response Rate	Difference vs. PBO	P-value
Study 1032 (Month 3)					
CP 5 mg	132	55	42 %	17 %	.0025
CP 10 mg	133	64	48 %	23 %	<.0001
PBO	131	32	25 %		
Study 1045 (Month 3)					
CP 5 mg	241	144	60 %	33 %	<.0001
CP 10 mg	242	159	66 %	39 %	<.0001
PBO	120	32	27 %		
Study 1046 (Month 6)					
CP 5 mg	311	164	53 %	22 %	<.0001
CP 10 mg	309	180	58 %	27 %	<.0001
PBO	157	49	31 %		
Study 1064 (Month 6)					
CP 5 mg	196	101	52 %	24 %	<.0001
CP 10 mg	196	103	53 %	25 %	<.0001
ADA 40 mg	199	94	47 %	19 %	.0008
PBO	106	30	28 %		

Excerpted from the clinical study reports A3921032, A3921045, A3921046, A3921064.

Table 4: Applicant's Analysis on HAQ-DI (FAS)

Treatment	N	LS Mean	Difference vs. PBO		
			LS Mean Difference	95% CI	P-value
Study 1032 (Month 3)					
CP 5 mg	117	-0.5	-0.3	(-0.4, -0.1)	.0002
CP 10 mg	125	-0.5	-0.3	(-0.4, -0.1)	<.0001
PBO	118	-0.2			
Study 1045 (Month 3)					
CP 5 mg	237	-0.5	-0.3	(-0.4, -0.2)	<.0001
CP 10 mg	227	-0.6	-0.4	(-0.5, -0.2)	<.0001
PBO	109	-0.2			
Study 1046 (Month 3)					
CP 5 mg	292	-0.5	-0.3	(-0.4, -0.2)	<.0001
CP 10 mg	292	-0.6	-0.4	(-0.5, -0.3)	<.0001

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PBO	147	-0.2			
Study 1064 (Month 3)					
CP 5 mg	188	-0.6	-0.3	(-0.4, -0.2)	<.0001
CP 10 mg	185	-0.7	-0.4	(-0.5, -0.3)	<.0001
ADA 40 mg	190	-0.5	-0.2	(-0.4, -0.1)	<.0001
PBO	98	-0.3			

Excerpted from the clinical study reports A3921032, A3921045, A3921046, A3921064.

Table 5: Applicant's Analysis on DAS28-4(ESR)<2.6 (FAS)

Treatment	N	n	Response Rate	Difference vs. PBO	P-value
Study 1032 (Month 3)					
CP 5 mg	119	8	7 %	5 %	.0497
CP 10 mg	125	11	9 %	7 %	.0105
PBO	120	2	2 %		
Study 1045 (Month 3)					
CP 5 mg	232	13	6 %	2 %	.6179
CP 10 mg	229	20	9 %	5 %	.1042
PBO	114	5	4 %		
Study 1046 (Month 6)					
CP 5 mg	263	24	9 %	6 %	.0038
CP 10 mg	270	36	13 %	10 %	<.0001
PBO	148	4	3 %		
Study 1064 (Month 6)					
CP 5 mg	177	11	6 %	5 %	.0151
CP 10 mg	176	22	13 %	12 %	<.0001
ADA 40 mg	178	12	7 %	6 %	.0091
PBO	92	1	1 %		

Excerpted from the clinical study reports A3921032, A3921045, A3921046, A3921064.

As noted earlier, the applicant's analyses were conducted on the FAS population, not on the ITT population. The applicant's analyses excluded non-ignorable number of patients as shown in the Table 2. Also in the analysis of HAQ-DI, the applicant assumed untestable MAR mechanism which is not supported because missing data from dropouts may arise from treatment-related reason such as adverse events. Therefore, BOCF imputation was applied in the analysis of HAQ-DI imputing '0' change from baseline to study endpoint or no improvement to patient with missing value at study endpoint and to those patients in ITT, but not in FAS set (Table 7). Results from my analyses of ACR20 and DAS28 conducted on the ITT population are presented in Table 6 and Table 8.

With the exception of DAS28 responder analysis, although there were small numerical differences, the overall conclusion for the ACR20 and HAQ-DI using the ITT population remains the same as that using the FAS population. In other words, there is significant treatment difference between tofacitinib and placebo in terms of ACR20 response and improvement in HAQ-DI. For DAS28 response, while there is consistent evidence that a significantly higher

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proportion of patients in the tofacitinib 10 mg group achieved DAS28 response compared to placebo, only one study showed a statistical significant difference between 5 mg and placebo (Table 8).

Table 6: Reviewer's Analysis on ACR20 (ITT)

Treatment	N	n	Response Rate	Difference vs. PBO	P-value
Study 1032 (Month 3)					
CP 5 mg	133	55	41 %	17 %	.0030
CP 10 mg	134	64	48 %	24 %	<.0001
PBO	132	32	24 %		
Study 1045 (Month 3)					
CP 5 mg	243	144	59 %	33 %	<.0001
CP 10 mg	245	159	65 %	39 %	<.0001
PBO	122	32	26 %		
Study 1046 (Month 6)					
CP 5 mg	315	164	52 %	21 %	<.0001
CP 10 mg	318	180	57 %	26 %	<.0001
PBO	159	49	31 %		
Study 1064 (Month 6)					
CP 5 mg	204	101	50 %	22 %	.0002
CP 10 mg	201	103	51 %	23 %	<.0001
ADA 40 mg	204	94	46 %	18 %	.0017
PBO	108	30	28 %		

Table 7: Reviewer's Analysis on HAQ-DI (ITT BOCF)

Treatment	N	LS Mean	Difference vs. PBO		
			LS Mean Difference	95% CI	P-value
Study 1032 (Month 3)					
CP 5 mg	133	-0.4	-0.2	(-0.3, -0.1)	.0007
CP 10 mg	134	-0.4	-0.2	(-0.3, -0.1)	.0001
PBO	132	-0.2			
Study 1045 (Month 3)					
CP 5 mg	243	-0.5	-0.3	(-0.4, -0.1)	.0001
CP 10 mg	245	-0.6	-0.4	(-0.5, -0.2)	<.0001
PBO	122	-0.2			
Study 1046 (Month 3)					
CP 5 mg	315	-0.4	-0.2	(-0.3, -0.1)	<.0001
CP 10 mg	318	-0.5	-0.3	(-0.4, -0.2)	<.0001
PBO	159	-0.2			
Study 1064 (Month 3)					
CP 5 mg	204	-0.4	-0.2	(-0.3, -0.1)	.0004
CP 10 mg	201	-0.5	-0.3	(-0.4, -0.2)	<.0001

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ADA 40 mg	204	-0.4	-0.2	(-0.3, -0.1)	.0003
PBO	108	-0.2			

Table 8: Reviewer's Analysis on DAS28-4(ESR)<2.6 (ITT)

Treatment	N	n	Response Rate	Difference vs. PBO	P-value
Study 1032 (Month 3)					
CP 5 mg	133	8	6 %	4 %	.0546
CP 10 mg	134	11	8 %	6 %	.0113
PBO	132	2	2 %		
Study 1045 (Month 3)					
CP 5 mg	243	13	6 %	2 %	.6025
CP 10 mg	245	20	8 %	5 %	.1454
PBO	122	5	4 %		
Study 1046 (Month 6)					
CP 5 mg	315	24	8 %	5 %	.0069
CP 10 mg	318	36	11 %	7 %	.0011
PBO	159	4	3 %		
Study 1064 (Month 6)					
CP 5 mg	204	11	5 %	4 %	.0510
CP 10 mg	201	22	11 %	10 %	.0014
ADA 40 mg	204	12	6 %	5 %	.0371
PBO	108	1	1 %		

In summary, data from these four studies provides evidence of efficacy in the domains of reducing signs and symptoms of RA, and improving physical function.

3.2.4.2 Results from Study 1044

The results of analyses by the applicant and me on ACR20 from study 1044 are presented in Table 9. Like studies 1032, 1045, 1046 and 1064, a statistically significantly higher proportion of patients in the tofacitinib group (CP5 or CP10) achieved ACR20 response compared to placebo in study 1044. This provided consistent data regarding improvement of signs and symptoms from RA.

Table 9: Analyses on Primary Endpoint

Treatment	N	n	Response Rate	Difference vs. PBO	P-value
ACR20 at Month 6 (Applicant's based on FAS)					
CP 5 mg	309	159	52 %	26 %	<.0001
CP 10 mg	309	191	62 %	36 %	<.0001
PBO	154	39	26 %		

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ACR20 at Month 6 (Reviewer's based on ITT)					
CP 5 mg	321	159	50 %	26 %	<.0001
CP 10 mg	316	191	60 %	36 %	<.0001
PBO	160	39	24 %		

As noted in Section 3.2.2, the primary analysis of radiographic data (mTSS) was ANCOVA (parametric analysis). Based on the applicant's analyses, the difference between tofacitinib 10 mg and placebo was statistically significant for mTSS score, while the difference was not statistically significant between 5 mg and placebo, at Month 6 and Month 12 (Table 10).

Table 10: Applicant's Analysis on mTSS (FAS)

Treatment	**N**	**LS Mean**	**Difference vs. PBO**		
			LS Mean Difference	**95% CI**	**P-value**
Study 1044 (primary at Month 6)					
CP 5 mg	278	0.12	-0.34	(-0.73, 0.04)	.0792
CP 10 mg	290	0.06	-0.40	(-0.79, -0.02)	.0376
PBO	140	0.47			
Study 1044 (Month 12)					
CP 5 mg	286	0.29	-0.63	(-1.27, 0.02)	.0558
CP 10 mg	295	0.05	-0.87	(-1.51, -0.23)	.0081
PBO	139	0.92			

Excerpted from the clinical study report A3921044.

The results from my analyses of radiographic data produced similar results from that of the applicant's analyses using ANCOVA, and therefore were not presented here. As noted, a sensitivity analysis was pre-specified in the protocol to evaluate treatment difference using ANCOVA model on the ranks with treatment as factor, and rank baseline modified Sharp score as covariate (a non-parametric analysis). The results from this analysis suggest no significant difference between tofacitinib 10 mg and placebo on mTSS at Month 6, while the difference was significant between tofacitinib 5 mg and placebo (Table 11). This is in reverse to what was shown in the primary (parametric) analysis. Both doses were not significantly different from placebo at Month 12. Other variations of rank sum test gave consistent results (Table 11).

Table 11: Analyses on mTSS based on the Ranks (FAS)

	N	**ANCOVA with ranked data P-value***	Wilcoxon test P-value†	Van der Waerden test P-value†	Van Elteren test P-value**†
Study 1044 (primary 6 months)					

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CP 5 mg	278	.0237	.0216	.0283	.0245
CP 10 mg	290	.1979	.1751	.1410	.1710
PBO	140				
Study 1044 (12 months)					
CP 5 mg	286	.0790	.0665	.0721	.0772
CP 10 mg	295	.0578	.0594	.0488	.0675
PBO	139				

*Source: Study Report Table 14.2.15.1.7
**van Elteren's test adjusted for the same covariates as in rank ANCOVA model.
† Reviewer's analyses

As noted in Section 0, some patients with observed radiographic data at Month 6 from the Sites 1048 and 1174 were excluded from the analysis. Including these patients in the analyses produced similar findings and did not change the overall conclusion. However, it is still concerning that 8 patients' radiographic data from Site 1155 were not reported. Although this does not appear to be excessive; given the small treatment effect size, it is unclear how this may affect the overall results.

The study was initially powered based on parametric ANCOVA model with assumed effect size of 0.8 units when comparing 10 mg dose to placebo. The planned study gives only 51% power for the rank ANCOVA with the same effect size (Table 12). The fact that the actual effect estimated from the study is 0.4 and the placebo group has much lower structural damage progression (assumed 1.4 units vs. actual 0.5 units) than assumed can be one of the explanations for why the analyses failed to show consistent results.

Table 12: Applicant's Power Analysis based on mTSS

	N	Mean (SD)	Power with ANOVA*	Power with Rank-ANOVA*
Study 044 (based on assumed parameters)				
CP 10 mg	300	0.6 (1.8)	88%	51%
	300	0.4 (1.5)	99%	84%
PBO	150	1.4 (3.4)		
Study 044 (based on results)				
CP 10 mg	316	0.1 (2.0)	P-value = 0.0376	P-value = 0.1979
PBO	160	0.5 (2.0)		

* Statistical Analysis Plan of study A3921044

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Table 13 gives an inferential result using a definition of "no progression," one by the applicant (defined as Change in mTSS ≤ 0.5) and the other by me (defined as Change in mTSS ≤ 0). With the applicant's definition of "no progression," both doses were significantly different from placebo while only 5 mg dose was different from placebo when my definition was applied. This further illustrates the lack of conclusiveness of the radiographic data when change in the definition of no progression resulted in a loss in statistical significance for the tofacitinib 10 mg dose group.

Table 13: Rates of 'No Progression' based on mTSS (rITT)

Treatment	N	N	Rate	Difference vs. PBO	P-value
No Progression defined by applicant as Change in mTSS ≤ 0.5					
CP 5 mg	278	246	88 %	11 %	.0028
CP 10 mg	290	252	87 %	9 %	.0167
PBO	140	108	77 %		
No Progression defined by reviewer as Change in mTSS ≤ 0					
CP 5 mg	278	233	84 %	10 %	.0200
CP 10 mg	290	229	79 %	5 %	.2766
PBO	140	104	74 %		

The cumulative distribution plot of mTSS at Month 6 is presented in Figure 2, without any specific cut-off for defining "no progression." The x-axis represents change from baseline and the y-axis represents cumulative percentage. Left of zero means improvement and right of zero means worsening. There appears to be a separation of curves between the tofacitinib doses and placebo (Figure 2). As shown in Table 14, a numerically higher proportion of patients in the tofacitinib group appears to improve compared to the placebo group. Likewise, a numerically smaller proportion of patients in the tofacitinib group appears to worsen compared to placebo group, suggesting some benefit of tofacitinib on structural damage score. However, the 5 mg dose appears to be numerically better than the 10 mg dose. This is consistent with the findings from the non-parametric analysis.

Figure 2: Cumulative Distribution of mTSS (rITT)

Reference ID: 3150054

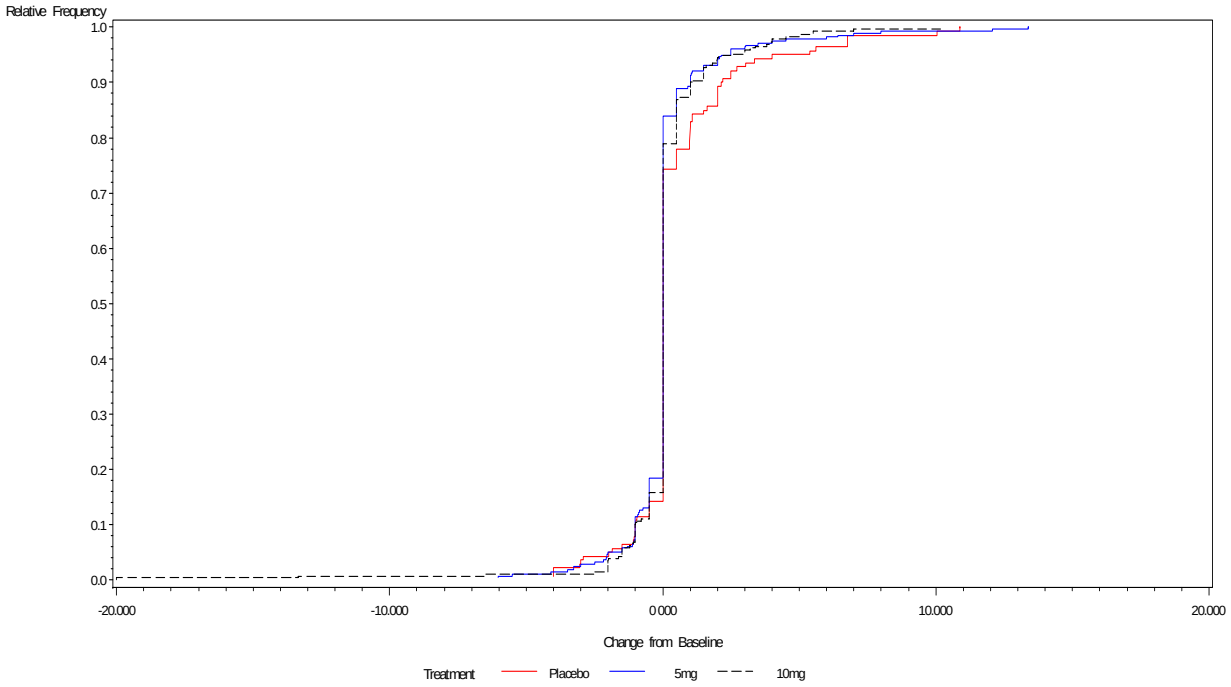

Table 14: Proportion of "Improved" or "No Change" or "Worsened" (rITT)

	PBO (N=140)	**CP 5 mg (N=278)**	**CP 10 mg (N=290)**
Improved (change in mTSS < 0)	20 (14%)	51 (18%)	46 (16%)
No Change	84 (60%)	182 (66%)	183 (63%)
Worsened (change in mTSS > 0)	36 (26%)	45 (16%)	61 (21%)

As noted in Table 14, about 63% of subjects had zero change from baseline, which implies that comparison between group means could be problematic because conclusion could be driven by a few outlying or extreme values.

Following are exploratory analyses on mTSS at Month 6 including outlier analyses conducted by me. This allows one to assess the impact of outliers or extreme observations on the applicant's analyses. Frequency distributions by treatment group are presented (

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Figure 3). The diagrams suggest that there were potential outliers especially in the tofacitinib groups. In consultation with the clinical team, extreme observations with absolute change greater than 7 units were identified with randomized treatment and extrapolated values were marked with asterisks (

Figure 3). Of note, some outliers at Month 6 are observed data and others are linearly extrapolated due to missing data at Month 6. The same parametric ANCOVA model was applied to the new data after excluding the outlying observations. In contrast with the results from the full ANCOVA model, the results from this new analysis showed no statistically significant differences between tofacitinib 10 mg and placebo, while the difference between tofacitinib 5 mg and placebo was statistically significant (Table 15). As expected, the same conclusion applies to nonparametric analyses regardless of whether outliers were excluded or not (data not shown). Similar analyses were conducted by excluding a patient with the most extreme observation. The results from the same ANCOVA model showed no statistically significant differences between tofacitinib groups and placebo (Table 16). The outlier analyses suggest that the significant findings based on group means using ANCOVA may be driven by a few extreme observations.

We acknowledge that inclusion or exclusion of outliers from data analysis can be done in many ways, and that it also depends on the reason why the case is an outlier. In this study, some of these values were not the actual observed values given that they were extrapolated values. There were also others that could be due to measurement errors. In summary, there is lack of consistent findings in the two tofacitinib dose groups when different statistical models were applied. Furthermore, based on the responder analysis (Table 14), 5 mg appears to be better than 10 mg.

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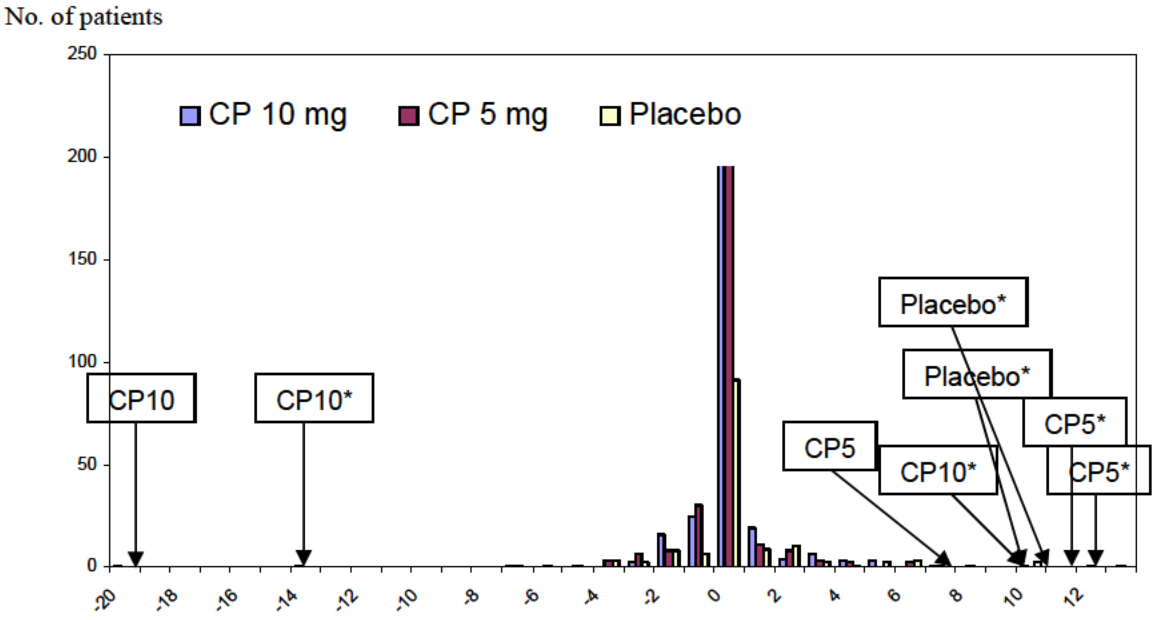
Figure 3: Frequency Distribution of Change from Baseline in mTSS at Month 6



*Extrapolated data

Table 15: ANCOVA on mTSS excluding outlying subjects (|Δ| greater than 7 units)

Treatment	N	LS Mean	Difference from PBO		
			LS Mean Difference	95% CI	P-value
Study 1044 (primary at Month 6)					

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CP 5 mg	275	-0.003	-0.32	(-0.59, -0.05)	0.021
CP 10 mg	287	0.14	-0.17	(-0.44, 0.09)	0.203
PBO	138	0.32			

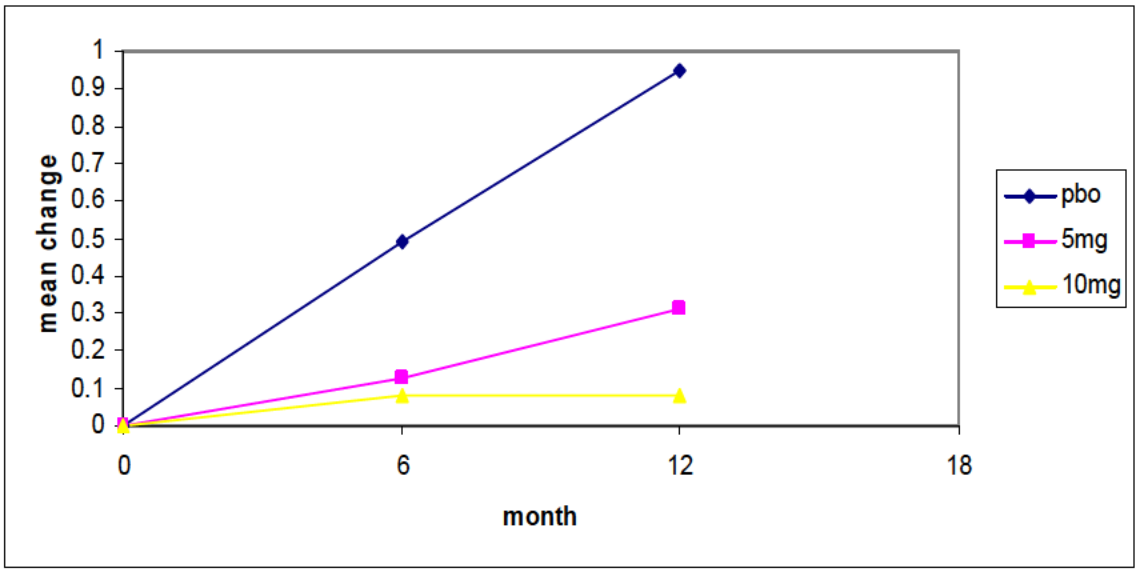
Table 16: ANCOVA on mTSS excluding outlying subjects (|Δ| greater than 20 units)

Treatment	N	LS Mean	Difference from PBO		
			LS Mean Difference	95% CI	P-value
Study 1044 (primary at Month 6) excluding patient 10421014 from CP 10 mg group					
CP 5 mg	278	0.11	-0.34	(-0.69, 0.01)	0.056
CP 10 mg	287	0.12	-0.33	(-0.68, 0.02)	0.061
PBO	138	0.45			

*Patient 10421014's baseline score is 42.5. At Month 6, her score is 22.5.

At the Pre-NDA meeting, the Division reminded the applicant that in order to support the primary radiographic endpoint, it will be important to show that the slope of structural damage over time does not increase from 6 to 12 months compared to 0 to 6 months as advised during the EOP2 meeting. The slope of radiographic damage progression over time is presented in Figure **4**. The slope of 10 mg dose from 6 month to 12 month is smaller when compared to the slope from baseline to 6 month whereas the slope of 5 mg dose gets steeper over time. Note that at Month 12, all placebo patients were advanced to tofacitinib by Month 6. Also, about 22% discontinued CP5 mg treatment and about 16% discontinued CP10 mg treatment. Therefore many of these patients' values at Month 12 are linearly extrapolated from the time they switched or discontinued treatments making it difficult to provide meaningful interpretation.

Figure 4: Radiographic Progression over Time (rITT)



In summary, based on the statistical assessment of radiographic data from study 1044, there is lack of consistent findings when different statistical models were applied to the radiographic data. In the primary analysis using parametric model, the difference between tofacitinib 10 mg and placebo was statistically significant for mTSS, while the difference was not statistically significant between 5 mg and placebo, at Month 6. In contrast, when non-parametric model was applied, the difference between tofacitinib 10 mg and placebo was not statistically significant for mTSS score, while the difference was statistically significant between 5 mg and placebo. In addition, based on the responder analysis, 5 mg appears to be numerically better than 10 mg, with lower proportion of patients experienced worsening and higher proportion of patients experienced improvement in the 5 mg group compared to 10 mg group.

Other than ACR20 and radiographic endpoints, the applicant also evaluated HAQ-DI and DAS-28. They applied gatekeeping strategy to control the type 1 error from multiple comparisons (Figure **5**). In this approach, treatment difference in ACR20 between 10 mg and placebo is tested first (Family 1). If it is significant at $p \leq 0.05$, then treatment differences in mTSS between 10 mg and placebo, and in ACR20 between 5 mg and placebo are tested each at the 0.05 level (Family 2). This method is problematic because two sets of comparisons are tested at this stage (i.e. Family 2) and it only requires a significant treatment difference in one (i.e. mTSS between 10 mg and placebo) to move to the next comparison (i.e. HAQ-DI) under Family 3. Two possible approaches to control the type 1 error are to either split the alpha level at Family 2 for each test comparison or to ensure that both tests are statistically significant at $p \leq 0.05$ before moving to Family 3.

Regardless of this problem, because the test failed to reject the hypothesis that tofacitinib 10 mg is not different from placebo in mTSS when non-parametric test was applied, the gatekeeping strategy does not allow one to continue testing.

Figure 5: Stepdown Procedure – Study 1044

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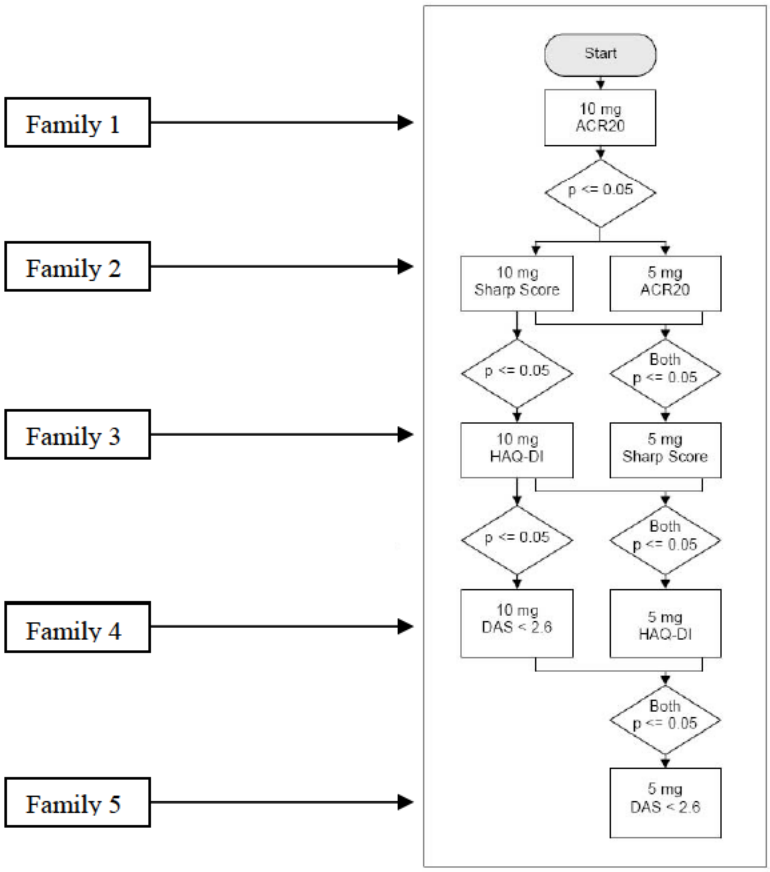

For completeness, treatment differences and 95% confidence intervals from the analyses of HAQ-DI and DAS28 are presented in Table 17.

Table 17: Analyses on Secondary Endpoints (Study 1044)

Treatment	N	LS Mean	LS Mean Difference vs. PBO	95% CI
HAQ-DI at Month 3 (Applicant's based on FAS)				
CP 5 mg	294	-0.4	-0.3	(-0.4, -0.2)
CP 10 mg	300	-0.6	-0.4	(-0.5, -0.3)
PBO	146	-0.2		
HAQ-DI at Month 3 (Reviewer's based on ITT BOCF)				
CP 5 mg	321	-0.4	-0.2	(-0.3, -0.1)
CP 10 mg	316	-0.5	-0.3	(-0.4, -0.2)
PBO	160	-0.2		

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Treatment	N	N	Response Rate	Difference vs. PBO
DAS28-4(ESR)<2.6 at Month 6 (Applicant's based on FAS)				
CP 5 mg	265	19	7 %	5 %
CP 10 mg	257	47	18 %	16 %
PBO	129	2	2 %	
DAS28-4(ESR)<2.6 at Month 6 (Reviewer's based on ITT)				
CP 5 mg	321	19	6 %	3 %
CP 10 mg	316	41	13 %	12 %
PBO	160	2	1 %	

Applicant's analyses excerpted from the clinical study report A3921044.

In summary, data from study 1044 provides evidence of efficacy in the domains of reducing signs and symptoms of RA. The evidence for an effect in radiographic progression is from a single study and statistical significance is sensitive to the statistical methods applied.

3.3 Evaluation of Safety

The assessment of the safety of the study drug was mainly conducted by the reviewing medical team. After the Advisory Committee meeting and after discussion among members of the clinical and statistics teams, it was found that additional safety analyses are needed to be able to determine the safety profile of tofacitinib 5 mg and tofacitinib 10 mg. The safety summaries that the applicant provided were not adequate to make regulatory decision regarding the safety of tofacitinib 5 mg or 10 mg doses. Because of the complexity of the study design, the Division asked the applicant to reconsider how best to analyze the safety data, particularly those major events of interest. The Division sent several information requests to the applicant requesting safety datasets with selected variables from existing database and additional analyses accounting for differences in length of exposure and the cross-over nature of the design. Teleconferences were held between the Division and the applicant to clarify some issues or roadblocks regarding the requests. The clinical and statistical teams will be reviewing the results from the applicant's re-analyses, and will be conducting their own analyses using the incoming datasets. A Type A meeting between the Division and the applicant will be scheduled in July to discuss the potential for alternative safety analyses to address the Agency's questions, and the potential impact of the submission timing on the review of the NDA, particularly in light of the August 21, 2012 action date.

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4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The following analyses are the subgroup analyses by demographics in terms of ACR20. Since majority of subjects (about 60%) were white, I do not present subgroup analyses by race and only present subgroup analyses by sex and age group (< 55 or ≥ 55).

The majority of the subjects (about 80%) were female and therefore the subgroup analyses were consistent with whole subjects for all studies (Table 18 and Table 19). In addition, there was no noticeable difference in terms of ACR20 between the age groups (Table 20 and Table 21).

Table 18: Reviewer's Subgroup Analysis on ACR20 (ITT Male)

Treatment	N	n	Response Rate	Difference vs. PBO
Study 1032 (Month 3)				
CP 5 mg	20	6	30 %	11 %
CP 10 mg	18	7	39 %	20 %
PBO	26	5	19 %	
Study 1044 (6 months)				
CP 5 mg	52	33	63 %	33 %
CP 10 mg	43	26	60 %	30 %
PBO	23	7	30 %	
Study 1045 (Month 3)				
CP 5 mg	36	17	47 %	29 %
CP 10 mg	29	19	66 %	48 %
PBO	17	3	18 %	
Study 1046 (Month 6)				
CP 5 mg	51	27	53 %	31 %
CP 10 mg	60	26	43 %	21 %
PBO	36	8	22 %	
Study 1064 (Month 6)				
CP 5 mg	30	15	50 %	31 %
CP 10 mg	33	21	64 %	45 %
ADA 40 mg	42	24	57 %	38 %
PBO	26	5	19 %	

Table 19: Reviewer's Subgroup Analysis on ACR20 (ITT Female)

Treatment	N	n	Response Rate	Difference vs. PBO
Study 1032 (Month 3)				
CP 5 mg	113	49	43 %	17 %
CP 10 mg	116	57	49 %	23 %
PBO	106	27	26 %	
Study 1044 (Month 6)				

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CP 5 mg	269	126	47 %	24 %
CP 10 mg	273	165	60 %	37 %
PBO	137	32	23 %	
Study 1045 (Month 3)				
CP 5 mg	207	127	61 %	33 %
CP 10 mg	216	140	65 %	37 %
PBO	105	29	28 %	
Study 1046 (Month 6)				
CP 5 mg	264	137	52 %	19 %
CP 10 mg	258	154	60 %	27 %
PBO	123	41	33 %	
Study 1064 (Month 6)				
CP 5 mg	174	86	49 %	18 %
CP 10 mg	168	82	49 %	18 %
ADA 40 mg	162	70	43 %	12 %
PBO	82	25	31 %	

Table 20: Reviewer's Subgroup Analysis on ACR20 (ITT Age ≥55)

Treatment	N	n	Response Rate	Difference vs. PBO
Study 1032 (Month 3)				
CP 5 mg	68	29	43%	19 %
CP 10 mg	76	38	50 %	26 %
PBO	62	15	24 %	
Study 1044 (Month 6)				
CP 5 mg	159	79	50 %	29 %
CP 10 mg	142	81	57 %	36 %
PBO	77	16	21 %	
Study 1045 (Month 3)				
CP 5 mg	102	58	57 %	37 %
CP 10 mg	113	71	63 %	43 %
PBO	46	9	20 %	
Study 1046 (Month 6)				
CP 5 mg	150	71	47 %	13 %
CP 10 mg	140	70	50 %	16 %
PBO	71	24	34 %	
Study 1064 (Month 6)				
CP 5 mg	93	45	48 %	16 %
CP 10 mg	99	41	41 %	9 %
ADA 40 mg	96	44	46 %	14 %
PBO	56	18	32 %	

Table 21: Reviewer's Subgroup Analysis on ACR20 (ITT Age <55)

Treatment	N	n	Response Rate	Difference vs. PBO
Study 1032 (Month 3)				
CP 5 mg	65	26	40 %	16 %

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CP 10 mg	58	26	45 %	21 %
PBO	70	17	24 %	
Study 1044 (Month 6)				
CP 5 mg	162	80	49 %	21 %
CP 10 mg	174	110	63 %	35 %
PBO	83	23	28 %	
Study 1045 (Month 3)				
CP 5 mg	141	86	61 %	31 %
CP 10 mg	132	88	67 %	37 %
PBO	76	23	30 %	
Study 1046 (Month 6)				
CP 5 mg	165	93	56 %	28 %
CP 10 mg	178	110	62 %	34 %
PBO	88	25	28 %	
Study 1064 (Month 6)				
CP 5 mg	111	56	51 %	28 %
CP 10 mg	102	62	61 %	38 %
ADA 40 mg	108	50	46 %	23 %
PBO	52	12	23 %	

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The primary analysis population or set (FAS) was defined by the applicant as all randomized patients who were treated and had post-baseline assessments. However, in my analyses, ITT population was used as the primary analysis population and treated the patients in FAS, but not in ITT as treatment failures for binary endpoints such as ACR20 and DAS28 and imputed the baseline scores for continuous endpoint such as HAQ-DI.

As explained in the statistical analysis plan (SAP), to assess robustness of efficacy data with respect to missing data, the applicant conducted sensitivity analysis on HAQ-DI. They varied the covariance structure from compound symmetry to auto-regressive. However, this approach is not an appropriate sensitivity analysis to assess missing at random (MAR) assumption. therefore, a conservative baseline observation carried forward approach (BOCF) was applied to the missing data to assess the robustness of their positive result against missing not at random scenario.

The primary parametric analysis and the pre-specified secondary non-parametric analysis on radiographic endpoint were not consistent. This led me to explore the distribution of the radiographic data and conduct some outlier analyses. This led me to find out that both CP 5 mg

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and 10 mg may have some activity on radiographic progression although it weakened the statistical significance of CP 10 mg dose.

The proposed gate-keeping method to adjust for multiplicity is problematic because two sets of comparisons are tested at the second stage and it only requires a significant treatment difference in HAQ-DI (or mTSS for study 1044) between 10 mg and placebo in order to move to the comparison of DAS28 (or HAQ-DI for study 1044). Two possible approaches to control the type 1 error are to either split the alpha level at Family 2 for each test comparison or to ensure that both tests are statistically significant at $p \leq 0.05$ before moving to stage 3.

5.2 Collective Evidence

Because the safety of tofacinitib 5 mg and 10 mg dose groups are still under review, it is premature to discuss the risk-benefit profile of tofacitinib at this time.

5.3 Conclusions and Recommendations

The efficacy data from 5 studies gave a strong evidence of tofacitinib 5 mg and 10 mg for treatment of signs and symptoms based on ACR20 and improvement in physical function based on HAQ-DI. However, the data supported only tofacitinib 10 mg for lowering disease activity based on DAS28. While radiographic data showed that tofacitinib 5 mg and 10 mg may have some activity on radiographic progression, the evidence for an effect is from a single study and statistical significance is sensitive to the statistical methods applied.

5.4 Labeling Recommendations

Following is an excerpt from the relevant clinical studies section in the proposed label. I generally agree with the study description and primary analysis results and their interpretation. I recommend removing the radiographic endpoint result, as well as results from the exploratory analyses. Of note, these comments are based on the original proposed label. The applicant is planning to submit a new proposed label; therefore, these comments may still change.

(b) (4)

[redacted]

4 Pages Of Draft Labeling Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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APPENDICES

Table 22 Patient Disposition

Study 1032:

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Screened: 589				
Assigned to Study Treatment	133	134	66	66
Treated	133	134	66	66
Completed	107 (80.5)	103 (76.9)	53 (80.3)	48 (72.7)
Discontinued	26 (19.5)	31 (23.1)	13 (19.7)	18 (27.3)
Patient Died	0	0	0	1 (1.5)
Related to Study Drug	10 (7.5)	12 (9.0)	6 (9.1)	8 (12.1)
Adverse event	8 (6.0)	7 (5.2)	3 (4.5)	0
Lack of efficacy	2 (1.5)	5 (3.7)	3 (4.5)	8 (12.1)
Not Related to Study Drug	16 (12.0)	19 (14.2)	7 (10.6)	9 (13.6)
Adverse event	4 (3.0)	5 (3.7)	1 (1.5)	4 (6.1)
Other	1 (0.8)	1 (0.7)	1 (1.5)	0
Protocol violation	2 (1.5)	8 (6.0)	3 (4.5)	4 (6.1)
Patient no longer willing to participate in study	9 (6.8)	5 (3.7)	2 (3.0)	1 (1.5)

Excerpted from the clinical study report, table 6 (page 105).

Study 1044:

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Screened: 1291				
Assigned to Study Treatment	321	319	81	79
Treated	321	316	81	79
Ongoing at Date of Cutoff[a]	250 (77.9)	265 (83.1)	64 (79.0)	64 (81.0)
Discontinued	71 (22.1)	51 (16.0)	17 (21.0)	15 (19.0)
Patient Died[b]	1 (0.3)	1 (0.3)	0	0
Related to Study Drug	35 (10.9)	22 (7.0)	10 (12.3)	6 (7.6)
Adverse event	27 (8.4)	19 (6.0)	5 (6.2)	4 (5.1)
Lack of efficacy	7 (2.2)	3 (0.9)	3 (3.7)	1 (1.3)
Study terminated by Sponsor[c]	1 (0.3)	0	2 (2.5)	1 (1.3)
Not Related to Study Drug	35 (10.9)	28 (8.8)	7 (8.6)	9 (11.4)
Adverse event	9 (2.8)	7 (2.2)	0	2 (2.5)
Lost to follow-up	5 (1.6)	0	0	3 (3.8)
Protocol violation	6 (1.9)	6 (1.9)	3 (3.7)	1 (1.3)
Pregnancy	1 (0.3)	1 (0.3)	0	0
Site closure[d]	1 (0.3)	0	0	1 (1.3)
Patient no longer willing to participate in study	8 (2.5)	11 (3.5)	2 (2.5)	2 (2.5)
Other	1 (0.3)[e]	1 (0.3)[f]	2 (2.5)[g]	0
Other: Patient moving	4 (1.2)	1 (0.3)	0	0
Other: Sponsor request	0	1 (0.3)	0	0

Excerpted from the clinical study report, table 7 (page 128).

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Study 1045:

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Screened: 954				
Assigned to Study Treatment	244	245	61	61
Treated	243[a]	245	61	61
Completed	232 (95.1)	218 (89.0)	54 (88.5)	51 (83.6)
Discontinued	11 (4.5)	27 (11.0)	7 (11.5)	10 (16.4)
Patient Died	0	1 (0.4)[b]	0	0
Related to Study Drug	4 (1.6)	7 (2.9)	5 (8.2)	5 (8.2)
Adverse event	3 (1.2)	6 (2.4)	2 (3.3)	1 (1.6)
Lack of efficacy	1 (0.4)	1 (0.4)	3 (4.9)	4 (6.6)
Not Related to Study Drug	7 (2.9)	19 (7.8)	2 (3.3)	5 (8.2)
Adverse event	0	3 (1.2)	1 (1.6)	1 (1.6)
Other	1 (0.4)	2 (0.8)	0	1 (1.6)
Protocol violation	2 (0.8)	8 (3.3)	1 (0.4)	1 (1.6)
Patient no longer willing to participate in study	4 (1.6)	6 (2.4)	0	2 (3.3)

Excerpted from the clinical study report, table 6 (page 100).

Study 1045:

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Screened: 1281				
Assigned to Study Treatment	318	318	79	80
Treated	315	318	79	80
Completed	261 (82.1)	252 (79.2)	71 (89.9)	67 (83.8)
Discontinued	54 (17.0)	66 (20.8)	8 (10.1)	13 (16.3)
Patient Died[a]	0	2 (0.6)	0	0
Related to Study Drug	31 (9.8)	34 (10.7)	3 (3.8)	4 (5.0)
Adverse event	14 (4.4)	20 (6.3)	0	0
Lack of efficacy	16 (5.1)	12 (3.8)	3 (3.8)	3 (3.8)
Other[b]	1 (0.3)	2 (0.6)	0	1 (1.3)
Not Related to Study Drug	23 (7.3)	30 (9.4)	5 (6.3)	9 (11.3)
Adverse event	6 (1.9)	9 (2.8)	2 (2.5)	3 (3.8)
Lost to follow-up	1 (0.3)	2 (0.6)	2 (2.5)	0
Other [b]	8 (2.5)	14 (4.4)	1 (1.3)	5 (6.3)
Patient no longer willing to participate in study	8 (2.5)	5 (1.6)	0	1 (1.3)

Excerpted from the clinical study report, table 6 (page 127).

Study 1064:

Reference ID: 3150054

Number (%) of Patients	CP-690,550 5 mg	CP-690,550 10 mg	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID	Adalimumab 40 mg SC q 2 weeks
Screened: 1042					
Assigned to study treatment	204	201	56	52	204
Treated	204	201	56	52	204
Completed	150 (73.5)	158 (78.6)	47 (83.9)	39 (75.0)	162 (79.4)
Discontinued	54 (26.5)	43 (21.4)	9 (16.1)	13 (25.0)	42 (20.6)
Patient died	0	0	0	0	1 (0.5)
Related to study drug	25 (12.3)	22 (10.9)	5 (8.9)	5 (9.6)	22 (10.8)
Adverse event	19 (9.3)	15 (7.5)	2 (3.6)	2 (3.8)	16 (7.8)
Lack of efficacy	6 (2.9)	7 (3.5)	3 (5.4)	3 (5.8)	6 (2.9)
Not related to study drug	29 (14.2)	21 (10.4)	4 (7.1)	8 (15.4)	19 (9.3)
Adverse event	5 (2.5)	9 (4.5)	0	3 (5.8)	6 (2.9)
Lost to follow-up	2 (1.0)	1 (0.5)	0	0	0
Other	18 (8.8)	9 (4.5)	4 (7.1)	4 (7.7)	12 (5.9)
Patient no longer willing to participate in study	4 (2.0)	2 (1.0)	0	1 (1.9)	1 (0.5)

Excerpted from the clinical study report, table 6 (page 110).

Table 23 Baseline Demographics

Study 1032:

Demographic Characteristic Parameter	CP-690,550 5 mg BID			CP-690,550 10 mg BID		
	Male N=20	Female N=113	Total N=133	Male N=18	Female N=116	Total N=134
Age (years), n (%):						
18-44	3 (15.0)	16 (14.2)	19 (14.3)	0	23 (19.8)	23 (17.2)
45-64	13 (65.0)	71 (62.8)	84 (63.2)	14 (77.8)	71 (61.2)	85 (63.4)
≥65	4 (20.0)	26 (23.0)	30 (22.6)	4 (22.2)	22 (19.0)	26 (19.4)
Mean (SD)	53.8 (12.2)	55.7 (11.4)	55.4 (11.5)	57.3 (6.9)	54.7 (11.8)	55.1 (11.3)
Range	29-72	20-83	20-83	46-65	21-84	21-84
Race, n (%):						
White	17 (85.0)	91 (80.5)	108 (81.2)	16 (88.9)	96 (82.8)	112 (83.6)
Black	2 (10.0)	9 (8.0)	11 (8.3)	1 (5.6)	6 (5.2)	7 (5.2)
Asian	1 (5.0)	10 (8.8)	11 (8.3)	0	8 (6.9)	8 (6.0)
Other	0	3 (2.7)	3 (2.3)	1 (5.6)	6 (5.2)	7 (5.2)
Weight (kg):						
Mean (SD)	87.7 (18.6)	75.8 (21.3)	77.6 (21.3)	90.0 (20.8)	77.0 (19.5)	78.8 (20.1)
Range	55.5-130.2	45.4-188.0	45.4-188.0	56.0-125.2	43.0-139.7	43.0-139.7
Body mass index (kg/m^2):						
Mean (SD)	27.9 (5.1)	29.4 (7.8)	29.2 (7.5)	28.8 (5.8)	29.5 (6.9)	29.4 (6.8)
Range	18.5-41.0	18.3-70.8	18.3-70.8	19.6-37.8	16.9-50.2	16.9-50.2

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Demographic Characteristic Parameter	Placebo → CP-690,550 5 mg BID			Placebo → CP-690,550 10 mg BID		
	Male N=13	Female N=53	Total N=66	Male N=13	Female N=53	Total N=66
Age (years) n (%):						
18-44	4 (30.8)	9 (17.0)	13 (19.7)	1 (7.7)	8 (15.1)	9 (13.6)
45-64	8 (61.5)	32 (60.4)	40 (60.6)	9 (69.2)	37 (69.8)	46 (69.7)
≥65	1 (7.7)	12 (22.6)	13 (19.7)	3 (23.1)	8 (15.1)	11 (16.7)
Mean (SD)	50.7 (10.9)	55.2 (11.8)	54.3 (11.7)	54.2 (9.9)	54.6 (11.4)	54.5 (11.0)
Range	34-69	31-82	31-82	40-72	22-80	22-80
Race n (%):						
White	12 (92.3)	47 (88.7)	59 (89.4)	11 (84.6)	42 (79.2)	53 (80.3)
Black	0	1 (1.9)	1 (1.5)	1 (7.7)	7 (13.2)	8 (12.1)
Asian	1 (7.7)	3 (5.7)	4 (6.1)	1 (7.7)	3 (5.7)	4 (6.1)
Other	0	2 (3.8)	2 (3.0)	0	1 (1.9)	1 (1.5)
Weight (kg):						
Mean (SD)	102.6 (35.3)	74.9 (22.8)	80.4 (27.7)	81.4 (14.9)	81.8 (21.9)	81.7 (20.6)
Range	47.0-175.1	45.5-134.7	45.5-175.1	63.0-110.0	49.7-163.3	49.7-163.3
Body Mass Index (kg/m^2):						
Mean (SD)	32.3 (10.4)	29.2 (7.9)	29.8 (8.4)	26.7 (4.5)	30.6 (8.1)	29.9 (7.6)
Range	17.7-53.8	19.1-50.4	17.7-53.8	19.4-37.6	19.6-54.6	19.4-54.6

Excerpted from the clinical study report, table 14 (page 114).

Study 1044:

Demographic Characteristic Parameter	CP-690,550 5 mg BID			CP-690,550 10 mg BID		
	Male N=52	Female N=269	Total N=321	Male N=43	Female N=273	Total N=316
Age (years) n (%):						
18-44	7 (13.5)	47 (17.5)	54 (16.8)	10 (23.3)	68 (24.9)	78 (24.7)
45-64	38 (73.1)	182 (67.7)	220 (68.5)	24 (55.8)	171 (62.6)	195 (61.7)
≥65	7 (13.5)	40 (14.9)	47 (14.6)	9 (20.9)	34 (12.5)	43 (13.6)
Mean (SD)	55.6 (10.1)	53.3 (11.8)	53.7 (11.6)	55.3 (11.9)	51.4 (11.3)	52.0 (11.4)
Range	27-74	20-82	20-82	35-81	18-77	18-81
Race n (%):						
White	34 (65.4)	118 (43.9)	152 (47.4)	23 (53.5)	121 (44.3)	144 (45.6)
Black	1 (1.9)	13 (4.8)	14 (4.4)	0	8 (2.9)	8 (2.5)
Asian	14 (26.9)	117 (43.5)	131 (40.8)	18 (41.9)	117 (42.9)	135 (42.7)
Other	3 (5.8)	21 (7.8)	24 (7.5)	2 (4.7)	27 (9.9)	29 (9.2)
Weight (kg):						
Mean (SD)	83.3 (20.5)	65.8 (18.4)	68.7 (19.8)	77.1 (18.1)	65.1 (17.9)	66.8 (18.4)
Range	47.8-149.2	36.2-158.7	36.2-158.7	45.0-117.1	38.1-128.3	38.1-128.3
Height (cm):						
Mean (SD)	173.8 (7.5)	158.0 (7.5)	160.5 (9.5)	172.6 (8.5)	158.3 (7.8)	160.2 (9.3)
Range	156.9-188.0	125.0-176.0	125.0-188.0	152.6-198.0	140.0-187.0	140.0-198.0

Reference ID: 3150054

Demographic Characteristic Parameter	Placebo → CP-690,550 5 mg BID			Placebo → CP-690,550 10 mg BID		
	Male N=16	Female N=65	Total N=81	Male N=7	Female N=72	Total N=79
Age (years) n (%):						
18-44	0	16 (24.6)	16 (19.8)	1 (14.3)	22 (30.6)	23 (29.1)
45-64	13 (81.3)	42 (64.6)	55 (67.9)	5 (71.4)	42 (58.3)	47 (59.5)
≥65	3 (18.8)	7 (10.8)	10 (12.3)	1 (14.3)	8 (11.1)	9 (11.4)
Mean (SD)	58.8 (8.2)	51.8 (11.8)	53.2 (11.5)	54.4 (15.6)	51.8 (11.4)	52.1 (11.8)
Range	46-78	22-81	22-81	21-70	23-76	21-76
Race n (%):						
White	12 (75.0)	24 (36.9)	36 (44.4)	4 (57.1)	32 (44.4)	36 (45.6)
Black	0	1 (1.5)	1 (1.2)	0	1 (1.4)	1 (1.3)
Asian	4 (25.0)	33 (50.8)	37 (45.7)	3 (42.9)	32 (44.4)	35 (44.3)
Other	0	7 (10.8)	7 (8.6)	0	7 (9.7)	7 (8.9)
Weight (kg):						
Mean (SD)	85.7 (21.1)	60.7 (14.4)	65.6 (18.7)	81.1 (24.7)	69.2 (21.6)	70.3 (21.9)
Range	55.0-135.0	41.0-122.5	41.0-135.0	50.4-119.6	41.0-159.2	41.0-159.2
Height (cm):						
Mean (SD)	172.6 (9.2)	156.6 (6.0)	159.7 (9.3)	170.5 (8.9)	159.3 (7.9)	160.3 (8.5)
Range	148.0-185.0	140.0-168.0	140.0-185.0	161.4-188.0	143.0-174.0	143.0-188.0

Excerpted from the clinical study report, table 12 (page 138).

Study 1045:

Demographic Characteristic Parameter	CP-690,550 5 mg BID			CP-690,550 10 mg BID		
	Male N=36	Female N=207	Total N=243	Male N=29	Female N=216	Total N=245
Age (years), n (%):						
18-44	7 (19.4)	48 (23.2)	55 (22.6)	3 (10.3)	60 (27.8)	63 (25.7)
45-64	21 (58.3)	136 (65.7)	157 (64.6)	23 (79.3)	119 (55.1)	142 (58.0)
≥65	8 (22.2)	23 (11.1)	31 (12.8)	3 (10.3)	37 (17.1)	40 (16.3)
Mean (SD)	54.4 (12.9)	51.9 (11.3)	52.2 (11.5)	54.3 (8.4)	52.1 (12.0)	52.4 (11.7)
Range	22-76	21-81	21-81	34-70	22-78	22-78
Race, n (%):						
White	28 (77.8)	125 (60.4)	153 (63.0)	20 (69.0)	148 (68.5)	168 (68.6)
Black	2 (5.6)	10 (4.8)	12 (4.9)	3 (10.3)	7 (3.2)	10 (4.1)
Asian	1 (2.8)	40 (19.3)	41 (16.9)	3 (10.3)	29 (13.4)	32 (13.1)
Other	5 (13.9)	32 (15.5)	37 (15.2)	3 (10.3)	32 (14.8)	35 (14.3)
Weight (kg):						
Mean (SD)	89.8 (20.0)	69.2 (18.7)	72.2 (20.2)	81.4 (17.4)	70.3 (19.6)	71.6 (19.6)
Range	55.0-157.0	38.4-135.2	38.4-157.0	40.0-130.0	32.4-142.6	32.4-142.6
Body Mass Index (kg/m²):						
Mean (SD)	28.8 (6.2)	26.9 (6.6)	27.2 (6.5)	27.0 (4.9)	27.6 (7.0)	27.5 (6.8)
Range	19.0-52.8	16.3-52.8	16.3-52.8	18.5-40.0	14.4-55.6	14.4-55.6
Height (cm):						
Mean (SD)	176.5 (6.5)	160.1 (7.3)	162.5 (9.2)	173.0 (7.6)	159.4 (7.9)	161.0 (9.0)
Range	161.8-192.0	140.0-178.0	140.0-192.0	147.0-184.0	125.3-185.0	125.3-185.0

Reference ID: 3150054

Demographic Characteristic Parameter	Placebo → CP-690,550 5 mg BID			Placebo → CP-690,550 10 mg BID		
	Male N=7	Female N=54	Total N=61	Male N=10	Female N=51	Total N=61
Age (years) n (%):						
18-44	2 (28.6)	16 (29.6)	18 (29.5)	4 (40.0)	16 (31.4)	20 (32.8)
45-64	5 (71.4)	30 (55.6)	35 (57.4)	5 (50.0)	31 (60.8)	36 (59.0)
≥65	0	8 (14.8)	8 (13.1)	1 (10.0)	4 (7.8)	5 (8.2)
Mean (SD)	47.9 (9.3)	51.1 (13.2)	50.7 (12.8)	46.3 (13.4)	49.3 (11.7)	48.8 (11.9)
Range	37-62	24-77	24-77	24-65	25-75	24-75
Race n (%):						
White	3 (42.9)	43 (79.6)	46 (75.4)	7 (70.0)	35 (68.6)	42 (68.9)
Black	2 (28.6)	1 (1.9)	3 (4.9)	1 (10.0)	2 (3.9)	3 (4.9)
Asian	1 (14.3)	6 (11.1)	7 (11.5)	1 (10.0)	7 (13.7)	8 (13.1)
Other	1 (14.3)	4 (7.4)	5 (8.2)	1 (10.0)	7 (13.7)	8 (13.1)
Weight (kg):						
Mean (SD)	67.8 (15.9)	70.0 (15.1)	69.8 (15.1)	85.6 (23.2)	73.2 (20.9)	75.3 (21.6)
Range	46.2-92.0	45.0-112.0	45.0-112.0	39.0-121.6	30.5-117.0	30.5-121.6
Body Mass Index (kg/m²):						
Mean (SD)	22.7 (4.3)	27.5 (5.6)	26.9 (5.7)	27.9 (7.1)	28.7 (7.6)	28.6 (7.5)
Range	17.0-29.0	17.4-41.1	17.0-41.1	15.4-37.6	14.6-45.9	14.6-45.9
Height (cm):						
Mean (SD)	172.5 (7.9)	159.6 (6.7)	161.1 (7.9)	174.4 (7.9)	159.3 (7.5)	161.8 (9.4)
Range	163.2-183.0	146.0-172.0	146.0-183.0	159.0-184.0	136.0-174.0	136.0-184.0

Excerpted from the clinical study report, table 12 (page 107).

Study 1046:

Demographic Characteristic Parameter	CP-690,550 5 mg BID			CP-690,550 10 mg BID		
	Male N=51	Female N=264	Total N=315	Male N=60	Female N=258	Total N=318
Page 1 of 3						
Age (years), n (%):						
18-44	11 (21.6)	64 (24.2)	75 (23.8)	12 (20.0)	66 (25.6)	78 (24.5)
45-64	32 (62.7)	162 (61.4)	194 (61.6)	40 (66.7)	158 (61.2)	198 (62.3)
≥65	8 (15.7)	38 (14.4)	46 (14.6)	8 (13.3)	34 (13.2)	42 (13.2)
Mean (SD)	53.7 (11.2)	52.5 (11.8)	52.7 (11.7)	52.8 (12.1)	51.7 (11.7)	51.9 (11.8)
Range	26-80	18-86	18-86	20-82	20-85	20-85
Race, n (%):						
White	32 (62.7)	141 (53.4)	173 (54.9)	40 (66.7)	134 (51.9)	174 (54.7)
Black	1 (2.0)	3 (1.1)	4 (1.3)	0	7 (2.7)	7 (2.2)
Asian	13 (25.5)	100 (37.9)	113 (35.9)	18 (30.0)	93 (36.0)	111 (34.9)
Other	5 (9.8)	20 (7.6)	25 (7.9)	2 (3.3)	24 (9.3)	26 (8.2)
Weight (kg):						
Mean (SD)	77.2 (16.1)	68.2 (18.9)	69.6 (18.8)	83.6 (16.7)	68.1 (18.0)	71.0 (18.7)
Range	46.1-117.5	38.0-186.9	38.0-186.9	52.0-124.7	34.7-148.8	34.7-148.8
Body mass index (kg/m²):						
Mean (SD)	25.8 (4.6)	26.7 (7.0)	26.6 (6.7)	27.6 (4.5)	26.7 (6.6)	26.9 (6.3)
Range	16.3-36.7	16.0-70.3	16.0-70.3	18.9-38.5	15.1-58.1	15.1-58.1
Height (cm):						
Mean (SD)	172.7 (6.2)	159.5 (6.5)	161.6 (8.1)	173.7 (7.1)	159.6 (6.9)	162.2 (8.8)
Range	157.0-188.0	143.0-178.0	143.0-188.0	157.0-191.0	138.0 (180.0)	138.0-191.0

Reference ID: 3150054

Demographic Characteristic Parameter	Placebo → CP-690,550 5 mg BID			Placebo → CP-690,550 10 mg BID		
	Male N=16	Female N=63	Total N=79	Male N=20	Female N=60	Total N=80
Page 2 of 3						
Age (years), n (%):						
18-44	2 (12.5)	16 (25.4)	18 (22.8)	3 (15.0)	13 (21.7)	16 (20.0)
45-64	10 (62.5)	43 (68.3)	53 (67.1)	15 (75.0)	37 (61.7)	52 (65.0)
≥65	4 (25.0)	4 (6.3)	8 (10.1)	2 (10.0)	10 (16.7)	12 (15.0)
Mean (SD)	57.9 (9.5)	49.1 (11.0)	50.8 (11.2)	53.8 (8.3)	53.2 (11.6)	53.3 (10.8)
Range	38-70	18-68	18-70	41-70	18-73	18-73
Race, n (%):						
White	13 (81.3)	35 (55.6)	48 (60.8)	14 (70.0)	30 (50.0)	44 (55.0)
Black	0	2 (3.2)	2 (2.5)	0	2 (3.3)	2 (2.5)
Asian	2 (12.5)	22 (34.9)	24 (30.4)	6 (30.0)	21 (35.0)	27 (33.8)
Other	1 (6.3)	4 (6.3)	5 (6.3)	0	7 (11.7)	7 (8.8)
Weight (kg):						
Mean (SD)	74.9 (16.4)	71.1 (19.8)	71.9 (19.1)	77.0 (18.2)	68.9 (21.4)	70.9 (20.8)
Range	48.0-104.8	40.0-138.5	40.0-138.5	47.0-117.9	35.0-158.3	35.0-158.3
Body mass index (kg/m^2):						
Mean (SD)	24.8 (4.3)	27.4 (7.4)	26.9 (7.0)	25.9 (5.7)	26.6 (7.0)	26.4 (6.7)
Range	17.2-32.7	15.8-54.1	15.8-54.1	16.7-40.8	16.2-54.1	16.2-54.1
Height (cm):						
Mean (SD)	173.2 (7.2)	161.0 (7.3)	163.5 (8.7)	172.2 (6.0)	160.2 (7.3)	163.2 (8.7)
Range	159.5-187.0	146.0-180.0	146.0-187.0	164.0-187.0	145.0-178.0	145.0-187.0

Excerpted from the clinical study report, table 13 (page 138).

Study 1064:

Demographic Characteristic Parameter	CP-690,550 BID					
	5 mg			10 mg		
	Male N=30	Female N=174	Total N=204	Male N=33	Female N=168	Total N=201
Age (years), n (%):						
18-44	6 (20.0)	40 (23.0)	46 (22.5)	6 (18.2)	42 (25.0)	48 (23.9)
45-64	18 (60.0)	104 (59.8)	122 (59.8)	23 (69.7)	97 (57.7)	120 (59.7)
≥65	6 (20.0)	30 (17.2)	36 (17.6)	4 (12.1)	29 (17.3)	33 (16.4)
Mean (SD)	53.9 (12.5)	52.9 (11.9)	53.0 (11.9)	53.3 (9.2)	52.8 (12.3)	52.9 (11.8)
Range	30-74	22-83	22-83	35-70	19-75	19-75
Race, n (%):						
White	26 (86.7)	125 (71.8)	151 (74.0)	26 (78.8)	117 (69.6)	143 (71.1)
Black	0	4 (2.3)	4 (2.0)	0	3 (1.8)	3 (1.5)
Asian	3 (10.0)	28 (16.1)	31 (15.2)	5 (15.2)	23 (13.7)	28 (13.9)
Other	1 (3.3)	17 (9.8)	18 (8.8)	2 (6.1)	25 (14.9)	27 (13.4)
Weight (kg):						
Mean (SD)	82.2 (14.8)	70.0 (18.9)	71.8 (18.9)	81.6 (17.6)	71.5 (17.4)	73.1 (17.8)
Range	49.0-122.2	38.0-162.0	38.0-162.0	48.0-113.0	34.5-145.1	34.5-145.1
Body Mass Index (kg/m^2):						
Mean (SD)	26.7 (4.5)	27.1 (6.9)	27.0 (6.6)	26.8 (4.9)	27.7 (6.4)	27.5 (6.2)
Range	18.7-40.8	17.8-53.4	17.8-53.4	17.2-33.7	16.2-46.3	16.2-46.3
Height (cm):						
Mean (SD)	175.3 (7.4)	160.7 (7.7)	162.9 (9.2)	174.2 (7.2)	160.7 (7.6)	162.9 (9.1)
Range	162.0-190.0	140.0-183.0	140.0-190.0	164.0-190.0	140.0-180.0	140.0-190.0

Reference ID: 3150054

Demographic Characteristic Parameter	Placebo → CP-690,550					
	5 mg			10 mg		
	Male N=13	Female N=43	Total N=56	Male N=13	Female N=39	Total N=52
Age (years) n (%):						
18-44	3 (23.1)	10 (23.3)	13 (23.2)	4 (30.8)	9 (23.1)	13 (25.0)
45-64	4 (30.8)	22 (51.2)	26 (46.4)	6 (46.2)	25 (64.1)	31 (59.6)
≥65	6 (46.2)	11 (25.6)	17 (30.4)	3 (23.1)	5 (12.8)	8 (15.4)
Mean (SD)	56.7 (15.8)	55.1 (13.2)	55.5 (13.7)	54.6 (13.5)	51.0 (13.7)	51.9 (13.7)
Range	26-74	23-76	23-76	33-79	18-75	18-79
Race n (%):						
White	113 (100.0)	27 (62.8)	40 (71.4)	13 (100.0)	22 (56.4)	35 (67.3)
Black	0	1 (2.3)	1 (1.8)	0	2 (5.1)	2 (3.8)
Asian	0	9 (20.9)	9 (16.1)	0	11 (28.2)	11 (21.2)
Other	0	6 (14.0)	6 (10.7)	0	4 (10.3)	4 (7.7)
Weight (kg):						
Mean (SD)	76.8 (13.1)	64.9 (13.5)	67.7 (14.2)	87.6 (28.9)	66.0 (20.3)	71.4 (24.3)
Range	50.2-105.0	40.0-106.0	40.0-106.0	66.7-151.9	35.0-135.2	35.0-151.9
Body Mass Index (kg/m^2):						
Mean (SD)	25.5 (3.9)	25.0 (4.4)	25.1 (4.3)	28.5 (7.1)	25.7 (5.5)	26.4 (6.0)
Range	19.1-33.4	16.4-38.0	16.4-38.0	22.4-43.0	16.6-41.7	16.6-43.0
Height (cm):						
Mean (SD)	173.5 (6.1)	160.8 (6.8)	163.8 (8.5)	173.9 (7.0)	159.2 (9.6)	162.9 (11.0)
Range	162.0-181.0	149.0-176.0	149.0-181.0	164.0-188.0	141.0-180.0	141.0-188.0

Demographic Characteristic Parameter	Adalimumab 40 mg SC q 2 weeks			Total		
	Male N=42	Female N=162	Total N=204	Male N=131	Female N=586	Total N=717
Age (years) n (%):						
18-44	6 (14.3)	44 (27.2)	50 (24.5)	25 (19.1)	145 (24.7)	170 (23.7)
45-64	30 (71.4)	94 (58.0)	124 (60.8)	81 (61.8)	342 (58.4)	423 (59.0)
≥65	6 (14.3)	24 (14.8)	30 (14.7)	25 (19.1)	99 (16.9)	124 (17.3)
Mean (SD)	54.8 (11.5)	51.9 (11.7)	52.5 (11.7)	54.4 (11.8)	52.6 (12.2)	52.9 (12.1)
Range	23-77	23-75	23-77	23-79	18-83	18-83
Race n (%):						
White	33 (78.6)	115 (71.0)	148 (72.5)	111 (84.7)	406 (69.3)	517 (72.1)
Black	0	3 (1.9)	3 (1.5)	0	13 (2.2)	13 (1.8)
Asian	6 (14.3)	23 (14.2)	29 (14.2)	14 (10.7)	94 (16.0)	108 (15.1)
Other	3 (7.1)	21 (13.0)	24 (11.8)	6 (4.6)	73 (12.5)	79 (11.0)
Weight (kg):						
Mean (SD)	79.3 (14.6)	70.7 (16.0)	72.4 (16.1)	81.1 (17.1)	70.0 (17.5)	72.0 (18.0)
Range	53.2-111.5	36.3-115.0	36.3-115.0	48.0-151.9	34.5-162.0	34.5-162.0
Body Mass Index (kg/m^2):						
Mean (SD)	26.1 (4.1)	27.4 (5.8)	27.1 (5.5)	26.6 (4.7)	27.1 (6.3)	27.0 (6.0)
Range	18.4-40.0	13.9-45.7	13.9-45.7	17.2-43.0	13.9-53.4	13.9-53.4
Height (cm):						
Mean (SD)	173.9 (7.9)	160.6 (7.3)	163.4 (9.2)	174.3 (7.3)	160.6 (7.6)	163.1 (9.2)
Range	156.0-194.0	144.0-180.0	144.0-194.0	156.0-194.0	140.0-183.0	140.0-194.0

Excerpted from the clinical study report, table 9 (page 121).

Table 24 Baseline Characteristics

<u>Study 1032:</u>

Reference ID: 3150054

Baseline Characteristic Parameter	CP-690,550 5 mg BID N=133	CP-690,550 10 mg BID N=134	Placebo → CP-690,550 5 mg BID N=66	Placebo → CP-690,550 10 mg BID N=66
Disease duration (rheumatoid arthritis) (duration since first diagnoses, years):				
Mean	13.0	12.6	11.3	11.2
Range	1.2-55.0	0.7-42.0	1.3-47.0	0.4-36.0
Rheumatoid factor:				
Negative	39.39	38.06	39.39	29.23
Positive	60.61	61.94	60.61	70.77
Anti-CCP:				
Negative	31.54	30.23	26.15	22.22
Positive	68.46	69.77	73.85	77.78
DAS28-3(CRP):				
Mean (SD)	5.38 (1.00)	5.31 (0.90)	5.23 (0.93)	5.55 (0.96)
Range	2.63-7.65	2.59-7.48	3.44-7.42	2.90-7.43
DAS28-4(ESR):				
Mean (SD)	6.48 (1.03)	6.40 (0.89)	6.29 (0.89)	6.64 (1.03)
Range	3.69-8.92	4.20-8.49	4.02-8.34	3.25-8.94
HAQ-DI:				
Mean (SD)	1.60 (0.66)	1.50 (0.61)	1.59 (0.62)	1.66 (0.69)
Range	0-3.0	0-3.0	0-2.8	0-2.9
Tender joint counts:				
Mean (SD)	28.40 (18.29)	27.55 (15.70)	26.68 (16.38)	29.70 (17.08)
Range	6.0-68.0	6.0-66.0	6.0-68.0	7.0-68.0
Swollen joint counts:				
Mean (SD)	16.20 (10.06)	16.57 (9.87)	15.05 (8.98)	19.29 (11.84)
Range	5.0-62.0	6.0-60.0	5.0-58.0	6.0-62.0
ESR (mm/Hr):				
Mean (SD)	47.83 (26.08)	45.16 (22.88)	43.74 (23.76)	49.66 (25.28)
Range	5.0-130.0	10.0-126.0	5.0-119.0	7.0-120.0
CRP (mg/L):				
Mean (SD)	19.33 (27.50)	15.73 (21.59)	15.40 (15.87)	17.98 (22.78)
Range	0.2-142.0	0.2-109.0	0.6-79.2	0.6-116.0

Excerpted from the clinical study report, table 15 (page 121).

Reference ID: 3150054

Study 1044:

Baseline Characteristic Parameter	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Disease duration (rheumatoid arthritis) (duration since first diagnosis, years):				
N	321	316	81	79
Mean	8.9	9.0	8.8	9.5
Range	0.3 – 43.0	0.3 – 42.0	0.6 – 30.8	0.4 – 43.5
Rheumatoid factor, n (%):				
N	315	308	79	77
Negative	78 (24.8)	69 (22.4)	16 (20.3)	19 (24.7)
Positive	237 (75.2)	239 (77.6)	63 (79.7)	58 (75.3)
Anti-CCP antibodies, n (%):				
N	320	315	81	79
Negative (<20 units)	45 (14.06)	49 (15.56)	13 (16.05)	14 (17.72)
Weak positive (20-39 units)	21 (6.56)	19 (6.03)	8 (9.88)	1 (1.27)
Moderate positive (40-59 units)	16 (5.0)	12 (3.81)	3 (3.70)	5 (6.33)
Strong positive (≥60 units)	238 (74.38)	235 (74.60)	57 (70.37)	59 (74.68)
DAS28-3(CRP):				
N	316	309	79	77
Mean (SD)	5.22 (0.88)	5.20 (0.87)	5.14 (0.89)	5.18 (0.86)
Range	2.86 – 7.55	2.92 – 7.93	3.27 – 6.70	3.22 – 7.17
DAS28-4(ESR):				
N	316	307	78	76
Mean (SD)	6.35 (0.90)	6.28 (0.94)	6.25 (0.95)	6.32 (0.97)
Range	2.84 – 8.67	3.79 – 8.69	4.12 – 8.42	4.27 – 8.56
Sharp Scores (mTSS):				
N	286	295	71	68
Mean (SD)	31.1 (47.71)	37.3 (54.10)	35.0 (43.20)	30.1 (40.45)
Range	0.0 – 337.0	0.0 – 311.5	0.0 – 170.5	0.0 – 208.5
HAQ-DI:				
N	315	309	79	77
Mean (SD)	1.41 (0.68)	1.39 (0.66)	1.40 (0.62)	1.23 (0.73)
Range	0.00 – 3.00	0.00 – 2.88	0.00 – 2.88	0.00 – 2.88
Tender joint counts:				
N	316	309	79	77
Mean (SD)	24.1 (14.01)	23.0 (14.52)	23.3 (13.48)	22.6 (12.87)
Range	6.0 – 68.00	6.0 – 68.00	6.0 – 68.00	6.0 – 58.00
Swollen joint counts:				
N	316	309	79	77
Mean (SD)	14.1 (8.21)	14.4 (7.74)	14.0 (7.90)	14.5 (8.89)
Range	6.0 – 58.00	6.0 – 47.00	6.0 – 45.00	6.0 – 55.00
ESR (mm/Hr):				
N	316	307	78	76
Mean (SD)	50.1 (24.48)	50.5 (26.99)	47.8 (22.14)	54.4 (26.94)
Range	3.0 – 135.00	3.0 – 140.00	12.0 – 115.00	12.0 – 126.00
CRP (mg/L):				
N	316	309	79	77
Mean (SD)	15.5 (19.07)	17.0 (26.93)	12.2 (14.54)	15.3 (15.05)
Range	0.2 – 174.00	0.2 – 360.00	0.2 – 94.50	0.4 – 77.50

Excerpted from the clinical study report, table 13 (page 142).

Study 1045:

Reference ID: 3150054

Baseline Characteristic Parameter	CP-690,550 5 mg BID N=243 n (%)	CP-690,550 10 mg BID N=245 n (%)	Placebo → CP-690,550 5 mg BID N=61 n (%)	Placebo → CP-690,550 10 mg BID N=61 n (%)
Disease duration (rheumatoid arthritis) (duration since first diagnoses, years):				
Mean	8.0	8.6	7.3	8.1
Range	0.2-42.3	0.2-49.0	0.3-28.0	0.1-28.0
Rheumatoid factor:				
Negative	69 (28.75)	84 (34.85)	26 (42.62)	32 (52.46)
Positive	171 (71.25)	157 (65.15)	35 (57.38)	29 (47.54)
Anti-CCP:				
Negative (<20 units)	70 (28.93)	75 (30.74)	17 (27.87)	27 (45.0)
Weak positive (20-39 units)	12 (4.96)	12 (4.92)	3 (4.92)	3 (5.00)
Moderate positive (40-59 units)	8 (3.31)	5 (2.05)	1 (1.64)	0
Strong positive (≥60 units)	152 (62.81)	152 (62.30)	40 (65.57)	30 (50.00)
DAS28-3(CRP):				
Mean (SD)	5.68 (0.90)	5.60 (0.91)	5.57 (0.76)	5.56 (0.94)
Range	3.21-7.90	3.22-7.75	4.01-7.38	3.11-7.91
DAS28-4(ESR):				
Mean (SD)	6.71 (0.91)	6.67 (0.91)	6.59 (0.83)	6.67 (1.06)
Range	3.56-8.56	4.40-8.61	4.14-8.42	4.49 (8.94)
HAQ-DI:				
Mean (SD)	1.53 (0.66)	1.50 (0.64)	1.48 (0.61)	1.58 (0.69)
Range	0.0-3.0	0.0-3.0	0.1-2.8	0.0-3.0
Tender joint counts:				
Mean (SD)	29.42 (14.98)	29.10 (15.59)	28.39 (15.31)	29.39 (16.59)
Range	6.0-68.0	6.0-68.0	8.0-68.0	5.0-67.0
Swollen joint counts:				
Mean (SD)	16.28 (8.58)	17.03 (10.38)	16.84 (9.96)	17.69 (11.53)
Range	5.0-59.0	1.0-63.0	4.0-50.0	2.0-57.0
ESR (mm/Hr):				
Mean (SD)	52.99 (27.52)	52.12 (27.03)	47.43 (25.04)	54.39 (33.80)
Range	5.0-130.0	6.0-160.0	5.0-108.0	3.0-141.0
CRP (mg/L):				
Mean (SD)	22.75 (27.00)	19.00 (19.85)	14.06 (12.99)	21.50 (32.66)
Range	0.2-137.0	0.2-113.0	0.2-45.6	0.3-153.0

Excerpted from the clinical study report, table 13 (page 110).

Study 1046:

Baseline Characteristic Parameter	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Disease duration (rheumatoid arthritis) (duration since first diagnoses, years):				
N	315	318	79	80
Mean	8.1	9.2	9.5	10.2
Range	0.2-39.9	0.2-41.0	0.3-39.3	0.3-49.0
Rheumatoid factor, n (%):				
N	307	313	78	79
Negative	80 (26.06)	85 (27.16)	21 (26.92)	22 (27.85)
Positive	227 (73.94)	228 (72.84)	57 (73.08)	57 (72.15)
Anti-CCP, n (%):				
N	309	316	78	80
Negative (<20 units)	72 (23.30)	75 (23.73)	19 (24.36)	19 (23.75)
Weak positive (20-39 units)	10 (3.24)	19 (6.01)	2 (2.56)	5 (6.25)
Moderate positive (40-59 units)	12 (3.88)	12 (3.80)	3 (3.85)	2 (2.50)
Strong positive (≥60 units)	215 (69.58)	210 (66.46)	54 (69.23)	54 (67.50)
DAS28-3(CRP):				
N	312	315	79	79
Mean (SD)	5.21 (0.92)	5.26 (0.96)	5.34 (0.85)	5.09 (0.97)
Range	1.60-7.62	2.64-7.66	3.51-7.11	2.58-7.37
DAS28-4(ESR):				
N	309	313	79	79
Mean (SD)	6.29 (0.96)	6.36 (1.01)	6.44 (0.90)	6.16 (0.92)
Range	2.68-8.86	3.00-9.03	4.68-8.51	3.92-8.60
HAQ-DI:				
N	311	315	79	78
Mean (SD)	1.44 (0.69)	1.43 (0.68)	1.45 (0.64)	1.24 (0.66)
Range	0-3.00	0-3.00	0-2.88	0-2.88
Tender joint counts:				
N	312	315	79	79
Mean (SD)	25.00 (15.26)	26.57 (16.10)	27.23 (16.78)	21.86 (13.01)
Range	4.00-68.00	4.00-68.00	5.00-68.00	5.00-67.00
Swollen joint counts:				
N	312	315	79	79
Mean (SD)	14.49 (10.26)	14.41 (9.72)	14.58 (9.65)	13.91 (8.62)
Range	4.00-56.00	4.00-54.00	4.00-56.00	4.00-51.00
ESR (mm/Hr):				
N	311	315	79	79
Mean (SD)	50.46 (28.71)	51.94 (28.46)	51.04 (23.72)	49.29 (27.72)
Range	5.00-150.00	2.00-130.00	6.00-114.00	12.00-116.00
CRP (mg/L):				
N	312	313	79	79
Mean (SD)	17.68 (21.44)	17.73 (21.88)	16.88 (16.47)	16.54 (18.20)
Range	0.30-168.00	0.20-149.00	0.53-92.80	0.36-85.50

Excerpted from the clinical study report, table 14 (page 142).

Study1 064:

Reference ID: 3150054

Baseline Characteristic Parameter	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID	Adalimumab 40 mg SC q 2 weeks
Disease duration (rheumatoid arthritis) (duration since first diagnoses, years):					
N	204	201	56	52	204
Mean	7.6	7.4	6.9	9.0	8.1
Range	0.3-39.0	0.3-49.0	0.3-40.0	0.3-49.4	0.2-36.3
Rheumatoid factor, n (%):					
N	199	198	56	51	201
Negative	66 (33.17)	67 (33.84)	16 (28.57)	20 (39.22)	64 (31.84)
Positive	133 (66.83)	131 (66.16)	40 (71.43)	31 (60.78)	137 (68.16)
Anti-CCP, n (%):					
N	202	197	55	50	202
Negative	58 (28.71)	71 (36.04)	13 (23.64)	19 (38.00)	51 (25.25)
Positive	144 (71.29)	126 (63.96)	42 (76.36)	31 (62.00)	151 (74.75)
DAS28-3(CRP)					
N	200	199	55	51	201
Mean (SD)	5.43 (0.89)	5.43 (0.83)	5.55 (0.95)	5.32 (0.79)	5.33 (0.92)
Range	2.08-7.18	3.10-7.58	3.72-7.34	3.81-6.72	2.39-7.30
DAS28-4(ESR):					
N	193	194	54	49	194
Mean (SD)	6.56 (0.89)	6.52 (0.84)	6.60 (1.04)	6.44 (0.73)	6.38 (0.87)
Range	3.21-8.42	4.16-9.01	4.11-8.50	5.08-7.82	3.56-8.81
HAQ-DI:					
N	201	199	55	51	201
Mean (SD)	1.50 (0.64)	1.53 (0.63)	1.47 (0.68)	1.36 (0.68)	1.50 (0.59)
Range	0.00-3.00	0.00-3.00	0.13-3.00	0.00-3.00	0.00-2.75
Tender joint counts:					
N	201	199	55	51	201
Mean (SD)	28.48 (15.03)	26.09 (14.13)	26.58 (14.36)	28.10 (14.43)	26.65 (15.34)
Range	0.00-68.00	6.00-66.00	9.00-68.00	7.00-60.00	6.00-67.00
Swollen joint counts:					
N	201	199	55	51	201
Mean (SD)	16.66 (8.76)	15.80 (7.82)	16.93 (9.98)	16.37 (7.51)	16.35 (8.65)
Range	0.00-54.00	6.00-48.00	6.00-58.00	6.00-34.00	6.00-50.00
ESR (mm/hr):					
N	195	194	55	49	194
Mean (SD)	48.56 (23.88)	49.90 (25.94)	52.65 (26.07)	42.88 (19.37)	48.48 (23.92)
Range	2.00-121.00	8.00-145.00	6.00-130.00	14.00-122.00	9.00-130.00
CRP (mg/L):					
N	200	199	56	51	201
Mean (SD)	14.89 (18.58)	17.27 (19.52)	20.29 (20.07)	11.57 (16.25)	17.48 (22.48)
Range	0.20-142.00	0.30-99.10	0.77-79.00	0.31-92.40	0.20-171.00

Excerpted from the clinical study report, table 10 (page 125).

Reference ID: 3150054

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

/s/

YONGMAN KIM
06/23/2012

JOAN K BUENCONSEJO
06/23/2012
I concur with Dr. Kim's review of (NDA 203214) Tofacitinib for the treatment of RA.

THOMAS J PERMUTT
06/25/2012
concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203214 **Applicant: Pfizer** **Stamp Date: 10/21/2011**

Drug Name: tofacitinib **NDA/BLA Type: NDA**

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	**No interim analysis is planned/conducted.**
Appropriate references for novel statistical methodology (if present) are included.	x			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				**Clinical reviewer's assessment is relevant.**
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

File name: Statistics Filing Checklist for a NDA 203214

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Yongman Kim	12/14/2011
Reviewing Statistician	Date
Joan Buenconsejo	12/14/2011
Supervisor/Team Leader	Date

File name: Statistics Filing Checklist for a NDA 203214

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

/s/

YONGMAN KIM
12/14/2011

JOAN K BUENCONSEJO
12/14/2011
I concur with Dr. Kim's review.