CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
ODE II / DPARP / HFD-570
10903 New Hampshire Ave.
Silver Spring, MD 20993

Memo to File

Addendum to Primary Clinical Review

NDA#: 203,214

SD#s: 30, 31, 33, 36, 37, 38, 39, 40, 41

Reviewer: Nikolay P. Nikolov, M.D., CDER/OND/DPARP

Submission: October 21, 2011 (Original NDA)
August 01, 2012 (Major Amendment Part 1, SD#36)
August 10, 2012 (Major Amendment Part 2, SD#38)

Reviewed: September 26, 2012

Product: Tofacitinib (CP-690,550), an inhibitor of Janus kinase (JAK) family of kinases

Proposed use: Treatment of rheumatoid arthritis (RA)

Sponsor: Pfizer

Summary: This is an addendum to the primary clinical review of NDA 203,214, tofacitinib for treatment of patients with RA, dated June 26, 2012. This document updates the primary review of the original NDA with:

- A review of the revised safety analyses included in the major NDA amendment,
- An updated risk-benefit assessment of tofacitinib for the intended indication, and
- Updated labeling recommendations based on the new data.

This document does not discuss issues covered in the primary review such as regulatory background, CMC, Pharmacology-Toxicology, Clinical Pharmacology, or clinical development. Efficacy is discussed in the context of the updated risk-benefit assessment.

Based on the information from this amendment, the PDUFA goal date was extended by three months from August 21, 2012 to November 21, 2012 and the Sponsor was formally notified of the action on August 20, 2012.

The results of the amended safety analyses are consistent with the results of the original NDA analyses. Further, the Agency's analyses are in general agreement with the sponsor's analyses of the safety data. The amended submission provided the data to refine the quantitative assessment of the relative risk of tofacitinib to placebo, adalimumab and between the two tofacitinib doses. No new or different safety issues were identified to significantly change the overall risk benefit assessment from the primary review.

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommend approval of NDA 203,214 for tofacitinib 5 mg BID with revisions to the proposed labeling, as outlined in Section 3. Labeling Recommendations.

1.2 Risk Benefit Assessment

Brief Overview of the Clinical Program

The original 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 patients with moderately-to-severely active 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 pivotal Phase 2 dose-ranging studies (1025 and 1035) and the five confirmatory Phase 3 studies are summarized in Table 1. For an overview of these studies, the reader is referred to the primary clinical review.

Summary of Efficacy Review and Conclusions

The amendment does not contain efficacy information. For review and conclusions regarding efficacy in this application, the reader is referred to the primary clinical review.

Summary of Safety Review and Conclusions

The review of tofacitinib clinical safety database, updated with the information in this amendment, identified several areas of major safety concerns potentially associated with tofacitinib administration:

1. An increased risk of solid and hematologic malignancies, including lymphoproliferative disorder (LPD) indicating a potential safety signal.
    a. Risk of malignancy, excluding NMSC, increased numerically in a dose and time-dependent fashion:
        i. Malignancy was numerically higher in the tofacitinib 10 mg BID compared to 5 mg BID group during the 0-12 month controlled period of the pivotal randomized clinical studies, assessed both by:
            - Incidence rate ratio of 1.38 with 95% CI (0.44, 4.35) and
            - Mantel-Haenszel risk ratio of 1.41 with 95% CI (0.45, 4.42) accounting for differences across trials.
        ii. Malignancy was also numerically higher in the tofacitinib compared to adalimumab group during the 0-12 month controlled period of study 1064, as assessed both by increased:
            - Incidence rate ratio of 1.77 with 95% CI (0.18, 16.99) and
            - Mantel-Haenszel risk ratio of 1.51 with 95% CI (0.16, 14.43).
        iii. Increased with prolonged tofacitinib exposure (from 0.8 events per 100 pt-yrs for <6 months exposure to 1.4 events per 100 pt-yrs for >24 months

exposure). The dose-relatedness in the long-term extension studies could not be adequately assessed due to study design limitations.

b. There appears to be an increased risk of lymphoma in particular.
    i. Seven cases of LPD occurred in the overall RA development program as of May 2012, all in tofacitinib-treated patients. Two of the cases occurred in highly atypical locations (CNS and breast).
    ii. Five lymphoma cases in 218 (2.3%) renal transplant patients who had received 15 mg BID. Four of 5 patients were on 15 mg BID for 6 months and one of 5 patients was on 15 mg BID for 3 months prior to maintenance treatment with 10 mg BID.
    iii. Lymphomas occurred in the highest dose group (3 of 8, 37%) of the chronic toxicology study in monkeys.

2. An increased risk of serious infections, including opportunistic infections, identifying a profile of tofacitinib as a major immunosuppressant.
    a. Serious infections associated with tofacitinib use were common in the RA program with pneumonia being the most common (occurring only in tofacitinib-treated patients).
    b. Tuberculosis occurred only in tofacitinib treated patients in a clearly dose-dependent fashion.
    c. Opportunistic infections were not uncommon and included cases of cryptococcal infections, Pneumocystis jiroveci pneumonia, and BK virus encephalitis, which are seen exclusively in severely immunocompromized patients.

3. Laboratory abnormalities, to include abnormal hematologic parameters, lipid parameter changes, liver enzymes, and serum creatinine elevation. Tofacitinib administration was associated with:
    a. Dose-dependent sustained neutropenia and progressive lymphopenia. Severe lymphopenia was also associated with increased risk of infections.
    b. Dose-dependent sustained elevations in total, LDL, and HDL cholesterol. Total and LDL cholesterol levels reversed with lipid-lowering therapy. These lipid abnormalities did not appear to translate into increases in cardiovascular events.
    c. Liver enzymes elevations which were observed mostly in patients on background DMARDs and significant liver abnormalities were uncommon. However, in one case, drug-induced liver injury could not be excluded and the case is considered to meet Hy's law criteria.
    d. Dose-dependent small but significant elevations of mean serum creatinine. These increases were associated with an increasing incidence of patients meeting the protocol criteria for discontinuation due to creatinine increases (confirmed creatinine increases of more than 50% of baseline). There did not otherwise appear to be an increase in the proportion of patients experiencing serious adverse events of renal failure.

In conclusion, the safety data from tofacitinib RA development program is consisted with the profile of a potent immunosuppressant, with associated inherent risks, such as serious infections, including opportunistic infections and tuberculosis. Tofacitinib administration was also associated with malignancy (excluding non-melanoma skin cancer, NMSC) in a manner that may be consistent with a dose- and duration of exposure- dependent manner.

Gastrointestinal perforations and interstitial lung disease were observed in the clinical trials, however the relative risk and role of tofacitinib treatment in the development of these adverse events is not well defined. Treatment with tofacitinib resulted in dose-dependent changes in laboratory parameters, such as sustained neutropenia and progressive lymphopenia, sustained elevations in total, LDL, and HDL cholesterol, small but significant elevations of mean serum creatinine, and liver enzymes elevations. While most of these were not associated with clinical adverse events in the controlled setting of the clinical trials, severe lymphopenia was associated with increased risk of infections. One case of Hy's law occurred with tofacitinib treatment. Using the estimate of severe drug-induced liver injury as occurring at 1/10th the rate of Hy's Law cases, 1 case of severe liver injury might be expected in 50,000 patients treated with tofacitinib.

Most of these potential safety issues are seen with other traditional and biologic DMARDs and have historically been handled via appropriate labeling and risk evaluation and mitigation strategies, which should also be adequate in this case. The clinical trial experience has been extensive, but may not be sufficient to capture the full extent of safety concerns that may arise with long-term JAK inhibition with tofacitinib, which is a new molecular entity.

The risk of malignancy and serious infections increased numerically with prolonged tofacitinib exposure; however due to limitations in the design of the long-term safety database, the incremental increase in risk associated with dose and duration of exposure could not be adequately characterized. However, as noted in the main clinical review, the long-term data submitted raise a concern that the risk could be increased in the higher dose with increasing duration of exposure. Therefore, to further address residual uncertainties regarding the long-term safety of tofacitinib, a long-term study of both tofacitinib doses 5 mg and 10 mg BID along with an active comparator is warranted, which will be consistent with the recommendations form the Arthritis Advisory Committee panel.

Risk Benefit Overview

Tofacitinib is a new molecular entity and if approved, would be the first in class of drugs, Janus associated kinase (JAK) inhibitors, for the treatment of patients with RA. Importantly, tofacitinib is an oral agent providing potential advantages over exiting injectable DMARDs.

At both tested doses, 5 mg and 10 mg BID, tofacitinib demonstrated clinical benefit on signs and symptoms and physical function in patients with established moderately-to-severely active RA, both as a monotherapy and in combination with MTX or other traditional DMARDs, with results in the range of approved biologic DMARDs such as TNF inhibitors. Tofacitinib, however did not show a clear evidence of radiographic benefit in this patient population, based on the results of a single study.

Tofacitinib has a safety profile of a potent immunosuppressant associated with increased risk of serious infections, including opportunistic infections and tuberculosis, solid and hematologic malignancy, possible idiosyncratic hepatotoxicity, and dose-dependent laboratory abnormalities, among which elevated LDL, HDL and total cholesterol.

The amended safety analyses of the major events of interest from the seven pivotal studies using Poisson regression analyses and accounting for differential study design were consistent with the observations in the original application.

During the 12 month controlled period of the seven pivotal studies, malignancy, excluding NMSC, serious infections, including tuberculosis, and opportunistic infections were identified as safety signals associated with the use of tofacitinib. Dose-dependent numerical increases in the relative risk of malignancies (excluding NMSC) and tuberculosis were observed, reaching statistical significance (p-value=0.03 before adjusting for multiplicity) only for tuberculosis.

In conclusion, the overall risk to benefit profile of tofacitinib in RA appears to be favorable, with many more patients potentially benefiting from treatment compared to those at potential risk. Most of the potential safety issues such as malignancy, tuberculosis, serious and opportunistic infections, hepatotoxicity and laboratory abnormalities are seen with other traditional and biologic DMARDs and have historically been handled via appropriate labeling and risk evaluation and mitigation strategies, which should also be adequate in this case.

Dosing Recommendations

The clinical benefit of tofacitinib 5 mg BID and 10 mg was generally comparable. Numerical differences were observed in ACR and DAS28 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 relatively small and of questionable clinical significance. (b) (4)

(b) (4)

herefore, based on the available data, the overall risk to benefit profile is more favorable for the 5 mg BID dose and until additional data are available to better characterize the long-term safety profile of the two doses, only the 5 mg BID dose should be approved.

Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is warranted and should assure communication to healthcare providers about the risks of:

- Serious infections, including opportunistic infections, and tuberculosis
- Malignancy
- Cardiovascular major adverse events associated with tofacitinib-induced elevation in lipid parameters
- Changes in laboratory parameters, such as decreases in neutrophil counts, lymphocyte counts, hemoglobin levels, increases in low density lipoprotein cholesterol (LDL-c), serum creatinine, transaminase elevations and potential hepatotoxicity associated with tofacitinib.

The risks of tofacitinib treatment, including malignancy, serious infections, hepatotoxicity, and necessity of laboratory monitoring should also be communicated to patients.

Recommendations for Postmarketing Requirements and Commitments

- A long-term prospective safety study:

A study of both tofacitinib doses 5 mg and 10 mg BID along with an active comparator to assess the safety for major AEs of interest that may manifest after prolonged tofacitinib exposure, such as cardiovascular adverse events, malignancies, serious infections, and hepatotoxicity. Such a study would help addressing residual uncertainties regarding the long-term safety of tofacitinib and would be consistent with the recommendations by the Arthritis Advisory Committee members for collecting long-term safety data.

- Studies to achieve compliance with PREA:
  Polyarticular juvenile idiopathic arthritis (pJIA) is considered to be the pediatric equivalent of adult RA. Therefore, in accordance with the Pediatric Research Equity Act (PREA) of 2003, studies in pJIA are mandated. With this submission, the applicant has requested a deferral for patients age 2-17 with pJIA, and a waiver for children 0-2, since pJIA is extremely rare in this age group. These requests have been granted for other therapeutic biologics, as, for ethical reasons, it is desirable to have an adequate experience with the safety profile of a treatment in adults before proceeding with extensive studies in children. The applicant has already discussed details of their proposed Phase 3 program in pJIA and systemic juvenile idiopathic arthritis (sJIA) with the Agency. (b) (4)

2. Review of the Amendment

2.1 Background

The original 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 patients with moderately-to-severely active 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.

The pivotal Phase 2 dose-ranging studies (1025 and 1035) and the five Phase 3 confirmatory studies are summarized in Table 1.

Table 1. Key Design Features of NDA 203,214 Pivotal Randomized Controlled Studies for Efficacy and Safety

Key Design Features of the Pivotal Randomized Controlled Studies in RA for Efficacy and Safety						
Protocol	**Patient Population**	**Design** ***Duration***	**Enrolled** ***Randomization***	**Treatment Arms (transition and escape for NR)**	**Primary Endpoints**	**Timepoint**
Patients with incomplete response to prior TNF inhibitor						
A3921025	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 2, 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 OD (→CP 5 mg BID @ Mo3 if NR)+ MTX Placebo (→CP 5 mg BID @ Mo3 if NR)+ MTX	ACR20	Month 3
A3921032	Moderate-to-severe RA TNF-IR, Stable background MTX	R, DB, PC Phase 3 *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	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
Patients with incomplete response to MTX or other DMARDs						
A3921035	Moderate-to-severe RA DMARD-IR, No background therapy	R, DB, AC Phase 2, Dose-ranging *6 months*	384 *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)	ACR20	Month 3
A3921044	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 3 *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	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6
A3921045	Moderate-to-severe RA DMARD-IR, No background to Month 3	R, DB, PC Phase 3 *6 months*	610 *4:4:1:1*	CP 5 mg BID CP 10 mg BID PBO → CP 5 mg BID @ Mo 3 PBO → CP 10 mg BID @ Mo 3	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
A3921046	Moderate-to-severe RA DMARD-IR, Stable background DMARDs[#]	R, DB, PC Phase 3 *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	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
A3921064	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, AC Phase 3 *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	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6

Source: Summary of Clinical Efficacy, Clinical Study Reports for studies A3921032, A3921044, A3921045, A3921046, A3921064

*-One year efficacy data submitted for Study A3921044; [#]-Background DMARD herapy in Study A3921046: 84% of subjects on MTX, –1/2 on combination DMARDs; AC-active control (adalimumab, study A3921064); BID-two imes daily; DMARDs-disease-modifying anti-rheumatic drugs; IR-incomplete response; MTX-methotrexate; mTSS-modified total Sharp Score; NR-non-responder defined as patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts over baseline at Month 3 visit; PBO-placebo; PC-placebo (add-on for studies A3921032, A3921044, A3921046, A3921064)-controlled; SC-subcutaneous; TNF-tumor necrosis factor. CP=CP-690,550/tofacitinib

The review of the efficacy data concluded that there is substantial evidence of efficacy of tofacitinib 5 mg or 10 mg for the treatment of rheumatoid arthritis 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 pooled safety data from five confirmatory double-blind phase 3 studies in RA (1032, 1044, 1045, 1046, and 1064). These data were supported by pooled data from five completed phase 2 studies (1025, 1039, 1019, 1035, and 1040) and pooled data from two ongoing long-term extension (LTE) studies (1024 and 1041). For an overview of these studies, the reader is referred to the primary clinical review.

The methods used in the safety analyses of the original NDA were consistent with those from other RA development programs. These safety analyses provided a qualitative but inadequate quantitative assessment of the long-term safety and the relative safety of the two dosing regimens (5 mg vs. 10 mg BID) of tofacitinib to allow for regulatory decision and accurate labeling.

Due to the complexity of the trial design, such as early escape options and unequal randomization, the following issues were identified as potential limitations with regard to the safety data presentation and analyses in the original application:

1. Data were analyzed for patients as randomized and not as treated. For example, patients who were on placebo and transition to active treatment at Months 3 or 6 were counted under the respective active treatment arm from that point on, instead of time "zero". Presenting the safety data for patients as treated may allow for a more precise assessment of crude proportions of patients with AEs for any given time period, even though this approach may not affect the incidence rates of AEs, adjusted for actual exposure to the drug, as discussed in this document. One important consideration with using this approach however, is that patients who escape from placebo to active treatment due to active disease represents a group of patients with more active disease who may have a different baseline risk of developing adverse events and therefore may represent a somewhat different population than the one originally randomized to active treatment.
2. It was not clear from the submission whether the rules for capturing and reporting of AEs were applied consistently within the RA development program which may introduce a bias in AE reporting. For example, only deaths were reported if they occurred on treatment or within 30 days of last dose.
3. Only safety data from the five Phase 3 randomized controlled trials were included in the pooled safety analyses (A3921032, A3921044, A3921045, A3921046, and A3921064). However, the two pivotal Phase 2 dose-ranging studies (A3921025, and A3921035) were of similar design and patient population and could be included in the pooled analyses to increase the overall sample size for assessment of controlled data.
4. Long-term extension study A3921041 included patients who completed Japanese Phase 2 studies which were not included in the pooled analyses of the controlled studies. Therefore, excluding these patients in the open label extension analyses may

allow for more accurate comparison with the analyses from the controlled studies. One caveat of this approach however, is that important safety information may be excluded.

To address these concerns, the Division had asked the sponsor 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 sponsor to clarify some issues or roadblocks regarding the requests.

At a Type A meeting on July 10, 2012, between the Division and the sponsor the following additional analyses were agreed upon as a path forward to addressing the information requests and the Agency's concerns:

- Seven trials to be included in integrated analysis:
  - Five phase 3 studies – 1032, 1046, 1044, 1045, 1064
  - Two phase 2 studies – 1025, 1035,
- Timing of Events . Events within 30 days of stopping treatment or decreasing dose. No 30 day window (hard stop) for placebo to tofacitinib cross over, increasing tofacitinib dose.
- Time Intervals
  - 0-3 months
  - 0-6 months
  - 0-12 months
- Events of interest
  - death
  - lymphoma
  - solid organ tumor
  - opportunistic infection
  - TB
  - SAE infection
  - herpes zoster
  - CV MACE events
- Events of interest for labeling (These events can be for 0-3 month time interval as long as laboratory changes have reached a plateau).
  - Hemoglobin
  - Lipids
  - Neutrophils
  - LFTs
  - Common AEs

For transparency, the Agency provided the sponsor with its plan for additional safety analyses to include.

1. Assessment of the safety profile of tofacitinib 5 mg BID relative to 10 mg BID for the 0-6 and 0-12 month periods of the 7 studies, with respect to events of interest, stratified by study, using Poisson regression with an offset term to account for differing exposure times, and study to account for differing patient populations and/or study designs.
   a. Only patients originally randomized to tofacitinib 5 and 10 mg BID

b. 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).

c. 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) + patients who escaped to tofacitinib 5 and 10 mg BID due to active disease.

2. Comparison of the safety profile of tofacitinib, relative to adalimumab, with respect to events of interest using data from studies 1035 and 1064, separately.

The Sponsor has submitted the requested analyses as a major NDA amendment on August 10, 2012 which was within three months of the user fee goal date. Therefore, the Agency extended the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 21, 2012.

Long-term extension studies considerations

Analyses of the long-term extension data from studies 1024 and 1041 proved to be challenging for quantitative assessment of the relative risk of the two tofacitinib doses for several reasons, including:

- The study design allowed for inconsistent dosing between the index and extension studies. For example:
    - In study 1024, following implementation of Protocol Amendment 3 (January 21, 2009), enrolling patients initiated open-label tofacitinib 10 mg BID at the baseline visit (except patients in China, who initiated open-label tofacitinib 5 mg BID at the baseline visit). Prior to implementation of Amendment 3, all patients initiated open-label tofacitinib 5 mg BID at the baseline visit. Patients who are taking tofacitinib 10 mg BID were allowed to decrease dosing to 5 mg BID for mild to moderate safety concerns and those who are taking 5 mg BID were allowed to increase their dose to 10 mg BID at the instruction of the investigator.
    - In study 1041, all patients were to initiate at a dose of tofacitinib 5 mg BID. The dosage may be increased from 5 mg BID to 10 mg BID, reduced from 10 mg BID to 5 mg BID, or temporarily discontinued (up to 28 consecutive days) based on consideration of the risks and benefits to the patient.
- The duration of exposure among patients in the extension studies was highly variable. For example, some patients may have had only 3 months of tofacitinib exposure (studies 1045 and 1032) versus 12 months for patients from studies 1044, 1046, and 1064.
- The overall duration of exposure to tofacitinib 5 mg BID dose was significantly longer compared with 10 mg BID (see Table 29 in the primary clinical review).

Because of these shortcomings in the design of the open label extension studies, quantitative assessment of the relative risk of the two tofacitinib doses was limited to assessment of safety data from the controlled periods of the pivotal randomized clinical trials.

To further address residual uncertainties regarding the long-term safety of tofacitinib, a long-term study of both tofacitinib doses 5 mg and 10 mg BID along with an active comparator is warranted. This will help assessing the safety for major AEs of interest that may manifest after prolonged tofacitinib exposure, such as cardiovascular adverse events, malignancies, serious infections, and hepatotoxicity as recommended in section *Recommendations for Postmarketing Requirements and Commitments*.

2.2 Methods

As agreed with the sponsor, the amended safety data analyses consist of an integrated analysis of the controlled periods of the seven pivotal studies (five confirmatory studies – 1032, 1046, 1044, 1045, 1064, and two dose-ranging studies – 1025, 1035) described in the primary clinical review and summarized in Table 1.

1. Analyses of major events of interest (death, malignancy excluding NMSC, serious and opportunistic infections, tuberculosis, herpes zoster, and MACE) to compare the relative safety profile of the two tofacitinib dosing regimens (5 mg vs. 10 mg BID) during the controlled periods of the studies, i.e. 0-12 months.

   To account for the differences in study design, i.e. patients transitioning to active treatment by design or due to active disease at either 3 or 6 months in the different studies, the Division's statistical review team identified and conducted three different analyses using Poisson regression modeling for:

   a) Only patients originally randomized to tofacitinib 5 and 10 mg BID (Analysis 1 population)
   b) Patients originally randomized to tofacitinib 5 and 10 mg BID + patients who transitioned to tofacitinib 5 and 10 mg BID by study design, i.e. month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064 (Analysis 2 population).
   c) 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) + patients who escaped to tofacitinib 5 and 10 mg BID due to active disease (Analysis 3 population).

   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 Rate Ratio (IRR). The Mantel-Haenszel Risk Ratio is also shown as a secondary analysis method. For rare events, 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.

2. Analyses of common AEs and laboratory parameters to compare the relative safety profile of tofacitinib (5 mg and 10 mg BID) to placebo during the controlled periods of the studies, i.e. 0-3 months:
    a) Patients originally randomized to tofacitinib 5 and 10 mg BID or placebo
    b) Patients originally randomized to tofacitinib 5 and 10 mg BID or placebo + patients who transitioned from placebo to tofacitinib 5 and 10 mg BID by study design at Month 3 (studies 1032 and 1045 only). This analysis did not include patients who transitioned to active treatment due to active disease because they may have a different baseline risk of developing adverse events. Similarly, this analysis did not include patients who continued to receive placebo through Month 6, as they did not have active disease and may represent a groups of patients with different baseline risk of developing adverse events.

3. Analyses of major events of interest (death, malignancy excluding NMSC, serious and opportunistic infections, tuberculosis, herpes zoster, and MACE) to compare the relative safety profile of tofacitinib (5 mg and 10 mg BID) to adalimumab during the controlled periods of studies 1035 and 1064, i.e. 0-12 months.

Ascertainment of the timing of events is based on sponsor's standard operating procedures:

- For deaths: All deaths are reported as SAEs and in the NDA were reported for deaths that occurred at any time after treatment and separately for deaths that occurred within 30 days of last dose. Furthermore, investigators are required, per protocol, to report all deaths (and SAEs) through 28 days after the last administration of tofacitinib, enhancing the reliability of accurate reporting of these events.
- For SAEs: The reporting period begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product.
- For AEs: Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit. For adverse events and/or clinically significant laboratory abnormalities, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. All treatment-emergent AEs that were reported to the study databases were included in the safety summaries, regardless of when the data were collected, up until database lock for the clinical study.
- For Laboratory tests: All laboratory data that was reported to the clinical database was included in the safety summaries, regardless of when the data were collected, until database lock for the clinical study.

2.3 Patient Populations Used for Safety Analyses

Based on the inclusion of safety data from the pivotal dose ranging studies 1025 and 1035 in the integrated safety analyses, the number of patients has changed compared with the pooled safety analyses in the review of the original application as summarized in Table 2. These numbers identify the denominator used in the revised safety analyses described in section 2.2 Methods.

"As randomized" population represents only patients as originally randomized and "As treated" represents 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) + patients who escaped to tofacitinib 5 and 10 mg BID due to active disease.

Table 2. Patient Populations and Exposure Used for Safety Analyses of Major Events of Interest in Tofacitinib Randomized Controlled Trials in RA, 0-12 Months

Patient Populations and Exposure Used for Safety Analyses of Major Events of Interest, 0-12 Months			
	Placebo	CP5 mg	CP10 mg
Safety population from the 5 confirmatory studies (Original application)			
As randomized, n	681	1216	1214
Exposure, Patient Years	203	904	910
Safety population from the 7 pivotal studies (Amended analyses)			
As randomized, n	809	1336	1349
Exposure, Patient Years	240	1056	1071
As randomized + transitioned from placebo by design only, n	809	1539	1542
Exposure, Patient Years	240	1143	1153
As treated, n	809	1689*	1639
Exposure, Patient Years	240	1240	1229

Source: Integrated Summary of Safety (clinical data cut-off March 29, 2011), Amendment August 2012,
*FDA statistical review team analyses; the number differs from the number provided in the amendment, i.e. 1814, where sponsor's revised analyses include all patients who transition not only from placebo but also from tofacitinib 1 and 3, mg BID and 20 mg QD dose (studies 1025 and 1035) or adalimumab (study 1035) to 5 mg BID
"As treated" population includes pa ients originally randomized to tofaci inib 5 and 10 mg BID + patients who transitioned only from placebo 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 from placebo to tofacitinib 5 and 10 mg BID due to active disease

Of note, the "As treated" population in the amended submission (n=1814) differ from the "As treated" population in the Agency's analyses (n=1689). The reason is that the sponsor's analyses include all patients who transition to 5 mg BID not only from placebo but also from tofacitinib 1 and 3, mg BID and 20 mg QD dose (studies 1025 and 1035) or adalimumab (study 1035) (see in Table 2). The analyses presented in this review use the Agency defined "As treated" population which includes patients originally randomized to tofacitinib 5 and 10 mg BID + patients who transitioned only from placebo 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 from placebo to tofacitinib 5 and 10 mg BID due to active disease. The intent is to minimize the confounding effect of other treatments of different prior dose of tofacitinib. In general, the results were consistent irrespective of the definition used for "As treated" population.

It is important to note that the listings of the adverse events have not changed; however depending on the patient population used for the different analyses, the events (numerator) may have been counted differently. For example,

- In the "As randomized" analyses, if a patient transitioned from placebo to tofacitinib 5 mg BID at Month 3 and the event occurred on active treatment at Month 5, this event would not be included in the analyses,
- In the "As treated" analyses, the same event would be counted as the numerator in the analyses under the tofacitinib 5 mg BID group with the actual exposure to the drug, i.e. 2 months.

2.4 Assessment of Safety of Tofacitinib 5 mg vs. 10 mg BID

The relative safety profile of tofacitinib 5 mg vs. 10 mg BID was compared primarily using data from the controlled periods of the pivotal studies, as this allowed for the longest controlled data comparison (up to 12 months). The focus of the quantitative analyses were major events of interest, defined as death, malignancy (excluding NMSC), serious and opportunistic infections, tuberculosis, herpes zoster, and MACE, as these were identified as potential safety issues based on the safety analyses covered in the primary review.

2.4.1 Comparison Between the Original and Amended Safety Analyses

To facilitate the comparison between the findings from the original application and the amended analyses, the head-to-head data are presented in the Table 3 using comparable statistics, i.e. incidence rates adjusted for the exposure.

As seen in Table 3, the inclusion of safety data from all the seven pivotal studies identified a few additional cases serious infections and Herpes zoster infections in both tofacitinib dose groups without significantly changing the distribution of the events based on the exposure-adjusted event rates. This was true for the comparison of patients as originally randomized ("As randomized") or also including patients who transitioned from placebo to tofacitinib by either design or by response ("As treated").

Both tofacitinib doses continue to show increased incidence of malignancy, excluding NMSC, serious infections, including tuberculosis and opportunistic infections compared with placebo.

Dose-dependent numerical differences between the tofacitinib 5 mg and 10 mg BID dose were observed for:

- Malignancy, excluding NMSC, in the total number of events (5 vs. (b) (4) and the exposure-adjusted incidence rates (0.47 vs. (b) (4) "As treated" and 0.40 vs. (b) (4) "As randomized)
- (b) (4)

In summary, the amended analyses of major events of interest of the 0-12 month controlled periods of the seven randomized controlled studies are consistent with the analyses from the original application.

Table 3. Summary of Major Events of Interest (Month 0-12 + 28 Days) in Tofacitinib Randomized Controlled Trials in RA, Comparison Between Original and Amended Analyses

Summary of Major Events of Interest (0-12 Months), Comparison Between Original and Amended Analyses									
	5 Confirmatory Studies (Original application)			7 Pivotal Studies (Amended analyses)					
	As randomized			As randomized		(b) (4)	As treated		(b) (4)
	PBO	CP5	CP10	PBO	CP5		PBO	CP5	
Number of patients, n	681	1216	1214	809	1336		809	1689	
Exposure, patient-years	203	904	910	240	1056		240	1240	
Deaths									
Number of deaths, n	1	5	4	1	5		1	5	
Incidence rate, per 100 PY	0.50	0.55	0.44	0.42	0.47		0.42	0.40	
Malignancy (excl. NMSC)									
Patients with ≥ 1 malignancy, n	0	5	8	0	5		0	5	
Incidence rate, per 100 PY	0	0.55	0.88	0	0.47		0	0.40	
Serious infectious events (SIE)									
Patients with ≥ 1 SIE, n (%)	3 (<1)	29 (2)	27 (2)	3	31 (2)		3 (<1)	34 (2)	
Incidence rate, per 100 PY	1.48	3.2	3.0	1.3	2.94		1.3	2.74	
Opportunistic infections (OI)									
Patients with ≥ 1 OI, n	-	4	4	-	3		-	4	
Incidence rate, per 100 PY	0	0.44	0.44	0	0.28		0	0.32	
Tuberculosis (TB)									
Patients with ≥ 1 TB, n (%)	-	-	6	-	-		-	-	
Incidence rate, per 100 PY	0	0	0.66	0	0		0	0	
Herpes zoster (HZ) infections									
Patients with ≥ 1 , n (%)	3 (<1)	39 (3)	38 (3)	5 (<1)	42 (2)		5 (<1)	47 (2)	
Incidence rate, per 100 PY	1.5	4.4	4.2	2.1	3.98		2.1	3.79	
MACE									
Patients with ≥ 1 MACE, n	2	4	6	2	4		2	6	
Incidence rate, per 100 PY	0.99	0.44	0.66	0.83	0.38		0.83	0.48	

Source: Integrated Summary of Safety, Section 2.1.2, Deaths, adapted from Tables 68-75; Amendment August 2012, Tables 1.1.3, 1.6.3, 1.4.3, 1.7 3, 1.8.3; FDA statistical review team analyses

Deaths

During the controlled periods of the seven pivotal studies, 5 patients died in the tofacitinib 5 mg BID compared with 5 in the 10 mg BID group (see Table 3). One new death in the tofacitinib 10 mg BID "As treated" group was included as it occurred in a patient who had transitioned from placebo to tofacitinib 10 mg BID for 47 days. No new deaths were included in the placebo group. Consistent with the findings in the primary review, the numerical imbalances between the three treatment arms do not indicate a clear dose-dependent increase in mortality rates.

Malignancy

The amended analyses of malignancy (excluding non-melanoma skin cancer, NMSC) differ from the original analyses because one case in the tofacitinib 10 mg BID dose group was excluded (see Table 3) because the case was diagnosed six months after the last dose of tofacitinib which is after the widow for ascertaining AEs in the amended analyses, i.e. 28 day from the last tofacitinib dose. No malignancies occurred in placebo-treated patients. Consistent with the observations from the original application, there continues to be a dose-related

numerical imbalance in the number of events and exposure-adjusted incidence rates between the two tofacitinib doses.

Serious Infections

The amended safety analyses identified a few additional cases of serious infections in both tofacitinib groups. Consistent with the observations from the original application, a higher proportion of patients in the tofacitinib groups experienced a serious infection compared to the placebo. The incidence rates between the two tofacitinib dose groups remained comparable and do not indicate a dose-dependent increase in the risk of serious infections.

Opportunistic Infections

No new cases of opportunistic infections were identified in the amended analyses and the incidence rates between the two tofacitinib dose groups remained comparable. No cases of opportunistic infections were the control groups. The number of opportunistic infections observed during the controlled periods of the pivotal studies is relatively small and does not allow drawing definitive conclusions regarding dose relatedness.

Tuberculosis

No new cases of tuberculosis were identified in the amended analyses. All tuberculosis cases occurred in the tofacitinib dose group during the controlled periods of the pivotal studies. (b) (4)

Herpes Zoster

The amended safety analyses identified a few additional cases of Herpes zoster infections in both tofacitinib groups. Consistent with the observations from the original application, a higher proportion of patients in the tofacitinib groups experienced a serious infection compared to the placebo. The incidence rates between the two tofacitinib dose groups remained comparable in the "As randomized" population. The analyses of "As treated" population identify some dose-dependent numerical increase in the incidence of Herpes zoster infections.

CV MACE

The amended analyses identified two additional cases of MACE, both in the tofacitinib 5 mg BID dose group. With these additional cases, the events and the incidence rates between the two tofacitinib groups become comparable and are still numerically lower than the placebo group. Consistent with the analyses of the original application, the available data on major adverse cardiovascular events do not indicate a clear safety signal of increased cardiovascular morbidity and mortality in patients treated with tofacitinib, compared with placebo.

2.4.2 Regression Analyses of Safety of Tofacitinib 5 mg vs. 10 mg BID

To further compare the relative safety of tofacitinib 5 mg and 10 mg BID dosing, the statistical review team, Drs. Andraca-Carrera, Kim and Buenconsejo, conducted additional analyses as described in Section 2.2 Methods. These included analyses of major events of interest using Poisson regression modeling stratified by study with an offset term given by the logarithm of time until first event or censoring to the following safety data for:

1) Only patients originally randomized to tofacitinib 5 and 10 mg BID at baseline (Analysis 1 population, "As randomized").
2) Patients originally randomized to tofacitinib 5 and 10 mg BID + patients who transitioned to tofacitinib 5 and 10 mg BID by study design, i.e. month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064 (Analysis 2 population).
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 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 (Analysis 3 population, "As treated").

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.

The results of Poisson regression analyses are presented as the Incidence Rate Ratio (IRR). A higher IRR indicates a higher risk of developing an adverse event in one group relative to the reference group. The Mantel-Haenszel Risk Ratio is also shown 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.

Summaries of the estimated incidence rate ratio for major events of interest are presented in:

- Table 4 (Analysis 1) for only patients originally randomized to tofacitinib 5 and 10 mg BID at baseline from the 7 pivotal studies
- Table 5 (Analysis 2) for 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)
- Table 6 (Analysis 3) for 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) + patients who escaped to tofacitinib 5 and 10 mg BID due to active disease.

Table 4. (Analysis 1) Incident Rate Ratio of Events of Interest, Comparing Tofacitinib 10 mg vs. 5 mg BID Based on Randomized Treatment Assignment

Risk of Major AEs of Interest of Tofacitinib 10 versus 5 mg BID, Analyses of "As Randomized" Safety Population				
	Incidence Rate Ratio (95% CI)	Mantel-Haenszel RR (95% CI)	5 mg BID[1] events/100 py	10 mg BID[2] events/100 py
Death	0.57 (b) (4) (b) (4)	0.57 (b) (4) (b) (4)	0.47	(b) (4)
MACE	1.49	1.50	0.38	
Malignancy excl. NMSC	1.38	1.41	0.47	
Lymphoma	*ND*	*ND*	*0*	
Solid organ tumors	*1.18* (b) (4)	*1.20* (b) (4)	*0.47*	
Opportunistic infections	1.31	1.34	0.28	
Tuberculosis	ND	ND	0	
Serious infections	0.95 (b) (4)	0.98 (b) (4)	2.94	
Herpes zoster	0.98	1.00	3.98	

Source: FDA statistical review team analyses
ND = not defined. Reference level is tofacitinib 5mg
[1]A total of 1055.5 years of exposure were observed among patients on tofacitinib 5mg (b) (4)
[2]Events in Tofacitinib 10mg per 100 py – Events in Tofacitinib 5mg per 100py, with MH study weights

(b) (4)

Table 5. (Analysis 2) Incident Rate Ratio of Events of Interest, Comparing Tofacitinib 10 mg vs. 5 mg BID 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)

Risk of Major AEs of Interest of Tofacitinib 10 versus 5 mg BID, Analyses of "As Randomized + Transitioned by Design" Safety Population				
	Incidence Rate Ratio (95% CI)	Mantel-Haenszel RR (95% CI)	5 mg BID[1] events / 100 py	10 mg BID[2] events / 100 py
Death	0.71 (b) (4) (b) (4)	0.72 (b) (4) (b) (4)	0.44	(b) (4)
MACE	1.00	1.01	0.53	
Malignancy excl. NMSC	1.38	1.41	0.44	
Lymphoma	*ND*	*ND*	*0*	
Solid organ tumors	*1.18* (b) (4)	*1.20* (b) (4)	*0.44*	
Opportunistic infections	0.99	1.01	0.35	
Tuberculosis	ND	ND	0	
Serious infections	0.93 (b) (4)	0.95 (b) (4)	2.98	
Herpes zoster	0.99	1.00	3.94	

Source: FDA statistical review team analyses
ND = not defined. Reference level is tofacitinib 5mg
[1]A total of 1142.7 years of exposure were observed among pa ients on tofaci inib 5mg (b) (4)

Table 6. (Analysis 3) Incident Rate Ratio of Events of Interest, Comparing Tofacitinib 10 mg vs. 5 mg BID Based on Randomized Treatment Assignment + Patients who Transitioned from Placebo to Tofacitinib at Either Month3 or Month 6 (by Design or by Response)

Risk of Major AEs of Interest of Tofacitinib 10 versus 5 mg BID, Analyses of "As Randomized + Transitioned by Design and by Response" Safety Population				
	Incidence Rate Ratio (95% CI)	Mantel-Haenszel RR (95% CI)	5 mg BID[1] events / 100 py	10 mg BID[2] events / 100 py
Death	0.45 (b) (4) (b) (4)	0.45 (b) (4) (b) (4)	0.40	(b) (4)
MACE	1.01	1.02	0.48	
Malignancy excl. NMSC	1.42	1.45	0.40	
Lymphoma	*ND*	*ND*	*0*	
Solid organ tumors	*1.21* (b) (4)	*1.25* (b) (4)	*0.40*	
Opportunistic infections	0.99	1.02	0.32	
Tuberculosis	ND	ND	0	
Serious infections	0.97 (b) (4	1.00 (b) (4)	2.74	
Herpes zoster	1.07	1.09	3.79	

Source: FDA statistical review team analyses
ND = not defined. Reference level is tofacitinib 5mg
[1]A total of 1240.1 years of exposure were observed among pa ients on tofaci inib 5mg (b) (4)

In summary, the three analyses comparing tofacitinib 5 mg to 10 mg BID show generally comparable risk of developing major event of interest during the controlled periods of the seven pivotal studies. Dose-dependent numerical increases in the relative risk of malignancies excluding NMSC and tuberculosis were observed, reaching statistical significance (p-value=0.03 before adjusting for multiplicity) only for tuberculosis. The lack of statistically significant differences between the two tofacitinib groups for the rest of the events of interest is not unexpected provided the relatively small number of events and the fact that the studies were not specifically designed to address this question.

Overall, the results from the Poisson regression analyses comparing the safety of tofacitinib 5 mg and 10 mg BID are consistent with the observations from the original application (see Table 3). Due to the relatively small number of events, definitive conclusions regarding the dose-relatedness of these observations are difficulty to be drawn.

It is important to note that the duration of the controlled periods used for these analyses (0-12 months) may not be sufficiently long to assess the potential dose-dependency of the major events of interest. For example, solid and hematologic malignancies, serious infections, opportunistic infections and tuberculosis, occurred later in the course of tofacitinib treatment; on average after about one year, as shown in Table 7 below based on the safety data from the entire tofacitinib RA development program.

Table 7. Duration of Exposure to Tofacitinib Prior to Diagnosis of Select Major Adverse Events in Tofacitinib RA Development Program

Duration of Exposure to Tofacitinib Prior to Diagnosis of Select Major Adverse Events		
	Median, days	**Mean, days**
Malignancy (excluding NMSC)	379	454
Lymphoproliferative disorder	365	409
Serious infections	286	346
Opportunistic infections	234	290
Tuberculosis	298	348

To address the residual uncertainty regarding the potential risk of long-term dose-related increases in major events such as malignancy and opportunistic infections, a long-term safety controlled study comparing both tofacitinib doses and an active comparator is warranted as discussed in section *Recommendations for Postmarketing Requirements and Commitments*.

2.5 Assessment of Safety of Tofacitinib vs. Adalimumab

In the tofacitinib RA development, adalimumab was used as the active comparator in studies 1035 and 1064. These studies were described in the primary clinical review and are summarized in Table 1.

The relative safety of tofacitinib to the active comparator adalimumab was previously assessed in the primary clinical review as part of the pooled analyses of safety, where the safety in adalimumab-treated patients from study 1064 was compared to the safety of tofacitinib, 5 mg BID, tofacitinib 10 mg BID and placebo from the five confirmatory studies. The limitations of this approach were that it did not account for the differences in the study design, such as study population and background therapy.

In order to more precisely compare the relative safety of tofacitinib to adalimumab, both adalimumab studies, 1035 and 1064, were analyzed separately for the major events of interest. Table 8 shows that there were more cases of tuberculosis, herpes zoster and serious infections reported among patients on tofacitinib than in patients on adalimumab. Table 9 shows that the estimated incidence rate ratio for 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 infections associated with the use of tofacitinib.

Table 8. Events of Interest Among Subjects Randomized to Tofacitinib and Adalimumab in Studies 1035 and 1064

Events of Interest Among Subjects Randomized to Tofacitinib and Adalimumab (Studies 1035 and 1064)										
Trial	N	Death	MACE	Lymphoma	Solid malignancy	Malignancy excl NMSC	OI	TB	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 (pooled 5 mg and 10 mg BID)										
A3921035[1]	110	0	0	0	0	0	0	0	0	0
A3921064[2]	405	0	2	0	3	3	0	2	15	19

Source: FDA statistical review team analyses
[1]Months 0-3 only
[2]Months 0-12
MACE-major adverse cardiovascular events; MNSC-non-melanoma skin cancer; OI-opportunis ic infections; TB-tuberculosis

Table 9. Incidence Rate Ratio of Events of Interest, Comparing Tofacitinib (5mg and 10mg) vs. Adalimumab During Months 0-12 + 28 Days in Study 1064

Risk of Major AEs of Interest of Tofacitinib versus Adalimumab, 0-12 Months				
	Incidence Rate Ratio (95% CI)	Mantel-Haenszel RR (95% CI)	Adalimumab[1] events / 100 py	Tofacitinib[2] events / 100 py
Death	ND	ND	0	0
MACE	0.39 (0.07, (b) (4)	0.34 (0.06, (b) (4)	1.54	0.53
Malignancy excl NMSC	1.77 (0.18	1.51 (0.16,	0.51	0.80
Lymphoma	*ND*	*ND*	*0*	*0*
Solid organ tumors	*1.77 (0.18 (b) (4))*	*1.51 (0.16, (b) (4)*	*0.51*	*0.80*
Opportunistic infections	ND	ND	0	0
Tuberculosis	ND	ND	0	0.53
Serious infections	2.59 (0.75, (b) (4)	2.52 (0.74 (b) (4)	1.54	3.98
Herpes zoster	1.98 (0.74,	1.91 (0.73	2.57	5.04

Source: FDA statistical review team analyses
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

2.6 Assessment of Safety of Tofacitinib vs. Placebo

To compare the relative safety profile of tofacitinib (5 mg and 10 mg BID) to placebo, major events of interest, common AEs and laboratory parameters were analyzed using safety data from the controlled periods of the studies, i.e. 0-3 months. This time period was selected for this comparison because it represented the true placebo-controlled data. Additional sensitivity analyses were conducted as described later in this section and in section 2.2 Methods.

2.6.1 Major Adverse Events of Interest

The major AEs of interest during the first 3 months of exposure are summarized in Table 10 and indicate a numeric imbalance in serious infections and Herpes zoster infections between tofacitinib-treated patients and placebo. Table 11 shows the corresponding estimated incidence rate ratio (IRR), Mantel-Haenszel risk ratio, and pooled incidence rate by treatment arm. Note that since the randomization ratio of patients to placebo or tofacitinib varied across trials, the pooled incidence rate of events should be considered exploratory. The pooled incidence rate 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 rate ratio and Mantel-Haenszel risk ratio, which account for differences across trials. While the difference in estimated incidence rate ratios was not statistically significant, it was consistent with the overall conclusion that tofacitinib-induced immunosuppression is associated with increased risk of serious infections and Herpes zoster infections.

Table 10. Major Adverse Events of Interest Among Subjects Randomized to Tofacitinib and Placebo, 0-3 Months

Events (N) of Interest Among Subjects Randomized to Tofacitinib and Placebo, 0-3 Months			
	Placebo N=809	**CP5 N=1336**	**CP10 N=1349**
Death	0	1	0
MACE	1	2	0
Malignancy excl. NMSC	0	1	1
Lymphoma	*0*	*0*	*0*
Solid organ tumors	*0*	*1*	*1*
Opportunistic infections	0	0	0
Tuberculosis	0	0	0
Serious infections	1	5	6
Herpes zoster	3	6	17

Source: FDA statistical review team analyses

Table 11. Incidence Rate Ratio of Events of Interest, Comparing Tofacitinib vs. Placebo During Months 0-3 Based on Randomized Treatment Assignment

Risk of Major AEs of Interest of Tofacitinib versus Placebo, 0-3 Months				
	Incidence Rate Ratio (95% CI)	Mantel-Haenszel RR (95% CI)	Placebo[1] events / 100 py	Tofacitinib[2] events / 100 py
Death	ND	ND	0	0.15
MACE	0.60 (0.01, 6.84)	0.66 (0.07, 6.07)	0.54	0.31
Malignancy excl. NMSC	ND	ND	0	0.31
Lymphoma	*ND*	*ND*	*0*	*0*
Solid organ tumors	*ND*	*ND*	*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)	0.54	1.70
Herpes zoster	2.11 (0.63, 7.06)	2.22 (0.66, 7.48)	1.63	3.55

Source: FDA statistical review team analyses
ND = not defined. Reference level is placebo
[1]A total of 183.9 patient years of exposure were observed among pa ients on placebo
[2]A total of 648.1 patient years of exposure were observed among pa ients on tofacitinib

2.6.2 Common Adverse Events

The clinical review of the original application listed the treatment-emergent AEs for the 0-12 month pooled data from the 5 confirmatory trials and the data were presented as exposure-adjusted rates. In this analysis however, the placebo group had a significantly shorter exposure (up to 3 months for the most part). To allow for more accurate comparison of the relative safety profile of the two tofacitinib dosing regimens (5 mg vs. 10 mg BID) to placebo with regard to the common AEs, the new analyses were focused on the head-to-head comparison during the controlled periods of the studies using:

- "As randomized": Patients originally randomized to tofacitinib 5 and 10 mg BID or placebo.
- "As treated": Patients originally randomized to tofacitinib 5 and 10 mg BID or placebo + patients who transitioned from placebo to tofacitinib 5 and 10 mg BID by study design at Month 3 (studies 1032 and 1045 only). This analysis did not include patients who transitioned to active treatment due to active disease because they may have a different baseline risk of developing adverse events. Similarly, this analysis did not include patients who continued to receive placebo through Month 6, as they did not have active disease and similarly may have a different baseline risk of developing adverse events.

A summary of common AEs comparing tofacitinib to placebo is presented in Table 12 below for both patient populations. Infection is the most common adverse event during the first 3 months of exposure. There is slightly greater number of patients who experienced adverse events in the "as treated" population compared to the "as randomized" population, however, the proportions are the same between the two populations. A slightly greater proportion of patients experienced infections in the tofacitinib group compared to placebo. No clear dose-dependent differences were observed between the two tofacitinib dose groups with the exception of

(b) (4)

Table 12. Summary of Common Adverse Events in Tofacitinib Randomized Controlled Trials in RA (0-3 Months Pooled Data)

Summary of Treatment-Emergent Adverse Events with ≥2% Occurrence in Any Treatment Group in Randomized Controlled Studies, Amended Analyses						
0-3 Months Pooled Safety Data	**7 Pivotal Studies (Amendment analyses)**					
	As randomized			**As treated**		
Treatment group	**PBO**	**CP5**	**CP10**	**PBO**	**CP5**	**CP10**
Number of patients, n	**809**	**1336**	**1349**	**809**	**1463**	**1476**
Total patients with ≥ 1 event, n (%)	**181 (22)**	**332 (25)**	**297 (22)**	**175 (22)**	**352 (24)**	**320 (22)**
Discontinued due to AE, n (%)	**12 (2)**	**13 (1)**	**9 (1)**	**11 (1)**	**13 (1)**	**11 (1)**
System Organ Class ≥2% in any treatment group, n (%)						
Preferred Term, n (%)						
Gastrointestinal Disorders, n (%)	**48 (6)**	**102 (8)**	**92 (7)**	**36 (4)**	**91 (6)**	**67 (5)**
Diarrhea, n (%)	*19 (2)*	*54 (4)*	*39 (3)*	*19 (2)*	*57 (4)*	*41 (3)*
Dyspepsia, n (%)	*13 (2)*	*19 (1)*	*27 (2)*	-	-	-
Nausea, n (%)	*19 (2)*	*36 (3)*	*33 (2)*	*19 (2)*	*40 (3)*	*33 (2)*
General Disorders Admin. Site Cond. , n (%)	**17 (2)**	**17 (1)**	**24 (2)**	**17 (2)**	**17 (1)**	**28 (2)**
Peripheral edema, n (%)	*17 (2)*	*17 (1)*	*24 (2)*	*17 (2)*	*17 (1)*	*28 (2)*
Infections and Infestation, n (%)	**77 (10)**	**152 (11)**	**129 (10)**	**77 (10)**	**164 (11)**	**134 (9)**
Bronchitis, n (%)	*12 (2)*	*17 (1)*	*15 (1)*	*12 (1)*	*19 (1)*	*16 (1)*
Nasopharyngitis, n (%)	*23 (3)*	*51 (4)*	*38 (3)*	*23 (3)*	*52 (4)*	*38 (3)*
Upper respiratory tract infection, n (%)	*27 (3)*	*60 (5)*	*51 (4)*	*27 (3)*	*66 (5)*	*53 (4)*
Urinary tract infection, n (%)	*15 (2)*	*34 (3)*	*27 (2)*	*15 (2)*	*37 (3)*	*29 (2)*
Investigations, n (%)	**-**	**-**	**-**	**3 (<1)**	**9 (<1)**	**29 (2)**
Blood creatine phosphokinase increased, n (%)	-	-	-	*3 (<1)*	*9 (<1)*	*29 (2)*
Musculoskeletal and Connective Tissue, n (%)	**36 (4)**	**32 (2)**	**16 (1)**	**36 (4)**	**36 (3)**	**19 (1)**
Arthralgia, n (%)	*17 (2)*	*14 (1)*	*11 (<1)*	*17 (2)*	*16 (1)*	*14 (1)*
Rheumatoid Arthritis, n (%)	*19 (2)*	*18 (1)*	*5 (<1)*	*19 (2)*	*20 (1)*	*5 (<1)*
Nervous System Disorders, n (%)	**17 (2)**	**58 (4)**	**46 (3)**	**17 (2)**	**59 (4)**	**51 (4)**
Headache, n (%)	*17 (2)*	*58 (4)*	*46 (3)*	*17 (2)*	*59 (4)*	*51 (4)*
Vascular Disorders, n (%)	**9 (1)**	**22 (2)**	**31 (2)**	**9 (1)**	**27 (2)**	**33 (2)**
Hypertension, n (%)	*9 (1)*	*22 (2)*	*31 (2)*	*9 (1)*	*27 (2)*	*33 (2)*

Source: Amendment August 2012, Tables 3.1.1 and 3.2.2

2.6.2 Laboratory Evaluations

The sponsor's amended analyses included comparisons of the laboratory parameters of interest between the treatment arms during the placebo-controlled period of the seven studies, i.e. 0-3 months. These analyses included "As randomized" and "As treated" population defined as in the Common AEs section above. The findings between the two patient populations were very similar and were consistent with the observations and conclusions from the review of the

original application.

Neutropenia

No new cases of confirmed neutropenia of <1000/mm^3 were identified in addition to the originally reported two cases.

Lymphocytopenia

(b) (4)

Consistent with the original analyses, the identified cases of mild, moderate, or severe lymphopenia were equally distributed among the treatment arms, including placebo.

Anemia

Four cases of life-threatening anemia (defined as hemoglobin decrease of ≥3 or absolute hemoglobin of ≤7 g/dL), occurred: (b) (4) two in placebo. Some dose-dependent numerical increases were seen for severe anemia (defined as hemoglobin decrease of >2 to <3 g/dL), consistent with a dose-dependent off-target toxicity of JAK2 inhibition. Same results were observed in both "As randomized" and "As treated" populations. These observations are generally consistent with the original analyses, where events of clinically significant hemoglobin decreases and severe values were small and proportionally equally distributed among the treatment arms.

Liver tests

With the inclusion of the laboratory data from the two dose-ranging studies, the amended analyses identified more cases of AST, ALT and total bilirubin elevations in all treatment arms, including in placebo. Similarly to the original analyses, most of the liver test elevations were observed in patients in the DMARD background studies with no cases of total bilirubin elevation greater than 3x ULN. No new cases of Hy's law were identified.

3. Labeling Recommendations

3.1 Proposed Labeling

(b) (4)

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

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/s/

NIKOLAY P NIKOLOV
09/26/2012

SARAH K YIM
09/26/2012

Food and Drug Administration
Center for Drug Evaluation and Research
ODE II / DPARP / HFD-570
10903 New Hampshire Ave.
Silver Spring, MD 20993

Memo to File

NDA: 203,214

SD #s: 0028, 0030, 0031

Reviewer: Nikolay P. Nikolov, M.D., CDER/OND/DPARP

Submitted: June 25, 2012

Reviewed: July 06, 2012

Product: Tofacitinib (CP-690,550), an inhibitor of Janus associated kinases (JAKs)

Proposed use: Treatment of rheumatoid arthritis (RA)

Sponsor: Pfizer

Submission: Type A Meeting package: Pfizer is requesting a Type A meeting to discuss and reach agreement on the safety analyses needed to support an assessment of the benefit-to-risk of tofacitinib and to support approval of the NDA during the first review cycle. Specifically, Pfizer proposes to discuss alternative strategies to respond to key elements of the 20 June Clinical Information Requests (IRs) in a more expeditious manner while still addressing the Agency's concerns.

Background Information*:*
After the Advisory Committee meeting on May 09, 2012, and after discussion among members of the clinical and statistics teams, several issues were identified as potential limitations with regard to the safety data presentation and analyses to better determine the safety profile of tofacitinib 5 mg and tofacitinib 10 mg. events of interest due to the complexity of the trial design (see , such as early escape options and unequal randomization. These issues included:

1. Data were analyzed for patients as randomized and not as treated. For example, patients who were on placebo and transition to active treatment at Months 3 or 6 were counted under the respective active treatment arm from that point on, instead of time "zero". Presenting the safety data for patients as treated may allow for a more precise assessment of crude proportions of patients with AEs for any given time period, even though this approach may not affect the incidence rates of AEs, adjusted for actual exposure to the drug.
2. From the submission, it was not clear whether the rules for capturing and reporting of AEs were applied consistently within the RA development program which may have introduced a bias in AE reporting. For example, a 30-day window from the last dose for capturing AE was applied only for deaths, and not other AEs.
3. Pooled safety analyses were presented for the five Phase 3 randomized controlled trials (A3921032, A3921044, A3921045, A3921046, and A3921064) and separately for the Phase 2

dose-ranging studies (A3921025, and A3921035). However, the two pivotal Phase 2 studies were of similar design and patient population to the Phase 3 studies and could be included in the pooled analyses to increase the overall sample size for assessment of controlled data.

4. Long-term extension study A3921041 included patients who completed Japanese Phase 2 studies which were not included in the pooled analyses of the controlled studies. Therefore, excluding these patients in the open label extension analyses may allow for more accurate comparison with the analyses from the controlled studies.

To address these points, the Sponsor was asked to provide additional analyses. 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 Type A meeting requested by the Sponsor is 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.

Summary of Meeting Package:

1.1. Assignment of events to treatment and pooling strategy

- Assignment of AEs to treatment: The Sponsor clarifies that events occurring on tofacitinib, regardless of previous placebo or adalimumab treatment, are attributed to tofacitinib at the administered dose.
- Assignment of AEs for time period: The Sponsor clarifies that assignment of AEs to treatment used the time period on study and not on treatment as requested in the Information Request. Pfizer has the following concerns with this approach based on study design considerations, as:
    - The tofacitinib Phase 3 trials were not designed as crossover studies. Patients were advanced, from placebo to tofacitinib only, based on disease activity at different timepoints. Pooling of these groups is therefore confounded by period effect over the short term.

Reviewer's comment: *This is a valid argument as patients who escape from placebo to active treatment due to active disease represents a group of patients with more active disease who may be more prone to developing adverse events and therefore may represent a somewhat different population than the one originally randomized to active treatment with a different baseline risk.*

    - Both patients and investigators were aware that only active drug was administered in the later portion of the clinical trials, making these time intervals essentially "open-label", further confounding the proposed pooling strategy.

Reviewer's comment: *The issue of open label is not as relevant for assessment of safety as it is for efficacy. It is unlikely that this would significantly affect the safety assessment of major events of interest. Further, the studies remain blinded and randomized to tofacitinib 5 mg and 10 mg BID.*

    - Data collection frequency was significantly different for the different time intervals, introducing acquisition bias into the proposed strategy. For example, study 1046 had visits at baseline, 2 weeks, 1 month, 2 months, 3 months, 4.5 months, 6 months, 9 months and 12 months. Thus, during Months 0-3, there were 5 visits (at baseline, 2 weeks, 1, 2, and 3 months), whereas during Months 3-6 there were 3 visits (at 3 months, 4.5 months and 6 months), and during the 6-9 month period there were 2 visits (at 6 and 9 months).

Reviewer's comment: *This is a valid argument as the different intensity of assessments may introduce bias in the AE assessment for patients who escape/transition from placebo to active treatment and pooling this way not be the most appropriate approach.*

Based on these concerns, Pfizer proposes that the most appropriate tofacitinib to placebo comparison is between originally randomized dose groups in months 0-3.

Reviewer's comment: *This is not unreasonable. We agreed internally on the 0-3 month's period to be the cleanest comparison to placebo. In addition, Pfizer will need to pool also Phase 2 studies, stratify by study, and include sensitivity analyses for months 0-3 to include "as treated" patients who transitioned from placebo to active treatment by study design (month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064), but excluding patients who escaped due to active disease. These analyses however, will only allow for tofacitinib to placebo comparison, which is needed for labeling.*

To assess the safety profile of tofacitinib 5 mg relative to 10 mg BID, for the 0-6 and 0-12 month periods of the 7 studies, with respect to major events of interest, a different approach was discussed internally, where the pooled data would be stratified by study, and analyzed using Cox proportional hazard model of:

- *Only patients originally randomized to tofacitinib 5 and 10 mg BID*
- *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).*
- *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) + patients who escaped to tofacitinib 5 and 10 mg BID due to active disease.*

These analyses represents a more scientifically sound approach to account for the complex trial design and to allow for comparative safety assessment of tofacitinib 5 mg vs. 10 mg BID. These analyses will be required for the regulatory decision on the NDA and will be conducted by the FDA statistical review team. This approach will be presented to the Sponsor as detailed in the Comment to Sponsor section to allow for further discussion at the meeting.

- Ascertainment of AEs: The reporting windows for reporting of AEs are based on company-wide standard operating procedures:
  - For deaths: All deaths are reported as SAEs and in the NDA were reported for deaths that occurred at any time after treatment and separately for deaths that occurred within 30 days of last dose. Furthermore, investigators are required, per protocol, to report all deaths (and SAEs) through 28 days after the last administration of tofacitinib, enhancing the reliability of accurate reporting of these events
  - For SAEs: The reporting period begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product.

Reviewer's comment: *If the window for reporting is 28 days after last administration, it is unclear how the Sponsor can ascertain that the death/SAE occurred within 30 days of last dose.*

  - For AEs: Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit. For adverse events and/or clinically significant laboratory abnormalities, follow-up

by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. All treatment-emergent AEs that were reported to the study databases were included in the safety summaries, regardless of when the data were collected, up until database lock for the clinical study.

- For Laboratory tests: All laboratory data that was reported to the clinical database was included in the safety summaries, regardless of when the data were collected, until database lock for the clinical study

Reviewer's comment: *From this description, it is not clear whether the 30-day post treatment applies to non-serious AEs and laboratory data and warrants clarification.*

- Incidence Rates by 6-month Time Intervals:
  - Pfizer has previously submitted to the NDA the non-cumulative incidence of the following safety events of interest broken down by 6-month intervals: Serious infections, Herpes zoster, Malignancies, Lung cancer, Breast cancer, and NMSC.
  - Pfizer proposes to provide similar analyses for opportunistic infections, tuberculosis, and gastrointestinal perforations

Reviewer's comment: *This is acceptable.*

  - Pfizer also proposes not to break down these periods to 3-month intervals.

Reviewer's comment: *This is acceptable, even though we have not specifically asked for this.*

1.2 Pfizer proposes not include the Phase 2 data in the pooled analyses with the justification that it represents only about 10% of the safety database and is unlikely to add substantially to the understanding of the benefit:risk assessment of tofacitinib.

Reviewer's comment: *Studies 1025 and 1035 however, are of sufficiently similar design and patient population to the Phase 3 studies and warrant inclusion in the integrated analyses.*

Comments to Sponsor:

1. Pfizer believes that the safety analyses agreed in the pre-NDA meeting and provided in the original submission are optimal for assessing the safety of tofacitinib. Based on our understanding of the Agency's current concerns, Pfizer proposes that supplementation of the NDA with alternative additional analyses will answer the key elements of the questions posed by the Agency in its 4 June IR (modified 20 June). Does FDA concur?

FDA Response:
We acknowledge your methodological considerations, but we do not agree with your proposal. One difference is the studies for inclusion in the safety analysis. Studies 1025 and 1035 are of sufficiently similar design and patient population to the Phase 3 studies. Therefore, we request that they are included in the integrated safety analyses. We do not agree with inclusion of the Japanese studies due to differences in patient population, background medication use, etc.

For transparency, we provided the following information on analyses we plan to conduct with the safety data.

1. **To assess the safety profile of tofacitinib 5 mg BID relative to 10 mg BID for the 0-6 and 0-12 month periods of the 7 studies, with respect to events of interest (listed in Question 1.4), stratified by study, using Cox proportional hazard model of:**
    a) **Only patients originally randomized to tofacitinib 5 and 10 mg BID**
    b) **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).**
    c) **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) + patients who escaped to tofacitinib 5 and 10 mg BID due to active disease.**
2. **We plan on comparing the safety profile of tofacitinib, relative to adalimumab, with respect to events of interest (listed in Question 1.4) using data from studies 1035 and 1064, separately.**

1.1. Assignment of events to treatments and pooling strategy:

FDA Response:
We agree that the least confounded tofacitinib to placebo comparison is between "originally randomized" dose groups in months 0-3. Summary statistics (counts and %) should be presented pooled to include all 7 studies. All statistical tests for events of interest (listed in Question 1.4) should be stratified by study. In addition, sensitivity analyses should be conducted, for months 0-3 including patients who transitioned from placebo to active treatment by study design (month 3 for studies 1032 and 1045) in months 3 to 6.

Your proposal to provide Kaplan-Meier plots by randomized sequence over 0-12 months for the 7 studies is acceptable.

From the description of reporting windows (Appendix 1 in the briefing package) several points need clarification:

- **If the window for reporting of death and SAE is 28 days after last dose administration,**

how can you ascertain that the event occurred within 30 days of last dose?

- **It is not clear whether the 30-day post treatment window applies to non-serious AEs and laboratory tests.**

1.2. Studies for inclusion in the safety analyses

FDA Response:
Refer to the Comments to Question 1 above.

1.3. Time periods and windows

FDA Response:
Refer to the Comments to Question 1.1 above.

1.4. Events for analysis

FDA Response:
Your proposal to include the following events in the requested analyses: death, lymphoma, solid organ tumor (malignancies), opportunistic infection, tuberculosis, serious infections, herpes zoster, and CV MACE events is acceptable.

2. Could the Agency provide insight into how the projected timelines for responding to the June information requests could impact the review of the NDA? For example, as long as the totality of the data support product safety and efficacy, could some of the desired analyses be performed as a post-approval commitment and be submitted to the agency as a labeling supplement after initial NDA approval?

Pfizer's response (to June4th and June 20th IRs) could not be provided to the Agency prior to September 2012, approximately 1 month after the PDUFA Action date. What would the implications be on the review of the NDA?

Following the teleconference on 19 June and the Clinical IR received on 20 June, Pfizer has considered the key components of the request and has made a proposal which Pfizer believes will address the intent of the 4 June and 20 June IRs. This proposal would result in submission of additional data by end of July 2012. If this proposal is reasonable and suitable to support an approval decision, would this timing permit completion of the review within the current PDUFA timeline, with any additional data provided post-approval?

FDA Response:
As a clarification, the June 20th IR supersedes the June 4th IR. The June 20th Clinical IR is focused on the information required for regulatory decision making. Therefore, the required analyses should be submitted as soon as possible to allow for a determination of a regulatory action on the application by the PDUFA goal, August 21, 2012.

Appendix 1. Key Design Features of NDA 203,214 Phase 2 and 3 Randomized Controlled Studies for Efficacy and Safety

Key Design Features of the Phase 3 Studies in RA for Efficacy and Safety

Protocol	Patient Population	Design *Duration*	Enrolled *Randomization*	Treatment Arms (transition and escape for NR)	Primary Endpoints	Timepoint
Patients with incomplete response to prior TNF inhibitor						
A3921032	Moderate-to-severe RA TNF-IR, Stable background MTX	R, DB, PC Phase 3 *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	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
Patients with incomplete response to MTX or other DMARDs						
A3921044	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 3 *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	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6
A3921045	Moderate-to-severe RA DMARD-IR, No background to Month 3	R, DB, PC Phase 3 *6 months*	610 *4:4:1:1*	CP 5 mg BID CP 10 mg BID PBO → CP 5 mg BID @ Mo 3 PBO → CP 10 mg BID @ Mo 3	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
A3921046	Moderate-to-severe RA DMARD-IR, Stable background DMARDs[#]	R, DB, PC Phase 3 *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	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
A3921064	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, AC Phase 3 *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	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6

Key Design Features of the Pivotal Phase 2 Studies in RA for Efficacy and Safety

Protocol	Patient Population	Design *Duration*	Enrolled *Randomization*	Treatment Arms (transition and escape for NR)	Primary Endpoints	Timepoint
A3921025	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 2, 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 OD (→CP 5 mg BID @ Mo3 if NR)+ MTX Placebo (→CP 5 mg BID @ Mo3 if NR)+ MTX	ACR20	Month 3
A3921035	Moderate-to-severe RA DMARD-IR, No background therapy	R, DB, AC Phase 2, Dose-ranging *6 months*	384 *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)	ACR20	Month 3

Source: Summary of Clinical Efficacy, Clinical Study Reports for studies A3921032, A3921044, A3921045, A3921046, A3921064

*-One year efficacy data submitted for Study A3921044; [#]-Background DMARD therapy in Study A3921046: 84% of subjects on MTX, ~1/2 on combination DMARDs; AC-active control (adalimumab, study A3921064); BID-two times daily; DMARDs-disease-modifying anti-rheumatic drugs; IR-incomplete response; MTX-methotrexate; mTSS-modified total Sharp Score; NR-non-responder defined as patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts over baseline at Month 3 visit; PBO-placebo; PC-placebo (add-on for studies A3921032, A3921044, A3921046, A3921064)-controlled; SC-subcutaneous; TNF-tumor necrosis factor. CP=CP-690,550/tofacitinib

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/s/

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07/06/2012

SARAH K YIM
07/06/2012

CLINICAL REVIEW

Application Type	NDA
Application Number	203,214
Priority or Standard	Standard
Submit Date	October 21, 2011
Received Date	October 21, 2011
PDUFA Goal Date	August 21, 2012
Division / Office	DPARP/OND
Reviewer Name	Nikolay P. Nikolov, M.D.
Review Completion Date	June 26, 2012
Established Name	Tofacitinib (CP-690,550)
Proposed Trade Name	Xeljanz (Proposed)
Therapeutic Class	Janus kinase (JAK) inhibitor
Applicant	Pfizer
Formulation(s)	Tablets
Dosing Regimen	5 or 10 mg BID
Indication	Rheumatoid Arthritis (RA)
Intended Population	Moderate-to-Severe RA

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommend approval of NDA 203,214 for tofacitinib 5 mg BID with revisions to the proposed labeling to include revision of the target patient population, as outlined in Section 9.2 Labeling Recommendations.

1.2 Risk Benefit Assessment

Brief Overview of the Clinical Program

Tofacitinib citrate film-coated tablets are an immediate-release (IR) formulation, intended to inhibit Janus associated kinases (JAK) family of kinases. JAKs mediate signal transduction activity through the common gamma chain family of cytokines including IL-2, -4, -7, -9, -15, and 21 which are integral to lymphocyte activation, proliferation and function, and play a role in pathogenesis of the target disease, rheumatoid arthritis (RA).

This NDA is comprised of 5 Phase 3, randomized, double blind, placebo-controlled trials, designed to assess clinical efficacy and safety of tofacitinib in the target population of adult patients with moderately-to-severely active established RA. The trials studied a range of patients, from those with more typical RA who have failed traditional DMARDs, mostly MTX (A3921044, A3921045, A3921046, an A3921064), to more refractory RA patients who have had inadequate response to prior TNF inhibitors (A3921032). Four studies assessed tofacitinib as an add-on in combination with MTX (A3921032, A3921044, and A3921064) and in combination with traditional DMARDs (A3921046). One study assessed tofacitinib as a monotherapy, following washout of other DMARDs (A3921045). Dose-selection and additional efficacy and safety information were derived from Phase 2 dose-ranging studies A3921025 (MTX background therapy) and A3921035 (monotherapy). Two of the Phase 2 and 3 studies had an adalimumab active comparator arm.

Summary of Efficacy Review and Conclusions

The five Phase 3 randomized controlled studies, A3921032, A3921044, A3921045, A3921046, an A3921064, provided efficacy data to assess the effect of tofacitinib on signs and symptoms of disease and physical function, as measured by three primary efficacy endpoints (in sequence):

1. Signs and symptoms as measured by ACR 20 at Month 3 (A3921045 and 1032) or at Month 6 (A3921046 and A3921064);
2. Physical function as measured by the HAQ-DI change from baseline at Month 3;
3. Incidence of DAS <2.6 at Month 3 (A3921045 and A3921032) or at Month 6 (A3921046 and A3921064).

Only a single study (A3921044) also provided data to assess the effect of tofacitinib on radiographic progression in addition to the other primary endpoints.

All studies had pre-specified statistical analysis plans accounting for multiplicity and handling of missing values.

Review of the efficacy data from these studies is summarized below:

1. Effects of tofacitinib on signs and symptoms of RA:
   All five Phase 3 studies provided consistent evidence of improvement on signs and symptoms of RA. In all studies, a statistically significantly higher proportion of patients in the tofacitinib group (CP5 or CP10) achieved ACR20 response compared to placebo. In addition, three studies (A3921032, A3921046, and A3921064) showed a significantly higher proportion of patients in the tofacitinib group (CP5 or CP10) achieved DAS28-4(ESR) <2.6 response compared to placebo. Major secondary endpoints evaluated in this review include the proportion of ACR50 and ACR70 responders and mean change from baseline in the individual ACR components. Results for these secondary endpoints are consistent with the primary results and support the conclusion that tofacitinib is efficacious in the treatment of RA. The clinical benefit of tofacitinib 5 mg BID and 10 mg was generally comparable. The observed numerical differences in ACR20 response rates between the two doses were small and of questionable clinical significance. Further the ACR50 and ACR70 responses were not consistently dose-dependent across the randomized controlled studies.

2. Effects of tofacitinib on physical function:
   Four studies (A3921032, A3921045, A3921046, and A3921064) also provided evidence of improvement in physical function as measured by HAQ-DI. Based on FDA statistical reviewer analyses, in all four studies, a statistically significant difference in HAQ-DI score was observed in patients treated with tofacitinib 5 mg (except in study A3921064) or tofacitinib 10 mg compared to placebo. The clinical benefit of tofacitinib 5 mg BID and 10 mg was generally comparable. The observed numerical differences in the mean change from baseline in HAQ-DI between the two doses were smaller than the minimal clinically meaningful difference.

3. Effects of tofacitinib on structural damage progression (study A3921044):
   It is not possible to make definitive conclusions about the treatment effect of tofacitinib on structural damage progression. Issues driving the uncertainty regarding these results include:
   a. A low amount of progression was observed in the placebo control group, limiting the treatment effect size that could be demonstrated
   b. The small apparent treatment effect size is susceptible to change depending on analytical approach, missing data, and missing data imputation method, and in this case appears to be driven by few extreme observations
   c. The data are not consistent with respect to dose (5 mg vs. 10 mg BID)
   d. Corroborating data (i.e., from another study) are not available to help resolve residual uncertainty.

In conclusion, the Phase 3 RA program provided replicate evidence of clinically meaningful efficacy (superiority) of tofacitinib 5 mg and 10 mg BID over placebo as monotherapy (A3921045), and in combination with MTX (A3921032, A3921044, and A3921064), or with DMARDs (A3921046) in the domains of:

- Signs and symptoms of RA as measured by ACR20, 50 and 70 responder rates and DAS28-4(ESR)<2.6 responder rates supporting the claim of improvement in Signs and Symptoms of RA
- Physical function as measured by the change from baseline in HAQ-DI, supporting the claim of improvement in physical function in RA

The radiographic data from study A3921044 however, did not provide a substantial evidence of efficacy to support a claim of radiographic benefit.

Summary of Safety Review and Conclusions

Safety data in this NDA submission were derived from Phase 2, 3, and open label, and long-term extensions (LTE) studies in RA. As of March 29th, 2011 (clinical data cut-off date), the RA Phase 2, 3 and LTE studies included 4816 patients across all treatment groups with 5716 patient-years of exposure to all doses as shown on Table 28. The submitted exposure data represents a safety database that meets the Agency's previously expressed expectations for a pre-marketing exposure of at least 1000 to 1500 patients treated for a minimum of one year to allow for reasonable safety assessment of a chronic immunosuppressive therapy with tofacitinib for the intended use. The overall study population in the RA development program was representative of the target patient population of adult patients with established moderately-to-severely active RA who have had inadequate response to at least one DMARD. Additional safety information was provided for adverse events of interest from studies in non-RA development programs, such as prevention of renal allograft rejection.

The five Phase 3 randomized controlled studies were of sufficiently similar design to allow for pooled analyses of the controlled data, by treatment group. Long-term safety

information from RA patients treated in the open-label LTE studies was also provided in this summary. To account for the differences in exposure among treatment groups, exposure-adjusted AE incidence rates are calculated as the number of patients with a new event (for that time period), divided by the total exposure in that treatment group in the pooled cohort, and multiplied by 100 (i.e., rate per 100 patient-years). This allowed for a standardized comparison of major safety events across treatment groups in the pooled safety analyses.

The review of tofacitinib clinical safety database identified several areas of major safety concerns associated with tofacitinib administration:

1. An increased risk of solid and hematologic malignancies, including lymphoproliferative disorder (LPD) indicating a potential safety signal.
    a. The risk of malignancy appeared to increase in a dose and time-dependent fashion. The exposure-adjusted incidence rate of malignancy:
        i. (b) (4)
            - Phase 3 studies (b) (4). 0.6 events per 100 pt-yrs) and
            - LTE studies (b) (4). 1.0 events per 100 pt-yrs)
        ii. Increased with prolonged tofacitinib exposure (from 0.8 events per 100 pt-yrs for <6 months exposure to 1.4 events per 100 pt-yrs for >24 months exposure)
    b. There appears to be an increased risk of lymphoma in particular.
        i. Seven cases of LPD occurred, all in tofacitinib-treated patients. Two of the cases occurred in highly atypical locations (CNS and breast)
        ii. Five lymphoma cases in 218 (2.3%) renal transplant patients who had received 15 mg BID. Four of 5 patients were on 15 mg BID for 6 months and one of 5 patients was on 15 mg BID for 3 months prior to maintenance treatment with 10 mg BID.
        iii. Lymphomas occurred in the highest dose group (3 of 8, 37%) of the chronic toxicology study in monkeys

2. An increased risk of serious infections, including opportunistic infections, identifying a profile of tofacitinib of a major immunosuppressant.
    a. Serious infections associated with tofacitinib use were common in the RA program with pneumonia being the most common (occurring only in tofacitinib-treated patients). These infections also appeared to be dose- and exposure-related.
    b. Tuberculosis occurred only in tofacitinib treated patients in a clearly dose-dependent fashion.
    c. Opportunistic infections were not uncommon and included cases of cryptococcal infections, Pneumocystis jiroveci pneumonia, and BK virus encephalitis, which are seen exclusively in severely immunocompromized

patients.

3. Laboratory abnormalities, to include abnormal hematologic parameters, lipid parameter changes, liver enzymes, and serum creatinine elevation. Tofacitinib administration was associated with:
    a. Dose-dependent sustained neutropenia and progressive lymphopenia. Severe lymphopenia was also associated with increased risk of infections.
    b. Dose-dependent sustained elevations in total, LDL, and HDL cholesterol. Total and LDL cholesterol levels reversed with lipid-lowering therapy. These lipid abnormalities did not appear to translate into increases in cardiovascular events.
    c. Liver enzymes elevations which were observed mostly in patients on background DMARDs and significant liver abnormalities were uncommon. However, in one case, drug-induced liver injury could not be excluded and the case is considered to meet Hy's law criteria.
    d. Dose-dependent small but significant elevations of mean serum creatinine. These increases were associated with an increasing incidence of patients meeting the protocol criteria for discontinuation due to creatinine increases (confirmed creatinine increases of more than 50% of baseline). There did not otherwise appear to be an increase in the proportion of patients experiencing serious adverse events of renal failure.

In conclusion, the safety data from tofacitinib RA development program identified the profile of a potent immunosuppressant, associated with inherent risks, such as serious infections, including opportunistic infections and tuberculosis. Tofacitinib administration was also associated with malignancy (excluding non-melanoma skin cancer) based on the increasing incidence rates in a dose-dependent manner and with prolonged duration of exposure likely due to a dose- and time-dependent immunosuppression. Gastrointestinal perforations and interstitial lung disease were observed in the clinical trials, however the relative risk and role of tofacitinib treatment in the development of these adverse events is not well defined. Treatment with tofacitinib resulted in dose-dependent changes in laboratory parameters, such as sustained neutropenia and progressive lymphopenia, sustained elevations in total, LDL, and HDL cholesterol, small but significant elevations of mean serum creatinine, and liver enzymes elevations. While most of these were not associated with clinical adverse events in the controlled setting of the clinical trials, severe lymphopenia was associated with increased risk of infections. One case of Hy's law occurred with tofacitinib treatment. Using the estimate of severe drug-induced liver injury as occurring at $1/10^{th}$ the rate of Hy's Law cases, 1 case of severe liver injury might be expected in 50,000 patients treated with tofacitinib.

Most of these potential safety issues are seen with other traditional and biologic DMARDs and have historically been handled via appropriate labeling and risk evaluation and mitigation strategies, which should also be adequate in this case. The clinical trial experience has been extensive, but may not be sufficient to capture the full

extent of safety concerns that may arise with long-term JAK inhibition with tofacitinib, which is a new molecular entity. Therefore, a prospective long-term safety assessment is warranted, which will be consistent with the recommendations form the Arthritis Advisory Committee panel.

Due to the complexity of the trial design, such as early escape options and unequal randomization, the following issues were identified as potential limitations with regard to the safety data presentation and analyses:

1. Data were analyzed for patients as randomized and not as treated. For example, patients who were on placebo and transition to active treatment at Months 3 or 6 were counted under the respective active treatment arm from that point on, instead of time "zero". Presenting the safety data for patients as treated may allow for a more precise assessment of crude proportions of patients with AEs for any given time period, even though this approach may not affect the incidence rates of AEs, adjusted for actual exposure to the drug, as discussed in this document. One important consideration with using this approach however, is that patients who escape from placebo to active treatment due to active disease represents a group of patients with more active disease who may be more prone to developing adverse events and therefore, and may represent a somewhat different population than the one originally randomized to active treatment.
2. It was not clear from the submission whether the rules for capturing and reporting of AEs were applied consistently within the RA development program which may introduce a bias in AE reporting. For example, only deaths were reported if they occurred on treatment or within 30 days of last dose.
3. Only safety data from the five Phase 3 randomized controlled trials were included in the pooled safety analyses (A3921032, A3921044, A3921045, A3921046, and A3921064). However, the two pivotal Phase 2 dose-ranging studies (A3921025, and A3921035) were of similar design and patient population and could be included in the pooled analyses to increase the overall sample size for assessment of controlled data.
4. Long-term extension study A3921041 included patients who completed Japanese Phase 2 studies which were not included in the pooled analyses of the controlled studies. Therefore, excluding these patients in the open label extension analyses may allow for more accurate comparison with the analyses from the controlled studies. One caveat of this approach however, is that important safety information may be excluded.

To address these points, the Sponsor was asked to provide additional analyses which are ongoing at this time and are not included in this document. These additional analyses may serve as sensitivity analyses and provide more quantitative safety information for the different time periods in the controlled studies, particularly for more common adverse events. However, since the major safety events associated with this application, such as malignancy and serious infections, are rare that tend to occur with prolonged exposure beyond the limited placebo-controlled period of the studies, the revised safety analyses are not expected to substantially change the overall conclusions

on safety and do not preclude the risk benefit analysis for tofacitinib discussed below. Long-term safety data would still need to be collected prospectively to further address the potential long-term toxicity associated with tofacitinib use.

Risk Benefit Overview

Tofacitinib is a new molecular entity and if approved, would be the first in class of drugs, Janus associated kinase (JAK) inhibitors, for the treatment of patients with RA. Importantly, tofacitinib is an oral agent providing potential advantages over exiting injectable DMARDs.

At both tested doses, 5 mg and 10 mg BID, tofacitinib demonstrated clinical benefit on signs and symptoms and physical function in patients with established moderately-to-severely active RA, both as a monotherapy and in combination with MTX or other traditional DMARDs, with results in the range of approved biologic DMARDs such as TNF inhibitors. Tofacitinib, however did not show a clear evidence of radiographic benefit in this patient population, based on the results of a single study.

Tofacitinib has a safety profile of a potent immunosuppressant associated with increased risk of serious infections, including opportunistic infections and tuberculosis, solid and hematologic malignancy, possible idiosyncratic hepatotoxicity, and dose-dependent laboratory abnormalities, among which elevated LDL, HDL and total cholesterol.

Table 1. describes the estimates of potential benefit, expressed as number-needed-to-treat (NNT) vs. potential risks, expressed as number-needed-to-harm (NNH). These calculations were based on comparison with pooled placebo data in the controlled period of the 5 Phase 3 studies. For NNT, a lower number indicates more “benefit”, and for NNH, a lower number indicates more “harm”.

Based on average proportion of responders in these studies, as few as 3 patients would need to be treated to have at least one patient experiencing a benefit on the level of an ACR20 response, and as few as 6 patients would need to be treated to have at least one patient experiencing a benefit of the magnitude of an ACR70 response.

During the 12 month controlled period of the Phase 3 studies, malignancy (excluding NMSC), serious infections, including tuberculosis, and opportunistic infections were identified as safety signals associated with the use of tofacitinib. With the exception of serious infections and opportunistic infections, which appeared to be similar with the 5 and 10 mg dose regimens, exposure-adjusted adverse events of interest appeared to occur more frequently in patients receiving 10 mg tofacitinib, resulting in lower numbers needed to “harm.” Importantly, in the long-term extension period the rates of serious infections and malignancy increased in a dose-dependent manner, while the rates of the other major events remained stable or decreased.

Table 1. Risk-Benefit Overview of Tofacitinib

Risk-Benefit Overview of Tofacitinib		
	CP5	**CP10**
NNT (95% CI)		
ACR20	4 (3, 5)	3 (3, 4)
ACR50	5 (4, 6)	4 (3, 4)
ACR70	8 (7, 10)	6 (5, 7)
NNH (95% CI)		
Malignancy (excl. NMSC)	181 (75, ∞)	(b) (4)
Serious Infections	58 (29, ∞)	67 (32, ∞)
Tuberculosis	n.a.	(b) (4)
Opportunistic infections	226 (88, ∞)	228 (89, ∞)
MACE	1995 (133, ∞)	600 (96, ∞)
GI perforations	n.a.	455 (125, ∞)

Source: Calculations by statistical reviewer, Dr. Yongman Kim, based on comparison with pooled placebo data using exposure-adjusted incidence rates from the 12-month pooled safety data from the five randomized controlled studies (A3921032, A3921044, A3921045, A3921046, and A3921064)
CP5 and CP10 columns represent data for patients as randomized and do not include patients who advanced to tofacitinib after receiving placebo for 3 to 6 months; ACR20, 50 and 70 responses were combined at the primary time point assessment;
NNT- number needed to treat, NNH-number needed to harm (0-12 months); n.a.-cannot be calculated because no cases were reported and the exposure-adjusted incidence rates were zero.

In conclusion, the overall risk to benefit profile of tofacitinib in RA appears to be favorable, with many more patients potentially benefiting from treatment compared to those at potential risk. Most of the potential safety issues such as malignancy, tuberculosis, serious and opportunistic infections, hepatotoxicity and laboratory abnormalities are seen with other traditional and biologic DMARDs and have historically been handled via appropriate labeling and risk evaluation and mitigation strategies, which should also be adequate in this case.

Dosing Recommendations

The clinical benefit of tofacitinib 5 mg BID and 10 mg was generally comparable. Numerical differences were observed in ACR and DAS28 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 relatively small and of questionable clinical significance. (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is warranted and should assure communication to healthcare providers about the risks of:

- malignancy,
- serious infections, including opportunistic infections, and tuberculosis
- changes in laboratory parameters, such as decreases in neutrophil counts, lymphocyte counts, hemoglobin levels, increases in low density lipoprotein cholesterol (LDL-c), serum creatinine, transaminase elevations and potential hepatotoxicity associated with tofacitinib.

The risks of tofacitinib treatment, including malignancy, serious infections, hepatotoxicity, and necessity of laboratory monitoring should also be communicated to patients.

1.4 Recommendations for Postmarket Requirements and Commitments

- A long-term prospective safety study:
  A study of both tofacitinib doses 5 mg and 10 mg BID along with an active comparator to assess the safety for major AEs of interest that may manifest after prolonged tofacitinib exposure, such as cardiovascular adverse events, malignancies, serious infections, and hepatotoxicity. Such a study would help addressing residual uncertainties regarding the long-term safety of tofacitinib and would be consistent with the recommendations by the Arthritis Advisory Committee members for collecting long-term safety data as discussed in Section 9.3 Advisory Committee Meeting.

- Studies to achieve compliance with PREA:
  Polyarticular juvenile idiopathic arthritis (pJIA) is considered to be the pediatric equivalent of adult RA. Therefore, in accordance with the Pediatric Research Equity Act (PREA) of 2003, studies in pJIA are mandated. With this submission,

the applicant has requested a deferral for patients age 2-17 with pJIA, and a waiver for children 0-2, since pJIA is extremely rare in this age group. These requests have been granted for other therapeutic biologics, as, for ethical reasons, it is desirable to have an adequate experience with the safety profile of a treatment in adults before proceeding with extensive studies in children. The applicant has already discussed details of their proposed Phase 3 program in pJIA and systemic juvenile idiopathic arthritis (sJIA) with the Agency. The (b) (4) The proposed study appears adequate to meet the requirements of PREA.

2 Introduction and Regulatory Background

Rheumatoid arthritis (RA) is a symmetric inflammatory polyarthritis, affecting approximately 1% of the adult population. Its etiology remains elusive, but pathogenic mechanisms have been studies extensively, and a number of effector mechanisms have been identified. Complex interactions between putative environmental triggers and epigenetic factors in genetically susceptible individuals lead to a multi-step process of loss of self-tolerance and abnormal innate and adaptive immune responses. This process involves multiple pro-inflammatory cytokines such as TNF-alpha, IL-1, and IL-6, intracellular signaling pathways (NF-κB, tyrosine kinases, such as JAK and Syk, and others), activated T and B lymphocytes, mononuclear phagocytes, fibroblasts and others. This cascade of events leads to synovial inflammation and proliferation resulting in joint pain and swelling, autoantibody production (rheumatoid factor and anti-citrullinated protein antibodies), bone erosions, joint space narrowing and joint destruction, and systemic features, including inflammation, cardiovascular, pulmonary, musculoskeletal, and other manifestations. Sustained RA activity results in irreversible joint destruction, functional impairment and increased morbidity and mortality, and significantly impacts society and the health care system.[1]

2.1 Product Information

Tofacitinib is intended to be a selective inhibitor of Janus associated kinases (JAK) family of kinases, which mediate signal transduction activity through the common gamma chain family of cytokines including IL-2, -4, -7, -9, -15, and 21. These cytokines are integral to lymphocyte activation, proliferation and function.

In kinase assays, tofacitinib inhibited JAK1, JAK2, JAK3 and, to a lesser extent, TyK2. The broad effect of JAK inhibition on multiple cytokine pathways provided the rationale

1 Scott SL and Steer S, The course of established rheumatoid arthritis, Best Practice & Research Clinical Rheumatology 2007, 21(5):943-967

for developing CP-690,550 as a treatment for RA in which lymphocyte activation and proliferation play a pathogenic role.

Tofacitinib citrate film-coated tablets are an immediate-release (IR) formulation designed to disintegrate and dissolve rapidly under physiological conditions in the stomach.

2.2 Tables of Currently Available Treatments for Proposed Indications

Many effective therapies have been already approved for the treatment of patients with RA as listed in Table 2 and Table 3. The classes of drugs used for treatment of RA include: nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, corticosteroids, and disease modifying anti rheumatic drugs (DMARDs). NSAIDs and COX-2 inhibitors are utilized primarily for symptomatic relief of pain and are useful co-therapies because of their anti-inflammatory and analgesic effects. Corticosteroids are versatile agents with potent anti-inflammatory effects, but their use is limited by long-term toxicity.

DMARDs are a diverse group of therapeutic agents that reduce signs and symptoms of RA as well as slow disease progression or produce a disease-modifying effect by retarding radiographic progression of joint damage. Methotrexate is the most commonly used DMARD because of its proven efficacy, and well-understood long term effects. Large molecule biologic products are considered to be DMARDs when they have been shown to inhibit progression of joint damage, which is the case for most of them (Table 3). In the treatment of RA, methotrexate is often the initial DMARD used and then combined with other DMARDs, commonly biologics, to enhance clinical effect.

Table 2. Small Molecule DMARDs Approved for Marketing in the United States

Product Name (Trade Name) [Sponsor]	Mechanism of Action in RA	Year of First Approval for RA
Sulfasalazine (AZULFIDINE) [Pfizer]	Anti-inflammatory and antimicrobial	1950
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	Anti-metabolite	1953
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	Interference with antigen processing (?)	1955
Azathioprine (IMURAN) [Prometheus Labs]	Cytostatic	1968
Penicillamine (CUPRIMINE) [Alton]	Unknown	1970
Auranofin (RIDAURA) [Prometheus Labs]	Unknown	1985
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]	T-cell activation inhibitor	1995, 1990
Leflunomide (ARAVA) [Sanofi-Aventis]	Anti-metabolite	1998

Table 3. Biologic DMARDs Approved for Marketing in the United States

Product Name (Trade Name) [Sponsor] {year} *	Presentation and *ROA* †	Description and *MOA* §	Claims for adult RA #
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Vial 25 mg Prefilled syringe 25 or 50 mg/mL SureClick Autoinjector 50 mg/mL *SC injection*	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Infliximab (REMICADE) [Centocor] {1999}	Vial 10 mg/mL *IV infusion*	Chimeric IgG1 k mAb *TNF inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Anakinra (KINERET) [Amgen] {2001}	Prefilled syringe 10 mg *SC injection*	Recombinant polypeptide *IL-1 receptor antagonist*	Clinical response Physical function response Radiographic response
Adalimumab (HUMIRA) [Abbott] {2002}	Prefiled syringe 40 mg/0.8 mL Humira Pen 40 mg/0.8 mL *SC injection*	Human IgG1 k mAb *TNF inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Lyophilized powder 250 mg/vial *IV infusion*	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor*	Clinical response Major clinical response Physical function response Radiographic response
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Vial 10 mg/mL *IV infusion*	Chimeric murine/human IgG1 k mAb *Anti CD20, B cell depletor*	Clinical response Physical function response Radiographic response
Golimumab (SIMPONI) [Centocor] {2009}	Prefiled syringe 50 mg/0.5 mL SmartJect Autoinjector 50 mg/0.5 mL *SC injection*	Humanized IgG1 k mAb *TNF inhibitor*	Clinical response Physical function response
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder 200 mg/vial *SC injection*	Humanized Fab fragment *TNF inhibitor*	Clinical response Major clinical response Radiographic response Physical function response
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Vial 20 mg/mL *IV infusion*	Humanized IgG1 k mAb *IL-6 receptor inhibitor*	Clinical response Radiographic response Physical function response

*Year = Year of first approval for RA
†ROA = Route of administration
§MOA= Mechanism of action
#Claims: Clinical response (or reducing signs and symptoms) assessed by ACR 20, 50, and 70 response over 6 month; Major clinical response defined as achieving ACR 70 response over 6 months period; Physical function response (or improving physical function) assessed by health assessment questionnaire (HAQ) over at least 6 month period; Radiographic response (or inhibiting progression of structural damage) assessed radiographically by Total Sharp Score (TSS) and sometimes its components of erosion score (ES) or joint space narrowing (JSN) score over at least 12 months

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

One conundrum associated with the assessment of efficacy in RA is the possible dissociation between clinical and radiographic outcomes. Radiographic progression may occur in people who have very low apparent disease activity and patients with clinical disease activity may have no evidence of radiographic progression.[2] Thus, documentation of a benefit of treatment on structural damage progression has been an important goal of clinical development programs for new products proposed for RA, particularly if the product has a novel target. This has become an increasingly important aspect of the risk-benefit assessment for new RA treatments in light of the many approved treatments that have documented beneficial effects in inhibiting the progression of structural damage.

2.3 Availability of Proposed Active Ingredient in the United States

Tofacitinib is not currently commercially available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Tofacitinib is in the same drug class with ruxolitinib (Jakafi), which is another Janus associated kinase (JAK) inhibitor, targeting JAK1 and JAK2, approved for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in November 2011. The major warnings and precautions identified in ruxolitinib's label include thrombocytopenia, anemia, neutropenia and infections.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

At the time the investigational new drug application (IND) for tofacitinib was submitted in 2004, Phase 1 clinical data were already available. Dose-ranging study A3921019 was the initial protocol submitted to the IND, which proposed monotherapy with CP-690,550 at doses of 5, 15, and 30 mg BID for a duration of 6 weeks. Lack of nonclinical coverage for the proposed doses was noted at that time. However, because there were pre-existing human data in approximately 180 patients at doses up to 50 mg BID for 14 days, the Agency at that time made an internal decision that the clinical data were adequate to support the safety of proceeding with the study, despite the lack of nonclinical support for all of the proposed doses, which would typically be required.

In January 2007, the Agency provided written feedback regarding the proposed design of Study A3921025 and an extension study. Study A3921025 included proposed doses of 1, 3, 5, 10, 15 mg BID and 20 mg QD, to be given with stable background methotrexate (MTX) for a duration of 6 months. The design of the studies was

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

considered generally acceptable, although it was noted that the nonclinical data appeared to only support chronic dosing in patients up to 5 mg BID. The review team at that time determined that previous clinical experience appeared to support the ability to proceed with the proposed studies.

In December 2008, an End of Phase 2 (EOP2) meeting took place to discuss the CP-690,550 development program. The Agency generally agreed with the proposed Phase 3 program elements and endpoints. Discussions included:

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

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

2.6 Other Relevant Background Information

There is no other pertinent background information.

3 Ethics and Good Clinical Practices

The Sponsor stated in the NDA submission that the studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants.

Written informed consent was obtained prior to the subject entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

3.1 Submission Quality and Integrity

3.1.1 OSI Inspection

The NDA submission was in electronic common technical document (eCTD) format and was adequately organized. The Office of Scientific Investigations (OSI) was consulted to conduct routine sponsor/monitor inspection for tofacitinib, as a new molecular entity.

The inspection audited all 5 Phase 3 studies, A3921032, A3921044, A3921045, A3921046, and A3921064. Three clinical sites (one in US, one in Brazil, and one in Poland), which were among the highest enrollers of patients and recruited for four of the five Phase 3 NDA studies, were selected for inspection. OSI inspection found minor and sporadic regulatory deficiencies and deficiencies in documentation at select study sites, but concluded that the studies appear to have been conducted adequately and the nature of the deficiencies is unlikely to significantly impact data integrity and reliability. OSI also concluded that the applicant appears to have taken appropriate preventive and corrective actions in response to the Form 483 findings. OSI inspection of the Sponsor did not identify major deficiencies in data quality and integrity and concluded that based on review of inspectional findings for these clinical investigators and the Sponsor, the study data collected appear generally reliable in support of the requested indication.

3.1.2 DAS28 calculation error

About three months into the NDA review, Pfizer informed the Division of identified programming error in the tofacitinib NDA submission. The error was related to the calculation of the 4 component Disease Activity Score (DAS28-4(ESR)) and its derivative values. Specifically, the Physician Global Assessment score was included in the calculation instead of the Patient Global Assessment score, resulting in incorrect values of the DAS28-4(ESR) included in the original application package. Upon further communication, the Sponsor clarified that:

- The issue was related to a transcription error in the programming code used to derive DAS28-4(ESR) rather than a data transcription error per se.
- The raw data for both the Physician Global Assessment and Patient Global Assessment were correct.
- Calculation of ACR responses (ACR20, ACR50, ACR70) was not affected.
- None of the population-based analyses or other parts of clinical pharmacology data were affected by this error.

The independent review of the error by the statistical review team was in general agreement with the Sponsor's findings. Subsequently, the Sponsor amended the NDA submission with the corrected DAS28-4:

- Data tables and figures containing DAS28-4(ESR) values

- CSRs for the 5 pivotal Phase 3 studies (A3921032, A3921044, A3921045, A3921046, A3921064); 2 Phase 2/3 long-term, open-label extension studies (A3921024, A3921041) and 2 Phase 2 studies (A3921109, A3921040)
- Summary documents including the Integrated Summary of Efficacy (ISE), the Summary of Clinical Efficacy SCE, the Clinical Overview (CO), and proposed labeling.

The Agency's review of the reported programming error concluded that it did not indicate a major deficiency with data quality or integrity and that the error would not affect the overall conclusions regarding efficacy, safety, or dose-selection.

3.2 Compliance with Good Clinical Practices

The applicant certified that all clinical investigations in the NDA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the US conducted under IND 70903 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP).

3.3 Financial Disclosures

The applicant submitted FDA Form 3454 (v.4/06) certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

4.1.1. Drug substance

CP-690,550-10 is a white to off-white (b) (4) The equilibrium solubility of CP-690,550-10 drug substance was evaluated in unbuffered water and standard aqueous buffers. (b) (4) No other polymorphs have been observed during development. CP-690,550-10 is non-hygroscopic and requires no special protection from humidity during handling, shipping, or storage.

4.1.2 Active Drug Product

Generic name:	tofacitinib citrate
Molecular Formula:	$C_{16}H_{20}N_6O \bullet C_6H_8O_7$ (citrate salt)
Molecular weight:	504.49 Daltons (citrate salt)
Pharmacology category:	Small molecule, BCS class 3
Route of administration:	Oral
Dose(s):	5 mg and 10 mg
Study Drug Formulation:	Film coated immediate release tablets
Mechanism of Action:	Competitive biding and inhibition of Janus associated kinases (JAK), discussed in detail in Section 4.4.1 Mechanism of Action

4.2 Clinical Microbiology

Not relevant to tofacitinib as an oral tablet.

4.3 Preclinical Pharmacology/Toxicology

Pivotal nonclinical toxicology studies were conducted in rats (6-month, doses of 0, 1, 10, 100 mg/kg/day) and cynomolgus monkeys (9-month, doses of 0, 0.5, 2, 10 mg/kg/day, 4 monkeys per sex per group). No-Observed-Adverse-Effect-Levels (NOAELs) could not be determined as adverse effects were noted in each of the lowest doses tested. Toxicities were associated with suppression of the immune and hematopoietic systems, to include suppression of myeloid and erythroid bone marrow production, reductions in circulating red and white blood cells, increased bacterial infections, and reduced or atrophied lymphoid organs. Reversibility of these findings was not evaluated in the chronic toxicity studies. However, shorter duration repeat-dose toxicity studies in rats and monkeys demonstrated that these findings were at least partially reversible.

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

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

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

Tofacitinib was determined not mutagenic or genotoxic based on the weight of evidence. Tofacitinib was negative in the in vitro test for gene mutations, positive in an in vitro test for chromosomal damage, and negative in the in vivo DNA damage assay. Two additional studies (in vitro CHO/HGPRT assay and an in vivo rat DNA synthesis assay) were negative for genetic toxicity. Carcinogenicity was assessed in a 6-month mouse study and a 2-year rat study. The mouse study did not suggest oncogenic potential related to tofacitinib. The rat study neoplastic findings included interstitial cell adenomas of the testes, and benign thymomas and malignant hibernomas in females.

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

4.4 Clinical Pharmacology

Much of this section has been excerpted and adapted from the clinical pharmacology review by Dr. Lokesh Jain.

The clinical pharmacology of tofacitinib has been studied in 13 in vitro, 21 Phase 1 clinical studies, and 5 Phase 2 dose ranging studies (including their corresponding 2 long term extension studies) providing population PK and exposure response (ER) information in healthy volunteers and patients with RA, psoriasis, and other populations.

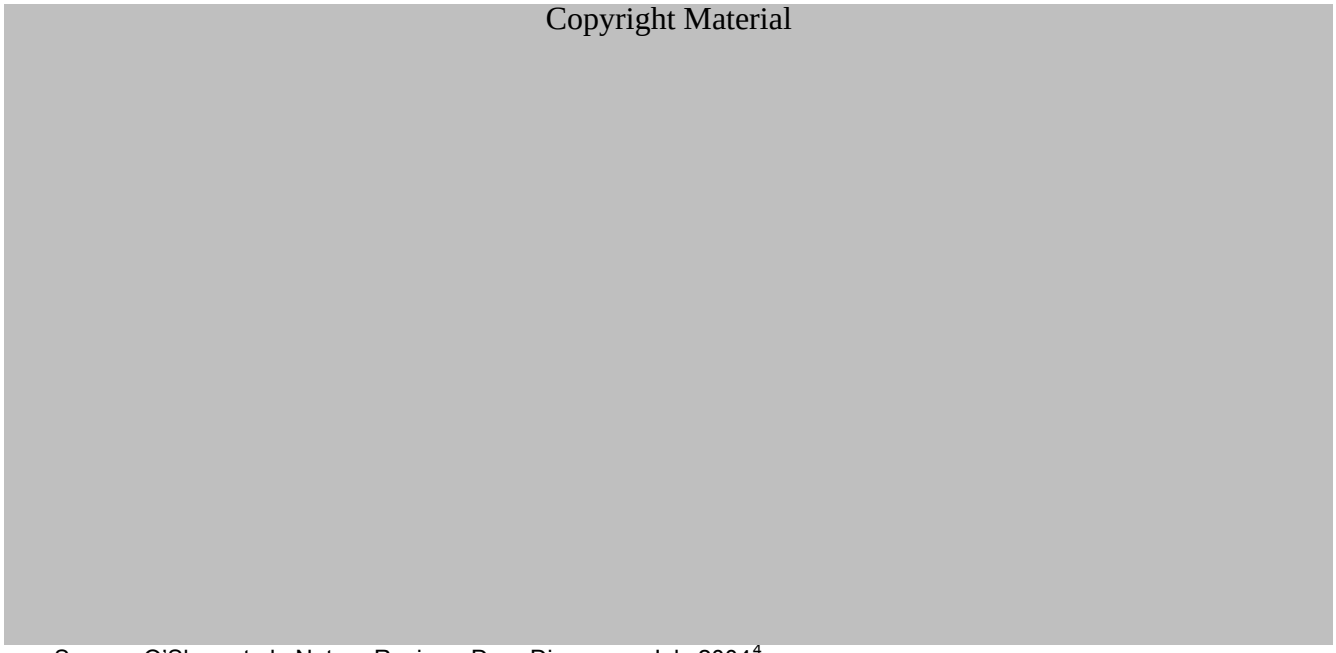
4.4.1 Mechanism of Action

Tofacitinib is intended to be a selective inhibitor of Janus kinase (JAK) family of kinases, which mediate signal transduction activity through the common gamma chain family of cytokines including IL-2, -4, -7, -9, -15, and 21. These cytokines are integral to lymphocyte activation, proliferation and function.

The Janus kinase (JAK) family, including JAK1, JAK2, JAK3 and tyrosine kinase 2 (TyK2), is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with type I and type II cytokine receptors. The biological importance of these kinases is elucidated by respective mouse knockout models as shown in Table 4. Further, the common gamma chain mutation, which is in the JAK3 signaling pathway, is also associated with X-linked severe combined immunodeficiency (SCID) phenotype in humans[3].

3 Noguchi M et al., Interleukin-1 receptor gamma chain mutations result in X-linked severe combined immunodeficiency in humans, Cell 1993 Apr 9;73(1):147-57

Table 4. Phenotype of Mouse JAK Knockout Models



Source: O'Shea et al., Nature Reviews Drug Discovery, July 2004[4]

Of the four family members, JAK1, JAK2 and TyK2 are ubiquitously expressed and associate with numerous types of cytokine receptors. JAK2 kinases are critical for the signaling of hematopoietic cytokines including erythropoietin and granulocyte/macrophage colony stimulating factor (GM-CSF).

JAK3 is preferentially expressed in lymphocytes and mast cells and pairs with JAK1 to mediate the common γ chain cytokines, including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21, which are integral to lymphocyte activation, proliferation, and function. Upon binding of the cytokine to its receptor, the associated JAKs are activated, and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the signal transducer and activator of transcription (STAT) family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) of transcription factors. The STATs are then phosphorylated by the co-localized JAKs, which stabilizes homo- or heterodimeric STAT complexes that translocate to the nucleus where they bind to specific gene promoters to activate transcription of a range of target genes.

In kinase assays, tofacitinib inhibits not only JAK3 but also JAK1, JAK2 and, to a lesser extent, TyK2 as shown in Table 5. This relatively non-specific JAK inhibition is relevant to the assessment of clinical safety, such as off-target effects on hematopoiesis, as discussed in the pertinent sections of this document.

4 O'Shea et al., New modality for immunosuppression: Targeting the JAK/STAT pathway, Nature Reviews Drug Discovery, July 2004;3:555-64

Table 5. IC_{50} and K_i of CP-690,550 for JAKs

	CP-690,550 (nM), n = 2 - 4	
Enzyme	**IC_{50} ± SEM**	**K_i ± SEM**
JAK 1	3.2 ± 1.4	0.68 ± 0.12
JAK 2	4.1 ± 0.4	0.97 ± 0.03
JAK 3	1.6 ± 0.2	0.24 ± 0.03
TyK 2	34 ± 6	4.4 ± 0.3

Source: Pharmacology/Toxicology review of pharmacodynamic studies
IC_{50}-50% inhibition concentration; K_i-inhibition constant; nM-nanomolar; SEM-standard error of the mean

4.4.2 Pharmacokinetics

The pharmacokinetic (PK) profile of CP-690,550 shows that peak plasma concentrations are reached within 0.5-1 hour following oral administration. Systemic exposure increased dose proportionally in the dose range of 1 to 100 mg. Steady state concentrations are achieved in 24-48 hours with minimal accumulation after BID administration. CP-690,550 is cleared via 70% hepatic metabolism and 30% renal excretion of the parent drug via glomerular filtration and active tubular secretion. The metabolism is primarily mediated by CYP3A4 with minor contribution from CYP2C19. Majority of metabolites are also eliminated through renal excretion (~51% of administered dose) with minor elimination in feces (~13%). The elimination half-life of tofacitinib is ~3 hours.

Absorption

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

Distribution

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

Metabolism and Transporters

- Tofacitinib was extensively metabolized, primarily by CYP3A4 enzyme with minor contribution from CYP2C19
- All metabolites have less than <8% of total drug exposure in circulation
- Based on in vitro studies, at therapeutic concentrations, it has low potential for inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 metabolic enzymes, low potential for induction of CYP1A2 and 3A4, and low potential of inhibition for P-gp, OCT2, OATP1B1, OATP1B3
- Based on in vitro studies, tofacitinib is not a substrate of BCRP transporter

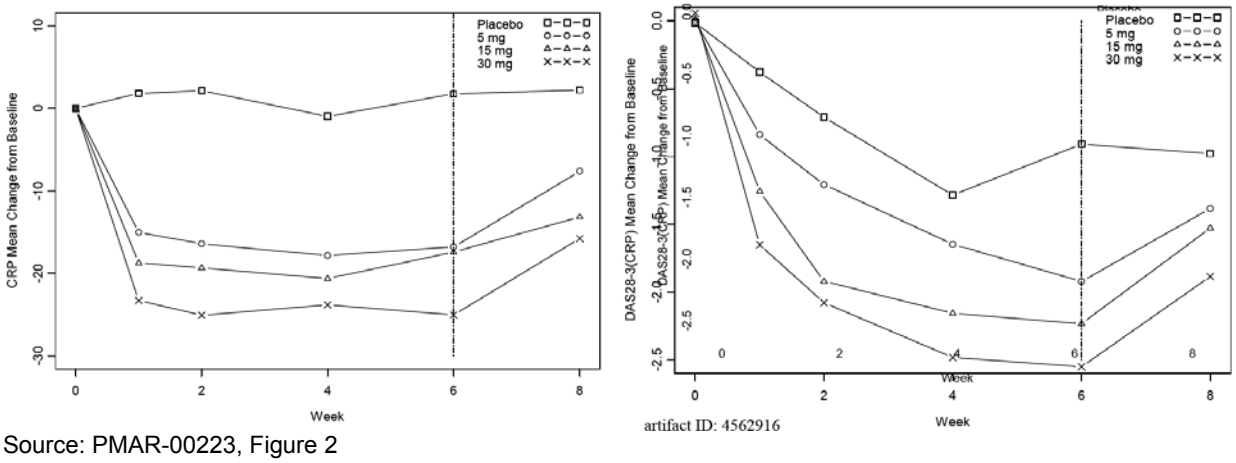
Elimination

- Of the 94% drug recovered following oral administration in a mass balance study, approximately 80% was recovered in urine, 29% as parent and 51% as metabolites. Remaining drug was recovered in feces, approximately 1% as parent and 13% as metabolites
- The terminal elimination half-life of tofacitinb was approximately 3 hours after single- or multiple-dose administration

4.4.3 Pharmacodynamics

The pharmacodynamic (PD) activity of tofacitinib however is longer relative to its PK half-life and is suggesting a prolonged effect on the immune system. For example, in a dose-ranging study A3921019 in RA, where patients were treated with three doses of tofacitinib or placebo for 6 weeks, changes observed with CP-690,550 treatment in C-reactive protein (CRP) and DAS28-3 (CRP) scores, and laboratory parameters, continued to show residual activity for at least 2 weeks after cessation of treatment, indicating prolonged pharmacodynamic activity (Figure 1).

Figure 1. Pharmacodynamic Activity of Tofacitinib in Study A3921019



Source: PMAR-00223, Figure 2

Collectively, the *in vitro*, nonclinical and clinical data indicate that partial and intermittent inhibition of multiple cytokine pathways is sufficient to elicit sustained pharmacodynamic

activity. One potential explanation of the prolonged PD activity relative to the PK profile is the slow recovery of downstream signaling and gene expression after competitive JAK inhibition with tofacitinib.

4.4.4. Dose Selection

Two dosing regimens, 5 mg BID and 10 mg BID, were selected for testing in the Phase 3 development based on analyses of data from non-clinical and dose-ranging clinical studies.

Multiple doses of tofacitinib were tested in non-clinical studies with mouse collagen-induced arthritis (CIA) model in QD and BID dosing regimen. Comparison of efficacious concentrations in these models with whole blood IC50 estimates for inhibition of various JAK dependent cytokines suggested that effective modulation of the inflammatory response through JAK1/3 did not require continuous coverage (i.e., plasma tofacitinib concentrations in excess of IC50) of the target over the day. Pharmacodynamic area under the curves calculated based on clinical scores f rom CIA model were used as efficacy endpoints. Based on sponsor's analysis, efficacy following various dosing schedules was better predicted by average concentration (C_{avg}) compared to peak or minimum concentrations (i.e., C_{max} or C_{min}). In these studies, the predicted tofacitinib dose to achieve 50% effectiveness (ED_{50}) in animal models for BID vs. QD dosing regimen were 6-12.8 mg/kg and 33.5-40.5 mg/kg, respectively. BID dosing was anticipated to provide the concentrations which were higher than the IC50 for JAK1/3 signaling for 12-13 hrs while this duration was 8.5-11 hrs for QD dosing. These observations supported the choice of BID dosing regimen, which was further tested in clinical programs.

The clinical development program was primarily designed to optimize a BID regimen for tofacitinib for the treatment of RA. Five Phase 2 clinical studies evaluated more than one dose levels of tofacitinib in RA patients ranging from 1 to 30 mg for 6 to 24-week duration.

Pfizer selected 5 and 10 mg BID doses of tofacitinib based on dose-response modeling of safety and efficacy data from Study A3921025, with supportive data from Study A3921019 and Study A3921035. The key design features of these studies and efficacy results for the American College of Rheumatology (ACR) Responses are summarized in Table 6 below. On background methotrexate (MTX) in Study 1025, the dose response was very flat across the range of doses from 3 mg BID to 20 mg QD. There was some suggestion in Study 1035 (a monotherapy evaluation) that 10 mg BID might result in additional responders over 5 mg BID.

Table 6. Summary of Dose-Ranging Studies A3921025, A3921035, and A3921019

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

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

Longitudinal dose-response modeling for data from study A3921025, was used to support the selection of dose for Phase 3 trials. In this placebo controlled study tofacitinib doses of 1, 3, 5, 10, 15 mg BID and 20 mg QD were administered to RA patients in background of methotrexate for 24 weeks to evaluate the efficacy (at week 12) and durability of effect (at week 24). Review of dose-responsiveness for safety data from this study suggested that except hemoglobin levels and LDL-c other adverse events within the study, i.e., changes in serum creatinine, neutrophils and other laboratory measures, did not provide sufficient dose discrimination. Therefore, dose selection was primarily based on ACR20, ACR50 and ACR70 response rates for efficacy and changes in hemoglobin for safety. Since the management of LDL-c requires individual patient specific considerations, it was not considered for dose-selection. Final doses were selected based on approximately 50% probability of achieving the target effect, which consisted of

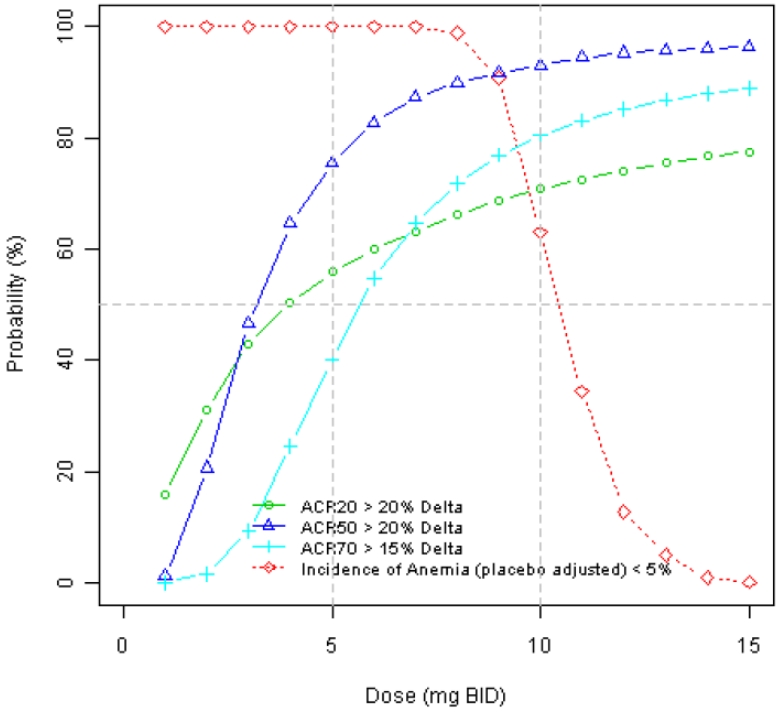
- placebo adjusted response rates of at least 20% for ACR20, 20% for ACR50, and

15% for ACR70 at week 12 and

- <5% placebo adjusted incidence rate of severe anemia through 24 weeks. Where, severe anemia was defined as >2 g/dL decrease in hemoglobin from baseline or an absolute hemoglobin level of <8 g/dL.

As shown in Figure 2, both 5 mg BID and 10 mg BID doses approximately met the target effect criteria and were thus selected for further evaluation in Phase 3 studies. The 10 mg BID dose was expected to provide additional benefit over 5 mg BID on ACR70 (probability of target effect 80% for 10 mg BID vs. 40% for 5 mg BID) while still maintaining >50% probability of having an acceptable incidence of anemia.

Figure 2. Probability of Achieving Target Effects for Efficacy (ACR20, ACR50 and ACR70 Response Rates) and Safety (Anemia) Endpoints Based on Dose-Response Modeling of A3921025 Data



Source: Pfizer study-pmar-00223/Figure 3/Page 14

Pfizer selected the doses of 5 mg BID and 10 mg BID for further study in Phase 3. The key drivers of their dose selection were ACR responses for efficacy and effect on hemoglobin (and associated anemia incidence) and LDL cholesterol as safety variables. Hemoglobin and LDL were chosen because, "effects on other endpoints were either clinically insignificant or the incidence of events were insufficient to model."[5] At End-Of-Phase 2 meeting, the Agency review team agreed that the selection of the 5 mg BID

5 Module 2.7.3 Summary of Clinical Efficacy, Section 2.7.3.4.2.1, Page 150

and 10 mg BID dose regimens appeared to be adequately justified, although 3 mg BID or QD regimens were also thought to warrant further consideration.

The safety parameter driving the original dose selection was the effect on hemoglobin and associated anemia incidence. Anemia however, is likely due to an off-target effect of tofacitinib on erythropoiesis via inhibition of JAK2 which is also supported by the observations in the Phase 3 program as discussed in Section 7.4.2.3 Hematologic Laboratory Parameters below. Therefore, anemia may not have been the most appropriate surrogate for safety in the dose-selection modeling. Further, using anemia in the dose-selection modeling, may underestimate the potential toxicity of tofacitinib as the in vitro activity of tofacitinib is about 2-3 fold higher for JAK3, than for JAK2 based on IC_{50} as shown in Table 5 above.

Based on the mechanism of action of inhibition of JAKs, which mediate signal transduction activity of multiple cytokines and thus affect lymphocyte activation, proliferation and function, it is important to explore the effects of tofacitinib on lymphocytes in relation to dose. From clinical safety perspective, investigating this relationship is particularly important in light of the observed increased incidence of serious infections, viral reactivations and opportunistic infections with tofacitinib use, suggesting lymphocyte functional impairment.

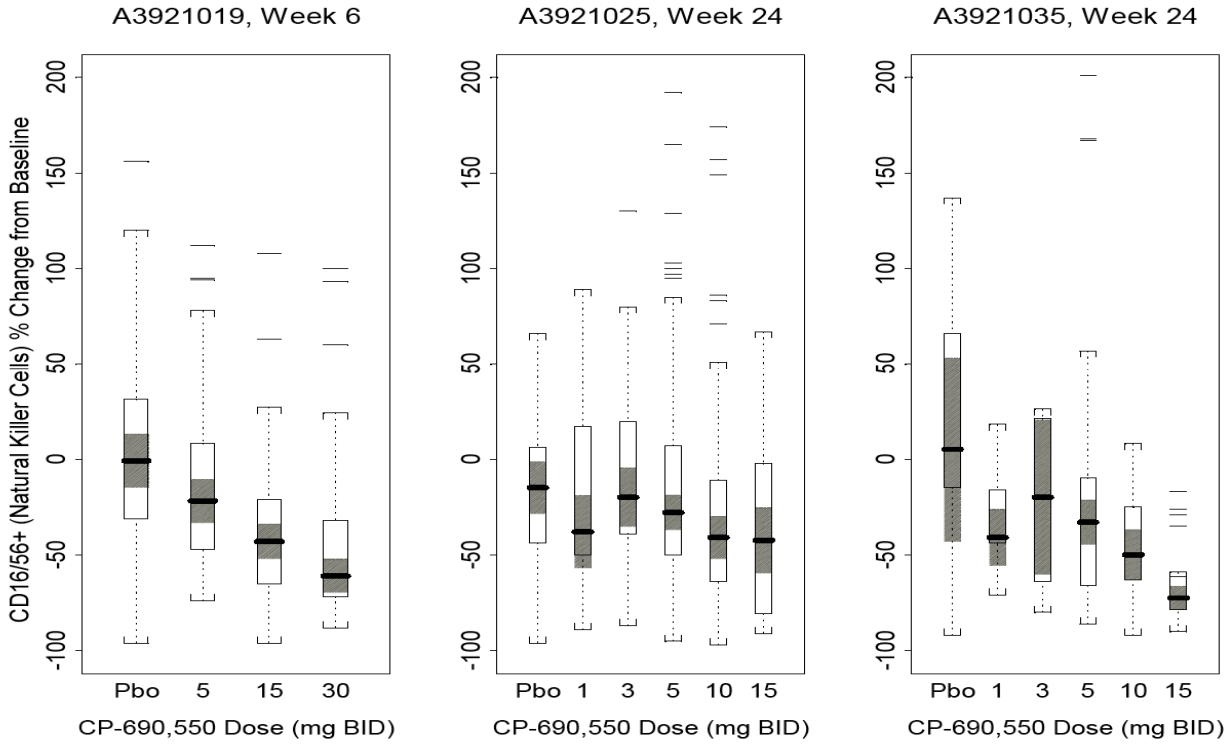
To provide some insights into this question, the Sponsor has collected data on lymphocyte subsets in the initial dose-ranging studies 1019, 1025 and 1035.

No consistent dose response in CD3+, CD4+, or CD8+ T lymphocyte counts was observed in these studies (data not shown) indicating that routine monitoring of lymphocyte subset counts (e.g. CD4+) is not supported by the available data and may not be helpful in identifying patients at risk of infections. Further, a functional, rather than cytotoxic effect of tofacitinib on CD4+ T cells was suggested by ex vivo experiments[6]

In contrast, NK cells counts (CD16+/56+) showed dose-dependent decreases as seen on Figure 3. However, the clinical significance of these observations remains unclear, as there was no clear association between lower NK call counts and increased incidence of serious infections, herpes zoster, and malignancy as reported by the Sponsor. Further, tofacitinib administration did not result in clinically significant reductions of serum immunoglobulin levels as measured in study 1025 (data not shown).

6 Measshima K, et al., The JAK inhibitor tofacitinib regulates synovitis through inhibition of interferon-γ and interleukin 17 production by human CD4+T cells, Arthritis Rheum, June 2012;64(6):1790-1798

Figure 3. Percent Change from Baseline in Lymphocyte Subsets Counts in RA Patients



Source: Summary of Clinical Pharmacology, Figures 25, 26.

Dose-selection discussion based on risk-benefit considerations for the proposed doses.

Review of the data supporting this NDA identified several areas of safety concern which appeared to be dose-dependent as discussed in detail in Section 7 Review of Safety. These major adverse events include:

- Solid and hematologic malignancies, including lymphoproliferative disorders
- Serious infections, including opportunistic infections and tuberculosis.
- Elevations of total cholesterol, LDL and HDL cholesterol levels
- Changes in other hematologic and select serum chemistry tests.

These potential safety signals, some of which major, appeared to be dose-dependent, which prompted the review team to re-visit the initial dose selection approach based on data from studies 1025 and 1035 to answer the question whether a lower nominal daily dose would provide clinically meaningful efficacy and potentially lower toxicity.

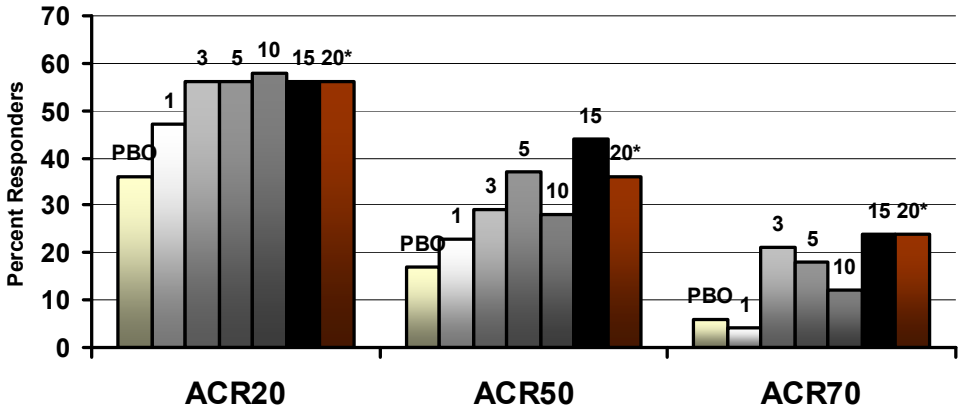
As discussed above, the pivotal dose-ranging studies 1025 and 1035 explored a wider range of doses to include 1, 3, 5, 10, 15 mg BID. In addition, study 1035 included an adalimumab arm. As seen in Figure 4:

- On background MTX in study 1025, the dose response was very flat across the range of doses from 3 mg twice daily to 20 mg once daily and the 3 mg twice daily showed efficacy, similar to 5 and 10 mg twice daily doses.
- With monotherapy use in study 1035, the 3 mg twice daily showed comparable or better efficacy to adalimumab as active comparator in all ACR responder categories.

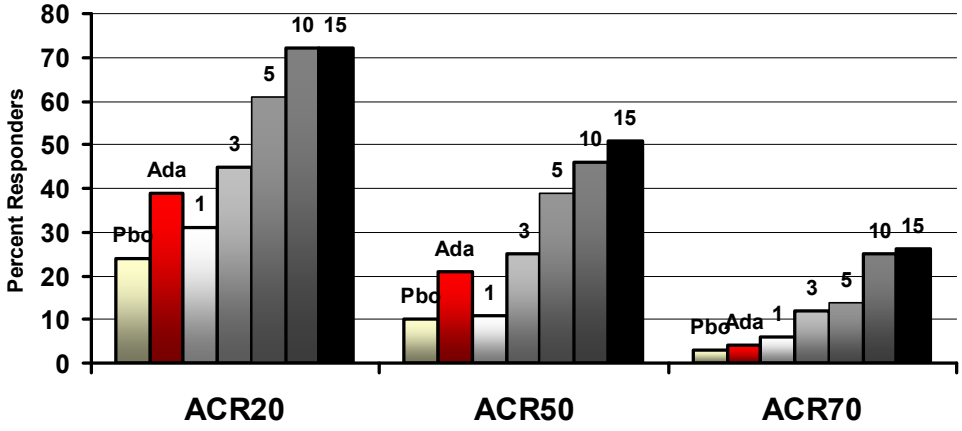
These data suggest that doses lower than proposed, such as 3 mg twice daily, may also be effective.

Figure 4. ACR Responder Categories in the Pivotal Dose-Ranging Studies

Study 1025



Study 1035



Numbers above the bars represent tofacitinib doses. *All tofacitinib doses are twice a day except for the 20 mg once daily dose in Study 1025

In the same dose ranging studies, only laboratory changes occurred in a manner that enabled a dose-relationship assessment. Exploration of laboratory parameters, such as serum creatinine, LDL and HDL cholesterol, and absolute neutrophil counts, also

showed consistent dose-dependent changes which also mirrored the dose-related efficacy parameters in study 1035. The 3 mg twice daily dose regimen was associated with a lower magnitude of abnormalities in LDL and HDL cholesterol, serum creatinine and absolute neutrophil counts, suggesting that this lower dose regimen has the potential for an improved safety profile with respect to dose-dependent toxicities.

5 Sources of Clinical Data

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 using the following path:
\\CDSESUB5\EVSPROD\NDA203214\203214.enx

The tofacitinib RA clinical development program, as of 29 March 2011 (the clinical data cut-off), consists of:

- Phase 1: 21 completed studies,
- Phase 2: 8 studies (6 completed, 2 ongoing),
- Phase 3: 6 studies (4 completed, 2 ongoing),
- Open label, long-term extension (LTE): 2 ongoing studies.

The nomenclature of all the clinical studies in the RA development consists of the prefix A392 followed by a four digit unique study number, i.e. A3921044. For simplicity, in this document, the studies will be referred to with the four digit unique study number, e.g. 1044. Also for simplicity, treatment groups of CP-690,550 5 mg BID and CP-690,550 10 mg BID may be referred to as CP5 and CP10, respectively. The terms CP-690,550 and tofacitinib are used interchangeably in this document.

This NDA is comprised of 5 Phase 3, controlled clinical trials, designed to assess clinical efficacy and safety of tofacitinib in adult patients with moderately-to-severely active established RA, either in combination with traditional DMARDs (MTX for the most part), or as a monotherapy (following washout of other DMARDs). The key design features of these studies are summarized in
Table 7. Detailed description of individual protocols is provided in Section 9.4 Individual Study Reports.

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.

Patients participating in Phase 3 studies had the option to enroll in the long-term extension (LTE) studies that were initiated in Phase 2 (1024 and 1041).

- Study 1024, is a long-term, open-label safety study, which allows patients from Phase 2 and 3 studies to "roll-over" and receive CP-690,550 (5 mg or 10 mg BID), thus providing the opportunity for patients to receive additional tofacitinib therapy for long-term effects assessment of tofacitinib.
- Study 1041 is similar in design to LTE Study 1024 and allows Japanese patients who have completed Japan Phase 2 studies 1039 and 1040 and global Phase 3 Study 1044 (restricted to patients enrolled in this study in Japan) to "roll-over" and continue receiving CP-690,550.

(b) (4)

5.1 Tables of Studies/Clinical Trials

Table 7. Key Design Features of NDA 203,214 Phase 2 and 3 Randomized Controlled Studies for Efficacy and Safety

Key Design Features of the Phase 3 Studies in RA for Efficacy and Safety						
Protocol	**Patient Population**	**Design** ***Duration***	**Enrolled** ***Randomization***	**Treatment Arms (transition and escape for NR)**	**Primary Endpoints**	**Timepoint**
Patients with incomplete response to prior TNF inhibitor						
A3921032	Moderate-to-severe RA TNF-IR, Stable background MTX	R, DB, PC Phase 3 *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	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
Patients with incomplete response to MTX or other DMARDs						
A3921044	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 3 *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	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6
A3921045	Moderate-to-severe RA DMARD-IR, No background to Month 3	R, DB, PC Phase 3 *6 months*	610 *4:4:1:1*	CP 5 mg BID CP 10 mg BID PBO → CP 5 mg BID @ Mo 3 PBO → CP 10 mg BID @ Mo 3	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
A3921046	Moderate-to-severe RA DMARD-IR, Stable background DMARDs[#]	R, DB, PC Phase 3 *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	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
A3921064	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, AC Phase 3 *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	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6

Key Design Features of the Pivotal Phase 2 Studies in RA for Efficacy and Safety

Protocol	Patient Population	Design *Duration*	Enrolled *Randomization*	Treatment Arms (transition and escape for NR)	Primary Endpoints	Timepoint
A3921025	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 2, 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 OD (→CP 5 mg BID @ Mo3 if NR)+ MTX Placebo (→CP 5 mg BID @ Mo3 if NR)+ MTX	ACR20	Month 3
A3921035	Moderate-to-severe RA DMARD-IR, No background therapy	R, DB, AC Phase 2, Dose-ranging *6 months*	384 *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)	ACR20	Month 3

Source: Summary of Clinical Efficacy, Clinical Study Reports for studies A3921032, A3921044, A3921045, A3921046, A3921064
*-One year efficacy data submitted for Study A3921044; #-Background DMARD therapy in Study A3921046: 84% of subjects on MTX, ~1/2 on combination DMARDs; AC-active control (adalimumab, study A3921064); BID-two times daily; DMARDs-disease-modifying anti-rheumatic drugs; IR-incomplete response; MTX-methotrexate; mTSS-modified total Sharp Score; NR-non-responder defined as patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts over baseline at Month 3 visit; PBO-placebo; PC-placebo (add-on for studies A3921032, A3921044, A3921046, A3921064)-controlled; SC-subcutaneous; TNF-tumor necrosis factor. CP=CP-690,550/tofacitin b

5.2 Review Strategy

The NDA submission was reviewed for content, format and overall data quality and integrity and found acceptable during the filing review.

Efficacy analyses were derived from 5 randomized controlled studies: 1032, 1044, 1045, 1046, and 1064. Each of the 5 pivotal studies was reviewed individually for the primary endpoints of:

- ACR20 response criteria were used to asses superiority of two doses of tofacitinib (5 mg and 10 mg BID) over placebo in all five Phase 3 studies at either Month 3 (studies 1032 and 1045) or Month 6 (studies 1044, 1046, and 1064) as the first of several primary endpoints. Key secondary endpoints, such as ACR50 and ACR70 responses at the same timepoints, change from baseline in ACR core variables, and time course of ACR20 and ACR50 responses were also assessed. Sensitivity analyses of the primary endpoint were also performed for each individual study.
- Change from baseline in Van der Heijde modified Sharp Scores (mTSS) at Month 6 (only study 1044) as the second primary endpoint in a sequence of four endpoints.
- Change from baseline in Health Assessment Questionnaire-Disability index (HAQ-DI) at month 3 in all five studies.
- The proportion of patients with low disease activity defined as DAS28-4(ESR) of less than 2.6 at Months 3 (studies 1032 and 1045) or Month 6 (studies 1044, 1046, 1064) was measured as the last in the sequence of primary endpoints in all Phase 3 studies.

Safety data in this submission were derived from:

- Phase 2 in RA: 8 studies:
  - 6 completed (1019, 1025, 1035, 1039, 1040, 1109)
  - 2 ongoing (1068, 1073)
- Phase 3 in RA: 6 studies:
  - 4 completed (1032, 1045, 1046, 1064)
  - 2 ongoing (1044 12-month interim data, (b) (4))
- Open label, long-term extensions (LTE) in RA: 2 ongoing studies (1024, 1041)
- Additional studies from non-RA populations, such as renal allograft patients.

To facilitate evaluation of rare adverse events, such as deaths, malignancy, serious infections, etc., and better understanding of the safety profile across the entire range of RA patients studied, the safety data from all 5 efficacy studies were pooled and integrated safety results displayed by treatment group for the 12-month safety population. Additionally, safety data from the long-term extension studies 1024 and 1041 were pooled and presented by treatment group for the open label period only.

Dose-selection for the Phase 3 program was reviewed in the context of the Phase 2 dose-ranging studies and the available efficacy and safety data from the RA development program.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1. Background DMARD Studies in RA

Study A3921032 (Phase 3) was a 6-month study in which 399 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to at least one approved TNF-inhibitor biologic agent received CP-690,550 5 or 10 mg BID or placebo added to background MTX. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of CP-690,550 5 or 10 mg BID. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in HAQ-DI and proportion with DAS28-4(ESR) less than 2.6. The last efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock.

Study A3921044 (Phase 3) is an ongoing 2-year study with a planned analysis at 1 year in which 797 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received CP-690,550 5 or 10 mg BID or placebo added to background MTX. At the Month 3 visit, non-responding placebo patients were advanced in a blinded fashion to a second predetermined treatment of CP-690,550 5 or 10 mg BID. At the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, change from baseline in mean modified Total Sharp Scores at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6. The last efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock.

Study A3921046 (Phase 3) was a 12-month study in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a nonbiologic DMARD received CP- 690,550 5 or 10 mg BID or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). Placebo patients were advanced as in Study A3921044. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3 and rates of DAS28-4(ESR) less than 2.6 at Month 6. The last efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock.

Study A3921064 (Phase 3) was a 12-month study in which 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received CP-690,550 5 or 10 mg BID, adalimumab 40 mg subcutaneously every other week, or

placebo added to background MTX. Placebo patients were advanced as in Study A3921044. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6. The last efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock.

Study A3921025 (Phase 2) was a 6-month dose-ranging study in which 507 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received one of the following doses of CP-690,550 (1, 3, 5, 10, or 15 mg BID or 20 mg QD) or placebo added to background MTX treatment. Non-responders to CP-690,550 doses of 1 or 3 mg BID or 20 mg QD or placebo were all advanced to CP-690,550 5 mg BID at 12 weeks. The primary endpoint was ACR20 response at Month 3.

Study A3921039 (Phase 2) was a 3-month dose-ranging study conducted in Japan in which 136 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received one of the following doses of CP-690,550 (1, 3, 5, or 10 mg BID) or placebo. ACR20 response was measured at Month 3. The primary endpoint was ACR20 response at Month 3. Data from this study were not included in the assessment of efficacy or in the pooled analyses of safety due to differences in trial design, patient population, and background therapies.

5.3.2. Monotherapy Studies in RA

Study A3921045 (Phase 3) was a 6-month monotherapy study in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic or biologic) received CP-690,550 5 or 10 mg BID or placebo. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of CP-690,550 5 or 10 mg BID. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in HAQ- DI, and rates of DAS28-4(ESR) <2.6. The last efficacy endpoint (DAS28-4(ESR) less than 2.6 response) was amended to the protocol prior to final database lock.

Study A3921035 (Phase 2) was a 6-month monotherapy study in which 384 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic or biologic) received one of the following doses of CP-690,550 (1, 3, 5, 10, or 15 mg BID) or adalimumab 40 mg SC injection (monotherapy) every other week or placebo. Patients on adalimumab, and non-responders to CP-690,550 dosed at 1 or 3 mg BID or to placebo were all advanced to CP-690,550 5 mg BID at 12 weeks. The primary endpoint was ACR20 response at Month 3.

Study A3921040 (Phase 2) was a 3-month monotherapy study conducted in Japan in which 317 patients with moderate to severe rheumatoid arthritis who had an inadequate response to at least 1 DMARD (nonbiologic or biologic, including MTX) received one of

the following doses of CP-690,550 (1, 3, 5, 10, or 15 mg BID) or placebo. The primary endpoint was ACR20 response at Month 3. Data from this study were not included in the assessment of efficacy or in the pooled analyses of safety due to differences in trial design, patient population, and background therapies.

5.3.3 Long-Term Extension Studies in RA

Study A3921024 is an ongoing long-term, open-label study to further assess the long-term safety and efficacy of CP-690,550 in patients with moderate to severe rheumatoid arthritis who have completed participation in a randomized study of CP-690,550 for the treatment of RA. Patients from Phase 2 studies receive CP-690,550 5 mg BID, and patients from Phase 3 studies receive CP-690,550 10 mg BID (with the exception of China, in which patients are dosed at 5 mg BID). CP-690,550 doses could be adjusted for safety concerns, lack of tolerance or lack of efficacy. As of 29 March 2011, 2823 patients were participating; 4000 patients are planned.

Study A3921041 is an ongoing long-term, open label study conducted in Japan to further assess the long-term safety and efficacy of CP-690,550 in patients with moderate to severe rheumatoid arthritis who have completed Japan Phase 2 studies A3921039 and A3921040 and global Phase 3 study A3921044. Patients continue to receive CP-690,550 5 mg BID. CP-690,550 doses could be adjusted for safety concerns, lack of tolerance or lack of efficacy. As of 29 March 2011, 404 patients were participating; 500 patients are planned.

5.3.4. Key eligibility criteria

Key eligibility criteria for enrollment in Phase 3 studies were:

- Men and women 18 years of age or greater who had been diagnosed as having rheumatoid arthritis (RA) and who had evidence of active RA as manifested by .6 out of 66 swollen and ≥6 out of 68 tender/painful joints and an elevated acute phase reactant test (CRP>7 mg/dL and/or ESR> 28 mm/h). For Study A3921046 the minimum swollen and tender/painful joint count is ≥4. Aside from RA, autoimmune rheumatic diseases other than Sjögren's Syndrome were exclusionary.
- Previous DMARD therapy and response eligibility criteria:
    - For 1035, 1045, and 1046 the patients must have had an inadequate therapeutic response to at least one traditional or biologic DMARD.
    - For 1025, 1044 and 1064 the patients must have had an inadequate therapeutic response to MTX.
    - For 1032 the patients must have had an inadequate response to at least one TNF inhibitor and must have had active disease despite stably dosed MTX.
- Appropriate contraceptive measures were required for men (when background traditional DMARD therapy was protocol mandated) and women of childbearing

potential (all studies). Pregnant and nursing women were excluded. Other exclusions were: serious, chronic or current infections, including tuberculosis, herpes zoster, hepatitis B or C, HIV; recent receipt of a live virus vaccine; a first degree relative with a hereditary immunodeficiency; evidence or history of a lymphoproliferative disorder; past treatment with lymphocyte depleting therapies other than B cell selective therapies (the latter was allowed with evidence of adequate B cell recovery); uncontrolled medical conditions; baseline clinically significant abnormalities in safety laboratory tests including hemoglobin, leukocyte, neutrophil and platelet counts, hepatic transaminases, serum creatinine; use of prohibited CYP3A inhibitors or inducers; recent history of alcohol or drug abuse.

Key eligibility criteria for enrollment into the LTE studies (1041 in Japan, 1024 the rest of the world) included:

- Patients must have previously completed participation in a randomized study of CP-690,550 for the treatment of RA, or required earlier discontinuation for reasons other than a treatment-related serious adverse event, and must have met safety related enrollment criteria.

Detailed Inclusion and Exclusion criteria for individual studies are presented in Section 9.4 Individual Study Reports.

6 Review of Efficacy

6.1 Indication

Sponsor's proposed indication is:
"Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs)".

6.1.1 Methods

All five Phase 3 studies were designed to establish superiority of two doses (5 mg and 10 mg BID) of CP-690,550 to placebo for all primary endpoints.

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

4. Signs and symptoms as measured by ACR 20 at Month 3 (Studies 1045 and 1032) or at Month 6 (Studies 1046 and 1064);
5. Physical function as measured by the HAQ-DI change from baseline at Month 3;

6. Incidence of DAS <2.6 at Month 3 (Studies 1045 and 1032) or at Month 6 (Studies 1046 and 1064).

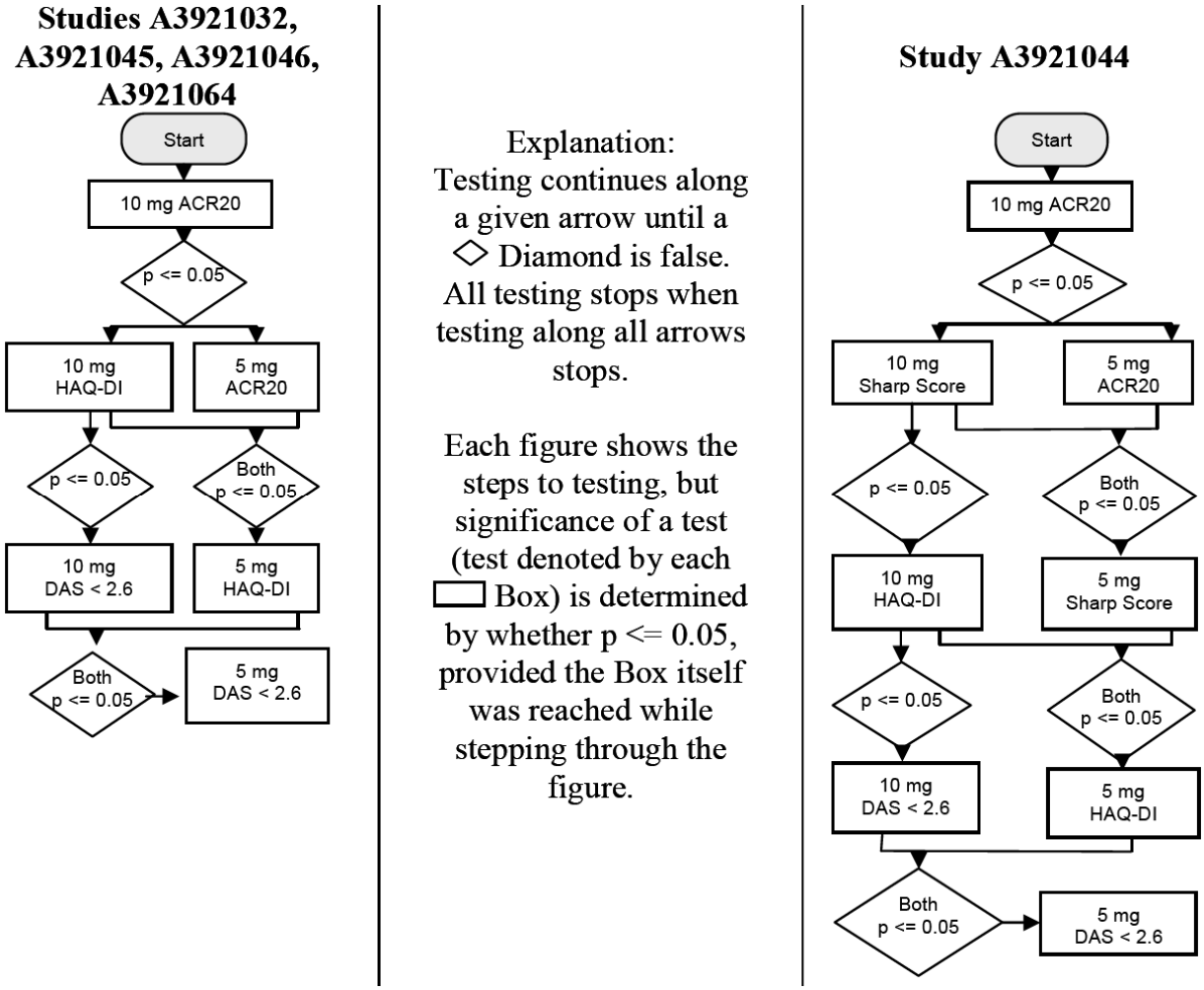
Study 1044 has four primary efficacy endpoints (in sequence):

1. Signs and symptoms as measured by ACR 20 at Month 6;
2. Structural preservation as measured by modified Sharp score 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.

Multiplicity adjustments

In order to control for multiplicity of endpoints and dosing regimens (the probability of type 1 error), the Sponsor assessed each endpoint sequentially using gate-keeping or step-down approach where 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 are two doses within each endpoint, the gate-keeping or step-down approach will also be applied, i.e., the high dose (10 mg BID) at a given endpoint can achieve significance only if the high dose at the prior endpoint is significant (Figure 5). For each endpoint, and for each dose group, the comparison with placebo will be conducted using a significance level (alpha) set at 0.05 (2-sided) or equivalently 0.025 (1-sided).

Figure 5. Primary Analyses Algorithm for Phase 3 Studies in RA



Source: Summary of Clinical Efficacy, Figure 1

Handling of missing data:

- For the primary analysis of ACR20, ACR50, ACR70 and DAS28-4(ESR)<2.6, the Non Responder Imputation (NRI) method was be used.
- For continuous endpoints, such as HAQ-DI, the missing values post-baseline were handled in a linear mixed-effect model with repeated measures where the values are assumed to be missing at random.
- For the mTSS and its components (erosion score and joint space narrowing score) in Study 1044, missing values due to patient advancement at Month 3 had have their Month 6 measurements imputed using a linear extrapolation based on radiographs at Month 3. Missing values due to patient dropout (before advancement, i.e. Month 3 or Month 6) were imputed using a linear extrapolation based on radiographs prior to withdrawal. For the Month 12 analyses, the missing values due to patient advancement at Month 3 or Month 6, or patient

withdrawal were imputed using linear extrapolation based on their radiographs prior to advancement or prior to withdrawal, respectively.

- In general, missing values were not imputed for descriptive statistics or laboratory values.

Key Secondary Endpoints

The following Table 8 summarizes the efficacy analyses for the key secondary endpoints in tofacitinib Phase 3 randomized controlled studies in RA

Table 8. Summary of Efficacy Analyses for Key Secondary Endpoints in Tofacitinib Phase 3 RA Development

Endpoint	Statistical Method	Interpretation
Mean change from baseline in DAS28-4(ESR)	mixed-effect model with repeated measures	Secondary analysis
Mean change from Baseline in DAS28-3(CRP)	mixed-effect model with repeated measures	Secondary analysis
Mean change from baseline in components of ACR	mixed-effect model with repeated measures	Secondary analysis
Rates of patients not progressing by mTSS	normal approximation for the difference in binomial proportions	Secondary analysis: Months 6, 12 and 24 (Study 1044)
Rates of patients with no progression in erosion score	normal approximation for the difference in binomial proportions	Secondary analysis: Months 6, 12 and 24 (Study 1044)
Rates of DAS28-3(CRP) <2.6	normal approximation for the difference in binomial proportions	Secondary analysis
Rates of DAS28-3(CRP) ≤3.2	normal approximation for the difference in binomial proportions	Secondary analysis
Rates of DAS28-4(ESR) ≤3.2	normal approximation for the difference in binomial proportions	Secondary analysis
Durability of ACR20, ACR50, ACR70, DAS28 response rates	N (%)	Secondary analysis
Rates of clinically meaningful decrease in the HAQ-DI (decrease of at least 0.22, 0.3, 0.5) "HAQ-DI (0.22)", etc.	normal approximation for the difference in binomial proportions	Secondary analysis
Actual and mean change from Baseline in the SF-36 8 domain scores and 2 component scores (separate analyses)	mixed-effect model with repeated measures	Secondary analysis
Actual and mean change from Baseline in the FACIT Fatigue Scale	mixed-effect model with repeated measures	Secondary analysis

Source: Summary of Clinical Efficacy, Table 4.

Patient population for primary and secondary efficacy analyses

The population for primary analyses was defined by the full analysis set (FAS) of patients that included all patients who:

- were randomized to the study,
- received at least one dose of the study drug and
- had at least one post-baseline measurement.

From the originally randomized patients who received at least one dose of the drug (intent-to-treat, ITT population), relatively few patients were excluded for the primary analyses as shown on Table 9 and these were generally equally distributed among the

treatment groups. Of note, in study 1044 the Sponsor has also excluded efficacy data for patients from sites that violated study procedures from the FAS dataset. For example, in study 1044, two sites were closed and 17 patients from these sites were excluded from FAS (Table 9).

Table 9. Patient Populations for Efficacy Analyses in Phase 3 Studies in RA

Patient Populations for Efficacy Analyses in Phase 3 Studies in RA					
	A3921032	A3921044	A3921046	A3921064	A3921045
Randomized and treated (ITT population)	399	797	792	717	610
Full analysis set (used for primary analyses)	399	781	785	708	606
Excluded for no post-BL measurement	0	0	7 (<1%)	9 (1%)	4 (<1%)
Excluded for procedural issues	0	17 (2%)*	0	0	0
Radiographic data missing	-	8**	-	-	-

Source: Summary of Clinical Efficacy, adapted from Data Sets Analyses sections Clinical Study Reports for studies A3921032, A3921044, A3921045, A3921046, A3921064;
*-Patients from Sites 1048 and 1174 were excluded from the Full Analysis set due to GCP violations
**-Only one out of nine patients from Site 1155 had radiographic data available in the dataset for analyses

6.1.2 Demographics

The population in the tofacitinib RA development program consisted of adult patients with long-standing, moderate-to-severely active RA who had inadequate response to one or more DMARDs or, in Study 1032, one or more TNF inhibitors. The five Phase 3 studies submitted enrolled predominantly female patients (~75-85%) with mean disease duration of ~7-13 years and high disease activity (mean DAS28-4 scores of over 6.3). Patients' mean age was 50-55 years ranging from 18 to 86 years. The baseline demographics and disease characteristics were well balanced between the treatment groups within each study (Table 11 and Table 12).

The RA development program was global and enrolled patients from predefined regions: US (20%), Europe/Canada (34%), Latin America (15%), and rest of the world (31%) as shown in Table 10.

Table 10. Geographical Distribution in Phase 2 and 3 RA Trials

Geographical Distribution (%) in Phase 2 and 3 RA Trials							
	TNFi IR	**DMARD/MTX Inadequate Responders (IR)**					
	A3921032	**A3921044**	**A3921045**	**A3921046**	**A3921064**	**A3921025**	**A3921035**
Enrolled, n	399	797	610	792	717	507	384
United States	42	17	25	17	15	25	22
Europe, Canada	46	24	34	25	56	44	48
Latin America	5	14	27	14	12	32	22
Rest of World	7	45	14	43	18	0	9

Source: Response to Information Request, May 22, 2012

Table 11. Summary of Baseline Demographics and Disease Characteristics by Trial and Treatment Assignment for All Phase 3 Studies

Summary of Baseline Demographics and Disease Characteristics by Phase 3 Trial (ITT Population)																	
	TNFi Inadequate			DMARD/MTX Inadequate													
	A3921032			A3921044			A3921046			A3921064				A3921045		
	PBO n (%) n=132	CP5 n (%) n=133	CP10 n (%) n=134	PBO n (%) n=160	CP5 n (%) n=321	CP10 n (%) n=316	PBO n (%) n=159	CP5 n (%) n=315	CP10 n (%) n=318	PBO n (%) n=108	CP5 n (%) n=204	CP10 n (%) n=201	ADA n (%) n=204	PBO n (%) n=122	CP5 n (%) n=243	CP10 n (%) n=245
Gender, n (%)																
Females	106 (80)	113 (85)	116 (87)	137 (86)	269 (84)	273 (86)	123 (77)	264 (84)	258 (81)	82 (76)	174 (85)	168 (84)	162 (79)	105 (86)	207 (85)	216 (88)
Age, years																
mean (SD)	55 (11)	55 (12)	55 (11)	52 (12)	54 (12)	52 (11)	52 (11)	53 (12)	52 (12)	54 (14)	53 (12)	53 (12)	53 (12)	50 (11)	52 (12)	52 (12)
Weight, kg																
mean (SD)	81 (24)	78 (21)	79 (20)	68 (20)	69 (20)	67 (18)	71 (20)	70 (19)	71 (19)	70 (19)	72 (19)	73 (18)	72 (16)	73 (19)	72 (20)	72 (20)
Height, cm																
mean (SD)	164 (9)	162 (10)	163 (9)	160 (9)	161 (10)	160 (9)	163 (9)	162 (8)	162 (9)	163 (10)	163 (9)	163 (9)	164 (9)	161 (9)	163 (9)	161 (9)
Race, n (%)																
White	112 (85)	108 (81)	112 (84)	72 (45)	152 (44)	144 (46)	92 (58)	173 (55)	174 (55)	75 (69)	151 (74)	143 (71)	148 (73)	88 (72)	153 (63)	168 (69)
Black	9 (7)	11 (8)	7 (5)	2 (1)	14 (4)	8 (3)	4 (3)	4 (1)	7 (2)	3 (3)	4 (2)	3 (2)	3 (2)	6 (5)	12 (5)	10 (4)
Asian	8 (6)	11 (8)	8 (6)	72 (45)	131 (41)	135 (43)	51 (32)	113 (36)	111 (35)	20 (19)	31 (15)	28 (14)	29 (14)	15 (12)	41 (17)	32 (13)
Other	3 (2)	3 (2)	7 (5)	14 (9)	24 (8)	29 (9)	12 (8)	25 (8)	26 (8)	10 (9)	18 (9)	27 (13)	24 (12)	13 (11)	37 (15)	35 (14)
Duration of RA, years, mean	11	13	13	9	9	9	10	8	9	8	8	7	8	8	8	9
Range	0.4-47	1.2-55	0.7-42	0.4-44	0.3-43	0.3-42	0.3-49	0.2-40	0.2-41	0.3-49	0.3-39	0.3-40	0.2-36	0.1-28	0.2-42	0.2-49
Rheumatoid Factor status																
% Positive	66	61	62	78	75	78	73	74	73	66	67	66	68	52	71	65
Anti-CCP Antibody status																
% Positive	76	68	70	86	84	83	76	77	76	68	71	64	75	64	71	69
MTX dose, mg/week																
mean (SD)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Prior TNF inhibitor																
Number of subjects, n (%)	132 (100)	133 (100)	134 (100)	15 (10)	62 (19)	50 (16)	10 (6)	23 (7)	19 (6)	9 (7)	12 (6)	14 (7)	16 (8)	24 (20)	34 (14)	41 (17)
Number of TNFi, Mean	1.48	1.51	1.43	1.3	1.4	1.3	1.2	1.2	1.3	1.0	1.2	1.2	1.1	1.4	1.5	1.5
Systemic GCS use																
Number of subjects, n (%)	83 (63)	85 (64)	81 (60)	94 (59)	216 (67)	207 (66)	92 (58)	186 (59)	175 (58)	69 (64)	117 (57)	121 (60)	116 (57)	77 (63)	140 (57)	148 (60)

Source: CSR A3921032, CSR A3921044, CSR A3921045, CSR A3921046, CSR A3921064

Table 12. Summary of Baseline Disease Activity by Trial and Treatment Assignment for All Phase 3 Studies

Summary of Baseline Disease Activity, by Phase 3 Trial (ITT Population)																	
	TNFi Inadequate			DMARD/MTX Inadequate													
	A3921032			A3921044			A3921046			A3921064				A3921045			
	PBO n (%) n=132	CP5 n (%) n=133	CP10 n (%) n=134	PBO n (%) n=160	CP5 n (%) n=321	CP10 n (%) n=316	PBO n (%) n=159	CP5 n (%) n=315	CP10 n (%) n=318	PBO n (%) n=108	CP5 n (%) n=204	CP10 n (%) n=201	ADA n (%) n=204	PBO n (%) n=122	CP5 n (%) n=243	CP10 n (%) n=245
DAS28-3(CRP) Mean (SD)	5.4 (1.0)	5.4 (0.9)	5.3 (1.0)	5.2 (0.9)	5.2 (0.9)	5.2 (0.9)	5.2 (0.9)	5.2 (0.9)	5.3 (1.0)	5.4 (0.8)	5.4 (0.9)	5.4 (0.8)	5.3 (0.9)	5.6 (0.8)	5.7 (0.9)	5.6 (0.9)
DAS28-4(ESR) Mean (SD)	6.5 (1.0)	6.5 (1.0)	6.4 (0.9)	6.3 (1.0)	6.4 (0.9)	6.3 (0.9)	6.3 (0.9)	6.3 (1.0)	6.4 (1.0)	6.5 (0.9)	6.6 (0.9)	6.5 (0.8)	6.4 (0.9)	6.6 (0.9)	6.7 (0.9)	6.7 (0.9)
ESR, mm/h (normal ≤ 24) Mean (SD)	47 (24)	48 (26)	44 (24)	51 (25)	50 (24)	51 (27)	50 (26)	50 (29)	52 (28)	48 (23)	49 (24)	50 (26)	48 (24)	51 (29)	53 (28)	52 (27)
CRP, mg/L (normal ≤ 7) Mean (SD)	17 (23)	19 (28)	15 (22)	14 (15)	16 (19)	17 (27)	17 (17)	18 (21)	17 (22)	16 (18)	15 (19)	17 (20)	17 (22)	18 (23)	23 (27)	19 (20)
Tender Joint Count (0-68 joints) Mean (SD)	28 (17)	28 (18)	28 (16)	23 (13)	24 (14)	23 (15)	25 (14)	25 (15)	27 (16)	27 (14)	28 (15)	26 (14)	27 (15)	29 (16)	29 (15)	29 (16)
Swollen Joint Count (0-66 joints) Mean (SD)	17 (10)	16 (10)	17 (10)	14 (8)	14 (8)	14 (8)	14 (9)	14 (10)	14 (10)	17 (9)	17 (9)	16 (10)	16 (9)	17 (10)	16 (9)	17 (10)
Physician Global (100 mm VAS) Mean (SD)	64 (17)	65 (18)	59 (19)	56 (17)	59 (16)	58 (17)	59 (17)	60 (18)	60 (17)	60 (17)	60 (17)	60 (17)	59 (16)	62 (17)	61 (17)	61 (17)
Subject Global (100 mm VAS) Mean (SD)	62 (23)	65 (23)	59 (24)	54 (23)	58 (24)	57 (23)	58 (23)	59 (23)	60 (23)	54 (21)	60 (21)	57 (24)	57 (22)	63 (22)	62 (22)	63 (23)
Subject Pain (100 mm VAS) Mean (SD)	61 (24)	66 (23)	60 (23)	55 (24)	58 (23)	57 (24)	57 (23)	57 (24)	59 (22)	55 (21)	59 (21)	59 (22)	56 (22)	62 (21)	61 (22)	62 (24)
Sharp Score (mTTS) Mean (SD)	-	-	-	33 (42)	31 (48)	37 (54)	-	-	-	-	-	-	-	-	-	-
HAQ-DI (max 3) Mean (SD)	1.6 (0.7)	1.6 (0.7)	1.5 (0.6)	1.4 (0.7)	1.4 (0.7)	1.3 (0.7)	1.3 (0.7)	1.4 (0.7)	1.4 (0.7)	1.4 (0.7)	1.5 (0.6)	1.5 (0.6)	1.5 (0.6)	1.5 (0.7)	1.5 (0.7)	1.5 (0.6)

Source: CSR A3921032, CSR A3921044, CSR A3921045, CSR A3921046, CSR A3921064

Table 13. Summary of Patient Disposition by Trial and Treatment Assignment in Phase 3 RA Trials

Summary of Patient Disposition by Trial and Treatment Assignment in Phase 3 RA Trials																
	TNFi Inadequate			DMARD/MTX Inadequate												
	A3921032			A3921044			A3921046			A3921064				A3921045		
	PBO n (%)	CP5 n (%)	CP10 n (%)	PBO n (%)	CP5 n (%)	CP10 n (%)	PBO n (%)	CP5 n (%)	CP10 n (%)	PBO n (%)	CP5 n (%)	CP10 n (%)	ADA n (%)	PBO n (%)	CP5 n (%)	CP10 n (%)
ITT Population	132	133	134	160	321	316	159	315	318	108	204	201	204	122	243	245
Completed	101 (75)	107 (81)	103 (77)	n.a.	n a.	n.a.	138 (86)	261 (82)	252 (84)	86 (80)	150 (74)	158 (79)	162 (79)	105 (86)	232 (95)	218 (89)
Total discontinued	14 (10)	26 (20)	31 (23)	32 (20)	71 (22)	51 (16)	21 (13)	54 (17)	66 (21)	22 (20)	54 (26)	43 (21)	42 (21)	17 (14)	11 (5)	27 (11)
Discontinuations due to AEs	8 (6)	12 (9)	13 (10)	12 (7)	41 (13)	27 (9)	5 (3)	22 (7)	31 (10)	7 (7)	25 (12)	24 (12)	25 (12)	5 (4)	3 (1)	10 (4)
Deaths	*0*	*0*	*1 (0.7)*[a]	*1 (0.6)*	*6 (1.9)*[b]	*1 (0.3)*	*0*	*2 (0.6)*	*2 (0.6)*	*0*	*1 (0.5)*	*0*	*3 (1.5)*	*0*	*0*	*1 (0.4)*
AEs (other than death)	*8*	*12 (9)*	*12 (9)*	*11 (7)*	*35 (11)*	*26 (8)*	*5 (3)*	*20 (6)*	*29 (9)*	*7 (7)*	*24 (12)*	*24 (12)*	*22 (11)*	*5 (4)*	*3 (1)*	*9 (4)*
Other withdrawals																
Insufficient treatment effect	11 (8)	2 (2)	5 (4)	4 (3)	7 (2)	3 (1)	6 (4)	16 (5)	12 (4)	6 (6)	6 (3)	7 (4)	6 (3)	7 (6)	1 (0.4)	1 (0.4)
Protocol violation	7 (5)	2 (2)	8 (6)	4 (3)	6 (2)	6 (2)	n.r.	n.r.	n.r.	n r.	n.r.	n.r.	n.r.	2 (2)	2 (1)	8 (3)
Lost to follow up	1 (2)	1 (1)	1 (1)	3 (2)	5 (2)	0	2 (1)	1 (0.3)	2 (1)	0	2 (1)	1 (1)	0	-	-	-
Consent withdrawn	3 (2)	9 (7)	5 (4)	4 (3)	8 (3)	11 (4)	1 (0.6)	8 (3)	5 (2)	1 (1)	4 (2)	2 (1)	1 (1)	2 (2)	4 (2)	6 (2)
Other	7 (5)	2 (2)	8 (6)	7 (4)	13 (4)	10 (3)	6 (4)	8 (3)	14 (4)	8 (7)	18 (9)	9 (5)	12 (6)	1 (1)	1 (0.4)	2 (1)

Source: CSR A3921032, CSR A3921044, CSR A3921045, CSR A3921046, CSR A3921064

[a] Subject 10721004 transitioned at Day 85 from placebo to CP10 for 46 days

[b] 3 of the patients died after withdrawing from study due to AEs

6.1.3 Subject Disposition

Table 13 summarizes patient disposition by trial and treatment assignment. Overall, more patients discontinued from Phase 3 studies in the tofacitinib and adalimumab groups compared with placebo, except in the monotherapy study 1045.

Higher proportions of tofacitinib- (6-12%) that placebo-treated (3-7%) patients discontinued study participation due to adverse events in a dose-dependent manner in all DMARD background studies. In the monotherapy study 1045 the rates were comparable among all groups. Reverse trends were observed for discontinuations due to lack of efficacy across all studies (1-4% in tofacitinib groups vs. 3-8% in placebo group).

6.1.4 Analysis of Primary Endpoint(s)

ACR20 Response Rates

ACR20 response criteria were used to assess superiority of two doses of tofacitinib (5 mg and 10 mg BID) over placebo in all five Phase 3 studies at either Month 3 (studies 1032 and 1045) or Month 6 (studies 1044, 1046, and 1064) as the first of several primary endpoints.

The American College of Rheumatology's response in RA (ACR20) is calculated as a ≥20% improvement in:

- tender joint count (68) and
- swollen joint counts (66) and
- 3 of the 5 remaining ACR-core set measures:
    - patient global assessments of arthritis on a visual analog scale (VAS),
    - physician global assessment of arthritis on a VAS,
    - patient reported pain on a VAS,
    - patient assessment of physical function (e.g., Health Assessment Questionnaire-Disability Index [HAQ-DI], and
    - acute-phase reactant (e.g., CRP).

Similarly, ACR50, and 70 are calculated with the respective percent improvement and were assessed as major secondary endpoints.

Tofacitinib administration at both doses (5 mg and 10 mg BID) showed statistical and clinically significant dose-related increases in ACR20 response rates in all 5 Phase 3 studies and were comparable to the adalimumab active comparator in study 1064, as summarized in Table 14. ACR50 and ACR70 response rates are also included for completeness, and were also higher in tofacitinib-treated patients.

Table 14. Summary of ACR Response Rates in the Phase 3 RA Studies

Percentage of ACR Responders in the Phase 3 RA Studies by Trial Treatment (FAS Population, NRI)								
	PBO[#] + DMARD	CP 5 mg BID + DMARD	CP 10 mg BID + DMARD	CP 5 mg BID Mono	CP 10 mg BID Mono	Adalimumab	p-value* (5mg BID)	p-value* (10mg BID)
Patients with incomplete response to prior TNF inhibitor therapy								
A3921032 (TNF-IR), MTX background Tx	(n=131)	(n=132)	(n=133)	-	-	-	Month 3	
ACR20	24	42	48				0.0025	<0.0001
ACR50	8	26	28				<0.0001	<0.0001
ACR70	2	14	11				0.0001	0.0017
Patients with incomplete response to MTX or other DMARDs								
A3921044 (MTX-IR), MTX background Tx	(n=154)	(n=309)	(n=309)	-	-	-	Month 6	
ACR20	25	51	62				<0.0001	<0.0001
ACR50	8	32	44				<0.0001	<0.0001
ACR70	1	15	22				<0.0001	<0.0001
A3921046 (DMARD-IR), DMARD background Tx	(n=157)	(n=311)	(n=309)	-	-	-	Month 6	
ACR20	31	53	58				<0.0001	<0.0001
ACR50	13	34	37				<0.0001	<0.0001
ACR70	3	13	16				<0.0001	<0.0001
A3921064 (MTX-IR), MTX background Tx	(n=106)	(n=196)	(n=196)	-	-	(n=199)	Month 6	
ACR20	28	52	53			47 (p=0.0008)*	<0.0001	<0.0001
ACR50	12	37	35			28 (p=0.0006)*	<0.0001	<0.0001
ACR70	2	20	22			9 (p=0.0031)*	<0.0001	<0.0001
A3921045 (DMARD-IR), No background Tx	(n=120)	-	-	(n=241)	(n=242)	-	Month 3	
ACR20	27			60	66		<0.0001	<0.0001
ACR50	13			31	37		<0.0001	<0.0001
ACR70	6			15	20		0.0026	<0.0001

Source: Summary of Clinical Efficacy, CSRs A3921032, A3921044, A3921045, A3921046, A3921064,
*p-value versus placebo; [#] -Placebo monotherapy in study A3921045, NRI-non-responder imputation; PBO-placebo

Tofacitinib-treatment was clearly associated with an increase in the proportion of responders at all levels of ACR responses, and the differences were statistically significant compared to the placebo control groups. There did not appear to be a consistent dose-response effect between the 5 mg and 10 mg BID doses. The clinical benefit of tofacitinib 5 mg BID and 10 mg was generally comparable. The observed numerical differences in ACR20 response rates between the two doses were small and of questionable clinical significance. Further the ACR50 and ACR70 responses were not consistently dose-dependent across the randomized controlled studies. For example, in study A3921032, ACR70 responses were numerically lower in the 10 mg BID dose group, consistent with the findings in dose-ranging study A3921025, where both ACR50 and ACR70 responses were numerically lower in the 10 mg BID dose group (see Figure 4).

In Study 1064, responses in the tofacitinib and adalimumab treatment groups were numerically higher in the tofacitinib groups compared with adalimumab control, consistent with the observations from the dose-ranging study 1035.

Sensitivity Analyses of ACR Response Rates

Sensitivity analyses of ACR20 response rates shown in Table 15 were conducted by the FDA statistical review team, Drs. Yongman Kim and Joan Buenconsejo, using the intent-to-treat (ITT) population. The results were consistent with the primary analyses where both tested tofacitinib doses were superior to placebo in all five efficacy studies, supporting the overall efficacy of tofacitinib in the domain of signs and symptoms of RA.

Further, in study 1064, ACR20 responses were numerically higher for both tofacitinib groups compared with active comparator adalimumab, also consistent with the primary analysis.

Table 15. Sensitivity Analysis of ACR20 Response Rates (ITT Population)

Sensitivity Analysis of ACR20 Response Rates (ITT Population)					
Treatment	**N**	**n**	**Response Rate**	**Difference vs. PBO**	**P-value**
Study A3921032 (Month 3)					
CP 5 mg	133	55	41 %	17 %	0.0030
CP 10 mg	134	64	48 %	24 %	<0.0001
PBO	132	32	24 %		
Study A3921044 (Month 6)					
CP 5 mg	321	159	50 %	26 %	<0.0001
CP 10 mg	316	191	60 %	36 %	<0.0001
PBO	160	39	24 %		
Study A3921045 (Month 3)					
CP 5 mg	243	144	59 %	33 %	<0.0001
CP 10 mg	245	159	65 %	39 %	<0.0001
PBO	122	32	26 %		
Study A3921046 (Month 6)					
CP 5 mg	315	164	52 %	21 %	<0.0001
CP 10 mg	318	180	57 %	26 %	<0.0001
PBO	159	49	31 %		
Study A3921064 (Month 6)					
CP 5 mg	204	101	50 %	22 %	0.0002
CP 10 mg	201	103	51 %	23 %	<0.0001
ADA 40 mg	204	94	46 %	18 %	0.0017
PBO	108	30	28 %		

Source: FDA Statistics Briefing Document, Arthritis Advisory Committee, May 09, 2012

Disease Activity Score (DAS)28<2.6

In addition to assessing ACR criteria for response to treatment, disease activity was also measured in all Phase 3 studies using Disease Activity Score (DAS) which is a composite endpoint with differential weighting given to each component. The components of the DAS28 arthritis assessment include:

- tender joint count (28 joints to include bilateral shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees.),
- swollen joint count (28),
- an acute phase reactant (ESR or CRP)
- patient's global assessment of arthritis.

There is a fair amount of overlap with the ACR response criteria, as DAS also uses tender and swollen joint counts, along with an inflammatory marker (ESR or CRP), and a physician's global assessment to calculate a disease activity score. However there are a number of important differences: 1) DAS describes disease activity at a given point in time, whereas ACR responses describe relative improvement; 2) DAS28 uses an abbreviated joint count that does not include the joints of the feet; 3) ACR responses incorporate patient-reported pain and an assessment of physical function as part of the core variables whereas the DAS does not.

The DAS components are summed mathematically into a single numerical value ranging from 0 to 10. A DAS28 score >5.1 is indicative of high disease activity, and <2.6 of low disease activity. A change of ≥1.2 in DAS28 score is considered clinically significant. DAS28-4(ESR) uses all 4 components listed above and ESR as the acute-phase reactant. DAS28-3(CRP) uses CRP as the acute-phase reactant but does not include the Patient's Global Assessment of Arthritis.

The proportion of patients with low disease activity defined as DAS28-4(ESR) of less than 2.6 at Months 3 (studies 1032 and 1045) or Month 6 (studies 1044, 1046, 1064) was measured as the last in the sequence of primary endpoints in all Phase 3 studies.

As shown in Table 16 below, the overall proportions of patients with DAS28-4(ESR) <2.6 were small (<16%) across treatment arms even though tofacitinib–treated patients had numerically higher proportions than placebo group. Statistical significance was reached only for studies 1032, 1046 and 1064 but not for study 1045. Note, for study 1044, this endpoint was the last in the hierarchy of endpoints and would not have been eligible for testing if the radiographic endpoints failed. The radiographic endpoint results are discussed below, in the Section Change in Modified Total Sharp Score from Baseline (Study 1044).

Table 16. Proportion of Patients Achieving DAS28-4(ESR)<2.6 in the Phase 3 RA Studies

Proportion of Patients Achieving DAS28-4(ESR) <2.6 in the Phase 3 RA Studies, by Trial Treatment (FAS Population, NRI)								
	PBO[#] + DMARD	CP 5 mg BID +DMARD	CP 10 mg BID +DMARD	CP 5 mg BID Mono	CP 10 mg BID Mono	Adalimumab	p-value* (5mg BID)	p-value* (10mg BID)
Patients with incomplete response to prior TNF inhibitor therapy								
A3921032 (TNF-IR) MTX background Tx, DAS28-4(ESR)<2.6, n (%)	(n=120) 2 (2)	(n=119) 8 (7)	(n=125) 11 (9)	-	-	-	Month 3 0.0497	0.0105
Patients with incomplete response to MTX or other DMARDs								
A3921044 (MTX-IR) MTX background Tx DAS28-4(ESR)<2.6, n (%)	(n=129) 2 (2)	(n=265) 19 (7)	(n=257) 47 (18)	-	-	-	Month 6 0.0035	<0.0001
A3921046 (DMARD-IR) DMARD background Tx DAS28-4(ESR)<2.6, n (%)	(n=148) 4 (3)	(n=263) 24 (9)	(n=270) 36 (13)	-	-	-	Month 6 0.0038	<0.0001
A3921064 (MTX-IR) MTX background Tx DAS28-4(ESR)<2.6, n (%)	(n=92) 1 (1)	(n=177) 11 (6)	(n=176) 22 (13)	-	-	(n=178) 12 (7) (p=0.0091)*	Month 6 0.0151	<0.0001
A3921045 (DMARD-IR) No background Tx DAS28-4(ESR)<2.6, n (%)	(n=114) 5 (4)	-	-	(n=232) 13 (6)	(n=229) 20 (9)	-	Month 3 0.6179	0.1042

Source: Summary of Clinical Efficacy (amended, February 08, 2012), CSRs A3921032, A3921044, A3921045, A3921046, A3921064,
*p-value versus placebo; [#] -Placebo monotherapy in study A3921045, NRI-non-responder imputation; PBO-placebo;
Grayed out-this endpoint was the last in the hierarchy of endpoints where radiographic endpoints failed; NRI-non-responder imputation

Sensitivity analyses of DAS29-4(ESR)<2.6 shown in Table 17, were conducted by the FDA statistical review team, using the intent-to-treat (ITT) population, instead of FAS population. These results were consistent with the primary analyses. However, in the case of ITT analyses tofacitinib 5 mg dose group reached statistical superiority to placebo only in study 1046.

In study 1064, adalimumab DAS28 responses were also statistically superior compared with placebo, and comparable to both tofacitinib groups.

Table 17. Sensitivity Analysis of DAS28-4(ESR)<2.6 Response Rates (ITT Population)

Sensitivity Analysis of DAS28-4(ESR)<2.6 Response Rates (ITT Population)					
Treatment	**N**	**n**	**Response Rate**	**Difference vs. PBO**	**P-value**
Study 1032 (Month 3)					
CP 5 mg	133	8	6 %	4 %	0.0546
CP 10 mg	134	11	8 %	6 %	0.0113
PBO	132	2	2 %		
Study 1044 (Month 6)					
CP 5 mg	321	19	6 %	5 %	n.r.
CP 10 mg	316	41	13 %	12 %	n.r.
PBO	160	2	1 %		
Study 1045 (Month 3)					
CP 5 mg	243	13	6 %	2 %	0.6025
CP 10 mg	245	20	8 %	5 %	0.1454
PBO	122	5	4 %		
Study 1046 (Month 6)					
CP 5 mg	315	24	8 %	5 %	0.0069
CP 10 mg	318	36	11 %	7 %	0.0011
PBO	159	4	3 %		
Study 1064 (Month 6)					
CP 5 mg	204	11	5 %	4 %	0.0510
CP 10 mg	201	22	11 %	10 %	0.0014
ADA 40 mg	204	12	6 %	5 %	0.0371
PBO	108	1	1 %		

Source: FDA Statistics Briefing Document, Arthritis Advisory Committee, May 09, 2012

DAS28 <2.6 indicates low disease activity but some patients continue to have active disease. Therefore, additional analyses were performed to assess the number of active (swollen and tender) joints (0, 1, 2, more than 2) as evidence of residual disease activity in patients who achieved DAS28 <2.6. This approach has been previously accepted by the Agency and serves to provide health care professionals with additional clinically useful information.

Among patients achieving DAS28 ESR <2.6, there were no consistent trends across the treatment groups with regards to the number of residual active joints with the caveat that this descriptive analysis is based on a small number of observations particularly in placebo groups.

Table 18. Percentage (Number) of Patients Achieving DAS28-4(ESR)<2.6 with Residual Active Joints in Phase 3 RA Studies

Percentage (Number) of Patients Achieving DAS28-4(ESR)<2.6 with Residual Active Joints in Phase 3 RA Studies						
Treatment	**N**	**n**	**0 Joints**	**1 Joint**	**2 Joints**	**>2 Joints**
Study 1032 (Month 3)						
CP 5 mg	133	8	38 (3)	0	38 (3)	25 (2)
CP 10 mg	134	16	38 (6)	13 (2)	19 (3)	31 (5)
PBO	132	2	0	0	0	100 (2)
Study 1044 (Month 6)						
CP 5 mg	321	19	42 (8)	5 (1)	32 (6)	21 (4)
CP 10 mg	316	41	36 (15)	17 (7)	7 (3)	40 (17)
PBO	160	2	50 (1)	0	0	50 (1)
Study 1045 (Month 3)						
CP 5 mg	243	14	43 (6)	3 (21)	3 (21)	2 (14)
CP 10 mg	245	22	50 (11)	18 (4)	14 (3)	18 (4)
PBO	122	5	60 (3)	20 (1)	0	20 (1)
Study 1046 (Month 6)						
CP 5 mg	315	33	45 (15)	9 (3)	18 (6)	27 (9)
CP 10 mg	318	41	46 (19)	15 (6)	5 (4)	34 (14)
PBO	159	3	100 (3)	0	0	0
Study 1064 (Month 6)						
CP 5 mg	204	12	8 (1)	0	8 (1)	83 (10)
CP 10 mg	201	24	58 (14)	8 (2)	8 (2)	25 (6)
ADA 40 mg	204	1	0	100 (1)	0	0
PBO	108	11	55 (6)	9 (1)	9 (1)	36 (4)

Source: Summary of Clinical Efficacy, adapted from Tables 3.3.A, 3.3.B, 3.4.A, 3.5.A, 3.6.A; N-number of treated patients; n-number of patients achieving DAS28-4(ESR)<2.6

Health Assessment Questionnaire-Disability Index (HAQ-DI)

Physical function was assessed using Health Assessment Questionnaire–Disability Index (HAQ-DI). The HAQ-DI assesses the degree of difficulty a patient has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

The change from baseline to Month 3 in HAQ-DI was used as a primary endpoint in all Phase 3 studies. As shown in Table 19 below, compared with placebo, statistically significant decreases in mean HAQ-DI at Month 3 were observed in both tofacitinib dose groups in all Phases 3 studies, except in study 1044 as this endpoint fell below the radiographic endpoints in the predefined hierarchical sequence for analysis. The HAQ-DI improvements were comparable between tofacitinib and adalimumab groups. The treatment effect sizes (improvement over placebo) were also clinically meaningful (>0.2 units) across all Phase 3 studies. In Phase 2 studies, the improvements in HAQ-DI were consistent with the findings in Phase 3 studies (data not shown).

Table 19. Mean Change from Baseline to Month 3 in HAQ-DI, in the Phase 3 RA Studies

Mean Changes from Baseline in HAQ-DI at Month 3 in the Phase 3 RA Studies, by Trial Treatment (FAS Population)								
	PBO[#] + DMARD	CP5 mg BID +DMARD	CP10 mg BID +DMARD	CP5 mg BID Mono	CP10 mg BID Mono	Adalimumab	p-value* (5mg BID)	p-value* (10mg BID)
Patients with incomplete response to prior TNF inhibitor therapy								
A3921032 (TNF-IR) MTX background Tx	(n=118)	(n=117)	(n=125)	-	-	-		
HAQ-DI Change	-0.23	-0.47	-0.49				0.0002	<0.0001
Patients with incomplete response to MTX or other DMARDs								
A3921044 (MTX-IR) MTX background Tx	(n=146)	(n=294)	(n=300)	-	-	-		
HAQ-DI Change	-0.15	-0.4	-0.57				<0.0001	<0.0001
A3921046 (DMARD-IR) DMARD background Tx	(n=147)	(n=292)	(n=292)	-	-	-		
HAQ-DI Change	-0.21	-0.47	-0.57				<0.0001	<0.0001
A3921064 (MTX-IR) MTX background Tx	(n=98)	(n=188)	(n=185)	-	-	(n=190)		
HAQ-DI Change	-0.25	-0.56	-0.64			-0.51 (p <0.0001)*	<0.0001	<0.0001
A3921045 (DMARD-IR) No background Tx	(n=109)	-	-	(n=237)	(n=227)	-		
HAQ-DI Change	-0.19			-0.50	-0.57		<0.0001	<0.0001

Source: Summary of Clinical Efficacy, CSRs A3921032, A3921044, A3921045, A3921046, A3921064;
*p-value versus placebo; [#] -Placebo monotherapy in study A3921045, NRI-non-responder imputation; PBO-placebo
Grayed out-this endpoint was the last in the hierarchy of endpoints where radiographic endpoints failed;

Sensitivity analyses of HAQ-DI shown in Table 20, conducted by the FDA statistical review team, using the intent-to-treat (ITT) population and baseline observation carried forward (BOCF) for handling missing values, also showed results consistent with the primary analyses and Sponsor's analyses as where both tofacitinib doses were superior to placebo in all five efficacy studies. In study 1064, adalimumab DAS28 responses were also statistically superior compared with placebo, and comparable to both tofacitinib group.

Table 20. Sensitivity Analysis of Change form Baseline in HAQ-DI at Month 3 (ITT Population, BOCF)

Sensitivity Analysis of Change form Baseline in HAQ-DI (ITT Population)					
Treatment	N	LS Mean	Difference vs. PBO		
			LS Mean Difference	95% CI	P-value
Study 1032					
CP 5 mg	133	-0.4	-0.2	(-0.3, -0.1)	0.0007
CP 10 mg	134	-0.4	-0.2	(-0.3, -0.1)	0.0001
PBO	132	-0.2			
Study 1044					
CP 5 mg	321	-0.4	-0.2	(-0.3, -0.1)	0.0001
CP 10 mg	316	-0.5	-0.3	(-0.4, -0.2)	0.0001
PBO	160	-0.2			
Study 1045					
CP 5 mg	243	-0.5	-0.3	(-0.4, -0.1)	0.0001
CP 10 mg	245	-0.6	-0.4	(-0.5, -0.2)	<0.0001
PBO	122	-0.2			
Study 1046					
CP 5 mg	315	-0.4	-0.2	(-0.3, -0.1)	<0.0001
CP 10 mg	318	-0.5	-0.3	(-0.4, -0.2)	<0.0001
PBO	159	-0.2			
Study 1064					
CP 5 mg	204	-0.4	-0.2	(-0.3, -0.1)	0.0004
CP 10 mg	201	-0.5	-0.3	(-0.4, -0.2)	<0.0001
ADA 40 mg	204	-0.4	-0.2	(-0.3, -0.1)	0.0003
PBO	108	-0.2			

Source: FDA Statistics Briefing Document, Arthritis Advisory Committee, May 09, 2012
BOCF-baseline observation carried forward

Change in Modified Total Sharp Score from Baseline (Study 1044)

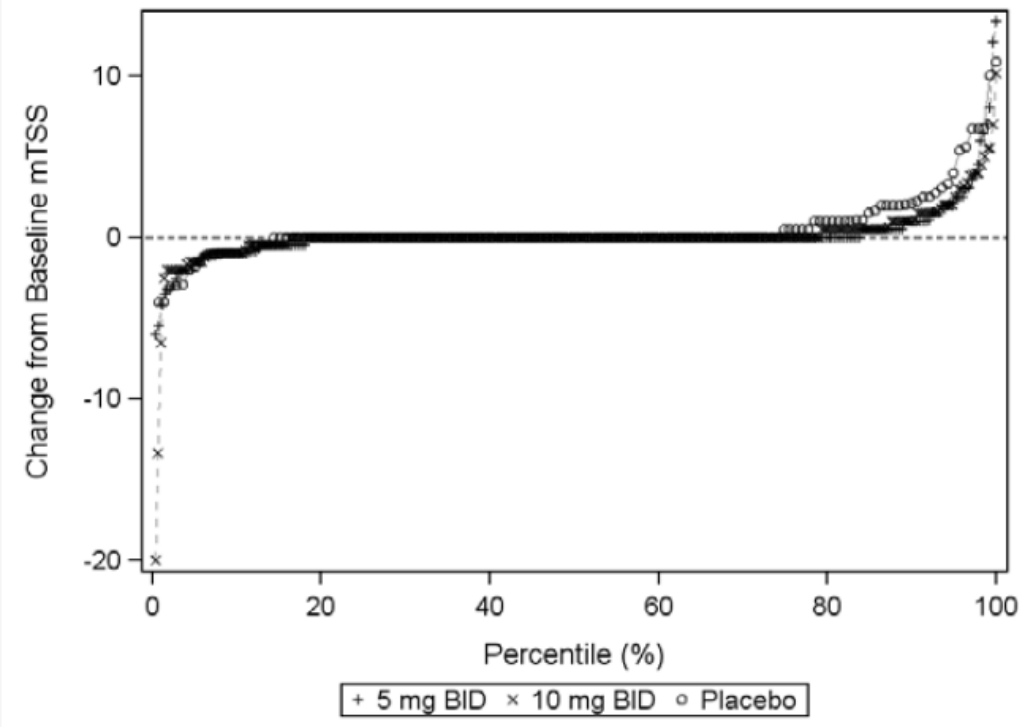
Radiographic outcomes were assessed only in Study 1044, using the change from baseline in Van der Heijde modified Sharp Scores (mTSS) at Month 6 as the second primary endpoint in a sequence of four endpoints. For this assessment, radiographs of hands and feet were obtained at Baseline (Visit 1), Month 6 (Visit 4), Month 12 (Visit 6) and Month 24 (Visit 10 or End of Study Visit). Patients who were identified as nonresponders, regardless of which treatment group to which the patient was assigned, were to have radiographs of hands and feet performed at Month 3 (Visit 3), but not Month 6.

The primary analysis of the radiographic outcome in Study 1044 excluded 17 patients from 2 sites with data integrity or procedural issues (see Table 9), as well as additional patients for whom valid post-baseline radiographs were not obtained. Thus the primary radiographic analysis excludes 21 (13%) placebo patients, 44 (14%) patients in the tofacitinib 5 mg group, and 24 (8%) patients in the tofacitinib 10 mg group. Scoring of all radiographs was done by two separate central, blinded assessors.

Cumulative Radiographic Data Distribution

As illustrated in Figure 6 below, which contains Study 1044 results and is consistent with the distribution observed in other RA programs, only a fraction (approximately 20%) of patients experience progression (above "0" on the graph) in the time frame of the study.

Figure 6. Cumulative Probability Plot of Radiograph Score Changes from Baseline to Month 6, Study 1044



Source: Figure 23 of the A3921044 Clinical Study Report

Placebo patients (designated by circles in Figure 6) did appear to have more worsening in mTSS scores than did tofacitinib-treated patients. However, based on the cumulative distribution data, patients in tofacitinib 5 mg BID dose group had numerically more radiographic benefit compared with patients in 10 mg BID group Table 21:

- More patients had no mTSS progression and
- Fewer patients had worsening mTSS.

This observation indicates inconsistency of the potential radiographic benefit with regards to dose.

Table 21. Cumulative Distribution of Patients Based on Radiographic Progression

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

Source: FDA Briefing Document, statistical analyses by Dr. Yongman Kim and Dr. Joan Buenconsejo

Analyses of the Primary Outcome

A primary analysis using analysis of covariance model and a sensitivity analysis using ANCOVA model on the rank were pre-specified in the protocol's statistical analysis plan.

In the primary analysis, only the change from baseline in mTSS for the tofacitinib 10 mg group achieved statistical significance compared to the placebo group (Table 22). Notably however, the estimated effect is smaller compared to what was assumed when powering for this study (0.4 versus 0.8 units, respectively). The placebo group also had less progression compared to what was assumed (0.5 versus 1.4 units, respectively).

Because the treatment effect is small, additional analyses were conducted to include a sensitivity analysis, which 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 22). Both doses were not significantly different from placebo at Month 12 based on the same analysis.

Results of the parametric primary analysis versus non-parametric analysis are summarized in Table 22 below.

(b) (4)

Table 22. Change from Baseline in mTSS, Study 1044

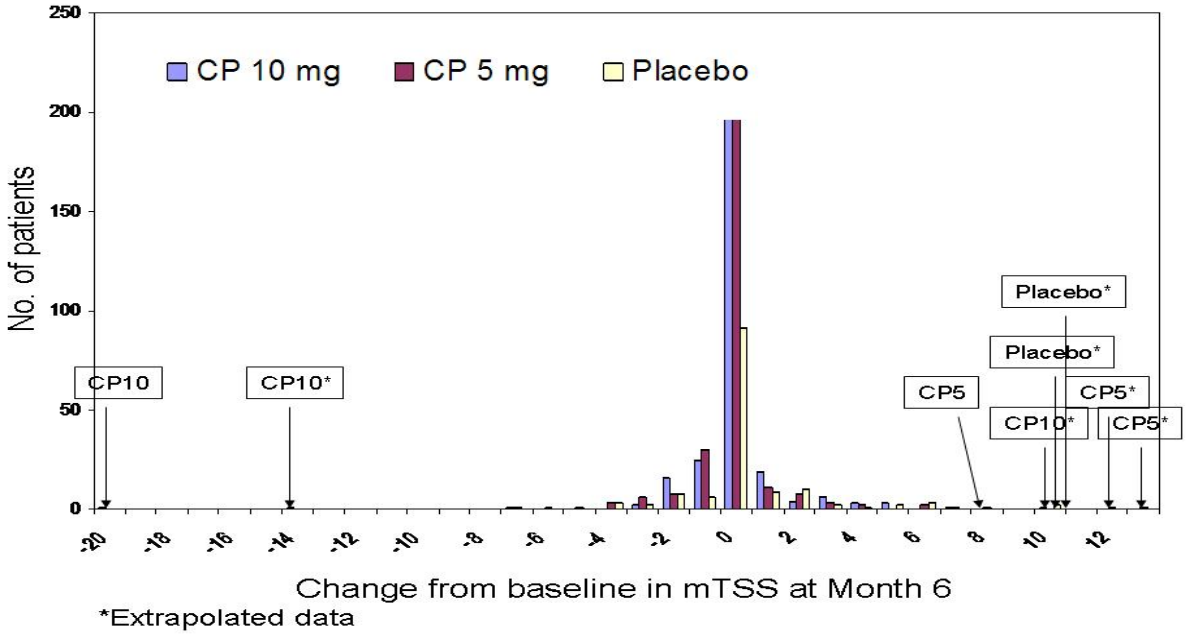
Analyses of Radiographic Outcomes: Change from Baseline in Modified Total Sharp Scores (mTSS) in Study A3921044			
	PBO + MTX	**CP5 mg BID + MTX**	**CP10 mg BID + MTX**
Assigned to study treatment (tx)	n=160	n=321	n=319
Received at least 1 dose of study tx	n=160	n=321	n=316
"Full Analysis Set"	n=156	n=316	n=309
Sponsor primary analysis (FAS, LEP, parametric)			
Month 6 (Primary Endpoint)	n=140*	n=278*	n=290*
mTSS LS means	0.47	0.12	0.06
p-value vs. placebo	-	0.0792	**0.0376**
Month 12	n=139*	n=286*	n=295*
mTSS LS means	0.92	0.29	0.05
p-value vs. placebo	-	0.0558	**0.0081**
FDA sensitivity analyses (FAS, LEP, non-parametric analyses)			
Month 6 (Primary Endpoint)	n=140*	n=278*	n=290*
ANCOVA with ranked data p-value	-	**0.0237**	0.1979
Month 12	n=139*	n=286*	n=295*
ANCOVA with ranked data p-value	-	0.0790	0.0578

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

Effect of Outliers

The magnitude of treatment effect in the CP 10 mg group is sensitive to outliers. The average change from baseline in the CP 10 mg group is 0.06. However, one patient in the 10 mg had a change of -20 units, and 3 patients had an absolute change of greater than 7 units (Figure 7). Of note, some outliers at Month 6 are observed data and others are linearly extrapolated (marked with asterisk in Figure 7) due to missing data at Month 6.

Figure 7. Frequency Distribution of Radiographic Data Showing Outliers



Source: FDA Slide Presentation, Arthritis Advisory Committee, May 09, 2012

To assess the significance of these outliers on the overall radiographic results, the primary parametric ANCOVA model was applied to the data after excluding observations with clinically unlikely degrees of change in mTSS at 6 months using two cutoffs:

- Outliers with extreme mTSS change from baseline >20 units (only one subject)
- Outliers with mTSS change from baseline >7 units (8 subjects across all treatment arms as marked in Figure 7).

Surprisingly, in contrast with the results from the full ANCOVA model, the results from this new analysis showed no statistically significant differences between either of tofacitinib doses and placebo (Table 23). Similar results were derived from nonparametric analyses of the same data (data not shown). This was mostly due to the fact that two patients in the tofacitinib 10 mg BID dose group had extreme values of "improving" mTSS score at 6 months.

The observations from the outlier analysis indicate that the apparent benefit on the mean change from baseline in the 10 mg BID dose group based on group means using ANCOVA may be driven by a few extreme observations and may not represent true overall benefit. This is of particular importance in the overall treatment benefit and risk-to-benefit assessment of tofacitinib.

Table 23. Sensitivity Analysis of Radiographic Outcomes, Month 6: Effect of Outliers

Sensitivity Analysis of Radiographic Outcomes, Month 6: Effect of Outliers, Study 1044			
	PBO + MTX	**CP5 mg BID + MTX**	**CP10 mg BID + MTX**
Primary analysis (FAS, LEP, parametric)			
Full Analysis Set	n=140*	n=278*	n=290*
mTSS LS means	0.47	0.12	0.06
LS Mean Difference	-	0.34	**0.40**
p-value vs. placebo	-	0.0792	**0.0376**
Excluding Subjects with mTSS change ≥ 20 units			
FAS excluding Subject 10421014*	n=140*	n=278*	n=289*
mTSS LS means	0.45	0.11	0.12
LS Mean Difference	-	0.34	**0.33**
p-value vs. placebo	-	0.056	**0.061**
Excluding Subjects with mTSS change ≥ 7 units			
Full Analysis Set excluding outliers	n=138*	n=275*	n=287*
mTSS LS means	0.32	-0.003	0.14
LS Mean Difference	-	0.32	**0.17**
p-value vs. placebo	-	0.021	**0.203**

Source: FDA Statistical analyses by Dr. Yongman Kim and Dr. Joan Buenconsejo
*Subject 10421014's baseline score is 42.5. At Month 6, patient's score is 22.5

Analysis of Patients with No Radiographic Progression

Further illustrating the lack of conclusiveness of the radiographic data, a change in the definition of "no progression" from a change in mTSS of ≤0.5 units to 0 units results in a loss in statistical significance for the tofacitinib 10 mg dose group, as shown in Table 24 below. Although the tofacitinib 10 mg dose group had the smallest mean change from baseline to Month 6 in mTSS (0.06 units), the tofacitinib 5 mg dose group had the higher proportion of patients experiencing no progression.

Table 24. Rates of "No Radiographic Progression"

Percentage of Patients with Radiographic Progression of ≤ 0.5 in Study 1044 at Month 6 (Imputation Using Linear Extrapolation, FAS Population)					
Study A3921044 (MTX-IR) MTX background Tx	**PBO + MTX**	**CP5 mg BID + MTX**	**CP10 mg BID + MTX**	**p-value* (5mg BID)**	**p-value* (10mg BID)**
No Progression defined by applicant as Change in mTSS ≤ 0.5					
Total umber of patients	139	277	290		
Patients with no progression, n (%)	108 (78)	246 (89)	252 (87)		
Difference from placebo	-	11%	9%	**0.0055**	**0.0230**
No Progression defined by FDA reviewer as Change in mTSS ≤ 0					
Total umber of patients	140	278	290		
Patients with no progression, n (%)	104 (74)	233 (84)	229 (79)		
Difference from placebo	-	10%	5%	**0.0200**	0.2766

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

Missing Radiographic Data

As noted in Table 9 above, some patients with observed radiographic data at Month 6 from 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.

Conclusion of Radiographic Outcomes

In summary, it is difficult to draw definitive conclusions regarding the treatment effect of tofacitinib on radiographic outcomes. Issues driving uncertainty regarding these results include:

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

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

In light of the uncertainties with the interpretation of the radiographic data from study 1044, it is important to address the biological plausibility of radiographic benefit with the use of tofacitinib. Structural damage in RA is manifested by: (1) cartilage damage, driven by inflammatory hyperplastic synovitis leading to apoptotic chondrocyte cell death and impaired cartilage regeneration, and (2) by bone erosions, resulting from cytokine (particularly receptor activator of NF-kB ligand, RANKL)-driven osteoclast differentiation and invasion of the subchondral periarticular bone.[7] As an inhibitor of JAK-STAT signaling pathway, tofacitinib inhibited multiple downstream pro-inflammatory molecules, including RANKL, providing a mechanistic rationale for its potential effect on bone erosions.[8] Suppressing synovial inflammation presents a rationale for tofacitinib's potential effect on cartilage loss. Recent experiments provide additional insights on the link between the RA synovitis and cartilage destruction and the dose-dependent effect of tofacitinib on those two components of structural damage.[9] Therefore, based on the general understanding of the pathogenesis of structural damage in RA, it is biologically plausible that tofacitinib may have an overall beneficial effect on structural damage. This however, would need to be substantiated in the clinical setting as also recommended by the Arthritis Advisory Committee (see Section 9.3 Advisory Committee Meeting)

6.1.5 Analysis of Secondary Endpoints(s)

ACR Response Rates

ACR50 and 70 Responses

ACR50 and 70 response categories are summarized in Table 14 above. All five Phase 3 controlled studies demonstrated superiority of tofacitinib over placebo for ACR50 and ACR70 categories. Similarly to ACR 20 category, there did not appear to be a consistent dose-response effect between the 5 mg and 10 mg BID doses.

ACR Components

Additional sensitivity analysis of mean change from baseline at Month 3 in all ACR components, was consistent with the results of the primary analysis of ACR20 response rates as shown in Table 25. Treatment with tofacitinib resulted in greater improvement

7 McInnes IB, Schett G, The pathogenesis of rheumatoid arthritis, N Engl J Med, 2011 Dec 8;365(23):2205-19
8 Mori T, et al.,IL-1β and TNFα-initiated IL-6-STAT3 pathway is critical in mediating inflammatory cytokines and RANKL expression in inflammatory arthritis, International Immunology 2011 Sept 21;23(11):701-712
9 Meashima K, et al., The JAK inhibitor tofacitinib regulates synovitis through inhibition of interferon-γ and interleukin 17 production by human CD4+T cells, Arthritis Rheum, June 2012;64(6):1790-1798

compared with control, in all ACR components, without a consistent dose-response (5 mg BID vs. 10 mg BID).

Table 25. Mean Change from Baseline in ACR Components at 3 Months, by Phase 3 Trial

Mean Change from Baseline in ACR Components at 3 Months, by Phase 3 Trial												
	Placebo			CP 5 mg BID			CP 10 mg BID			Adalimumab		
Study	N	LS Mean	SE	N	LS Mean	SE	N	LS Mean	SE	N	LS Mean	SE
Tender painful joint count												
1032	118	-6.74	1.27	119	-12.49	1.25	125	-14.12	1.28			
1044	146	-5.66	0.83	294	-11.33	0.59	300	-12.99	0.59			
1046	148	-8.57	0.85	294	-13.62	0.62	292	-15.6	0.63			
1064	98	-6.83	1.09	188	-14.21	0.81	185	-14.77	0.81	190	-13.52	0.81
1045*	109	-9.14	1.14	237	-15.01	0.79	229	-16.41	0.8			
Swollen joint count												
1032	118	-4.78	0.8	119	-9.28	0.79	125	-10	0.8			
1044	146	-4.06	0.54	294	-8.35	0.38	300	-8.72	0.38			
1046	148	-5.09	0.6	294	-7.76	0.43	292	-8.71	0.44			
1064	98	-5.98	0.63	188	-10.15	0.47	185	-9.89	0.47	190	-9.28	0.46
1045*	109	-5.14	0.74	237	-9.62	0.51	229	-10.52	0.52			
Patient's assessment of arthritis pain												
1032	115	-8.26	2.41	114	-27.16	2.43	119	-24.95	2.48			
1044	146	-8.88	1.75	295	-23.32	1.24	300	-28.05	1.24			
1046	148	-11.38	1.72	293	-24.18	1.24	292	-26.78	1.25			
1064	98	-9.57	2.17	188	-26.85	1.61	185	-28.11	1.62	190	-22.26	1.6
1045*	108	-10.71	2.14	237	-26.94	1.47	228	-31.06	1.5			
Patient's global assessment of arthritis												
1032	117	-9.19	2.42	114	-23.39	2.43	120	-25.05	2.48			
1044	146	-8.59	1.73	295	-22.31	1.22	299	-27.67	1.22			
1046	148	-12.54	1.72	293	-24.82	1.24	292	-28.19	1.25			
1064	98	-7.37	2.22	188	-23.89	1.65	185	-26.6	1.66	190	-21.37	1.64
1045*	108	-11.19	2.1	237	-26.99	1.45	229	-30.94	1.47			
Physician's global assessment of arthritis												
1032	115	-19.26	2.18	111	-30.26	2.2	119	-30.14	2.22			
1044	146	-13.5	1.45	294	-28.93	1.03	300	-33.83	1.02			
1046	148	-21.22	1.42	291	-30.37	1.03	290	-33.25	1.04			
1064	98	-16.76	1.91	184	-31.61	1.43	185	-31.47	1.43	189	-28.85	1.42
1045*	109	-18.44	1.81	238	-32.39	1.24	229	-36.8	1.27			
C-reactive protein												
1032	118	3.12	1.4	118	-11.77	1.39	124	-12.17	1.41			
1044	145	-0.81	1.1	296	-8.91	0.77	299	-11.53	0.77			
1046	147	-1.99	0.99	281	-11.79	0.72	273	-12.22	0.73			
1064	99	1.42	1.61	186	-9.66	1.2	184	-8.97	1.21	190	-8.24	1.19
1045*	108	-3.26	1.25	237	-12.6	0.85	228	-15.02	0.87			
HAQ-DI												
1032	118	-0.18	0.04	117	-0.43	0.04	125	-0.46	0.04			
1044	146	-0.15	0.04	294	-0.4	0.03	300	-0.54	0.03			
1046	147	-0.21	0.04	292	-0.46	0.03	292	-0.56	0.03			
1064	98	-0.24	0.05	188	-0.55	0.04	185	-0.61	0.04	190	-0.49	0.04
1045*	109	-0.19	0.05	237	-0.5	0.03	227	-0.57	0.03			

Source: Summary of Clinical Efficacy, adapted from Tables 16 and 34; *-Study 1045 is a monotherapy study

Time Course of ACR Response

The time course of ACR responses is discussed in Section 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects and presented graphically in Figure 11

Disease Activity Score (DAS)28

Secondary analyses on DAS28

The proportion of patients in the Phase 3 RA studies experiencing a clinically meaningful reduction in disease activity, as defined by improvement in DAS28-4 (ESR) of ≥1.2, is summarized in Table 26. A higher proportion of tofacitinib-treated patients experienced this level of improvement, supporting the overall treatment benefit of tofacitinib on signs and symptoms of disease.

Table 26. Proportion of Patients with DAS28-4(ESR) ≥1.2 Improvement in Phase 3 RA Trials

Proportion of Patients with DAS28-4(ESR) ≥1.2 Improvement in Phase 3 RA Trials, by Trial Treatment (FAS Population, NRI)								
	PBO + DMARD	CP 5 mg BID +DMARD	CP 10 mg BID +DMARD	CP 5 mg BID Mono	CP 10 mg BID Mono	Adalimumab	p-value* (5mg BID)	p-value* (10mg BID)
Patients with incomplete response to prior TNF inhibitor therapy								
A3921032 (TNF-IR) MTX background Tx	(n=120)	(n=119)	(n=125)	-	-	-	Month 3	
% Improved ≥1.2	28	59	69				<0.0001	<0.0001
Patients with incomplete response to MTX or other DMARDs								
A3921044 (MTX-IR) MTX background Tx	(n=129)	(n=265)	(n=257)	-	-	-	Month 6	
% Improved ≥1.2	23	54	66				<0.0001	<0.0001
A3921046 (DMARD-IR) DMARD background Tx	(n=148)	(n=263)	(n=270)	-	-	-	Month 6	
% Improved ≥1.2	32	57	64				<0.0001	<0.0001
A3921064 (MTX-IR) MTX background Tx	(n=92)	(n=177)	(n=176)	-	-	(n=178)	Month 6	
% Improved ≥1.2	32	54	55			50 (p<0.0026)*	0.0002	0.0001
A3921045 (DMARD-IR) No background Tx	(n=114)	-	-	(n=232)	(n=229)	-	Month 3	
% Improved ≥1.2	38			62	62		<0.0001	<0.0001

Source: Summary of Clinical Efficacy (amended submission 0008, February 08, 2012), CSRs A3921032, A3921044, A3921045, A3921046, A3921064,
*p-value versus placebo Grayed out-this endpoint was the last in the hierarchy of endpoints where radiographic endpoints failed; NRI-non-responder imputation

Time Course of DAS Response

The time course of DAS responses is discussed in Section 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects and presented graphically in Figure 11.

6.1.6 Other Endpoints

Change from baseline in SF-36 and FACIT-Fatigue scores

The applicant has submitted data for secondary endpoints of mean changes from baseline in SF-36 and Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) scale scores at Month 3.

SF-36 Health Survey: The SF-36 v.2 (Acute) is a 36-item generic health status measure. It measures 8 general health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. These domains can also be summarized as physical and mental component scores.

FACIT-Fatigue Scale: This is a patient completed questionnaire consisting of 13 items that assess fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better patient status (less fatigue).

The SF-36 was not developed specifically for RA, and there are features of the SF-36 that make it less desirable as a patient reported outcome measure. For example, there is not a clear separation of mental and physical components in the summary scores. (b) (4)

The Agency has not historically recognized improvement in fatigue as a distinct claim for RA, as fatigue and inflammation (reflected in the signs and symptoms claim for which ACR response criteria is used as the primary outcome measure) are intertwined, and treatments effective for reducing signs and symptoms would be expected to improve fatigue as well. The FACIT-F is a 13-item scale originally developed to measure fatigue in patients with cancer. Some validation work for this scale in RA patients has been published[10]; however further work on divergent validity and stability of the instrument in RA needs to be performed.

As the SF-36 and FACIT-F endpoints (b) (4) they were not reviewed in detail. However, the applicant's submitted analyses of these endpoints were consistent with the overall conclusion of treatment benefit associated with tofacitinib treatment.

6.1.7 Subpopulations

Explorations of efficacy were conducted by the Sponsor for subpopulations by age (18-44, 45-64 and .65 years), gender, weight (<60, 60 to 100, and >100 kg), BMI (<18.5, 18.5 to <25, 25 to <30, and ≥30), race (white, black, Asian, other), region (United States

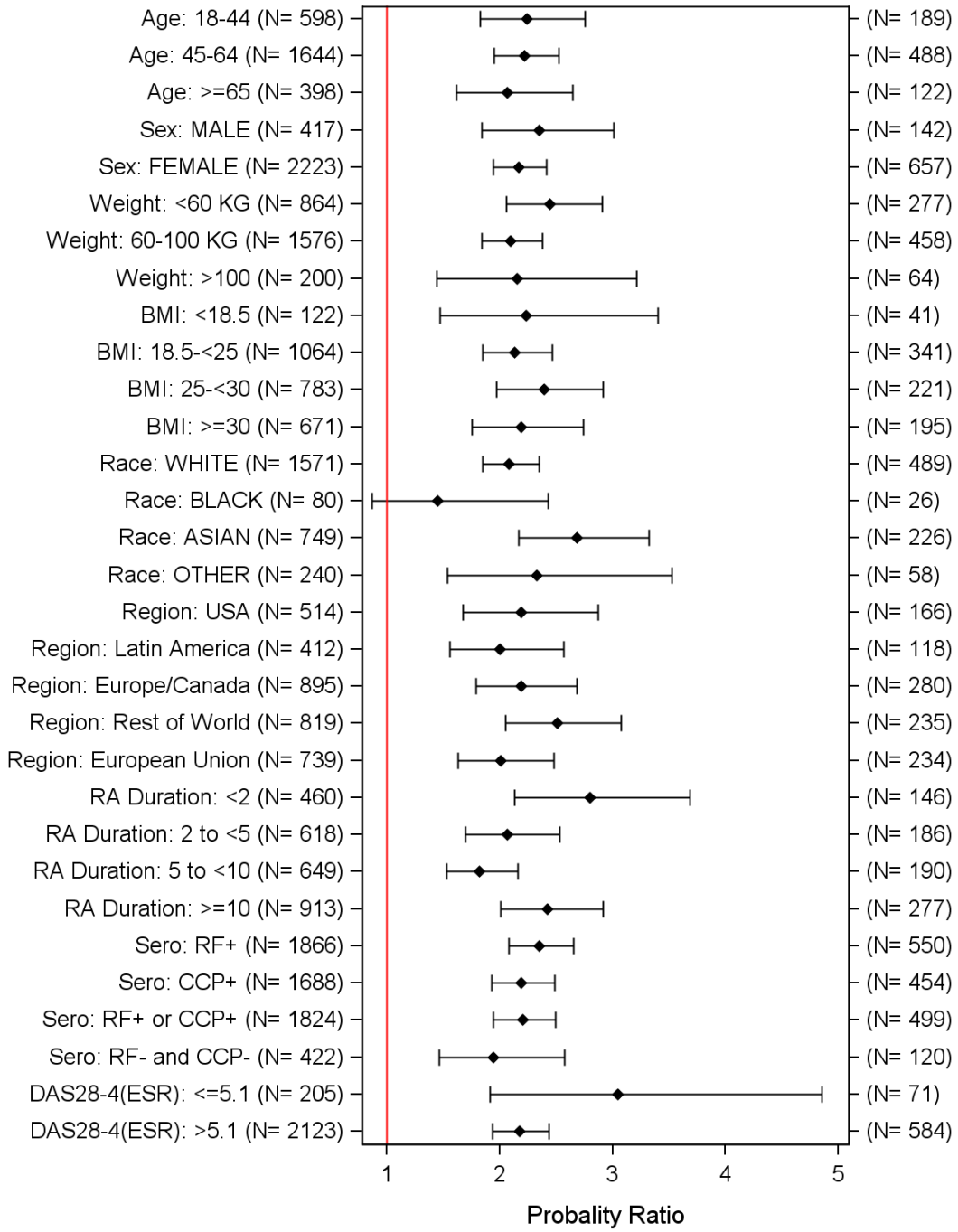
10 Hewlett S, Dures E, Almeida C, Measures of fatigue, Arthritis Care Res, 2011 Nov:63 Suppl 11:A263-86

of America, Latin America, Europe/Canada, rest of the world, and European Union), RA duration (<2, 2 to <5, 5 to <10 and ≥10 years), serological status (RF positive, CCP positive, either RF positive or CCP positive, both RF negative and CCP negative), DAS28-4(ESR) (≥5.1 and >5.1). Efficacy results were analyzed by these factors using pooled Phase 2 and Phase 3 data on ACR20 (Figure 8), and HAQ-DI (Figure 9) at Month 3.

Efficacy on signs and symptoms (ACR20) and physical function (HAQ-DI) appeared to be consistent with all the subgroups. Even though consistent with the overall benefit, the treatment effect was somewhat lower in blacks. This may be a result of insufficient power to demonstrate benefit in this subgroup as the sample size was small. Further, the Sponsor reported that black patients had similar RA disease characteristics, e.g. seropositivity, baseline ACR component scores, but had somewhat higher mean baseline DAS28-4(ESR) and HAQ-DI and higher mean body mass and BMI than the white, Asian and other race categories. Also, PK have been shown to be consistent across racial categories and unlikely to explain this observation.

Further, the Sponsor has presented subgroups analysis for each of the proposed doses, 5 mg and 10 mg BID, which is consistent with the analysis presented in Figure 8 and Figure 9.

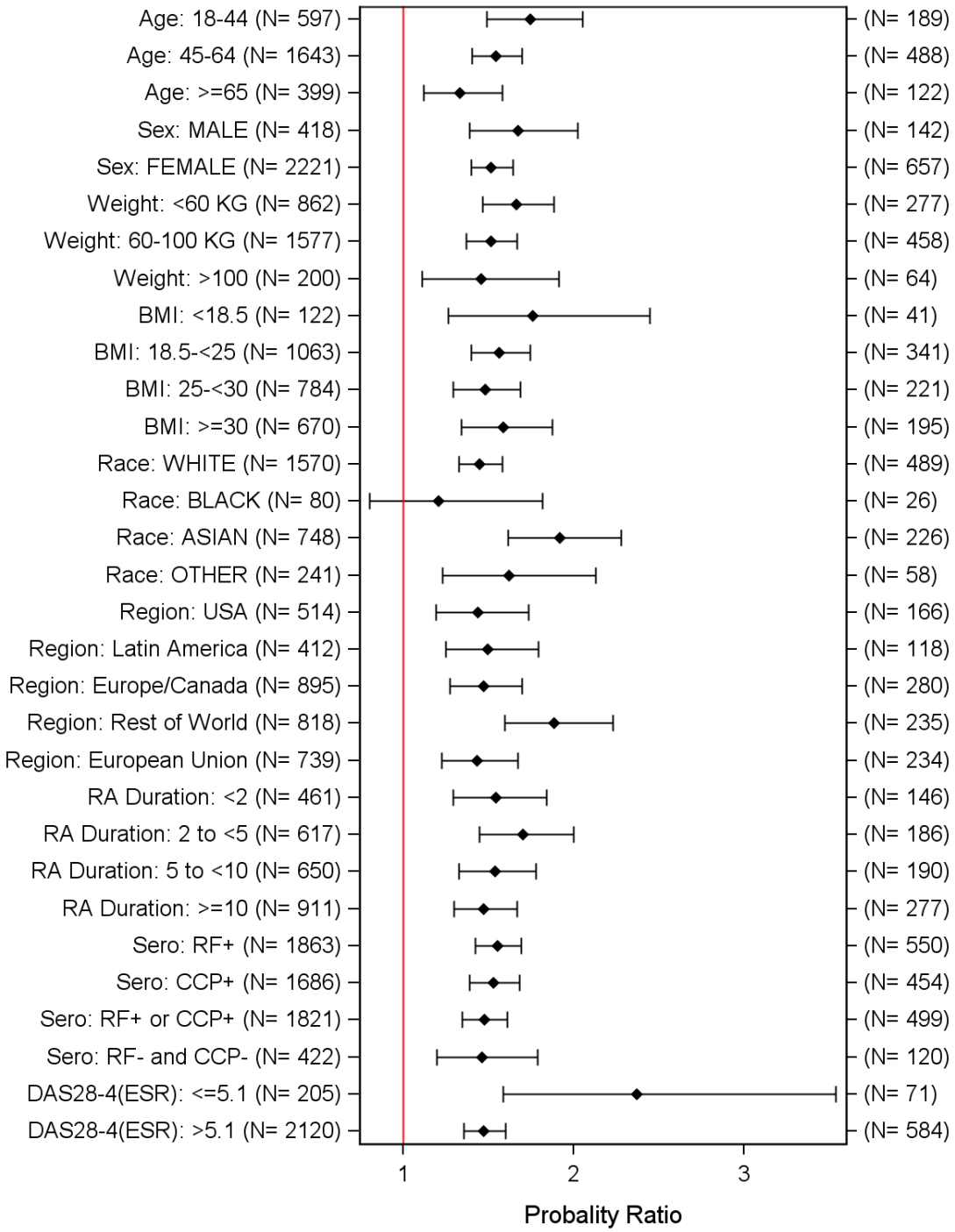
Figure 8. ACR20 Probability Ratio for Subpopulations, Pooled Phase 2 and Phase 3 RA Studies



Left Vertical Axis is CP-690,550 Combined sample size.
Right Vertical Axis is Placebo sample size.

Source: Summary of Clinical Efficacy, Figure 29

Figure 9. HAQ-DI Probability Ratio for Subpopulations, Pooled Phase 2 and Phase 3 RA Studies



Left Vertical Axis is CP-690,550 Combined sample size.
Right Vertical Axis is Placebo sample size.

Source: Summary of Clinical Efficacy, Figure 29

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Analysis of Information Relevant to Dosing Recommendations

Sponsor selected 5 and 10 mg BID doses of tofacitinib based on dose-response modeling of safety and efficacy data from Study A3921025, with supportive data from Study A3921019 and Study A3921035. The key design features of these studies and efficacy results for the ACR responses are summarized in Table 6 and Figure 4. On background methotrexate (MTX) in Study 1025, the dose response was very flat across the range of doses from 3 mg BID to 20 mg QD. There was some suggestion in Study 1035 (a monotherapy evaluation) that 10 mg BID might result in additional responders over 5 mg BID.

In the Phase 3 randomized controlled studies, ACR responses were generally comparable between both tofacitinib groups with the 10 mg BID group being slightly better in some studies as discussed in Section ACR20 Response Rates above. Importantly, in studies 1064 and 1035, both doses (5 and 10 mg BID) were numerically better than the active comparator adalimumab. Similar trends were seen for DAS28-4(ESR)<2.6 responders and HAQ-DI responses.

Taken together, these observations suggest some dose-dependency in the clinical outcomes in the domains of signs and symptoms and physical function. However, the potential added benefit of the 10 mg BID dose over the 5 mg BID dose is minimal and not consistent across the randomized controlled studies. Further, no dose-dependent benefits on radiographic endpoints were observed as discussed in detail in Section Change in Modified Total Sharp Score from Baseline (Study 1044) above.

Therefore, the potential benefit on signs and symptoms and physical function should be interpreted in the context of risk-benefit considerations in light of the significant dose-dependent safety findings, such as malignancy and serious infection which are discussed in detail in Section 7 Review of Safety below.

Dose Escalation

The Sponsor has proposed the following dosing regimen:
"The recommended starting dose of TRADE is 5 mg two times a day. (b) (4)

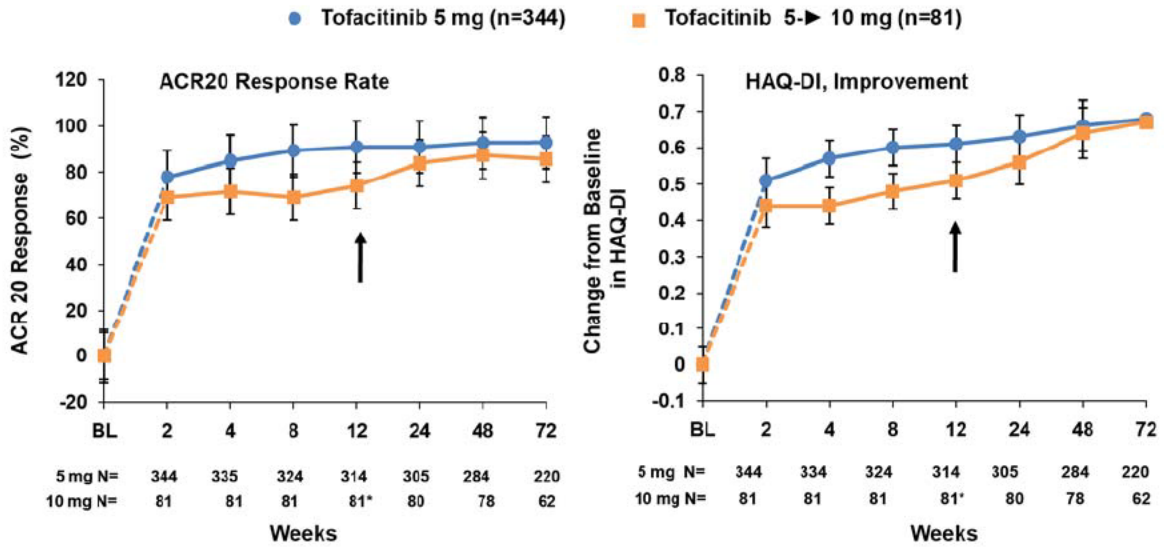
[redacted]

[redacted]

[redacted]

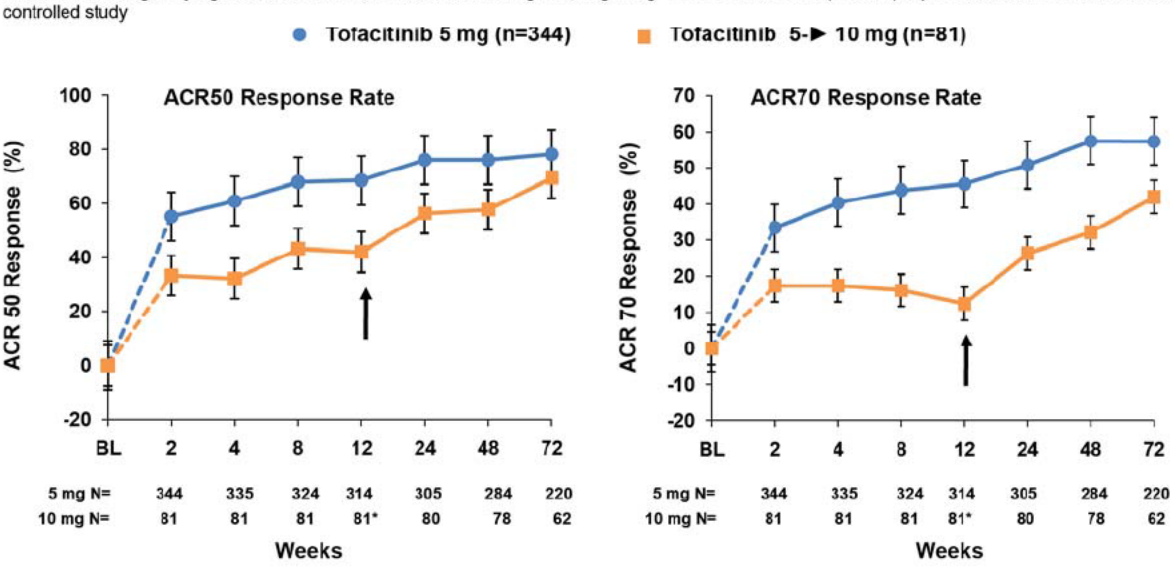
(b) (4)

Figure 10. ACR20/50/70 and HAQ-DI Responses Following Tofacitinib Dose Increase to 10 mg BID in Open-Label Extension Study 1041 (Japan)



A3921041 patients started open-label tofacitinib at 5 mg BID.
*Based on investigator judgment, dose could be increased to 10 mg BID, beginning ~Week 12. Baseline (Week 0) is pre-treatment in the randomized controlled study

E 6



A3921041 patients started open-label tofacitinib at 5 mg BID.
*Based on investigator judgment, dose could be increased to 10 mg BID, beginning ~Week 12. Baseline (Week 0) is pre-treatment in the randomized controlled study

E 7

Source: May 09, 2012 Arthritis Advisory Committee Meeting, Pfizer slide presentation, Slides E6 and E7

(b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

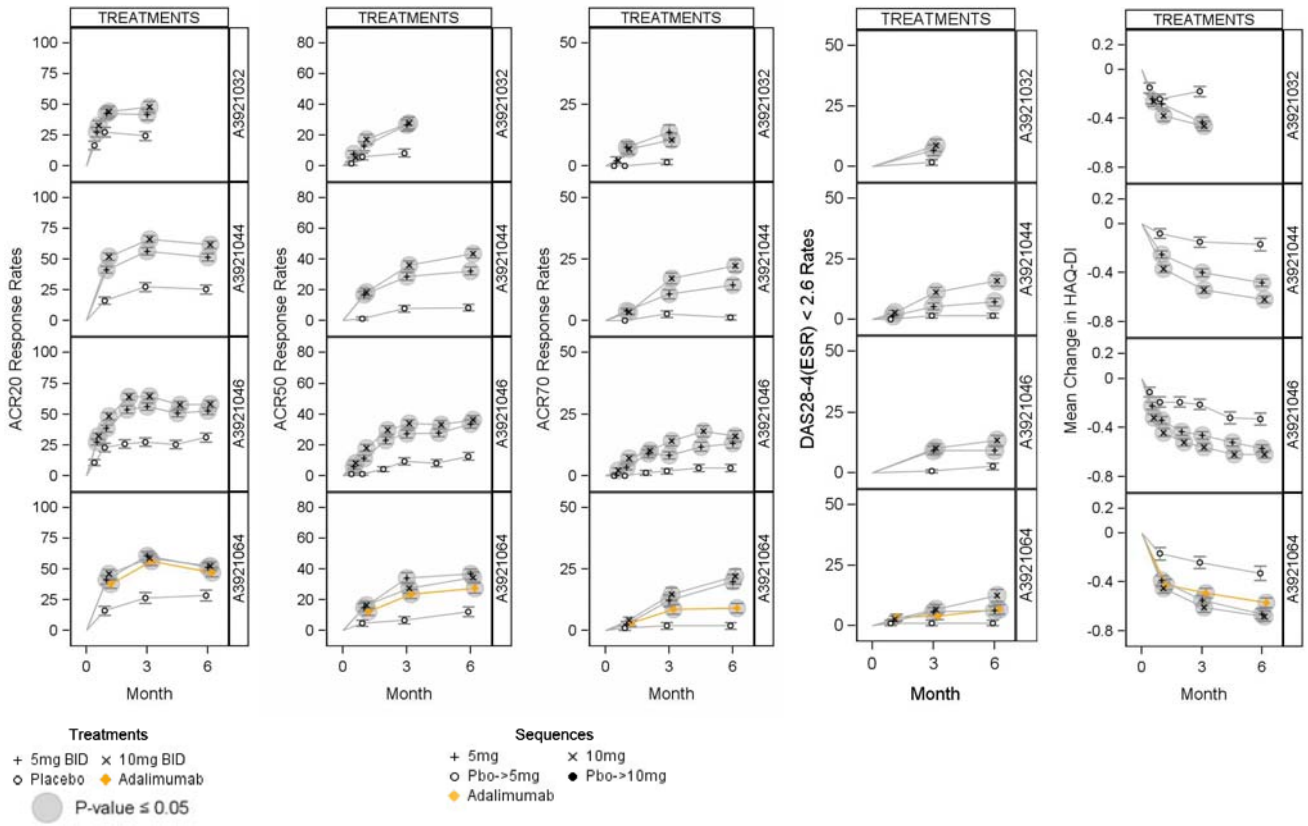
ACR, DAS28, and HAQ-DI responses were examined over time in Phase 3 randomized controlled studies as shown in Figure 11. Significant differences from placebo in ACR20, ACR50, HAQ-DI and DAS28 were observed as early as Week 2. Maximal ACR20 responses were achieved by Month 2 and continued at the same level through the rest of the studies. The proportion of ACR50 and ACR70 responders increased slightly numerically at each timepoint up to Mont 6 after which time point plateaued in the 1-year studies 1044, 1046 and 1064, but remained lower than the proportion of ACR20 responders. These trends were also observed in patients treated with adalimumab, even though their ACR50 and ACR70 responses were numerically lower than both tofacitinib doses, reaching statistical significance at Month 6.

The proportion of patients achieving DAS28-4(ESR) <2.6 increased generally by Month 6 and plateaued afterwards. The changes from baseline in mean DAS28-4(ESR) decreased steadily through Month 6 after which plateaued through the remainder of the 1 year studies 1044, 1046 and 1064. Similar decreases from baseline in mean HAQ-DI were observed over time in the same studies.

The time course of ACR20 responses, DAS28, and HAQ-DI changes, supports the conclusion that tofacitinib treatment was effective up to 1 year in the randomized controlled studies.

In the open-label, long-term extension studies, ACR20, ACR50, ACR70, mean DAS28 and HAQ-DI scores remained stable for up to 36 months indicating persistence of efficacy with chronic tofacitinib administration (data not shown).

Figure 11. Efficacy Over Time of ACR20, ACR50, ACR70, DAS28, HAQ-DI Responses in DMARD Background Phase 3 RA Studies



Source: Summary of Clinical Efficacy, Adapted from Figures 2, 3, 4, 6, 8

6.1.10 Additional Efficacy Issues/Analyses

Efficacy issues and analyses are discussed in Section 6 Review of Efficacy above.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data in this submission are derived from:

- Phase 2 in RA: 8 studies:
  - 6 completed (1019, 1025, 1035, 1039, 1040, 1109)
  - 2 ongoing (1068, 1073)
- Phase 3 in RA: 6 studies:

  - 4 completed (1032, 1045, 1046, 1064)
  - 2 ongoing (1044 12-month interim data, (b) (4))
- Open label, long-term extensions (LTE) in RA: 2 ongoing studies (1024, 1041)
- Additional studies from non-RA populations, such as renal allograft patients.

This submission contained 12-month safety data from 5 pivotal trials (see Table 7), including 12-month interim data from study 1044, which is designed as a 2-year study. (b) (4) These studies were of sufficiently similar design to allow for pooled analyses of the controlled data, by treatment group.

Long-term safety information from RA patients treated in the open-label LTE studies was also provided in this summary. The data are derived from two-open label extension studies, 1024 and 1041, which are ongoing. The clinical cut-off date for the provision of data from the extension study program was March 29th, 2011, with updated data through September 29th, 2011 submitted in the 120-day safety update.

Additional safety information was provided for adverse events of interest from studies in non-RA development programs, such as prevention of renal allograft rejection.

7.1.2 Categorization of Adverse Events

Adverse events were coded by using the MedDRA version 13.1.

SAEs were defined as any event that resulted in death, was life-threatening, resulted in a persistent or significant disability or incapacity, required in-patient hospitalization or prolongation of existing hospitalization, or resulted in a congenital anomaly or birth defect. In addition, other important medical events were considered SAEs if they jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed in this definition. The reporting of SAEs began at the time the patient provided informed consent through 28 days after the last study dose, or at any time after the last dose if a causal relationship to study medication was suspected.

Severity of AEs was recorded as mild, moderate, or severe, as judged by the investigator as shown in Table 27.

Table 27. Severity Grading for Adverse Events in RA Development Program

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

If the same patient in a given treatment group had more than one occurrence of the same event (preferred term), the AE is reported once at the maximum severity reported; patients were counted only once for each event. Missing severities are shown as severe unless the patient experienced another occurrence of the same event in a given treatment for which severity was recorded. AEs other than SAEs were recorded by the investigator from the time the patient took the first dose of study treatment through the last patient visit.

Treatment-related AEs, were those that the investigator judged were at least possibly related to treatment or for which information was insufficient to determine relationship.

The coding of adverse events was applied consistently across the treatment groups allowing for comparative assessment within the RA program. In this review, to minimize underestimation of the true incidence, some events were presented both by the "narrow" preferred term and pooled by a common term; for example, pneumonia viral and bronchopneumonia were also counted under the common term pneumonia.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This submission contained 12-month safety data from five Phase 3 randomized controlled trials (see
Table 7), including 12-month interim data from study 1044, which is designed as a 2-year study.

Pooling data from the 12 month safety data from these clinical trials was used to improve the precision of an incidence estimate. This was considered particularly important for detecting a potential safety signal for rare events, such as malignancy, serious infections, gastrointestinal perforations, which were events of special interest based on the immunosuppressive properties of tofacitinib.

These studies were of sufficiently similar design to allow for pooled analyses of the controlled data, by treatment group. The Phase 3 safety analyses are presented as 12-month pooled safety data, however notable differences between the safety profile in monotherapy study (1045) and DMARD background studies (1032, 1044, 1046, and 1064) are reflected in the text. Observed differences in rates of adverse events in individual studies are reflected in the text.

Safety data from Phase 2 dose-ranging studies were reviewed individually for assessment of dose-response for efficacy and safety. To increase the precision of an incidence estimate for events of interest, additional analyses were requested from the Sponsor. More specifically, since studies 1025 and 1035 were of similar design and duration with the Phase 3 studies and enrolled similar target population with comparable demographics, the Sponsor was asked to include the safety data (limited to patients exposed to placebo, tofacitinib 5 mg and 10 mg BID dosing) from these dose-ranging

studies in the pooled analyses of the five Phase 3 safety data. These analyses are ongoing at this time and are not included in this document.

Long-term safety data were also pooled by dosing regimen for studies 1024 and 1041. Notably, study 1041 is a long-term open label extension study of patients who have completed Japan Phase 2 studies 1039 and 1040 and global Phase 3 study 1044 and the majority of these patients (from studies 1039 and 1040) were not included in the pooled safety analyses of Phase 3 studies. Including these patients only in long-term extension studies was identified as a potential issue for appropriate assessment the incidence of AEs and events of special interest over time and comparison to the analyses of the controlled studies. Therefore, the Sponsor was asked to revise the analyses by providing the pooled long-term extension safety data as a continuation of the pooled safety analyses of patients from the randomized controlled studies. These analyses are ongoing at this time and are not included in this document.

Due to differences in the patient population, safety data from non-RA development programs, such as prevention of renal allograft rejection were reviewed individually.

Exposure-adjusted incidence rates (IR, number of events per patient-years of exposure) for all Phase 3 studies were calculated for selected AEs. The exposure time and AEs for patients randomized to placebo, for purposes of IR calculations, are counted in the PBO group only until they advanced (at month 3 or 6) to the CP-690,550 groups. The IRs for the CP-690,550 groups are displayed as IR in the CP5 group (only patients originally randomized to that dose group), CP10 group (only patients originally randomized to that dose group), and All Doses (includes patients who received CP-690,550 regardless of dose or original randomization; i.e. includes the AEs and exposure time in the placebo patients who crossed over to CP-690,550).

To account for the differences in exposure among treatment groups, exposure-adjusted AE incidence rates are calculated as the number of patients with a new event (for that time period), divided by the total exposure in that treatment group in the pooled cohort, and multiplied by 100 (i.e., rate per 100 patient-years). This allows for a standardized comparison between treatment groups in the pooled safety analyses.[11]

During the NDA review, it was noted that, when placebo-treated patients escaped or crossed over to active treatment (at either Month 3 or 6) their exposure to tofacitinib was counted from that point onwards, when in fact this should have been “zero” timepoint for tofacitinib exposure. To illustrate this observation, two hypothetical examples are presented below:

1. In a 12 month study, patient A was in placebo for first 3 months, and escaped to CP 5 mg at month 3, and diagnosed with malignancy at month 5. Patient A will be double counted in the denominator at the 0 to 3 months interval, with 0 event

11 Liu GF, et al., Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials, Statist Med 2006; 25:1275-1286

in the placebo numerator, and 1 malignancy event in the CP 5 mg numerator with exposure time being month 2. Furthermore, patient A should be counted in the placebo denominator at the following time intervals: 0 to 3 months, 0 to 6 months, and 0 to 12 months. Patient A should also be counted in the CP 5 mg denominator at the following time intervals: 0 to 3 months, 3 to 6 months (if applicable), 6 to 9 months (if applicable), 0 to 6 months and 0 to 12 months.

2. In a 12 month study, patient B was in placebo for first 6 months, and switched over to CP 10 mg at month 6. Patient B should be counted in the placebo denominator at the following time intervals: 0 to 3 months, 3 to 6 months, 0 to 6 months, and 0 to 12 months. Patient B should also be counted in the CP 10 mg denominator at the following time intervals: 0 to 3 months, 3 to 6 months, 0 to 6 months, and 0 to 12 months.

While, this may not have affected the incidence rates adjusted for actual exposure in the pooled safety analyses, it may not allow for accurate assessment of crude percentage rates of the different time periods, e.g. 0 to 3 months, 3 to 6 months, etc.

To allow for accurate assessment of crude percentage rates of the different time periods, the Sponsor was asked to revise the safety analyses where placebo patients who escaped or crossed over to tofacitinib should be counted in the denominator in both groups based on their on-treatment time. The numerator count will depend on the timing of event. These analyses are ongoing at this time and are not included in this document.

7.2 Adequacy of Safety Assessments

As of March 29th, 2011 (clinical data cut-off date of the original NDA submission), the RA Phase 2, 3 and LTE studies included 4816 patients across all treatment groups with 5716 patient-years of exposure to all doses as shown on Table 28.

As of March 29th, 2011 (clinical data cut-off date), the RA Phase 2, 3 and LTE studies included 4816 patients across all treatment groups with 5716 patient-years of exposure to all doses as shown on Table 28. The submitted exposure data represents a safety database that meets the Agency's previously expressed expectations for a pre-marketing exposure of at least 1000 to 1500 patients treated for a minimum of one year to allow for reasonable safety assessment of a chronic immunosuppressive therapy with tofacitinib for the intended use.

The overall study population in the RA development program was representative of the target patient population of adult patients with established moderately-to-severely active RA who have had inadequate response to at least one DMARD.

Clinical safety assessments in the RA development program were based on the knowledge from the non-clinical program, extensive clinical pharmacology characterization and dose-selection exploration studies, as discussed in the respective sections of this document. In addition, adverse events of interest were selected

appropriately for generally appropriate for the target study population and the mechanism of action (immunosuppressive small molecule drug). These included infections, including severe and opportunistic infections, malignancy, gastrointestinal perforations, and interstitial lung disease. Appropriate in vitro studies of drug-drug interactions were carried out according to current guidelines.

Ascertainment of AE reporting
The submission is not clear regarding how and when were the adverse events captured and ascertained following discontinuation of treatment except for the SAEs, where the reporting began at the time the patient provided informed consent through 28 days after the last study dose, or at any time after the last dose if a causal relationship to study medication was suspected. This raises questions about the procedures for collection, reporting, and analyses of adverse events and laboratory data. To address these questions the Sponsor was asked to provide a summary with specific focus on collection and handling of adverse events and laboratory data after treatment ends and revise the safety analysis of all adverse events using the following criteria:

- Events reported on treatment only
- Events reported within 30 days of stopping treatment. In cases where patients have crossed over from placebo to tofacitinib, this 30 day window would not exist as events that occur on tofacitinib should be counted as a tofacitinib event.

These analyses are ongoing at this time and are not included in this document.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As of March 29th, 2011 (clinical data cut-off date of the original NDA submission), the RA Phase 2, 3 and LTE studies included 4816 patients across all treatment groups with 5716 patient-years of exposure to all doses as shown on Table 28. indicating that at least 1000 to 1500 patients were treated for a minimum of one year to allow for reasonable safety assessment of a chronic immunosuppressive therapy with tofacitinib for the intended use.

Table 28. Summary of Exposure to Tofacitinib in Phase 2, Phase 3 and Long-Term Extension Trials in RA

Exposure to Tofacitinib in Phase 2, Phase 3 and LTE Trials in RA		
	Number of patients	Patient-years
Overall exposure at any dose		
Phase 2 exposure	1369	420
Phase 3 exposure	3030	2211
Long-Term Extension studies	3227*	3085
Total exposure at any dose	4816	5716
Exposure at any dose, by duration		
≥ 1 month	4664	5320
≥ 3 months	4213	4580
≥ 6 months	3768	3565
≥ 12 months	2703	1897
≥ 18 months	905	1008
≥ 24 months	696	623

Source: Integrated Summary of Safety (clinical data cut-off March 29, 2011); Studies included: A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (data up to 1 year), A3921045, A3921046, A3921064.
* Patients in LTE studies were previously enrolled in Phase 2 or 3 study and are not new patients

7.2.2 Explorations for Dose Response

A wide range of doses were explored in the dose-ranging studies providing preliminary evidence of dose-response in doses above 1 mg BID as discussed in Section 4.4.4. Dose Selection. Since two of these doses were selected for further Phase 3 testing, this allowed for further assessment of dose-response in a much larger patient population. The vast majority of patients in the RA development were exposed to tofacitinib 5 and/or 10 mg BID, the two doses tested in the Phase 3 trials, with 5483 patient-years of exposure. Overall, higher proportion of patients was exposed to 5 mg BID than to 10 mg BID dose, as shown in Table 29, because 5 mg BID was the starting dose for patients enrolling in the LTE studies from the Phase 2 index studies.

As seen in this table, exposure to both 5 mg and 10 mg BID was fairly balanced for the first 12 months to allow for exploration of dose-response with regard to safety findings. In contrast, beyond 24 months, the 10 mg BID dose is significantly under-represented which limits the dose comparisons of adverse events beyond 24 months.

Table 29. Exposure to Tofacitinib by Dose and Duration in Phase 2, Phase 3 and LTE Trials in RA

Exposure to Tofacitinib by Dose and Duration in Phase 2, Phase 3 and LTE Trials in RA			
Duration of exposure	5 mg BID (n=1677)	10 mg BID (n=1755)	5 mg/10 mg BID* (n=1178)
≥ 6 months	1366	1321	1135
≥ 12 months	1107	939	905
≥ 24 months	580	8	105

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

In comparison, the exposure to both placebo and adalimumab controls, is significantly lower (see Table 30) because of trial design aspects, such as:

- Unequal allocation by randomization for most of the trials, providing only limited numbers of controls
- Duration of placebo-controlled periods limited to 3 to 6 months.
- Placebo-treated non-responders crossed over to active treatment after 3 months

This unbalanced exposure to treatment and control is an important consideration when comparing safety data, particularly rare events (<5% crude percentage), such as malignancy, mortality, and serious infections.

Table 30. Exposure to Placebo and Adalimumab Controls in Phase 2, Phase 3 and LTE Trials in RA

Exposure to Tofacitinib, Placebo and Adalimumab Controls in Phase 2, Phase 3 and LTE Trials in RA					
Placebo (Max. duration 3 to 6 months)		**Adalimumab** (Max. duration 1 year)		**Tofacitinib, Any Dose** (Max. duration > 2 years)	
Patients, n	Exposure, PY	Patients, n	Exposure, PY	Patients, n	Exposure, PY
954	265	257	190	4816	5716

Source: Summary of Clinical Safety (clinical data cut-off March 29, 2011)

To account for the differences in exposure among treatment groups, exposure-adjusted AE incidence rates are calculated as the number of patients with a new event (for that time period), divided by the total exposure in that treatment group in the pooled cohort, and multiplied by 100 (i.e., rate per 100 patient-years). This allows for a standardized comparison among treatment groups in the pooled safety analyses. This approach was used to identify potential safety signals of rare events, such as malignancy, mortality, and serious infections.[12]

12 Liu GF, et al., Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials, Statist Med 2006; 25:1275-1286

Updated safety information was reviewed as a part of the 120-day safety update with a clinical data cut-off of September 29, 2011.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was considered necessary to further explore the safety profile of tofacitinib, which is primarily based on human clinical data.

The non-clinical program was generally comprehensive and was considered acceptable to explore potential safety adverse reactions. For further details, the reader is referred to Section Preclinical Pharmacology/Toxicology.

7.2.4 Routine Clinical Testing

The type and frequency of routine clinical testing of patients in the RA development program was considered adequate. It was based on the knowledge of tofacitinib's mechanism of action, non-clinical safety findings and the target patient population. For details, see Section 9.4 Individual Study Reports.

7.2.5 Metabolic, Clearance, and Interaction Workup

The clinical pharmacology of CP-690,550 has been studied in 13 in vitro, 21 Phase 1 clinical studies, and 5 Phase 2 dose ranging studies (including their corresponding 2 long term extension studies) providing population PK and exposure response (ER) information in healthy volunteers and patients with RA, psoriasis, and other populations. For further discussion, the reader is referred to Section Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Tofacitinib is in the same drug class with ruxolitinib, which is another Janus associated kinase (JAK) inhibitor, targeting JAK1 and JAK2, approved for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in November 2011. The major warnings and precautions identified in ruxolitinib's label include thrombocytopenia, anemia, neutropenia and infections.[13]

Tofacitinib's safety data were assessed in the context of what is known about the safety profile of other traditional and biologic DMARDs. Therefore the data were evaluated with special attention to serious infections, malignancies. However JAK inhibition may pose unique risks, such as neutropenia, lymphopenia, elevated serum creatinine, and elevated lipid parameters. These potential concerns are also addressed below.

13 USPI Jakafi (ruxolibinib), November 2011

7.3 Major Safety Results

Exposure-adjusted incidence rates of deaths, serious adverse events (SAEs), serious infectious events (SIEs), malignancy (excluding non-melanoma skin cancer, NMSC), AEs leading to withdrawal, and major cardiovascular adverse endpoints (MACE) during the Phase 3 and LTE studies in RA are summarized in Table 31.

There were numerical imbalances in these safety endpoints among treatment groups; however the overall exposure-adjusted rates were not elevated in tofacitinib-treated patients with the important exception of the rates of serious infectious events and malignancy. The malignancy rates also increased over time with prolonged exposure in the LTE studies, which appears to be a trend unique to malignancy and suggests a potential safety signal associated with tofacitinib use. Detailed analyses of Malignancy are provided in Section 7.3.2.1 Malignancy.

Table 31. Overview of Deaths, SAEs, and Events of Interest, Phase 3 Studies and LTE

Overview of Deaths (All and within 30 days of last dose), SAEs, and Events of Interest, All Phase 3 Studies (0-12 Months) and LTE studies							
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies	
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All Doses*	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Total Number of Patients Total Exposure, PY	681 203	204 179	1216 904	1214 910	3030 2098	3227 3118	3515 4410
Deaths within 30 days of last dose, n (%) Rate per 100 PY	1 (0.1) 0.50	1 (0.5) 0.56	5 (0.4) 0.55	4 (0.3) 0.44	10 (0.3) 0.48	10 (0.3) 0.32	14 (0.4) 0.32
All deaths, n (%) Rate per 100 PY	1 (0.1) 0.50	3 (1.5) 1.67	8 (0.7) 0.88	4 (0.3) 0.44	13 (0.4) 0.62	20 (0.6) 0.64	29 (0.8) 0.66
No with ≥ 1 SAE, n (%) Rate per 100 PY	30 (4.4) 15.0	19 (9.3) 10.9	104 (8.6) 11.9	87 (7.2) 9.8	211 (7.0) 10.3	337 (10.4) 11.3	446 (12.7) 10.7
No with ≥ 1 SIE, n (%) Rate per 100 PY	3 (0.4) 1.5	3 (1.5) 1.7	29 (2.4) 3.2	27 (2.2) 3.0	61 (2.0) 2.9	93 (2.9) 3.0	131 (3.7) 3.0
No with ≥ 1 Malignancy (excluding NMSC), n (%) Rate per 100 PY	0 0	1 (0.5) 0.56	5 (0.4) 0.55	8 (0.7) 0.88	13 (0.4) 0.62	35 (1.1) 1.12	50 (1.4) 1.14
No of Pts with AEs leading to withdrawal, n (%) Rate per 100 PY	25 (3.7) 12.4	22 (10.8) 12.3	95 (7.8) 10.6	99 (8.2) 10.9	205 (6.8) 9.8	223 (6.9) 7.2	318 (9.0) 7.3
No with ≥ 1 MACE event, n Rate per 100 PY	2 (0.3) 0.99	3 (1.5) 1.68	4 (0.3) 0.44	6 (0.5) 0.66	12 (0.4) 0.57	5 (0.15) 0.19	9 (0.26) 0.23

Source: Summary of Clinical Safety, 120 Day Safety Update (data cut-off September 29, 2011), Tables 13, 19, 22, 23, 35
*CP All Doses group includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months.

7.3.1 Deaths

As of September 29, 2011 (120-day safety update clinical data cut-off), a total of 49 deaths were reported in tofacitinib RA development program. Of these, 45 occurred in tofacitinib-, one in placebo-, and three in adalimumab-treated patients. There were no deaths in Phase 1 studies. Summaries of all reported deaths and deaths in the Phase 3 and LTE studies are provided in Table 32 and Supplementary Table 99 respectively. The death listings in Table 32 also indicate the AE that were present at the time of death or within 30 days of last treatment and lead to death irrespective of time of death.

The causes of death are consistent with the profile of an immunosuppressant drug, and also with those seen in the underlying population with comparable disease and demographic characteristics. Among tofacitinib-treated patients, infections, malignancies, and cardiovascular disorders were the most common causes of death. In the Phase 3 and LTE studies 15 patients died from infection, with pneumonia being the most common (12 cases); 12 patients died from malignancies; 11 patients died of cardiovascular etiologies (4 cardiac arrests, 2 cerebrovascular accidents, 2 arrhythmias, 1 cardiac failure, 1 pulmonary embolism, 1 pulmonary hypertension); other deaths are summarized in Table 32.

Table 32. Listings of Deaths in Tofacitinib RA Development Program

Listings of Deaths in the Tofacitinib RA Development Program

Study-Subject ID	Age/ Gender	Total CP exposure, days	Days after last treatment	Cause of death [CV-SEAC Adjudication]	AE leading to death present on Tx or within 30 days of last dose
Placebo + MTX (n=681)					
1044-11821007	51/F	191	13	Pyelonephritis, sepsis, ARF [Non-CV, other]	Pyelonephritis, sepsis
Adalimumab + MTX (n=204)					
1064-11131005	68/M	71	1	Cardiac arrest [Sudden cardiac death]	Cardiac arrest
1064-10461047#	62/M	265	215	Non-small cell lung cancer	Non-small cell lung cancer
1064-11371004#	64/F	211	248	Bone marrow hypoplasia	No
CP3 mg BID + MTX (n=68)					
1025-11031001	40/F	36	14	Pneumonia	Pneumonia
CP5 mg BID + MTX/DMARD (n=1216)					
1044-10191001	73/M	203	13	Pneumonia [Infection]	Pneumonia
1044-10401028	74/M	42	8	Viral pneumonia/ARDS [Infection]	Viral pneumonia
1044-11081030	69/F	307	25	Metastatic lung cancer, MOF [n.a.]	Metastatic lung cancer
1044-11171004	75/F	41	31	Pneumonia (PCP?), MOF [Infection]	Pneumonia
1044-11731006#†	77/F	352	~35	Pneumonia, heart failure, atherosclerosis	Pneumonia
1044-11701010#	70/F	368	~60	COPD worsening	n.a.
1046-10291010	81/M	170	22	Traumatic intracranial hemorrhage	Traumatic intracranial hemorrhage
1046-11431005	49/M	303	54	Interstitial lung disease [Infection]	No
1064-11361006	54/F	372	35	Pneumonia	Bronchitis
CP10 mg BID + MTX/DMARD (n=1214)					
1044-10621016	74/M	157	8	Aspiration [Non-CV, other]	Aspiration
1045-10941004*	78/F	102	5	Cardiac arrest [Coronary heart disease]	Cardiac arrest
1046-10091004	58/M	357	17	Pulmonary hypertension, Respiratory failure	Pulmonary hypertension, Respiratory failure
1046-11111007	37/M	173	1	Cardiac failure, acute [Valvular heart disease]	Cardiac failure, acute
1032-10721004**	51/F	47	1	Pulmonary embolism [Unknown reason]	Pulmonary embolism
CP15 mg BID (n=249)					
1035-10811003	68/F	140	46	Cerebrovascular accident, hemorrhagic	Cerebrovascular accident, hemorrhagic
LTE CP5 mg BID (n=1321)					
1024-10031004	49/M	1354	1	Arrhythmia, coronary artery disease	Arrhythmia, coronary artery disease
1024-10161006	69/F	579	113	Lung neoplasm, malignant	Lung neoplasm, malignant
1024-10181004	60/F	773	33	Brain injury, post surgery [non-CV, Other]	Brain injury, post surgery
1024-10271003	57/M	416	0	Arrhythmia, hypertension, atherosclerosis [CV]	Arrhythmia, hypertension, atherosclerosis
1024-10431005	46/M	833	19	Appendicitis, sepsis [Infection]	Appendicitis, sepsis
1024-10441004	70/F	256	92	Pulmonary infection, multi-organ failure	Pulmonary infection, cardiac failure
1024-10551020	72/F	812	2	COPD, respiratory failure	COPD, respiratory failure
1024-10751011	62/M	650	34	Metastatic lung neoplasm	Metastatic lung neoplasm
1024-10781004	61/F	203	771	Metastatic breast cancer	Metastatic breast cancer
1024-10811010	62/F	668	0?	Cardio-respiratory arrest [Sudden cardiac death]	Cardio-respiratory arrest
1024-10831011	70/F	200	0?	Unknown, found dead in her sleep	n.a.
1024-10901005	74/F	878	14	Cerebrovascular accident	Cerebrovascular accident
1024-11251018	78/M	246	~60	Colon cancer	Colon cancer
1024-11271012	71/M	986	18	Suicide/gunshot wound	Suicide/gunshot wound
1024-11361010	64/F	277	37	Pneumonia, acute renal failure [Infection]	No
1024-10831008#	66/F	1313	0	Sepsis, Pneumonia	Sepsis, Pneumonia
1024-11731014#	73/F	980	10	Gallbladder cancer	Gallbladder cancer
1024-11811020#	68/F	583	38	Synovial sarcoma	Synovial sarcoma
1024-11881004#	67/F	453	34	Sepsis, septic arthritis	Septic arthritis
1041-10061003	58/F	671	327	Metastatic ovarian cancer, pneumonia	Metastatic ovarian cancer
1041-10211003	59/F	245	69	Thrombotic thrombocytopenic purpura, MOF	Interstitial lung disease/pneumonia
LTE CP10 mg BID (n=1906)					
1024-11221065	35/M	1	0	Suicide	Suicide
1024-11271015	67/M	207	4	Pneumonia, septic shock [Infection]	Pneumonia, septic shock
1024-14901003	64/F	242	39	Malignant hepatic and lung neoplasm	Malignant hepatic and lung neoplasm
1024-10021018#	58/F	558	5	Cardio-respiratory arrest	Cardio-respiratory arrest
1024-11341005#	64/M	110	37	Lung malignancy	Lung malignancy
1024-11911007#	80/F	527	100	Lung adenocarcionma [Cancer]	Lung adenocarcionma
1024-12431003#	64/M	372	87	Lung cancer, small cell, metastatic	Lung cancer, small cell, metastatic
1024-13381005#	71/M	374	84	Pneumonia	Pneumonia

Source: Integrated Summary of Safety, Section 2.1.2, Deaths; #120-Day Safety Update (clinical data cut-off September 29, 2011)
* Study 1045 was a monotherapy study; ** Subject 10721004 transitioned from placebo to CP10 on Day 85; †-Patient died after the clinical data cut-off date, September 29, 2012
COPD-chronic obstructive pulmonary disease; CV-SEAC-cardiovascular safety endpoint adjudication committee; MOF-multiorgan failure; PCP-Pneumocystis jiroveci pneumonia

The Sponsor proposed a timeframe of 30 days for assessing association between death and potential direct tofacitinib toxicity. This is not unreasonable based on the known PK/PD characteristics of the drug (PK $t_{1/2}$ ~3 hours, and relatively longer PD effect as summarized in Section Clinical Pharmacology). Summaries of all deaths occurring within 30 days of last treatment in the Phase 3 and LTE studies are provided in Table 33. Cardiovascular events were the leading cause of death followed by infections across all treatment groups, which is consistent with the causes of mortality in the underlying population. Due to the relatively small number of events in each broad category, it is difficult to draw definitive conclusions on dose-relatedness.

Table 33. Summary of Deaths within 30 Days of Last Dose in the Phase 3 and LTE Studies in RA

Integrated Summary of Deaths Within 30 Days of Last Treatment in the Phase 3 and LTE Studies in RA

	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Total number of patients	681	204	1216	1214	3030	1321	1906	3227	3515
Total exposure, patient-years	203	179	904	910	2098	2236	882	3118	4410
Number of events, n (%)	1 (0.1)	1 (0.5)	5 (0.4)	4 (0.3)	10 (0.3)	8 (0.6)	2 (0.1)	10 (0.3)	13 (0.4)
Rate per 100 patient-years	0.50	0.56	0.55	0.44	0.48	0.36	0.23	0.32	0.30
Cause of death, n (event/100 PY)									
Infections	**1 (0.5)**	**-**	**3 (0.3)**	**-**	**3 (0.1)**	**1 (<0.1)**	**1 (<0.1)**	**2 (<0.1)**	**3 (<0.1)**
Pneumonia	-	-	*3*	-	*3*	-	*1*	*1*	*2*
Appendicitis	-	-	-	-	-	*1*	-	*1*	*1*
Pyelonephritis	*1*	-	-	-	-	-	-	-	-
Septic arthritis	-	-	-	-	-	-	-	-	*1*
Malignancy	**-**	**-**	**1 (0.1)**	**-**	**1 (<0.1)**	**-**	**-**	**-**	**1 (<0.1)**
Lung cancer	-	-	*1*	-	*1*	-	-	-	-
Gallbladder cancer	-	-	-	-	-	-	-	-	*1*
Cardiovascular Disorders	**-**	**1 (0.6)**	**-**	**3 (0.3)**	**4 (0.2)**	**4 (0.2)**	**-**	**4 (0.1)**	**5 (0.1)**
Arrhythmia, atherosclerosis	-	-	-	-	-	*2*	-	*2*	*2*
Cardiac arrest	-	*1*	-	*1*	*1*	*1*	-	*1*	*1*
Cardiac failure, valvular	-	-	-	*1*	*1*	-	-	-	-
Diastolic heart failure	-	-	-	-	-	-	-	-	*1*
Cerebrovascular accident	-	-	-	-	-	*1*	-	*1*	*1*
Pulmonary hypertension	-	-	-	*1*	*1*	-	-	-	-
Pulmonary embolism	-	-	-	-	*1*	-	-	-	-
Pulmonary	**-**	**-**	**-**	**-**	**-**	**1 (<0.1)**	**-**	**1 (<0.1)**	**1 (<0.1)**
COPD exacerbation	-	-	-	-	-	*1*	-	*1*	*1*
Suicide	**-**	**-**	**-**	**-**	**-**	**1 (<0.1)**	**1 (<0.1)**	**2 (<0.1)**	**2 (<0.1)**
Aspiration	**-**	**-**	**-**	**1 (0.1)**	**1 (<0.1)**	**-**	**-**	**-**	**-**
Traumatic intracranial hemorrhage	**-**	**-**	**1 (0.1)**	**-**	**1 (<0.1)**	**-**	**-**	**-**	**-**
Unknown	**-**	**-**		**-**	**-**	**1 (<0.1)**	**-**	**1 (<0.1)**	**1 (<0.1)**

Source: Integrated Summary of Safety, Section 2.1.2, Deaths, adapted from Tables 68-75; 120-Day Safety Update (clinical data cut-off September 29, 2011), adapted from Tables 13-17
Note: Four deaths were not included in the incidence calculations: three were reported after the reporting window for safety analyses, on occurred after clinical data cut-off September 29, 2011

Table 34 provides a summary of exposure-adjusted incidence rates of deaths in Phase 3 and LTE studies by different attribution windows. The data are presented separately for deaths:

- that occurred within the reporting period
- that occurred within 30 days of the last dose
- due to AEs that occurred within the 30 days of last dose.

Note: One death listed in Table 32 (PID 1044-11731006) occurred after the last clinical cut-off date of September 29, 2011 and was not included in the incidence rate calculations in Table 34.

Table 34. Integrated Summary of Deaths in the Phase 3 and LTE Studies in RA

Integrated Summary of Deaths in the Phase 3 and LTE Studies in RA									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses*	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept. 29, 2011)
Total Number of Patients	681	204	1216	1214	3030	1321	1906	3227	3515
Total Exposure, patient-years	203	179	904	910	2098	2236	882	3118	4410
Deaths within 30 days of last dose									
Number of events, n (%)	1 (0.1)	1 (0.5)	5 (0.4)	4 (0.3)	10 (0.3)	8 (0.6)	2 (0.1)	10 (0.3)	13 (0.4)
Rate per 100 PY	0.50	0.56	0.55	0.44	0.48	0.36	0.23	0.32	0.30
Deaths due to AEs that occurred within 30 days of last dose									
Number of events, n (%)	1 (0.1)	2 (1.0)	6 (0.5)	4 (0.3)	11 (0.4)	16 (1.2)	3 (0.2)	19 (0.6)	28 (0.8)
Rate per 100 PY	0.50	1.12	0.66	0.44	0.52	0.71	0.34	0.61	0.63
All deaths									
Number of events, n (%)	1 (0.1)	3 (1.5)	8 (0.7)	4 (0.3)	13 (0.4)	17 (1.3)	3 (0.2)	20 (0.6)	29 (0.8)
Rate per 100 PY	0.50	1.67	0.88	0.44	0.62	0.76	0.34	0.64	0.69

Source: Integrated Summary of Safety, Section 2.1.2, Deaths, adapted from Tables 68-75; 120-Day Safety Update (clinical data cut-off September 29, 2011), adapted from Tables 13-17
Note: One death occurred after data cut-off September 29, 2011 and was not included in the incidence calculations (PID 1044-11731006 as listed in Table 32)
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized

Irrespective of the death attribution window, there were numerical imbalances in the number of deaths between the tofacitinib and control groups (Table 34) in the pooled Phase 3 controlled studies, without clear dose-related increases in mortality rates. Due to the relatively small number of events, it is difficult to draw definitive conclusions on dose-relatedness. During the long-term exposure studies, more deaths occurred in the 5 mg BID dose group, which is the dose which had the largest clinical experience. Despite the numerical imbalance, the overall exposure-adjusted death rates are numerically comparable between the tofacitinib all-dose group and placebo- and adalimumab-control groups, in the Phase 3 program and have not increased substantially with prolonged exposure in the LTE studies as shown in Table 34 above.

7.3.2 Nonfatal Serious Adverse Events

An SAE was defined as any untoward medical occurrence at any dose that:

- Resulted in death;
- Was life-threatening (immediate risk of death);
- Required inpatient hospitalization or prolongation of existing hospitalization;
- Resulted in persistent or significant disability/incapacity; and/or
- Resulted in congenital anomaly/birth defect.

Treatment-emergent nonfatal SAEs were observed in all treatment groups with comparable rates during the Phase 3 studies as shown in Table 35. The most common nonfatal SAEs were reported in the Infections and Infestation system organ class, with exposure-adjusted rates ranging between 1.7 events/100 patient-years for adalimumab and 6.7 events/100 patient-years for tofacitinib 10 mg BID dose in the LTE studies.

During the LTE studies, the exposure-adjusted rates of all SAEs, Infections and Infestation, and Neoplasms increased for the 10 mg BID dose group compared with the with the 5 mg dose group and with the Phase 3 rates indicating a dose-dependent increased risk of infections and neoplasms with prolonged exposure. These potential safety signals are discussed in the separate sections later in this document.

Table 35. Integrated Summary of All Nonfatal SAEs in the Phase 3 and LTE Studies in RA

Integrated Summary of All Nonfatal SAEs in the Phase 3 and LTE Studies in RA									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Total number of SAEs	31	20	122	108	230	363	181	544	711
Total patients with ≥ 1 SAE, n (%)	30 (4.4)	19 (9.3)	104 (8.6)	87 (7.2)	211 (7.0)	217 (16.4)	120 (6.3)	337 (10.4)	446 (12.7)
Exposure for event, patient-years	200	175	873	890	2044	2111	860	2971	4172
Incidence of SAEs, event per 100 patient-years (95% CI)	**15.02** (10.51, 21.49)	**10.87** (6.93, 17.04)	**11.87** (9.79, 14.38)	**9.76** (7.91, 12.04)	**10.30** (8.99, 11.78)	**10.28** (8.99, 11.74)	**13.96** (11.67, 16.69)	**11.34** (10.20, 12.62)	**10.69** (9.74, 11.73)
System Organ Class, n (event/100 PY)									
Infections and Infestation**	4 (2.0)	3 (1.7)	33 (3.8)	30 (3.4)	63 (3.1)	76 (3.6)	58 (6.7)	134 (4.5)	177 (4.2)
Musculoskeletal and Connective Tissue	5 (2.5)	3 (1.7)	14 (1.6)	9 (1.0)	23 (1.1)	39 (1.8)	10 (1.2)	49 (1.6)	75 (1.8)
Injury, Poisoning, Procedural Complications	8 (4.0)	2 (1.1)	20 (2.3)	14 (1.6)	34 (1.7)	35 (1.7)	23 (2.7)	58 (2.0)	70 (1.7)
Neoplasms, Benign, Malignant**	2 (1.0)	2 (1.2)	9 (1.0)	12 (1.3)	21 (1.0)	33 (1.6)	17 (1.97)	50 (1.7)	65 (1.6)
Gastrointestinal Disorders	1 (0.5)	2 (1.1)	6 (0.7)	11 (1.2)	17 (0.8)	27 (1.3)	12 (1.4)	39 (1.3)	48 (1.2)
Cardiac Disorders**	2 (0.1)	4 (2.3)	5 (0.6)	13 (1.5)	17 (0.8)	26 (1.2)	7 (0.8)	33 (1.1)	46 (1.1)
Respiratory, Thoracic, Mediastinal Disorder	2 (1.0)	1 (0.6)	11 (1.3)	9 (1.0)	20 (1.0)	16 (0.8)	7 (0.8)	23 (0.8)	29 (0.7)
Nervous System Disorders	7 (3.5)	0	8 (0.9)	7 (0.8)	15 (0.7)	11 (0.5)	10 (1.2)	21 (0.7)	43 (1.0)
Vascular Disorders	1 (0.5)	0	2 (0.2)	4 (0.5)	6 (0.3)	16 (0.8)	4 (0.5)	20 (0.7)	31 (0.7)
Hepatobiliary Disorders**	2 (1.0)	1 (0.6)	7 (0.8)	4 (0.5)	11 (0.5)	10 (0.5)	6 (0.7)	16 (0.5)	19 (0.5)
Renal and Urinary Disorders**	4 (2.0)	1 (0.6)	1 (0.1)	2 (0.2)	3 (0.1)	10 (0.5)	4 (0.5)	14 (0.5)	20 (0.5)
General Disorders Admin. Site Conditions	1 (0.5)	1 (0.6)	7 (0.8)	9 (1.0)	16 (0.8)	13 (0.6)	2 (0.2)	15 (0.5)	21 (0.5)
Metabolism and Nutrition	2 (1.0)	0	2 (0.2)	5 (0.6)	7 (0.3)	6 (0.3)	3 (0.3)	9 (0.3)	9 (0.2)
Blood and Lymphatic	0	1 (0.6)	3 (0.3)	4 (0.4)	7 (0.3)	8 (0.4)	3 (0.3)	11 (0.4)	13 (0.3)
Reproductive System, Breast Disorders	3 (1.5)	0	4 (0.5)	0	4 (0.2)	8 (0.4)	1 (0.1)	9 (0.3)	11 (0.2)
Eye Disorders	0	0	0	3 (0.3)	3 (0.1)	4 (0.2)	3 (0.3)	7 (0.2)	7 (0.2)
Ear and Labyrinth	0	0	0	2 (0.2)	2 (0.1)	5 (0.2)	1 (0.1)	6 (0.2)	6 (0.1)
Psychiatric Disorders	0	0	1 (0.1)	0	1 (<0.1)	1 (<0.1)	3 (0.3)	4 (0.1)	6 (0.1)
Skin and Subcutaneous Tissue Disorders	0	0	4 (0.5)	0	4 (0.2)	1 (<0.1)	0	1 (<0.1)	4 (0.1)
Endocrine Disorders	0	0	0	0	0	0	2 (0.2)	2 (<0.1)	3 (<0.1)
Immune system disorders	0	0	0	0	0	0	0	0	3 (<0.1)
Investigations	0	0	1 (0.1)	0	1 (<0.1)	0	0	0	6 (0.1)
Pregnancy, Puerperium, Perinatal Conditions	1 (0.5)	0	0	2 (0.2)	2 (0.1)	3 (0.1)	0	3 (<0.1)	3 (<0.1)
Social circumstances	0	0	0	1 (0.1)	1 (<0.1)	0	0	0	0
Surgical and Medical Procedures	0	0	0	1 (0.1)	1 (<0.1)	0	0	0	1 (<0.1)

Source: Summary of Clinical Safety (data cut-off March 29, 2011), adapted from Tables 93-106 and 120-Day Safety Update, adapted from tables 21-23
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized; **-Separate table and review

7.3.2.1 Malignancy

Overall Malignancy (Excluding Non-Melanoma Skin Cancer, NMSC)

In the RA clinical development program, including Phase 2 studies, a total of 67 patients were diagnosed with solid tumors or hematologic malignancy (see Table 100). In addition, three cases of neoplasms that could not be defined as malignant were reported in the RA development program: one case of thyroid hyperplastic nodule in a patient on tofacitinib 10 mg BID, one case of breast atypical ductal hyperplasia in a patient on tofacitinib 5 mg BID, and one case of ovarian mucinous cystadenoma patient on tofacitinib 10 mg BID (Table 100).

During the controlled periods of Phase 3 randomized controlled studies, 13 cases occurred in tofacitinib-treated, one case occurred in adalimumab-controlled group as shown in Table 36. No malignancies occurred in placebo-treated patients. During the 12-month pooled safety period, the rates of malignancy were numerically similar between the adalimumab and tofacitinib 5 mg BID group but higher in the tofacitinib 10 mg BID group.

Table 36. Number of Patients with Malignancy (Excluding Non-Melanoma Skin Cancer) in Phase 3 Randomized Controlled Studies, by Trial Period

Summary of Malignancy (Excluding Non-Melanoma Skin Cancer) in Phase 3 Randomized Controlled Studies, by Trial Period					
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses
0-3 Months	**681**	**204**	**1216**	**1214**	**2430**
Total patients with ≥ 1 malignancy, n (%)	**0**	**0**	**2 (0.17)**	**3 (0.25)**	**5 (0.2)**
Breast cancer	-	-	-	1	1
Gastric cancer	-	-	1	-	1
Renal cell carcinoma, metastatic	-	-	1	-	1
Metastatic neoplasm, NOS	-	-	-	1	-
Cervix carcinoma	-	-	-	1	1
3-6 Months	**221**	**204**	**1451**	**1439**	**2890**
Total patients with ≥ 1 malignancy, n (%)	**0**	**0**	**1 (<0.1)**	**3 (0.2)**	**4 (0.1)**
Lung cancer	-	-	-	1	1
Non-small cell	-	-	-	*1*	*1*
Breast cancer	-	-	-	1	1
Cervix carcinoma	-	-	-	1	1
Squamous cell carcinoma, metastatic	-	-	1	-	1
> 6 Months	**N.A.**	**204**	**1056**	**1046**	**2102**
Total patients with ≥ 1 malignancy, n (%)	**N.A.**	**1 (0.5)**	**2 (0.2)**	**2 (0.2)**	**4 (0.2)**
Lung cancer	N.A.	1 (0.5)	2 (0.2)	-	2 (0.1)
Metastatic	N.A.	-	*1*	-	*1*
Non-small cell	N.A.	*1*	*1*	-	*1*
Breast cancer	N A.	-	-	1 (0.1)	1 (<0.1)
Lymphoma	N.A.	-	-	1 (0.1)	1 (<0.1)
Pooled 0-12 Months RCT Studies	**681**	**204**	**1216**	**1214**	**3030**
Total patients with ≥ 1 malignancy, n (%)	**0**	**1 (0.5)**	**5 (0.4)**	**8 (0.7)**	**13 (0.4)**
Exposure, patient-years	203	178	904	910	2098
Incidence rate, per 100 PY (95%CI)	0	0.56 (0.08, 3.97)	0.55 (0.23, 1.33)	0.88 (0.44, 1.76)	0.62 (0.36, 1.07)

Source: Integrated Analyses of Malignancy, adapted from Tables 15-18, 20-22

The types of malignancies in the Phase 3 RA and LTE studies are described in Table 37 below. Five malignancies, not included in Table 37, were reported in the Phase 2 RA development program: well differentiated adenocarcinoma of the colon, malignant melanoma, basal cell carcinoma, and squamous cell carcinoma of the skin, all in tofacitinib-treated patients and renal cell carcinoma in one adalimumab-treated patient.

The types of malignancies in the RA development program are consistent with the overall pattern that would be expected for the study population even though unusual malignancies, such as liposarcoma and synovial sarcoma, were also reported. As seen in Table 37, lung cancer was the most common malignancy in 16 patients (15 on tofacitinib and 1 on adalimumab), followed by breast cancer in 11 patients. Gastric cancer occurred in 5 patients. Renal cell carcinoma was reported in four patients (3 on tofacitinib and one on adalimumab). Lymphoma and prostate cancer occurred in 3 patients each on tofacitinib. Malignant melanoma occurred in 3 tofacitinib-treated patients. Colon, bladder, ovarian, cervical carcinoma occurred in 2 patients each. The remaining 11 malignancies occurred in 1 patient each. There were also additional concerns pertaining to lymphoma, which will be discussed in greater detail below.

Table 37. Summary of Malignancies in the Phase 3 and LTE Studies in RA.

Integrated Summary of Malignancies (Excluding Non-Melanoma Skin Cancer) in Phase 3 and LTE Studies in RA									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept. 29, 2011)
Enrolled, n	681	204	1216	1214	3030	1321	1906	3227	3515
Total patients with ≥ 1 malignancy, n (%)	-	1 (0.5)	5 (0.4)	8 (0.7)	13 (0.4)	23 (1.7)	12 (0.6)	35 (1.1)	50 (1.4)
Exposure, patient-years	203	178	904	910	2098	2235	881	3116	4407
Incidence rate, per 100 PY (95%CI)	0	0.56 (0.08, 3.97)	0.55 (0.23, 1.33)	0.88 (0.44, 1.76)	0.62 (0.36, 1.07)	1.03 (0.68, 1.55)	1.36 (0.77, 2.40)	1.12 (0.81, 1.56)	1.14 (0.86, 1.50)
Solid tumors, n (incidence per 100 PY)	-	1 (0.6)	5 (0.6)	7 (0.8)	12 (0.6)	21 (1.0)	12 (1.4)	33 (1.1)	48 (1.1)
Lung cancer	-	1 (0.6)	3 (0.3)	1 (0.1)	4 (0.2)	3 (0.1)	5 (0.6)	8 (0.3)	12 (0.3)
Adenocarcinoma	-	-	-	-	-	-	2	2	2
Bronchial	-	-	-	-	-	1	1	2	4
Lung cancer, NOS	-	-	-	-	-	-	-	-	1
Metastatic	-	-	2	-	2	-	-	-	-
Non-small cell, NOS	-	1	1	1	2	2	1	3	3
Small cell	-	-	-	-	-	-	1	1	2
Breast cancer	-	-	-	3 (0.3)	3 (0.1)	5 (0.2)	1 (0.1)	6 (0.2)	8 (0.2)
Metastatic	-	-	-	-	-	2	-	2	2
Paget's disease of the breast	-	-	-	-	-	1	-	1	1
Not specified	-	-	-	3	3	2	1	3	5
Gastric cancer	-	-	1 (0.1)	-	1 (<0.1)	2 (0.1)	-	2 (0.1)	4 (0.1)
Prostate cancer	-	-	-	-	-	-	3 (0.3)	3 (0.1)	3 (0.1)
Renal cell carcinoma	-	-	1 (0.1)	-	1 (<0.1)	1 (<0.1)	1 (0.1)	2 (0.1)	2 (<0.1)
Malignant melanoma	-	-	-	-	-	-	1 (0.1)	1 (<0.1)	2 (<0.1)
Colon cancer	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	2 (<0.1)
Bladder cancer	-	-	-	-	-	-	-	-	2 (<0.1)
Ovarian cancer	-	-	-	-	-	2 (0.1)	-	2 (0.1)	2 (<0.1)
Cervix carcinoma	-	-	-	2 (0.2)	2 (0.1)	-	-	-	-
Squamous cell carcinoma	-	-	-	-	-	-	1 (0.1)	1 (<0.1)	1 (<0.1)
Metastatic neoplasm, NOS	-	-	-	1 (0.1)	1 (<0.1)	-	-	-	-
Thyroid cancer	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Choroid plexus papilloma	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Ureteric cancer	-	-	-	-	-	-	-	-	1 (<0.1)
Uterine cancer	-	-	-	-	-	-	-	-	1 (<0.1)
Endometrial cancer	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Gallbladder cancer	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Laryngeal cancer	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Liposarcoma	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Synovial sarcoma	-	-	-	-	-	-	-	-	1 (<0.1)
Vulvar cancer	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Hematologic, n (incidence per 100 PY)	0	0	0	1 (0.1)	1 (<0.1)	2 (<0.1)	0	2 (<0.1)	2 (<0.1)
CNS lymphoma, NHL, B-cell	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Lymphoma	-	-	-	1 (0.1)	1 (<0.1)	-	-	-	-
Lymphoproliferative disorder	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)

Source: Integrated Safety Analysis on Malignancies (data cut-off March 29, 2011), adapted from Tables 12, 13, 14, 26, 40; Summary of Clinical Safety, adapted from Tables 110-112; 120-Day Safety Update, adapted from tables 34-47
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

Immunosuppression is generally regarded as a factor in carcinogenesis. This is also reflected by the fact that all solid malignancies occurred in patients on active treatment, either tofacitinib or adalimumab. However, about one third of the cases occurred in patients who were on tofacitinib monotherapy and were not receiving additional immunosuppression with concomitant DMARD suggesting that tofacitinib alone may be a potent immunosuppressant conferring increased risk of malignancy.

Notably, the exposure-adjusted incidence rates of solid tumors and hematologic malignancies numerically increased in a dose-dependent fashion (Table 37) and with prolonged exposure (Table 38 and Figure 12 A) suggesting the possibility of additional risk attributable to tofacitinib. In the LTE studies, compared with controlled periods in the Phase 3 studies, the rate of malignancies numerically increased for both tofacitinib groups. The fact that the confidence intervals of the incidence rates are overlapping should be interpreted with caution, as the trials were not designed to specifically assess statistical significance of safety events such as malignancy.

Furthermore, malignancy was reported as the cause of death in a significant proportion, 27% (12/45), of all deaths in the tofacitinib-treated patients (Table 32).

Table 38. Incidence Rates of Malignancy (Excluding NMSC) Over Time in Tofacitinib Phase 2, 3 and LTE RA Studies

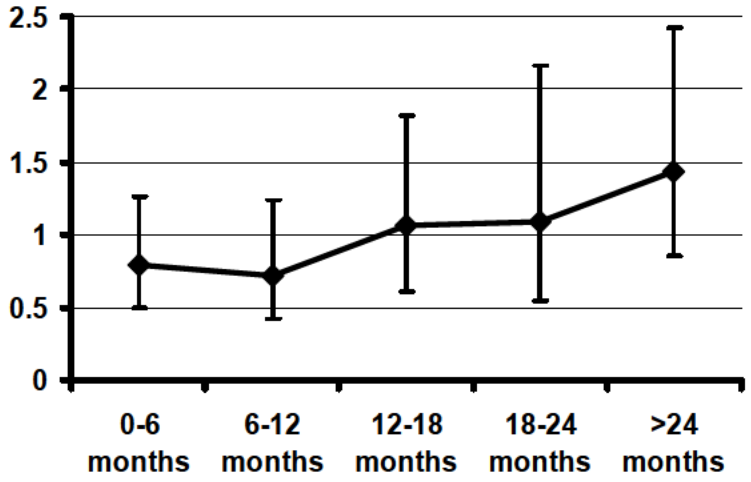
Incidence Rates of Malignancy (Excluding Non-melanoma Skin Cancer, NMSC) Over Time in Tofacitinib Phase 2, 3 and LTE RA Studies					
	0-6 months	**6-12 months**	**12-18 months**	**18-24 months**	**>24 months**
Enrolled, n	4791	4012	3126	2054	941
Total patients with ≥ 1 malignancy, n (%)	17 (0.4)	13 (0.3)	13 (0.4)	8 (0.4)	14 (1.5)
Exposure for event, patient-years	2166.0	1811.0	1229.1	736.7	976.1
Incidence rate, per 100 patient-years (95% CI)	**0.79** (0.49, 1.26)	**0.72** (0.42, 1.24)	**1.06** (0.61, 1.82)	**1.09** (0.54, 2.17)	**1.43** (0.85, 2.42)

Source: 120 Day Safety Update, adapted from Table 36

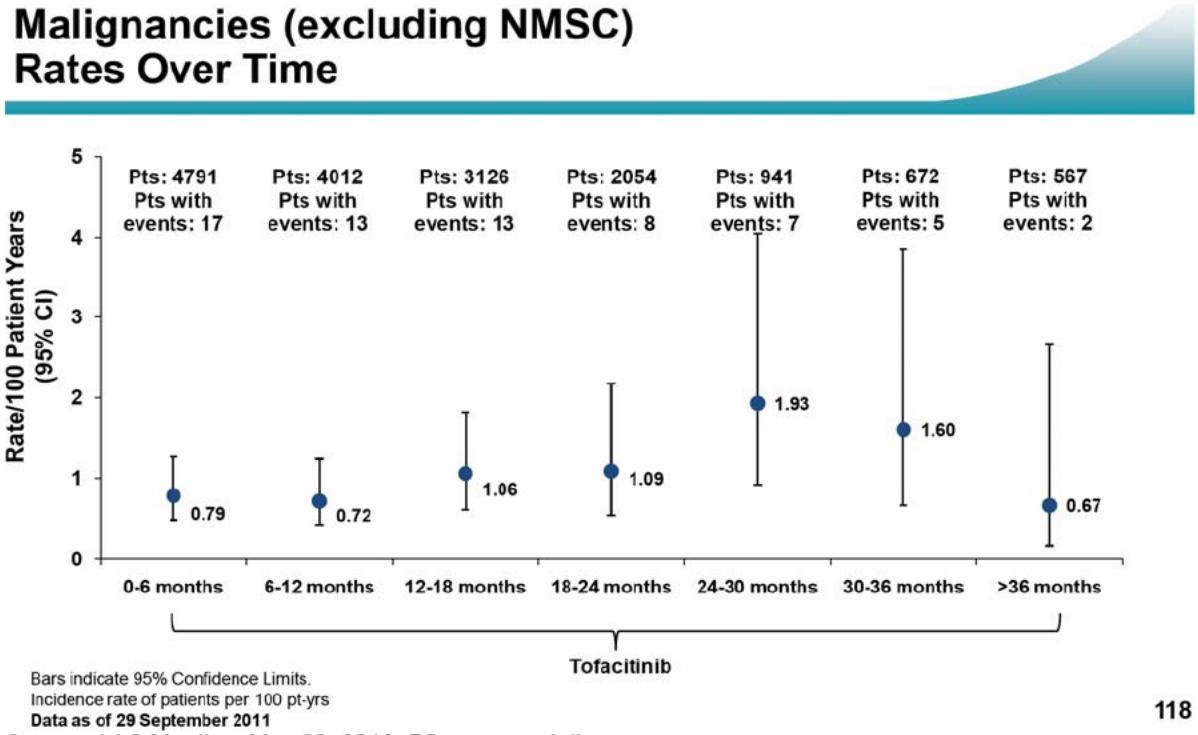
At the Arthritis Advisory Committee meeting on May 09, 2012, the Sponsor presented an alternative figure of the same data, where the incidence of malignancy was further broken down by 6 month periods for patients exposed to tofacitinib beyond 24 months (Figure 12 B). The figure suggested a decrease in the incidence of malignancy beyond month 30 of tofacitinib exposure. This observation however may be misleading, as in this time period, the majority of patients have been exposed to 5 mg BID dose (see Table 29 above) and the 10 mg BID dose groups is significantly underrepresented. If there was a dose-dependent (5 mg vs 10 mg BID) increase in the risk of developing malignancy as suggested by the controlled period of the Phase 3 studies, this figure may significantly underestimate the true incidence of malignancy in the 10 mg BID dose group beyond the 24-month tofacitinib exposure.

Figure 12. Non-cumulative Incidence Rates of Malignancy (Excluding Non-melanoma Skin Cancer, NMSC) Over Time in Tofacitinib Phase 2, 3 and LTE RA Studies

A. Data from the NDA submission



B. Data presented by Sponsor at the AAC, May 09, 2012



Source: AAC Meeting, May 09, 2012, Pfizer presentation

The unexpected observation of malignancy rates increasing over time is of particular concern and indicates a potential safety signal.

This observation could be specific to tofacitinib, as malignancy was not identified as a safety concern with the approved ruxolitinib[14] with the caveat that this drug was approved for an unmet medical need and based on a relatively small safety database.

Lung cancer

Lung cancer was the most prevalent type of cancer in the RA development program with a total of 16 cases: 15 in tofacitinib-treated patients and one in adalimumab control group Table 39. Only three of these patients were never smokers and the rest were active smokers or had a history of long-term smoking.

Table 39. Integrated Summary of Lung Cancer in Phase 3 and LTE Studies in RA

Integrated Summary of Lung Cancer in Phase 3 and LTE Studies in RA								
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies		
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	Updated LTE, All Doses (cut-off Sept. 29, 2011)
Enrolled, n	681	204	1216	1214	3030	1370	2145	3515
Exposure, patient-years	203	178	904	910	2098	2726	1683	4409
Patients with ≥ event, n		1	3	1	4	4	8	12
Incidence rate, per 100 PY	0	0.56	0.33	0.11	0.22	0.15	0.48	0.27

Source: Integrated Analysis of Malignancy, adapted from Table 33; 120 Day Safety Update, adapted from Table 37
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

The incidence of lung cancer also increased numerically over time for the first 24 months (Table 40) in parallel with the overall cancer incidence. During the Phase 3 controlled period, three cases of lung cancer occurred in the 5 mg group and one in the 10 mg group with comparable incidence rates. However, in the long-term exposure period, more cases accumulated in the 10 mg BID dose group with increasing rates compared with the 5 mg BID group. This suggests the possibility of increased risk of lung cancer with prolonged and higher tofacitinib exposure, albeit the numbers of these events are small to make definitive conclusions.

14 USPI Jakafi (ruxolitinib), November 2011

Table 40. Incidence Rates of Lung Cancer Over Time in Tofacitinib Phase 2, 3 and LTE RA Studies

Incidence Rates of Lung Cancer Over Time in Tofacitinib Phase 2, 3 and LTE RA Studies					
	0-6 months	6-12 months	12-18 months	18-24 months	>24 months
Enrolled, n	4791	4013	3126	2056	941
Total patients with ≥ 1 malignancy, n (%)	5 (0.1)	3 (0.1)	4 (0.1)	3 (0.2)	1 (0.1)
Exposure for event, patient-years	2166	1811	1229	737	977
Incidence rate, per 100 patient-years	0.23	0.17	0.33	0.41	0.10

Source: 120 Day Safety Update, adapted from Table 38

Lung cancer has been recognized as more prevalent in the RA population relative to the general population based on published literature.[15] The Standardized Incidence Ratio (SIR) for lung cancer is 2.35 (95% CI 1.34 to 3.82) based on comparisons with the NCI Surveillance Epidemiology and End Results (SEER) general population database and is consistent with comparable historical control, whose SIR was in the range of 1.6[16] to 3.5[17].

Breast Cancer

Breast cancer was the second most prevalent cancer in tofacitinib RA development with all the cases occurring in tofacitinib-treated patients and none in placebo or adalimumab controls as shown in Table 41. During the controlled period, all cases were reported in the 10 mg BID dose, however, in the long-term exposure, more cases occurred with a higher incidence in the 5 mg BID dose group. Based on the small numbers and inconsistent trends, it is difficult to draw definitive conclusions regarding the dose-dependency (5 mg vs 10 mg BID) of breast cancer.

15 Abasolo L et al., Cancer in rheumatoid arthritis, Semin Arthritis Rheum, 2008 Jun;37(6):388-97
16 Smitten A et al., A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis, Arthritis Research & Therapy 2008, 10:R45
17 Abasolo L et al., Cancer in rheumatoid arthritis, Semin Arthritis Rheum, 2008 Jun;37(6):388-97

Table 41. Integrated Summary of Breast Cancer in Phase 3 and LTE Studies in RA

Integrated Summary of Breast Cancer in Phase 3 and LTE Studies in RA								
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies		
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	Updated LTE, All Doses (cut-off Sept. 29, 2011)
Enrolled, n	681	204	1216	1214	3030	1370	2145	3515
Exposure, patient-years	203	178	904	910	2098	2726	1683	4409
Patients with ≥ event, n	-	-	-	3	3	6	2	8
Incidence rate, per 100 PY	0	0	0	0.39	0.17	0.27	0.14	0.22

Source: Integrated Analysis of Malignancy, adapted from Table 36; 120 Day Safety Update, adapted from Table 40
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

Importantly, the trends over time also suggest that longer tofacitinib exposure may be associated with increasing incidence of breast cancer as shown in Table 42.

Table 42. Incidence Rates of Breast Cancer Over Time in Tofacitinib Phase 2, 3 and LTE RA Studies

Incidence Rates of Breast Cancer Over Time in Tofacitinib Phase 2, 3 and LTE RA Studies					
	0-6 months	6-12 months	12-18 months	18-24 months	>24 months
Enrolled, n	4017	3358	2608	1718	772
Total patients with ≥ 1 malignancy, n (%)	1	3	2	2	3
Exposure for event, patient-years	1812	1513	1027	611	806
Incidence rate, per 100 patient-years	0.06	0.20	0.20	0.33	0.37

Source: 120 Day Safety Update, adapted from Table 38

The SIR for lung cancer is 0.82 (95% CI 0.41-1.46) based on comparisons with the SEER database and is consistent with comparable historical control, whose SIR was in the range of 0.84[18] to 0.53[19].

Lymphoproliferative Disorders, Including Lymphoma

A total of 13 cases of lymphoproliferative disorder (LPD) were reported in the tofacitinib clinical development program:

- 7 in the RA program, all in tofacitinib-treated patients (Table 43)
- 5 in the renal allograft rejection program (Table 45)

18 Smitten A et al., A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis, Arthritis Research & Therapy 2008, 10:R45
19 Abasolo L et al., Cancer in rheumatoid arthritis, Semin Arthritis Rheum, 2008 Jun;37(6):388-97

- 1 in psoriasis program, which occurred prior to randomization.

LPD in RA development program:
A total of seven cases of LPD were reported in the RA development program, all of which occurred in tofacitinib-treated patients participating in Phase 3 efficacy or LTE studies (summarized in Table 43).

Table 43. Summary of Lymphoproliferative Disorders, Including Lymphoma in Tofacitinib RA Clinical Development

Summary of Lymphoproliferative Disorders, Including Lymphoma in Tofacitinib RA Clinical Development					
Study-Subject ID	**Age/Gender**	**CP Dose (Background DMARD)**	**Duration of Exposure**	**Preferred Term**	**Description**
1024-10361009	78/F	5 mg BID (MTX)	807 days	Central nervous system lymphoma	Primary CNS, diffuse B-cell lymphoma; EBV negative
1041-10281005	51/F	5 mg BID	226 days	Lymphoproliferative disorder	Abdominal lymph nodes; EBV positive
1044-11901002	47/F	10 mg BID (MTX)	206 days	Lymphoma	Thymus
1044-10041006	69/F	10 mg BID (MTX)	365 days	Breast lymphoma	Diffuse large B cell lymphoma
(b) (4)-11571001	65/M	10 mg BID	149 days	Non-Hodgkin's lymphoma	High grade B-cell Burkitt-like lymphoma;
(b) (4)11931002#	63/M	CP dose and MTX blinded	449 days	Lymphoproliferation	Hematologic
1024-11271019#	61/F	5 mg BID	660 days	Mantle cell lymphoma	Mantle cell lymphoma-blastoid variant

Source: Integrated Safety Analysis on Malignancies; 120-Day Safety Update; #-Cases reported after the 120-Day Safety Update

While the histopathological diagnoses are consistent with the types of lymphoma seen in the comparable RA population, primary central nervous system lymphoma (PCNSL) and breast lymphoma are atypical locations.

Analysis of the seven LPD cases in the RA program does not suggest an apparent pattern in relation to dose (5 vs 10 mg BID) or background immunosuppression, e.g. MTX. However, most of the cases have occurred later in the course of treatment with tofacitinib (median of one year, mean of 14 months) which would be consistent with a scenario where prolonged tofacitinib exposure is associated with an increased risk of developing LPD in this patient population.

The incidence of LPD in the RA program, based on the point estimates, numerically increased with prolonged exposure as shown on Table 44. Similarly, the standardized incidence ratios (SIR) have also increased over time. The fact that the confidence intervals of the incidence rates at the different timepoints are overlapping should be interpreted with caution, as the trials were not designed to specifically assess statistical significance of safety events such as LPD.

Table 44. Exposure-adjusted Incidence of LPD in RA Phase 2, Phase 3, and LTE Studies Over Time (All Doses)

Exposure-adjusted Incidence of LPD in RA Phase 2, Phase 3, and LTE Studies Over Time (All Doses)				
	March 29, 2011	September 29, 2011	January 12, 2012	March 8, 2012
Enrolled	4789	5563	5677	n.r.
Patients with LPD, n (%)	3 (<0.1)	5 (<0.1)	6 (0.11)	7
Exposure for event (PY)	5650.7	7977.2	9070.6	n.r.
Incidence, event per 100 PY (95% CI)	0.053 (0.02, 0.17)	0.063 (0.02, 0.15)	0.066 (0.03, 0.15)	n.r.
SIR (95% CI)	1.74 (0.36, 5.10)	2.35 (0.76, 5.50)	n.r.	n.r.

Source: Integrated Safety Analysis on Malignancies; 120-Day Safety Update; Response to Information Request and MedWatch reports (July, 18, 2011, January 24, 2012, March 8, 2012)

LPD in Prevention of renal allograft rejection development program

Five cases of post-transplant LPD (PTLD) have been reported in 218 tofacitinib-treated patients in the Phase 2b renal allograft program (Table 45) for a cumulative incidence of 2.3%. In study 1030, patients were randomized 1:1:1 to one of two tofacitinib regimens or to a cyclosporine control regimen. One tofacitinib arm was dosed at 15 mg BID for the first 6 months, then reduced to 10 mg BID, and the other arm received 15 mg BID for the first 3 months, then reduced to 10 mg BID. Study 1050 was an open-label extension study.

Table 45. Summary of Lymphoproliferative Disorders, Including Lymphoma in Tofacitinib Renal Allograft Clinical Development

Summary of Lymphoproliferative Disorders, Including Lymphoma in Tofacitinib Renal Allograft Clinical Development					
Study-Subject ID	**Age/Gender**	**CP Dose**	**Duration of Exposure**	**Preferred Term**	**Location *Description***
1030-10901001	62/M	15 mg BID x 6 months then reduced	~9 months	Lymphoproliferative disorder	Brain, stomach, colon, pericardial; *EBV-positive*
1030-10661002	39/M	15 mg BID x 3 months then reduced	~10 months	Non-Hodgkin's lymphoma	Brain *EBV-positive*
1030-11001005	53/M	15 mg BID x 6 months then reduced	~10 months	Post-transplant Hodgkin's lymphoma	Lungs *EBV-positive*
1050-10321006	71/M	15 mg BID x 6 months then reduced	~19 months	Non-Hodgkin's lymphoma	Brain *EBV-positive*
1050-10571001	46/M	15 mg BID x 6 months then reduced	~29 months	Large B-cell lymphoma	Brain *EBV-positive*

Source: Integrated Safety Analysis on Malignancies; 120-Day Safety Update

Notably, four out of the five PTLD cases have featured CNS involvement. In the general transplant population, by comparison, the CNS is involved in approximately 15% of PTLD events. No PTLD events have been reported among the patients randomized to the cyclosporine control regimen. These observations suggest an increased risk of PTLD with tofacitinib treatment.

The concern about the potential tofacitinib effect on lymphoma-genesis is further supported by findings in the pivotal 39-week cynomolgus monkey study (see also Section Preclinical Pharmacology/Toxicology above) Three of eight monkeys in the high dose group (10 mg/kg) had lymphomas and multiple monkeys of all treated groups had lymphocyte hyperplasia in lymphoid tissue. Two were B cell lymphomas and one was T cell lymphoma in the peri-thymic fat.

In summary, there appears to be a consistent safety signal of increased risk of LPD with tofacitinib use. In the RA development program, seven cases of LPD have been observed with tofacitinib treatment versus no cases in the placebo- and adalimumab-control control groups. In two of the cases, the lymphoma location was highly atypical (central nervous system and breast). Further, findings in the transplant program corroborate an increased risk of PTLD, with an unusual predominance of CNS PTLD. Findings in the RA and post-renal transplant indications are supported by a signal of lymphomas in the high-dose tofacitinib group in the chronic monkey study, suggesting a consistent signal of increased risk.

Melanoma

Three cases of melanoma were reported in tofacitinib RA development, two in patients receiving 5 mg BID and one on 10 mg BID. No cases occurred during the control periods of the Phase 3 studies. One of the cases occurred in study 1025 and the rest, during the long-term extension studies. In light of the small number of events and no cases in the controlled periods, it is difficult to draw conclusions on the significance of melanoma in the tofacitinib RA development. Further, patients with methotrexate-treated RA may be at a two-to-three fold increased risk of melanoma.[20]

Non-Melanoma Skin Cancer (NMSC)

A total of 33 cases non-melanoma skin cancer (NMSC) were reported in the RA clinical development, including Phase 2 studies as shown in Table 46. Majority of these were basal cell carcinomas. There were some dose-dependent increases in the numbers and exposure-adjusted incidence between the two tofacitinib doses; however, the incidence of NMSC in tofacitinib groups remained comparable to placebo and adalimumab controls and there was no consistent trend over time (Table 47).

20 Buchbinder M, et al., Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate, Arthritis Rheum 2008 Jun 15;59(6):794-9

Table 46. Summary of Non-Melanoma Skin Cancer in Phase 3 and LTE Studies in RA

Integrated Summary of NMSC Cancer in Phase 3 and LTE Studies in RA								
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies		
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	Updated LTE, All Doses (cut-off Sept. 29, 2011)
Enrolled, n	681	204	1216	1214	3030	1370	2145	3515
Exposure, patient-years	202	177	902	909	2095	2717	1677	4394
Patients with ≥ event, n	2	2	3	5	8	10	15	25
Incidence rate, per 100 PY	0.99	1.13	0.33	0.55	0.44	0.37	0.89	0.57
Basal cell carcinoma	1	1	2	4	6	6	11	17
Atypical fibroxanthoma	-	-	1	-	1	-	-	-
Bowen's disease	-	-	-	1	1	-	1	1
Keratoacanthoma	-	-	-	-	-	2	-	2
Molluscum contagiosum	-	-	-	-	-	1	-	1
Squamous cell carcinoma, skin	1	1	-	-	-	1	3	4

Source: Integrated Analysis of Malignancy, adapted from Table 40; 120 Day Safety Update, adapted from Table 46
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

Table 47. Incidence Rates of Non-Melanoma Skin Cancer Over Time in Tofacitinib Phase 2, 3 and LTE RA Studies

Incidence Rates of Breast Cancer Over Time in Tofacitinib Phase 2, 3 and LTE RA Studies					
	0-6 months	6-12 months	12-18 months	18-24 months	>24 months
Enrolled, n	4791	4007	3117	2054	937
Total patients with ≥ 1 malignancy, n (%)	9	6	8	2	6
Exposure for event, patient-years	2164	1808	1224	733	967
Incidence rate, per 100 patient-years	0.42	0.33	0.65	0.27	0.62

Source: 120 Day Safety Update, adapted from Table 37

Based on these data for NMSC and the small number of melanomas in tofacitinib RA development, it is difficult to draw definitive conclusions about tofacitinib-induced photosensitivity as a potential safety issue.

7.3.2.2 Infections

Overall Infections

Phase 3 and LTE studies generally excluded patients at increased infection risk, such as patients who had a significant infection within 6 months, a WBC of $<3 \times 10^3/mm^3$, an ANC $<1.2 \times 10^3/mm^3$, evidence of infection with TB (by X-ray, and/or skin testing, and/or Quantiferon), repeated episodes of VZV or HSV infections, or evidence of HCV, HBV or HIV infection.

Despite theses measures, infections occurred with overall higher incidence in tofacitinib-treated patients, without a clear dose-relationship, as shown in Table 48 below. The most common treatment-emergent infections, occurring in at least 2% of patients in any treatment group, were upper respiratory tract infections, urinary tract infections, herpes zoster and influenza. The proportion of patients with moderate and severe infections in tofacitinib groups appears comparable to the control groups in the 12-month pooled Phase 3 studies (Table 49). The data on infection severity were not reported by the Sponsor for the LTE studies.

Table 48. Summary of Treatment-Emergent Infections with ≥2% Occurrence in All Phase 3 Studies and LTE by Trial Period

Integrated Summary of Treatment-Emergent Infections and Infestation SOC AEs by Preferred Term with ≥2% Occurrence in All Phase 3 Studies and LTE by Trial Period, Number of Patients (%)					
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses
0-3 months					
Enrolled	681	204	1216	1214	2430
Number of patients with AEs	67 (10)	23 (11)	131 (11)	119 (10)	250 (10)
Upper respiratory tract infection	51 (7)	18 (9)	111 (9)	93 (8)	204 (8)
Urinary tract infection	12 (2)	7 (3)	25 (2)	24 (2)	49 (2)
Viral infections	4 (1)	0	2 (0.2)	4 (0.3)	6 (0.2)
Influenza	4 (1)	0	2 (0.2)	4 (0.3)	6 (0.2)
3-6 months					
Enrolled	221	204	1451	1439	2890
Number of patients with AEs	7 (3)	15 (7)	115 (8)	97 (7)	212 (7)
Upper respiratory tract infection	5 (2)	9 (4)	87 (6)	71 (5)	158 (5)
Urinary tract infection	2 (1)	6 (3)	25 (2)	24 (2)	49 (2)
Influenza	0	0	5 (0.3)	6 (0.4)	11 (0.3)
> 6 months					
Enrolled	-	204	1056	1046	2102
Number of patients with AEs	-	21 (10)	115 (11)	145 (14)	260 (12)
Upper respiratory tract infection	-	13 (6)	90 (9)	100 (10)	190 (9)
Urinary tract infection	-	5 (3)	15 (1)	31 (3)	46 (2)
Herpes zoster	-	4 (2)	20 (2)	22 (2)	42 (2)
LTE Studies					
Enrolled	-	-	1321	1906	3227
Number of patients with AEs	-	-	567 (43)	433 (23)	1000 (31)
Gastroenteritis	-	-	39 (3)	17 (1)	56 (2)
Upper respiratory tract infection	-	-	520 (39)	336 (18)	856 (27)
Urinary tract infection	-	-	119 (9)	85 (4)	204 (6)
Herpes zoster	-	-	90 (7)	43 (2)	133 (4)
Influenza	-	-	75 (6)	30 (2)	105 (3)

Source: Integrated Safety Analysis on Infections, Adapted from Tables 11, 12, 13.

Table 49. Summary of Treatment-Emergent Infections by Severity in All Phase 3 Studies by Trial Period and Treatment Received

Integrated Summary of Treatment-Emergent Infections and Infestation SOC AEs by Severity in All Phase 3 and LTE Studies by Trial Period, Number of Patients (%)					
	PBO	**ADA**	**CP5 mg BID**	**CP10 mg BID**	**CP, All doses**
0-3 months					
Enrolled	681	204	1216	1214	2430
All AEs	125 (18)	33 (16)	243 (20)	257 (21)	500 (21)
Mild	82 (12)	20 (10)	148 (12)	166 (14)	314 (13)
Moderate	39 (6)	13 (6)	85 (7)	79 (7)	164 (7)
Severe	4 (0.6)	0	10 (0.8)	12 (1.0)	22 (0.9)
3-6 months					
Enrolled	221	204	1451	1439	2890
All AEs	20 (9)	28 (14)	249 (17)	244 (17)	493 (17)
Mild	14 (6)	13 (6)	144 (10)	148 (10)	292 (10)
Moderate	5 (2)	13 (6)	96 (7)	90 (6)	186 (6)
Severe	1 (0.5)	2 (1.0)	9 (0.6)	6 (0.4)	15 (0.5)
> 6 months					
Enrolled	-	204	1056	1046	2102
All AEs	-	36 (18)	193 (18)	238 (23)	431 (21)
Mild	-	28 (14)	122 (12)	138 (13)	260 (12)
Moderate	-	8 (4)	66 (6)	92 (9)	158 (8)
Severe	-	0	5 (0.5)	8 (0.8)	13 (0.6)
LTE Studies					
Enrolled	-	-	1321	1906	3227
All AEs	-	-	n.r.	n.r.	n.r.
Mild	-	-	n.r.	n.r.	n.r.
Moderate	-	-	n.r.	n.r.	n.r.
Severe	-	-	n.r.	n.r.	n.r.

Source: Integrated Safety Analysis on Infections, Adapted from Table 14.

Serious infections

Serious infection was defined as any infection that required hospitalization for treatment, required parenteral antimicrobial therapy, or met other criteria that required it to be classified as an SAE. A patient who experienced a serious infection was to be discontinued from the study. This infection was to be reported as an SAE and listed as the reason for discontinuation in the CRF. Appropriate laboratory investigations including, but not limited to, cultures were to be performed to establish the etiology of any serious infection.

In the tofacitinib RA development program, including Phase 1, 2, 3, and LTE studies, a total of 206 serious infections were reported in tofacitinib-treated patients across all tested doses. Of these, three occurred in placebo-treated patients (bronchiectasis, pyelonephritis with bacterial sepsis, and sialoadenitis), three in adalimumab-treated

patients (breast abscess, bursitis, gallbladder empyema) and 197 occurred in patients treated with one of the two doses proposed for approval (5 and 10 mg BID). The most common serious infection was pneumonia accounting for approximately 27% of all serious infections, followed by herpes zoster, urinary tract infections, gastroenteritis, and cellulitis. The serious infections occurred generally later in the course of tofacitinib treatment (median exposure of approximately 10 months, mean of about 12 months). This observation should be taken into account when comparing the rates is serious infections to placebo-treated patients whose exposure was limited to only 3 to 6 months. Comparisons to adalimumab-treated patients may be more informative as their exposure was up to one year in study 1064.

A summary of nonfatal serious infectious events (SIE) during Phase 3 and LTE studies is provided in Table 50 and in Supplementary Table 102. During the Phase 3 studies, a higher proportion of patients in the tofacitinib groups experienced a serious infection compared to the placebo and adalimumab control groups. In the LTE studies, the incidence rates of SIE remained stable in the 5 mg BID dose group but increased numerically in the 10 mg BID dose group suggesting a dose-dependent increase in SIE risk as shown in Figure 13 and Table 50.

Figure 13. Incidence of Serious Infectious Events in Phase 3 and LTE Studies in RA, by Dose

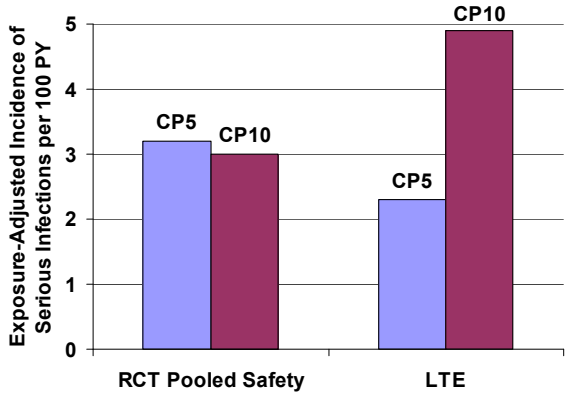


Table 50. Summary of Serious Infectious Events (SIE) (All Causality) in Phase 3 and LTE Studies in RA

Integrated Summary of Serious Infectious Events (SIE) (All Causality) in Phase 3 and LTE Studies in RA

	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Total number of SIEs	6	4	33	30	63	76	58	134	172
Total patients with ≥ 1 SIE, n (%)	3 (0.4)	3 (1.5)	29 (2.4)	27 (2.2)	61 (2.0)	50 (3.8)	43 (2.3)	93 (2.9)	131 (3.7)
Exposure, patient-years	202.5	178.7	900.9	909.1	2093.8	2222	878.9	3100 9	4377.7
Incidence of SIE terms, per 100 patient-years	3.0	2.2	3.7	3.3	3.0	3.4	6.6	4.3	3.9
Incidence of SIE, pa ient per 100 patient-years (95%CI)	1.48 (0.5, 4.6)	1.7 (0.5, 5.2)	3.2 (2.2, 4.6)	3.0 (2.0, 4.3)	2.9 (2.3, 3.7)	2.3 (1.7, 3.0)	4.9 (3.6, 6.6)	3.0 (2.4, 3.7)	3.0 (2.5, 3.6)
Types of Infections, n (event/100 PY)									
Pneumonia	-	-	11 (1.2)	6 (0.7)	17 (0.8)	17 (0.8)	13 (1.5)	30 (1.0)	40 (0.9)
Cellulitis	-	2 (1.1)	6 (0.7)	1 (0.1)	7 (0.3)	3 (0.1)	4 (0.5)	7 (0.2)	9 (0.2)
Herpes zoster	-	-	4 (0.4)	1 (0.1)	5 (0.2)	7 (0.3)	1 (0.1)	9 (0.3)	10 (0.2)
Abscess	-	1 (0.6)	3 (0.3)	1 (0.1)	4 (0.2)	3 (0.1)	8 (1.0)	11 (0.4)	11 (0.3)
Gastroenteritis	1 (0.5)	-	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)	3 (0.3)	6 (0.2)	11 (0.3)
Urinary tract infec ion	-	-	-	2 (0.2)	2 (0.1)	6 (0.3)	2 (0.2)	8 (0.3)	9 (0.2)
Tuberculosis	-	-	-	4 (0.4)	4 (0.2)	3 (0.1)	-	3 (0.1)	7 (0.2)
Sepsis	2 (1.0)	-	2 (0.2)	-	2 (0.1)	3 (0.1)	5 (0.6)	8 (0.3)	9 (0.2)
Bronchitis, bronchiolitis, bronchiectasis	1 (0.5)	-	1 (0.1)	2 (0.2)	3 (0.1)	2 (0.1)	3 (0.3)	5 (0.2)	6 (0.1)
Pyelonephritis	1 (0.5)	-	1 (0.1)	2 (0.2)	3 (0.1)	2 (0.1)	1 (0.1)	3 (0.1)	5 (0.1)
Diverticulitis	-	-	-	2 (0.2)	2 (0.1)	5 (0.2)	1 (0.1)	6 (0.2)	6 (0.1)
Appendicitis	-	-	-	-	-	4 (0.2)	1 (0.1)	5 (0.2)	5 (0.1)
Sinusitis	-	-	-	-	-	2 (0.1)	3 (0.3)	5 (0.2)	5 (0.1)
Enterocolitis	-	-	-	1 (0.1)	1 (<0.1)	2 (0.1)	1 (0.1)	3 (0.1)	4 (0.1)
Herpes simplex	-	-	-	-	-	1 (<0.1)	2 (0.2)	3 (0.1)	3 (0.1)
Cytomegalovirus infec ion	-	-	-	1 (0.1)	1 (<0.1)	2 (0.1)	-	2 (0.1)	2 (<0.1)
Device-related infec ion	-	-	-	-	-	2 (0.1)	-	2 (0.1)	2 (<0.1)
Meningitis	-	-	-	-	-	-	2 (0.2)	2 (0.1)	2 (<0.1)
Arthritis bacterial	-	-	-	1 (0.1)	1 (<0.1)	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
BK virus infection	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Bursitis, infective	-	-	-	-	-	-	-	-	1 (<0.1)
Cholecystitis, infective	-	-	1 (0.1)	-	1 (<0.1)	-	-	-	-
Clostridium difficile colitis	-	-	-	1 (0.1)	1 (<0.1)	-	1 (0.1)	1 (<0.1)	1 (<0.1)
Dengue fever	-	-	1 (0.1)	-	1 (<0.1)	-	-	-	-
Diabetic foot infection	-	-	-	1 (0.1)	1 (<0.1)	-	-	-	-
Esophageal Candidiasis	-	-	-	-	-	-	1 (0.1)	1 (<0.1)	1 (<0.1)
Gallbladder empyema	-	1 (0.6)	-	-	-	-	-	-	-
Hepatitis B	-	-	-	-	-	-	1 (0.1)	1 (<0.1)	1 (<0.1)
Infective spondylitis	-	-	-	-	-	-	1 (0.1)	1 (<0.1)	1 (<0.1)
Influenza	-	-	-	1 (0.1)	1 (<0.1)	1 (<0.1)	-	1 (<0.1)	2 (<0.1)
Labyrin hitis	-	-	-	1 (0.1)	1 (<0.1)	-	-	-	-
Mycobacterium avium complex	-	-	-	-	-	-	1 (0.1)	1 (<0.1)	1 (<0.1)
Necrotizing fascii is	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Osteomyelitis	-	-	1 (0.1)	-	1 (<0.1)	-	-	-	1 (<0.1)
Peritoneal infection	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	2 (<0.1)
Pertussis	-	-	-	-	-	-	1 (0.1)	1 (<0.1)	1 (<0.1)
Respiratory tract infection, NOS	-	-	-	-	-	-	1 (0.1)	1 (<0.1)	2 (<0.1)
Salpingo-oophoritis	-	-	1 (0.1)	-	1 (<0.1)	-	-	-	1 (<0.1)
Sialoadenitis	1 (0.5)	-	-	1 (0.1)	1 (<0.1)	-	-	-	-
Syphilis, secondary	-	-	-	-	-	1 (<0.1)	-	1 (<0.1)	1 (<0.1)
Tonsillitis	-	-	-	-	-	1 (<0.1)	1 (0.1)	2 (0.1)	2 (<0.1)

Source: Integrated Summary of Clinical Safety on Infections (data cut-off March 29, 2011), adapted from Tables 18, Summary of Clinical Safety adapted from Tables 68 and 93; and 120-Day Safety Update, adapted from Tables 18, 23

*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those pa ients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized. NOS-not otherwise specified;

Pneumonia was the most common nonfatal SIE, and was reported only in tofacitinib-treated patients. Other common SIE included cellulitis, herpes zoster, abscess, gastroenteritis, and urinary tract infection. Opportunistic infections, including tuberculosis were not uncommon, and will be discussed in further detail below. One case of Legionella pneumonia was reported in a patient in the LTE studies (subject ID 1024-12741007). The patient was a 62-year-old female who was treated with tofacitinib 10 mg BID for 95 days in Study 1024 when tofacitinib was discontinued due to three days of pyrexia. On Day 97, the patient was diagnosed with severe Legionella pneumonia and was hospitalized. She developed acute respiratory distress syndrome (ARDS) and was permanently withdrawn from the study. She recovered from ARDS on Day 109 and the pneumonia was resolved on Day 122.

Overall, the pattern of SIE is consistent with the profile of a product that induces significant immunosuppression.

To explore the potential for additive/synergistic immunosuppression with background DMARDs, the incidence of serious infections was assessed separate for monotherapy study 1045 and pooled DMARD background studies (1032, 1044, 1046, and 1064) and summarized in Table 51. The monotherapy study 1045 was of shorter duration (6 months) and the incidence rates in this study are based on small number of single events. However, there was a clear dose-dependent numerical imbalance in both proportions of patients with serious infections and incidence rates of serious infections over the 6 month trial consistent with dose-dependent immunosuppression by tofacitinib. While these data are not directly comparable to the 12 month data from the DMARD background studies, both tofacitinib dose groups had a higher overall incidence rate of serious infections compared with placebo add-on and adalimumab active control, suggesting that tofacitinib has a more potent immunosuppressive effect compared with traditional and biologic DMARDs.

Table 51. Summary of Serious Infectious Events in Phase 3 RA Development, by Background DMARD Treatment

Summary of Serious Infectious Events in Phase 3 RA Development, by Background DMARD Treatment					
	PBO	ADA	CP5	CP10	CP, All doses
DMARD background studies (0-12 months)					
Enrolled, n	559	204	973	969	2435
Patients with ≥1 SIE, n (%)	3 (0.5)	3 (1.5)	28 (2.9)	23 (2.4)	55 (2.3)
Exposure for event	175	179	784	795	1836
Incidence Rate per 100 PY	1.7	1.7	3.6	2.9	3.0
Monotherapy study 1045 (0-6 months)					
Enrolled, n	122	N.A.	243	245	595
Patients with ≥1 SIE, n (%)	0	N.A.	1 (0.4)	4 (1.6)	6 (1)
Exposure for event	0	N.A.	117	114	257
Incidence Rate per 100 PY	0	N.A.	0.9	3.5	2.3

Source: Integrated Summary Analyses of Infections, adapted from Table 25

Additional explorations of potential demographic factors and concomitant corticosteroid use on the incidence of serious infections were also undertaken. The results indicate that age ≥65 years, male gender and concomitant corticosteroid use confer increased risk as summarized in Table 52. Importantly, the trends of increased overall incidence of serious infections with tofacitinib dose and duration of exposure continued to hold for each of the explored parameters, indicating a dose (5 mg BID vs. 10 mg BID) and time (12-month pooled Phase 3 data vs. LTE)-dependent immunosuppression by tofacitinib.

Table 52. Incidence Rate (per 100 Patient Years) of Serious Infectious Events in Phase 3 Development, by Demographics and Corticosteroid Use

Incidence Rate (per 100 Patient Years) of Serious Infectious Events in Phase 3 Development, by Demographics and Corticosteroid Use						
	Phase 3 Studies, 12-Month Pooled Safety				LTE Studies	
	PBO	ADA	CP5	CP10	CP5	CP10
Age						
< 65 years	1.7	0.7	2.5	2.7	2.0	3.5
≥ 65 years	0	7.9	7.6	4.7	3.5	12.4
Gender						
Males	0	0	5.0	5.7	2.6	8.0
Females	1.8	2.1	2.9	2.5	2.2	4.3
Glucocorticosteroids						
Yes	2.6	2.0	5.0	2.8	2.6	5.9
No	0	1.3	1.0	3.2	1.9	3.8

Source: Integrated Summary Analyses of Infections, adapted from Tables 35 and 36

Additionally, infections were the most common AE leading to study discontinuation in the Phase 3 and LTE studies as summarized in Table 61 below. The exposure-adjusted

incidence rates of infections leading to discontinuation were also disproportionately high in tofacitinib groups compared with both placebo- and adalimumab-controls, without clear relation to dose (5 mg vs. 10 mg BID).

Tuberculosis

Phase 2 and 3 protocols in RA excluded patients with evidence of active or inadequately treated active or latent infection with Mycobacterium tuberculosis (TB). LTE studies did not require for TB screening before rolling over from Phase 2 and 3 studies.

Despite excluding patients at risk for developing tuberculosis, a total of 12 cases of tuberculosis were reported in the RA development program as summarized in Table 53. All cases occurred in tofacitinib groups, most on background DMARD therapy. Eleven of the 12 cases occurred in countries with high prevalence of TB. Consistent with dose-dependent immunosuppression, the majority of cases occurred in the high dose tofacitinib group. In the Phase 3 program, all cases occurred in the 10 mg BID dose group. Three cases of TB occurred in the 5 mg BID dose group in the LTE studies, all of which were disseminated. No patients died due to TB. In two additional patients (not included in Table 53) initially reported as suspected cases, tuberculosis was excluded upon follow up procedures as reported by the Sponsor in the 120-day safety update.

Table 53. Listing of TB Cases in Tofacitinib RA Development Program

Listing of TB Cases in Tofacitinib RA Development Program						
Study-subject ID	Age/Gender	Last CP dose	Total CP exposure days	TB description	Bacteriology	Country
1044-11491008	42/F	10	269	Lymph node	Confirmed	India
1045-10301004	48/M	10	152	Pleural effusion	Not confirmed	India
1046-11211015	51/M	10	325	Pulmonary	Confirmed	China
1046-11491017	51/F	10	201	Pulmonary	Confirmed	Thailand
1064-10461036	63/M	10	305	Pulmonary	Confirmed	Korea
1064-11401010	67/F	10	290	Pulmonary	Not confirmed	Philippines
1024-14111003	43/F	10	446	Pulmonary	Not confirmed	Philippines
1024-14141004	73/F	10	366	Pulmonary	Not confirmed	Philippines
1024-14131003	71/F	10	421	Pulmonary	Not confirmed	Philippines
1024-10551011	42/F	5	240	Disseminated	Confirmed	Mexico
1024-10941002	73/F	5	196	Disseminated	Confirmed	US
1024-11361014	61/F	5	960	Disseminated	Confirmed	Korea

Source: Integrated Summary of Safety on Infections, adapted from Table 27; 120 Day Safety Update; Response to information request, June 05, 2012

In most of the cases, tuberculosis was diagnosed later in the course of treatment (median of approximately 10 months, mean of one year) and the exposure-adjusted incidence did not appear to increase significantly after this time period in the LTE studies (Table 54).

Table 54. Exposure-Adjusted Incidence of TB in Phase 3 and LTE studies in RA

Exposure-Adjusted Incidence of TB in Phase 3 and LTE studies in RA									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Total patients with ≥ 1 event of TB, n	-	-	-	6	6	1	1	2	5
Exposure for event, patient-years	-	-	-	910	2098	2236	882	3118	4409
Incidence of TB, per 100 patient-years (95%CI)	0	0	0	0.66 (0.3, 1.5)	0 29 (0.1, 0.6)	0.05 (0.01, 0.3)	0.11 (0.02, 0.8)	0 06 (0.02, 0.3)	0.11 (0.05, 0.3)

Source: Integrated Safety Analysis on Infections (data cut-off March 29, 2011), adapted from Table 26, 120-Day Safety Update, adapted from Table 26
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 mon hs; the rest of the dose groups are pooled as randomized.

Opportunistic Infections

In the RA development program, there were a total of 22 reported opportunistic infections, all of which occurred in tofacitinib-treated patients listed in Table 55. The pattern of reported opportunistic infections is consistent with the profile of a potent immunosuppressive drug and some of these infections, such as BK virus encephalitis, CMV and cryptococcal infections are seen exclusively in severely immunocompromized patients, such as advanced acquired immunodeficiency syndrome patients. This is reflective of the mechanism of action of tofacitinib and its effect on T lymphocytes. As discussed in Section 4.4.4. Dose Selection, tofacitinib-induced JAK inhibition of T lymphocytes is likely associated with functional CD4 impairment rather than direct cytotoxicity. Therefore, routine monitoring of CD4 counts in patients treated with tofacitinib is not likely to identify patients at risk. Further, the value of monitoring with functional assays to identify patients at risk is currently unknown and not widely available outside of the research settings, therefore limiting its utility in routine patient care.

Table 55. Listing of Opportunistic Infections (Excluding TB Infections) in Tofacitinib RA Development Program

Listing of Opportunistic Infections (Excluding TB Infections) in Tofacitinib RA Development Program						
Study-subject ID	Infection	Age/Gender	Last CP dose, mg BID	Total CP exposure, days	Microbiology	Outcome
1044-10381007	Esophageal candidiasis	60/F	5	172	No	Not resolved
1024-11741008	Esophageal candidiasis	48/F	5	467	No	Resolved
1024-12341010	Esophageal candidiasis	58 F	10	129	No	Not resolved
1024-12621006	Esophageal candidiasis	47/M	10	487	No	Resolved
1044-10801001	Esophageal candidiasis	61/F	10	264	No	Resolved
1044-11781008	Esophageal candidiasis	64/F	5	139	No	Not resolved
1041-10271018	Esophageal candidiasis	54/F	5	197	No	Resolved
1024-14411012	Esophageal candidiasis	53/F	10	166	No	Resolved
1044-10381009	CMV sialoadenitis	66/F	10	135	Biopsy	Resolved
1044-11681009	CMV viremia	55/F	10	132	CMV antigen+	Resolved
1041 10111001	CMV infection	68/F	5	226	n.a.	Resolved
1024 11741006	CMV hepatitis	56/F	5	698	CMV antigen+	Not resolved
1044-11171004	PCP	75/F	5	41	No	Death
1041-10121004	PCP	61/F	5	295	No	Resolved
1024-11451015	PCP	64/F	10	454	PCR+	Resolved
1046-10681009	Cryptococcal pneumonia	68/F	10	236	Microscopy+	Not resolved
1024-11371009	Cryptococcal meningitis	60/F	10	480	CSF culture+	Not resolved
1041-10051007	Cryptococcal pneumonia	61/F	5	232	Cryptococcal Ag+	Resolved
1041-10251004	MAC infection	63/F	10	253	AFB+, DNA+	Not resolved
1041-10431005	Atypical mycobacterial	60/F	5	413	n.a.	Not resolved
1046-10141006	H. zoster disseminated	59/F	5	93	VZV antigen+	Resolved
1024-10441008	BK virus encephalitis	64/F	5	678	CSF PCR+	Not resolved

Source: Integrated Safety Analysis on Infections (data cut-off March 29, 2011), adapted from Table 34; 120-Day Safety Update; Response to information request, June 05, 2012
AFB-acid fast bacilli, Ag-antigen; CMV-cytomegalovirus, CSF-cerebrospinal fluid, DNA-deoxyribonucleic acid, H. zoster-Herpes zoster, MAC-mycobacterium avium complex, PCP-Pneumocystis jiroveci pneumonia, PCR-polymerase chain reaction, VZV-Varicella zoster virus,
Note: TB infections are presented in separate listing (Table 53 above)

Opportunistic infections generally occurred with prolonged tofacitinib exposure (median of 8 months, mean of 10 months), consistent with the observations for overall serious infections and tuberculosis, supporting the concern that tofacitinib-induced immunosuppression is associated with prolonged tofacitinib exposure. The number and pattern of opportunistic infections observed with tofacitinib treatment suggests significant immunosuppression that is apparent with both doses.

The estimated exposure-adjusted incidence rates of opportunistic infections in the RA Phase 3 trials and LTE are summarized in Table 56 below. Again, consistent with dose-dependent immunosuppression, a numeric increase in the exposure-adjusted incidence rates of opportunistic infections is seen in a dose-dependent manner during the long-term extension studies.

Table 56. Exposure-Adjusted Incidence of Opportunistic Infections (Excluding Tuberculosis) in Phase 3 and LTE Studies in RA

Exposure-Adjusted Incidence of Opportunistic Infections (Excluding Tuberculosis) in Phase 3 and LTE Studies in RA									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
All Opportunistic infection									
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Total pa ients with ≥ 1 event, n (%)	-	-	4	4	8	7	5	12	14
Exposure for event, patient-years	-	-	904	910	2097	2232	881	3114	4403
Incidence, per 100 patient-years	0	0	0.44	0.44	0 38	0.31	0.57	0.38	0.32

Source: Integrated Safety Analysis on Infections (data cut-off March 29, 2011), adapted from Table 33; 120-Day Safety Update, adapted from Table 32; Response to Information Request, June 05, 2012
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

Herpes Zoster

Herpes zoster was a common adverse event with higher incidence in tofacitinib groups (around 4.3 events/100 patient-years) than in placebo- (1.5 events/100 patient-years) and adalimumab (2.8 events/100 patient-years) without apparent dose dependence (Table 57). The median time of exposure at the time of diagnosis was approximately 6 months and did not appear to increase with prolonged exposure.

There were relatively few serious Herpes zoster infections, most of which occurred in the lower tofacitinib dose group. Age over 65 years was associated with higher incidence (6.3 events/100 patient-years) of herpes zoster infections.

Table 57. Exposure-Adjusted Incidence of Herpes Zoster Infections in Phase 3 and LTE studies in RA

Exposure-Adjusted Incidence of Herpes Zoster Infections in Phase 3 and LTE studies in RA									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
All Herpes zoster viral infection									
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Total pa ients with ≥ 1 event, n (%)	3 (<1)	5 (2)	39 (3)	38 (3)	90 (3)	91 (7)	34 (2)	134 (4)	184 (5)
Exposure for event, patient-years	202	177	886	895	2060	2140	869	3009	4239
Incidence, per 100 patient-years (95%CI)	1 5 (0.5, 4.6)	2 8 (1.2, 6.8)	4.4 (3.2, 6.0)	4 2 (3.1, 5.8)	4.4 (3.5, 5.4)	4.3 (3.5, 5.2)	4.9 (3.7, 6.7)	4.5 (3.8, 5.3)	4.3 (3.8, 5.0)
Serious Herpes zoster infection									
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Total pa ients with ≥ 1 event, n	-	-	4	1	5	7	1	8	11
Exposure for event, patient-years	-	-	904	910	2098	2235	882	3117	4407
Incidence, per 100 patient-years (95%CI)	0	0	0.44 (0.2, 1.2)	0.11 (0.02, 0.8)	0 24 (0.1, 0.6)	0.31 (0.2, 0.7)	0.11 (0.02, 0.8)	0.26 (0.1, 0.5)	0.25 (0.1, 0.5)

Source: Integrated Safety Analysis on Infections (data cut-off March 29, 2011), adapted from Table 28, 120-Day Safety Update, adapted from Tables 28, 29
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

To explore the potential for additive immunosuppression with background DMARDs, the incidence of Herpes zoster was assessed separate for monotherapy study 1045 and pooled DAMRD background studies (1032, 1044, 1046, and 1064) and summarized in Table 58. in monotherapy study 1045, there was a clear dose-dependent numerical imbalance in the exposure-adjusted incidence rates of Herpes zoster over the 6 month trial consistent with dose-dependent immunosuppression by tofacitinib. In the 12 month DAMRD background studies, both tofacitinib dose groups had a higher overall incidence rate of serious infections compared with placebo add-on and adalimumab active control, suggesting that tofacitinib has a more potent immunosuppressive effect compared with traditional and biologic DMARDs. These observations are consistent with viral reactivation related to tofacitinib's functional effect of on CD4 T lymphocytes.

Table 58. Summary of Herpes Zoster in Phase 3 Development by Background DMARD Treatment

Summary of Herpes Zoster in Phase 3 Development, by Background DMARD Treatment					
	PBO	ADA	CP5	CP10	All CP
DMARD background studies (0-12 months)					
Patients with ≥ 1 event, n (%)	3 (<1)	5 (2)	38 (4)	35 (4)	84 (3)
Incidence rate per 100 PY	1.7	2.8	4.9	4.4	4.6
Monotherapy study 1045 (0-6 months)					
Patients with ≥ 1 event, n (%)	0	N.A.	1 (<1)	3 (1)	6 (1)
Incidence rate per 100 PY	0	N.A.	0.9	2.6	2.3

Source: Integrated Analyses of Infections, adapted from Table 28
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

Additional explorations of potential demographic factors and concomitant corticosteroid use on the incidence of H. zoster infections were also undertaken. The results indicate that female gender and concomitant corticosteroid use confer somewhat increased risk as summarized in Table 59.

Table 59. Incidence Rate (per 100 Patient Years) of All Herpes Zoster Infections in Phase 3 Development, by Demographics and Corticosteroid Use

Incidence Rate (per 100 Patient Years) of All Herpes Zoster Infections in Phase 3 Development, by Demographics and Corticosteroid Use						
	Phase 3 Studies, 12-Month Pooled Safety				LTE Studies	
	PBO	ADA	CP5	CP10	CP5	CP10
Age						
< 65 years	1.7	2.6	4.6	4.0	3.9	4.5
≥ 65 years	0	3.9	3.1	5.5	5.8	7.4
Gender						
Males	2.7	8.1	2.9	2.9	3.5	4.7
Females	1.2	1.4	4.7	4.5	4.4	5.0
Glucocorticosteroids						
Yes	0.9	2.9	5.0	4.2	4.7	6.2
No	2.3	2.6	3.6	4.3	3.7	3.6

Source: Integrated Summary Analyses of Infections, adapted from Tables 38 and 40

7.3.3 Dropouts and/or Discontinuations

The proportion of patients with AE leading to withdrawal was small (<5%) and generally comparable among all treatment groups in the Phase 3 studies. In LTE studies, this proportion was higher for the 5 mg BID dose group, possibly because of the longer

exposure in that group. The proportions of patients, who experienced AE that lead to dose reduction or temporary interruption, were numerically higher in tofacitinib-treated groups.

Table 60. Patient Disposition by Treatment-Emergent AEs (All Causality) in All Phase 3 and LTE Studies in RA by Trial Period and Treatment Assignment

Patient Disposition by Treatment-Emergent AEs (All Causality) in All Phase 3 and LTE Studies in RA by Trial Period and Treatment Assignment					
	PBO	ADA	CP 5 mg BID	CP 10 mg BID	CP, All doses
Phase 3 studies (0-3 months), n (%)					
Enrolled, n	681	204	1216	1214	2430
Number of AEs	690	182	1321	1348	2669
Subjects with AEs	363 (53)	105 (52)	624 (51)	653 (54)	1277 (53)
Subjects with SAE	25 (4)	5 (3)	36 (3)	35 (3)	71 (3)
Subjects with severe AE	28 (4)	6 (3)	49 (4)	39 (3)	88 (4)
Subjects discontinued due to AE	22 (3)	10 (5)	52 (4)	49 (4)	101 (4)
Subjects with dose reduced/interrupted due to AE	38 (6)	15 (7)	103 (9)	99 (8)	202 (8)
Phase 3 studies (3-6 months), n (%)					
Enrolled, n	221	204	1451	1439	2890
Number of AEs	97	120	1061	1067	2128
Subjects with AEs	58 (26)	68 (33)	579 (40)	556 (39)	1135 (39)
Subjects with SAE	7 (3)	6 (3)	47 (3)	37 (3)	84 (3)
Subjects with severe AE	5 (2)	8 (4)	55 (4)	37 (3)	92 (3)
Subjects discontinued due to AE	4 (2)	9 (4)	36 (3)	45 (3)	81 (3)
Subjects with dose reduced/interrupted due to AE	4 (2)	10 (5)	96 (7)	90 (6)	186 (6)
Phase 3 studies (>6 months), n (%)					
Enrolled, n	-	204	1056	1046	2102
Number of AEs	-	142	883	1001	1884
Subjects with AEs	-	83 (41)	445 (42)	478 (46)	923 (44)
Subjects with SAE	-	7 (3)	34 (3)	32 (3)	66 (3)
Subjects with severe AE	-	5 (3)	23 (2)	27 (3)	50 (2)
Subjects discontinued due to AE	-	4 (2)	18 (2)	24 (2)	42 (2)
Subjects with dose reduced/interrupted due to AE	-	6 (3)	69 (7)	85 (8)	154 (7)
LTE studies (as of September 29, 2011), n (%)					
Enrolled, n	-	-	1321	1906	3227
Number of AEs	-	-	4899	2848	7747
Subjects with AEs	-	-	1047 (79)	1088 (57)	2135 (66)
Subjects with SAE	-	-	209 (16)	114 (6)	323 (10)
Subjects with severe AE	-	-	153 (12)	98 (5)	251 (8)
Subjects discontinued due to AE	-	-	148 (11)	75 (4)	223 (7)
Subjects with dose reduced/interrupted due to AE	-	-	353 (27)	259 (14)	612 (19)

Source: Integrated Summary of Safety, adapted form Tables P3ALL 4.1.1, 4.1.2, 4.1.3; and LTE 4.1.1, 4.9.1
Note: AE data for LTE studies is presented as the total number of events and exposure-adjusted AE rates rather than percent of patients with AE to account for unequal exposure to the 5 and 10 mg BID dose groups; AE data are presented as the total number of events and percent of patients with AE; Exposure-adjusted rates for AE are presented elsewhere.

The discontinuations due to adverse events that occurred in the Phase 3 RA trials and LTE are summarized in Table 61 and detailed in Table 103 below. Infections were the most common reason for discontinuation with pneumonia and herpes zoster being the

most common in tofacitinib-treated patients. However, investigations were also a common reason, and there were pre-specified laboratory abnormalities that were to trigger discontinuation, as follows:

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

Discontinuations otherwise mirrored the pattern observed with SAE in the studies.

Table 61. Integrated Summary of All AEs Leading to Discontinuation in the Core Phase 3 (0-12 Months) and LTE Studies in RA

Integrated Summary of All AEs Leading to Discontinuation in the Core Phase 3 (0-12 Months) and LTE Studies in RA									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Total number of AEs causing discontinuation	35	28	138	163	301	210	88	298	412
Total patients discontinuing due to AE, n (%)	26 (3.7)	22 (10.8)	95 (7.8)	99 (8 2)	205 (6.8)	148 (11.2)	75 (3.9)	223 (6.9)	318 (9.1)
Exposure for event, patient-years	202	178	898	906	2087	2222	878	3100	4382
Incidence of discontinuation per 100 patient-years (95% CI)	12.41 (8.38, 18 36)	12.35 (8.13, 18.75)	10.58 (8 65, 12.94)	10.93 (8.98, 13.31)	9.82 (8.57, 11.26)	6.66 (5.67, 7 82)	8.54 (6.81, 10.71)	7.19 (6 31, 8 20)	7.26 (6.50, 8.10)
MedDRA SOC AE Term, n (%)									
Infections and Infestation	2 (0.3)	4 (0.2)	30 (2.5)	33 (2.7)	63 (2.1)	48 (3.6)	38 (2.0)	86 (2.7)	117 (3.3)
Investigations	3 (0.4)	0	18 (1.5)	24 (2.0)	42 (1.4)	22 (1.7)	8 (0.4)	30 (0.9)	53 (1.5)
Gastrointestinal Disorders	5 (0.7)	2 (0.1)	12 (1.0)	18 (1 5)	30 (1.0)	16 (1.2)	3 (0.2)	19 (0.6)	22 (0.6)
Neoplasms, Benign, Malignant, Unspecified	1 (0.1)	1 (0.5)	5 (0.4)	7 (0.6)	12 (0.4)	24 (1.8)	9 (0.5)	33 (1.0)	48 (1.4)
Nervous System Disorders	2 (0.3)	1 (0.5)	8 (0.7)	4 (0 3)	12 (0.4)	10 (0.8)	2 (0.1)	12 (0.4)	16 (0.5)
Respiratory, Thoracic, Mediastinal Disorders	0	0	5 (0.4)	7 (0.6)	12 (0.4)	6 (0.5)	6 (0.3)	12 (0.4)	17 (0.5)
Skin and Subcutaneous Tissue Disorder	0	3 (1.5)	12 (1.0)	3 (0.3)	15 (0.5)	3 (0.2)	3 (0.2)	6 (0.2)	11 (0.3)
Blood and Lymphatic System Disorders	0	1 (0.5)	6 (0.5)	6 (0.5)	12 (0.4)	6 (0.5)	3 (0.2)	9 (0.3)	10 (0.3)
Musculoskeletal, Connective Tissue Disorders	9 (1.3)	4 (2.0)	6 (0.5)	7 (0.6)	13 (0.4)	5 (0.4)	2 (0.1)	7 (0.2)	12 (0.3)
Cardiac Disorders	2 (0.3)	2 (0.1)	1 (0.1)	5 (0.4)	6 (0.2)	12 (0.9)	2 (0.1)	14 (0.4)	14 (0.4)
Vascular Disorders	0	0	0	4 (0.3)	4 (0.1)	2 (0.2)	1 (0.1)	3 (0.1)	6 (0.2)
Ear and Labyrinth	0	0	1 (0.1)	3 (0.2)	4 (0.1)	1 (0.1)	0	1 (<0.1)	2 (0.1)
Eye Disorders	0	0	1 (0.1)	2 (0.2)	3 (0.1)	2 (0.2)	0	2 (0.1)	3 (0.1)
General Disorders and Admin. Site Cond.	1 (0.1)	0	4 (0.3)	3 (0.2)	8 (0.3)	5 (0.4)	0	5 (0.2)	7 (0.2)
Hepatobiliary Disorders	0	0	4 (0.3)	0	4 (0.1)	6 (0.5)	2 (0.1)	8 (0.2)	8 (0.2)
Immune system disorders	0	0	1 (0.1)	1 (0.1)	2 (0.1)	0	0	0	1 (<0.1)
Injury, Poisoning, Procedural Complication	1 (0.1)	0	4 (0.3)	1 (0.1)	5 (0.2)	5 (0.4)	2 (0.1)	7 (0.2)	9 (0.3)
Metabolism and Nutrition	2 (0.3)	0	1 (0.1)	4 (0 3)	5 (0.2)	0	1 (0.1)	1 (<0.1)	2 (0.1)
Pregnancy, Puerperium, Perinatal Cond.	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)	0	0	0	1 (<0.1)
Psychiatric Disorders	0	1 (0.5)	1 (0.1)	0	1 (<0.1)	0	2 (0.1)	2 (0.1)	2 (0.1)
Renal and Urinary Disorders	2 (0.3)	1 (0.5)	0	4 (0.3)	4 (0.1)	3 (0.2)	0	3 (0.1)	5 (0.1)
Reproductive System and Breast Disorders	0	0	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)	0	1 (<0.1)	2 (0.1)

Source: Summary of Clinical Safety (data cut-off March 29, 2011), adapted from Tables 93-106 and 120-Day Safety Update, adapted from tables 21-23
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

7.3.4 Adverse Events of Special Interest

Gastrointestinal Perforations

Gastrointestinal perforations were previously observed in the target patient population treated with immunosuppressives and are reported here as one of the events of interest.

A total of ten patients were diagnosed with definite or probable gastrointestinal perforation in the Phase 2 (1 case), Phase 3 (2 cases) and LTE (7 cases) studies. Nine of the ten cases involved the lower GI tract anatomical location; five of which were

reported as perforated diverticulitis, three as appendicitis, and one which was not specified. The only case of upper GI (gastric ulcer) perforation was reported in a patient treated with a low dose (3 mg BID) of tofacitinib in a Phase 2 study who had a history of prior recurrent gastric ulcer complication. All cases occurred in patients taking concomitant NSAID and/or systemic corticosteroids, which have been independently associated with increased risk of GI perforation. The distribution of the cases by time and treatment assignment is summarized in Table 62. The overall incidence rate of 0.144 per 100 patient-years of GI perforations reported in the tofacitinib RA development program is below rates for corticosteroids in RA patients (0.39 per 100 patient-years) and comparable to rates for TNF inhibitors (0.13 per 100 patient-years), based on estimates derived from evaluation of large healthcare databases.

Table 62. Exposure-Adjusted Incidence Rates of Gastrointestinal Perforations in Phase 3 and LTE Studies in RA

Exposure-Adjusted Rates of Gastrointestinal Perforations in Phase 3 and LTE Studies in RA by Treatment Assignment									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept. 29, 2011)
Enrolled, n	681	204	1216	1214	3030	1321	1906	3227	3515
Exposure, patient-years	203	179	904	910	2098	2236	8812	3118	4409
No (%) of patients with event	-	-	-	2 (0.2)	2 (<0.1)	4 (0.3)	3 (0.2)	7 (0.2)	7 (0.2)
Incidence, events per 100 PY (95%CI)	0	0	0	0.22 (0.06, 0.88)	0.095 (0.03, 0.38)	0.18 (0.07, 0.48)	0.34 (0.11, 1.06)	0.23 (0.11, 0.47)	0.16 (0.08, 0.33)

Source: Integrated Summary of Safety, adapted from Tables 162, 164; 120-Day Safety Update, adapted from Table 52.
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

Interstitial Lung Disease

A total of 26 potential cases of interstitial lung disease (ILD) were identified in tofacitinib RA safety database of which 13 were adjudicated to be possible or probable ILD cases, 10 of which were on background methotrexate. More cases occurred in tofacitinib 10 mg BID dose; however exposure-adjusted incidence rates in tofacitinib-treated groups were comparable the placebo during the Phase 3 and LTE studies as shown in Table 63. The association of tofacitinib with the reported cases of ILD is currently unclear due to the relatively small numbers and individual case characteristics. Furthermore, ILD is a recognized extraarticular manifestation of RA particularly in patients with long-standing active disease, such as the population in tofacitinib development program.

Table 63. Exposure-Adjusted Rates of Treatment-Emergent Interstitial Lung Disease in Phase 3 and LTE Studies in RA by Treatment Assignment

Exposure-Adjusted Rates of Treatment-Emergent Interstitial Lung Disease in Phase 3 and LTE Studies in RA by Treatment Assignment									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept. 29, 2011)
Enrolled, n	681	204	1216	1214	3030	1321	1906	3227	3515
Exposure, patient-years	202.6	178.9	903.7	910.4	2098.2	2236.2	881.7	3117.8	4409
No (%) of patients with event	1 (0.2)	0	1 (<1)	1 (<1)	4 (0.1)	1 (<1)	4 (0.2)	5 (0.2)	7 (0.2)
Incidence, events per 100 PY	0.49	0	0.11	0.11	0.19	0.05	0.45	0.16	0.16
(95%CI)	(0.1, 3.5)		(0.02, 0.8)	(0.02, 0.8)	(0.1, 0.5)	(0.01, 0.3)	(0.2, 1.2)	(0.1, 0.4)	(0.1, 0.3)

Source: Integrated Summary of Safety, adapted from Tables 197-199; 120-Day Safety Update, adapted from Tables 58, 59.
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

7.3.5 Submission Specific Primary Safety Concerns

See Summary of Safety Review and Conclusions.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A majority of patients experienced at least one AE during the course of the Phase 3 and LTE studies with an overall higher proportion in tofacitinib and adalimumab-treated patients, as summarized in Table 64 and Table 60 below. However, exposure-adjusted rates are comparable between the treatment groups with the highest rate in the placebo group. The most common AEs (occurring in ≥2% in any treatment group) were in Infections and infestations system organ class, followed by Gastrointestinal disorders. The most frequently reported AEs in the CP All doses group were upper respiratory tract infection, headache, nasopharyngitis, and diarrhea.

Table 64. Integrated Summary of Treatment-Emergent AEs (All Causality) by System Organ Class in the Phase 3 and LTE Studies in RA

Integrated Summary of Treatment-Emergent AEs in the Phase 3 and LTE Studies in RA									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Number of AEs	787	302	3265	3416	6681	4899	2848	7747	
Total patients with ≥ 1 AEs, n (%)	337 (55)	149 (73)	874 (72)	878 (72)	2057 (68)	1047 (79)	1088 (57)	2135 (66)	n.r.
Exposure for event, patient-years	128	86	394	388	783	766	473	1239	n.r.
Incidence of AEs, event per 100 patient-years (95% CI)	295.7 (267, 327)	173.6 (148, 204)	201.6 (189, 220)	206.1 (193, 220)	203.8 (194, 213)	136.7 (129, 145)	230.1 (217, 244)	172.4 (165, 180)	n.r.
System Organ Class ≥2% in any treatment group, n (%)									
Blood and Lymphatic System Disorders	<2%	<2%	<2%	<2%	<2%	93 (7)	52 (3)	145 (4)	n.r.
Ear and Labyrinth Disorders	<2%	<2%	<2%	<2%	<2%	66 (5)	19 (1)	85 (3)	n.r.
Gastrointestinal Disorders	97 (14)	21 (10)	204 (17)	189 (16)	393 (13)	388 (29)	220 (12)	608 (19)	n.r.
General Disorders Admin. Site Cond.	36 (5)	13 (6)	53 (4)	52 (4)	105 (3)	138 (10)	80 (4)	218 (7)	n.r.
Infections and Infestation	145 (21)	97 (48)	685 (56)	739 (61)	1424 (47)	698 (53)	583 (31)	1281 (40)	n.r.
Injury, Poisoning and Procedural Complications	<2%	<2%	<2%	<2%	<2%	195 (15)	110 (6)	305 (9)	n.r.
Investigations	34 (5)	11 (5)	71 (6)	101 (8)	172 (6)	224 (17)	155 (8)	379 (12)	n.r.
Metabolism and Nutrition Disorders	<2%	<2%	<2%	<2%	<2%	138 (10)	91 (5)	229 (7)	n.r.
Musculoskeletal and Connective Tissue	78 (11)	25 (12)	170 (14)	157 (13)	327 (11)	308 (23)	205 (11)	513 (16)	n.r.
Nervous System Disorders	46 (7)	11 (5)	91 (7)	78 (6)	169 (6)	199 (15)	116 (6)	315 (10)	n.r.
Respiratory, Thoracic, Mediastinal Disorder	25 (4)	12 (5)	50 (4)	48 (4)	98 (3)	172 (13)	120 (6)	292 (9)	n.r.
Skin and Subcutaneous Tissue Disorders	35 (5)	11 (5)	51 (4)	64 (5)	115 (4)	175 (13)	130 (7)	305 (10)	n.r.
Vascular Disorders	10 (1)	2 (1)	28 (2)	42 (3)	70 (2)	129 (10)	45 (2)	137 (4)	n.r.

Source: Integrated Summary of Safety, adapted from Tables 44-54 and P3ALL Tables 4.1.1, 4.1.2, 4.1.3
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

7.4.2 Laboratory Findings

Tofacitinib treatment resulted in dose-dependent changes of certain hematologic, hepatobiliary, serum chemistry (creatinine and creatine phosphokinase) and lipid parameters. Overall, relatively small numbers of patients met the pre-specified protocol criteria for monitoring or discontinuation due to laboratory abnormalities (Table 65). Anemia (defined as Hgb <8 g/dL or ↓≥ 2 mg/dL) and liver enzyme elevations (defined as AST or ALT > 3 x ULN) were the most common protocol criteria requiring further monitoring in Phase 3 and LTE studies and were fairly balanced among treatment groups. Increases in serum creatinine were the most common laboratory abnormality meeting criteria for discontinuation later in Phase 3 and during LTE studies and are discussed in detail in 7.4.2.1 Serum Creatinine Elevations and Renal Disorders section below.

Table 65. Subjects with Laboratory Values Meeting Protocol Criteria for Monitoring and Discontinuation in Phase 3 and LTE Studies in RA

Number of Patients (%) with Laboratory Values Meeting Protocol Criteria for Monitoring and Discontinuation in Phase 3 and LTE Studies in RA					
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses
0-3 months, enrolled n	**681**	**204**	**1216**	**1214**	**2430**
Monitoring criteria					
ANC <1,000/mm^3	0	1 (<1)	4 (<1)	3 (<1)	7 (<1)
Platelets <100,000/mm^3	2 (<1)	0	3 (<1)	4 (<1)	7 (<1)
Hgb <8 g/dL or ↓≥ 2 mg/dL	14 (2.1)	0	12 (<1)	21 (1.7)	33 (1.4)
AST/ALT >3xULN	8 (1.2)	0	14 (1.1)	12 (<1)	26 (1.1)
Discontinuation criteria					
ANC <500/mm^3 (confirmed x 2)	0	0	0	0	0
Hgb ≤8 g/dL or ↓≥ 30% (confirmed x 2)	1 (<1)	0	0	3 (<1)	3 (<1)
Platelets <75,000/mm^3 (confirmed x 2)	0	0	1 (<1)	0	1 (<1)
↑AST/ALT >3xULN and T Bilirubin >2xULN	0	0	0	0	0
↑AST/ALT >3xULN and ↑INR	0	0	1 (<1)	0	1 (<1)
↑AST/ALT >5xULN	2 (<1)	0	1 (<1)	0	1 (<1)
↑Creatinine >50% of baseline (confirmed x 2)	2 (<1)	0	3 (<1)	2 (<1)	5 (<1)
↑Creatinine ≥ 30% at end of study	1 (<1)	1 (<1)	0	2 (<1)	2 (<1)
3-6 months, enrolled n	**221**	**204**	**1451**	**1439**	**2890**
Monitoring criteria					
ANC <1,000/mm^3	0	0	1 (<1)	5 (<1)	6 (<1)
Platelets <100,000/mm^3	0	0	5 (<1)	3 (<1)	8 (<1)
Hgb <8 g/dL or ↓≥ 2 mg/dL	6 (2.7)	3 (1.5)	20 (1.4)	41 (2.8)	61 (2.1)
AST/ALT >3xULN	0	1 (<1)	17 (1.2)	20 (1.4)	37 (1.3)
Discontinuation criteria					
ANC <500/mm^3 (confirmed x 2)	0	0	0	0	0
Hgb ≤8 g/dL or ↓≥ 30% (confirmed x 2)	0	0	1 (<1)	1 (<1)	2 (<1)
Platelets <75,000/mm^3 (confirmed x 2)	0	0	1 (<1)	0	1 (<1)
↑AST/ALT >3xULN and T Bilirubin >2xULN	0	0	0	0	0
↑AST/ALT >3xULN and ↑INR	0	0	0	0	0
↑AST/ALT >5xULN	0	1 (<1)	1 (<1)	1 (<1)	2 (<1)
↑Creatinine >50% of baseline (confirmed x 2)	0	0	4 (<1)	2 (<1)	6 (<1)
↑Creatinine ≥ 30% at end of study	0	0	24 (1.6)	37 (2.6)	61 (2.1)
> 6 months, enrolled n	**-**	**204**	**1056**	**1046**	**2102**
Monitoring criteria					
ANC <1,000/mm^3	-	0	0	4 (<1)	4 (<1)
Platelets <100,000/mm^3	-	1 (<1)	3 (<1)	3 (<1)	6 (<1)
Hgb <8 g/dL or ↓≥ 2 mg/dL	-	5 (2.5)	18 (1.7)	33 (3.1)	51 (2.4)
AST/ALT >3xULN	-	3 (1.5)	21 (2.0)	20 (1.9)	41 (1.9)
Discontinuation criteria					
ANC <500/mm^3 (confirmed x 2)	-	0	0	0	0
Hgb ≤8 g/dL or ↓≥ 30% (confirmed x 2)	-	0	0	2 (<1)	2 (<1)
Platelets <75,000/mm^3 (confirmed x 2)	-	1 (<1)	0	1 (<1)	1 (<1)
↑AST/ALT >3xULN and T Bilirubin >2xULN	-	0	0	0	0
↑AST/ALT >3xULN and ↑INR	-	0	0	0	0
↑AST/ALT >5xULN	-	1 (<1)	1 (<1)	1 (<1)	2 (<1)
↑Creatinine >50% of baseline (confirmed x 2)	-	0	3 (<1)	2 (<1)	5 (<1)
↑Creatinine ≥ 30% at end of study	-	4 (2.0)	30 (2.8)	32 (3.1)	62 (2.9)
LTE Studies, enrolled n	**-**	**-**	**1321**	**1906**	**3227**
Monitoring criteria					
ANC <1,000/mm^3	-	-	6 (<1)	6 (<1)	12 (<1)
Platelets <100,000/mm^3	-	-	6 (<1)	4 (<1)	10 (<1)
Hgb <8 g/dL or ↓≥ 2 mg/dL	-	-	113 (8.6)	76 (4.0)	189 (5.9)
AST/ALT >3xULN	-	-	45 (3.4)	37 (1.9)	82 (2.5)
Discontinuation criteria					
ANC <500/mm^3 (confirmed x 2)	-	-	0	0	0
Hgb ≤8 g/dL or ↓≥ 30% (confirmed x 2)	-	-	5 (<1)	0	5 (<1)
Platelets <75,000/mm^3 (confirmed x 2)	-	-	0	0	0
↑AST/ALT >3xULN and T Bilirubin >2xULN	-	-	1 (<1)	0	1 (<1)
↑AST/ALT >3xULN and ↑INR	-	-	0	0	0
↑AST/ALT >5xULN	-	-	2 (<1)	3 (<1)	5 (<1)
↑Creatinine >50% of baseline (confirmed x 2)	-	-	30 (2.3)	30 (1.6)	60 (1.9)
↑Creatinine ≥ 30% at end of study	-	-	39 (3.0)	12 (<1)	51 (1.6)

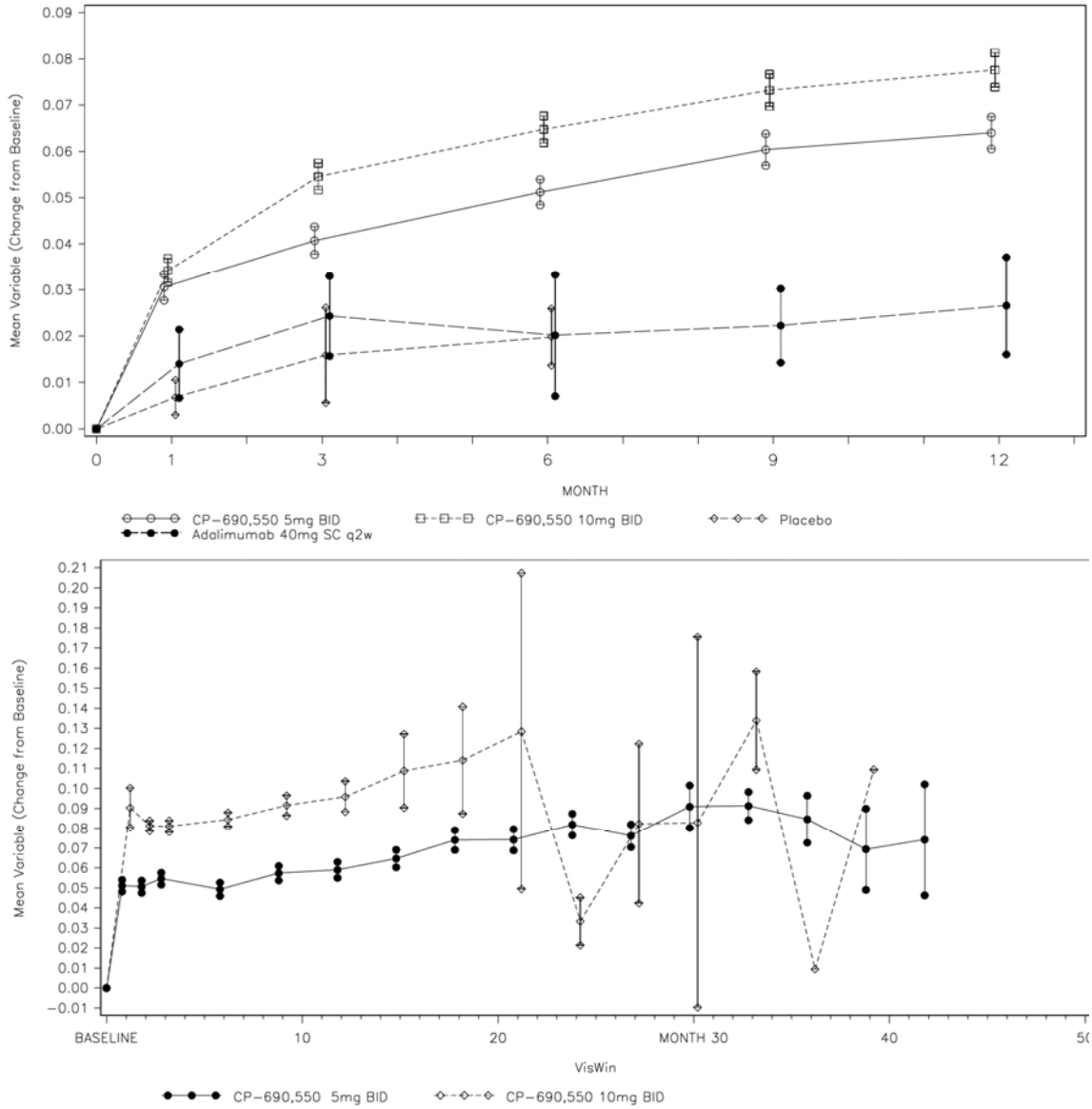
Source: Integrated Summary of Safety, Adapted from P3ALL Table 14.6.1, and LTE Table 14.6.1

7.4.2.1 Serum Creatinine Elevations and Renal Disorders

Serum Creatinine

Tofacitinib administration resulted in small (<0.1 mg/dL) but significant dose- and length of exposure-dependent elevations of serum creatinine (Figure 14). Mean serum creatinine appeared to plateau with prolonged exposure in the Phase 3 and during the LTE studies.

Figure 14. Mean Changes From Baseline in Serum Creatinine (mg/dL) in All Phase 3 Studies (Upper Panel) and LTE Studies (Lower Panel)



Source: Integrated Summary of Safety, Figures 41 and 42.

A higher proportion (20% vs 15%) of patients in the 10 mg BID groups compared with 5 mg BID groups had a deterioration of calculated creatinine clearance from normal (>90 ml/min) to mildly impaired (60-90 ml/min) across all Phase 3 studies but did not progress further (data not shown).

Renal Failure

Table 66. summarizes the treatment-emergent AEs and SAEs related to renal dysfunction from the tofacitinib clinical program in RA. The renal dysfunction in these cases appeared to be mostly reversible back to baseline within 6 weeks of tofacitinib discontinuation. These cases were also confounded by comorbidities such as hypertension, diabetes, CHF, sepsis and dehydration. Almost all patients were taking concomitant medications with effect on renal function, such as ACE inhibitors, ARBs, NSAIDs and diuretics.

The observed dose- and time-dependent increases in mean serum creatinine levels were associated with increasing incidence of patients meeting the protocol criteria for discontinuation (confirmed creatinine increases ≥ 50% from baseline) as shown in Table 65 above. Also, exposure-adjusted rates of SAEs of acute renal failure were more common with prolonged exposure, particularly in the 10 mg dose group (Table 66 below). Based on the relatively small number of events and significant confounding factors, it is difficult to draw definite conclusions about the clinical significance of these observations.

Table 66. Summary of Renal Failure AEs in Phase 3 and LTE Studies in RA

Summary of Renal Failure AEs in Phase 3 and LTE Studies in RA by Treatment Group									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Exposure for event, patient-years	203	179	1045	779	2085	2215	871	3085	4365
Total patients with ≥ event, n (%)	2	2	12	22	34	38	20	58	81
Incidence rate, per 100 patient-years	1.0	1.1	1.1	2.8	1.7	1.7	2.3	1.9	1.9
Investigations AEs, n	1	3	10	13	23	20	10	30	52
(incidence rate per 100 PY)	(0.5)	(1.7)	(1.0)	(1.7)	(1.1)	(1.0)	(1.1)	(1.0)	(1.2)
Blood creatinine increased	1	2	3	10	13	12	8	20	38
Blood urea increased	-	1	4	3	7	7	2	9	12
Creatinine clearance decreased	-	-	-	-	-	1	-	1	2
Protein urine present	-	-	3	-	3	-	-	-	-
Renal Disorders AEs, n	1	1	2	7	9	22	11	33	36
(incidence rate per 100 PY)	(0.5)	(0.6)	(0.2)	(0.9)	(0.4)	(1.0)	(1.3)	(1.1)	(0.8)
Albuminuria	-	-	-	-	-	-	1	1	1
Azotemia	-	-	-	-	-	1	-	1	1
Nephritis	-	-	-	-	-	-	1	1	1
Proteinuria		1	1	2	3	13	2	15	15
Renal failure	-	-	-	3	3	2	2	4	5
Renal failure acute	1	-	-	2	2	5	4	9	10
Renal impairment	-	-	1	-	1	1	1	2	3
Patients with SAE Renal Failure, n	1	0	0	2	2	6	4	10	11
(incidence rate per 100 PY)	(0.5)			(0.3)	(0.1)	(0.3)	(0.5)	(0.3)	(0.2)

Source: Summary of Clinical Safety, adapted from Tables189-192; 120 Day Safety Update, adapted from Table 56
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as hose patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

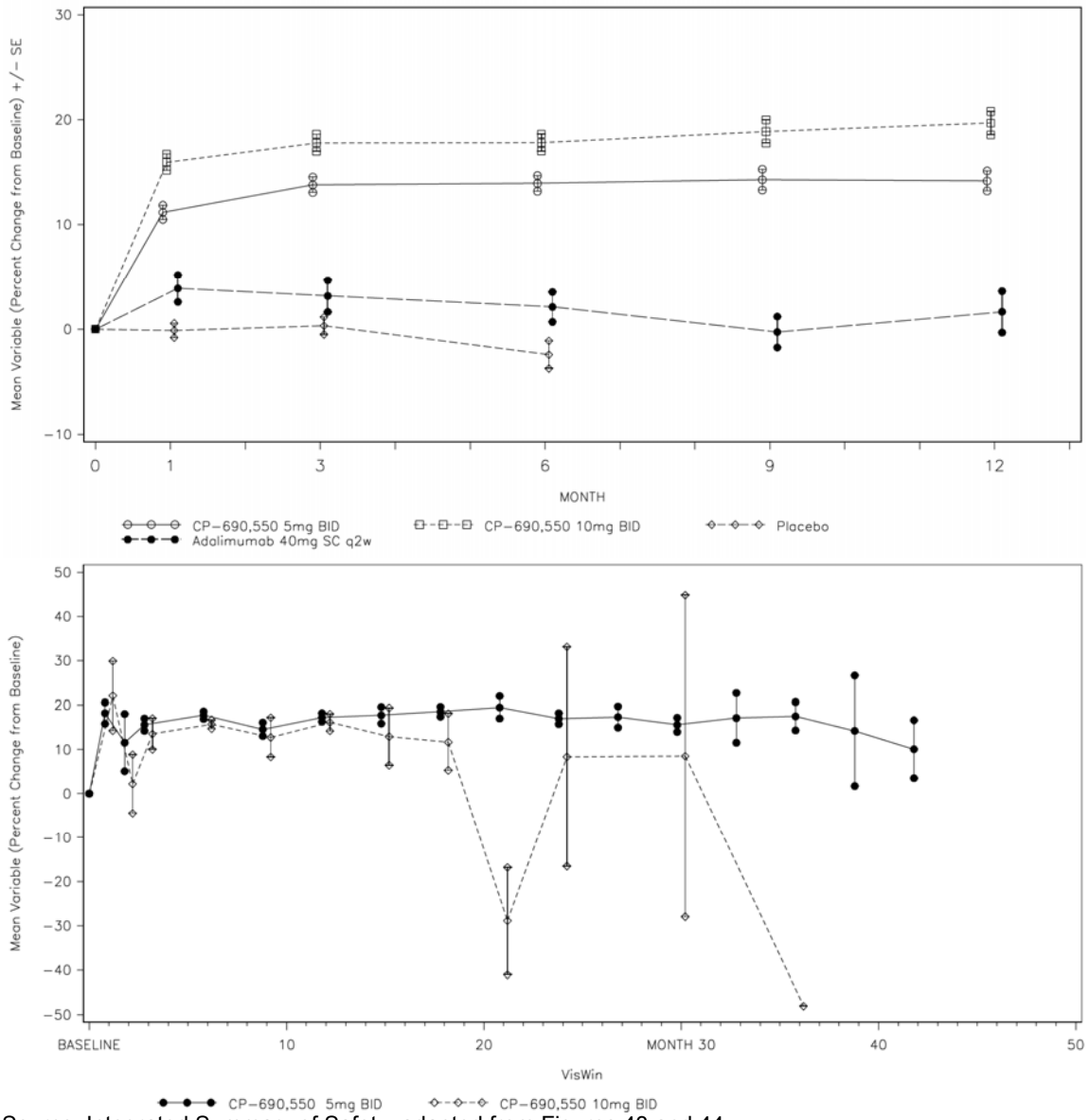
To further explore the effects of tofacitinib on renal function, the Sponsor conducted a 14-day repeat dose (15 mg BID) study 1033, in healthy volunteers and reported that tofacitinib administration did not affect renal function (measured GFR using iohexol serum clearance), renal plasma flow, or 24-hour urinary creatinine clearance for the short study duration. While reassuring, the results of this study do not address the long-term effects of tofacitinib on creatinine clearance in the target population. This could still be a concern, as the proportion of patients with serum creatinine elevations increased after Month 3 in the Phase 3 studies as well as in LTE studies, as shown above in Table 65 above. This may warrant inclusion of serum creatinine monitoring in labeling and in communications to health care providers as part of REMS and to patients as part Medication Guide.

7.4.2.2 Lipid Abnormalities and Cardiovascular Disorders

Lipid Abnormalities

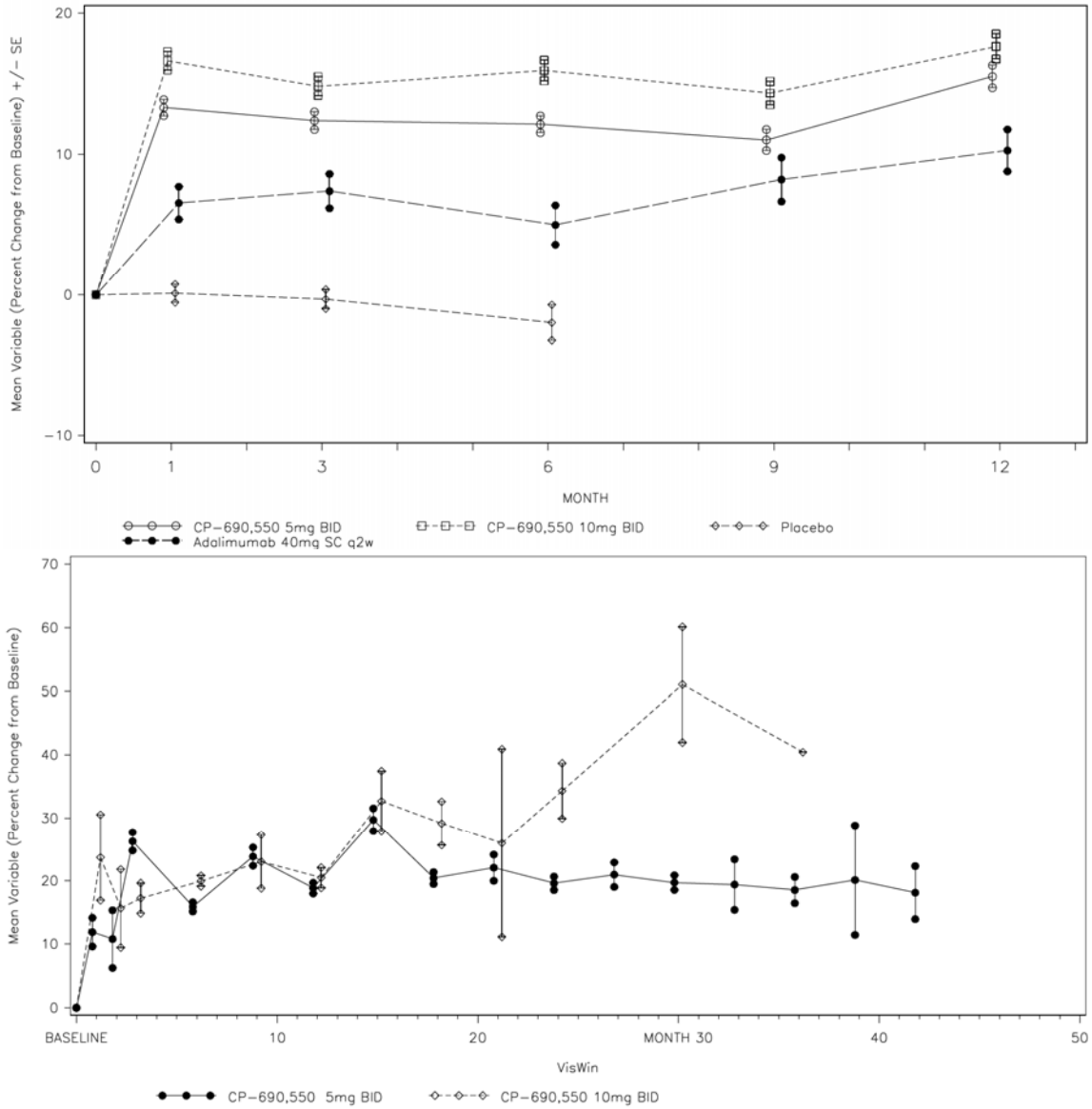
Tofacitinib administration was associated with dose-dependent increases in total, LDL, as well as HDL cholesterol that appeared to occur within one month of treatment and then plateaued. Mean LDL levels increased by approximately 14-18% from baseline, in contrast to adalimumab and placebo which remained largely unchanged throughout the Phase 3 studies as seen in Figure 15. The overall magnitude and trends of the changes in total cholesterol paralleled the changes in LDL. Similarly, in Phase 3 studies, mean HDL levels also increased by approximately 12-15% from baseline in the tofacitinib groups, whereas levels increased to a lesser extent (10%) in adalimumab group, and remained unchanged in placebo group (Figure 16). Triglycerides also increased by 10-20% from baseline in tofacitinib groups without clear dose-dependence and remained stable with prolonged exposure (data not shown). The overall LDL/HDL ratios were small and remained unchanged over time even though the clinical significance of this is unknown.

Figure 15. Mean Changes From Baseline in LDL (mg/dL) in All Phase 3 Studies (Upper Panel) and LTE Studies (Lower Panel)



Source: Integrated Summary of Safety, adapted from Figures 43 and 44

Figure 16. Mean Changes From Baseline in HDL (mg/dL) in All Phase 3 Studies (Upper Panel) and LTE Studies (Lower Panel)



Source: Summary of Clinical Safety, adapted from Figure 30;

Lipid Shifts on Treatment

The Sponsor submitted analyses of categorical changes in LDL-c as a function of baseline values using the following cut-off values recommended in the Adult Treatment Panel III (ATP III) guidelines for the treatment of high blood cholesterol (National Cholesterol Education Program [NCEP] ATP III, 2001): <100, 100 to <130, 130 to <160, 160 to <190, and over 190 mg/dL.

The proportion of patients with baseline LDL cholesterol in each of the categories was comparable among all treatment groups in the Phase 3 studies.

Overall, in the first three months of the Phase 3 studies, higher proportions of patients moved from baseline to a higher category while on treatment with tofacitinib than did patients in placebo or adalimumab groups consistent with the documented increases in the mean LDL cholesterol levels shown in Figure 15 above. This was particularly evident in the patients in the lower baseline LDL categories. However, no dose-dependent (5 vs. 10 mg BID) category shifts were observed as shown in Table 67. The data beyond the 3 month timepoint were consistent with the findings during the first 3 months.

Table 67. LDL Shifts on Treatment vs Baseline, All Phase 3 Studies (Month 0-3)

Number (%) of Patients with LDL Shifts on Treatment vs Baseline, All Phase 3 Studies (Month 0-3)					
	Maximum On-Treatment LDL Cholesterol				
Baseline	<100	100 to <130	130 to <160	160 to <190	≥190
CP5					
<100 mg/dL	204 (16.78)	169 (13.90)	52 (4.28)	8 (0.66)	4 (0.33)
100 mg/dL to <130 mg/dL	16 (1.32)	155 (12.75)	153 (12.58)	48 (3.95)	13 (1.07)
130 mg/dL to <160 mg/dL	2 (0.16)	20 (1.64)	107 (8.80)	87 (7.15)	29 (2.38)
160 mg/dL to <190 mg/dL	1 (0.08)	1 (0.08)	16 (1.32)	30 (2.47)	36 (2.96)
≥190 mg/dL	0 (0.00)	1 (0.08)	2 (0.16)	5 (0.41)	26 (2.14)
CP10					
<100 mg/dL	200 (16.47)	180 (14.83)	66 (5.44)	12 (0.99)	2 (0.16)
100 mg/dL to <130 mg/dL	15 (1.24)	112 (9.23)	175 (14.42)	56 (4.61)	13 (1.07)
130 mg/dL to <160 mg/dL	4 (0.33)	15 (1.24)	93 (7.66)	92 (7.58)	36 (2.97)
160 mg/dL to <190 mg/dL	0 (0.00)	1 (0.08)	8 (0.66)	35 (2.88)	37 (3.05)
≥190 mg/dL	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.08)	27 (2.22)
CP All					
<100 mg/dL	404 (16.63)	349 (14.36)	118 (4.86)	20 (0.82)	6 (0.25)
100 mg/dL to <130 mg/dL	31 (1.28)	267 (10.99)	328 (13.50)	104 (4.28)	26 (1.07)
130 mg/dL to <160 mg/dL	6 (0.25)	35 (1.44)	200 (8.23)	179 (7.37)	65 (2.67)
160 mg/dL to <190 mg/dL	1 (0.04)	2 (0.08)	24 (0.99)	65 (2.67)	73 (3.00)
≥190 mg/dL	0 (0.00)	1 (0.04)	2 (0.08)	6 (0.25)	53 (2.18)
PBO					
<100 mg/dL	153 (22.47)	73 (10.72)	6 (0.88)	2 (0.29)	0 (0.00)
100 mg/dL to <130 mg/dL	28 (4.11)	160 (23.49)	46 (6.75)	4 (0.59)	0 (0.00)
130 mg/dL to <160 mg/dL	3 (0.44)	22 (3.23)	74 (10.87)	22 (3.23)	3 (0.44)
160 mg/dL to <190 mg/dL	0 (0.00)	1 (0.15)	13 (1.91)	23 (3.38)	6 (0.88)
≥190 mg/dL	0 (0.00)	0 (0.00)	0 (0.00)	6 (0.88)	18 (2.64)
ADA					
<100 mg/dL	36 (17.65)	24 (11.76)	1 (0.49)	1 (0.49)	0 (0.00)
100 mg/dL to <130 mg/dL	12 (5.88)	35 (17.16)	25 (12.25)	3 (1.47)	0 (0.00)
130 mg/dL to <160 mg/dL	0 (0.00)	3 (1.47)	22 (10.78)	13 (6.37)	2 (0.98)
160 mg/dL to <190 mg/dL	0 (0.00)	0 (0.00)	7 (3.43)	9 (4.41)	4 (1.96)
≥190 mg/dL	0 (0.00)	0 (0.00)	1 (0.49)	0 (0.00)	4 (1.96)

Source: Integrated Analysis of Cardiovascular Safety, adapted from Tables 14.8.11; Only subjects with both a valid baseline and an on-treatment value for the parameter of interest are included in table.

The documented dose-dependent lipid abnormalities are of concern, as the relationship between LDL and risk for cardiovascular disease is direct and linear. One percent increase in the level of LDL is associated with a 1% increase in the risk for CVD. Therefore, on a population level, the average increase in LDL-C observed following treatment with 10 mg BID tofacitinib may potentially increase the risk for cardiovascular

disease by as much as 20%. This warrants inclusion of lipid monitoring in labeling and in communications to health care providers as part of REMS and to patients as part Medication Guide.

With regard to the documented tofacitinib-induced concomitant elevations in HDL, their clinical significance is currently unclear as studies have shown no clinically meaningful benefit from drug-induced increasing HDL-cholesterol.[21]

Cardiovascular Disorders

Cardiovascular disorders were identified as events of interest for monitoring and analyses because of tofacitinib-induced change in lipid parameters (an approximate 15% increase in triglycerides, LDL, and HDL), which are discussed in detail in Lipid Abnormalities section above.

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

The adjudication of CV events was performed in a blind fashion by an external Cardiovascular Safety Endpoint Adjudication Committee (CV-SEAC) consisting of three cardiologists and governed by a Charter.

Tofacitinib administration resulted in reduction in C-reactive protein as shown in Table 25 above. However, the effect of tofacitinib on hs-CRP was not reported in this submission.

Major Cardiovascular Events

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

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

Table 68 summarizes the MACE and other relevant cardiovascular events by treatment assignment. The few MACE events, including fatal events, non-fatal myocardial infarction, and cerebrovascular accidents, were proportionally distributed among the treatment arms and were comparable to placebo- and adalimumab-comparator arms. These rates were also comparable to background rates in the RA population of 1.2 and 2.0 per 100 patient-years for women and men respectively.[22] Importantly, the exposure-

21 AIM-HIGH Investigators, Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy, N Engl J Med, 2011 Dec 15;365(24):2255-67
22 Solomon DH et al., Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis 2006;65:1608-12

adjusted rates from the LTE studies remained consistent with the rates observed during the controlled Phase 3 studies.

Table 68. Summary of Major Adverse Cardiovascular Events in Phase 3 and LTE RA Studies by Treatment Assignment

Summary of Major Cardiovascular Adverse Events in Phase 3 and LTE Studies in RA by Treatment Assignment									
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept. 29, 2011)
Enrolled, n **Exposure, patient-years**	**681** **203**	**204** **179**	**1216** **904**	**1214** **910**	**3030** **2098**	**1321** **1743**	**1906** **880**	**3227** **2622**	**3515** **3907**
MACE									
Events, n Patients, n Incidence rate per 100 PY (95%CI)	2 2 0.99 (0.25, 3.95)	3 3 1.68 (0.54, 5.20)	6 4 0.44 (0.17, 1.18)	6 6 0.66 (0.3, 1.47)	14 12 0.57 (0.33, 1.01)	3 3 0.17 (0.06, 0.53)	2 2 0 23 (0.06, 0.91)	5 5 0.19 (0.08, 0.46)	9 9 0.23 (0.12, 0.44)
Cardiovascular Mortality									
Events, n Patients, n Incidence rate per 100 PY (95%CI)	- - 0	1 1 0.56 (0.08, 3.97)	- - 0	2 2 0.22 (0.06, 0.88)	2 2 0.1 (0.02, 0.38)	1 1 0.06 (0.01, 0.41)	- - 0	1 1 0.04 (0.01, 0.27)	1 1 0.03 (0.004, 0.81)
Non-fatal Myocardial Infarction									
Events, n Patients, n Incidence rate per 100 PY (95%CI)	- - 0	2 2 1.12 (0.28, 4.47)	2 2 0.22 (0.06, 0.89)	2 2 0.22 (0.06, 0.89)	4 4 0.19 (0.07,0.51)	1 1 0.06 (0.01, 0.41)	- - 0	1 1 0.04 (0.01, 0.27)	2 2 0.05 (0.01, 0.21)
Non-fatal CVA									
Events, n Patients, n Incidence rate per 100 PY (95%CI)	2 2 0.99 (0.25, 3.95)	- - 0	4 3 0.33 (0.11, 1.03)	2 2 0.22 (0.06, 0.89)	8 7 0.33 (0.16, 0.70)	1 1 0.06 (0.01, 0.41)	2 2 0 23 (0.06, 0.91)	3 3 0.11 (0.04, 0.36)	6 6 0.15 (0.01, 0.34)
Congestive Heart Failure									
Events, n Patients, n Incidence rate per 100 PY (95%CI)	- - 0	- - 0	- - 0	6 5 0.55 (0.23, 1.32)	7 6 0.29 (0.13, 0.64)	3 2 0.12 (0.03, 0.46)	- - 0	3 2 0.08 (0.02, 0.31)	7 5 0.13 (0.05, 0.31)

Source: Integrated Summary of Safety, adapted from Table 160; 120- Day Safety Update, adapted from Table 49.
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

Myocardial Infarction

There were 6 adjudicated cases of myocardial infarction in tofacitinib-treated patients in the Phase 3 and LTE studies, with estimated rate of 0.10 per 100 patient-years, which is comparable with the published rates of MI in RA patients (0.53 per 100 patient-years).[23]

Cerebrovascular accidents

Similarly, the rate of cerebrovascular accident events in tofacitinib-treated patients was not elevated compared to published rates. Fourteen CVA events were reported in the

23 Solomon DH et al., Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis 2006;65:1608-12

Phase 3 and LTE studies with exposure-adjusted rate of 0.23 per 100 patient-years, which is also consistent with published rates of stroke in RA patients (0.51 per 100 patient-years).[24]

Congestive Heart Failure

A total of 14 events of congestive heart failure were reported in 11 patients in the Phase 3 and LTE studies. While these events occurred in tofacitinib-treated patients, all cases were significantly confounded by prior medical history, co-morbidities and concomitant medications. The overall congestive heart failure rate of 0.23 per 100 patient-years in tofacitinib-treated patients is comparable to published rates of around 2.0 per 100 patient-years.[25]

In summary, the available data on major adverse cardiovascular events do not indicate a clear safety signal of increased cardiovascular morbidity and mortality in patients treated with tofacitinib, compared with placebo and adalimumab controls. However, the duration of controlled period is relatively short to allow for accurate assessment of the effect of lipid elevations on the long-term cardiovascular disease in tofacitinib-treated patients. The optimal approach to address this question is to prospectively assess cardiovascular outcomes in a clinical trial. Additionally, labeling should include the observed changes in lipids and instruction for routine monitoring of lipid levels and management according to National Cholesterol Education Program recommendations.

Effects of Lipid-Lowering Therapy

To document the ability of lipid-lowering agents to ameliorate these changes, the Sponsor conducted study 1109, designed as a randomized, double-blind trial of atorvastatin 10 mg/day or placebo in addition to tofacitinib 10 mg BID for 6 weeks, to evaluate the safety and efficacy in reducing LDL in 111 patients with active RA. As expected, treatment with atorvastatin significantly reduced mean LDL levels in patients with tofacitinib-induced LDL elevations (data not shown) without unexpected or additional toxicity.

7.4.2.3 Hematologic Laboratory Parameters

The overall rates of severe and potentially life-threatening hematologic abnormalities was low in the Phase 3 studies and LTE, as summarized in Table 69 below.

24 Solomon DH et al., Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis 2006;65:1608-12
25 Nicola PJ et al. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. Arthritis Rheum 2006; 54:60-67

Table 69. Summary of Patients with Confirmed Hematologic Abnormalities by Severity and Treatment Sequence in Phase 3 and LTE Studies in RA

Confirmed Hematologic Abnormalities by Severity and Treatment Sequence in Phase 3 and LTE Studies in RA								
	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies		
	PBO→ CP5 mg BID	PBO→ CP10 mg BID	ADA	CP5 mg BID	CP10 mg BID	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)
Enrolled, n	**343**	**338**	**204**	**1216**	**1214**	**1321**	**1906**	**3227**
Anemia, n (%)								
Mild to Moderate (Hgb ↓≥1 to ≤2 g/dL)	30 (9)	33 (10)	10 (5)	95 (8)	130 (11)	164 (12)	156 (8)	320 (10)
Severe (Hgb ↓>2 to <3 g/dL)	1 (<1)	9 (3)	0	8 (<1)	21 (2)	37 (3)	21 (1)	58 (2)
Life-threatening (Hgb ↓≥3 or absolute ≤7 g/dL)	1 (<1)	3 (<1)	0	0	1 (<1)	17 (1)	6 (<1)	23 (<1)
Neutropenia, n (%)								
Mild (ANC ≥1.5 to <2 x 1000/mm^3)	8 (2)	9 (3)	5 (<3)	29 (2)	33 (3)	55 (4)	37 (2)	92 (3)
Moderate to Severe (ANC <1.5 to ≥0.5 x 1000/mm^3)	2 (<1)	3 (<1)	2 (<1)	4 (<1)	19 (2)	8 (<1)	8 (<1)	16 (<1)
Life-threatening (ANC <0.5 x 1000/mm^3)	0	0	0	0	0	0	0	0
Lymphopenia, n (%)								
Mild (ALC ≥1.5 to <2 x 1000/mm^3)	95 (28)	92 (27)	64 (31)	356 (29)	347 (29)	318 (24)	486 (26)	804 (25)
Moderate to Severe (ALC <1.5 to ≥0.5 x 1000/mm^3)	128 (37)	132 (39)	43 (21)	462 (38)	461 (38)	773 (59)	591 (31)	1364 (42)
Life-threatening (ALC <0.5 x 1000/mm^3)	0	0	0	0	5 (<1)	6 (<1)	4 (<1)	10 (<1)

Source: Integrated Summary of Safety, adapted from Tables 201-211; Integrated Summary of Safety on Infections, adapted from Table 23

Leukocyte Abnormalities

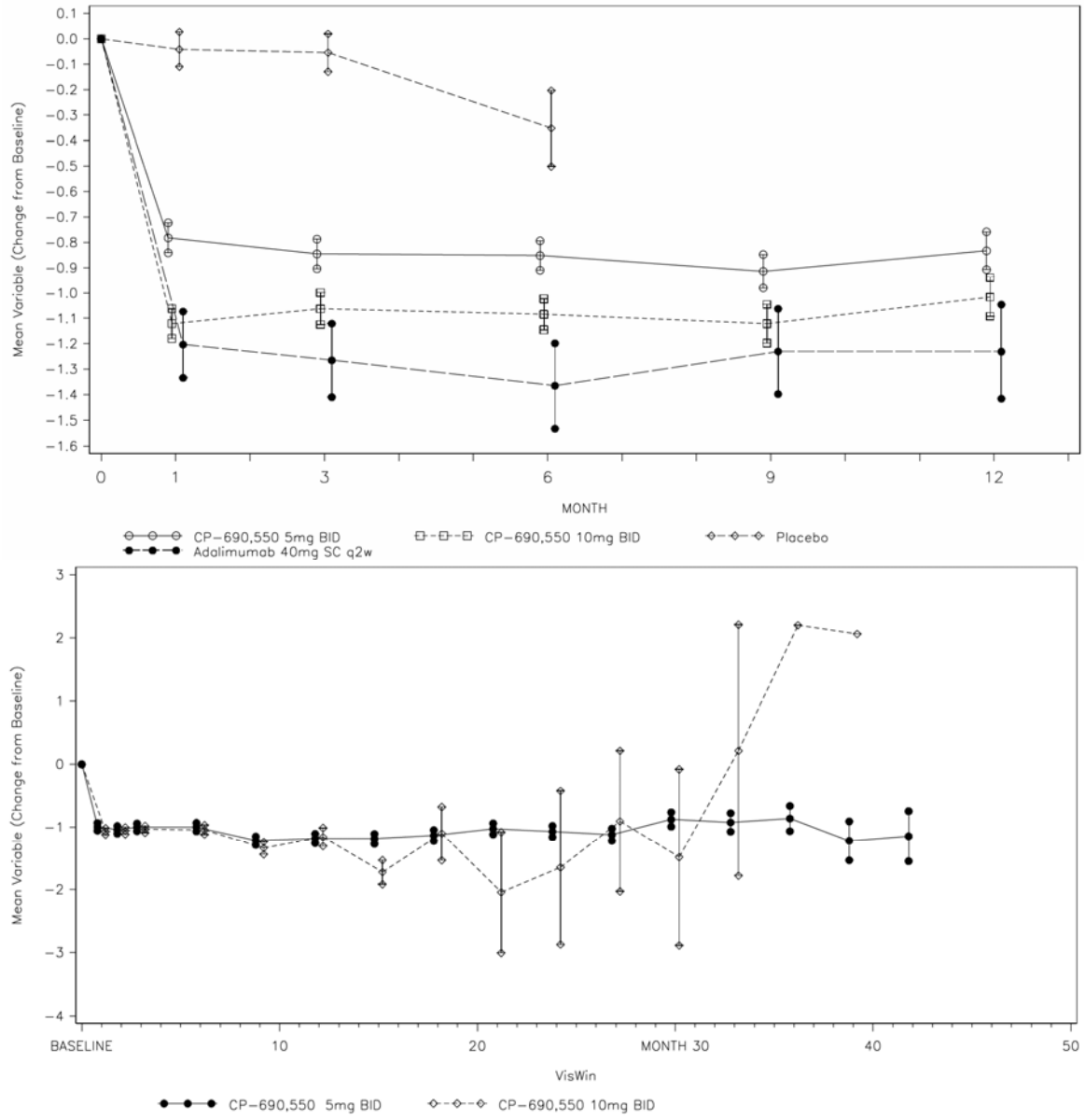
This section provides an assessment of leukocyte abnormalities observed in the RA development program and a discussion on the potential association of infections with tofacitinib-induced changes in neutrophils and lymphocytes.

Tofacitinib use was associated with dose-dependent decreases in both neutrophil and lymphocyte counts.

Neutrophils:

Tofacitinib administration resulted in rapid and dose-dependent decreases in mean peripheral absolute neutrophil counts (ANC) over the first month of treatment without further declines, which is comparable to adalimumab (Figure 17).

Figure 17. Mean Changes From Baseline in Neutrophil Counts (x1000/mm^3) in All Phase 3 Studies (Upper Panel) and LTE Studies (Lower Panel)



Source: Integrated Summary of Safety, adapted from Figures 30 and 31;

No life-threatening neutropenias (two consecutive ANC <500/mm^3) were reported and only 2 cases (0.08%) of confirmed ANC count <1000/mm^3 were reported in the Phase 3 controlled studies, one in each tofacitinib dose group (Source Tables s19.4 and s19.16 P3ALL).

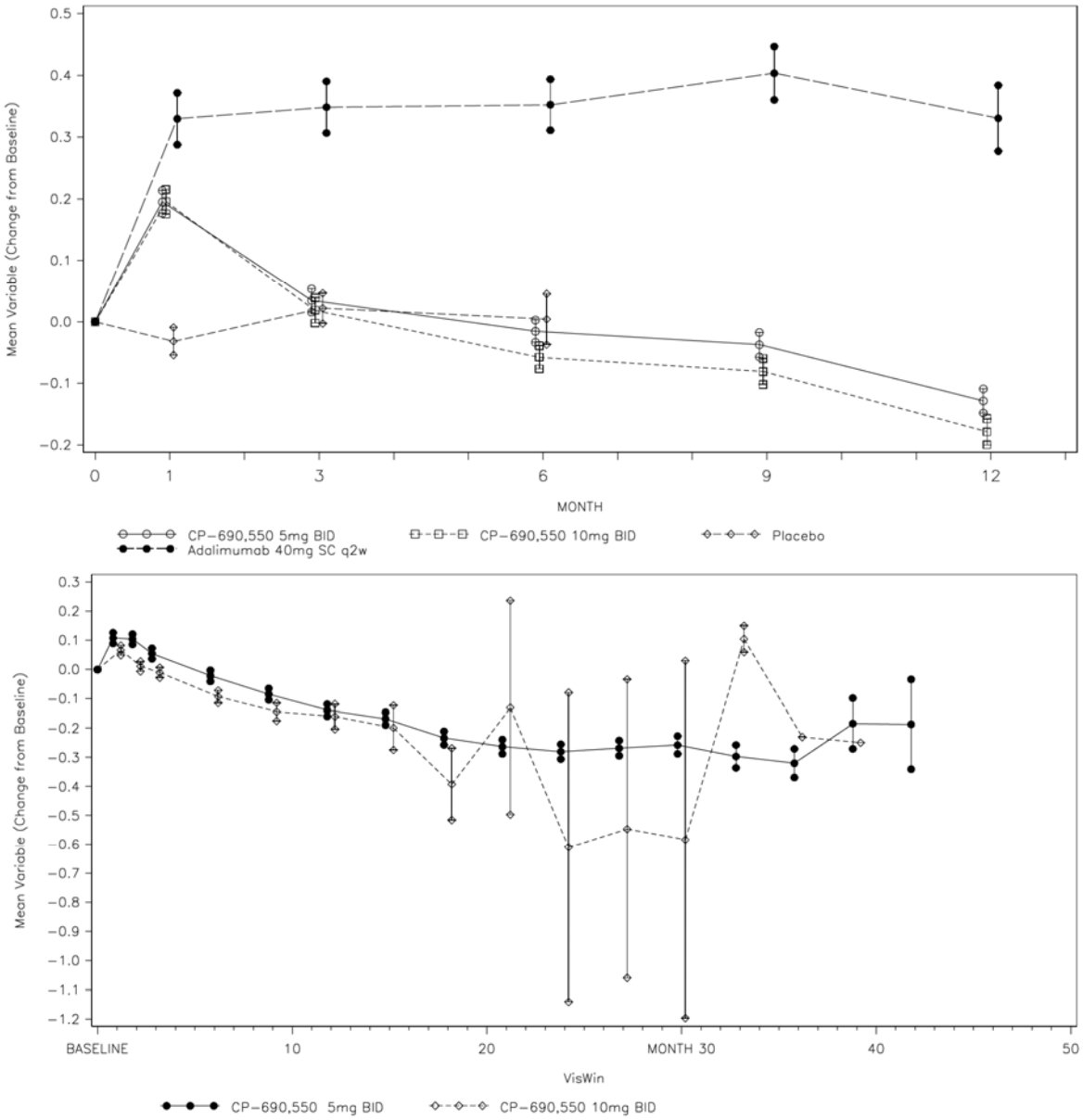
There was no clear association between neutropenia (defined as ANC<2,000/mm^3) and infections; similar proportions of patients developed infections (~20-30%) or serious

infections (1-2%) among patients with or without confirmed neutropenia, in the Phase 3 and LTE studies.

Lymphocytes:

Tofacitinib use resulted in initial lymphocytosis for the first month, followed by gradual decline in mean counts which continued for at least 12 months. These changes are in contrast to the changes caused by adalimumab use which was associated with sustained lymphocytosis (Figure 18). One potential pathogenic mechanism of the observed lymphopenia may be an off-target tofacitinib effect of JAK2 inhibition.

Figure 18. Mean Changes From Baseline in Lymphocyte Counts (x1000/mm^3) in All Phase 3 Studies (Upper Panel) and LTE Studies (Lower Panel)



Source: Integrated Summary of Safety, adapted from Figures 33 and 34

Five patients treated with tofacitinib 10 mg BID in the Phase 3 studies (all on background DMARD) experienced marked lymphopenia (two consecutive ALC <500/mm^3). Of these, 3 (60%) developed infections (periodontitis, Herpes simplex, and a urinary tract infection).

In the LTE studies, 10 patients experienced marked lymphopenia. Notably, 80% (8/10) of these patients developed infections, including 4 serious infections (3 cases of herpes zoster, 1 of which later developed disseminated TB, and 1 case each of pyelonephritis,

urinary tract infection, pneumonia and erysipelas). In contrast, the incidence of infections was 24% and serious infections 2.8%, among patients who did not develop life-threatening lymphopenia.

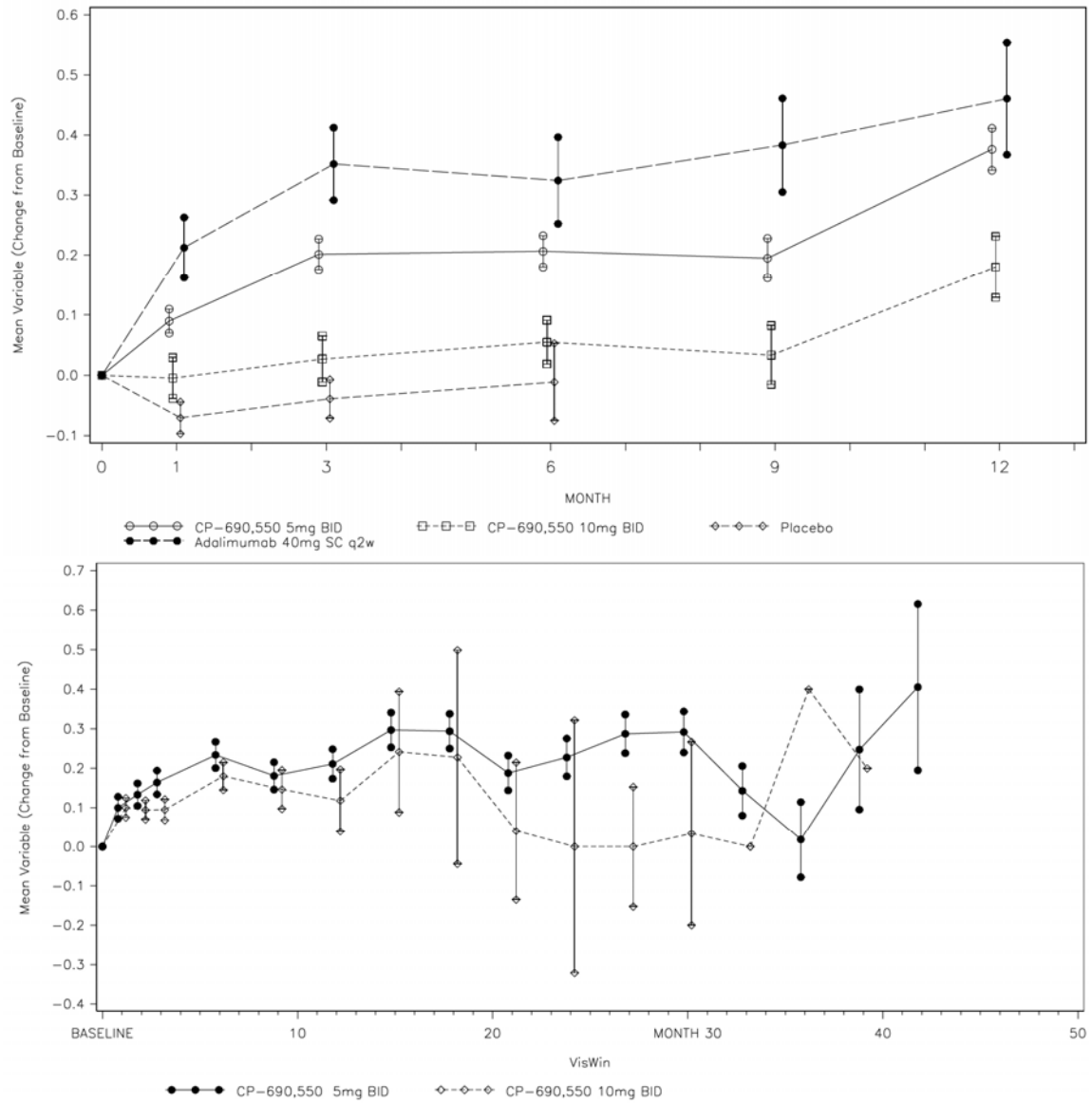
These observations indicate that tofacitinib-induced lymphopenia confers an increased risk of infections, including serious ones. Despite these observations however, only NK cell counts showed dose-dependent decreases, but not CD3+, CD4+, or CD8+ lymphocyte subsets, as discussed in detail in Section 4.4.4. Dose Selection. This suggests functional rather than cytotoxic effect of tofacitinib. Based on these considerations, it is unclear whether monitoring of total lymphocyte or lymphocyte subset counts, may be helpful to identify patients at risk of developing infections, but since this is a routine hematology lab test, it should be considered as a part of the routine clinical assessment of patients taking tofacitinib.

Hemoglobin Abnormalities

Mean hemoglobin concentrations increased in the tofacitinib 5 mg BID and adalimumab groups, in parallel with improvement in disease activity, suggesting an improvement in anemia related to chronic disease (Figure 19). However, in the tofacitinib 10 mg BID dose group, mean hemoglobin concentrations remained unchanged from baseline, despite the observed clinical response in disease activity, which may reflect the inhibition of JAK2 effects. These observations are consistent with the findings from Phase 2 dose-ranging studies and the modeling used for dose-selection. Notably, this represents an off-target toxicity of tofacitinib and may not have been the optimal safety parameter for inclusion in the dose-selection modeling, as discussed in detail in Section 4.4.4. Dose Selection above.

Events of clinically significant hemoglobin decreases and severe or life-threatening values were small and proportionally equally distributed among the treatment arms (Table 69). However, since anemia may represent an off-target toxicity associated with tofacitinib use, this warrants inclusion of hemoglobin monitoring in labeling and in communications to health care providers as part of REMS and to patients as part Medication Guide.

Figure 19. Mean Hemoglobin Changes from Baseline in All Phase 3 Studies (Upper Panel) and LTE Studies (Lower Panel)

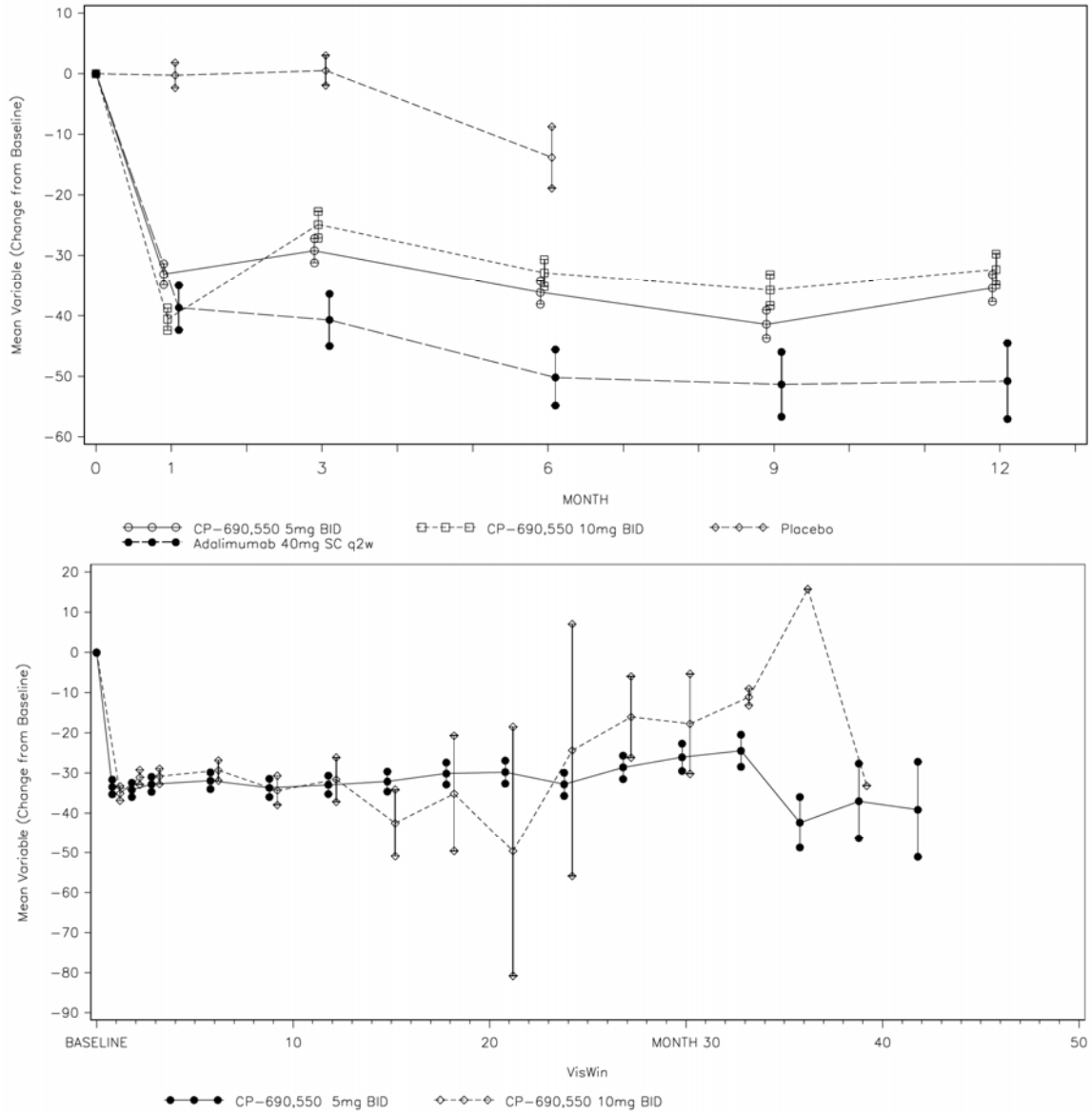


Source: Integrated Summary of Safety, adapted from Figures 25 and 26

Platelet Abnormalities

Tofacitinib administration, lead to small decreases from baseline of about 30-40,000 in mean platelet counts, comparable to adalimumab Figure 20. Few patients developed thrombocytopenia of <75,000/mm^3, none of which was associated with clinically significant bleeding.

Figure 20. Mean Changes From Baseline in Platelet Counts (x 1,000/mm^3) in All Phase 3 Studies (Left Panel) and LTE Studies (Right Panel)



Source: Integrated Summary of Safety, adapted from Figures 37 and 38

In summary, most of the hematologic abnormalities showed dose-dependent changes. However, only tofacitinib-induced lymphopenia appeared to be associated with a clinically relevant outcome of infections. Among lymphocyte subsets measured in the dose-ranging studies however, the CD4 cell counts which are routinely available for routine clinical monitoring, did not show dose-dependency and may not be helpful in identifying patients at risk of infection.

7.4.2.4 Liver Test Abnormalities and Hepatobiliary Disorders

Liver Test Abnormalities

Liver test abnormalities were observed in less than 20% of tofacitinib-treated patients in RA clinical development. Most of these abnormalities occurred in studies with background DMARD (methotrexate for the most part) therapy. Tofacitinib administration was associated with small (<10 IU/L) elevations of mean ALT and AST. Small elevations in total bilirubin (~0.05 mg/dL) were also documented which were comparable to the changes with adalimumab (0.08 mg/dL). In monotherapy study 1045, there were minimal, no clinically significant changes in the mean values of ALT, AST and total bilirubin (data not shown), which is consistent with data from Phase 2 monotherapy studies (1019, 1035, and 1040). In LTE studies, similar small increases were documented in ALT, AST (both <5 IU/L) and total bilirubin (~0.05 mg/dL). Significant liver test abnormalities were uncommon and remained balanced among treatment groups throughout the Phase 3 background DMARD studies and LTE studies as shown in Table 70.

Table 70. Incidence of Liver Test Abnormalities, Change from Baseline in Phase 3 Background DMARD Studies

Incidence of Liver Test Abnormalities, Change from Baseline in Phase 3 Background DMARD Studies				
	PBO	ADA	CP5 mg BID	CP10 mg BID
0-3 months, n (%)	**554**	**204**	**986**	**962**
Total bilirubin				
≥1 x ULN	8 (1)	6 (3)	17 (2)	17 (2)
≥2 x ULN	0	1 (<1)	1 (<1)	1 (<1)
≥3 x ULN	0	0	0	0
AST				
≥1 x ULN	54 (10)	25 (12)	166 (17)	187 (19)
≥2 x ULN	6 (1)	2 (1)	7 (1)	12 (1)
≥3 x ULN	2 (<1)	0	3 (<1)	2 (<1)
ALT				
≥1 x ULN	67 (12)	32 (17)	172 (18)	204 (21)
≥2 x ULN	12 (2)	0	18 (2)	28 (3)
≥3 x ULN	0	0	5 (<1)	7 (<1)
3-6 months, n (%)	**185**	**187**	**1048**	**1047**
Total bilirubin				
≥1 x ULN	1 (1)	5 (3)	18 (2)	15 (1)
≥2 x ULN	0	0	0	0
≥3 x ULN	0	0	0	0
AST				
≥1 x ULN	11 (6)	20 (11)	148 (14)	157 (15)
≥2 x ULN	1 (1)	1 (1)	16 (2)	16 (2)
≥3 x ULN	0	1 (1)	6 (1)	4 (<1)
ALT				
≥1 x ULN	15 (8)	17 (9)	144 (14)	152 (15)
≥2 x ULN	3 (2)	1 (1)	15 (1)	19 (2)
≥3 x ULN	1 (1)	0	5 (<1)	9 (1)
> 6 months, n (%)	**-**	**178**	**905**	**905**
Total bilirubin				
≥1 x ULN	-	5 (3)	19 (2)	31 (3)
≥2 x ULN	-	1 (1)	0	0
≥3 x ULN	-	0	0	0
AST				
≥1 x ULN	-	16 (9)	174 (19)	207 (23)
≥2 x ULN	-	2 (1)	19 (2)	30 (3)
≥3 x ULN	-	1 (1)	10 (1)	8 (1)
ALT				
≥1 x ULN	-	26 (15)	140 (15)	189 (21)
≥2 x ULN	-	3 (2)	28 (3)	47 (5)
≥3 x ULN	-	1 (1)	8 (1)	14 (2)
LTE Studies, n (%)	**-**	**-**	**1321**	**1906**
Total bilirubin				
≥1 x ULN	-	-	108 (8)	52 (3)
≥2 x ULN	-	-	2 (<1)	1 (<1)
≥3 x ULN	-	-	2 (<1)	0
AST				
≥1 x ULN	-	-	387 (29)	440 (24)
≥2 x ULN	-	-	54 (4)	35 (2)
≥3 x ULN	-	-	18 (1)	12 (1)
ALT				
≥1 x ULN	-	-	377 (29)	411 (22)
≥2 x ULN	-	-	80 (6)	74 (4)
≥3 x ULN	-	-	24 (2)	21 (1)

Source: Integrated Summary of Safety Hepatic, Adapted from Tables 24-26, 31

Further analysis of ALT changes, separately for patients with normal versus abnormal baseline ALT values in the pooled Phase 3 RCT and LTE studies is presented in Table 71. These data indicate that significant ALT shifts were rare and balanced across treatment arms, suggesting that tofacitinib administration was associated with low level

of liver test abnormalities. Majority of patients with confirmed ALT elevations from baseline >3xULN were taking concomitant methotrexate alone or in combination with leflunomide.

Table 71. Summary of ALT Shifts from Baseline in Phase 3 (0-12 Months) and LTE Studies

Integrated Summary of the Incidence of Confirmed ALT Elevations (IU/L) by Baseline Status in Phase 3 (0-12 Months) and LTE Studies							
	RCT 12-Month Pooled Safety				LTE Studies		
	PBO	ADA	CP5	CP10	CP5	CP10	CP, All doses
Normal Baseline, n (%)	**633**	**177**	**1090**	**1101**	**1205**	**1692**	**2897**
≥1 x ULN	51 (8)	15 (9)	119 (11)	150 (14)	151 (13)	173 (10)	324 (11)
≥3 x ULN	3 (<1)	1 (<1)	6 (<1)	6 (<1)	6 (<1)	9 (<1)	15 (<1)
≥5 x ULN	1 (<1)	0	3 (<1)	1 (<1)	1 (<1)	2 (<1)	3 (<1)
≥10 x ULN	0	0	2 (<1)	0	1 (<1)	1 (<1)	2 (<1)
Abnormal Baseline, n (%)	**47**	**27**	**120**	**110**	**65**	**163**	**228**
≥1 x ULN	22 (47)	12 (44)	70 (58)	65 (59)	35 (54)	67 (41)	102 (45)
≥3 x ULN	2 (4)	1 (4)	7 (6)	6 (6)	8 (12)	2 (1)	10 (4)
≥5 x ULN	1 (2)	1 (4)	0	1 (<1)	1 (2)	0	1 (<1)
≥10 x ULN	0	0	0	0	0	0	0

Source: Integrated Analyses of Hepatic Events, Adapted from Tables 35 and 38

Hepatotoxicity

Table 72. provides an overview of the treatment-emergent hepatic disorders AEs, SAEs, AEs leading to temporary and permanent discontinuation and hepatic-related deaths. The overall proportions of AEs in the Hepatic Disorders AEs was balanced among all treatment during the first six months and remained stable in the tofacitinib groups until one year in the Phase 3 studies. In the LTE studies, the incidence rates of AEs increased numerically in a dose-dependent manner. SAEs were infrequent (<0.5%) and exposure-adjusted rates remained stable in the LTE studies suggesting that the documented liver test abnormalities were rarely associated with clinically significant hepatic events rare, including with prolonged tofacitinib exposure. The one death reported as hepatic disorder AE in the LTE studies (1024-14901003) occurred in a 64 year-old white woman in the CP10 group was temporarily withdrawn on Day 90 due to SAEs of hepatic and lung neoplasm malignant (primary unknown); the patient died on Day 129 (Table 32).

There were no cases of fulminant hepatic failure or cases requiring liver transplantation in the RA development program to date.

Table 72. Summary of Hepatic Disorder by Trial Period and Treatment Assignment

Summary of AEs in the Standardized MedDRA Query (SMQ) of Drug-Related Hepatic Disorders in Phase 3 and LTE Studies in RA					
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses
0-3 months, n (%)					
Enrolled, n	681	204	1216	1214	2430
Patients with AE	15 (2.2)	2 (1.0)	30 (2.5)	33 (2.7)	63 (2.6)
Patients with SAE	1 (0.1)	0	0	0	0
Patients who discon inued due to AE	2 (0.3)	0	6 (0.5)	3 (0.2)	9 (0.4)
Patients who interrupted dosing due to AE	0	0	4 (0.3)	4 (0.3)	8 (0.3)
Deaths due to hepatic disorder	0	0	0	0	0
3-6 months, n (%)					
Enrolled, n	221	204	1451	1439	2890
Patients with AE	1 (0.5)	3 (1.5)	24 (1.7)	32 (2.2)	56 (1.9)
Patients with SAE	0	0	2 (0.1)	0	2 (0.1)
Patients who discon inued due to AE	0	1 (0.5)	4 (0.2)	5 (0.3)	9 (0.3)
Patients who interrupted dosing due to AE	0	0	3 (0.1)	4 (0.3)	7 (0.2)
Deaths due to hepatic disorder	0	0	0	0	0
> 6 months, n (%)					
Enrolled, n	-	204	1056	1046	2102
Patients with AE	-	1 (0.5)	25 (2.4)	34 (3.3)	59 (2.8)
Patients with SAE	-	0	0	0	0
Patients who discon inued due to AE	-	0	1 (0.1)	1 (0.1)	2 (0.1)
Patients who interrupted dosing due to AE	-	1 (0.5)	2 (0.2)	3 (0.3)	5 (0.2)
Deaths due to hepatic disorder	-	0	0	0	0
LTE Studies, n (exposure adjusted incidence rate, per 100 patient years)					
Enrolled, n	-	-	1321	1906	3227
Exposure, patient-years	-	-	2215	871	3085
Patients with AE	-	-	92 (4.2)	71 (8.2)	163 (5.3)
Patients with SAE	-	-	6 (0.3)	4 (0.5)	10 (0.3)
Patients who discon inued due to AE	-	-	15 (0.7)	8 (1.0)	23 (0.7)
Patients who interrupted dosing due to AE	-	-	12 (0.5)	11 (1.3)	23 (0.7)
Deaths due to hepatic disorder	-	-	0	1 (<0.1)	1 (<0.1)

Source: Integrated Safety Analysis on Hepatic adverse events, Adapted from Tables 13-17 and P3ALL Table 12.10.1
Note: Data for LTE studies are presented as the total number and exposure-adjusted incidence rates to account for differences in exposure

Potential Hy's Law Cases

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

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

Six patients, all in the LTE studies, met the laboratory criteria for Hy's law, but five of these cases did not meet the third criterion due to the presence of significant confounding factors as described in the narratives below:

- 1024-11361014: A case of a 61-year-old female patient with RA and Sjögren's

syndrome who was diagnosed with miliary TB and TB meningoencephalitis in January 2011 while being treated with tofacitinib since March 03, 2008. Tofacitinib was permanently discontinued on January 13, 2011 at the time of TB diagnosis and on February 09, 2011 liver tests were reported to be normal. A combination anti-TB treatment was initiated with isoniazid, ethambutol, rifampicin, pyrazinamide, pyridoxine, levofloxacine and amikacin, with recovery from the infection. On (b) (6), the subject was admitted with jaundice and LFT elevations: ALT 432 IU/L (normal 0-40 IU/L), AST 416 IU/L (normal 0-40 IU/L), and Total bilirubin 20.8 mg/dL (normal 0.2-1.2 mg/dL). The clinical scenario is consistent with drug-induced hepatotoxicity; however, the case is significantly confounded by the use of combination anti-TB medications, well known to be associated with such toxicity. Therefore, the case does not meet the definition of Hy's law.

- 1041-10211003: A case of a 59-year-old female with history of RA, HTN, gastric ulcer, mediastinal tumor and osteoporosis, who was diagnosed with interstitial pneumonia and acute hepatitis after being treated with tofacitinib for about six months. Concomitant medications included diclofenac, celecoxib, loxoprofen, prednisolone. Tofacitinib was discontinued as of 08/18/2010 after the diagnosis of interstitial pneumonia. Liver enzymes were normal at that time. The patient was admitted for shortness of breath on 09/04 and was found to have acute hepatitis (reportedly LFTs were normal on 08/18/2010) with ALT-2000, AST-2300, AP-1500, LDH-800, GGT-600, Bilirubin from 1.4 to 3.2. Therapeutic measures from 04 Sept. 2010 to 06 Sept. 2010 included the following: prednisolone 5 mg daily, isoniazid, 100 mg twice daily, loxoprofen sodium 60 mg twice daily and celecoxib 200 mg BID. On 07 Sept. 2010, the prednisolone, isoniazid, loxoprofen sodium and celecoxib were discontinued. However, diclofenac was continued. Subsequently the patient developed disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and multiorgan failure and died 69 days after tofacitinib discontinuation. This event is significantly confounded by concomitant medications, such as NSAIDs and isoniazid, and concurrent illness (interstitial pneumonia) of potentially viral etiology; also the laboratory assessment suggests a cholestatic rather than hepatocellular pattern of liver injury. Therefore, the case does not meet the definition of Hy's law.

- 1024-11521020: A case of a 63-year-old male with RA and multiple co-morbidities treated concomitantly with leflunomide, allopurinol and ramipril, who developed acute polyserositis with pericardial tamponade, right heart failure and congested hepatopathy with ascites and liver enzyme elevations while being treated with tofacitinib for 2 months. Therefore, the case does not meet the definition of Hy's law.

- Patient 1041-10061023: A case of a 70 year-old female who was treated with tofacitinib 5 mg BID for 161 days prior to being found to have increased alanine aminotransferase. On Day 196, 35 days after discontinuing study drug, the

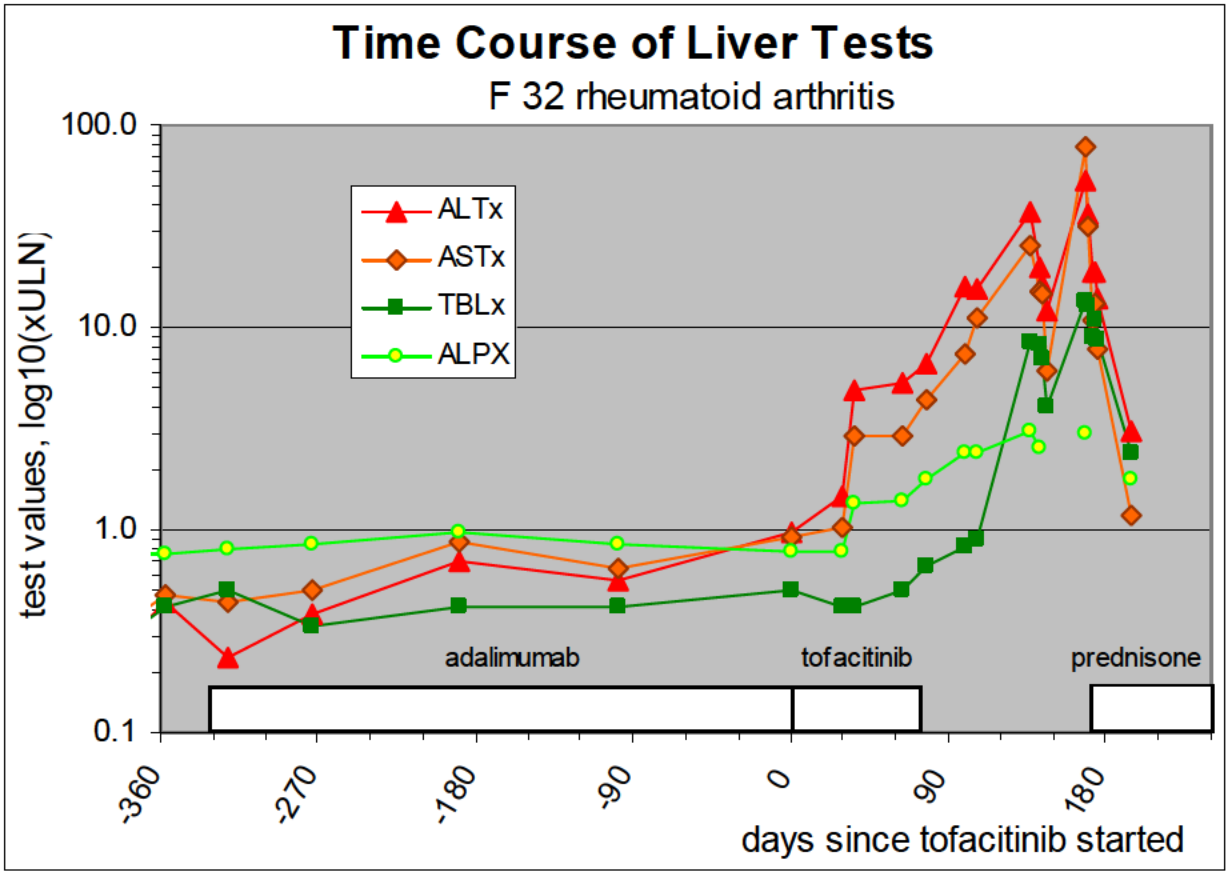
patient had an ALT of 577 IU/L (reference range 5 to 40 IU/L), AST of 300 IU/L (reference range 10 to 40 IU/L), total bilirubin of 6.4 mg/dL (reference range 0.2 to 1 mg/dL) and alkaline phosphatase of 742 IU/L (reference range 115 to 359 IU/L). The patient was diagnosed with obstructive jaundice with compression of the common bile duct on CT scan. Therefore, the case does not meet the definition of Hy's law.

- Patient 1024-10431005: A case of a 46-year-old male who developed liver enzyme elevations in the setting of appendicitis with septicemia and necrosis of the ascending colon. Therefore, the case does not meet the definition of Hy's law. On Day 679 of tofacitinib treatment, the patient presented to the hospital with diffuse abdominal pain and abdominal distention, and had an ALT of 100 U/L (reference range 5 to 50 U/L), AST of 90 U/L (reference range 4 to 46 U/L) and total bilirubin of 9.7 mg /dL (reference range 0.22 to 1.28 mg/dL). Background immunosuppressive treatment included MTX 15 mg/week and prednisone 5 mg bid. His condition deteriorated and he underwent surgery diagnosed with retrocecal necrotizing appendicitis, necrosis of ascending colon. The cause of death was attributed to appendicitis and necrosis of the ascending colon.

One of the six cases that met Hy's law laboratory criteria, was identified as a potential case of Drug-Induced Liver Injury (DILI):

- Patient 1024-15081007: A case of a 32-year-old female with RA diagnosed in 09/2006. There is no medical history of liver disease in the subject or family. She received tofacitinib at 10 mg BID for RA from 02/24/2011 to 05/05/2011. On 05/06/2011 tofacitinib was decreased to 5 mg BID due to asymptomatic transaminitis initially documented on 04/19/2011 (see Figure 21). Methotrexate was stopped on 05/05/2011 and the subject was withdrawn from the study, and study drug was permanently discontinued. On (b) (6), the subject was hospitalized due to jaundice and high transaminase levels (see Figure 21). Starting on (b) (6), the subject was treated with prednisolone 60 mg/day and azathioprine 100 mg/day and reportedly experienced a clinical and laboratory response. On (b) (6) she was discharged from the hospital recovering.

Figure 21. Time Course of Liver Test for Patient 1024-15081007



Source: Liver Consult, Figure courtesy of Dr. John Senior

Additional studies included:

- On (b) (6)
  - Fine needle biopsy of the liver (interpreted as non-specific, but consistent with an idiosyncratic drug-related hepatocellular injury).
  - Anti-hepatitis C virus (HCV) antibody (AB) reactive at 3.41 index, and ribonucleic acid (RNA) HCV was non-reactive/negative.
- On (b) (6)
  - Antinuclear antibody (ANA) negative,
  - Liver kidney microsomal (LKM) antibodies negative,
  - Hepatitis B core antibody was positive but Hepatitis B surface antigen was negative.

The event was initially classified as autoimmune hepatitis based on clinical picture, course of disease, and reportedly very good response to immunosuppression with high doses systemic corticosteroids and azathioprine.

Internal review of the case by the Hepatology consultant Dr. John Senior concluded that this acute, serious hepatitis may have been caused by idiosyncratic response of this woman to tofacitinib, as it was temporally related to

> treatment. Although her course was not primarily cholestatic, but rather hepatocellular in development, it included three hospitalizations, serious jaundice and other expressions of whole-organ liver dysfunction, clinical illness, and a liver biopsy. These criteria do fulfill the requirements for a "Hy's Law" case. Further follow up on the case is requested from the Sponsor but is not available at the time of this review.
>
> Based on the conclusions from the internal review of the case, inclusion of this Hy's law case in labeling and communication to health care providers and patients is warranted and monitoring of liver tests is justified. Further, hepatotoxicity should be one of the safety parameters for monitoring in a long-term safety outcomes study as a post-marketing requirement.

In summary, the relatively low incidence of significant liver test abnormalities seen in tofacitinib RA development and the fact that no cases of fulminant hepatic failure or cases requiring liver transplantation were reported is somewhat reassuring. However, as discussed above, one case meeting Hy's criteria in a patient treated with the 10 mg BID dose, was observed in approximately 5000 patients in the tofacitinib global RA program as of the 120-days safety update. Therefore, using the estimate of severe drug-induced liver injury as occurring at $1/10^{th}$ the rate of Hy's Law cases, 1 case of severe liver injury might be expected in 50,000 patients treated with tofacitinib. This by itself may not be a sufficient justification to require liver test monitoring more frequently than routinely done in the clinical practice for the target patient population, which is generally every 3 to 6 months. However, if liver test abnormalities are noted, these patients should be monitored closely and considered for alternative RA treatment. Health care providers should be watchful for early evidence of liver injury, investigate promptly the possible cause, and interrupt drug administration until alternate cause are found the be very likely.

7.4.2.5 Serum Creatine Phosphokinase

Serum creatine phosphokinase (CPK) was routinely monitored in all Phase 3 studies and open-label study 1024. Treatment with tofacitinib resulted in dose-dependent increases in mean CK levels from a baseline within the first 6 months (increases of about 40-60 IU/L) and remained relatively stable thereafter. The mean values remained within normal limits. Similar increases were seen in the LTE study 1024. There was no change in the mean CPK levels for placebo patients over the 6 months of therapy, whereas the adalimumab group mean CPK levels increased by about 20 IU/L.

Overall, a higher proportion of tofacitinib-treated patients developed AEs related to CPK increases rated as mild or moderate, and only a few resulted in permanent discontinuation (2 patients at 10 mg BID dose in Phase 3 studies and in LTE studies 3 patients at 5 mg and 1 patient at 10 mg BID dose).

Rhabdomyolysis in RA clinical development:

One SAE of rhabdomyolysis (highest CPK level was 2942) occurred in the context of a critically ill patient (1046-10091004) with severe pulmonary hypertension, congestive heart failure, and respiratory failure who died. The cause of death was adjudicated as non-cardiovascular event of infection by the CV adjudication committee. No SAE of rhabdomyolysis were reported in the LTE studies.

Myopathy in RA clinical development:
Two SAEs of myopathy were reported in tofacitinib RA development program: one in a patient with CMV hepatitis (1024-11741006) and normal CPK levels; and one in patient who was diagnosed with polymyositis, likely present prior to enrollment in a Phase 2 study (1040-10061009). A total of 8 patients in Phase 3 and 10 patients in LTE studies, had AE indentified by SMQ (standard MedDRA Query) of rhabdomyolysis/myopathy with concomitant elevation of CPK ≥5 x ULN. Of these patients, only one discontinued (1024-11921005) diagnosed subsequently with biopsy-proven polymyositis.

In summary, it did not appear that elevations of CPK related to tofacitinib-treatment resulted in an increased risk of myopathic adverse events.

7.4.3 Vital Signs

Blood Pressure

Baseline mean systolic blood pressure (BP) was comparable in all treatment groups. Changes from baseline in BP were small in all treatment groups during the first 3 months of treatment. However, a higher proportion of patients in tofacitinib-treated groups compared to placebo, experienced hypertension, new onset hypertension, elevations of 10 mmHg or more, and discontinuation due to hypertension (Table 73). Eleven tofacitinib-treated patients experienced SAE of hypertension or were discontinued from the studies due to hypertension (Table 74). Factors predisposing to hypertension were >65 years of age, hypertension and use of antihypertensive medications at baseline.

There were no significant differences in diastolic BP (DBP) elevations between tofacitinib-, placebo-, and adalimumab-treated groups.

Table 73. Effects of Tofacitinib on Blood Pressure

Effects of Tofacitinib on Blood Pressure					
	PBO	ADA	CP 5 mg BID	CP 10 mg BID	CP, All doses
Phase 3 studies (0-3 months)					
Enrolled, n	681	204	1216	1214	3030
Patients with confirmed hypertension, n (%)	92 (14)	33 (17)	214 (18)	212 (18)	426 (18)
Patients with SBP > 10 mmHg, n (%)	36 (5)	14 (7)	84 (7)	79 (7)	163 (7)
Patients with SBP > 15 mmHg, n (%)	31 (4.6)	8 (3.9)	59 (4.9)	64 (5.3)	123 (5.1)
Patients with AE hypertension, n (%)	10 (1.5)	0	25 (2.1)	35 (2.9)	60 (2.0)
Discontinuations due to hypertension AE, n (%)	0	0	1 (0.1)	1 (0.1)	2 (0.1)
LTE studies (as of September 29, 2011)					
Enrolled, n	-	-	1370	2145	3515
Exposure for event, patient-years	-	-	2703	1662	4365
Patients with AE hypertension, n (incidence rate, per 100 PY)	-	-	125 (4.6)	80 (4.8)	205 (4.7)
Discontinuations due to hypertension AE, n (%)	-	-	1 (<0.1)	1 (<0.1)	2 (<0.1)

Source: Integrated Summary of Safety, adapted form Tables 156-158; 120 Day Safety Update, Adapted from Table 48
*-CP All Doses group represents data for patients as treated and includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; the rest of the dose groups are pooled as randomized.

Table 74. Listing of Serious Adverse Events and Discontinuations Due to Adverse Events of Hypertension

Listing of Serious Adverse Events and Discontinuations Due to Adverse Events of Hypertension				
	AE Preferred Term	Day of Event	Outcome	SAE
Phase 3 studies				
1032-11231003	Hypertensive crisis	113	Resolved	Yes
1044-11621008	BP increased	69	Ongoing	No
1064-10051009	Hypertension	9	Resolved	Yes
1064-10371003	BP increased	135	Ongoing	No
LTE studies				
1024-10271003	Worsening hypertension	247	Fatal	Yes
1024-10451015	Hypertension	808	Resolved	Yes
1024-11251012	Accelerated hypertension	715	Resolved	Yes
1024-11641001	Hypertensive crisis	471	Resolved	Yes
1024-11651007	Hypertensive crisis	5 events	Resolved	Yes
1024-10431018	Hypertension	382	Ongoing	Yes
1024-11571010	Hypertensive crisis	2 events	Ongoing	Yes

Source: Integrated Summary of Safety, Adapted from Table 157

Weight

In the Phase 3 studies, small dose-dependent increases in mean weight over time were observed in tofacitinib treatment patients compared with placebo; smaller increases in weight were also observed in the adalimumab group, as described in Table 75. The clinical significance of these findings is unclear, as these changes were small and

patients had a concomitant dose-dependent improvement in physical function as measured by HAQ-DI.

Table 75. Mean Change from Baseline in Weight (kg) in Phase 3 RA Studies

Mean Change from Baseline in Weight (kg) in Phase 3 Studies					
	PBO	ADA	CP 5 mg BID	CP 10 mg BID	CP, All doses
0-6 months	**177**	**186**	**1270**	**1259**	**2529**
Mean change, kg (SD)	0.5 (2.4)	0.8 (2.9)	1.4 (1.2)	1.7 (3.1)	1.6 (3.1)
0-12 months	**N.A.**	**160**	**845**	**834**	**1679**
Mean change, kg (SD)	-	0.6 (3.6)	1.9 (3.9)	2.2 (4.0)	2.0 (3.9)

Source: Integrated Summary of Safety, adapted form Table 233

Similarly small dose-dependent increases in body mass index (BMI) were also reported. At Month 6, mean increases in BMI were 0.5 and 0.7 in the CP5 and CP10 groups, respectively, compared with 0.2 for placebo and 0.3 for adalimumab. By Month 12, mean BMI in the CP groups had increased by 0.7 and 0.9 in the CP5 and CP10 groups, respectively. This clinical significance of these observations is currently unclear, as this was not mirrored by increased incidence of cardiovascular adverse events as discussed in the subsection on Cardiovascular Disorders.

These findings may reflect a dose-dependent improvement on systemic inflammation resulting in a decreased catabolic state, previously driven by proinflammatory cytokines.

7.4.4 Electrocardiograms (ECGs)

ECG Findings and QTc study

A thorough QTc study (A3921028) showed that administration of a single, supra-therapeutic dose of CP-690,550 (100 mg) was not associated with QTc prolongation in healthy volunteers, which is consistent with the low number of cardiac arrhythmias reported in the RA development program.

7.4.5 Special Safety Studies/Clinical Trials

To investigate the observed dose-dependent increases in serum creatinine levels associated with tofacitinib administration, the Sponsor conducted a 14-day repeat dose (15 mg BID) study A3921033, in healthy volunteers and reported that tofacitinib administration did not affect renal function (measured GFR using iohexol serum clearance), renal plasma flow, or 24-hour urinary creatinine clearance for the short study duration. This study is further discussed in Section 7.4.2.1 Serum Creatinine Elevations and Renal Disorders above.

7.4.6 Immunogenicity

Use of tofacitinib, as an oral small molecule, is not expected to be associated with induction of immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The integrated safety analyses of major safety events are displayed as incidence rate per 100 patient-years of exposure by treatment group as shown in Table 76 and Figure 22 allowing for examination of potential differences in the safety profiles of tofacitinib 5 mg and 10 mg BID. With respect to deaths, AEs leading to discontinuation and major cardiovascular adverse events (MACE) these two treatment groups were similar and comparable to placebo and adalimumab control groups.

In contrast, the rates of malignancy (excluding non-melanoma skin cancer, NMSC) were higher in tofacitinib 10 mg BID dose compared with the lower dose of 5 mg BID and adalimumab group suggesting dose-dependency of malignancy. In addition, the incidence rates increased in a dose-dependent fashion in the long-term studies.

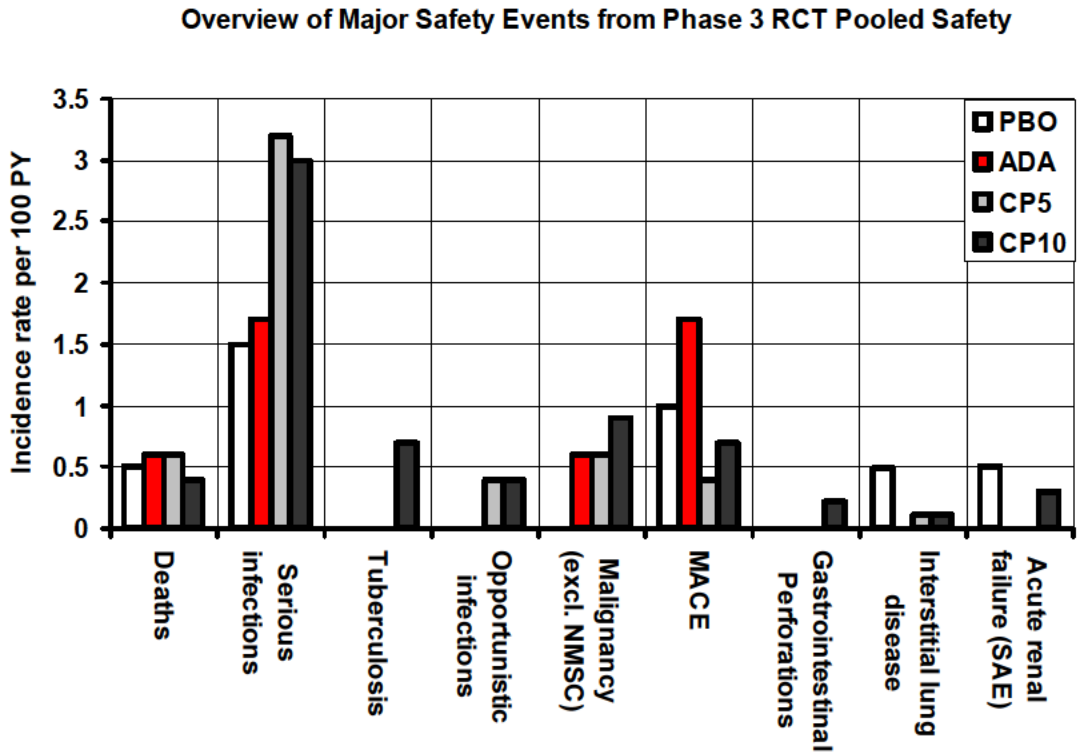
With regard to serious infections and opportunistic infections, the incidence rates were comparable between the two tofacitinib doses in the controlled studies, however, the incidence increased in a dose-dependent fashion in the long-term extension studies, which is consistent with dose-dependent cumulative immunosuppression which may not be evident during the limited controlled period.

Table 76. Dose-Dependency in Incidence Rates (per 100 PY) of Major Safety Events in RA Development, by Treatment Group

Incidence Rates (per 100 PY) of Major Safety Events in RA Development, by Treatment Group						
	RCT Pooled Safety				LTE Studies	
	PBO	ADA	CP5	CP10	CP5	CP10
Deaths (within 30 days of last dose)	0.5	0.6	0.6	0.4	0.4	0.2
Serious Infections	1.5	1.7	3.2	3.0	2.3	4.9
Tuberculosis	0	0	0	0.7	0.1	0.1
Opportunistic infections	0	0	0.4	0.4	0.3	0.6
Malignancy (excluding NMSC)	0	0.6	0.6	0.9	1.0	1.4
AEs leading to withdrawal	12.4	12.3	10.6	10.9	6.7	8.5
MACE	1.0	1.7	0.4	0.7	0.2	0.2

Source: Summary of Clinical Safety, 120 Day Safety Update (data cut-off September 29, 2011), Tables 13, 19, 22, 23, 35; MACE-major adverse cardiovascular events; NMSC-non-melanoma skin cancer

Figure 22. Dose-Dependency in Incidence Rates (per 100 PY) of Major Safety Events in RA Development, by Treatment Group



These data indicate dose-dependency of malignancy (excluding NMSC) during both the controlled Phase 3 studies and long-term extensions studies. A clear dose-dependency is also observed for tuberculosis during the Phase 3 studies. The data suggest dose-dependent increases in the incidence of serious infections, including opportunistic infections during the long-term extension studies, based on exposure-adjusted incidence rates. Importantly, while this is consistent with the mechanism of action and the profile of a potent immunosuppressive drug, this dose-dependency that increased over time in the long-term extension studies appears unique for malignancy and serious infections and is of particular concern.

Laboratory data provides further evidence of dose-dependent changes associated with tofacitinib use. This was evident in Phase 2 dose-ranging studies as discussed in Section 4.4.4. Dose Selection and in all Phase 3 studies as discussed in Section Laboratory Findings. While most of these laboratory changes did not translate in clinically significant adverse events, tofacitinib-induced lymphopenia was associated with infections.

7.5.2 Time Dependency for Adverse Events

As shown in Table 77, solid and hematologic malignancies, serious infections, opportunistic infections and tuberculosis, occurred later in the course of tofacitinib treatment, on average after about one year.

Table 77. Duration of Exposure to Tofacitinib Prior to Diagnosis of Select Major Adverse Events

Duration of Exposure to Tofacitinib Prior to Diagnosis of Select Major Adverse Events		
	Median, days	Mean, days
Malignancy (excl NMSC)	379	454
Lymphoproliferative disorder	365	409
SIE	286	346
Opportunistic infections	234	290
TB	298	348

As discussed in the respective sections above, the estimated exposure-adjusted incidence rates of solid and hematologic malignancies and serious infections, also increased in the long-term extension studies. Further analyses to assess the non-cumulative rate of adverse events by 6-month periods identified two major adverse events of interest that increased over time with long-term tofacitinib use:

- Malignancy (excluding NMSC) as shown in Table 38 and Figure 12 and
- Serious infections as shown in Table 50 and Figure 13.

These trends appeared to be unique to malignancy and serious infections and suggest an increased risk of these events attributable to long-term exposure to tofacitinib.

However, based on these analyses, inclusion of solid and hematologic malignancy in addition to serious infections in the boxed warning section on the product label is warranted.

7.5.3 Drug-Demographic Interactions

Adverse events, SAEs and AEs leading to discontinuation, by age, gender, and race are summarized in Table 78, Table 79, and Table 80 respectively.

Tofacitinib use was associated with SAEs and AEs leading to discontinuation, that were somewhat higher in patients older than 65 years of age, as compared with younger patients which may reflect the higher rate of comorbidities in the older population. No consistent gender or racial differences for AEs, SAEs and AEs leading to discontinuation were observed throughout the different treatment periods.

Analyses of serious infections by age and gender are presented in Table 52 above, and indicate that age ≥65 years and male gender confer a higher risk of serious infections.

Asian patients had a higher incidence of H. zoster infections, Pneumocystis jiroveci pneumonia, and gastric cancer, compared with other races, potentially reflecting a higher background rate of some of these events in Japanese patients. Due to the small number of these events however, it is difficult to draw definitive conclusions on their association with tofacitinib use in Asian race.

Table 78. Overview of Adverse Events in Tofacitinib RA Development by Age

Overview of Adverse Events in Tofacitinib RA Development by Age				
	PBO	**ADA**	**CP5 mg BID**	**CP10 mg BID**
0-3 months, n (%)	**681**	**204**	**1216**	**1214**
AEs				
< 65 years	312 (54)	87 (50)	520 (51)	540 (52)
≥ 65 years	51 (51)	18 (60)	104 (55)	113 (61)
SAEs				
< 65 years	17 (3)	3 (2)	23 (2)	26 (3)
≥ 65 years	8 (8)	2 (7)	13 (7)	9 (5)
AEs leading to discontinuation				
< 65 years	19 (3)	8 (5)	41 (4)	34 (3)
≥ 65 years	3 (3)	2 (7)	11 (6)	15 (8)
3-6 months, n (%)	**221**	**204**	**1451**	**1439**
AEs				
< 65 years	52 (28)	55 (32)	490 (40)	461 (38)
≥ 65 years	6 (17)	13 (43)	89 (39)	95 (45)
SAEs				
< 65 years	7 (4)	5 (3)	35 (3)	27 (2)
≥ 65 years	0	1 (3)	12 (5)	10 (5)
AEs leading to discontinuation				
< 65 years	3 (2)	8 (5)	30 (3)	33 (3)
≥ 65 years	1 (3)	1 (3)	6 (3)	12 (6)
> 6 months, n (%)	**-**	**204**	**1056**	**1046**
AEs				
< 65 years	N.A.	70 (40)	383 (43)	406 (45)
≥ 65 years	N.A.	13 (43)	62 (38)	72 (49)
SAEs				
< 65 years	N.A.	5 (3)	26 (3)	24 (3)
≥ 65 years	N.A.	2 (7)	8 (5)	8 (5)
AEs leading to discontinuation				
< 65 years	N.A.	4 (2)	13 (2)	17 (2)
≥ 65 years	N.A.	0	5 (3)	7 (5)

Source: Integrated Summary of Safety, adapted from Table 235

Table 79. Overview of Adverse Events in Tofacitinib RA Development by Gender

Overview of Adverse Events in Tofacitinib RA Development by Gender				
	PBO	**ADA**	**CP5 mg BID**	**CP10 mg BID**
0-3 months, n (%)	**681**	**204**	**1216**	**1214**
AEs				
Males	60 (47)	17 (41)	78 (41)	106 (58)
Females	303 (55)	88 (54)	546 (53)	547 (53)
SAEs				
Males	4 (3)	3 (7)	6 (3)	5 (3)
Females	21 (4)	2 (1)	30 (3)	30 (3)
AEs leading to discontinuation				
Males	4 (3)	2 (5)	6 (3)	8 (4)
Females	18 (3)	8 (5)	46 (5)	41 (4)
3-6 months, n (%)	**221**	**204**	**1451**	**1439**
AEs				
Males	7 (16)	10 (24)	74 (32)	80 (36)
Females	51 (29)	58 (34)	505 (42)	476 (39)
SAEs				
Males	0	1 (2)	5 (2)	12 (5)
Females	7 (4)	5 (3)	42 (3)	25 (2)
AEs leading to discontinuation				
Males	0	2 (5)	3 (1)	5 (2)
Females	4 (2)	7 (4)	33 (3)	40 (3)
> 6 months, n (%)	**-**	**204**	**1056**	**1046**
AEs				
Males	N.A.	20 (48)	59 (33)	86 (49)
Females	N.A.	63 (39)	386 (44)	392 (45)
SAEs				
Males	N.A.	2 (5)	7 (4)	10 (6)
Females	N.A.	5 (3)	27 (3)	22 (3)
AEs leading to discontinuation				
Males	N.A.	2 (5)	1 (1)	5 (3)
Females	N.A.	2 (1)	17 (2)	19 (2)

Source: Integrated Summary of Safety, adapted from Table 236

Table 80. Overview of Adverse Events in Tofacitinib RA Development by Race

Overview of Adverse Events in Tofacitinib RA Development by Race				
	PBO	**ADA**	**CP5 mg BID**	**CP10 mg BID**
0-3 months, n (%)	**681**	**204**	**1216**	**1214**
AEs				
White	234 (53)	74 (50)	373 (51)	401 (54)
Black	17 (71)	2 (67)	33 (73)	24 (69)
Asian	86 (52)	17 (59)	160 (49)	165 (53)
Other	26 (50)	12 (50)	58 (54)	63 (51)
SAEs				
White	18 (4)	3 (2)	22 (3)	21 (3)
Black	0	0	2 (4)	0
Asian	5 (3)	2 (7)	9 (3)	10 (3)
Other	2 (4)	0	3 (3)	4 (3)
AEs leading to discontinuation				
White	15 (3)	7 (5)	29 (4)	29 (4)
Black	1 (4)	1 (33)	3 (7)	0
Asian	5 (3)	2 (7)	19 (6)	13 (4)
Other	1 (2)	0	1 (1)	7 (6)
3-6 months, n (%)	**221**	**204**	**1451**	**1439**
AEs				
White	29 (25)	50 (34)	362 (40)	355 (40)
Black	1 (20)	1 (33)	24 (47)	24 (50)
Asian	23 (30)	10 (35)	145 (39)	124 (35)
Other	5 (23)	7 (30)	48 (40)	53 (38)
SAEs				
White	3 (3)	2 (1)	28 (3)	22 (3)
Black	0	0	2 (4)	2 (4)
Asian	3 (4)	3 (10)	14 (4)	9 (3)
Other	1 (5)	1 (4)	3 (3)	4 (3)
AEs leading to discontinuation				
White	1 (1)	4 (3)	20 (2)	27 (3)
Black	0	0	1 (2)	2 (4)
Asian	3 (4)	3 (10)	13 (4)	12 (3)
Other	0	2 (8)	2 (2)	4 (3)
> 6 months, n (%)	**-**	**204**	**1056**	**1046**
AEs				
White	N.A.	66 (45)	262 (44)	272 (47)
Black	N.A.	1 (33)	15 (58)	14 (61)
Asian	N.A.	10 (35)	137 (40)	148 (43)
Other	N.A.	6 (25)	31 (37)	44 (44)
SAEs				
White	N.A.	5 (3)	23 (4)	18 (3)
Black	N.A.	0	3 (12)	0
Asian	N.A.	2 (7)	7 (2)	11 (3)
Other	N.A.	0	1 (1)	3 (3)
AEs leading to discontinuation				
White	N.A.	3 (2)	6 (1)	9 (2)
Black	N.A.	0	1 (4)	1 (4)
Asian	N.A.	1 (3)	11 (3)	12 (4)
Other	N.A.	0	0	2 (2)

Source: Integrated Summary of Safety, adapted from Table 237

7.5.4 Drug-Disease Interactions

Potential drug-disease interactions were explored for patients with co-morbidities that may affect the metabolism and extraction of tofacitinib as descried below:

Renal Impairment

- Mean percentage change in AUC (90%CI), for subjects with mild, moderate, and severe renal impairment compared to normal renal function were respectively: 41% (-5%, 109%), 71% (14%, 157%), and 156% (69%, 287%). Mean percentage changes in Cmax (90% CI) for these cases were respectively: 1% (-31%, 49%), 2% (-31%, 52%), and 21% (-19%, 81%). These data indicate that dose adjustment/reduction is indicated for treatment of patients with moderate and severe renal impairment.
- A 14 days study was conducted to assess the impact of tofacitinib on renal function by measuring the glomerular filtration rate (iohexol serum clearance), effective renal plasma flow (p-aminohippuric acid (PAH) clearance), and creatinine clearance (CLCr, based on 24-hour urine collection) on day 1 and day 15. No significant change in iohexol serum clearance, PAH clearance, and CLCr were observed with mean change of less than 10% for comparison of Day 15 vs. Day 1.

Hepatic Impairment

- Mean percentage change in AUC (90%CI) for subjects with mild and moderate hepatic impairment vs. normal hepatic function were respectively: 3% (-22%, 36%) and 65% (25%, 117%). Mean fold change in C_{max} (90% CI) for these cases were respectively: -1% (-25%, 32%) and 49% (12%, 97%).
- A significant portion of tofacitinib is cleared through hepatic metabolism; therefore, tofacitinib was not evaluated in patients with severe hepatic impairment because potential for high systemic exposures may pose the risk of immunosuppression in patients who are already at risk of infection from their hepatic disease.
- These data indicate that dose adjustment/reduction is indicated for treatment of patients with moderate hepatic renal impairment.

Based on these observations dose reductions in patients with moderate and severe renal impairment and moderate liver impairment are justified and warrant inclusion in labeling.

7.5.5 Drug-Drug Interactions

Effect of co-administered drugs on tofacitinib exposure

- Tofacitinib co-administration with a strong CYP3A inhibitor, ketoconazole, increased the mean tofacitinib AUC (90%CI) by 103% (91%, 116%) and C_{max} by 16% (5%, 29%).

- Co-administration with a moderate CYP3A4 and strong CYP2C19 inhibitor, fluconazole, increased mean tofacitinib AUC (90%CI) by 79% (64%, 96%) and C_{max} by 27% (12%, 44%).
- Co-administration with a strong CYP3A inducer, rifampin, resulted in substantial decreases in mean tofacitinib AUC (90%CI) by -84% (-86%, -82%) and in C_{max} by -74% (-77%, -69%).
- Co-administration with tacrolimus, a CYP3A substrate with narrow therapeutic index, increased mean tofacitinib AUC (90%CI) by 21% (13%, 30%) and decreased C_{max} by -9% (-17%, -1%).
- Co-administration with cyclosporine, a CYP3A substrate with narrow therapeutic index and also an inhibitor of P-gp, BCRP, OATP1B1, and OATP1B3, increased mean tofacitinib AUC (90%CI) by 73% (62%, 85%) and decreased C_{max} by -17% (-29%, -3%).
- Co-administration with methotrexate, had no significant effect on mean tofacitinib AUC and C_{max}

Effect of tofacitinib on exposure of co-administered drugs

- Concomitant use of oral contraceptives (OC) with tofacitinib did not have any significant effect on AUC and C_{max} of ethinyloestradiol and levonorgestrel
- Concomitant use with tofacitinib had no substantial effect on AUC and C_{max} of midazolam, a sensitive CYP3A substrate
- Concomitant use of tofacitinib and methotrexate, decreased mean methotrexate AUC (90% CI) by -10% (-23%, 4%) and C_{max} by -13% (-24%, 0%)

Based on these considerations there are clinically relevant drug-drug interactions which are important to be included in the labeling.

7.6 Additional Safety Evaluations

Safety evaluations have been covered in the other subsections of Section 7 Review of Safety.

7.6.1 Human Carcinogenicity

Safety data on malignancy and neoplasms is discussed in detail in Section 7.3.2.1 Malignancy above.

7.6.2 Human Reproduction and Pregnancy Data

As of the data cut-off for the 120 day safety update, a total of 23 cases of exposure in utero were reported during RA studies, 8 were in patients receiving CP5 (7 maternal exposures), 6 were in patients receiving CP10 (5 maternal), 1 was in a patient receiving CP15 (maternal), 1 was in a patient receiving placebo (maternal), 1 was in a patient

receiving adalimumab (paternal), and 2 were in patients whose treatment is still blinded (1 maternal).

In the 17 pregnancies where the outcome was known, 5 were ongoing, 5 had a full—term normal newborn, and 1 ended with a pre-term normal birth, 2 had elective terminations, and 4 had spontaneous abortions.

This small cohort of patients is not sufficient to draw definitive conclusions about the possible effect of tofacitinib on human reproduction and pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Tofacitinib has not been tested in pediatric population.

This submission for the adult RA indication invokes a requirement for a pediatric assessment in polyarticular juvenile idiopathic arthritis (pJIA) patients, as per the Pediatric Research Equity Act (PREA). In this submission, the Sponsor has provided a request for deferral of studies in pJIA patients 2-17, and a waiver for the 0-2 year old age group, providing the rationale that JIA is extremely rare in very young children. In

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The requested deferral of studies in pJIA patients 2-17 years old, and a waiver for the 0-2 year old age group, and the proposed pediatric plan have not been reviewed by the Pediatric Review Committee (PeRC) at the time of this review. However, similar requests have been granted for other immunosuppressive therapeutics, because for ethical reasons, it is desirable to have an adequate experience with the safety profile of a treatment in adults before proceeding with extensive studies in children. The proposed pediatric plan is consistent with the pediatric development for other products and would be generally acceptable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Sponsor has not reported cases of drug abuse or dependence, withdrawal and rebound or other information relevant to the potential for drug abuse in these studies.

Overdose was defined as an adverse event and reported in six patients (3 in the CP5 group, 2 in the CP10 group, and 1 in the placebo to CP10 sequence). No AEs of overdose were serious. In 5 of the patients, the overdoses were attributed to patient forgetfulness or misunderstanding the dosing instructions. One case was attributed to the patient lacking understanding of the role of tofacitinib in RA therapy and was taking it as needed “to help with her tiredness”.

7.7 Additional Submissions / Safety Issues

120-Day Safety Update (Submission 0005, February 16, 2012)

This safety update provided new safety data from tofacitinib studies obtained between the date of the initial submission data cutoff (March 29, 2011) and the safety update data cutoff date of September 29, 2011. New data for events of special interest (as defined in the initial submission and below) are presented and summarized, new serious adverse events are tabulated and incidence rates of events of special interest have been updated with cumulative data. The dataset for this safety update includes the same patients in Phase 2 and Phase 3 studies in the initial submission.

Integrated data from the 2 ongoing open-label LTE studies have been updated and now include 3515 patients, representing an additional 288 patients who have been enrolled in these studies and 1291 additional patient-years of drug exposure since the initial submission data cutoff date of 29 March 2011. The 120-day safety update and additional information from amendments to the original NDA submission have been incorporated into the applicable safety sections of this review.

8 Postmarket Experience

To date tofacitinib it has not been approved anywhere in the world and no post-marketing information is available.

9 Appendices

9.1 Literature Review/References

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USPI Jakafi (ruxolitinib), November 2011

9.2 Labeling Recommendations

9.2.1 Trade Name

The Sponsor has originally proposed a different trade name, (b) (4) which was found unacceptable (b) (4)

(b) (4)

The currently proposed trade name for tofacitinib, Xeljanz, was reviewed by the Division of Medication Error and Prevention and Analysis (DMEPA) and was determined to be acceptable.

9.2.2 Suggested Revisions to Proposed Labeling

Box Warning Section:

I recommend the following major safety-related revisions:

- (b) (4)

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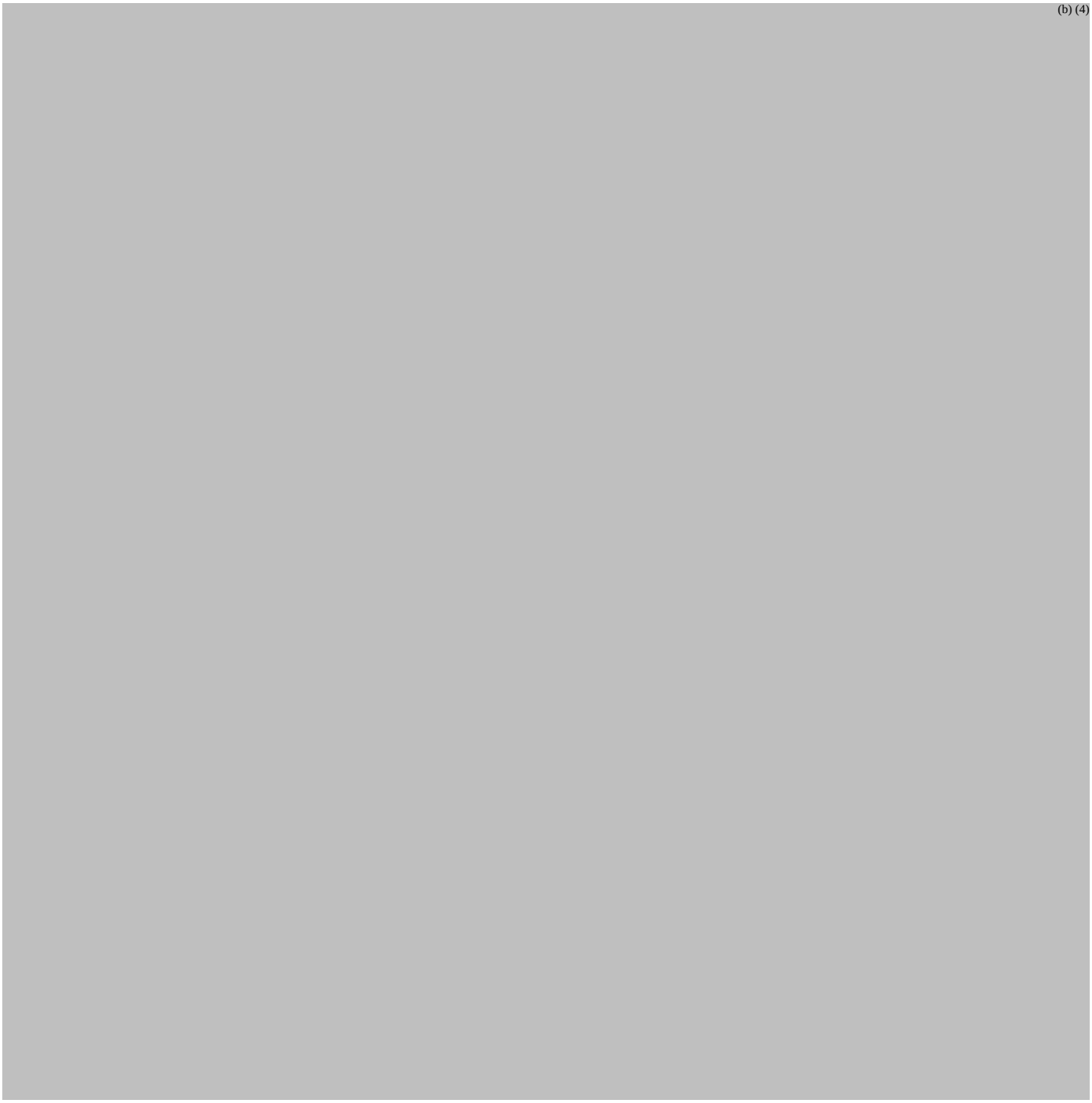
(b) (4)



9.3 Advisory Committee Meeting

An Arthritis Advisory Committee meeting was convened on May 09, 2012 to discuss this NDA. The following section summarizes the Committee's discussion on the topics and voting questions:

Questions to the Committee:

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

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

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

   a. Address the following safety issues:

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

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

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

      Committee Discussion: *Given the overall safety profile of the 5 mg and 10 mg dose, the committee agreed that the safety data are more favorable for the 5 mg dose. The committee agreed that there was a concern for over-immunosuppression and*

malignancy with the 10 mg dose, especially if given with other immunologics. However, the committee agreed that the 10mg dose might be a viable option for refractory patients who are willing to accept the risk of treatment.

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

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

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

Vote: Yes= 2 No = 8 Abstain = 0

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

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

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

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

Vote: Yes= 10 No = 0 Abstain = 0

Committee Discussion: *The committee unanimously agreed that the data provide substantial evidence of the efficacy of tofacitinib for the treatment of moderately to severely*

active rheumatoid arthritis in patients who have had inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). The committee agreed that the efficacy of tofacitinib was compelling across all five studies and was demonstrated to be at least as good as the comparators.

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

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

Please see the transcript for details of the committee discussion.

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

Vote: Yes= 7 No = 2 Abstain = 1

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

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

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

Please see the transcript for details of the committee discussion.

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

Vote: Yes= 8 No = 2 Abstain = 0

Committee Discussion: *The majority of the committee agreed that the efficacy and safety data provide substantial evidence to support the approval of tofacitinib for the*

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

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

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

9.4 Individual Study Reports

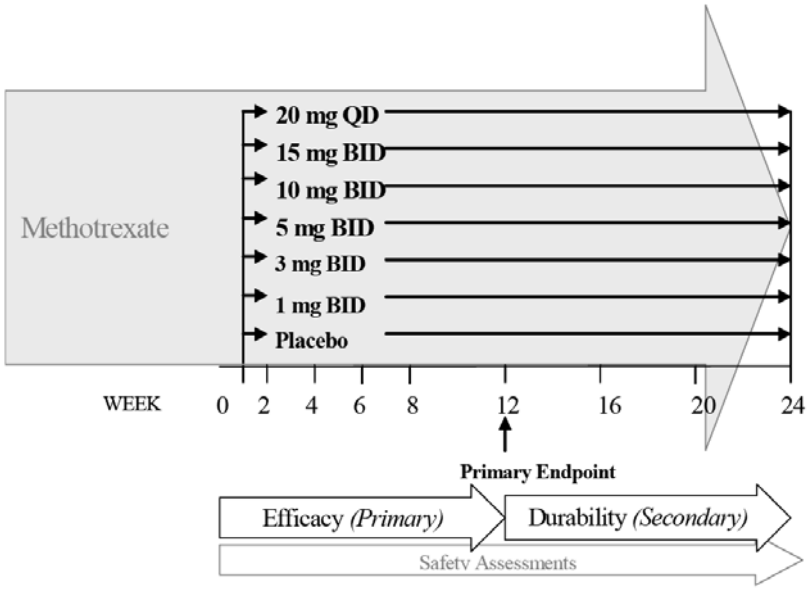
9.4.1 Study A3921025 (Phase 2 Dose-Ranging)

Study Protocol

Overall Study Design

This was a Phase 2b, randomized, double-blind, placebo-controlled, parallel group study. It was planned to randomize 483 subjects with RA, who had had an inadequate response to MTX alone, in a 1:1:1:1:1:1:1 ratio to receive 1 of 6 dose regimens of CP-690,550 (20 mg QD; 15 mg, 10 mg, 5 mg, 3 mg and 1 mg BID) or placebo tablets.

Figure 23. Study 1025 Design Schema



Source: CSR A3921025

Subjects randomized to the CP-690,550 3 mg BID, 1 mg BID, 20 mg QD and placebo groups, who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts over baseline at the Week 12 visit, were labeled "non-responders" and automatically reassigned, for the remaining 12 weeks of their study participation, to the dose of 5 mg BID (a dose already demonstrated to be efficacious in Study A3921019). Subjects randomized to the 15, 10 and 5 mg BID groups who failed to achieve a minimum improvement remained on their originally assigned dose. No other dose adjustments of CP-690,550 were allowed. Subjects, investigators and Pfizer study personnel were blinded to reassignment.

During the study subjects remained on stable background arthritis therapy, which had to include MTX (supplemented with folic acid).

Inclusion Criteria

- Subjects had to be at least 18 years of age.
- Sexually active woman of childbearing potential and any male partner were required to simultaneously use 2 effective contraceptive methods.
- Non-vasectomized men had to be willing to abstain from sexual intercourse or willing to use a condom in addition to having their female partner use another form of contraception such as an intrauterine device, barrier method with spermicide, oral contraceptive, injectable progesterone, sub-dermal implant, or a tubal ligation, if the woman could become pregnant from the time of the first dose of study drug until completion of follow-up procedures.
- The subject had a diagnosis of RA based upon the American College of Rheumatology (ACR; formerly American Rheumatism Association) 1987 Revised Criteria8, i.e., fulfilling at least 4 of the following 7 criteria for at least 6 consecutive months preceding randomization:
    - morning stiffness in and around any joint for more than 1 hour;
    - soft tissue swelling of 3 or more joint areas;
    - swelling of the proximal interphalangeal (PIP), metacarpophalangeal (MCP) or wrist joints;
    - symmetrical joint swelling;
    - rheumatoid nodules;
    - serum rheumatoid factor positive;
    - radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.
- The subject had active disease at both screening and baseline visits, as defined by both:
    - ≥6 joints tender or painful on motion, and
    - ≥6 joints swollen;

  and fulfilled 1 of the following 2 criteria at screening:
    - erythrocyte sedimentation rate (ESR) (Westergren method) >ULN in the local laboratory;
    - C-reactive protein (CRP) >7 mg/L in the central laboratory
- The subject met ACR 1991 Revised Criteria for Global Functional Status in RA, Class I, II or III.
- Subjects had been taking oral or parenteral MTX continuously for at least 4 months and on a stable dosage of 7.5 to 25 mg weekly for at least 6 weeks prior to first dose of study drug. Stable weekly doses less than 15 mg were allowed only in the presence of documented intolerance to or toxicity from higher doses. Subjects must have an inadequate clinical response to MTX, defined, for the purpose of this study, by the Investigator's and subject's opinions that the subject did not experience adequate benefit from MTX plus the presence of sufficient residual disease activity to meet the entry criteria.

- Folic acid had been dosed per local standards of care stably for at least 4 weeks before first dose of study drug.
- Subjects receiving non-prohibited concomitant medications for any reason must have been on a stable regimen, defined as not starting a new drug or changing dosage within 7 days or 5 half lives (whichever was longer) prior to first dose of study drug.
- Subjects who had received the following treatment regimens were eligible, providing defined discontinuation periods were observed. Note that none of these therapies should have been discontinued by a subject to allow participation in this study if they were currently effective and tolerated.
    - Biologics - anakinra (Kineret.), etanercept (Enbrel.);
    - DMARDS-leflunomide (Arava.), auranofin (oral gold), injectable gold (aurothioglucose or aurothiomalate), sulfasalazine, and d-penicillamine, minocycline, antimalarials (chloroquine and hydroxychloroquine);
    - Immunosuppressive/Immunomodulatory therapies - azathioprine, cyclosporine, and staphylococcal protein A immuno-absorbant pheresis columns (such as PROSORBA® device/column);
    - NSAIDs - any experimental non selective or selective NSAID (COX 2 inhibitor) within a clinical study;
    - Other - herbal medications, immunization with any live virus vaccination (eg, FluMist.), intra articular, intramuscular, or intravenous corticosteroids;
    - Infliximab (Remicade.), adalimumab (Humira.);
    - Abatacept (Orencia.);
    - Any experimental therapy for RA other than an experimental non selective or selective NSAID.

Exclusion Criteria

- Subjects with evidence of hematopoietic disorders or evidence of hemoglobin levels <9.0 g/dL or hematocrit <30 % at screening or within the 3 months prior to first dose of study drug.
- An absolute white blood cell (WBC) count of $<3.0 \times 10^9$/L ($<3000/mm^3$) or absolute neutrophil count of $<1.2 \times 10^9$/L ($<1200/mm^3$) at screening visit or within the 3 months prior to first dose of study drug.
- Thrombocytopenia, as defined by a platelet count $<100 \times 10^9$/L ($<100,000/mm^3$) at screening visit or within the 3 months prior to first dose of study drug.
- Estimated glomerular filtration rate ≤ 50 mL/min based on Cockcroft Gault calculation.
- Pregnant or lactating women.
- Total bilirubin, AST or ALT >1.5 x ULN at screening.
- Current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, or neurological disease.
- History of an infected joint prosthesis at any time, with the prosthesis still in situ.
- Current routine household contact with individuals who have received varicella or FluMist® vaccine within 4 weeks or oral polio vaccine within 8 weeks prior to first

dose of study drug, during the 24 weeks of treatment and for 8 weeks following completion of the study.

- History of any lymphoproliferative disorder (such as EBV-related lymphoproliferative disorder, as reported in some subjects on other immunosuppressive drugs), history of lymphoma, leukemia, myeloproliferative disorders, multiple myeloma, or signs and symptoms suggestive of current lymphatic disease.
- History of previously untreated infection with Mycobacterium tuberculosis (TB) or current treatment for same, as defined by any of the following:
    - A positive Mantoux Purified Protein Derivative (PPD) skin test, performed within the 3 months prior to screening with .5 mm of induration without adequate anti-TB therapy. If a subject had had prior Bacille Calmette Guerin (BCG) vaccination, the subject could be tested using an ex vivo method (eg, QuantiFERON. TB Gold [QFT Gold test]) and was excluded if determined to be immunoreactive to TB by that method;

    Or

    - Chest radiograph, which must have been taken within the 3 months prior to screening, that had changes suggestive of active TB infection;
    - If a subject had received a previous 9 month course of TB prophylaxis with isoniazid (or an acceptable alternative regimen), a PPD test did not need to be obtained, but a chest radiograph was obtained if a recent chest radiograph (with the prior 3 months) was not available.
- Subjects with clinically significant infections currently or within 6 months of first dose of study drug (eg, those requiring hospitalization or parenteral antimicrobial therapy or opportunistic infections), or those with a history of more than 1 episode of herpes simplex or zoster, a history of disseminated zoster, a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study or any infection requiring antimicrobial therapy within 2 weeks of screening.
- Failure of prior treatment with 3 TNF inhibitors: etanercept (Enbrel.), infliximab (Remicade.) and adalimumab (Humira.).
- Any prior treatment with lymphocyte depleting agents/therapies (such as CamPath. [alemtuzab], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc). Subjects who had received rituximab or other selective B lymphocyte depleting agents were eligible if they had not received such therapy for at least 1 year prior to study baseline and had normal CD19/20+ counts by Fluorescence-Activated Cell Sorting (FACS) analysis.
- Subjects with any condition possibly affecting oral drug absorption, gastrectomy, or clinically significant diabetic gastroenteropathy.
- History of alcohol or drug abuse with less than 6 months of abstinence prior to first dose of study drug.
- Screening 12-lead ECG that demonstrated clinically relevant abnormalities which may have affected subject safety or interpretation of study results.
- Donation of blood in excess of 500 mL within 2 months prior to first dose of study drug.

- Subjects with an oral or tympanic temperature at baseline of 38 .C or higher at screening.
- Subjects with a first-degree relative with a hereditary immunodeficiency.
- Subjects with malignancies or with a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
- Significant trauma or major surgery within 4 weeks of screening.
- Subjects who required prohibited concomitant medications listed in Appendix 5 of the protocol or subjects unwilling to discontinue herbal medications for at least 4 weeks prior to the first dose of study drug. Subjects who received non-prohibited concomitant medications for any reason must be on a stable regimen, which was defined as not starting a new drug or changing dosage within 7 days or 5 half lives (whichever was longer) prior to first dose of study drug.
- Subjects infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses.
- Subjects who had previously participated in any study of CP-690,550.
- Subjects with allergy/hypersensitivity to MTX, or previous serious toxicity with this medication.
- Subjects who, in the opinion of the investigator or sponsor, were uncooperative or unable to comply with study procedures.
- Any other condition which made the subject unsuitable for inclusion in the study.

Concomitant Medications

Subjects continued on their stable background arthritis therapy, which had to include MTX (supplemented with folic acid) and could include NSAIDs, selective COX-2 inhibitors, opioids, acetaminophen, and/or low dose oral corticosteroids (≤10 mg prednisone or equivalent per day) throughout the 24-week treatment period.

Intravenous or intramuscular corticosteroids, DMARDs other than MTX and biologic response modifiers were not allowed during this study. Intra-articular corticosteroids were allowed in a cumulative dose of no more than 40 mg methylprednisolone or its equivalent throughout the study in no more than 2 joints, and were not to be administered between the Week 6 and 12 visits, inclusive. Injected joints were also considered as having their pre-injection status (swollen and/or tender) for the remainder of the study.

Assignment to Treatment Group

Subjects were randomized in a 1:1:1:1:1:1:1 ratio to receive 1 of 6 doses of CP-690,550 (dose levels 20 mg QD, 15 mg BID, 10 mg BID, 5 mg BID, 3 mg BID and 1 mg BID) or placebo. It was planned to randomize 69 subjects in each treatment group. Subjects received study drug as an outpatient, returning to the study site for evaluations at baseline and at the end of Weeks 2, 4, 6, 8, 12, 16, 20 and 24/early termination.

Blinding

The study was subject, investigator, and Pfizer study personnel blinded. An interim analysis was performed after 100% of subjects had enrolled and either discontinued or completed their Week 12 visit. Efficacy was reported up to the Week 12 visit and safety was reported for all data available. The final analysis contained all data for the full 24 weeks of the study.

Criteria for Withdrawal from Treatment

Subjects who developed a serious infection during the study, defined as any infection (viral, bacterial, or fungal) that required hospitalization or parenteral antimicrobials, and subjects who required rescue doses of acetaminophen/paracetamol or opioid for more than 7 consecutive days, were discontinued. All abnormal laboratory events of clinical significance were followed until the laboratory values returned to normal or baseline levels or were deemed clinically stable. In addition, any subject with a confirmed increase in serum creatinine at end of study or at discontinuation of at least 0.2 mg/dL and at least 10% above baseline value was followed up with retesting every 1 to 2 weeks until the creatinine elevation had fully reversed to within 10% of the subject's baseline value or had stabilized.

Schedule of Assessments

Table 81. Schedule of Assessments for Study 1025

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SCHEDULE OF EVENTS	Screening[a]	Base line	Week Visits							End of Treatment
	Day -28	Day 0	2	4	6	8	12	16	20	Week 24 / ET
Informed Consent	X									
Rheumatoid Arthritis Diagnosis	X									
Tender/Painful Joint Count and Swollen Joint Count	X									
Medical History[b] and Current Medication	X									
Complete Physical Examination[c]	X	X								X
Targeted Physical Examination[c]			X	X	X	X	X	X	X	
History of Alcohol and Drug Abuse	X									
Mantoux PPD or QuantiFERON[d]	X									
Chest Radiograph	X									
Erythrocyte Sedimentation rate	X	X					X			
HBsAg, HCVAb	X									
(Brazil Only) Stool examination for parasites	X									
Rheumatoid Factor	X									
Anonymized Pharmacogenomic Sampling	X									
American College of Rheumatology Assessments[e]		X	X	X	X	X	X	X	X	X
C-Reactive Protein	X	X	X	X	X	X	X	X	X	X
Vital Signs and Oral or Tympanic Temperature	X	X	X	X	X	X	X	X	X	X
12-Lead Electrocardiogram	X	X			X		X			X
Hematology[f]	X	X	X	X	X	X	X	X	X	X

Source: Appendix A1

ET = early termination, FACS = Fluorescence-Activated Cell Sorting, PPD = purified protein derivative, HBsAg = Hepatitis B Surface Antigen , HCVAb = Hepatitis C Anti-body, IgM = Immunioglobulin M, IgG = Immunioglobulin G, IgA = Immunioglobulin A, EQ-5D = EuroQol EQ-5D health state profile, SF-36 = Short Form - 36, MOS = Medical Outcomes Study, FACIT = Function Assessment of Chronic Illness Therapy.

[a] Screening visit took place between 14-28 days prior to the baseline visit.

[b] Medical history included smoking status and average weekly alcohol consumption. Family history of premature coronary heart disease (CHD): CHD in a male first degree relative <55 years, CHD in a female first-degree relative <65 years, and waist circumference (a cardiovascular risk factor).

[c] Complete physical examination included weight, examination of heart, lungs, abdomen, and lymph nodes. Height and waist circumference were measured at screening only. Targeted physical examination consisted of weight and examination of heart, lungs, abdomen, and lymph nodes.

[d] Only subjects who had not had a tuberculin skin test within 3 months of screening visit. Subjects could have had either a Mantoux Purified Protein Derivative (PPD) test or a QuantiFERON®-TB Gold Test. Subjects who had a Mantoux PPD test returned within 48-72 hours for induration evaluation.

[e] Included Tender /Painful Joint Count (68), Swollen Joint Count (66), Patient's Assessment of Arthritis Pain visual analog scale (VAS), Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, Health Assessment Questionnaire Disability Index (visit window ±3 days).

[f] Hematology: Complete blood count, white blood cell differential, hemoglobin, hematocrit, reticulocyte and platelet count.

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SCHEDULE OF EVENTS	Screening[a]	Base line	Week Visits							End of Treatment
	Day -28	Day 0	2	4	6	8	12	16	20	Week 24 / ET
Lipid Profile (fasting)[g]		X	X		X		X			X
Safety Chemistry Panel 1(fasting)[h]	X	X								X
Safety Chemistry Panel 2[i]			X	X	X	X	X	X	X	
Serum Pregnancy Test	X									X
Urine Tests: Urinalysis Urine/ Pregnancy Test[j]	X	X	X	X	X	X	X	X	X	X
Blood Epstein-Barr Virus DNA		X					X			X
FACS Analysis: Lymphocyte subset markers		X								X
Serum IgG, IgM and IgA levels		X								X
Pharmacokinetic Samples[k]					X		X			
Retained Urine and Serum and Plasma Biomarker Sample		X					X			X
Dosing[l]		X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X	X
EQ-5D		X					X			X
SF-36		X					X			X
MOS-Sleep		X	X				X			X
FACIT-Fatigue		X	X				X			X
Drug Dispensing		X			X		X	X	X	
Drug Accountability					X		X	X	X	X
Review Subject's Entry Criteria for Follow-up Study									X	X

Source: Appendix A1

ET = early termination, FACS = Fluorescence-Activated Cell Sorting, PPD = purified protein derivative, HBsAg = Hepatitis B Surface Antigen , HCVAb = Hepatitis C Anti-body, IgM = Immunioglobulin M, IgG = Immunioglobulin G, IgA = Immunioglobulin A, EQ-5D = EuroQol EQ-5D health state profile, SF-36 = Short Form - 36, MOS = Medical Outcomes Study, FACIT = Function Assessment of Chronic Illness Therapy.

[a] Screening visit took place between 14-28 days prior to the baseline visit.

[g] Fasting total cholesterol, low density lipoprotein , high density lipoprotein and triglycerides. Subjects fasted for 9 hours. Apolipoprotein A1 and B measures were performed at baseline and Week 24/early termination visits only.

[h] Panel 1 (full serum chemistry) consisted of blood urea nitrogen and creatinine, glucose (fasting), calcium, sodium, potassium, chloride, total carbon dioxide, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, uric acid, albumin, total protein, lactic dehydrogenase. Panel 2 consisted of serum hepatic function testing (AST / ALT / total bilirubin / albumin), and serum creatinine.

[i] Pregnancy tests were only for women of child bearing potential. Follicle stimulating hormone test was optional.

[j] Pharmacokinetic sampling at Weeks 6 and 12: subjects remained in the study center for 4 hours and provided samples at predose and 1, 2, and 4 hours postdose. Subjects who were unable to remain in the study center for up to 4 hours provided at least the predose, 1 hour and 2 hour samples and returned to the study center for a sample any time prior to administering the evening dose on the same day of the pharmacokinetic visit.

[k] Dosing occurred during the visit at baseline, and at Weeks 6, 12, 16, and 20. The subject took study drug at home before study visits on Weeks 2, 4, 8 and 24.

Pharmacokinetic sampling:
Plasma samples for population PK and PK/pharmacodynamic modeling were collected at Week 6 and 12 visits as shown in Table 82

Table 82. Timepoints for Pharmacokinetic Sampling in study 1025

Study Visit	Pre AM Dosing	hours post AM dose		
	0 hr[1]	1 hr (± 15 min)	2 hrs (±30 min)	4 hrs (± 30 min)
Week 6	X	X	X	X
Week 12	X	X	X	X

Source : Appendix A1

[1] The Pre AM Dosing PK sample was collected at 12 (± 2) hours postdose administered on the evening prior to the visit.

Efficacy Parameters

- The primary analysis was that of ACR20 at Week 12.

- Secondary analyses included 4-parameter Emax models for the ACR variables in separate analyses, as well as descriptive statistics. These were based on the full analysis set (FAS).
- Pharmacokinetic parameter values were derived from the analysis of plasma concentration-time data of CP-690,550 using nonlinear mixed effects modeling approaches.
- An interim analysis at 100% accrual at the completion of Week 12 was performed.

Study Conduct

Started 01.30.2007, Completed 08.12.2008

Amendments:
There were 3 amendments to the protocol; 2 were global and 1 was specific to Sweden:

- Protocol Amendment 1 - February 06, 2007: The protocol was amended as per recommendations from the FDA for changes to the statistical section, to revise criteria for discontinuation and to specify follow-up procedures for specific laboratory abnormalities.
- Protocol Amendment 2 – April 24, 2007 (Sweden only): The protocol was updated in response to a request from the Swedish Regulatory Authorities for further information as to how the relationship between dose, concentration and efficacy/safety was to be characterized.
- Protocol Amendment 3 – August 22, 2007: The protocol was amended to allow flexibility for analysis of lymphocyte markers by FACS. The interim analyses were clarified and analyses of the DAS28-4 (ESR) were added. Changes to the exclusion criteria section included clarification of excluded vaccines and vaccine use, conditions affecting absorption of orally administered drugs and minimum background MTX dose criteria. Requirements for allowed dietary supplements were added to the lifestyles section. Erythrocyte sedimentation rate assessments were added at baseline and Week 12 visits.

The protocol amendments did not negatively impact the study conduct, efficacy or safety evaluations.

Patient Disposition

A total of 685 subjects were screened, and 509 were randomized to treatment. Of these 509 subjects, 507 took study drug. Overall, similar proportions of patients completed the study. There was no clear dose-relation for discontinuations across the range of tested tofacitinib doses. More patients in placebo group discontinuing due to lack of efficacy as shown on Table 83.

Table 83. Patient Disposition for Study 1025

	CP-690,550						
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg QD	Placebo
Number (%) of Subjects							
Screened: N=685							
Randomized to Study Treatment	71	68	71	75	75	80	69
Treated	70	68	71	74	75	80	69
Completed	61 (85.9)	57 (83.8)	56 (78.9)	66 (88.0)	60 (80.0)	66 (82.5)	54 (78.3)
Discontinued	9 (12.7)	11 (16.2)	15 (21.1)	8 (10.7)	15 (20.0)	14 (17.5)	15 (21.7)
Reason for discontinuation							
Related to study drug	4 (8.2)	3 (5.5)	2 (2.8)	4 (5.4)	7 (9.3)	5 (7.5)	8 (15.7)
Adverse event	2 (4.1)	3 (5.5)	1 (1.4)	4 (5.4)	7 (9.3)	5 (7.5)	3 (5.9)
Lack of efficacy	2 (4.1)	0	1 (1.4)	0	0	0	5 (9.8)
Not related to study drug	5 (10.2)	8 (14.5)	13 (18.3)	4 (5.4)	8 (10.7)	8 (11.9)	6 (11.8)
Adverse event	1 (2.0)	0	2 (2.8)	1 (1.4)	3 (4.0)	1 (1.5)	0
Lost to follow-up	0	2 (3.6)	1 (1.4)	0	1 (1.3)	0	0
Other	4 (8.2)	3 (5.5)	9 (12.7)	1 (1.4)	3 (4.0)	5 (7.5)	4 (7.8)
No longer willing	0	3 (5.5)	1 (1.4)	2 (2.7)	1 (1.3)	2 (3.0)	2 (3.9)

Source: CSR A3921025, Table 7

Subjects randomized to placebo, 1 mg BID, 3 mg BID and 20 mg QD who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts (a measure of efficacy) over baseline at Week 12 visit were labeled “non responders” and were automatically reassigned for the remaining 12 weeks of their participation. Based on these criteria, the proportion of patients reassigned to tofacitinib 5 mg BID appeared to be somewhat dose-dependent as shown in Table 84.

Table 84. Rate of Non-Responder Reassignment at Week 12 in Study 1025

					Difference from Placebo				
							95% Confidence Interval		
Treatment	N	n	n/N%	Std Error	Difference	Std error of difference	Lower	Upper	p-Value
1 mg BID	70	21	30.00	5.48	3.91	7.61	-11.01	18.83	0.6072
3 mg BID	68	13	19.12	4.77	-6.97	7.12	-20.92	6.98	0.3276
20 mg QD	80	13	16.25	4.12	-9.84	6.70	-22.98	3.30	0.1423
Placebo	69	18	26.09	5.29					

Baseline Demographics and Disease Characteristics

The baseline demographic and disease characteristics were summarized in Table 85. Overall, these are representative of the target patient population in the Phase 3 development.

Table 85. Baseline Demographic and Disease Characteristics for Study 1025

	Range of mean values across treatment groups
Female	74-88%
White	79-90%
Age	50.8-56.0 years
Rheumatoid arthritis disease duration	7.5-11.8 years
Tender joint count (68)	21.5-24.8
Swollen joint count (66)	14.1-16.5
HAQ-DI	1.2-1.6
DAS28-3 (CRP)	5.1-5.5
DAS28-3 (ESR)	6.07-6.40
Glucocorticoid use	45-64%

Source: CSR A3921025, Table 10.

Efficacy Results

For discussion on efficacy, refer to Table 6, which contains the individual study results for study 1025 along with the results from the pivotal Phase 2 dose-ranging studies.

Safety Results

A summary of all causality treatment-emergent AEs is presented in Table 86. During the first three months of the study, some dose-dependent increases were observed in the proportions of patients with any AE and discontinuations due to AE. During the 0-3 months period the 10 and 15 mg BID treatment groups had the highest proportion of subjects reporting an AE.

Table 86. Summary of Treatment-Emergent Adverse Events (All Causality) in Study 1025

Summary of Treatment-Emergent AEs (All Causality) in Study 1025							
	PBO	CP1 mg BID	CP3 mg BID	CP5 mg BID	CP10 mg BID	CP15 mg BID	CP20 mg QD
0-3 Months							
Enrolled, n	69	70	68	71	74	75	80
Total number of AEs	72	89	79	96	108	96	104
Subjects with ≥ AE	37 (54)	34 (49)	40 (59)	39 (55)	48 (65)	45 (60)	44 (55)
Subjects with ≥ SAE	0	1 (1)	3 (4)	1 (1)	1 (1)	1 (1)	1 (1)
Deaths	0	0	1 (2)	0	0	0	0
Discontinued due to AE	3 (4)	1 (1)	2 (3)	2 (3)	5 (7)	8 (11)	5 (6)
Subjects with dose reduction or temporary discontinuation due to AE	4 (6)	5 (7)	4 (6)	5 (7)	7 (10)	6 (8)	5 (6)
0-6 Months							
Evaluable as randomized, n, n	51	49	55	71	74	75	67
Total number of AEs	69	65	78	135	157	138	118
Subjects with ≥ AE	29 (67)	29 (59)	38 (69)	47 (66)	50 (68)	57 (76)	41 (61)
Subjects with ≥ SAE	0	1 (2)	4 (7)	4 (6)	1 (1)	6 (8)	4 (6)
Deaths	0	0	1 (2)	0	0	0	0
Discontinued due to AE	3 (6)	3 (6)	2 (4)	3 (4)	5 (7)	10 (13)	6 (9)
Subjects with dose reduction or temporary discontinuation due to AE	7 (14)	4 (8)	5 (9)	10 (14)	10 (14)	6 (8)	7 (10)

Source: CSR A3921025, adapted from Tables 39-41

Two deaths were reported in this study. One was before randomization, the other was attributed to the events of respiratory failure and cardiac failure secondary to bilateral pneumonia and occurred in the 3 mg BID treatment group (see also Table 32).

Throughout the study, all 21 SAEs occurred in tofacitinib-treated patients without clear dose-dependence. There were 5 subjects serious infections during the study. Three subjects had pneumonia (one of whom died), 1 had a urinary tract infection and 1 had a respiratory tract infection.

Two patients developed malignancy. One colon cancer in a patient on tofacitinib 1 mg BID dose, and one case of melanoma in a patient on tofacitinib 5 mg BID dose (see also Table 100).

Consistent with the findings from Phase 3 studies, dose related changes in hemoglobin, neutrophils and serum creatinine, LDL, HDL, and total cholesterol were observed. An increase in incidences of ALT >3xULN was observed in the 15 mg BID treatment group. No IgG level was <300 mg/dL at Week 24 and only 1 subject in the 10 mg BID treatment group experienced a drop to <50% of baseline value. Further laboratory abnormalities pertinent to dose-selection and mechanism of action were discussed in Section 4.4.4. Dose Selection.

The overall safety in this dose-ranging study is consistent with the safety profile of tofacitinib in the Phase 3 program.

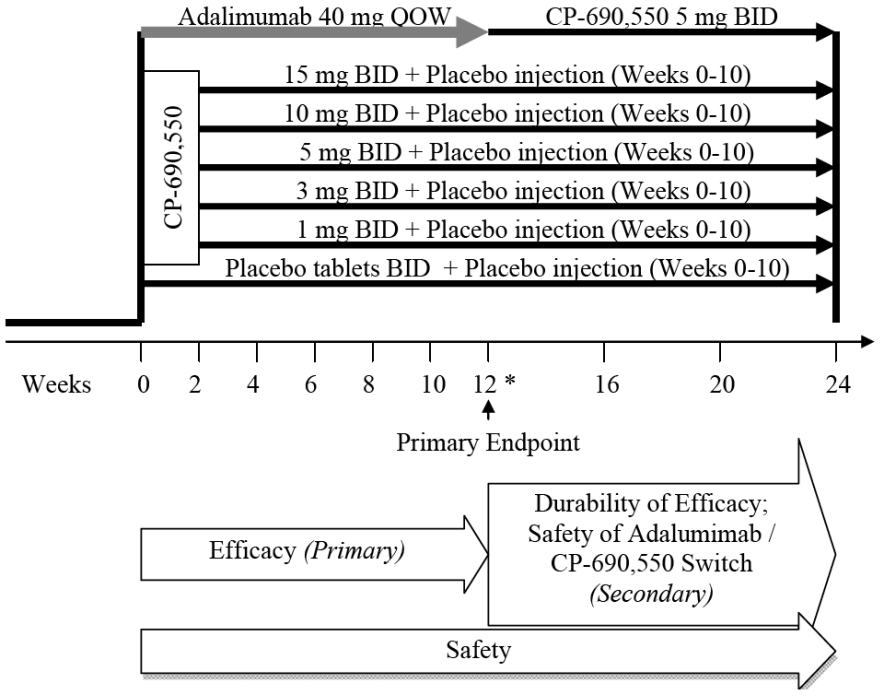
9.4.2 Study A3921035 (Phase 2 Dose-Ranging)

Study Protocol

Overall Study Design

This was a Phase 2B, randomized, double-blind, placebo-controlled, active comparator (adalimumab), parallel group study. Subjects were randomized to 1 of: oral CP-690,550 (1, 3, 5, 10 or 15 mg BID), adalimumab 40 mg sc QOW for 10 weeks followed by CP-690,550 5 mg BID for 12 weeks, or placebo. A total of 350 subjects were required; 50 subjects for each study group.

Figure 24. Study 1035 Design Schema



Source: CSR A3921035

Inclusion Criteria

- Evidence of a signed and dated informed consent document indicating that the subject had been informed of all pertinent aspects of the study.
- Subjects had to be at least 18 years of age.

- If the subject was a sexually active woman of childbearing potential, she and any male partner were required to simultaneously use 2 effective contraceptive methods.
- Non vasectomized men had to be willing to abstain from sexual intercourse or willing to use a condom in addition to having their female partner use another form of contraception such as an intrauterine device, barrier method with spermicide, oral contraceptive, injectable progesterone, sub dermal implant, or a tubal ligation, if the woman could become pregnant from the time of the first dose of study medication until completion of follow-up procedures.
- The subject had a diagnosis of RA based upon the ACR (formerly American Rheumatism Association) 1987 Revised Criteria 5 ie, fulfilling at least 4 of the following 7 criteria for at least 6 consecutive months preceding randomization:
    - morning stiffness in and around any joint for more than 1 hour;
    - Soft tissue swelling of 3 or more joint areas;
    - swelling of the proximal interphalangeal (PIP), metacarpophalangeal (MCP) or wrist joints;
    - symmetrical joint swelling;
    - rheumatoid nodules;
    - serum rheumatoid factor positive;
    - radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.
- The subject had active disease at both screening and baseline, as defined by both:
    - ≥6 joints tender or painful on motion, AND
    - ≥6 joints swollen;

  and fulfilled 1 of the following 2 criteria at screening:
    - Erythrocyte sedimentation rate (ESR) (Westergren method) above the upper limit of normal (ULN) in the local laboratory;
    - C-reactive protein (CRP) >7 mg/L in the central laboratory.
- The subject met ACR 1991 Revised Criteria for Global Functional Status in RA, Class I, II or III.
- Subjects receiving non prohibited concomitant medications for any reason must have been on a stable regimen, which was defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever was longer) prior to first study dose, or as defined in Concomitant Medications.
- Subjects must have failed an adequate study of therapy with at least 1 DMARD due to lack of efficacy or toxicity.
- Subjects who received the following treatment regimens were eligible, provided the following discontinuation periods were observed. Note that none of these therapies were to be discontinued by a subject to allow participation in this study if they were currently effective and tolerated.
    - Within 4 weeks of first dose of study drug:
        - DMARDS – Leflunomide (Arava®), methotrexate, sulfasalazine, and d-penicillamine, minocycline; etanercept (Enbrel®); anakinra (Kineret®);
        - Immunosuppressive/Immunomodulatory therapies - azathioprine, cyclosporine, and PROSORBA® device/column;

- Non-steroidal anti-inflammatory drugs (NSAIDs) - any experimental NSAIDs or experimental selective cyclooxygenase 2 (COX 2) inhibitors;
- Other-herbal medications, immunization with any live virus vaccination (eg, FluMist™) other than oral polio vaccine, intra articular, intramuscular, or intravenous corticosteroids.

o Within 8 weeks of first dose: Infliximab (Remicade®), auranofin (Ridaura®), injectable gold (aurothioglucose or aurothiomalate), or immunization with oral polio vaccine.
o Within 3 months of first dose: Abatacept (Orencia®).
o Within 6 months of first dose: Any experimental therapy for RA (other than experimental NSAIDs, selective COX 2 inhibitors and selective B lymphocyte depleting agents).

Exclusion Criteria

- Subjects who discontinued any previous TNFi therapy for either lack of efficacy or adverse events (AEs). Subjects who previously received adalimumab therapy for any reason were not allowed in the study.
- Subjects with evidence of hematopoietic disorders:
  o hemoglobin levels <9.0 gm/dL or hematocrit <30% at screening visit or within the 3 months prior to first study dose.
  o an absolute white blood cell (WBC) count of <3.0 x 10^9/L (<3000/mm^3) or absolute neutrophil count of <1.2 X 10^9/L (<1200/mm^3) at screening visit or within the 3 months prior to first study dose.
  o thrombocytopenia, as defined by a platelet count <100 x 10^9/L (<100,000/mm^3) at screening visit or within the 3 months prior to first study dose.
- Estimated glomerular filtration rate (GFR) ≤50 mL/min based on Cockcroft-Gault calculation.
- Pregnant or lactating women.
- Total bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 2 times the ULN at screening visit.
- Current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, or neurological disease.
- History of an infected joint prosthesis at any time, with the prosthesis still in situ.
- Current routine household contact with individuals who had received either varicella or FluMist® (within 4 weeks) or oral polio vaccine (within 8 weeks), prior to first study dose.
- History of any lymphoproliferative disorder (such as Epstein-Barr Virus [EBV]-related lymphoproliferative disorder, as reported in some subjects on other immunosuppressive drugs), history of lymphoma, leukemia, myeloproliferative disorders, multiple myeloma, or signs and symptoms suggestive of current lymphatic disease.
- Evidence of active or latent infection with Mycobacterium tuberculosis (TB), as defined by any of the following:

  - a subject had a positive Mantoux Purified Protein Derivative (PPD) skin test result of ≥5 mm of induration within the 3 months prior to screening, OR;
  - a subject was immunoreactive for TB using an ex vivo method (eg, QuantiFERON-TB Gold (QFT Gold) or T-Spot test), OR;
  - a subject had a chest radiograph (taken within the 3 months prior to screening) that had changes suggestive of active TB infection.

  If a subject had a positive PPD or was immunoreactive for TB using an ex vivo method, (s)he may have been eligible if (s)he had completed an appropriate treatment regimen for TB and had a chest radiograph within the 3 months prior to screening that had no evidence of active TB. A subject who was currently being treated for TB infection could only be enrolled with prior approval by the Sponsor.
- Subjects with clinically significant infections currently or within 6 months of first dose of study drug (eg, those requiring hospitalization or parenteral antimicrobial therapy or opportunistic infections), or those with a history of more than one episode of herpes simplex or zoster, a history of disseminated zoster, a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study or any infection requiring antimicrobial therapy within 2 weeks of screening.
- Any prior treatment with lymphocyte-depleting agents/therapies (such as CamPath® [alemtuzab], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc). Subjects who had received rituximab or other selective B lymphocyte depleting agents were eligible if they had not received such therapy for at least 1 year prior to first dose.
- Subjects with any condition possibly affecting oral drug absorption, gastrectomy, or clinically significant diabetic gastroenteropathy.
- History of alcohol or drug abuse with less than 6 months of abstinence prior to first dose of study drug.
- Screening 12-lead electrocardiogram (ECG) that demonstrated clinically relevant abnormalities which may have affected subject safety or interpretation of study results.
- Donation of blood in excess of 500 mL within 2 months prior to first study dose.
- Subjects with an oral, tympanic, or axillary temperature of 38°C or higher at screening.
- Subjects with a first-degree relative with a hereditary immunodeficiency.
- Subjects with malignancies or with a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
- Significant trauma or major surgery within 4 weeks of screening visit.
- Subjects requiring prohibited concomitant medications.
- Subjects infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses.
- Subjects who had previously participated in any study of CP-690,550.
- Subjects who, in the opinion of the investigator or sponsor, would be uncooperative or unable to comply with study procedures.
- Subjects in violation of the local label requirements for adalimumab.

- Any other condition which would make the subject unsuitable for inclusion in the study.

Concomitant Medications

Subjects continued on their stable background arthritis therapy, which could include antimalarials, NSAIDs, selective COX 2 inhibitors, opioids, acetaminophen, and/or low dose oral corticosteroids (≤10 mg prednisone or equivalent per day) throughout the 24-week treatment period. Dosages of antimalarials must have been stable for at least 8 weeks prior to first study dose and had to remain so during the study treatment period. Dosages of NSAIDs/COX 2 inhibitors, opioids, acetaminophen, and corticosteroids must have been stable for at least 4 weeks prior to first study dose and had to remain so during the study treatment period.

Intravenous or intramuscular corticosteroids, DMARDs (other than antimalarials) were not allowed during this study. Intra-articular corticosteroids were allowed.

Assignment to Treatment Group

Subjects were randomized in a 1:1:1:1:1:1:1 ratio to receive 1 of 5 doses of CP-690,550 (1, 3, 5, 10, and 15 mg BID), placebo or adalimumab followed by CP-690,550 5 mg BID. It was planned to randomize 50 subjects in each treatment group.

Blinding

The study was subject, investigator, and sponsor-blinded. The investigative staff member responsible for administration of subcutaneous drug (adalimumab or placebo injection) was unblinded. The blind was not broken during the study. Blood specimens for pharmacokinetic (PK) analysis were obtained from all subjects and were maintained in a blinded fashion.

Criteria for Withdrawal from Treatment

Subjects who required rescue doses of acetaminophen/paracetamol or opioid for more than 7 consecutive days, and subjects interrupting study drug for more than 10 consecutive days or for a total of 14 nonconsecutive days were discontinued from the study.

All abnormal laboratory events of clinical significance were followed until the laboratory values had returned to normal or baseline levels. In addition, any subject with a confirmed increase in serum creatinine at end of study or at discontinuation of at least 0.2 mg/dL and at least 10% above baseline value, was retested every 1 to 2 weeks until the creatinine elevation had fully returned to within 10% of the subject's baseline value, or had stabilized.

If a subject had any clinically significant, study-related abnormalities at the conclusion of the study, the sponsor’s clinical monitor (or designated representative) was notified and every

effort made to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

Dose Modification

Subjects randomized to the CP-690,550 3 mg BID, 1 mg BID, and placebo groups, who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts over baseline at the Week 12 visit, were to be labeled “non-responders” and automatically reassigned, for the remaining 12 weeks of their study participation to the dose of 5 mg BID.

Subjects randomized to the 15, 10 and 5 mg BID groups were to remain on their originally assigned doses and not be reassigned. Other than this automatic reassignment, dose adjustments of CP-690,550 were not allowed.

Schedule of Assessments

Table 87. Schedule of Activities in Study 1035

Procedures	Visits									
	1	2	3	4	5	6	7	8	9	10
		Weeks								
	Screen[a]	Baseline Day 0	2	4	6	8	10	12	16	20	24/early term
Informed Consent	X									
RA Diagnosis/Medical History[b]	X									
Complete Physical Examination[c]	X	X									X
Targeted Physical Examination[d]			X	X	X	X	X	X	X	X	
Vital Signs/Oral, Tympanic, or Axillary Temperature	X	X	X	X	X	X	X	X	X	X	X
Mantoux PPD or QuantiFERON[e]	X										
Chest Radiograph	X										
12 Lead Electrocardiogram	X	X			X			X			X
HBsAg, HCV Ab; Rheumatoid Factor	X										
Hematology[f]	X	X	X	X	X	X	X	X	X	X	X
Lipid Profile (fasting)[g]		X	X		X			X			X
Safety Chemistry Panel 1[h]	X	X									X
Safety Chemistry Panel 2[i]			X	X	X	X	X	X	X	X	
Follicle Stimulating Hormone[j]	X										
FACS: Lymphocyte Subset Markers		X									X
Blood EBV DNA		X			X[k]			X			X
Serum IgG, IgM and IgA Levels		X									X
Urinalysis[l]; Urine Pregnancy Test[m]	X	X	X	X	X	X	X	X	X	X	X
Stool Exam for Parasites (Brazil Only)	X										
HIV Serology (Germany Only)	X										
Pharmacogenomic Sample (DNA)[n]		X									
Exploratory RNA Sample[n]		X		X				X	X		
Retain Urine/Serum/Plasma Sample[n]		X						X			X
Pharmacokinetic Samples[o]				X					X		
Tender/Painful Joint Count Swollen Joint Count Patient Assessment of Arthritis Pain Patient Global Assessment Physician Global Assessment HAQ-DI[p]		X----------									----------X
CRP, ESR	X----------										----------X
Randomization		X									
EQ-5D[q] and SF-36[q]		X						X			X
MOS-Sleep[r] and FACIT-Fatigue[r]		X	X					X			X
Oral Dosing[s]		X	X	X	X	X	X	X	X	X	
Sub-Cutaneous Dosing		X	X	X	X	X	X				
Drug Dispensing		X		X		X		X	X	X	
Drug Accountability				X		X		X	X	X	X
Adverse Event Assessment		X----------									----------X
Prior and Concomitant Medication	X----------										----------X
Review Entry Criteria for A3921024										X	X

[a] Screening visit took place up to 28 days prior to the baseline visit/Day 0,
[b] Medical history included smoking status, average weekly alcohol consumption: units/week, where a unit contains 12 g of pure alcohol, an amount equivalent to that contained in 5 oz (a glass) of wine, 12 oz of beer, or 1.5 oz of 90 proof of spirits. Family history of premature CHD: CHD in a male first degree relative <55 years of age, CHD in a female first degree relative <65 years of age, and waist circumference (a cardiovascular risk factor),
[c] Complete physical examination included weight, examination of heart, lungs, abdomen, and lymph nodes, performed at screening, baseline, and Week 24/early termination. Height and waist circumference measured at screening only,
[d] Targeted physical examination consistes of weight and examination of heart, lungs, abdomen, and lymph nodes, performed Weeks 2, 4, 6, 8, 10, 12, 16, and 20. (See Appendix A8 of the protocol [Appendix 1] for details for suspicious lymphadenopathy),
[e] If PPD skin test performed – this was read by the investigator within 48 to 72 hours (additional visit),
[f] Hematology: CBC (WBC Differential, hemoglobin, hematocrit, reticulocyte, and platelet count). Sites from which specimens could not be transported to the central lab rapidly enough to perform valid reticulocyte counts were not required to perform reticulocyte counts,
[g] Lipid Profile: Fasting total cholesterol, LDL, HDL, and triglycerides. Subjects fasted for 9 hours. Apolipoprotein A1 and B measures were performed at Baseline and Week 24/early termination visits only,
[h] Safety Chemistry Panel 1 (Full Serum Chemistry) consisted of (BUN and creatinine, glucose (fasting), Ca++, Na+, K+, Cl , total CO_2, AST, ALT, total bilirubin, alkaline phosphatase, uric acid, albumin, total protein, and LDH,
[i] Safety Chemistry Panel 2 consists of serum hepatic function testing (AST/ALT/total bilirubin/albumin), and serum creatinine,
[j] FSH testing was performed at screening to confirm postmenopausal status,
[k] Additional Blood EBV DNA level at 6 weeks (Germany Only),
[l] Urinalysis: dipstick in all cases. Microscopy and/or culture if clinically indicated or if dipstick results were positive for blood or protein,
[m] Urine pregnancy test: only for women of child bearing potential.
[n] For de-identified pharmacogenomic (DNA) sampling, de-identified exploratory RNA sampling, and the retained de-identified urine/serum/plasma sample a separate molecular profiling consent was obtained. RNA analysis was performed on a limited number of subjects at selected sites,
[o] Pharmackinetic sampling was done on Weeks 4 and 16, on a limited number of subjects at selected sites. Samples were obtained at predose (Study Drug tablet) and 1, 2, and 4 hours postdose. For those subjects unable to remain in the clinic for up to 4 hours, subjects providid at least the predose, 1 hour and 2 hour samples and returned to the clinic for a sample any time prior to administering the evening dose on the same day of the pharmacokinetic visit,
[p] HAQ-DI is in Appendix 2 of the protocol (Appendix A1),
[q] EQ 5D is in Appendix 11 of the protocol (Appendix A1) and SF 36 is in Appendix 3 of the protocol (Appendix A1)
[r] MOS Sleep is in Appendix 12 of the protocol (Appendix A1)and FACIT Fatigue is in Appendix 13 of the protocol (Appendix A1),
[s] On study visit days, subjects were instructed to take morning dose in the office.
RA = rheumatoid arthritis, PPD = purified protein derivative, HBsAg = Hepatitis B surface antigen, HCV Ab = Hepatitis C antibody, FACS = fluorescence activated cell sorting, EBV = Epstein-Barr Virus, DNA = deoxyrisbose nucleic acid, IgG = immunoglobulin G, IgM = immunoglobulin M, IgA = immunoglobulin A, HIV = human immunodeficiency virus, RNA = ribonucleic acid, HAQ-DI = health assessment questionnaire disability index, CRP = C-reactive protein, ESR = Erythrocyte sedimentation rate, EQ-5D = EuroQol EQ-5D health state profile, SF-36 = Short Form - 36, MOS = Medical Outcomes Study, FACIT = Function Assessment of Chronic Illness Therapy, FSH = follicle stimulating hormone, CHD = coronory heart disease, CBC = complete blood count, WBC = white blood cell, LDL = low density lipoprotein, HDL = high density lipoprotein, BUN = blood urea nitrogen, Ca = calcium, Na – sodium, K = potassium, Cl = chlorine, AST = aspartate aminotransferase, ALT – alanine aminotransferase, LDH = lactate dehydrogenase,
Source: CSR A3921035, Table 2

Efficacy Parameters
Primary efficacy parameter was ACR20 response rate at Month 3.

Study Conduct

Started 09.05.2007, Completed 01.14.2009

Amendments:
There were 3 amendments to the protocol; 1 was global and 2 were country specific.

- Protocol Amendment 1 - 30 July 2007: Several amendments were made to different sections of the protocol, including the schedule of activities and inclusion and exclusion criteria. The changes to eligibility criteria were for clarification did not significantly impact the study population.
- Protocol Amendment 2 – 28 May 2008 (Bulgaria, Chile, Greece, Mexico and Ukraine): The protocol was amended to reflect that sites would not have to perform reticulocyte counting if transportation of the specimens to the laboratory could not be completed rapidly enough.
- Protocol Amendment 3 – 23 October 2008 (Brazil and Greece): The protocol was updated to allow axillary temperature measurements in recording body temperature in countries where that method is standard medical practice.

The protocol amendments did not negatively impact the study conduct, efficacy or safety evaluations.

Patient Disposition

A total of 555 subjects were screened and 386 were randomized to treatment (Table 88). Of these subjects, 384 took study drug and were evaluated for safety and efficacy. Subjects randomized to tofacitinib 3 mg BID, 1 mg BID, and placebo groups, who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts over baseline at the Week 12 visit, were to be labeled "non-responders" and automatically blind-reassigned, for the remaining 12 weeks of their study participation to the dose of 5 mg BID (labeled as "r" in Table 88). Subjects randomized to the 15, 10 and 5 mg BID groups were to remain on their originally assigned doses and not be reassigned.

Table 88. Patient Disposition in Study 1035

	CP-690,550 BID										
	1 mg		3 mg		5 mg	10 mg	15 mg	Adalimumab[a]		Placebo	
Number of Subjects (%)											
Screened 555											
Randomized to study treatment	54		52		50	61	57	53		59	
Treated	54		51		49	61	57	53		59	
Completed	40 (74.1)		43 (82.7)		43 (86.0)	55 (90.2)	52 (91.2)	37 (69.8)		43 (72.9)	
Discontinued	14 (25.9)		8 (15.4)		6 (12.0)	6 (9.8)	5 (8.8)	16 (30.2)		16 (27.1)	
Discontinuation from double-blind treatment period											
	N = 37	**r = 17**	**N = 34**	**r = 17**	**N = 49**	**N = 61**	**N = 57**	**N = 9**	**r = 44**	**N = 34**	**r = 25**
Related to study drug	5 (13.5)	1 (5.9)	1 (2.9)	1 (5.9)	2 (4.1)	2 (3.3)	2 (3.5)	6 (66.7)	2 (4.5)	3 (8.8)	1 (4.0)
Adverse event	2 (5.4)	0	0	0	1 (2.0)	1 (1.6)	2 (3.5)	3 (33.3)	0	0	0
Lack of efficacy	3 (8.1)	1 (5.9)	1 (2.9)	1 (5.9)	1 (2.0)	1 (1.6)	0	3 (33.3)	2 (4.5)	3 (8.8)	1 (4.0)
Not related to study drug	8 (21.6)	0	5 (14.7)	1 (5.9)	4 (8.2)	4 (6.6)	3 (5.3)	3 (33.3)	5 (11.4)	12 (35.3)	0
Adverse Event	2 (5.4)	0	3 (8.8)	0	0	0	1 (1.8)	0	4 (9.1)	1 (2.9)	0
Lost to follow-up	0	0	1 (2.9)	0	1 (2.0)	1 (1.6)	1 (1.8)	1 (11.1)	0	3 (8.8)	0
Other	4 (10.8)	0	1 (2.9)	1 (5.9)	0	1 (1.6)	0	1 (11.1)	1 (2.3)	5 (14.7)	0
No longer willing to participate	2 (5.4)	0	0	0	3 (6.1)	2 (3.3)	1 (1.8)	1 (11.1)	0	3 (8.8)	0

Source: Table 13.1.1 and Table 13.1.2.A
N = total number of evaluable subjects, r = reassigned after Week 12 to CP-690.550 5 mg BID
Discontinuations ocurring outside the lag period were attributed to the last study treatment receieved.
[a] Adalimumab 40 mg every other week from baseline to Week 10, CP-690,550 5 mg BID from Week 12 to 24.
Source: CSR A3921035, Table 7

Baseline Demographics and Disease Characteristics

The baseline demographic and disease characteristics were summarized in Table 89. Overall, these are representative of the target patient population in the Phase 3 development.

Table 89. Baseline Demographic and Disease Characteristics in Study 1035

	Range of mean values across treatment groups
Female	85%-88%
White	72%-82%
Age	52.4-55.1 years
Rhematoid arthritis disease duration	7.7-10.8 years
Tender joint count	24.1-27.1
Swollen joint count	14.9-17.4
HAQ-DI	1.4-1.6
DAS28-3 (CRP)	5.4-5.6
DAS28-4 (ESR)	6.3-6.6
Glucocorticoid use	51.0%-61.1%

Source: Tables 13.2.1, 13.2.2, 13.2.4, 13.3.8.A, 13.4.12.2 and 13.4.12.7
HAQ-DI = health assessment questionnaire disability index, DAS = disease activity score, CRP = C-reactive protein, ESR = erythrcyte sedimentation rate
Source: CSR A3921035, Table 10

Efficacy Results

For discussion on efficacy, refer to Table 6, which contains the individual study results for study 1035 along with the results from the pivotal Phase 2 dose-ranging studies.

Safety Results

All causality treatment-emergent AEs in study 1035 were fairly balanced among the treatment arms as shown in Table 90.

Table 90. Summary of Treatment-Emergent Adverse Events (All Causality) in Study 1035

Summary of Treatment-Emergent AEs (All Causality) in Study 1035							
	PBO	ADA	CP1 mg BID	CP3 mg BID	CP5 mg BID	CP10 mg BID	CP15 mg BID
0-3 Months							
Enrolled, n	59	53	54	51	49	61	57
Total number of AEs	46	42	39	33	47	70	73
Subjects with ≥ 1 AE	24 (41)	27 (51)	19 (35)	19 (37)	24 (49)	31 (51)	30 (53)
Subjects with ≥ 1 SAE	1 (2)	1 (2)	0	1 (2)	0	0	1 (2)
Deaths	0	0	0	0	0	0	0
Discontinued due to AE	1 (2)	4 (8)	2 (4)	2 (4)	0	1 (2)	2 (4)
Subjects with dose reduction or temporary discontinuation due to AE	0	0	1 (2)	2 (4)	1 (2)	2 (3)	3 (5)
0-6 Months							
Evaluable as randomized, n	34	9	37	34	49	61	57
Total number of AEs	28	5	42	39	68	93	103
Subjects with ≥ 1 AE	16 (47)	5 (56)	19 (51)	18 (53)	27 (55)	36 (59)	35 (61)
Subjects with ≥ 1 SAE	0	0	1 (3)	2 (6)	1 (2)	0	5 (9)
Deaths	0	0	0	0	0	0	1
Discontinued due to AE	1 (3)	3 (33)	4 (11)	3 (9)	1 (2)	1 (2)	3 (5)
Subjects with dose reduction or temporary discontinuation due to AE	1 (3)	0	1 (3)	2 (6)	3 (6)	2 (3)	5 (9)

Source: CSR A3921025, adapted from Tables 43 and 45

One patient died from a hemorrhagic cerebrovascular accident (Table 32) while being treated with tofacitinib 15 mg BID dose. Three serious infections developed, all pneumonias developed (two in patients on 1 mg BID and on in a patient on 15 mg BID). One patient developed renal cell carcinoma while being treated with adalimumab.

Dose related changes in neutrophils were observed and 2 incidences of sever neutropenia were reported by 2 subjects. Small mean increases in serum creatinine from baseline were observed across all treatment groups. Dose dependent increases in LDL, HDL, and total cholesterol were observed; these increases appeared to plateau by Week 6. ALT levels >3 x ULN were observed in 2 subjects each in the 15 mg BID and adalimumab dose groups, respectively. No IgG level was below 300 mg/dL at Week 24 and only 1 subject experienced a drop to <50% of baseline value while receiving 5 mg BID of tofacitinib. Further laboratory abnormalities pertinent to dose-selection and mechanism of action were discussed in Section 4.4.4. Dose Selection.

The overall safety in this dose-ranging study is consistent with the safety profile of tofacitinib in the Phase 3 program.

9.4.3 Study A3921032 (Phase 3)

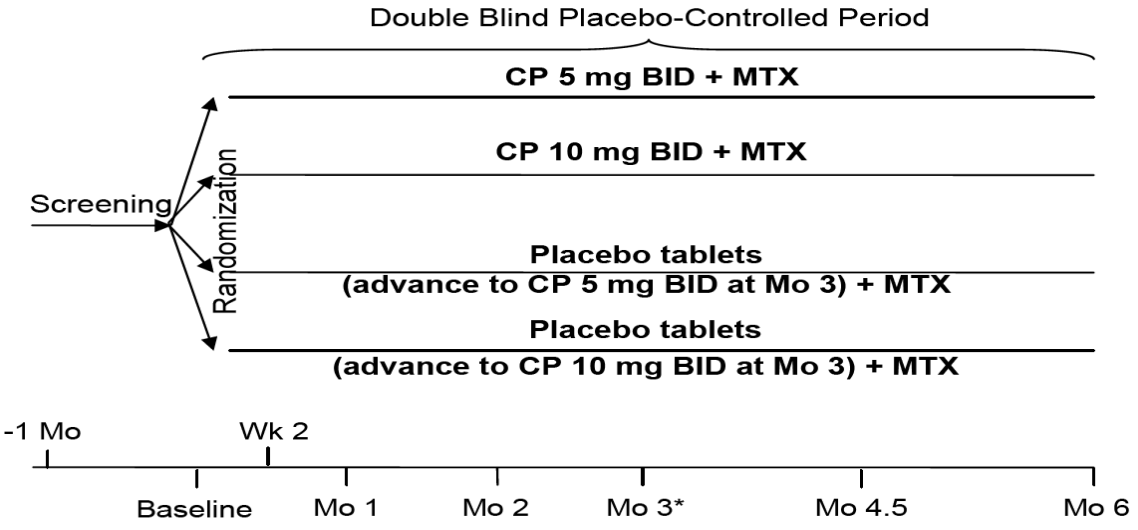
Study Protocol

Overall Study Design

This is a Phase 3, randomized, 6-month, double-blind, placebo-controlled, parallel study of CP-690,550, in doses of 5 or 10 mg BID, versus placebo in patients on background adequate doses of MTX (7.5-25 mg weekly) who have had inadequate response or could not tolerate prior TNF inhibitor using a 2:2:1:1 randomization schema as follows (Figure 25). Primary outcome measures are assessed at Month 3 visit. At that visit previously randomized patients in the placebo arms are advanced to receive CP-690,550, in doses of 5 or 10 mg BID.

Figure 25. Study 1032 Design Schema

Sequence Number	Treatment Sequence	Planned Number of Randomized Patients
1	CP-690,550 5 mg BID	132
2	CP-690,550 10 mg BID	132
3	Placebo (advanced to CP-690,550 5 mg BID at Month 3)	66
4	Placebo (advance to CP-690,550 10 mg BID at Month 3)	66



Inclusion Criteria

- Rheumatoid arthritis with evidence of disease activity by joint counts and laboratory markers of inflammation as described in Section 4.1.1 (below).

- The patient must meet the American College of Rheumatology (ACR) classification criteria for the diagnosis of rheumatoid arthritis (RA) by satisfying at least four of the seven criteria as described in Appendix 1 of the protocol.
- The patient must have active disease at both screening and baseline, as defined by having both:
  - >6 tender/painful joints on motion (out of 68 joints assessed); *and;*
  - >6 swollen joints (out of 66 joints assessed)
  - The patient must also have active disease, as defined by one of the following criteria at screening: Erythrocyte sedimentation rate (ESR) (Westergren method) >28 mm/hr; *or* C-reactive protein (CRP) >7 mg/L in the central laboratory.
- The patient must meet Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA.

- Ongoing treatment with an adequate and stable dose of methotrexate. All local standard-of-care practices for the administration of methotrexate, including laboratory testing, follow-up care, contraindications, and folic acid administration should be performed according to local standards of care throughout the study. Minimum guidelines for methotrexate and folic acid therapy during study:
  - The patient must have taken oral or parenteral methotrexate continuously for at least 4 months prior to the first dose of study medication and be on a stable dose of 7.5 mg to 25 mg weekly, for at least 6 weeks prior to the first dose of study medication. Stable weekly doses less than 15 mg are allowed only in the presence of intolerance to or toxicity from higher doses or where higher doses would violate the local label. Doses higher than 25 mg weekly are not permitted under any circumstances.
  - Patients should be on an adequate and stable dose of folic acid (not less than 5 mg weekly, unless higher doses would violate the local label) for at least 4 weeks prior to the first dose of study medication.
- Other Inclusion Criteria
  - Evidence of a signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study
  - Patients must be at least 18 years of age.
  - Sexually active women of childbearing potential and men whose partners are women of childbearing potential are required to use adequate contraceptive methods during participation in this study.
  - No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by all of the following:
    - A negative QuantiFERON-Gold®™ test or, if unavailable, a Mantoux Purified Protein Derivative skin test using 5 tuberculin units per 0.1 mL (5 TU PPD) result of <5 mm of induration performed within the 3 months prior to screening. [It is strongly

recommended that patients with a history of Bacille Calmette Guérin (BCG) vaccination be tested with the QuantiFERON-Gold®™ test].
    - A chest radiograph taken within the 3 months prior to screening without changes suggestive of active TB infection.
    - No history of either untreated or inadequately treated latent or active TB infection.
    - If a patient has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug TB resistance are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a PPD test nor a QuantiFERON TB Gold (QFT Gold test) need be obtained, but a chest radiograph must still be obtained if not done within the prior 3 months. A patient who is currently being treated for either latent or active TB infection can only be enrolled with confirmation of current incidence rates of multi-drug resistant TB infection, documentation of an adequate treatment regimen, and with prior approval by the Sponsor.
- For traditional DMARDS, the following minimum washout criteria apply:
    - Minocycline, Penicillamine, Sulfasalazine: must have been discontinued for 4 weeks prior to the first dose of study drug.
    - Leflunomide (Arava®) must have been discontinued 8 weeks prior to the first dose of study drug if no elimination procedure is followed. Alternately, it should have been discontinued with the following elimination procedure at least 4 weeks prior to the first dose of study drug: Cholestyramine at a dosage of 8 grams three times daily for at least 24 hours, or activated charcoal at a dosage of 50 grams 4 times a day for at least 24 hours.
    - Auranofin (Ridaura®), Injectable Gold (aurothiglucose or aurothiomalate): must have been discontinued for 8 weeks prior to first dose of study drug.
    - Antimalarials (Hydroxychloroquine, Chloroquine): Antimalarials will be allowed in this study. If discontinued, they must be discontinued for 4 weeks prior to the first dose of study drug. If continued, the dose must be stable for at least 8 weeks prior to first dose of study drug.
- Biologic Response Modifiers. All must be discontinued for entry into this study:
    - Anakinra (Kineret®), Enbrel (Etanercept®), Golimumab (Simponi TM): Discontinued for 4 weeks prior to the first dose of study drug;
    - Adalimumab (Humira®): Discontinued for 6 weeks prior to first dose of study drug;

- Infliximab (Remicade®): Discontinued for 8 weeks prior to the first dose of study drug;
- Abatacept (Orencia®), Tocilizumab (Actemra®), Certolizumab pegol (Cimzia®): Discontinued for 12 weeks prior to first dose of study drug;
- Rituximab or other selective B lymphocyte depleting agents (either marketed or investigational): Discontinued for 1 year prior to the first dose of study drug and if CD19/20+ counts are normal by FACS analysis;

o Other:
- Oral corticosteroids: Patients who are already on oral corticosteroids must be on a stable dose of ≤10 mg/day of prednisone or equivalent for 4 weeks prior to first dose of study drug.
- Intraarticular, intramuscular, or intravenous corticosteroids: None may be administered within 4 weeks prior to first dose of study drug.
- Cyclosporine, Tacrolimus, Azathioprine: All must be discontinued 4 weeks prior to the first dose of study drug.
- Prosorba Device/Column: This must be discontinued 4 weeks prior to the first dose of study drug.
- Experimental NSAIDS (including Cox-2 inhibitors): These must be discontinued 4 weeks prior to the first dose of study drug.
- Any investigational treatment not mentioned elsewhere must be discontinued for 4 weeks or 5 half lives, whichever is longer. Exposure to investigational biologics should be discussed with the Sponsor.

o Patients receiving non-prohibited concomitant medications for any reason must be on a stable regimen, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to first study dose.

Exclusion Criteria

- Any prior treatment with non B lymphocyte-selective lymphocyte depleting agents/therapies, such as alemtuzumab (Campath®) OR alkylating agents (eg, cyclophosphamide or chlorambucil) OR total lymphoid irradiation, etc. Patients who have received rituximab or other selective B lymphocyte depleting agents (including experimental agents) are eligible if they have not received such therapy for at least 1 year prior to study baseline and have normal CD 19/20+ counts by FACS analysis (Section 4.2. Number 6 Biologics)
- Pregnant or lactating females.
- Blood dyscrasias including confirmed:
  - Hemoglobin <9 g/dL or Hematocrit <30%;

  - White blood cell count <3.0 x 10^9/L;
  - Absolute neutrophil count <1.2 x 10^9/L;
  - Platelet count <100 x 10^9/L.
- Estimated GFR less than 40 ml/min based on Cockcroft-Gault calculation (Appendix 3).
- AST or ALT more than 1.5 times the upper limit of normal at screening visit.
- Current or recent history of uncontrolled clinically significant renal, hepatic, hematological, gastrointestinal, endocrine, metabolic, pulmonary, cardiac, or neurological disease.
- History of any other autoimmune rheumatic disease other than Sjögren's syndrome.
- History of an infected joint prosthesis at any time, with the prosthesis still in situ.
- History of any lymphoproliferative disorder, such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.
- History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study drug.
- History of any infection requiring antimicrobial therapy within 2 weeks prior to the first dose of study drug.
- A history of recurrent (more than one episode) herpes zoster, disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
- A patient who was vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of study drug, expects to be vaccinated or exposed to these vaccines during treatment, or during the 6 weeks following discontinuation of study drug.
- A patient with any condition possibly affecting oral drug absorption, eg, gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. *Procedures such as gastric* banding*, that simply divide the stomach into separate chambers, are NOT exclusionary.*
- History of alcohol or substance abuse, unless in full remission for greater than 6 months prior to first dose of study drug.
- Screening 12-lead ECG that demonstrates clinically relevant abnormalities which may affect patient safety or interpretation of study results
- A patient with a first-degree relative with a hereditary immunodeficiency.
- A patient with a malignancy or with a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ
- Significant trauma or major surgery within 1 month of screening visit.
- A patient requiring prohibited concomitant medications including prohibited dietary supplements. Prohibited concomitant medications must be

discontinued at least 4 weeks prior to the first dose of study drug, with the exception of amiodarone which must be discontinued for at least 290 days prior to the first dose of study drug.
- A patient infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses
- A patient who has previously participated in any study of CP-690,550.
- A patient who has an allergy/hypersensitivity to methotrexate, or previous serious toxicity when administered methotrexate.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
- A patient who, in the opinion of the Investigator or Pfizer, will be uncooperative or unable to comply with study procedures.

Concomitant Medications

1. Required concomitant medications:
   - Background MTX is well defined and appropriate for the study design: Patients need to have received continuous oral or parenteral MTX for at least 4 months, and be on stable doses of 7.5 to 25 mg (higher doses are not permitted) weekly for at least 6 weeks, prior to the first dose of the study drug.
   - Folic acid in usual doses for at least 4 weeks prior to the first dose of the study drug.
2. Stable background pain and other arthritis therapy, are defined. Steroids use at stable doses is allowed but i.v. and i.m. steroids are not allowed. Intra-articular steroids (40 mg maximum) are allowed as a rescue therapy.
3. Other concomitant medications, including use of herbals are detailed in the protocol.
4. Rescue therapies are detailed in the protocol.
5. Disallowed concomitant medications. A list of prohibited medications is provided and appears inclusive and acceptable (Appendix 4).

Assignment to Treatment Group

A patient who had signed an informed consent document to participate in the study, had undergone all screening procedures, and had met all inclusion and none of the exclusion criteria for participation in the study at the baseline visit was eligible to be randomized into this study. Patient randomization was accomplished using Impala (an automated web/telephone randomization system provided by the Sponsor).

Blinding

This study was patient-, investigator-, and Sponsor-blinded. The DSMB had access to unblinded treatment information during the clinical study. At the initiation of the study, the study site was instructed on using Impala for breaking the blind. Blinding was only to be broken in emergency situations for reasons of patient safety. The investigator was required to attempt to contact the Sponsor before breaking the blind. When the blind for a patient had been broken, the reason was to be fully documented. At all times, treatment and randomization information was to be kept confidential and was not to be released to the investigator/study staff until the conclusion of the study.

Schedule of Assessments

Table 91. Schedule of Assessments in Study 1032

SCHEDULE OF ACTIVITIES

Protocol Activity		Screening[1]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
			Baseline Day 0	2 wks	1 mo	3 mo	4.5 mo	6 mo or Early Termination
Informed Consent RA Diagnosis, Family and Medical History[2]		X						
Prior/Concomitant Medications		X	X	X	X	X	X	X
Complete Physical Examination		X	X					X
Targeted Physical Examination[3]				X	X	X	X	
Vital Signs, Temperature		X	X	X	X	X	X	X
QuantiFERON-Gold®™ or PPD		X						
Radiograph of Chest[11]		X						
12-lead Electrocardiogram		X						X
Blood/Urine	Hematology,[4] Urinalysis	X	X	X	X	X	X	X
	Lipid Profile (fasting)[5,10]		X		X	X		X
	Chemistry [6, 10]	X	X	X	X	X	X	X
	Urine Pregnancy Test (HCG)[7]	X	X	X	X	X	X	X
	HIV, HBsAg, HCV Ab	X						
	Rheumatoid Factor / Anti CCP Antibodies		X					X
	Stool Examination for Parasites (Brazil only)	X						
	Molecular Profiling[8]		X	X	X	X		X
	C-Reactive Protein (CRP)	X	X	X	X	X	X	X
ACR/DAS	Erythrocyte Sedimentation Rate (ESR)[9]	X	X			X		X
	Tender/Painful Joint Count, Swollen Joint Count	X	X	X	X	X	X	X
	Patient Assessment of Arthritis Pain		X	X	X	X	X	X
	Patient Global Assessment of Arthritis		X	X	X	X	X	X
	Physician Global Assessment of Arthritis		X	X	X	X	X	X
	Health Assessment Questionnaire – Disability Index		X	X	X	X	X	X
SF-36 (Version 2, Acute)			X	X	X	X		X
MOS Sleep Scale/FACIT-Fatigue Scale			X	X	X	X		X
EuroQol EQ-5D			X		X	X		X
Work Limitations and RA Healthcare Resource Utilization Questionnaires			X			X		X
Randomization			X					
Drug Dispensing			X			X		
Drug Accountability				X	X	X	X	X
Adverse Event Reporting			X	X	X	X	X	X
Review Entry Criteria for A3921024/A3921029								X

The protocol provides for independent DSMB which will review the accumulated safety data on ongoing basis and make recommendations that may impact the conduct of the study.

Efficacy Parameters

- Primary Endpoints:
  1. ACR 20 responder rate versus placebo at the Month 3 visit.

2. Change from baseline in the HAQ-DI versus placebo at the Month 3 visit.
3. Rate of patients achieving a DAS28-4(ESR) <2.6 at Month 3 visit

- Secondary Efficacy Endpoints.
  1. ACR20 responder rates at all time points other than Month 3.
  2. ACR 50 and ACR 70 responder rates at all time points.
  3. DAS28 at all time points.
  4. HAQ-DI at all time points other than Month 3.
- Safety Endpoints:
  1. All AEs will be summarized descriptively to include: Incidence and severity; Incidence of adjudicated cardiovascular events; Incidence of adjudicated malignancies; Incidence and severity of clinical laboratory abnormalities; Summary of changes in physical examination compared to baseline by subject; Mean change from baseline in vital signs (BP, HR, and Temperature)

Study Conduct

Started 10.12.2009, Completed 03.17.2011

Amendments:

- Protocol Amendment 1 (December 04, 2009): The purpose of this amendment was to specify a maximum allowable dose of MTX for patients in Ireland, and to ensure adherence to contraception requirements for MTX in these patients. Additionally, the amendment outlined an exclusion for patients in Ireland being actively treated for latent or active TB.
- Protocol Amendment 2 (May 10, 2010; 154 patients enrolled): The main purpose of this amendment was to add an additional primary objective and endpoint in order to compare the rate of achieving DAS28-4(ESR) <2.6 at Month 3 in patients with active RA on background MTX who have had an inadequate response to a TNF inhibitor, after administration of CP 690,550 in doses of 5 mg BID and 10 mg BID vs placebo.
- Protocol Amendment 3 (December 13, 2010, 399 patients enrolled, recruitment closed) Text regarding the follow-up of AEs and laboratory abnormalities was updated; and a section for potential cases of drug-induced liver injury was added.

The protocol amendments did not negatively impact the study conduct, efficacy or safety evaluations.

Patient Disposition

Patient disposition in study 1032 is presented in Table 13 above and was consistent with the patient disposition in the rest of the Phase 3 studies in RA as summarized in above in Section 6.1.3 Subject Disposition.

Baseline Demographics and Disease Characteristics

Patient baseline demographics in study 1032 is presented in Table 11 and Table 12 above and are representative of adult patients with moderately-to-severely active RA who have failed at least one TNF inhibitor. The baseline disease characteristics were well balanced across the treatment arms and generally consistent with the rest of the Phase 3 studies.

Efficacy Results

For discussion on efficacy, refer to Section 6 Review of Efficacy, which contains the individual study results for study 1032 along with the results from the Phase 3 efficacy studies.

Safety Results

For discussion on safety, refer to Section 7 Review of Safety.

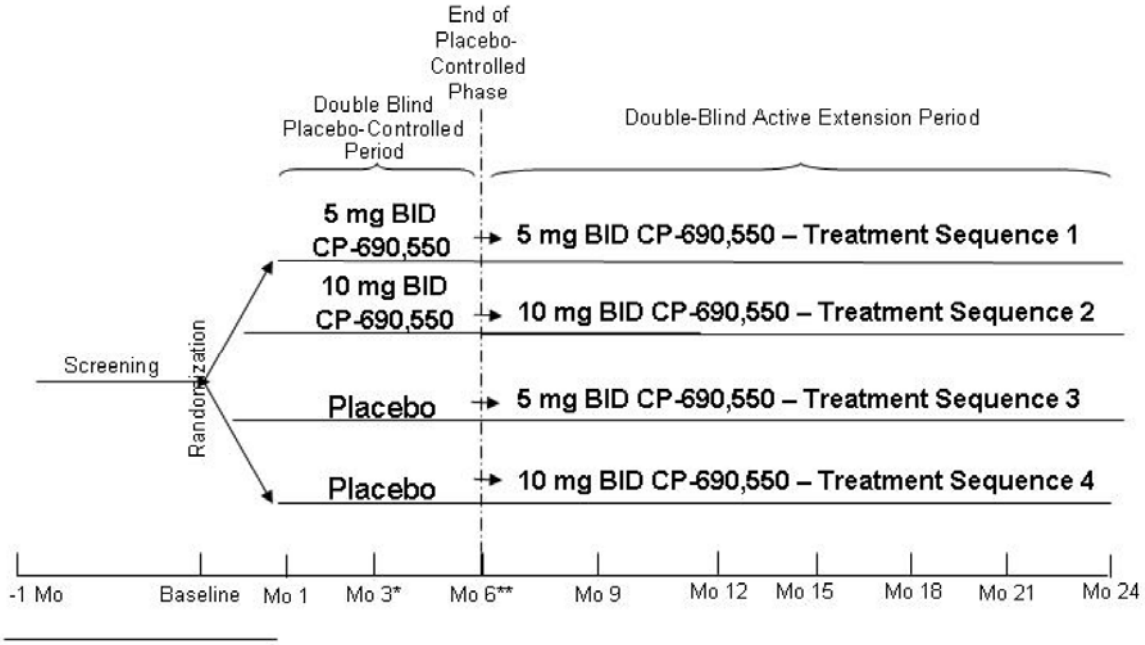
9.4.4 Study A3921044 (Phase 3)

Study Protocol

Overall Study Design

This is a Phase 3 randomized, 2-year, double-blind, placebo-controlled, parallel group study. Patients were randomized in a 4:4:1:1 ratio to 1 of the following 4 parallel treatment sequences as shown in Figure 26. At the Month 3 visit, if there was not at least a 20% improvement in both the tender/painful and swollen joint counts as reported in the study database, the patient was considered a nonresponder who was then advanced in a blinded fashion to a pre-randomized treatment with either tofacitinib 5 or 10 mg BID.

Figure 26. Study 1044 Design Schema



* At Mo 3 nonresponders will be blindly advanced to the active extension period of their respective Treatment Sequence.

** At Mo 6 all subjects, not previously advanced, will be blindly advanced to their active extension period of their respective Treatment Sequence.

Inclusion Criteria

Major inclusion criteria included:

- The patient was required to meet the ACR classification criteria for the diagnosis of RA
- Evidence of at least 3 distinct joint erosions on posteroanterior (PA) hand and wrist or anteroposterior (AP) foot radiographs (locally read) OR if radiographic evidence of joint erosion was not available, the patient must have had an RF+, as determined by an acceptable laboratory method, OR antibodies to anti-CCP+, as determined by an acceptable laboratory method;
- The patient must have had active disease at both Screening and Baseline, as defined by having both:
  - ≥6 tender/painful joints on motion, and;
  - ≥6 swollen joints.
- The patient must have had 1 of the following criteria at Screening:
  - ESR (Westergren method) >28 mm/hr, or;
  - C-Reactive protein (CRP) >7 mg/L in the central laboratory.
- The patient must have met Class I, II, or III of the ACR 1991 Revised Criteria for Global Functional Status in RA
- The patient must have taken oral or parenteral MTX continuously for at least 4 months prior to the first dose of study drug and have been on a stable weekly dose for at least 6 weeks prior to the first dose of study drug. Stable weekly doses less than 15

mg were allowed only in the presence of intolerance to or toxicity from higher doses or where higher doses would violate the local label. Doses higher than 25 mg weekly were not permitted under any circumstances.

- Patients were to be on an adequate and stable dose of folic acid (not less than 5 mg weekly, unless higher doses would violate the local label) for at least 4 weeks prior to the first dose of study drug.
- The patient must have had an inadequate clinical response to MTX defined as the presence of sufficient residual disease activity to meet the entry criteria.
- The patient was required to be at least 18 years of age or older;
- The patient must have discontinued all disallowed concomitant medications for the required time prior to the first dose of study drug and must have been taking only those concomitant medications in doses and frequency allowed by the protocol
- Women of childbearing potential must have tested negative for pregnancy prior to enrollment in this study;
- Sexually active women of childbearing potential and men whose partners were women of childbearing potential were required to use adequate contraceptive methods during participation in this trial, as required for men and women on MTX therapy.
- No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by all of the following:
    - A negative QuantiFERON-TB Gold In-Tube test or, if unavailable, a Mantoux Purified Protein Derivative (PPD) skin test using 5 tuberculin units per 0.1 mL (5 TU PPD) result of <5 mm of induration (<20 mm erythema in Japan), performed within 3 months prior to Screening. (It was strongly recommended that patients with a history of Bacille Calmette Guérin [BCG] vaccination be tested with the QuantiFERON-TB Gold In-Tube test);
    - A chest radiograph taken within 3 months prior to Screening without changes suggestive of active TB infection;
    - No history of either untreated or inadequately treated latent or active TB infection;
    - If a patient had previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a PPD test nor a QuantiFERON-TB Gold In-Tube test needed to be obtained, but a chest radiograph must still have been obtained if not done within the previous 3 months. A patient who was currently being treated for either latent or active TB infection could only have been enrolled with confirmation of current incidence rates of multi-drug resistant TB infection, documentation of an adequate treatment regimen, and prior approval of the Sponsor.

Exclusion Criteria

Major exclusion criteria were:

- Pregnancy or currently lactating;
- Blood dyscrasias, including confirmed:
  - Hemoglobin <9 g/dL or Hematocrit <30%;
  - White blood cell (WBC) count $<3.0\times10^9$/L;
  - Absolute neutrophil count (ANC) $<1.2\times10^9$/L; and
  - Platelet count $<100\times10^9$/L.
- Estimated glomerular filtration rate (GFR) <40 mL/min based on Cockcroft-Gault calculation
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 1.5× the upper limit of normal (ULN) at Screening or any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the patient's participation in the study;
- Current or recent history of uncontrolled clinically significant renal, hepatic, hematological, gastrointestinal, endocrine, metabolic (including uncontrolled clinically significant hypercholesterolemia), pulmonary, cardiac, or neurological disease;
- History of any other rheumatic autoimmune disease, other than Sjögren's syndrome;
- History of an infected joint prosthesis at any time, with the prosthesis still in situ;
- History of any lymphoproliferative disorder, such as EBV-related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease;
- History of recurrent (more than 1 episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex;
- History of any infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study drug;
- History of any infection requiring antimicrobial therapy within 2 weeks prior to the first dose of study drug;
- Any prior treatment with non B cell-specific lymphocyte depleting agents/therapies [eg, alemtuzumab (Campath), alkylating agents (eg, cyclophosphamide or chlorambucil), total lymphoid irradiation, etc]. Patients who had received rituximab or other selective B lymphocyte depleting agents (including experimental agents) were eligible if they had not received such therapy for at least 1 year prior to study Baseline and had normal CD 19/20+ counts by fluorescence activated cell sorting (FACS) analysis;
- Any patient who had been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study drug or was to be vaccinated with these vaccines at any time during treatment or within 6 weeks following discontinuation of study drug. (See protocol, Section 16.1.1, for further information regarding avoidance of household contacts who may have been vaccinated);
- A patient with any condition possibly affecting oral drug absorption, eg, gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding, that simply divide the stomach into separate chambers, were NOT exclusionary;
- History of alcohol or drug abuse with less than 6 months of abstinence prior to first dose of study drug;

- Screening 12-lead electrocardiogram (ECG) that demonstrated clinically relevant abnormalities that may affect patient safety;
- A patient with a first-degree relative with a hereditary immunodeficiency;
- A patient with a malignancy or with a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ;
- Significant trauma or surgery procedure within 1 month prior to first dose of study drug;
- A patient requiring prohibited concomitant medications including prohibited dietary supplements listed in the protocol (Section 16.1.1);
- A patient known to be infected with human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus;
- A patient who had previously participated in any study of CP-690,550;
- A patient who had an allergy/hypersensitivity to MTX, or previous serious toxicity when administered MTX;
- Participation in studies of investigational compounds within 4 weeks or 5 half-lives (whichever was longer) prior to the first dose of study drug.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study;
    - In Japan, because of the higher risk of interstitial pneumonia in Japanese RA patients than in Western patients with RA, investigators were to carefully evaluate patients who exhibited symptoms, especially fever or cough. If clinical laboratory findings (serum ß-D-glucan, KL-6) or findings on the chest radiograph (taken within 3 months prior to Screening) were suggestive of serious lung disease, such as interstitial pneumonia, the patient was to be excluded from enrollment in this study. If uncertainty still existed, the investigator may have considered obtaining a chest computed tomography (CT) scan for further evaluation in consultation with the Sponsor's study clinician.

Concomitant Medications

Patients continued on their stable background arthritis therapy, which must have included MTX supplemented with folic acid and could have included nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, opioids, acetaminophen, and/or low dose oral corticosteroids (≤10 mg prednisone or equivalent per day) throughout the study.

Assignment to Treatment Group

A patient who had signed an informed consent document to participate in the study, had undergone all Screening procedures, and had met all inclusion and none of the exclusion criteria for participation in the study at the Baseline visit was eligible to be randomized into

this study. Patient randomization was accomplished using Impala (an automated web/telephone randomization system).

Blinding

This study was patient-, investigator-, and Sponsor-blinded. At all times, treatment and randomization information was to be kept confidential and was not to be released to the investigator/study staff until the conclusion of the study.

Schedule of Assessments

Table 92. Schedule of Assessments in Study 1044

		Screening[a]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
			Baseline Day 0	1 mo	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	21 mo	24 mo/ EOS
Informed Consent, RA Activity, Medical History[b]		X										
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination		X	X					X				X
Targeted Physical Examination[c]				X	X	X	X		X	X	X	
Vital Signs, Temperature		X	X	X	X	X	X	X	X	X	X	X
QuantiFERON-Gold or PPD, Radiograph of Chest		X										
12-lead Electrocardiogram		X						X				X
Radiograph of Hands & Feet[d]			X		X[e]	X		X				X
Blood/Urine	Rheumatoid Factor, anti-CCP	X	X									X
	Hematology[f], Chemistry Panel[g]	X	X	X	X	X	X	X	X	X	X	X
	Lipid Profile (fasting)[h]		X	X	X	X	X	X		X		X
	CBC with Differential & Chemistry Labs[i]	As appropriate for Standard of Care										
	Urine/Urine Pregnancy Test (HCG)[j]	X	X	X	X	X	X	X	X	X	X	X
	Stool Examination for Parasites (Brazil only)	X										
	Molecular Profiling Sampling (pharmacogenomic)[k]		X	X	X	X		X		X		X
	HIV Serology, HBsAg, HCV Ab	X										
ACR/ DAS	C-Reactive Protein (CRP)	X	X	X	X	X	X	X	X	X	X	X
	Erythrocyte Sedimentation Rate (ESR)[l]	X	X	X	X	X	X	X	X	X	X	X
	Tender/Painful Joint Count, Swollen Joint Count	X	X	X	X	X	X	X	X	X	X	X
	Patient Assessment of Arthritis Pain		X	X	X	X	X	X	X	X	X	X
	Patient Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X	X
	Physician Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X	X
	Health Assessment Questionnaire – Disability Index		X	X	X	X	X	X	X	X	X	X
SF-36 (Version 2, Acute)			X	X	X	X	X	X	X	X	X	X
MOS Sleep Scale/FACIT- Fatigue Scale			X	X	X	X		X		X		X
EuroQol EQ-5D, Work Limitations Questionnaire			X		X	X		X		X		X
RA Healthcare Resource Utilization Questionnaire			X		X	X		X		X		X
Randomization			X									
Drug Dispensing			X		X	X	X	X	X	X	X	
Drug Accountability					X	X	X	X	X	X	X	X
Adverse Event Reporting			X	X	X	X	X	X	X	X	X	X
Review Entry Criteria for A3921024/A3921041 (in Japan only)												X

Abbreviations: ACR=American College of Rheumatology, DAS=disease activity score, mo=month, EOS=end of study, RA=rheumatoid arthritis, LDL=low density lipoprotein, HDL=high density lipoprotein, RBC=red blood cell, WBC=white blood cell, CCP=cyclic citrullinated peptide, FACIT=Functional Assessment of Chronic Illness Therapy, SF-36=Short Form-36, MOS=Medical Outcomes Study, EuroQol EQ-5D=European Quality of Life 5-dimension scale, HIV=human immunodeficiency virus, HBsAg=hepatitis B surface antigen, HCV Ab=hepatitis C virus antibody, HCG=human chorionic gonadotropin, PPD=purified protein derivative, CBC=complete blood count

[a]Screening Visit occurred within 1 month prior to the Baseline Visit.

[b]Medical History included smoking status, average weekly alcohol consumption, family history of premature coronary heart disease (CHD).

[c]Targeted physical exam consisted of weight, examination of heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes.

[d]Hand and foot radiographs were read and scored centrally.

[e]Only nonresponders who were identified at Month 3 had hand and feet radiographs taken.

[f]Hematology included RBC, WBC with differential, hemoglobin, hematocrit, and platelet count.

[g]Chemistry Panel included blood urea nitrogen (BUN), creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma glutamyl transferase (GGT), albumin, creatine kinase (CK). In Japan, serum β-D-glucan and KL-6 were also obtained at Screening.

[h]Lipid Profile included fasting total cholesterol, LDL, HDL, and triglycerides; apolipoprotein A1 and B and other lipoprotein tests potentially including particle size measurements were obtained at Baseline and Months 3, 6, 9, 12, 18, and 24.

[i]Chemistry laboratories as appropriate for standard of care in patients receiving methotrexate; may have included creatinine, albumin and liver tests.

[j]Urinalysis included specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase. Urine pregnancy testing (β-HCG) was required only for women who were of childbearing potential; may have been repeated more frequently if required by local practices, if a menstrual cycle was missed, or if potential pregnancy was otherwise suspected.

[k]Only at sites participating in the molecular profiling (pharmacogenomic) research component. Refer to Molecular Profiling Supplement (Section 16.1.1) for further details.

[l]At sites where local laboratory had the capability of reporting results only to the central lab.

Efficacy Parameters

This study had 4 primary efficacy endpoints in the following hierarchical order:

- Signs and symptoms as measured by ACR20 at Month 6;

- Structure preservation as measured by the modified Total Sharp Score (mTSS) change from Baseline at Month 6;
- Physical function as measured by the HAQ-DI change from Baseline at Month 3; and
- Incidence of DAS28-4(ESR) <2.6 at Month 6.

Secondary endpoints are summarized in Table 8.

Study Conduct

Started 03.31.2009, Ongoing (NDA submission cut-off date 04.01.2011)

Amendments:

There were five global amendments:

- Protocol Amendment 1 (January 21, 2009, prior to starting the study):
  - Removed primary objective to compare the incidence of major clinical response and clarified secondary objectives;
  - Clarified guidelines for background therapy and safety guidelines
- Protocol Amendment 2 (July 06, 2009, 59 subjects enrolled):
  - Clarified analyses of HAQ-DI;
  - Clarified guidelines for background therapy and safety guidelines
- Protocol Amendment 3 (September 14, 2009, 285 subjects enrolled):
  - Clarified guidelines on concomitant and prohibited therapies
- Protocol Amendment 4 (May 10, 2010, 800 subjects enrolled, enrollment closed):
  - Clarified provisions for long-term extension
  - Added the fourth primary outcome of DAS28-4(ESR)<2.6
- Protocol Amendment 5 (June 10, 2010) was country-specific for Japan: added details to the guidelines for assessment and treatment of Japanese patients with low lymphocyte counts or symptoms related to interstitial pneumonia.
- Protocol Amendment 6 (December 13, 2010, 800 subjects enrolled, enrollment closed):
  - Added description of statistical analyses.

While the protocol and the statistical analysis plan were amended, including after all patients were enrolled, the implementation of these amendments did not negatively impact the study conduct, efficacy or safety evaluations.

Patient Disposition

Patient disposition in study 1044 is presented in Table 13 above and was consistent with the patient disposition in the rest of the Phase 3 studies in RA as summarized in above in Section 6.1.3 Subject Disposition.

Baseline Demographics and Disease Characteristics

Patient baseline demographics in study 1044 is presented in Table 11 and Table 12 above and are representative of adult patients with moderately-to-severely active RA. The baseline disease characteristics were well balanced across the treatment arms and generally consistent with the rest of the Phase 3 studies.

Efficacy Results

For discussion on efficacy, refer to Section 6 Review of Efficacy, which contains the individual study results for study 1044 along with the results from the Phase 3 efficacy studies.

Safety Results

For discussion on safety, refer to Section 7 Review of Safety.

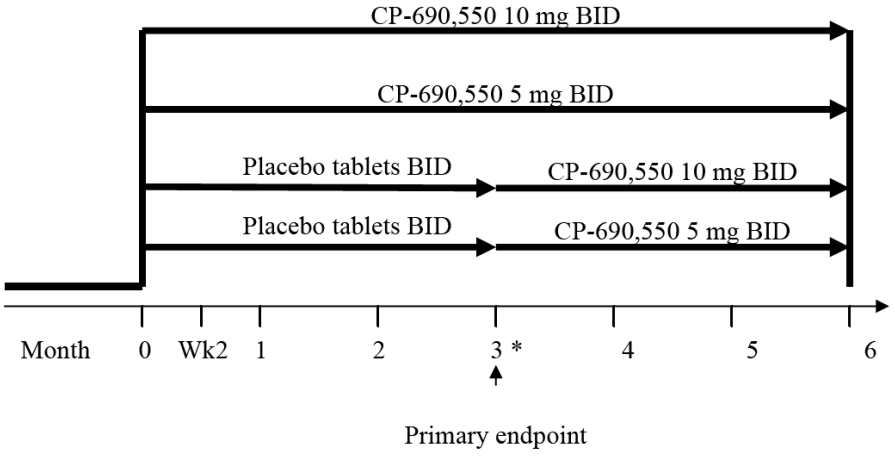
9.4.5 Study A3921045 (Phase 3)

Study Protocol

Overall Study Design

This was a Phase 3, randomized, 6-month, double-blind, placebo-controlled, parallel-group study. Patients were randomized in a 4:4:1:1 ratio to 1 of the following 4 parallel treatment sequences shown in Figure 27

Figure 27. Study 1045 Design Schema



Inclusion Criteria

Major inclusion criteria were:

- Evidence of a signed and dated informed consent document indicating that the patient had been informed of all pertinent aspects of the study.
- At least 18 years of age.
- Sexually active women of childbearing potential and men whose partners were women of childbearing potential were required to use adequate contraceptive methods during participation in this study. Further description of the requirements and a list of contraceptives considered effective and acceptable for use in this study are outlined in the protocol.
- Diagnosis of RA based upon the ACR 1987 Revised Criteria
- Active disease at both Screening and Baseline, as defined by both
    - ≥6 joints tender or painful on motion; AND
    - 6 joints swollen.
    - and fulfilled 1 of the following 2 criteria at Screening:
        - ESR (Westergren method) >28 mm in the local laboratory; or
        - CRP >7 mg/L in the central laboratory.
- Met ACR 1991 Revised Criteria for Global Functional Status in RA,6 Class I, II, or III
- No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by all of the following:
    - A negative QuantiFERON-Gold test or, if unavailable, a Mantoux Purified Protein Derivative (PPD) skin test using 5 tuberculin units (TU) per 0.1 mL (5 TU PPD) with a result of <5 mm of induration performed within the 3 months before Screening. It was strongly recommended that patients with a history of Bacille Calmette Guérin (BCG) vaccination be tested with the QuantiFERON-Gold test.
    - A chest radiograph taken within the 3 months before Screening without changes suggestive of active TB infection.
    - No history of either untreated or inadequately treated latent or active TB infection.
    - If a patient had previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multidrug TB resistance were <5% or an acceptable alternative regimen) or active (acceptable multidrug regimen) TB infection, neither a PPD test nor a QuantiFERON TB Gold (QFT-G) test need to have been obtained, but a chest radiograph must still have been obtained if not done within the previous 3 months. A patient who was currently being treated for either latent or active TB infection could only have been enrolled with confirmation of current incidence rates of multidrug resistant TB infection, documentation of an adequate treatment regimen, and with prior approval by the Sponsor.
- Inadequate response to at least 1 DMARD (traditional or biologic) due to lack of efficacy or toxicity.
- For traditional DMARDs, the following minimum washout criteria applied:
    - MTX, minocycline, penicillamine, and sulfasalazine must have been discontinued for 4 weeks before the first dose of study drug.
    - Leflunomide must have been discontinued 8 weeks before the first dose of study drug if no elimination procedure was followed. Alternately, it should have

been discontinued with the following elimination procedure at least 4 weeks before the first dose of study drug: cholestyramine at a dosage of 8 grams 3 times daily for at least 24 hours, or activated charcoal at a dosage of 50 grams 4 times daily for at least 24 hours.
    - Auranofin (Ridaura) or injectable gold (aurothiglucose or aurothiomalate) must have been discontinued for 8 weeks before first dose of study drug.
    - Antimalarials (hydroxychloroquine, chloroquine): antimalarials were allowed in this study. If discontinued, they were required to be discontinued for 4 weeks before the first dose of study drug. If continued, the dose was required to be stable for at least 8 weeks before the first dose of study drug.
- Biologic response modifiers were required to be discontinued for entry into this study:
    - Anakinra (Kineret) and Enbrel (etanercept) were to be discontinued 4 weeks before the first dose of study drug;
    - Adalimumab (Humira) was to be discontinued for 6 weeks before the first dose of study drug;
    - Infliximab (Remicade) was to be discontinued 8 weeks before the first dose of study drug;
    - Certolizumab pegol (Cimzia) and golimumab (Simponi) were to be discontinued for 10 weeks before the first dose of study drug;
    - Abatacept (Orencia) and tocilizumab (Actemra) were to be discontinued 12 weeks before the first dose of study drug; and
    - Rituximab or other selective B lymphocyte depleting agents (both marketed or investigational) were to be discontinued for 1 year before the first dose of study drug and CD19/20+ counts were required to be normal by fluorescence activated cell sorting (FACS) analysis.
- Other:
    - Oral corticosteroids: Patients who were already on oral corticosteroids were required to be on a stable dose of .10 mg/day of prednisone or equivalent for 4 weeks before the first dose of study drug;
    - Intra-articular, intramuscular, or intravenous corticosteroids: None were allowed to be administered within 4 weeks before the first dose of study drug;
    - Cyclosporine, tacrolimus, and azathioprine were to be discontinued 4 weeks before the first dose of study drug;
    - Prosorba Device/Column was to be discontinued 4 weeks before the first dose of study drug;
    - Experimental nonsteroidal anti-inflammatory drugs (NSAIDs; including cyclooxygenase-2 [COX-2] inhibitors) were to be discontinued 4 weeks before the first dose of study drug; and
    - Any investigational or marketed treatment not mentioned elsewhere was required to be discontinued for 4 weeks or 5 half lives, whichever was longer, before the first dose of study drug. Exposure to investigational biologics was required to be discussed with the Sponsor.
- Patients receiving allowed concomitant medications for any reason were required to be willing to stay on a stable regimen.

Exclusion Criteria

Major exclusions criteria were:

- Any prior treatment with non-B lymphocyte-selective lymphocyte depleting agents/therapies, such as alemtuzumab (Campath), alkylating agents (eg, cyclophosphamide or chlorambucil), or total lymphoid irradiation.
- Pregnant or lactating females.
- Blood dyscrasias, including confirmed
    - Hemoglobin <9 g/dL or hematocrit <30%;
    - White blood cell (WBC) count <3.0 × 109/L;
    - Absolute neutrophil count (ANC) <1.2 × 109/L; or
    - Platelet count <100 × 109/L.
    - Estimated glomerular filtration rate (GFR) ≤40 mL/min based on Cockcroft-Gault calculation.
- Total bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) >1.5 × the upper limit of normal (ULN) at the Screening visit.
- Current or recent history of uncontrolled clinically significant renal, hepatic, hematological, gastrointestinal, endocrine, metabolic, pulmonary, cardiac, or neurological disease.
- History of any other autoimmune rheumatic disease other than Sjogren's syndrome.
- History of an infected joint prosthesis at any time, with the prosthesis still in situ.
- History of any lymphoproliferative disorder, such as Epstein Barr virus (EBV)-related lymphoproliferative disorder, or history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.
- History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months before the first dose of study drug.
- History of any infection requiring antimicrobial therapy within 2 weeks before the first dose of study drug.
- History of recurrent (more than 1 episode) herpes zoster, disseminated (a single episode) herpes zoster, or disseminated (a single episode) herpes simplex.
- Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks before the first dose of study drug, or expected to be vaccinated or exposed to these vaccines during treatment or during the 6 weeks following discontinuation of study drug.
- Any condition possibly affecting oral drug absorption (eg, gastrectomy), clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery (eg, gastric bypass). Procedures such as gastric banding, that simply divide the stomach into separate chambers, were NOT exclusionary.
- History of alcohol or drug abuse with less than 6 months of abstinence before the first dose of study drug.
- Screening 12-lead electrocardiogram (ECG) that demonstrated clinically relevant abnormalities that may have affected patient safety or interpretation of the study results.

- First-degree relative with a hereditary immunodeficiency.
- Malignancy or history of malignancy, with the exception of adequately treated or excised nonmetastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
- Significant trauma or major surgery within 1 month of the Screening visit.
- Required prohibited concomitant medications, including prohibited dietary supplements.
- Infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses.
- Had previously participated in any study of CP-690,550.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or study drug administration, or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.

Concomitant Medications

Patients were allowed to remain on antimalarial medications during the study. The antimalarial therapy was required to be stable for at least 8 weeks before the first dose of study drug, and must remain so during the study treatment period, except if an adjustment was needed to protect a patient's safety. No other DMARDs (traditional or biologic) were allowed as concomitant therapy during the study. All other DMARDs (traditional and biologic) were required to be washed out as per the Inclusion/Exclusion criteria.

Patients were required to remain on stable dosages of NSAIDs, selective COX-2 inhibitors, and/or low dose oral corticosteroids (.10 mg prednisone or equivalent per day) throughout the study.

Intravenous or intramuscular corticosteroids were not allowed during this study either as a stable concomitant medication or as rescue medication.

Assignment to Treatment Group

A patient who had signed an informed consent document to participate in the study, had undergone all Screening procedures, and had met all inclusion and none of the exclusion criteria for participation in the study at the Baseline visit was eligible to be randomized into this study.

Patient randomization was accomplished using Impala (an automated web/telephone randomization system).

Blinding

This study was patient-, investigator-, and sponsor-blinded. At all times, treatment and randomization information was to be kept confidential and was not to be released to the investigator/study staff until the conclusion of the study.

Schedule of Assessments

Table 93. Schedule of Assessments in Study 1045

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Protocol Activity	Screening[a]	Visits							
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
		Baseline Day 0	2 W	1 M	2 M	3 M	4 M	5 M	6 M or Early Termination
Informed consent	X								
RA diagnosis; family and medical history[b]	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Complete physical examination	X	X							X
Targeted physical examination[c]			X	X	X	X	X	X	
Vital signs, temperature	X	X	X	X	X	X	X	X	X
QuantiFERON-Gold or PPD/ radiograph of chest	X								
12-lead electrocardiogram	X								X
Hematology,[d] urinalysis	X	X		X	X	X	X	X	X
Lipid profile (fasting)[e]		X		X		X			X
Chemistry 1[f]	X	X							X
Chemistry 2[g]				X	X	X	X	X	
Urine pregnancy test (HCG)[h]	X	X	X	X	X	X	X	X	X

Source: protocol (Section 16.1.1)
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CBC = complete blood count, CK = creatine kinase, CO_2 = carbon dioxide, GGT = gamma glutamyl transferase, HCG = human chorionic gonadotropin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, M = month, PPD = purified protein derivative, RA = rheumatoid arthritis, RBC = red blood cell count, W = week, WBC = white blood cell
[a] Screening visit occurred within 1 month (±10 days) before the Baseline Visit.
[b] Medical history included smoking status, average weekly alcohol consumption, and family history of premature coronary heart disease.
[c] Targeted physical examination consisted of weight and examination of heart, lungs, abdomen, and lymph nodes.
[d] Hematology included CBC (RBC count, WBC count with differential, hemoglobin, hematocrit, and platelet count).
[e] Lipid profile included fasting total cholesterol, LDL, HDL, and triglycerides. Additional lipoprotein tests, potentially including apolipoprotein A1, apolipoprotein B, and particle size measurements were performed at Baseline, Month 3, and Month 6/Early termination.
[f] Chemistry 1 (full serum chemistry) included blood urea nitrogen, creatinine, glucose (fasting), calcium, sodium, potassium, chloride, total CO_2, AST, ALT, total bilirubin, alkaline phosphatase, albumin, GGT, and CK.
[g] Chemistry 2 included serum hepatic function testing (AST, ALT, total bilirubin, GGT, alkaline phosphatase, and albumin), serum creatinine, and CK.
[h] Urinary pregnancy testing (HCG) was required only for women who were of childbearing potential; may have been repeated more frequently if required by local practices, if a menstrual cycle was missed, or if potential pregnancy was otherwise suspected.

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Protocol Activity		Screening[a]	Visits							
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
			Baseline Day 0	2 W	1 M	2 M	3 M	4 M	5 M	6 M or Early Termination
HIV, HBsAg, HCV Ab		X								
Rheumatoid factor/ anti-CCP antibodies			X							X
Stool examination for parasites (Brazil only)		X								
Molecular profiling[i]			X	X	X		X			X
ACR/DAS	C-reactive protein (CRP)	X	X	X	X	X	X	X	X	X
	ESR[j]	X	X				X			X
	Tender/ painful joint count, swollen joint count	X	X	X	X	X	X	X	X	X
	Patient assessment of arthritis pain		X	X	X	X	X	X	X	X
	Patient global assessment of arthritis		X	X	X	X	X	X	X	X
	Physician global assessment of arthritis		X	X	X	X	X	X	X	X
	HAQ-DI		X	X	X	X	X	X	X	X
PRO scales[k]			X				X			X
Randomization			X							
2 Week IVRS diary instruction (US only)[l]			X							
Drug dispensing			X				X			
Drug accountability				X	X	X	X	X	X	X
Adverse event reporting			X	X	X	X	X	X	X	X
Review entry criteria for A3921024/ A3921029									X	X

Source: protocol (Section 16.1.1)
Abbreviations: CCP = cyclic citrullinated peptide, EQ-5D = self-report questionnaire (quality of life instrument) developed by the European Quality of Life (EuroQoL) Group, ESR = erythrocyte sedimentation rate, EuroQoL = European Quality of Life [Group], FACIT = Functional Assessment of Chronic Illness Therapy, HAQ-DI = Health Assessment Questionnaire-Disability Index, HBsAg = hepatitis B surface antigen, HCV Ab = hepatitis C virus antibody, HIV = human immunodeficiency virus, IVRS = Interactive Voice Response System, M = month, MOS-SS = Medical Outcomes Study Sleep Scale, PRO = patient-reported outcomes, RA = rheumatoid arthritis, SF-36 = Short Form-36, US = United States, W = week
[a] Screening visit occurred within 1 month (+10 days) before the Baseline visit.
[i] See Molecular Profiling Protocol Supplement (Appendix 16.1.1).
[j] All ESR tests performed after Screening were to be done at a local laboratory that had the capability of reporting directly to the central laboratory, keeping the results blinded from the site personnel. If ESR could not be performed in a blinded manner, the site was not to perform ESR after Screening.
[k] SF-36 (Version 2, Acute), MOS-SS, FACIT-Fatigue Scale, EuroQoL EQ-5D, Work Limitations Questionnaire, and RA Healthcare Resource Utilization Questionnaire
[l] Patients in the United States reported daily via IVRS for 2 weeks (Patient's Assessment of Arthritis Pain and Patient's Global Assessment of Arthritis).

Efficacy Parameters

The primary efficacy endpoints were in the hierarchical order:

- ACR20 responder rate at the Month 3 visit;

- Change from Baseline in the HAQ-DI vs placebo at the Month 3 visit; and
- Rate of patients achieving a DAS28-4(ESR) <2.6 vs placebo at the Month 3 visit

Secondary endpoints are summarized in Table 8.

Study Conduct

Started 02.09.2009, Completed 06.23.2010

Amendments:

There were two global amendments:

- Protocol Amendment 1 (January 30, 2009, prior to starting the study): Clarified timing of primary endpoints and handling placebo.
- Protocol Amendment 2 (March 12, 2010, 611 enrolled, enrollment closed):
    - An additional objective and endpoint were added to compare the rate of achieving DAS28-4(ESR) <2.6 at Month 3

While the protocol was amended after all patients were enrolled, the amendment implementation did not negatively impact the study conduct, efficacy or safety evaluations.

Patient Disposition

Patient disposition in study 1045 is presented in Table 13 above and was consistent with the patient disposition in the rest of the Phase 3 studies in RA as summarized in above in Section 6.1.3 Subject Disposition.

Baseline Demographics and Disease Characteristics

Patient baseline demographics in study 1045 is presented in Table 11 and Table 12 above and are representative of adult patients with moderately-to-severely active RA. About 15-20% of patients have failed one TNF inhibitor, which is higher that in studies 1044, 1046, and 1064. The baseline disease characteristics were well balanced across the treatment arms and generally consistent with the rest of the Phase 3 studies.

Efficacy Results

For discussion on efficacy, refer to Section 6 Review of Efficacy, which contains the individual study results for study 1045 along with the results from the Phase 3 efficacy studies.

Safety Results

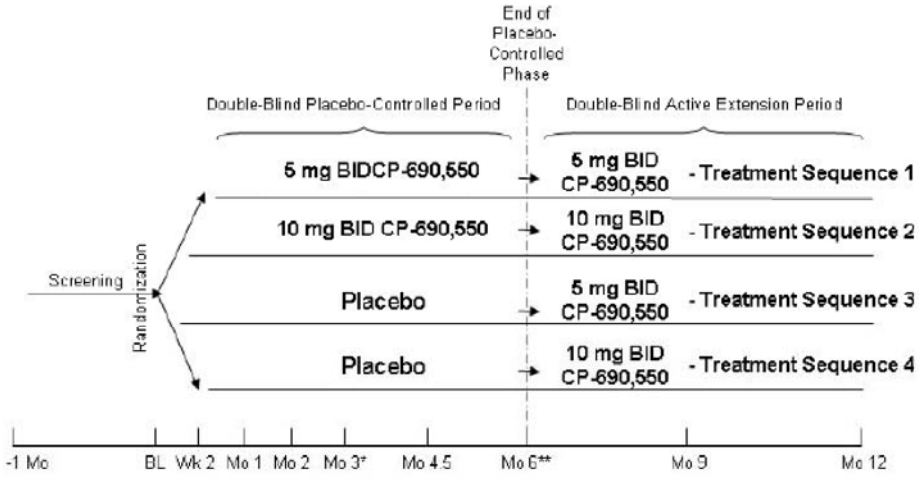
For discussion on safety, refer to Section 7 Review of Safety.

9.4.6 Study A3921046 (Phase 3)

Study Protocol

Overall Study Design
This was a Phase 3 randomized, 1-year, double-blind, placebo-controlled, parallel group study. Patients were randomized in a 4:4:1:1 ratio to 1 of the 4 parallel treatment sequences presented in

Figure 28. Study 1046 Design Schema



Source: Section 16.1.1
BID = twice daily; BL = baseline; Mo = month
*At Month 3, nonresponders were blindly advanced to the active extension period of their respective treatment sequence.
** At Month 6, all patients not previously advanced were blindly advanced to their active extension period of their respective treatment sequence.

Inclusion Criteria

Major inclusion criteria were:

- The patient must have met the ACR classification criteria for the diagnosis of RA by satisfying at least 4 of the 7 criteria
- The patient must have had active disease at both screening and baseline, as defined by having both:
  - ≥4 tender/painful joints on motion (out of 68 joints assessed); and
  - ≥4 swollen joints (out of 66 joints assessed).
- The patient must also have had active disease as defined fulfilling 1 of the 2 following criteria at screening only:
  - ESR (Westergren method) >28 mm/hr; or
  - C-reactive protein (CRP) >7 mg/L in the central laboratory.

- The patient must have met Class I, II, or III of the ACR 1991 Revised Criteria for Global Functional Status in RA.
- Patient must have had an inadequate response to at least 1 DMARD (traditional or biologic) due to lack of efficacy or toxicity.
- Patient must have remained on at least 1 background traditional DMARD and be dosed in accordance with the local regulatory label and willing to remain on that traditional DMARD throughout the course of the study. Combination therapy was allowed as consistent with local standards.
    - Methotrexate: maximum dose of 25 mg/week. Minimum duration of therapy was 4 months and the dose had to be stable for 6 weeks prior to first dose of study drug. Patients on methotrexate should have been on an adequate and stable dose of folic acid (not less than 5 mg weekly, unless higher doses violated the local label) for at least 4 weeks prior to the first dose of study drug.
    - Sulfasalazine: maximum dose of 3 g/day. Minimum duration of therapy was 2 months and dose had to be stable for 4 weeks prior to first dose of study drug.
    - Leflunomide: maximum dose of 20 mg/day. Minimum duration of therapy was 4 months and dose had to be stable for 4 weeks prior to first dose of study drug.
    - Hydroxychloroquine sulfate: maximum dose of 400 mg/day. Minimum duration of therapy was 2 months and dose had to be stable for 4 weeks prior to first dose of study drug.
    - Injectable Gold: maximum dose of 50 mg/week. Minimum duration of therapy was 6 months and dose had to be stable for 3 months prior to first dose of study drug.
    - Penicillamine: maximum dose of 1000 mg/day. Minimum duration of therapy was 6 months and dose had to be stable for 3 months prior to first dose of study drug.
    - Other traditional DMARDs may have been considered after discussion with the Sponsor.
- Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
- Patient must have been at least 18 years of age or older.
- Patient had discontinued all disallowed concomitant medications for the required time prior to the first dose of study drug and was taking only those concomitant medications in doses and frequency allowed by the protocol.
- Women of childbearing potential must have tested negative for pregnancy prior to enrollment in this study.
- Sexually active women of childbearing potential and men whose partners were women of childbearing potential were required to use adequate contraceptive methods during participation in this study. Further description of the requirements and a list of contraceptives considered effective and acceptable for use in this study can be found in the protocol
- No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by all of the following:

  - A negative QuantiFERON-Gold test or, if unavailable, a Mantoux Purified Protein Derivative (PPD) skin test using 5 tuberculin units (TU) per 0.1 mL (5 TU PPD) result of <5 mm of induration performed within the 3 months prior to screening. It was strongly recommended that patients with a history of Bacille Calmette Guérin vaccination were tested with the QuanitFERON-Gold test.
  - A chest radiograph taken within the 3 months prior to screening without changes suggestive of active TB infection.
  - No history of either untreated or inadequately treated latent or active TB infection.
  - If a patient had previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug TB resistance were <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a PPD test nor a QuantiFERON TB Gold needed to be obtained, but a chest radiograph must have been obtained if not done so within the prior 3 months. A patient who was currently being treated for either latent or active TB infection could only be enrolled with confirmation of current incidence rates of multi-drug resistant TB infection, documentation of an adequate treatment regimen, and with prior approval by the Sponsor.
- Patients receiving non-prohibited concomitant medications for any reason must have been on a stable regimen, which was defined as not having started a new drug or having changed dosage within 7 days or 5 half-lives (whichever was longer) prior to first study dose, or as defined in Concomitant Medications (See Section 9.4.7).

Exclusion Criteria

Major exclusion criteria were:

- Any DMARD use that would be contraindicated according to the local prescribing information, including use as a background medication.
- Pregnant or lactating females.
- Blood dyscrasias including confirmed:
  - Hemoglobin <9 g/dL or Hematocrit <30%
  - White blood cell count <3.0 x 10^9/L;
  - Absolute neutrophil count <1.2 x 10^9/L;
  - Platelet count <100 x 10^9/L
- Estimated glomerular filtration rate <40 mL/min based on Cockcroft-Gault calculation
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 1.5 times the upper limit of normal (ULN) at screening or any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the patient's participation in the study.
- Current or recent history of uncontrolled clinically significant renal, hepatic, hematological, gastrointestinal, endocrine, metabolic, pulmonary, cardiac, or neurological disease.
- History of any other rheumatic autoimmune disease other than Sjogren's syndrome.
- History of an infected joint prosthesis at any time, with the prosthesis still in situ.

- History of any lymphoproliferative disorder (LPD), such as EBV related LPD, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.
- History of recurrent (more than 1 episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
- History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study drug.
- History of any infection requiring antimicrobial therapy within 2 weeks prior to the first dose of study drug.
- Any prior treatment with non B-cell-specific lymphocyte depleting agents/therapies (e.g., alemtuzumab [Campath®]), alkylating agents (eg, cyclophosphamide or chlorambucil), total lymphoid irradiation, etc]. Patients who had received rituximab or other selective B lymphocyte depleting agents (including experimental agents) were eligible if they had not received such therapy for at least 1 year prior to study baseline and had normal CD 19/20+ counts by fluorescence activated cell sorting (FACS) analysis
- Any patient who had been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study drug or was to be vaccinated with these vaccines at any time during treatment or within 6 weeks following discontinuation of study drug.
- A patient with any condition possibly affecting oral drug absorption, e.g., gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding, that simply divide the stomach into separate chambers, were NOT exclusionary.
- History of alcohol or drug abuse with less than 6 months of abstinence prior to first dose of study drug.
- Screening 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities which may have affected patient safety or interpretation of study results.
- A patient with a first-degree relative with a hereditary immunodeficiency.
- A patient with a malignancy or with a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
- Significant trauma or major surgery within 1 month of screening visit.
- A patient requiring prohibited concomitant medications including prohibited dietary supplements
- A patient known to be infected with human immunodeficiency virus (HIV) or hepatitis B or C virus.
- A patient who had previously participated in any study of CP-690,550.
- Participation in studies of other investigational compounds within 4 weeks or 5 half-lives (whichever was longer) prior to the first dose of study drug. Patients could not participate in studies of other investigational compounds at any time during their participation in this study. Exposure to investigational biologics was to be discussed with the Sponsor's Medical Monitor.

- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.

Concomitant Medications

Patients continued on their stable background arthritis therapy which may have included any of the traditional DMARDs at the dosage range and intervals mentioned in the inclusion criteria. All patients were required to follow the standard of care monitoring required for such background therapies. Stable background arthritis therapy could include nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, opioids, acetaminophen, and/or low dose oral corticosteroids (≤10 mg prednisone or equivalent per day) throughout the study. Intravenous or intramuscular corticosteroids and biologic response modifiers were not allowed during this study.

Assignment to Treatment Group

A patient who had signed an informed consent document to participate in the study, had undergone all Screening procedures, and had met all inclusion and none of the exclusion criteria for participation in the study at the Baseline visit was eligible to be randomized into this study. Patients were randomized in a 4:4:1:1 ratio. Randomization was accomplished using IVRS, an automated web/telephone randomization system.

Blinding

This study was patient-, investigator-, and Sponsor-blinded. Blinding was only to be broken in emergency situations for reasons of patient safety. At all other times, treatment and randomization information was kept confidential and was not released to the investigator/study staff until the conclusion of the study.

Schedule of Assessments

Table 94. Schedule of Assessments in Study 1046

Schedule of Events		Visits								
	Screening[a]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
		Baseline Day 0	Wk 2	Mo 1	Mo 2	Mo 3	Mo 4.5	Mo 6	Mo 9	Mo 12 or End of Study
Page 1 of 3										
Informed Consent	X									
RA Diagnosis, Medical History[b]	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X	X								X
Targeted Physical Examination[c]			X	X	X	X	X	X	X	
Vital Signs, Temperature	X	X	X	X	X	X	X	X	X	X
QuantiFERON-Gold or PPD	X									
Radiograph of Chest	X									
12-lead Electrocardiogram										X
Blood/Urine: Rheumatoid Factor		X								X
Blood/Urine: Antibodies to Cyclic Citrullinated Peptide (anti-CCP)		X								X
Blood/Urine: Hematology[d], Urinalysis, Safety Chemistry Panel[e]	X	X	X	X	X	X	X	X	X	X
Blood/Urine: Lipid Profile (fasting)[f]		X		X		X		X	X	X
Blood/Urine: Safety laboratories[g]		As appropriate for Standard of Care								
Blood/Urine: Urine Pregnancy Test (HCG)[h]	X	X	X	X	X	X	X	X	X	X
Blood/Urine: Stool Examination for Parasites (Brazil only)	X									
Blood/Urine: HIV, HBsAg, HCV Ab	X									
Blood/Urine: Molecular Profiling[i]		X	X	X		X		X		X
Blood/Urine: C-Reactive Protein (CRP)	X	X	X	X	X	X	X	X	X	X
Blood/Urine: Erythrocyte Sedimentation Rate (ESR)[j]	X	X				X		X		X
ACR/DAS: Tender/Painful Joint Count, Swollen Joint Count	X	X	X	X	X	X	X	X	X	X
ACR/DAS: Patient Assessment of Arthritis Pain		X	X	X	X	X	X	X	X	X
ACR/DAS: Patient Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X
ACR/DAS: Physician Global Assessment of Arthritis		X	X	X	X	X	X	X	X	X
ACR/DAS: Health Assessment Questionnaire – Disability Index		X	X	X	X	X	X	X	X	X
SF-36 (Version 2, Acute)	X			X		X		X	X	X
MOS-Sleep and FACIT- Fatigue Scale	X			X		X		X		X
EuroQoL EQ-5D	X					X		X		X
RA Healthcare Resource Utilization Questionnaire	X					X		X		X
Work Limitations Questionnaire	X					X		X		X
Randomization	X									
2 Week IVRS Diary Instructions[k]	X									
Drug Dispensing	X					X		X	X	
Drug Accountability						X		X	X	X
Adverse Event Reporting	X	X	X	X	X	X	X	X	X	X
Review Entry Criteria for A3921024										X

Abbreviations: CCP = cyclic citrullinated peptide, EQ-5D = self-report questionnaire (quality of life instrument) developed by the European Quality of Life (EuroQoL) Group, ESR = erythrocyte sedimentation rate, EuroQoL = European Quality of Life [Group], FACIT-Fatigue Scale = Functional Assessment of Chronic Illness Therapy-Fatigue Scale, HAQ-DI = Health Assessment Questionnaire-Disability Index, HBsAg = hepatitis B surface antigen, HCG = human chorionic gonadotropin, HCV Ab = hepatitis C virus antibody, HIV = human immunodeficiency virus, IVRS = Interactive Voice Response System, Mo = month, MOS Sleep Scale = Medical Outcomes Study Sleep Scale, PPD = purified protein derivative, RA = rheumatoid arthritis, SF-36 = Short Form (36 questions) Health Survey, Wk = week

[a] Screening Visit occurred within 1 month (30 days + 10 day window) prior to the Baseline Visit.

[b] Medical history included smoking status, average weekly alcohol consumption, family history of premature coronary heart disease (CHD).

[c] Targeted physical examination consisted of weight, examination of heart, lungs, abdomen, lower extremities (peripheral oedema) and lymph nodes.

[d] Hematology included red blood cell count, white blood cell count with differential, hemoglobin, hematocrit and platelet count.

[e] Chemistry panel included sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, creatine kinase, aspartate aminotransferase, alanine aminotransferase, albumin, total protein, bilirubin (direct, indirect and total), alkaline phosphatase, and gamma glutamyl transferase.

[f] Lipid profile included fasting total cholesterol, low density lipoprotein, high density lipoprotein, and triglycerides. Fasting apolipoprotein A-1 and B and other lipoprotein tests potentially including particle size measurements were obtained at Baseline and Month 3, 6, 9 and 12/End of Study.

[g] Safety laboratories as appropriate for standard of care.

[h] Urinary pregnancy testing (human chorionic gonadotropic) was required only for women who were of childbearing potential; may have been repeated more frequently if required by local practices, if a menstrual cycle was missed, or if potential pregnancy was otherwise suspected.

[i] Molecular profiling included deoxyribonucleic acid sample at baseline, and plasma and serum biomarker samples at baseline and other timepoints. Only at sites participating in the Molecular Profiling (pharmacogenomic) research component.

[j] All ESR tests performed after screening must have been done at a local laboratory that had the capability of reporting directly to the central laboratory, keeping the results blinded from the site personnel. If ESR could not be performed in a blinded manner, the site was not to perform ESR after screening.

[k] Patients in the United States reported daily via interactive voice response system for 2 weeks both the Patient's Assessment of Arthritis Pain and the Patient's Global Assessment of Arthritis.

Efficacy Parameters

This study has 3 primary efficacy endpoints in the following hierarchical order:

- Signs and symptoms as measured by ACR20 at Month 6
- Physical function as measured by the HAQ-DI change from baseline at Month 3;
- Incidence of DAS28-4 (ESR) <2.6 at Month 6

Secondary endpoints are summarized in Table 8.

Study Conduct

Started 05.18.2009, Completed 01.17.2011

Amendments:

There were three global amendments:

- Protocol Amendment 1 (January 28, 2009, prior to starting the study): included CK assessment and Apolipoprotein measurements
- Protocol Amendment 2 (March 22, 2010, 795 subjects enrolled, enrollment closed):
    - An additional primary objective and endpoint were added to compare the rate of achieving DAS28-4(ESR) <2.6 at Month 3
- Protocol Amendment 3 (December 01, 2010, 795 subjects enrolled, enrollment closed):
    - Strengthened language regarding follow-up for AEs and clinically significant laboratory abnormalities.
    - Added text regarding potential cases of drug-induced liver injury.

While the protocol was amended after all patients were enrolled, the amendments implementation did not negatively impact the study conduct, efficacy or safety evaluations.

Patient Disposition

Patient disposition in study 1046 is presented in Table 13 above and was consistent with the patient disposition in the rest of the Phase 3 studies in RA as summarized in above in Section 6.1.3 Subject Disposition.

Baseline Demographics and Disease Characteristics

Patient baseline demographics in study 1046 is presented in Table 11 and Table 12 above and are representative of adult patients with moderately-to-severely active RA. The baseline disease characteristics were well balanced across the treatment arms and generally consistent with the rest of the Phase 3 studies.

Efficacy Results

For discussion on efficacy, refer to Section 6 Review of Efficacy, which contains the individual study results for study 1046 along with the results from the Phase 3 efficacy studies.

Safety Results

For discussion on safety, refer to Section 7 Review of Safety.

9.4.7 Study A3921064 (Phase 3)

Study Protocol

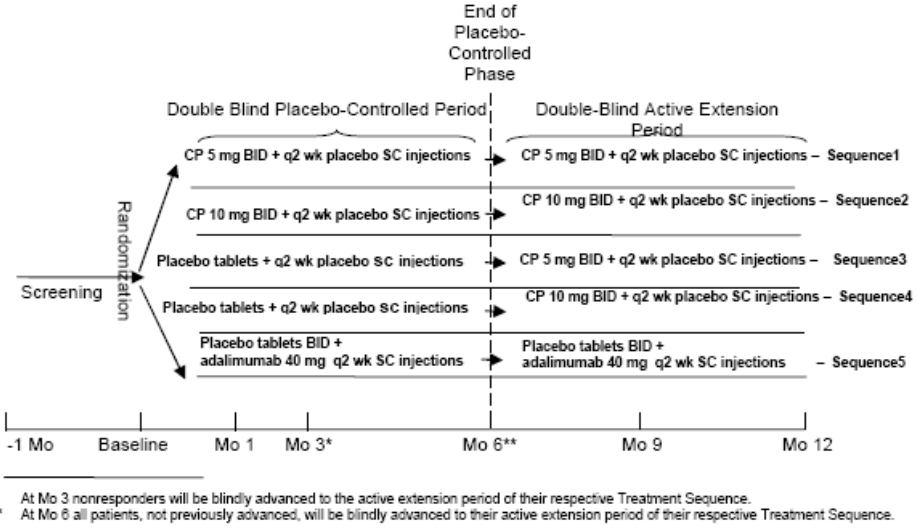
Overall Study Design

Study Design: This was a Phase 3 randomized, 1-year, double-blind, placebo-controlled, parallel-group study. Patients were randomized in a 4:4:1:1:4 ratio to 1 of the 5 parallel treatment sequences, as shown on Figure 29. Of note, this study includes an active comparator arm adalimumab, 40 mg SC injections once every two weeks (q2 week).

Figure 29. Study 1064 Design Schema

Treatment Sequence	N	Double-Blind Placebo-Controlled Period[a]	Double-Blind Active-Extension Period[b]
Sequence 1	200	CP-690,550 5 mg BID + q 2 week placebo SC injections	CP-690,550 5 mg BID + q 2 week placebo SC injections
Sequence 2	200	CP-690,550 10 mg BID + q 2 week placebo SC injections	CP-690,550 10 mg BID + q 2 week placebo SC injections
Sequence 3	50	Placebo + q 2 week placebo SC injections	CP-690,550 5 mg BID + q 2 week placebo SC injections
Sequence 4	50	Placebo + q 2 week placebo SC injections	CP-690,550 10 mg BID + q 2 week placebo SC injections
Sequence 5	200	Placebo + adalimumab 40 mg q 2 week SC injections	Placebo + adalimumab 40 mg q 2 week SC injections

Abbreviations: BID = twice daily; N = the planned number of subjects for each treatment sequence; q = every; SC = subcutaneous
[a] 3- to 6-month duration; response was assessed at Month 3, and nonresponsive patients were advanced to the double-blind, active-extension period.
[b] All patients had entered this period by Month 6.



At the Month 3 visit, the tender/painful and swollen joint counts were calculated and compared to the patient's individual Baseline values. If there was not a 20% improvement in both the tender/painful and swollen joint counts, the patient was considered a nonresponder patient. If a nonresponder patient was randomized to active treatment (Treatment Sequences 1, 2, or 5), that patient was to remain on the same treatment, at the same dose, for the duration of the study. If a nonresponder patient was randomized to Treatment Sequences 3 or 4, that patient was to be advanced to the second predetermined treatment in a blinded manner for the remainder of the study by the drug allocation system. At the end of Month 6, all patients were automatically advanced to their second predetermined treatment in a blinded fashion for the remainder of the study.

Inclusion Criteria

- RA with evidence of disease activity by joint counts and laboratory markers of inflammation:

  - The patient was required to meet the ACR classification criteria for the diagnosis of RA3 by satisfying at least 4 of the 7 criteria as described in Appendix 1 of the protocol (Section 16.1.1).
  - The patient was required to have active disease at both Screening and Baseline, as defined by having both:
    - ≥6 tender/painful joints on motion (of 68 joints assessed); and
    - ≥6 swollen joints (of 66 joints assessed).
  - The patient must also have active disease, as defined by one of the following criteria at Screening:
    - ESR (Westergren method) >28 mm/hr; or
    - C-reactive protein (CRP) >7 mg/L in the central laboratory.
  - The patient must meet Class I, II, or III of the ACR 1991 Revised Criteria for Global Functional Status in RA.
- Ongoing treatment with an adequate and stable dose of 7.5 to 25 mg weekly of MTX, inclusive.
- Other inclusion criteria:
  - Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative) had been informed of all pertinent aspects of the study.
  - Patient was required to be at least 18 years of age or older.
  - Patient had discontinued all disallowed concomitant medications for the required time prior to the first dose of study medication and was taking only those concomitant medications in doses and frequency allowed by the protocol.
  - Women of childbearing potential were required to test negative for pregnancy prior to enrollment in this study.
  - Sexually active women of childbearing potential and men whose partners are women of childbearing potential were required to use adequate contraceptive methods during participation in this study, as required for men and women on MTX therapy.
  - No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by all of the following:
    - A negative QuantiFERON.-TB Gold (QFT-G) In-Tube®™ or, if unavailable, a Mantoux purified protein derivative (PPD) skin test using 5 tuberculin units per 0.1 mL (5 tuberculin units PPD) result of <5 mm of induration, performed within the 3 months prior to Screening.
    - A chest radiograph taken within the 3 months prior to Screening without changes suggestive of active TB infection;
    - No history of either untreated or inadequately treated latent or active TB infection;
    - If a patient had previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a PPD test nor a QFT-G In-Tube needed to be obtained, but a chest

radiograph was still required if not done so within the prior 3 months. A patient who was currently being treated for either latent or active TB infection could only have been enrolled with confirmation of current incidence rates of multi-drug resistant TB infection, documentation of an adequate treatment regimen, and prior approval of the Sponsor.

- Patients receiving non-prohibited concomitant medications for any reason were required to be on a stable regimen, which was defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to first study dose, or as defined in concomitant medications section of the protocol.

Exclusion Criteria

- Pregnant or lactating females.
- Blood dyscrasias within 3 months prior to the first dose of study medication, including confirmed:
  - Hemoglobin <9 g/dL or hematocrit <30%;
  - White blood cell count <3.0 x 10^9/L;
  - Absolute neutrophil count <1.2 x 10^9/L;
  - Platelet count <100 x 10^9/L.
- Estimated glomerular filtration rate <40 mL/min based on Cockcroft-Gault calculation.
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 1.5x the upper limit of normal (ULN) or any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the patient's participation in the study.
- Current or recent history of uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, or neurological disease.
- History of any other autoimmune rheumatic disease, other than Sjogren's syndrome.
- History of an infected joint prosthesis at any time, with the prosthesis still in situ.
- History of any lymphoproliferative disorder, such as Epstein Barr virus related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.
- History of recurrent (more than one episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
- History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study medication.
- History of infection requiring antimicrobial therapy within 2 weeks prior to the first dose of study medication.
- Patients who have failed any TNFi for either lack of efficacy or a TNFi mechanism related AE.
- Patients who have previously received adalimumab therapy for any reason.
- Patients who are contraindicated for treatment with adalimumab in accordance with the approved local label. Patients meeting the New York Heart Association Class III and Class IV congestive heart failure:

    - Class III: patients with marked limitation of activity; they are comfortable only at rest;
    - Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.
- Any prior treatment with non-B-cell-specific lymphocyte depleting agents/therapies (eg, alemtuzumab [Campath®]), alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc). Patients who have received rituximab or other selective B lymphocyte depleting agents (including experimental agents) were eligible if they had not received such therapy for at least 1 year prior to study Baseline and had normal CD 19/20+ counts by fluorescence-activated cell sorting analysis.
- Any patient who has been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study medication or is to be vaccinated with these vaccines at any time during treatment or within 6 weeks following discontinuation of study medication.
- A patient with any condition possibly affecting oral drug absorption, eg, gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding, that simply divide the stomach into separate chambers, were not exclusionary.
- History of alcohol or drug abuse with less than 6 months of abstinence prior to first dose of study medication.
- Screening 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities which may affect patient safety or interpretation of study results.
- A patient with a first degree relative with a hereditary immunodeficiency.
- A patient with a malignancy or with a history of malignancy, with the exception of adequately treated or excised non metastatic basal cell or squamous cell cancer of the skin, cervical carcinoma in situ.
- Significant trauma or surgery procedure within 1 month prior to first dose of study medication.
- A patient requiring prohibited concomitant medications.
- A patient known to be infected with human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus.
- A patient who had previously participated in any study of CP-690,550.
- Participation in studies of other investigational compounds within 4 weeks or 5 half-lives (whichever was longer) prior to the first dose of study medication. Patients could not participate in studies of other investigational compounds at any time during their participation in this study. Exposure to investigational biologics was to be discussed with the Sponsor's medical monitor.
- A patient who had an allergy/hypersensitivity to MTX, or previous serious toxicity when administered MTX.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.

Concomitant Medications

Patients continued on their stable background arthritis therapy, which was required to include MTX supplemented with folic acid and could have included nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, opioids, acetaminophen, and/or low dose oral corticosteroids (.10 mg prednisone or equivalent per day) throughout the trial. Dosages of NSAIDs/COX-2 inhibitors, opioids, acetaminophen, and corticosteroids were required to have been stable for at least 4 weeks prior to first study dose and were to remain so during the study treatment period, except if adjustment was needed to protect a patient's safety.

Intravenous or intramuscular corticosteroids, biologic response modifiers, and DMARDs other than MTX were not allowed during this study. Topical NSAIDs were allowed.

Patients who have received the following treatment regimens were eligible to participate in the study, providing the following discontinuation periods were observed prior to the first dose of study medication:

- Anakinra (Kineret®) and etanercept (Enbrel®) were required to be discontinued for 4 weeks prior to the first dose of study medication.
- Infliximab (Remicade®) was required to be discontinued for 8 weeks prior to the first dose of study medication.
- Abatacept (Orencia®) and tocilizumab (Actemra.) were required to be discontinued for 12 weeks prior to the first dose of study medication.
- Rituximab or other selective B lymphocyte depleting agents (both marketed and investigational) were required to be discontinued for 1 year prior to the first dose of study medication and if CD19/20+ counts were normal by fluorescence activated cell sorting (FACS) analysis.
- Auranofin (oral gold), aurothioglucose (injectable gold), aurothiomalate (injectable gold) were required to be discontinued for 8 weeks prior to the first dose of the study medication.
- Sulfasalazine, d-penicillamine, bucillamine, mizoribin, azathioprine, chloroquine, hydroxychloroquine, cyclosporine, tacrolimus, and staphylococcal protein A immuno-absorbant pheresis columns (eg, PROSORBA. device/column) were required to be discontinued for 4 weeks prior to the first dose of study medication.
- Leflunomide (Arava®) was required to be discontinued 8 weeks prior to the first dose of study medication if no elimination procedure is followed. Alternately, it was to be discontinued with the following elimination procedure at least 4 weeks prior to the first dose of study medication:
    - Cholestyramine at a dosage of 8 g three times daily for at least 24 hours, or activated charcoal at a dosage of 50 g four times a day for at least 24 hours (US package insert, Elimination Procedure to significantly lower leflunomide drug levels).
- Tetracyclines and minocycline, unless prescribed for the treatment of acne or other dermatologic disorders, were required to be discontinued for 4 weeks prior to the first dose of study medication.

Assignment to Treatment Group

Patients were randomized in a 4:4:1:1:4 ratio to 1 of the 5 parallel treatment sequences for the 2 periods (double-blind, placebo-controlled period, then double-blind, active-extension period).

A patient who had signed an informed consent document to participate in the study, had undergone all Screening procedures, and had met all inclusion and none of the exclusion criteria for participation in the study at the Baseline visit was eligible to be randomized into this study.

Randomization was accomplished using the IVRS, which contains the randomization schedule. At the Screening Visit, the investigative site contacted the IVRS (online or by telephone call). The site enrolled the patient into the IVRS by indicating minimal information sufficient to distinguish one patient from another (e.g., date of birth) and received the patient identification (ID) number. At the Baseline Visit, the system associated that patient with the next available treatment on the randomization schedule and provided the randomization number.

Blinding

This study was patient-, investigator-, and sponsor-blinded. At the initiation of the study, the study site was instructed on using IVRS for breaking the blind. Blinding was only to be broken in emergency situations for reasons of patient safety. The Investigator was to attempt to contact the study team of the Sponsor before breaking the blind. If the blind for a patient was broken, the reason was required to be fully documented and entered on the CRF. At all other times, treatment and randomization information was kept confidential and was not released to the investigator/study staff until the conclusion of the study.

Schedule of Assessments

Table 95. Schedule of Assessments in Study 1064

		Screening[a]	Visits					
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
			Baseline Day 0	1 Mo	3 Mo	6 Mo	9 Mo	12 Mo or End of Study
Informed consent		X						
RA Diagnosis, medical history[b]		X						
Concomitant medications		X	X	X	X	X	X	X
Complete physical examination		X	X					X
Targeted physical examination[c]				X	X	X	X	
Vital signs, temperature		X	X	X	X	X	X	X
QuantiFERON-TB Gold®™ or PPD		X						
Radiograph of chest[d]		X						
12-lead electrocardiogram		X						X
Blood/Urine	Rheumatoid factor, anti-CCP		X					X
	Hematology[e] and chemistry panel[f]	X	X	X	X	X	X	X
	Lipid profile (fasting)[g]		X	X	X	X	X	X
	Hematology & chemistry laboratory tests[h]		As appropriate for standard of care					
	Urinalysis/urine pregnancy test (HCG)[i]	X	X	X	X	X	X	X
	Stool examination for parasites (Brazil only)	X						
	Molecular Profiling Sampling (pharmacogenomic)[j]		X	X	X	X		X
	CP-690,550 and adalimumab pharmacokinetics[k]				X	X		X
	HIV serology, HbsAg, HCV Ab,	X						
ACR/DAS	C-reactive protein	X	X	X	X	X	X	X
	Erythrocyte sedimentation rate[l]	X	X	X	X	X	X	X
	Tender/painful joint count, swollen joint count	X	X	X	X	X	X	X
	Patient Assessment of Arthritis Pain		X	X	X	X	X	X
	Patient Global Assessment of Arthritis		X	X	X	X	X	X
	Physician Global Assessment of Arthritis		X	X	X	X	X	X
	Health Assessment Questionnaire – Disability Index		X	X	X	X	X	X
SF-36 (version 2, acute)			X	X	X	X	X	X
MOS Sleep Scale/ FACIT - Fatigue Scale			X	X	X	X		X
EuroQoL EQ-5D			X	X	X	X		X
RA Healthcare Resource Utilization Questionnaire			X		X	X		X
Work Limitations Questionnaire			X		X	X		X
Randomization			X					
Drug dispensing			X		X	X	X	
Drug accountability					X	X	X	X
Adverse event reporting			X	X	X	X	X	X
Review entry criteria for A3921024								X

Source: Section 16.1.1.
Abbreviations: ACR = American College of Rheumatology; CCP = cyclic citrullinated peptide; DAS = disease activity score; EQ-5D = self-report questionnaire (quality of life instrument) developed by the European Quality of Life (EuroQoL) Group; EuroQoL = European Quality of Life [Group]; FACIT = Functional Assessment of Chronic Illness Therapy; HBsAg = hepatitis B surface antigen; HCG = human chorionic gonadotrophin; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; Mo = month; MOS = Medical Outcomes Study; PPD = purified protein derivative Tuberculin test; RA = rheumatoid arthritis; SF-36 = Short Form-36.
[a] Screening Visit occurred within 1 month prior to the Baseline Visit.
[b] Medical history included smoking status, average weekly alcohol consumption, and family history of premature coronary heart disease.
[c] Targeted physical examination consisted of weight, examination of heart, lungs, abdomen, lower extremities for peripheral edema, and lymph nodes.
[d] Radiograph of chest was to be performed unless performed and documented within 3 months of Screening Visit.
[e] Hematology included red blood cell count, white blood cell count (with differential), hemoglobin, hematocrit, and platelet count.
[f] Safety chemistry laboratories included: sodium, potassium, chloride, bicarbonate, calcium, glucose, blood urea nitrogen, total protein, creatinine, creatine kinase, bilirubin (direct, indirect, and total), alkaline phosphatase, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, albumin and serum creatinine.
[g] Lipid profile included fasting total cholesterol, low- and high-density lipoprotein cholesterol, and triglycerides, and may have included fasting apolipoprotein A-1 and B and other lipoprotein tests, potentially including particle size measurements.
[h] Hematology & safety chemistry laboratory tests as appropriate for standard of care in patients receiving methotrexate; may have included creatinine, albumin, and liver function tests.
[i] Urinalysis included specific gravity, pH, protein, glucose, ketones, and blood. Urinary pregnancy testing (HCG) was required only for women who were of childbearing potential, and may have been repeated more frequently if required by local practices, if a menstrual cycle was missed, or if potential pregnancy was otherwise suspected.
[j] Only at participating sites (please refer to the Molecular Profiling Supplement for details).
[k] Serum samples were collected to determine CP-690,550 or adalimumab pharmacokinetics prior to dosing.
[l] Collected only at sites where local laboratory has the capability of reporting results to the central laboratory.

An independent Data Safety Monitoring Board (DSMB), a group of experts external to the Sponsor, reviewed accumulating safety data from this study on an ongoing basis. Review of

efficacy data was not a responsibility of this committee. The DSMB had access to unblinded treatment information during the clinical study. The operating procedures of the DSMB were documented in the DSMB charter.

Efficacy Parameters

Primary Efficacy Endpoints: Signs and symptoms as measured by ACR20 at Month 6, physical function as measured by the HAQ-DI change from Baseline at Month 3, and incidence of DAS28-4(ESR) <2.6 at Month 6.

Study Conduct

Started 05.20.2009, Completed 03.10.2011

Amendments
All amendments in the study were done after all 717 patients were enrolled:

- Protocol Amendment 1 (15 April 2010): An additional primary objective and endpoint were added to compare the rate of achieving DAS28-4(ESR) <2.6 at Month 3 in patients with active RA after administration of CP-690,550, in doses of 5 mg BID and 10 mg BID versus placebo BID.
- Protocol Amendment 2 (17 December 2010): Strengthened the language regarding follow-up for adverse events and clinically significant laboratory abnormalities and included information regarding cases of potential drug-induced liver injury and guide investigators on mitigating the associated risk.
- Protocol Amendment 3 (7 February 2011): This was a country specific protocol amendment (Korea) The protocol was amended to delete a redundancy.

While the protocol was amended after all patients were enrolled, their implementation did not negatively impact the study conduct, efficacy or safety evaluations.

Patient Disposition

Patient disposition in study 1064 is presented in Table 13 above and was consistent with the patient disposition in the rest of the Phase 3 studies in RA as summarized in above in Section 6.1.3 Subject Disposition.

Baseline Demographics and Disease Characteristics

Patient baseline demographics in study 1064 is presented in Table 11 and Table 12 above and are representative of adult patients with moderately-to-severely active RA. The baseline disease characteristics were well balanced across the treatment arms and generally consistent with the rest of the Phase 3 studies.

Efficacy Results

For discussion on efficacy, refer to Section 6 Review of Efficacy, which contains the individual study results for study 1064 along with the results from the Phase 3 efficacy studies.

Safety Results

For discussion on safety, refer to Section 7 Review of Safety.

9.4.8 Study A3921024 and A3921041 (Long-Term Extension Studies)

Study Protocol 1024

Overall Study Design

This is an ongoing, long-term, open-label, follow-up study. Patients must have previously participated in randomized studies of CP-690,550.

Following implementation of Protocol Amendment 3 (January 21, 2009), enrolling patients initiated open-label tofacitinib 10 mg BID at the baseline visit (except patients in China, who initiated open-label tofacitinib 5 mg BID at the baseline visit. Prior to implementation of Amendment 3, all patients initiated open-label tofacitinib 5 mg BID at the baseline visit. Patients who are taking tofacitinib 10 mg BID were allowed to decrease dosing to 5 mg BID for mild to moderate safety concerns and those who are taking 5 mg BID were allowed to increase their dose to 10 mg BID at the instruction of the investigator.

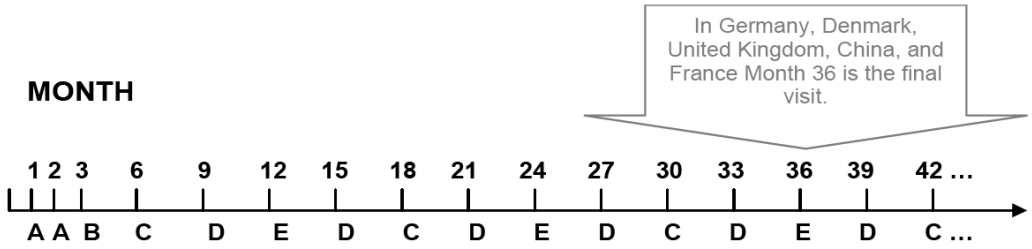
Concomitant Medications

Patients were to continue on their stable background arthritis therapy, which could include nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, and opioids (.30 mg oral morphine/day potency), certain allowed DMARDs (methotrexate [MTX], leflunomide, sulfasalazine, anti-malarials, auranofin and injectable gold preparations at approved doses), and corticosteroids (≤10 mg prednisone or equivalent/day).

Schedule of Assessments

Visits occurred at 1, 2, and 3 months after baseline, then every 3 months (13 weeks) as long as the patient remains in the study for efficacy and safety as shown in Table 96.

Table 96. Schedule of Assessments in Study 1024



Protocol Activity	Patients >14 days after EOS Visit		Combined with EOS Visit	Separate Visit within 14 days after EOS Visit	Mo 1, 2	Mo 3	Mo 6 Q12 mos [a]	Mo 9 Q6 mos [b]	Mo 12 Q12 mos [c]	End of Treatment (Month 36 in Germany, Denmark, United Kingdom,China, and France)
					A	B	C	D	E	
	Screen	Baseline	Screening /Baseline	Screening /Baseline	*See Figure 1 for applicable assessments grouped by letter.*					
Informed Consent	X		X	X						
Medical History	X									
CV Risk Assessment[1]	X						X		X	
Complete Physical Exam	X								X	X
Targeted Physical Exam[2]		X		X	X	X	X	X		
Mantoux PPD or QuantiFERON/Chest Radiograph, if Necessary[3]	X									
Weight	X					X	X	X	X	X
Height[4]	X								X	X
Temperature, Vital Signs	X	X		X	X	X	X	X	X	X
Laboratory Testing[5]	X	X[d]		X	X	X	X[d]	X	X[d]	X[d, e]
HIV Serology, HBsAg, HCV Ab	X									
Rheumatoid factor, anti-CCP	X									
ESR (obtained at local lab)	X	X		X	X	X	X	X	X	X
12-Lead ECG	X	X							X	X
Radiographs of Hands and Feet[f]							X[f]		X[f]	X[f]
Adverse Event Assessment		X		X	X	X	X	X	X	X
Prior/Concomitant Medication	X	X		X	X	X	X	X	X	X
ACR and DAS28 Assessment[6]	X	X		X	X	X	X	X	X	X

Protocol Activity	Patients >14 days after EOS Visit		Combined with EOS Visit	Separate Visit within 14 days after EOS Visit	Mo 1, 2	Mo 3	Mo 6 Q12 mos ([a])	Mo 9 Q6 mos ([b])	Mo 12 Q12 mos ([c])	End of Treatment (Month 36 in Germany, Denmark, United Kingdom,China, and France)
					A	B	C	D	E	
	Screen	Baseline	Screening /Baseline	Screening /Baseline	*See* Figure 1 *for applicable assessments grouped by letter.*					
SF-36 Health Survey		X		X		X	X	X	X	X
FACIT-Fatigue Scale, EuroQol EQ-5D, Work Limitations Questionnaire, RA Healthcare Resource Utilization Questionnaire		X					X		X	X
Dispense/Collect Drug		X	X	X	X	X	X	X	X	X
Stool Examination (Brazilian and Peruvian Sites Only)	X									
CP-690,550 Pharmacokinetics[7]										

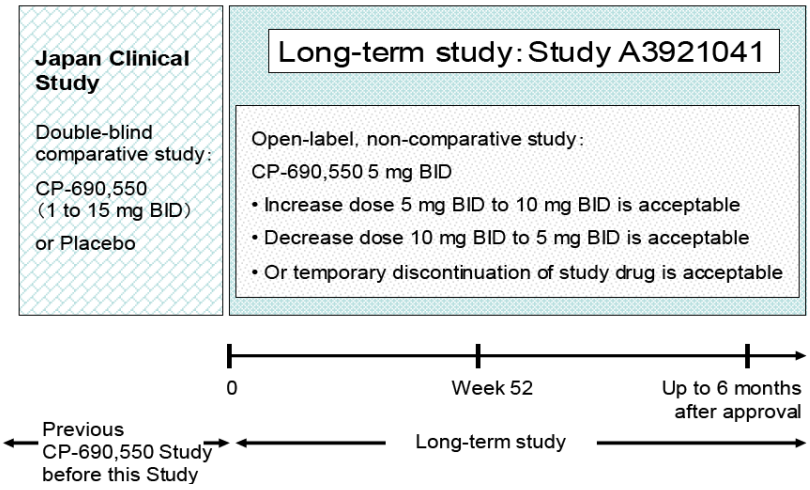
Mo=month; mos=months; EOS=end of study; LDL-c=low density lipoprotein; HDL-c=high density lipoprotein; CCP=cyclic citrullinated peptide; FACIT=Functional Assessment of Chronic Illness Therapy; SF-36=Short Form-36; EuroQol EQ-5D=European Quality of Life 5-dimension scale; HIV=human immunodeficiency virus; HbsAg=hepatitis B surface antigen; HCV Ab=hepatitis C virus antibody; uHCG=urine human chorionic gonadotropin; PPD=purified protein derivative; CBC=complete blood count; CV=cardiovascular; CHD=coronary heart disease; AST=aspartate aminotranferase; ALT=alanine aminotransferase; GGT=gamma-glutamyl transferase; CK=creatine kinase; U/A=urinalysis; DMARD=disease modifying anti-rheumatic drug; ACR=American College of Rheumatology; DAS28= Disease Activity Score defined using 28 joint counts; VAS=visual analog scale; CRP=C-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index; ESR=erythrocyte sedimentation rate; PK=pharmacokinetics; ECG=electrocardiogram; RA=rheumatoid arthritis
Source: Protocol A3921024 (Section 16.1.1)
[1.] Cardiovascular (CV) Risk Factor Assessment includes smoking status, average weekly alcohol consumption, and family history of premature coronary heart disease (CHD). Only to be done every 6 months through Month 24 and then yearly after Month 24.
[2.] Targeted physical exam consists examination of heart, lungs, lower extremeties for peripheral edema, abdomen, and lymph nodes.
[3.] If not completed in the last 3 months. Patients having a PPD must return with 48-72 hours for evaluation.
[4.] Height is collected at Screening for patients who enroll more than 14 days after their EOS visit from the qualifying study and at annual visits for all patients.
[5.] Laboratory testing includes hematology (complete blood count [CBC] with differential); Chemistry Panel includes urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), albumin, and creatine kinase (CK); urinalysis (U/A), and urine pregnancy test (urine human chorionic gonadotropin [uHCG]) for females of childbearing potential. In addition, a fasting lipid panel (cholesterol, low density lipoprotein [LDL-c], high density lipoprotein [HDL-c], triglycerides) will be collected at the baseline visit for patients who enroll more than 14 days after their EOS visit from their qualifying study, and every 6 months throughout the course of the study for all patients. Safety laboratory testing as appropriate for standard of care for patients receiving background DMARDs.
[6.] ACR and DAS28 Assessment includes Tender/Painful Joint Count (68), Swollen Joint Count (66), Patient's Assessment of Pain (visual analog scale [VAS]), Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Arthritis, CRP, HAQ-DI.
Note that the DAS28 Assessments include measures already done within the ACR assessment: Tender/Painful Joint Counts (28), Swollen Joint Counts (28), and Patient Global Assessment of Disease Activity. In addition, ESR is to be completed, and it is listed separately above.
[a.] Every 12 months after Month 6 (eg, Month 6, 18, 30, etc). See Figure 1.
[b.] Every 6 months after Month 9 (eg, Month 9, 15, 21, etc). See Figure 1.
[c.] This annual visit occurs every 12 months after Month 12 (eg, month 12, 24, 36, etc), except in Germany, Denmark, United Kingdom, China, and France where Month 36 is the end of study. See Figure 1.
[d.] Includes a fasting lipid panel; apolipoprotein A and B and other lipoprotein tests potentially including particle size measurements will be obtained at End of Study Visit (Month 36 in Germany, Denmark, United Kingdom, China, and France).
[e.] Refer to Protocol A3921024 (Section 16.1.1) for additional laboratory monitoring if necessary.
[f.] Radiographs of hands and feet will be read and scored centrally; they will be obtained every 6 months (except in Germany where they will be obtained annually) only for patients who had obtained baseline films that were read and scored centrally in their qualifying study.
[7.] A predose sample and a 2 hour (±20 min) postdose sample will be collected at any one of the scheduled visits, or a separate pharmacokinetics (PK) visit can be scheduled. Additionally, in a percentage (5%-10%) of participating patients, 2 more samples (a predose sample and a 2 hour (±20 min) postdose sample) will be collected at another visit, separated by at least 1 month from the first PK visit. (See Protocol A3921024 [Section 16.1.1] Pharmacokinetic Sampling).

Study Protocol 1041

Overall Study Design

This is an ongoing Japanese, multi-center, open-label, non-comparative, long-term study, designed as a continuation of studies 1039 and 1040. For individual patients, participation in this study is to be initiated on the day of the final visit (i.e., last dose) of their participation in their previous study as shown in Figure 30.

Figure 30. Study 1041 Design Schema

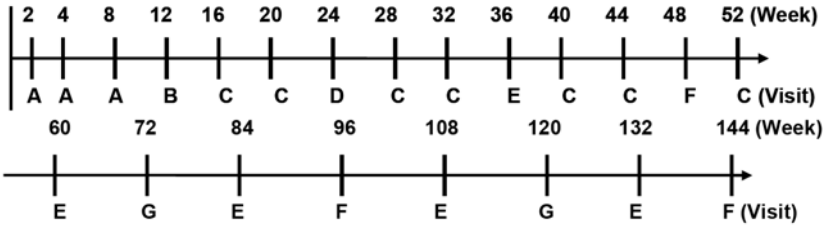


All patients were to initiate at a dose of tofacitinib 5 mg BID. The dosage may be increased from 5 mg BID to 10 mg BID, reduced from 10 mg BID to 5 mg BID, or temporarily discontinued (up to 28 consecutive days) based on consideration of the risks and benefits to the patient.

Schedule of Assessments

Table 97. Schedule of Assessments in Study 1041

First 1 year (Week 52):



	Items	Baseline Day 0	Visit points (Long term) W2 (A)	W4 (A)	W8 (A)	W12 (B)	W16 (C)	W20 (C)	W24 (D)	W28 (C)	W32 (C)	W36 (E)	W40 (C)	W44 (C)	W48 (F)	W52 (C)	W60 (E)	W72 (G)	W84 (E)	End of Treatment (Early term)
Informed Consent		X																		
Patient background	Eligibility confirmation (eg, inclusion/exclusion criteria)	X																		
	Background investigation (eg, complications, medical history, treatment conditions) [1]	X													X			X		X
	Questions/Examinations by physician (physical examination, joint palpation) [2]	X	X	X	X	X			X			X			X		X	X	X	X
	Questions/Examinations by physician (including lung and heart auscultation)						X	X		X	X		X	X		X	will be performed as a standard test [10]			
Observation items	ACR Assessments [3]	X	X	X	X	X			X			X			X		X	X	X	X
	DAS28-3(CRP), DAS28-4(ESR)	X	X	X	X	X			X			X			X		X	X	X	X
	QOL (SF-36v2)	X				X			X						X			X		X
	HAQ-DI	X	X	X	X	X			X			X			X		X	X	X	X
	Body weight, Vital signs (sitting blood pressure/ pulse rate, axillary body temperature)	X	X	X	X	X			X			X			X		X	X	X	X
	Adverse events assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab tests	Tuberculosis test [4]	X																		
	ESR (Westergren method)	X	X	X	X	X			X			X			X		X	X	X	X
	CRP (C-reactive protein)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Hematology [5]	X	X	X	X	X			X			X			X		X	X	X	X
	Biochemistry: standard (fasting) [6]	X	X	X	X	X			X			X			X		X	X	X	X
	Biochemistry: hematological including differential [10]						X	X		X	X		X	X		X	will be performed as a standard test [10]			
	Biochemistry: lipid special (fasting) [7]	X				X			X			X			X		X	X	X	X
	Pregnancy test (serum) [8]	X				X			X			X			X		X	X	X	X
	Urinalysis (general/pregnancy) [8]	X	X	X	X	X			X			X			X		X	X	X	X
	Standard 12-lead ECG	X							X						X			X		X
	SpO_2	X	X	X	X	X			X			X			X		X	X	X	X
	Chest X-rays	X													X					X
Drug supplies	Study drug dispensing	X				X			X			X			X		X	X	X	
	Study drug recovery, remaining drug check		X	X	X	X			X			X			X		X	X	X	X
	Confirmation of concomitant medications	X	X	X	X	X			X			X			X		X	X	X	X
	Instructions on the use of drugs [9]	X	X	X	X	X			X			X			X		X	X	X	

TB=tuberculosis; CRP=C-reactive protein; Na^+=sodium; Ca^{++}=calcium; K^+=potassium; LDL-c=low density lipoprotein; HDL-c=high density lipoprotein; RBC=red blood cell; WBC=white blood cell; SF-36=Short Form-36; CV=cardiovascular; CHD=coronary heart disease; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ACR=American College of Rheumatology; DAS28-3(CRP)=Disease Activity Score defined using 28 joint counts and C-reactive protein; DAS28-4(ESR)=Disease Activity Score defined using 28 joint counts and erythrocyte sedimentation rate ; VAS=visual analog scale; CRP=C-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index; ESR=erythrocyte sedimentation rate; T-Chol=total cholesterol; TG=triglycerides; ALP=alkaline phosphatase; BUN=blood urea nitrogen; LDH=lactate dehydrogenase; FSH=follicle-stimulating hormone; QOL=quality of life; W=week; ECG=electrocardiogram; SpO_2=partial pressure of oxygen; term=termination
Source: Protocol A3921041 (Section 16.1.1)
[1.] Medical history, complications, treatment conditions, etc utilize previous study data. Cardiovascular (CV) Risk Factor Assessment includes smoking status, average weekly alcohol consumption, family history of premature coronary heart disease (CHD), and waist circumference. This information should be updated at annual visits (Weeks 48, 72, etc) (See Protocol A3921041 [Section 16.1.1]).
[2.] Questioning/examination by physician consists of weight, examination of heart, lungs, abdomen, and lymph nodes. At Baseline and Week 96/Early termination should be monitored carefully.
[3.] ACR Assessments include Tender /Painful Joint Count (68), Swollen Joint Count (66), Patient's Assessment of Arthritis Pain (VAS), Patient's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, HAQ-DI.
[4.] Confirmation of tuberculosis (TB) infection by means of QuantiFERON-TB or tuberculin skin test will be performed only if a tuberculin test has not been performed during the previous study (the assessment of tuberclin test will be made within 48-72 hours).
[5.] WBC; differential WBC; RBC; hemoglobin; hematocrit; reticulocytes; platelet count.
[6.] Biochemistry tests (standard): protein, total bilirubin, albumin, ALP, BUN, creatinine, blood glucose, AST, ALT, LDH, Na^+, K^+, Cl^-, Ca^{++}, HCO_3^- (all measured at fasting at least 9 hours after eating).
[7.] Biochemistry tests (lipid): T-Chol, LDL-c, HDL-c, TG, apolipoprotein A-I and A-II, apolipoprotein B (all measured at fasting at least 9 hours after eating).
[8.] Pregnancy tests will be performed for women of child bearing potential (serum FSH [test] is optional). Urinalysis will be performed using dipsticks and, if a clinically significant abnormality is observed or at the discretion of the investigator, additional examination by means of, for example, microscopy will be performed.
[9.] The final visit of the previous randomized study can be combined with the baseline visit for this study. If it is the same day, the investigator will instruct the patient to take the tablets to start in the next morning. Patients will be instructed to return the remaining study medication every 3 months and at the end of treatment (including visit after discontinuation).
[10.] Visit for ensuring safety of patients will be added as patient status dictates. Questions/examinations (including lung and heart auscultation), CRP, hematological biochemistry including differential (serum creatinine, AST, ALT and albumin etc) should be confirmed.

Study Conduct for Studies 1024 and 1041

Patient Disposition

Table 98. Patient Disposition in LTE Studies 1024 and 1041

No. (%) of Patients	CP-690,550		
	5 mg BID	10 mg BID	All Doses
Screened: 3268			
Assigned to Study Treatment	1321	1906	3227
Treated	1321	1906	3227
Ongoing at Date of Cutoff	1022 (77.4)	1768 (92.8)	2790 (86.5)
Discontinued	299 (22.6)	138 (7.2)	437 (13.5)
Patient Died	9 (0.7)	2 (0.1)	11 (0.3)
Related to Study Drug	100 (7.6)	44 (2.3)	144 (4.5)
Adverse event	100 (7.6)	44 (2.3)	144 (4.5)[a]
Not Related to Study Drug	54 (4.1)	31 (1.6)	85 (2.6)
Adverse event	54 (4.1)	31 (1.6)	85 (2.6)[a]
Relation to study drug not defined	139 (10.5)	62 (3.3)	201 (6.2)
Did not meet entrance criteria	1 (0.1)	0	1 (0.5)
Insufficient clinical response	34 (2.6)	8 (0.4)	42 (1.3)
Lost to follow-up	10 (0.8)	8 (0.4)	18 (0.6)
No longer willing to participate in study	47 (3.6)	31 (1.6)	78 (2.4)
Protocol violation	17 (1.3)	3 (0.2)	20 (0.6)
Withdrawn due to pregnancy	6 (0.5)	2 (0.1)	8 (0.2)
Other	24 (1.8)	10 (0.5)	34 (1.1)

Source: CSR A3921024 and A3921041, Table 6.

It is important to note that even though more patients were enrolled in the tofacitinib 10 mg BID dose group, their exposure is significantly lower as patients in the 5 mg BID dose group have started earlier enrollment from the index Phase 2 studies. The significance of this observation is discussed in Section Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations. Therefore, comparing crude proportions of these events may not be accurate. To account for the differences in exposure, most of the major events of interest were presented as exposure-adjusted incidence rates.

Baseline Demographics and Disease Characteristics

The baseline demographic characteristics for the LTE studies are mostly consistent with those from the Phase 2 and 3 studies.

Safety Results

For discussion on safety, refer to Section 7 Review of Safety.

9.5 Supplementary Tables

Table 99. Summary of All Deaths in the Phase 3 and LTE Studies in RA

Integrated Summary of All Deaths in the Phase 3 and LTE Studies in RA

	Phase 3 Studies, 12-Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Total number of patients	681	204	1216	1214	3030	1321	1906	3227	3515
Total exposure, patient-years	203	179	904	910	2098	2236	882	3118	4410
Number of events, n (%)	1 (0.1)	3 (1.5)	7 (0.6)	4 (0.3)	12 (0.4)	17 (1.3)	3 (0.2)	20 (0.6)	28 (0.8)
Rate per 100 patient-years	0.50	1.67	0.77	0.44	0.57	0.76	0.34	0.64	0.63
Cause of death, n (event/100 PY)									
Infections	**1 (0.5)**	**-**	**5 (0.6)**	**-**	**5 (0.2)**	**4 (0.2)**	**1 (<0.1)**	**5 (0.2)**	**8 (0.2)**
Pneumonia	-	-	*5**	-	*5**	*3*	*1*	*4*	*6*
Appendicitis	-	-	-	-	-	*1*	-	*1*	*1*
Pyelonephritis	*1*	-	-	-	-	-	-	-	-
Septic arthritis	-	-	-	-	-	-	-	-	*1*
Malignancy	**-**	**1 (0.5)**	**1 (0.1)**	**-**	**1 (<0.1)**	**4 (0.2)**	**1 (<0.1)**	**5 (0.2)**	**10 (0.2)**
Lung cancer	-	*1*	*1*	-	*1*	*1*	*1*	*2*	*5**
Breast cancer	-	-	-	-	-	*1*	-	*1*	*1*
Colon cancer	-	-	-	-	-	*1*	-	*1*	*1*
Gallbladder cancer	-	-	-	-	-	-	-	-	*1*
Ovarian cancer	-	-	-	-	-	*1*	-	*1*	*1*
Synovial sarcoma		-	-	-	-	-	-	-	*1*
Cardiovascular Disorders	**-**	**1 (0.5)**	**-**	**3 (0.3)**	**4 (0.2)**	**4 (0.2)**	**-**	**4 (0.1)**	**5 (0.1)**
Arrhythmia, atherosclerosis	-	-	-	-	-	*2*	-	*2*	*2*
Cardiac arrest	-	*1*	-	*1*	*1*	*1*	-	*1*	*2*
Cardiac failure, valvular	-	-	-	*1*	*1*	-	-	-	-
Cerebrovascular accident	-	-	-	-	-	*1*	-	*1*	*1*
Pulmonary hypertension	-	-	-	*1*	*1*	-	-	-	-
Pulmonary embolism	-	-	-	-	*1*	-	-	-	-
Pulmonary	**-**	**-**	**2 (0.2)**	**-**	**2 (0.1)**	**1 (<0.1)**	**-**	**1 (<0.1)**	**1 (<0.1)**
COPD exacerbation	-	-	*1**	-	*1**	*1*	-	*1*	*1*
Interstitial lung disease	-	-	*1*	-	*1*	-	-	-	-
Suicide	**-**	**-**	**-**	**-**	**-**	**1 (<0.1)**	**1 (<0.1)**	**2 (0.1)**	**2 (<0.1)**
Aspiration	**-**	**-**	**-**	**1 (0.1)**	**1 (<0.1)**	**-**	**-**	**-**	**-**
Bone marrow hypoplasia	**-**	**1 (0.5)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Traumatic intracranial hemorrhage	**-**	**-**	**1 (0.1)**	**-**	**1 (<0.1)**	**-**	**-**	**-**	**-**
Brain injury, post-surgery	**-**	**-**	**1 (0.1)**	**-**	**-**	**1 (<0.1)**	**-**	**1 (<0.1)**	**1 (<0.1)**
Unknown	**-**	**-**		**-**	**-**	**1 (<0.1)**	**-**	**1 (<0.1)**	**1 (<0.1)**

Source: Integrated Summary of Safety, Section 2.1.2, Deaths, adapted from Tables 68-75; 120-Day Safety Update (clinical data cut-off September 29, 2011), adapted from Tables 13-17
Note: *-Four deaths were not included in the incidence calculations: three were reported after the reporting window for safety analyses, on occurred after clinical data cut-off September 29, 2011

Table 100. Listings of Malignancy (Excluding Non-Melanoma Skin Cancer) in the Tofacitinib RA Development Program

Listings of Malignancy (Excluding Non-Melanoma Skin Cancer) in the Tofacitinib RA Development Program					
Study-Subject ID	**Age/ Gender**	**Total CP exposure, days**	**Backgroun d DMARD**	**Primary**	**Histology**
RCT Adalimumab					
1064- 10461047	62/M	253	MTX	Lung cancer (NSCLC)	Adenocarcinoma
1035- 10891008	53/F	79	Mono	Kidney	Renal cell carcinoma
RCT CP1 mg BID					
1025- 10961004	57/F	165	MTX	Colon	Well differentiated adenocarcinoma, Dukes C1
RCT CP5 mg BID					
1025- 10991004	53/M	169	MTX	Melanoma	Superficially expanding malignant melanoma (Clark II, Braslow 0.5 mm)
1044- 11101006	68/F	36	MTX	Gastric cancer	Adenocarcinoma of the stomach
1044- 10021007	63/F	135	MTX	Probable lung cancer (NSCLC)	Metastatic squamous cell cancer (bone); Squamous cell carcinoma NOS
1044- 11081030	69 F	307	MTX	Lung cancer (SCLC)	Metastatic small cell cancer and bronchoalveolar cell cancer;
1064- 10461020	62/F	85	MTX	Possible renal cell cancer	Skin biopsy: Poorly differentiated carcinoma with clear cytoplasm (note: possible metastatic renal cell carcinoma).
1064- 11631002	55/F	171	MTX	Lung cancer (NSCLC)	Non-small cell carcinoma
RCT CP10 mg BID					
1044- 10421022	59/F	117	MTX	Cervix	Intraepithelial squamous cell carcinoma
1044- 10621024	67/F	124	MTX	Breast cancer	Low grade ductal carcinoma with mucinous features; Mucinous adenocarcinoma
1045- 10151003	60/M	174	Mono	Lung cancer (NSCLC)	Highly suspicious for non-small cell carcinoma.
1045- 10551001	30/F	181	Mono	Breast cancer	N.A.
1046- 11001001	49/F	280	MTX, SSZ	Breast cancer	Invasive ductal carcinoma Carcinoma, NOS
1046- 11561012	56/F	59	MTX	Unknown primary (lung or pancreas suspected)	Cancer cells most likely originating from pancreas or lung
1064- 11321003	50/F	150	MTX	Cervical carcinoma	Squamous cell carcinoma definitively invasive, moderately differentiated, consistent with a cervical carcinoma. Squamous cell carcinoma NOS
1044- 11901002#	46/F	206	MTX	B-Cell lymphoma	Malignant lymphoma, B-cell type non-Hodgkin's, NOS; EBV?
1032- 10181005*	75/F	143	MTX	Thyroid	Hyperplastic nodule; Neoplasm, uncertain whether benign or malignant
LTE CP5 mg BID					
1024- 10101010	63/F	947	MTX	Vulvar cancer	Squamous cell carcinoma NOS
1024- 10161006	67/F	578	Mono	Lung cancer	Squamous cell carcinoma
1024- 10571003	51/F	1060	MTX	Breast cancer	Ductal carcinoma grade II
1024- 10631010	51/M	781	MTX	Laryngeal cancer	Squamous cell carcinoma NOS
1024- 10751011	60/M	649	MTX	Lung cancer (NSCLC)	Poorly differentiated non-small cell carcinoma
1024- 10781004	59/F	197	MTX	Breast cancer	Ductal carcinoma
1024- 10811001	51/F	756	MTX	Endometrial cancer	Moderately differentiated endometrioid papillary adenocarcinoma
1024- 10831009	52/F	863	MTX	Ovarian cancer	Moderately differentiated serous-type adenocarcinoma; Serous cystadenocarcinoma
1024- 10831012	55/F	1071	MTX	Breast cancer	Breast ductal cancer with adenocarcinoma lymph node metastases
1024- 10901001	62/F	508	MTX	Renal cell carcinoma (+ lung metastases)	Renal cell adenocarcinoma, well-differentiated
1024- 10951003	51/F	798	Mono	Thyroid cancer	Focus of follicular variant of papillary carcinoma
1024- 11251009	61/M	411	MTX	Lung cancer	Bronchogenic carcinoma
1024- 11251018	77/M	239	Mono	Sigmoid carcinoma with metastases	Sigmoid carcinoma
1024- 11361010	63/F	277	Mono	Atypical choroid plexus papilloma	Choroid plexus papilloma, WHO grade II
1024- 11651002	46/F	567	Mono	Liposarcoma	Liposarcoma, well differentiated
1024- 11731014	71/F	978	Mono	Gall bladder cancer with hepatic infiltration	N.A.
1041- 10051002	55/F	586	MTX	Breast cancer	Paget's disease of the breast with infiltrating ductal carcinoma

1041- 10061003	56/F	670	MTX	Ovarian cancer (metastases to LN, lung, omentum)	Stage IV ovarian cancer
1041- 10101011	68/F	204	Mono	Gastric cancer	Tubular adenocarcinoma, well differentiated
1041- 10271005	55/F	279	Mono	Gastric cancer	Adenocarcinoma
1041- 10321001	59/F	380	Mono	Breast cancer	Ductal carcinoma
1041- 10031002	51/M	1183	MTX	Lung cancer (SCLC)	Lung cancer (SCLC)
1024- 10751015	71/M	1058	MTX	Bladder cancer	Bladder cancer
1024- 10091004	50/F	1211	MTX	Breast cancer	Breast cancer
1041- 10521003	69/F	447	Mono	Gastric cancer	Gastric cancer
1024- 11811020	67/F	538	MTX	Synovial sarcoma	Synovial sarcoma
1024- 11741016	66/F	503	N.A.	Melanoma	Melanoma
1024- 10361009#	76/F	807	MTX	CNS lymphoma	Diffuse large B cell lymphoma. Malignant lymphoma, large B-cell, diffuse, EBV neg
1041- 10281005#	51/F	226	Mono	Lymphoma	Lymphoproliferative disorder; Hodgkin's lymphoma; EBV positive
1024- 10031001*	58/F	785	MTX	Breast	Core Biopsy- Local lab report: Atypical ductal hyperplasia Central lab report: Carcinoma in situ: Excisional Biopsy- Local lab report: Atypical ductal hyperplasia (without CIS or invasion) Central lab report: Dysplasia
LTE CP10 mg BID					
1024- 10181015	67/M	372	Leflunomide	Prostate cancer	Prostate adenocarcinoma
1024- 10311014	54/M	148	Mono	Unknown primary	Squamous cell carcinoma
1024- 11131019	71/M	113	Mono	Lung cancer (NSCLC)	Metastatic adenocarcinoma
1024- 11911007	79/F	526	Mono	Lung cancer (NSCLC)	Poorly differentiated adenocarcinoma
1024- 12431003	63/M	372	MTX	Small cell lung cancer	Small cell lung cancer
1024- 12511001	60/F	561	MTX	Breast cancer	Non-invasive cancer
1024- 12711004	46/M	449	MTX	Melanoma	N.A.
1024- 14581003	65/M	278	MTX	Lung cancer	N.A.
1024- 14901003	63/F	242	MTX	Probable lung cancer	Poorly differentiated non-small cell cancer
1024- 14921009	47/F	82	Mono	Renal cell carcinoma	Renal cell carcinoma, stage II
1024- 14981001	71/M	11	MTX	Prostate cancer	Prostate adenocarcinoma
1024- 15251002	68/M	177	MTX	Prostate cancer	N.A.
1024- 11521029	70/F	528	Leflunomide	Lung cancer (NSCLC)	Lung cancer (NSCLC)
1024- 11521018	68/F	607	Mono	Lung cancer (NSCLC)	Lung cancer (NSCLC)
1024- 10061011	65/F	582	Mono	Endometrial adenocarcinoma	Endometrial adenocarcinoma
1024- 15681010	77/F	340	Mono	Bladder cancer	Bladder cancer
1024- 11341005	64/M	110	MTX	Lung cancer	Lung cancer
1024- 15681006	61/F	378	Mono	Gastric cancer	Gastric cancer
1024- 12981017	66/F	511	MTX	Breast cancer	Breast cancer
1024- 13091002	49/F	757	Mono	Ureter cancer	Ureter cancer
1024- 11231020	72/F	743	MTX	Colon cancer	Colon cancer
1024- 11911002*	49/F	610	Mono	Ovary	Mucinous cystadenoma; Mucinous cystic tumor of borderline malignancy

Source: Integrated Summary of Malignancy, Adapted from Tables 20 and 21; 120-Day Safety Update (clinical data cut-off September 29, 2011), adapted from Table 34; Case Narra ives;; Response to Information Request June 05, 2012
#-LPD (Lymphoproliferative Disorder)
*-Uncertain weather benign or malignant

Table 101. Integrated Detailed Summary of All Nonfatal SAEs in the Phase 3 and LTE Studies in RA

Integrated Summary of All Nonfatal SAEs in the Phase 3 and LTE Studies in RA									
	Phase 3 Studies 0-12 Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Total number of SAEs	31	20	122	108	230	363	181	544	711
Total patients with ≥ 1 SAE, n (%)	30 (4.4)	19 (9.3)	104 (8.6)	87 (7.2)	211 (7.0)	217 (16.4)	120 (6.3)	337 (10.4)	446 (12.7)
Exposure for event, patient-years	199.7	174.8	872.6	890.4	2044.4	2111 0	859.8	2970.8	4172.3
Incidence of SAEs, event per 100 patient-years (95% CI)	15.02 (10.51, 21.49)	10.87 (6.93, 17.04)	11.87 (9.79, 14.38)	9.76 (7.91, 12.04)	10.30 (8.99, 11.78)	10.28 (8.99, 11.74)	13.96 (11.67, 16.69)	11.34 (10.20, 12.62)	10.69 (9.74, 11.73)
System Organ Class, n (event/100 PY) *Preferred term event, n*									
Blood and Lymphatic	**0**	**1 (0.6)**	**3 (0.3)**	**4 (0.4)**	**7 (0.3)**	**8 (0.4)**	**3 (0.3)**	**11 (0.4)**	**13 (0.3)**
Cardiac Disorders**	**2 (0.1)**	**4 (2.3)**	**5 (0.6)**	**13 (1.5)**	**17 (0.8)**	**26 (1.2)**	**7 (0.8)**	**33 (1.1)**	**46 (1.1)**
Ear and Labyrinth	**0**	**0**	**0**	**2 (0.2)**	**2 (0.1)**	**5 (0.2)**	**1 (0.1)**	**6 (0.2)**	**6 (0.1)**
Endocrine Disorders	**0**	**0**	**0**	**0**	**0**	**0**	**2 (0.2)**	**2 (<0.1)**	**3 (<0.1)**
Eye Disorders	**0**	**0**	**0**	**3 (0.3)**	**3 (0.1)**	**4 (0.2)**	**3 (0.3)**	**7 (0.2)**	**7 (0.2)**
Gastrointestinal Disorders	**1 (0.5)**	**2 (1.1)**	**6 (0.7)**	**11 (1.2)**	**17 (0.8)**	**27 (1.3)**	**12 (1.4)**	**39 (1.3)**	**48 (1.2)**
Abdominal hernia	-	*1*	-	-	-	*3*	*1*	*4*	*7*
Abdominal pain	-	-	-	-	-	*2*	*2*	*4*	*4*
Anal polyp	-	-	-	*1*	*1*	-	-	-	-
Ascites	-	-	-	-	-	*1*	*1*	*2*	*2*
Colitis	-	-	*1*	-	*1*	-	-	-	-
Colonic polyp	-	-	-	-	-	*1*	-	*1*	*2*
Constipation	-	-	-	*1*	*1*	-	-	-	-
Diarrhea	-	-	-	-	-	*2*	*1*	*3*	*5*
Diverticular perforation	-	-	-	*1*	*1*	*1*	*2*	*3*	*3*
Duodenal polyp	-	-	-	-	-	*1*	-	*1*	*1*
Duodenal ulcer hemorrhage	-	-	*1*	-	*1*	-	-	-	*1*
Enterocele	-	-	-	-	-	*1*	-	*1*	*1*
Gastric ulcer	-	-	-	-	-	*1*	-	*1*	*1*
Gastric ulcer hemorrhage	-	-	-	-	-	*1*	-	*1*	*1*
Gastritis	-	-	-	-	-	*2*	*1*	*3*	*4*
Gastritis, erosive	-	-	-	*1*	*1*	*1*	-	*1*	*1*
Gastritis hemorrhagic	-	-	-	-	-	*1*	-	*1*	*1*
Gastrointestinal disorder, NOS	-	-	-	-	-	-	-	-	*1*
Hematemesis	-	-	-	*1*	*1*	-	-	-	-
Hematochezia	-	-	-	-	-	*2*	-	*2*	*1*
Ileus	-	-	-	*1*	*1*	*1*	*1*	*2*	*3*
Intestinal fistula	-	-	-	-	-	-	-	-	*1*
Intestinal perforation	-	-	-	-	-	*1*	-	*1*	*1*
Inflammatory bowel disease	-	-	-	*1*	*1*	-	-	-	-
Melena	-	*1*	-	-	-	-	-	-	-
Nausea	-	-	*1*	-	*1*	-	-	-	-

Pancreatitis	-	-	*2*	-	*2*	*2*	*2*	*4*	*4*
Peptic ulcer hemorrhage	-	-	-	*1*	*1*	-	-	-	-
Peritonitis	-	-	-	*1*	*1*	-	*1*	*1*	*1*
Rectal hemorrhage	-	-	-	-	-	-	-	-	*1*
Reflux esophagitis	-	-	-	-	-	*2*	-	*2*	*2*
Salivary gland calculus	*1*	-	-	-	-	-	-	-	-
Salivary gland enlargement	-	-	*1*	-	*1*	-	-	-	-
Vomiting	-	-	-	*2*	*2*	*1*	-	*1*	*1*
General Disorders Admin. Site Cond.	**1 (0.5)**	**1 (0.6)**	**7 (0.8)**	**9 (1.0)**	**16 (0.8)**	**13 (0.6)**	**2 (0.2)**	**15 (0.5)**	**21 (0.5)**
Hepatobiliary Disorders (separate)	**2 (1.0)**	**1 (0.6)**	**7 (0.8)**	**4 (0.5)**	**11 (0.5)**	**10 (0.5)**	**6 (0.7)**	**16 (0.5)**	**19 (0.5)**
Immune system disorders	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3 (<0.1)**
Infections and Infestation (separate)	**4 (2.0)**	**3 (1.7)**	**33 (3.8)**	**30 (3.4)**	**63 (3.1)**	**76 (3.6)**	**58 (6.7)**	**134 (4.5)**	**177 (4.2)**
Injury, Poisoning, Procedural Complic.	**8 (4.0)**	**2 (1.1)**	**20 (2.3)**	**14 (1.6)**	**34 (1.7)**	**35 (1.7)**	**23 (2.7)**	**58 (2.0)**	**70 (1.7)**
Investigations	**0**	**0**	**1 (0.1)**	**0**	**1 (<0.1)**	**0**	**0**	**0**	**6 (0.1)**
ECG T-wave inversion	-	-	-	-	-	-	-	-	*1*
Metamyelocyte count increased	-	-	-	-	-	-	-	-	*1*
Myelocyte count increased	-	-	-	-	-	-	-	-	*1*
Transaminase increases	-	-	*1*	-	*1*	-	-	-	*3*
Metabolism and Nutrition	**2 (1.0)**	**0**	**2 (0.2)**	**5 (0.6)**	**7 (0.3)**	**6 (0.3)**	**3 (0.3)**	**9 (0.3)**	**9 (0.2)**
Musculoskeletal and Connective Tissue	**5 (2.5)**	**3 (1.7)**	**14 (1.6)**	**9 (1.0)**	**23 (1.1)**	**39 (1.8)**	**10 (1.2)**	**49 (1.6)**	**75 (1.8)**
Neoplasms, Benign, Malignant**	**2 (1.0)**	**2 (1.2)**	**9 (1.0)**	**12 (1.3)**	**21 (1.0)**	**33 (1.6)**	**17 (1.97)**	**50 (1.7)**	**65 (1.6)**
Nervous System Disorders	**7 (3.5)**	**0**	**8 (0.9)**	**7 (0.8)**	**15 (0.7)**	**11 (0.5)**	**10 (1.2)**	**21 (0.7)**	**43 (1.0)**
Amnesia	-	-	-	*1*	*1*	*1*	-	*1*	*1*
Brain injury	-	-	-	-	-	*1*	-	*1*	*1*
Brain edema	-	-	-	-	-	*1*	-	*1*	*1*
Carotid artery disease	-	-	-	*2*	*2*	*1*	-	*1*	*2*
Carpal, cubital tunnel syndrome	-	-	-	-	-	*2*	-	*2*	*2*
Cerebrovascular accident	-	-	*4*	-	*4*	*1*	*3*	*4*	*4*
Cranial nerves paralysis	-	-	-	-	-	*1*	*2*	*3*	*4*
Dysarthria	*1*	-	-	-	-	-	-	-	-
Epilepsy	*1*	-	-	-	-	*2*	-	*2*	*3*
Encephalopathy	-	-	-	-	-	*1*	-	*1*	*1*
Grand mal convulsion	*1*	-	-	-	-	-	-	-	-
Headache	-	-	-	*1*	*1*	-	*1*	*1*	*1*
Hemorrhage, intracranial	-	-	*1*	-	*1*	*2*	-	*2*	*2*
Ischemic stroke	*1*	-	-	-	-	-	-	-	*1*
Loss of consciousness	-	-	-	-	-	*2*	-	*2*	*2*
Monoplegia	-	-	-	-	-	*1*	-	*1*	*1*
Nerve root compression	-	-	-	-	-	-	-	-	*1*
Neuritis	-	-	-	-	-	*1*	-	*1*	*1*
Polyneuropathy	*1*	-	-	-	-	-	-	-	-
Radicular syndrome	-	-	-	-	-	*1*	*1*	*2*	*3*
Sciatica	-	-	*1*	*1*	*2*	-	*1*	*1*	*3*
Sensory loss	-	-	-	-	-	-	-	-	*1*
Serotonin syndrome	-	-	-	-	-	-	*1*	*1*	*1*
Spinal claudication	-	-	-	-	-	-	-	-	*1*
Spinal cord compression	-	-	-	-	-	-	*1*	*1*	*1*
Syncope	-	-	-	*1*	*1*	*1*	*1*	*2*	*2*
Thalamic infarction	-	-	-	*1*	*1*	-	-	-	-
Transient ischemia attack	*1*	-	*2*	-	*2*	-	*1*	*1*	*3*
Uremic encephalopathy	*1*	-	-	-	-	-	-	-	-
Pregn., Puerperium, Perinatal Cond.**	**1 (0.5)**	**0**	**0**	**2 (0.2)**	**2 (0.1)**	**3 (0.1)**	**0**	**3 (<0.1)**	**3 (<0.1)**
Psychiatric Disorders	**0**	**0**	**1 (0.1)**	**0**	**1 (<0.1)**	**1 (<0.1)**	**3 (0.3)**	**4 (0.1)**	**6 (0.1)**
Alcoholism	-	-	-	-	-	-	-	-	*1*
Anxiety	-	-	-	-	-	-	*1*	*1*	*1*
Completed suicide	-	-	-	-	-	*1*	*1*	*2*	*2*

Depression	-	-	-	-	-	-	*1*	*1*	*1*
Mental disorder	-	-	*1*	-	*1*	-	-	-	-
Post-traumatic stress disorder	-	-	-	-	-	-	-	-	*1*
Renal and Urinary Disorders**	**4 (2.0)**	**1 (0.6)**	**1 (0.1)**	**2 (0.2)**	**3 (0.1)**	**10 (0.5)**	**4 (0.5)**	**14 (0.5)**	**20 (0.5)**
Reproductive System, Breast Disorders	**3 (1.5)**	**0**	**4 (0.5)**	**0**	**4 (0.2)**	**8 (0.4)**	**1 (0.1)**	**9 (0.3)**	**11 (0.2)**
Respiratory, Thoracic, Mediastinal Dz	**2 (1.0)**	**1 (0.6)**	**11 (1.3)**	**9 (1.0)**	**20 (1.0)**	**16 (0.8)**	**7 (0.8)**	**23 (0.8)**	**29 (0.7)**
Acute respiratory distress syndrome	-	-	*1*	-	*1*	-	*1*	*1*	*2*
Adenoidal hypertrophy	-	-	-	-	-	*1*	-	*1*	*1*
Aspiration	-	-	-	*1*	*1*	-	-	-	-
Asthma	-	-	*1*	-	*1*	*1*	-	*1*	*1*
Bronchiectasis	-	-	-	-	-	-	-	-	*1*
Chronic obstructive pulmonary dz	-	-	*1*	*2*	*3*	*2*	*2*	*4*	*4*
Dyspnea	-	-	-	-	-	*3*	*1*	*4*	*4*
Hydrothorax	-	*1*	-	-	-	-	-	-	-
Interstitial lung disease	-	-	*2*	*2*	*4*	*1*	*1*	*2*	*2*
Lung infiltration	-	-	-	-	-	-	*1*	*1*	*1*
Organizing pneumonia	-	-	-	-	-	*1*	-	*1*	*1*
Pleural effusion	-	-	-	*1*	*1*	-	-	-	*1*
Pleuritic pain	-	-	*1*	-	*1*	*1*	-	*1*	*1*
Pneumonia, aspiration	-	-	*1*	-	*1*	-	-	-	-
Pneumothorax	-	-	-	-	-	-	*1*	*1*	*1*
Pulmonary embolism	*1*	-	*2*	-	*2*	*1*	-	*1*	*2*
Pulmonary fibrosis	-	-	-	*1*	*1*	-	-	-	-
Pulmonary hypertension	-	-	-	*1*	*1*	-	-	-	-
Pulmonary sarcoidosis	-	-	*1*	-	*1*	-	-	-	-
Respiratory arrest	-	-	-	-	-	*1*	-	*1*	*1*
Respiratory disorder, NOS	-	-	*1*	-	*1*	-	-	-	
Respiratory distress/failure	-	-	-	*1*	*1*	*4*	-	*4*	*4*
Rhinitis, allergic	-	-	-	-	-	-	*1*	*1*	*1*
Sleep apnea syndrome	*1*	-	-	-	-	-	-	-	*1*
Skin and Subcutaneous Tissue Dz	**0**	**0**	**4 (0.5)**	**0**	**4 (0.2)**	**1 (<0.1)**	**0**	**1 (<0.1)**	**4 (0.1)**
Social circumstances	**0**	**0**	**0**	**1 (0.1)**	**1 (<0.1)**	**0**	**0**	**0**	**0**
Surgical and Medical Procedures	**0**	**0**	**0**	**1 (0.1)**	**1 (<0.1)**	**0**	**0**	**0**	**1 (<0.1)**
Vascular Disorders	**1 (0.5)**	**0**	**2 (0.2)**	**4 (0.5)**	**6 (0.3)**	**16 (0.8)**	**4 (0.5)**	**20 (0.7)**	**31 (0.7)**
Aortic aneurysm	-	-	-	*1*	*1*	-	-	-	-
Atherosclerosis, NOS	-	-	-	-	-	*2*	-	*2*	*2*
Circulatory collapse	-	-	-	-	-	-	*1*	*1*	*1*
Deep vein thrombosis	*1*	-	-	-	-	*5*	*1*	*6*	*9*
Extremity necrosis	-	-	-	-	-	*1*	-	*1*	*2*
Hematoma	-	-	-	-	-	*1*	-	*1*	*2*
Hypertension	-	-	-	-	-	*4*	*1*	*5*	*5*
Hypertensive crisis	-	-	*1*	-	*1*	*4*	-	*4*	*6*
Hypovolemic shock	-	-	-	-	-	-	-	-	*1*
Infarction, NOS	-	-	-	*1*	*1*	-	-	-	-
Peripheral vascular disease	-	-	-	*1*	*1*	-	-	-	-
Thrombophlebitis	-	-	-	-	-	-	-	-	*1*
Venous insufficiency	-	-	-	-	-	-	*1*	*1*	*1*
Venous thrombosis	-	-	-	-	-	*1*	-	*1*	*1*

Source: Summary of Clinical Safety (data cut-off March 29, 2011), adapted from Tables 93-106 and 120-Day Safety Update, adapted from tables 21-23
*-CP All Doses group includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months; **-Separate table and review

Table 102. Number of Patients Serious Infections in Phase 3 Randomized Controlled Studies, by Trial Period

Number of Patients with Infections and Infestations SOC Serious Adverse Events by Preferred Term (All Causalities) for All Terms - Phase 3 Randomized Controlled Studies, by Trial Period

	Phase 3 Studies				
MedDRA PT, Number of patients (%)	**PBO**	**ADA**	**CP5 mg BID**	**CP10 mg BID**	**CP, All doses**
0-3 Months, Number of patients	**681**	**204**	**1216**	**1214**	**2430**
Patients with ≥ 1 SIE, n (%)	2 (0.3)	0	11 (0.9)	12 (1.0)	23 (0.9)
Abscess jaw	-	-	1 (0.1)	-	1 (<0.1)
Arthritis bacterial	-	-	-	1 (0.1)	1 (<0.1)
Bronchitis	-	-	1 (0.1)	-	1 (<0.1)
Cellulitis	-	-	2 (0.2)	1 (0.1)	3 (0.1)
Cholecystitis, infective	-	-	1 (0.1)	-	1 (<0.1)
Cytomegalovirus infection	-	-	-	1 (0.1)	1 (<0.1)
Dengue fever	-	-	1 (0.1)	-	1 (<0.1)
Diabetic foot infection	-	-	-	1 (0.1)	1 (<0.1)
Herpes zoster	-	-	1 (0.1)	1 (0.1)	2 (0.1)
Herpes zoster, NOS	-	-	-	*1 (0.1)*	*1 (<0.1)*
Herpes zoster disseminated	-	-	*1 (0.1)*	-	*1 (<0.1)*
Gastroenteritis	1 (0.1)	-	-	-	-
Urinary tract infection	-	-	-	1 (0.1)	1 (<0.1)
Influenza	-	-	-	1 (0.1)	1 (<0.1)
Labyrinthitis	-	-	-	1 (0.1)	1 (<0.1)
Liver abscess	-	-	-	1 (0.1)	1 (<0.1)
Osteomyelitis	-	-	1 (0.1)	-	1 (<0.1)
Pneumonia	-	-	3 (0.3)	2 (0.2)	5 (0.2)
Pneumocystis jiroveci pneumonia	-	-	*1 (0.1)*	-	*1 (<0.1)*
Pneumonia, NOS	-	-	*1 (0.1)*	*2 (0.2)*	*3 (0.1)*
Pneumonia viral	-	-	*1 (0.1)*	-	*1 (<0.1)*
Sialoadenitis	1 (0.1)	-	-	1 (0.1)	1 (<0.1)
3-6 months	**221**	**204**	**1451**	**1439**	**2890**
Patients with ≥ 1 SIE, n (%)	3 (1.4)	2 (1.0)	10 (0.7)	8 (0.6)	18 (0.6)
Bacterial sepsis	1 (0.5)	-	-	-	-
Breast abscess	-	1 (0.5)	-	-	-
Bronchiectasis	1 (0.5)	-	-	1 (<0.1)	1 (<0.1)
Bronchitis	-	-	-	1 (<0.1)	1 (<0.1)
Pneumonia	-	-	1 (<0.1)	1 (<0.1)	2 (<0.1)
Bronchopneumonia	-	-	*1*	-	*1*
Lower respiratory tract infection	-	-	-	*1*	*1*
Cellulitis	-	1 (0.5)	4 (0.3)	-	4 (0.1)
Cellulitis, NOS	-	-	*4*	-	*4*
Breast cellulitis	-	*1 (0.5)*	-	-	-
Clostridium difficile colitis	-	-	-	1 (<0.1)	1 (<0.1)
Diverticulitis	-	-	-	1 (<0.1)	1 (<0.1)
Enterocolitis	-	-	-	1 (<0.1)	1 (<0.1)
Gastroenteritis	-	-	1 (<0.1)	-	1 (<0.1)
Herpes zoster	-	-	2 (0.1)	-	2 (<0.1)
Localized infection, NOS	-	-	1 (<0.1)	-	1 (<0.1)
Pyelonephritis	1 (0.5)	-	-	2 (0.1)	2 (<0.1)
Sepsis	-	-	1 (<0.1)	-	1 (<0.1)
> 6 months	**N.A.**	**204**	**1056**	**1046**	**2102**
Patients with ≥ 1 SIE, n (%)	N.A.	2 (1.0)	12 (1.1)	10 (1.0)	22 (1.0)
Diverticulitis	N.A.	-	-	1 (0.1)	1 (<0.1)
Erysipelas	N A.	1 (0.5)	-	-	-
Gallbladder empyema	N.A.	1 (0.5)	-	-	-
Gastroenteritis	N A.	-	-	1 (0.1)	1 (<0.1)
Herpes zoster	N.A.	-	1 (0.1)	-	1 (<0.1)
Lung abscess	N.A.	-	1 (0.1)	-	1 (<0.1)
Pneumonia	N.A.	-	7 (0.7)	3 (0.3)	10 (0.5)
Pneumonia, NOS	N.A.	-	*6*	*2*	*8*
Pneumocystis cryptococcal	N.A.	-	-	*1*	*1*
Pneumonia, primary atypical	N.A.	-	*1*	-	*1*
Pulmonary tuberculosis	N.A.	-	-	4 (0.4)	4 (0.2)
Pyelonephritis, acute	N A.	-	1 (0.1)	-	1 (<0.1)
Salpingo-oophoritis	N A.	-	1 (0.1)	-	1 (<0.1)
Septic shock	N A.	-	1 (0.1)	-	2 (0.1)
Urinary tract infection	N.A.	-	-	1 (0.1)	1 (<0.1)

Pooled 0-12 Months	681	204	1216	1214	2430
Total number of SIEs	5	4	33	30	63
Total patients with ≥ 1 SIE, n (%)	3 (0.4)	3 (1.5)	29 (2.4)	27 (2.2)	61 (2.0)
Exposure, patient-years	202.5	178.7	900.9	909.1	2093.8
Incidence of SIE, patient per 100 patient-years (95%CI)	1.5 (0.5, 4.6)	1.7 (0.5, 5.2)	3.2 (2.2, 4.6)	3.0 (2.0, 4.3)	2.9 (2.3, 3.7)

Source: Integrated Analyses of Infections, adapted from Table 18

Table 103. Integrated Summary of All AEs Leading to Discontinuation in the Core Phase 3 (0-12 Months) and LTE Studies in RA

Integrated Summary of All AEs Leading to Discontinuation in the Core Phase 3 (0-12 Months) and LTE Studies in RA									
	Phase 3 RCT 0-12 Month Pooled Safety					LTE Studies			
	PBO	ADA	CP5 mg BID	CP10 mg BID	CP, All doses	CP5 mg BID	CP10 mg BID	LTE, All Doses (cut-off March 29, 2011)	Updated LTE, All Doses (cut-off Sept 29, 2011)
Enrolled	681	204	1216	1214	3030	1321	1906	3227	3515
Total number of AEs causing discontinuation	35	28	138	163	301	210	88	298	412
Total patients discontinuing due to AE, n (%)	26 (3.7)	22 (10.8)	95 (7.8)	99 (8.2)	205 (6.8)	148 (11.2)	75 (3.9)	223 (6.9)	318 (9.1)
Exposure for event, patient-years	201.5	178.2	897.8	905.5	2086.9	2222.4	878.1	3100.5	4381.9
Incidence of discontinua ion per 100 patient-years	12.41	12.35	10.58	10.93	9 82	6.66	8.54	7.19	7.26
(95% CI)	(8.38, 18.36)	(8.13, 18.75)	(8.65, 12.94)	(8.98, 13.31)	(8.57, 11.26)	(5.67, 7.82)	(6.81, 10.71)	(6.31, 8.20)	(6.50, 8.10)
System Organ Class, n (event/100 PY) *Preferred term event, n*									
Blood and Lymphatic System Disorders, n (%)	**0**	**1 (0.5)**	**6 (0.5)**	**6 (0.5)**	**12 (0.4)**	**6 (0.5)**	**3 (0.2)**	**9 (0.3)**	**10 (0.3)**
Anemia	-	-	3	3	6	3	2	5	
Leukocytosis	-	-	1	-	1	-	-	-	
Leukopenia	-	1	-	-	-	1	-	1	
Lymphadenitis	-	-	1	-	1	-	-	-	
Neutropenia	-	-	-	-	-	1	1	2	
Pancytopenia	-	-	-	1	1	1	-	1	
Thrombocytopenia	-	-	2	2	4	-	-	-	
Cardiac Disorders, n (%)	**2 (0.3)**	**2 (0.1)**	**1 (0.1)**	**5 (0.4)**	**6 (0.2)**	**12 (0.9)**	**2 (0.1)**	**14 (0.4)**	**14 (0.4)**
Acute myocardial infarction/MI	-	1	1	1	2	3	-	3	
Angina (unstable, pectoris, PM)/ACS	-	-	-	-	-	3	-	3	
AV Block, complete	1	-	-	-		-	-	-	
Arrhythmia	-	-	-	1	1	4	-	4	
Cardiac arrest	1	1	-	1	1	-	-	-	
Cardiac failure	-	-	-	3	3	1	1	2	
Ischemic cardiomyopahy	-	-	-	-	-	1	-	1	
Long QT syndrome	-	-	-	-	-	-	1	1	
Myocardial ischemia	-	-	-	-	-	1	-	1	
Pericarditis	-	-	-	1	1	-	-	-	
Ear and Labyrinth, n (%)	**0**	**0**	**1 (0.1)**	**3 (0.2)**	**4 (0.1)**	**1 (0.1)**	**0**	**1 (<0.1)**	**2 (0.1)**
Vertigo	-	-	1	3	4	1	-	1	
Eye Disorders, n (%)	**0**	**0**	**1 (0.1)**	**2 (0.2)**	**3 (0.1)**	**2 (0.2)**	**0**	**2 (0.1)**	**3 (0.1)**
Dry eye	-	-	1	-	1	-	-	-	
Glaucoma	-	-	-	-	-	1	-	1	
Necrotizing retinitis	-	-	-	1	1	1	-	1	
Retinal ischemia	-	-	-	-	-	1	-	1	
Ulcerative keratitis	-	-	-	1	1	-	-	-	

Gastrointestinal Disorders, n (%)	**5 (0.7)**	**2 (0.1)**	**12 (1.0)**	**18 (1.5)**	**30 (1.0)**	**16 (1.2)**	**3 (0.2)**	**19 (0.6)**	**22 (0.6)**
Abdominal distension/discomfort	1	-	-	2	2	-	-	-	
Abdominal hernia	-	-	-	-	-	1	-	1	
Abdominal pain	-	-	5	1	6	6	-	6	
Ascites	-	-	-	-	-	-	1	1	
Constipation	-	-	-	2	2	2	-	2	
Diarrhea	2	1	2	2	4	3	-	3	
Diverticular perforation	-	-	-	1	1	2	2	4	
Dry mouth	-	-	1	-	1	-	-	-	
Duodenal ulcer	-	-	-	-	-	1	-	1	
Duodenitis erosive	-	-	-	-	-	1	-	1	
Dyspepsia	1	1	2	-	2	-	-	-	
Enteritis, enterocoli is	-	-	-	1	1	1	-	1	
Gastric ulcer	-	-	-	-	-	1	-	1	
Gastritis hemorrhagic	-	-	-	-	-	1	-	1	
Gastrointestinal hemorrhage	-	-	-	1	1	1	-	1	
Glossodynia	1	-	-	1	1	-	-	-	
Hematemesis	-	1	-	-	-	-	-	-	
Hematochezia	-	1	-	-	-	-	-	-	
Hemorrhoidal hemorrhage	-	-	1	-	1	-	-	-	
Ileus	-	-	-	1	1	1	-	1	
Mouth ulcera ion	-	-	1	-	1	-	-	-	
Nausea	-	-	2	6	8	-	-	-	
Pancreatitis	-	-	1	-	1	-	-	-	
Peritonitis	-	-	-	1	1	-	-	-	
Tongue edema	-	-	1	-	1	-	-	-	
Vomiting	-	-	1	4	5	1	-	1	
General Disorders and Admin. Site Cond., n (%)	**1 (0.1)**	**0**	**4 (0.3)**	**3 (0.2)**	**8 (0.3)**	**5 (0.4)**	**0**	**5 (0.2)**	**7 (0.2)**
Chest pain	-	-	1	-	1	-	-	-	
Edema	-	-	2	1	3	-	-	-	
Multiorgan failure	-	-	-	1	1	-	-	-	
Pyrexia	-	-	1	1	2	4	-	4	
Other	1	1	-	2	3	1	-	1	
Hepatobiliary Disorders, n (%)	**0**	**0**	**4 (0.3)**	**0**	**4 (0.1)**	**6 (0.5)**	**2 (0.1)**	**8 (0.2)**	**8 (0.2)**
Cholecystitis	-	-	2	-	2	1	1	2	
Cholelithiasis	-	-	-	-	-	1	-	1	
Hepatic congestion	-	-	-	-	-	-	1	1	
Hepatic cyst	-	-	-	-	-	1	-	1	
Hepatic pain	-	-	-	-	-	1	-	1	
Hepatitis	-	-	-	-	-	2	-	2	
Hepatosplenomegaly	-	-	1	-	1	-	-	-	
Hepatotoxicity	-	-	1	-	1	-	-	-	
Immune system disorders, n (%)	**0**	**0**	**1 (0.1)**	**1 (0.1)**	**2 (0.1)**	**0**	**0**	**0**	**1 (<0.1)**
Drug hypersensitivity	-	-	1	-	1	-	-	-	
Lupus-like syndrome	-	-	-	1	1	-	-	-	
Infections and Infestation (separate) , n (%)	**2 (0.3)**	**4 (0.2)**	**30 (2.5)**	**33 (2.7)**	**63 (2.1)**	**48 (3.6)**	**38 (2.0)**	**86 (2.7)**	**117 (3.3)**
Abscess	-	1	2	1	3	3	4	7	
Acarodermatitis	-	-	-	-	-	1	-	1	
Appendicitis	-	-	-	-	-	1	1	2	
Arthritis bacterial	-	-	-	-	-	1	-	1	
Aspergilloma	-	-	-	1	1	-	-	-	

Bronchitis, bronchiolitis, bronchiectasis	1	-	1	-	1	-	1	1	
Cellulitis	-	2	4	-	4	3	3	6	
Dengue fever	-	-	1	-	1	-	-	-	
Device-related infection	-	-	-	-	1	2	-	2	
Diabetic foot infection	-	-	-	1	-	-	-	-	
Diverticulitis	-	-	-	3	3	3	1	4	
Enterocolitis	-	-	-	1	1	-	-	-	
Esophageal Candidiasis	-	-	1	-	1	-	-	-	
Gallbladder empyema	-	1	-	-	-	-	-	-	
Gastroenteri is	-	-	-	1	1	-	1	1	
Haemophilus infection, NOS	-	-	-	-	-	1	-	1	
Hematoma infection	-	-	1	-	1	-	-	-	
Herpes simplex	-	-	-	1	1	2	1	3	
Herpes zoster	-	1	4	7	11	8	2	10	
Infective spondylitis	-	-	-	-	-	-	1	1	
Influenza	-	-	-	1	1	-	-	-	
Labyrinthitis	-	-	-	1	1	-	-	-	
Mycobacterium avium complex infection	-	-	-	-	-	1	1	2	
Necrotizing fasciitis	-	-	-	-	-	1	-	1	
Onychomycosis	-	-	-	-	-	-	1	1	
Osteomyelitis	-	-	1	-	1	-	1	1	
Paronychia	-	-	1	-	1	-	-	-	
Peritoneal infection	-	-		-	-	1	1	2	
Pneumonia, NOS	-	-	4	5	9	7	13	20	
Pneumonia, cryptococcal	-	-	-	1	1	-	-	-	
Pneumonia, Pneumocystis jiroveci	-	-	1	-	1	-	-	-	
Pneumonia, primary atypical	-	-	1	-	1	1	-	1	
Pneumonia, viral	-	-	1	-	1	-	-	-	
Pyelonephritis	1	-	1	1	2	3	1	4	
Salpingo-oophorirtis	-	-	1	-	1	-	-	-	
Sepsis	1	-	2	-	2	1	3	4	
Sialoadenitis	1	-	-	-	-	-	-	-	
Sinusitis	-	-	-	1	1	-	2	2	
Sinusitis, aspergillus	-	-	-	-	-	1	-	1	
Skin infection, NOS	1	-	-	1	-	1	-	1	
Syphilis, secondary	-	-	-	-	-	1	-	1	
Staphylococcal infection	-	-	-	-	-	1	-	1	
Streptococcal infection	-	-	-	-	-	1	-	1	
Tinea pedis	-	-	-	-	-	-	1	1	
Tonsillitis	-	-	-	-	-	1	-	1	
Tuberculosis	-	-	-	5	5	1	-	1	
Upper respiratory tract infection	-	-	5	-	5	2	1	3	
Urinary tract infection	-	-	-	3	3	3	2	5	
Injury, Poisoning, Procedural Complications, n (%)	**1 (0.1)**	**0**	**4 (0.3)**	**1 (0.1)**	**5 (0.2)**	**5 (0.4)**	**2 (0.1)**	**7 (0.2)**	**9 (0.3)**
Investigations	**3 (0.4)**	**0**	**18 (1.5)**	**24 (2.0)**	**42 (1.4)**	**22 (1.7)**	**8 (0.4)**	**30 (0.9)**	**53 (1.5)**
ALT increased	-	-	3	6	9	8	2	10	
AST increased	-	-	2	6	8	4	-	4	
Blood alkaline phosphatase increased	-	-	-	1	1	2	-	2	
Blood creatine phosphokinase increased	-	-	-	2	2	3	1	4	
Blood creatinine increased	1	-	2	7	9	3	-	3	
Blood pressure increased	-	-	1	1	2	-	-	-	
Blood triglycerides increased	-	-	-	-	-	1	-	1	
Blood urea increased	-	-	-	-	-	1	-	1	

ECG T-wave inversion	-	-	-	-	-	1	-	1	
Gamma-glutamyltransferase increased	-	-	1	4	5	3	-	3	
Hemoglobin decreased	1	-	-	1	1	2	-	2	
Hepatic enzyme increased	1	1	3	1	4	1	3	4	
International normalized ratio increased	-	-	1	-	1	-	-	-	
Liver function test abnormal	-	-	-	1	1	2	-	2	
Lymphocyte count decreased	-	-	-	1	1	-	1	1	
Neutrophil count decreased	-	-	3	-	3	-	-	-	
Platelet count decreased	-	-	1	-	1	-	-	-	
Transaminase increased	1	-	2	-	2	-	1	1	
Weight increased	-	-	2	1	3	-	-	-	
White blood count decreased	-	-	3	2	5	-	-	-	
Metabolism and Nutrition, n (%)	**2 (0.3)**	**0**	**1 (0.1)**	**4 (0.3)**	**5 (0.2)**	**0**	**1 (0.1)**	**1 (<0.1)**	**2 (0.1)**
Musculoskeletal and Connective Tissue Disorders, n (%)	**9 (1.3)**	**4 (2.0)**	**6 (0.5)**	**7 (0.6)**	**13 (0.4)**	**5 (0.4)**	**2 (0.1)**	**7 (0.2)**	**12 (0.3)**
Neoplasms, Benign, Malignant and Unspecified, n (%)	**1 (0.1)**	**1 (0.5)**	**5 (0.4)**	**7 (0.6)**	**12 (0.4)**	**24 (1.8)**	**9 (0.5)**	**33 (1.0)**	**48 (1.4)**
Basal cell carcinoma	1	-	-	-	-	1	-	1	
Breast cancer	-	-	-	2	2	5	-	5	
Cervix carcinoma	-	-	-	2	2	-	-	-	
Choroid plexus papilloma	-	-	-	-	-	1	-	1	
Colon cancer	-	-	-	-	-	1	-	1	
Endometrial cancer	-	-	-	-	-	1	-	1	
Gastric cancer	-	-	-	-	-	2	-	2	
Hair follicle tumor, benign	-	-	1	-	1	-	-	-	
Laryngeal cancer	-	-	-	-	-	1	-	1	
Liposarcoma	-	-	-	-	-	1	-	1	
Lung cancer	-	1	2	1	3	4	4	8	
Lymphoproliferative disorder	-	-	-	1	1	2	-	2	
Malignant ascites	-	-	-	-	-	1	-	1	
Malignant melanoma	-	-	-	-	-	1	1	2	
Malignant pleural effusion	-	-	-	-	-	1	-	1	
Metastatic neoplasm, NOS	-	-	-	1	1	3	-	3	
Myelodysplastic syndrome	-	1	-	-	-	-	-	-	
Ovarian cancer	-	-	-	-	-	2	-	2	
Peritoneal neoplasm	-	-	-	-	-	1	-	1	
Prostate cancer	-	-	-	-	-	-	2	2	
Renal cell carcinoma	-	-	1	-	1	-	1	1	
Squamous cell carcinoma, NOS	-	-	1	-	1	-	1	1	
Thyroid cancer	-	-	-	-	-	1	-	1	
Vulvar cancer	-	-	-	-	-	1	-	1	
Nervous System Disorders, n (%)	**2 (0.3)**	**1 (0.5)**	**8 (0.7)**	**4 (0.3)**	**12 (0.4)**	**10 (0.8)**	**2 (0.1)**	**12 (0.4)**	**16 (0.5)**
Carotid artery aneurysm	-	-	-	-	-	1	-	1	
Carpal, cubital tunnel syndrome	-	1	-	-	-	-	-	-	
Cervical cord compression	-	-	-	-	-	-	1	1	
Cranial nerves paralysis	-	-	-	-	-	1	1	2	
Dizziness	1	-	1	-	1	-	-	-	
Epilepsy	-	-	-	-	-	3	-	3	
Headache	-	-	5	1	6	1	-	1	
Hemorrhage, intracranial	-	-	-	-	-	2	-	2	
Hypoesthesia	-	-	-	1	1	-	-	-	
Ischemic stroke	-	-	-	1	1	-	-	-	

Loss of consciousness	-	-	-	-	-	2	-	2	
Neuropathy	-	-	1	-	1	-	-	-	
Somnolence	-	-	-	1	1	-	-	-	
Syncope	-	-	-	1	1	1	-	1	
Tremor	-	-	1	-	1	1	-	1	
Uremic encephalopathy	1	-	-	-	-	-	-	-	
Pregnancy, Puerperium and Perinatal Conditions, n (%)	**1 (0.1)**	**0**	**1 (0.1)**	**1 (0.1)**	**2 (0.1)**	**0**	**0**	**0**	**1 (<0.1)**
Unintended pregnancy	1	-	1	1	2	-	-	-	
Psychiatric Disorders, n (%)	**0**	**1 (0.5)**	**1 (0.1)**	**0**	**1 (<0.1)**	**0**	**2 (0.1)**	**2 (0.1)**	**2 (0.1)**
Alcoholism	-	-	-	-	-	-	1	1	
Anxiety	-	1	-	-	-	-	-	-	
Completed suicide	-	1	-	-	-	-	1	1	
Mental disorder	-	-	1	-	1	-	-	-	
Renal and Urinary Disorders, n (%)	**2 (0.3)**	**1 (0.5)**	**0**	**4 (0.3)**	**4 (0.1)**	**3 (0.2)**	**0**	**3 (0.1)**	**5 (0.1)**
Diabetic nephropathy	1	-	-	-	-	-	-	-	
Dysuria	-	-	-	1	1	-	-	-	
Goodpasture's syndrome	1	-	-	-	-	-	-	-	
Hydronephrosis	1	-	-	-	-	-	-	-	
IgA nephropathy	-	1	-	-	-	-	-	-	
Nephrolithiasis	-	-	-	1	1	-	-	-	
Renal failure, acute and chronic	1	-	-	3	3	3	-	3	
Reproductive System and Breast Disorders, n (%)	**0**	**0**	**1 (0.1)**	**1 (0.1)**	**2 (0.1)**	**1 (0.1)**	**0**	**1 (<0.1)**	**2 (0.1)**
Respiratory, Thoracic and Mediastinal Disorders, n (%)	**0**	**0**	**5 (0.4)**	**7 (0.6)**	**12 (0.4)**	**6 (0.5)**	**6 (0.3)**	**12 (0.4)**	**17 (0.5)**
Acute respiratory distress syndrome	-	-	1	-	1	-	1	1	
Asthma	-	-	-	-	-	1	-	1	
Chronic obstructive pulmonary disease	-	-	-	-	-	1	2	3	
Dry throat	-	-	1	-	1	-	-	-	
Dyspnea	-	-	1	3	4	1	1	2	
Inters itial lung disease	-	-	1	1	2	1	-	1	
Pleural effusion	-	-	-	-	-	-	1	1	
Pneumonia, aspiration	-	-	1	-	1		-	-	
Pulmonary embolism	-	-	-	2	2	1	-	1	
Pulmonary fibrosis	-	-	-	1	1	-	1	1	
Respiratory distress/failure	-	-	-	-	-	2	-	2	
Sleep apnea syndrome	-	-	-	-	-	-	-	-	
Skin and Subcutaneous Tissue Disorder, n (%)	**0**	**3 (1.5)**	**12 (1.0)**	**3 (0.3)**	**15 (0.5)**	**3 (0.2)**	**3 (0.2)**	**6 (0.2)**	**11 (0.3)**
Vascular Disorders, n (%)	**0**	**0**	**0**	**4 (0.3)**	**4 (0.1)**	**2 (0.2)**	**1 (0.1)**	**3 (0.1)**	**6 (0.2)**
Aortic aneurysm	-	-	-	1	1	-	-	-	
Deep vein hrombosis	-	-	-	-	-	1	1	2	
Hypertension	-	-	-	1	1	-	-	-	
Hypertensive crisis	-	-	-	-	-	1	-	1	
Infarc ion, NOS	-	-	-	1	1	-	-	-	
Venous thrombosis	-	-	-	1	1	-	-	-	

Source: Summary of Clinical Safety (data cut-off March 29, 2011), adapted from Tables 93-106 and 120-Day Safety Update, adapted from tables 21-23

*CP All Doses group includes patients originally assigned to CP5 or CP10 at the start of the study as well as those patients advanced to CP-690,550 after receiving placebo for 3 to 6 months.

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

/s/

NIKOLAY P NIKOLOV
06/26/2012

SARAH K YIM
06/26/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 203,214 **Applicant: Pfizer** **Stamp Date: 10/21/2011**

Drug Name: tofacitinib **NDA Type: Standard** **MO: Nikolay P. Nikolov, M.D.**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD Format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? • Study Number: A3921025 Study Title: "A Phase 2b, Randomized, Double Blind, Placebo Controlled, Multicenter Study to Compare 6 Dose Regimens of CP-690,550 Versus. Placebo, Each Combined with Methotrexate, Administered for 6 Months in the Treatment of Subjects with Active Rheumatoid Arthritis Who Have Had An Inadequate Response to Methotrexate Alone" Sample Size: 507 Arms: 20 mg QD; and 15 mg, 10 mg, 5 mg, 3 mg, 1 mg BID, and PBO Location in submission: 5.3.5.1, CSR A3921035	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	• Study Number: A3921035 Study Title: "A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Active Comparator, Multicenter Study to Compare 5 Dose Regimens of CP-690,550 and Adalimumab versus Placebo, Administered for 6 Months in the Treatment of Subjects with Active RA" Sample Size: 384 Arms: 15 mg, 10 mg, 5 mg, 3 mg, 1 mg BID, Adalimumab, and PBO Location in submission: 5.3.5.1, CSR A3921035				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? • Pivotal Study #1: A3921032 • Pivotal Study #2: A3921045 • Pivotal Study #3: A3921046 • Pivotal Study #4: A3921064 Indications: - (b) (4) • Pivotal Study #4: A3921064 Indications: - (b) (4)	X			The Sponsor provides five core studies to support the proposed claims
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			The Phase 2/3 studies were global and include 20% US patients
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			The NDA format and content were discussed at Pre-NDA meeting, February 16, 2011
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Comprehensive QT study A3921028; reviewed by FDA in March 2009
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Separate proposed pediatric study request was submitted under IND 70,903
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

1. Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. If submitting as a PDF document, include mapping in both directions (verbatim -> preferred and preferred -> verbatim).

Nikolay P. Nikolov, M.D.	December 14, 2011
Reviewing Medical Officer	Date
Sarah Yim, M.D.	December 14, 2011
Clinical Team Leader	Date

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

/s/

NIKOLAY P NIKOLOV
12/14/2011

SARAH K YIM
12/14/2011
I concur. NDA 203214 is fileable from a clinical standpoint.