APPLICATION NUMBER:

208246Orig1s000

MEDICAL REVIEW(S)
Clinical Investigator Financial Disclosure
Review Template

Application Number: 208246
Submission Date(s): April 24, 2015
Applicant: Pfizer
Product: Tofacitinib XR 11mg
Reviewer: Juwaria Waheed, MD
Date of Review: 01/20/2016
Covered Clinical Study (Name and/or Number): See Summary below

<table>
<thead>
<tr>
<th>Was a list of clinical investigators provided:</th>
<th>Yes ☒</th>
<th>No ☐ (Request list from applicant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of investigators identified:</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Number of investigators who are sponsor employees (including both full-time and part-time employees):</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:</td>
<td>N.A.</td>
<td></td>
</tr>
<tr>
<td>Significant payments of other sorts:</td>
<td>N.A.</td>
<td></td>
</tr>
<tr>
<td>Proprietary interest in the product tested held by investigator:</td>
<td>N.A.</td>
<td></td>
</tr>
<tr>
<td>Significant equity interest held by investigator in sponsor of covered study:</td>
<td>N.A.</td>
<td></td>
</tr>
<tr>
<td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td>
<td>Yes ☐</td>
<td>No ☐ (Request details from applicant)</td>
</tr>
<tr>
<td>Is a description of the steps taken to minimize potential bias provided:</td>
<td>Yes ☐</td>
<td>No ☐ (Request information from applicant)</td>
</tr>
<tr>
<td>Number of investigators with certification of due diligence (Form FDA 3454, box 3):</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Is an attachment provided with the reason:</td>
<td>Yes ☐</td>
<td>No ☐ (Request explanation from applicant)</td>
</tr>
</tbody>
</table>
Pfizer Inc. submitted financial disclosure information for the covered studies in Table 1. The financial disclosure information covers the time period from the start of the study through one year after the completion of the study.

### Table 1. List of Covered Studies

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Study Name</th>
<th>Disclosure Start Date</th>
<th>Disclosure Cut-Off Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3921131</td>
<td>A PHASE 1, RANDOMIZED, OPEN LABEL, PARTIAL CROSSOVER STUDY TO EVALUATE THE PHARMACOKINETICS (PK), SAFETY, AND SAFETY OF THREE MODIFIED RELEASE (MR) AND ONE IMMEDIATE RELEASE (IR) FORMULATIONS OF TOFACTINIB (CP-690,550) IN HEALTHY VOLUNTEERS</td>
<td>25-NOV-2011</td>
<td>02-JAN-2012</td>
</tr>
<tr>
<td>A3921132</td>
<td>A PHASE 1, RANDOMIZED, OPEN-LABEL, 2-WAY CROSSOVER STUDY TO EVALUATE THE PHARMACOKINETICS (PK), SAFETY, AND BIOAVAILABILITY OF TOFACTINIB FOLLOWING SINGLE ORAL DOSE OF MR 11 MG COMPARED TO MR 22 MG IN HEALTHY VOLUNTEERS</td>
<td>14-NOV-2012</td>
<td>12-DEC-2012</td>
</tr>
<tr>
<td>A3921163</td>
<td>A PHASE 1, RANDOMIZED, OPEN-LABEL, SINGLE DOSE, 2-WAY CROSSOVER IN HEALTHY VOLUNTEERS TO EVALUATE THE PHARMACOKINETICS, BIOAVAILABILITY, AND SAFETY OF A MODIFIED RELEASE FORMULATION OF TOFACTINIB COMPARED TO THE IMMEDIATE RELEASE FORMULATION OF TOFACTINIB</td>
<td>26-JUL-2013</td>
<td>26-SEP-2013</td>
</tr>
<tr>
<td>A3921180</td>
<td>A PHASE 1, RANDOMIZED, OPEN-LABEL, SINGLE DOSE, 2-PERIOD CROSSOVER STUDY TO INVESTIGATE THE EFFECT OF FOOD ON THE PHARMACOKINETICS OF TOFACTINIB MODIFIED RELEASE (MR) 11 MG TABLETS IN HEALTHY WESTERN AND JAPANESE VOLUNTEERS</td>
<td>11-APR-2014</td>
<td>01-JUL-2014</td>
</tr>
<tr>
<td>A3921195</td>
<td>A PHASE 1, RANDOMIZED, OPEN-LABEL, SINGLE DOSE, CROSSOVER STUDY TO INVESTIGATE THE EFFECT OF DISSOLUTION RATE ON THE BIOAVAILABILITY OF MODIFIED RELEASE FORMULATIONS OF TOFACTINIB IN HEALTHY VOLUNTEERS</td>
<td>25-MAY-2014</td>
<td>31-JUL-2014</td>
</tr>
<tr>
<td>A3921212</td>
<td>A PHASE 1, RANDOMIZED, OPEN-LABEL, 2-PERIOD CROSSOVER STUDY TO EVALUATE SINGLE DOSE AND STEADY STATE PHARMACOKINETICS AND BIOAVAILABILITY OF THE MODIFIED RELEASE FORMULATION OF TOFACTINIB COMPARED TO THE IMMEDIATE RELEASE FORMULATION OF TOFACTINIB IN HEALTHY VOLUNTEERS</td>
<td>09-APR-2014</td>
<td>27-MAY-2014</td>
</tr>
</tbody>
</table>

**Sponsor summary of Certification – FDA Form 3454**

Certification, using FORM FDA 3454, that none of the financial interests or arrangements described in 21 CFR Part 54 exists, is provided for 30 of the 30 clinical investigators who participated in the covered studies listed above. Pfizer Inc. has identified 14 clinical investigators who were full-time or part-time employees of the sponsor of the covered studies. Due Diligence activities were required for 0 of the 30 clinical investigators.

**Reviewer’s Comments**

The Applicant has adequately disclosed financial interests and/or arrangements with clinical investigators by having submitted a signed Form FDA 3454. The applicant states that none of the 30 investigators, of whom 14 were full-time or part-time employees of the Applicant, had financial information to disclose.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUWARIA F WAHEED
02/22/2016

NIKOLAY P NIKOLOV
02/22/2016
Application Type: NDA
Application Number(s): 208246
Priority or Standard: Standard
Submit Date(s): April 24, 2015
Received Date(s): April 24, 2015
PDUFA Goal Date: February 24, 2016
Division / Office: DPARP/OND
Reviewer Name(s): Juwaria Waheed, MD
Review Completion Date: January 20, 2016
Established Name: Xeljanz (Tofacitinib)
(Proposed) Trade Name: Xeljanz XR
Therapeutic Class: Janus Kinase (JAK) inhibitor
Applicant: Pfizer
Formulation(s): Tablets
Dosing Regimen: 11mg once a day (QD)
Indication(s): Rheumatoid Arthritis (RA)
Intended Population(s): Moderate-to-Severe RA

Template Version: March 6, 2009
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NDA 208,246
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommend approval of NDA 208,246 for tofacitinib 11 mg XR extended-release tablets with revisions to the proposed labeling, as outlined in Section 9.2 Labeling Recommendations.

1.2 Risk Benefit Assessment

Brief overview of clinical program

The clinical program for tofacitinib XR (extended-release) comprised of seven phase 1 PK studies to characterize the biopharmaceutical aspects of tofacitinib XR with the goal of establishing PK bioequivalence between the XR and the approved immediate-release (IR) formulations of tofacitinib. Consistent with the pre-NDA submission discussions, clinical efficacy and safety studies were not assessed in the RA indication. Instead, as discussed, the current tofacitinib XR NDA submission cross-references to NDA 203,214, tofacitinib IR, for safety and efficacy of the active moiety. Safety and efficacy of tofacitinib IR has been originally reviewed under NDA 203,214, approved on November 6, 2012. As such, data previously reviewed under NDA 203,214 will be cross-referenced and will not be reviewed under this NDA.

Risk Benefit Assessment

Tofacitinib, a first in class, Janus associated kinase (JAK) inhibitor is approved at 5mg BID dosing after demonstrating a positive benefit-risk balance for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to MTX, as a monotherapy or in combination with a nonbiological DMARD. Efficacy and safety of the 5mg BID dose in the adult RA population has been established as reviewed under NDA 203,214. The proposed tofacitinib XR formulation has been developed to provide a once-daily dosing alternative with the same exposure as to the tofacitinib IR 5mg BID (twice a day) dosing regimen.

The clinical development plan of tofacitinib XR 11mg formulation is predicated on establishing pharmacokinetic (PK) equivalence to tofacitinib IR formulation. The seven studies that comprise the clinical program are biopharmaceutical (clinical-pharmacology) studies in healthy volunteers designed to characterize the PK profile of the XR formulation and subsequently demonstrate equivalent bioavailability (BA) as measured by PK parameters of area under the plasma concentration-time curve (AUC) between XR (11mg administered QD) and IR (5 mg administered BID) formulations.
Additionally, PK similarity between the XR and IR formulations was assessed for other PK parameters such as Cmax (maximum plasma concentration) and Cmin (minimum plasma concentration) at steady-state relative to that of the IR formulation.

The clinical development program for the XR formulation demonstrated equivalent AUC and Cmax for the XR 11mg formulation compared to the tofacitinib IR 5 mg formulation in the pivotal PK study (A3921212) as well as other studies. Cmin at steady state for the XR formulation was ~30% lower compared to the IR formulation, however, this did not impact efficacy. Exposure-response analysis with the IR formulation showed that efficacy endpoints of ACR20 and DAS28 were unaffected by a lower Cmin. This is also supported by the similar clinical efficacy observed with IR 20 mg QD dose compared to IR 10 mg BID despite a large difference in Cmin; and the improved goodness-of-fit characteristics with Cav compared to Cmax or Cmin (Dr. Chen, clinical pharmacology review).

Given the PK characterization of the XR formulation, and the known exposure-response relationships from the approved IR formulation, it was determined that a phase 3 clinical safety and efficacy study may not add any further meaningful information to the development program. Therefore, an independent clinical safety and efficacy program for tofacitinib XR was not conducted in the RA indication. Instead, the applicant will cross-reference safety and efficacy studies from the tofacitinib IR program (NDA 203,214).

Further, with the adequate PK bridging between the XR and IR formulations, and evaluation of exposure-response (E-R) relationships for the IR formulation in the RA population, it is anticipated that the safety and efficacy of the tofacitinib XR 11mg daily in the RA indication will be consistent with that of tofacitinib IR 5mg BID. The safety profile of tofacitinib XR in the healthy volunteer PK studies was consistent with the known safety profile of tofacitinib IR and no new safety signals were identified.

Overall, the risk to benefit profile of tofacitinib XR in RA patients seems favorable. The 11mg once a day regimen may have the potential to improve compliance and thus may represent an advantage over the twice a day dosing regimen currently approved for the IR formulation.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Currently there is an approved Risk Evaluation and Mitigation Strategy (REMS) for tofacitinib IR for use in RA. The tofacitinib IR REMS, at approval on 6 November 2012, included a Medication Guide and a Communication Plan. FDA has requested the Medication Guide be removed from the REMS and the modification was approved on 11
February 2015, [NDA 203214/S-006;008]). The REMS addresses serious risks associated with tofacitinib, including serious infections, including opportunistic infections, tuberculosis, malignancy, and changes in laboratory parameters such as decreases in lymphocytes, neutrophils, and hemoglobin levels, and increases in lipids, which will require monitoring.

As agreed upon during the pre-NDA interaction (24 November, 2014), the applicant provided an assessment report of the ongoing REMS program for tofacitinib IR in the current NDA dossier (Module 1, Section 1.16) that concludes that the goals of the current REMS are being met. Upon complete review of the tofacitinib IR REMS, the applicant proposes to incorporate the tofacitinib XR tablet formulation into the current REMS for NDA 203,214 to address the safety risks associated with tofacitinib.

1.4 Recommendations for Postmarket Requirements and Commitments

- Studies to achieve compliance with PREA:

Tofacitinib XR represents a new dosage form and a new dosing regimen and approval of this NDA would trigger PREA. With this submission, the applicant has requested a waiver for children 0 to less than 2 years old, since pJIA is extremely rare in this age group and a deferral of studies for patients age 2-17 years old with pJIA until the completion of PREA requirements for tofacitinib IR formulation under NDA 203,214. The assessment of PK, efficacy and safety data from tofacitinib IR JIA program will determine the need for any pediatric studies with XR formulation. These requests have been included in the agreed initial Pediatric Study Plan (iPSP) on March 20, 2015.

As part of this agreed upon (iPSP), the applicant committed to pursue the development of an age-appropriate tofacitinib XR formulation to enable QD dosing in pediatric patients requiring doses lower than 11 mg and/or pediatric patients who are unwilling/unable to swallow the current XR 11 mg tablet. During the NDA review cycle, the applicant amended the iPSP with proposed studies and timelines for feasibility assessment and development of age-appropriate XR formulation. The proposed pediatric study plan was discussed at the FDA Pediatric Review Committee (PeRC) on January 06, 2016 and while PeRC agreed with the overall proposal they recommended that the timelines for the development of the age-appropriate XR formulation be shortened. At the time of this review these timelines have not been finalized.

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.

2.1 Product Information

XELJANZ® (tofacitinib, CP-690,550) 5 mg twice daily (BID) using the immediate release (IR) tablet formulation was approved in the United States for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) on November 6, 2012 under NDA 203,214.

The applicant, Pfizer, submitted the current NDA to seek licensure for once daily (QD) dosing using a modified release (XR) formulation; tofacitinib XR 11mg tablets. The once daily dosing is anticipated to enhance patient convenience and potentially compliance with treatment regimen.

Tofacitinib is an 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 for developing CP-690,550 as a treatment for RA in which lymphocyte activation and proliferation play a pathogenic role. (NDA 203,214).

2.2 Tables of Currently Available Treatments for Proposed Indications

Rheumatoid Arthritis: Many effective therapies are approved for the treatment of patients with RA including nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, corticosteroids, disease modifying anti rheumatic drugs (DMARDs) and biologics. Currently approved DMARDs and biologic therapies are listed in Table 1 and Table 2, respectively.
Table 1. Small Molecule DMARDs Approved for RA in the United States

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

Table 2. Biologic DMARDs Approved for RA in the United States

<table>
<thead>
<tr>
<th>Product Name (Trade Name) [Applicant] [year]</th>
<th>Presentation and ROA †</th>
<th>Description and MOA §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept (ENBREL) [Immunex/Amgen] (1998)</td>
<td>Vial 25 mg Prefilled syringe 25 or 50 mg/mL SC injection</td>
<td>Fusion protein consisting of TNF-R and human IgG1 Fc TNF inhibitor</td>
</tr>
<tr>
<td>Infliximab (REMICADE) [Centocor] (1999)</td>
<td>Vial 10 mg/mL IV infusion</td>
<td>Chimeric IgG1 k mAb TNF inhibitor</td>
</tr>
<tr>
<td>Anakinra (KINERET) [Amgen] (2001)</td>
<td>Prefilled syringe 10 mg SC injection</td>
<td>Recombinant polypeptide IL-1 receptor antagonist</td>
</tr>
<tr>
<td>Adalimumab (HUMIRA) [Abbott] (2002)</td>
<td>Prefilled syringe 40 mg/0.8 mL Humira Pen 40 mg/0.8 mL SC injection</td>
<td>Human IgG1 k mAb TNF inhibitor</td>
</tr>
<tr>
<td>Abatacept (ORENCIA) [Bristol Myers Squibb] (2005)</td>
<td>Lyophilized powder 250 mg/vial IV infusion</td>
<td>Fusion protein consisting of CTLA-4 and human IgG1 Fc T cell activation inhibitor</td>
</tr>
<tr>
<td>Rituximab (RITUXAN) [Genentech and Biogen] (2006)</td>
<td>Vial 10 mg/mL IV infusion</td>
<td>Chimeric murine/human IgG1 k mAb Anti CD20, B cell depletor</td>
</tr>
<tr>
<td>Golimumab (SIMPONI) [Centocor] (2009)</td>
<td>Prefilled syringe 50 mg/0.5 mL SmartJect Autoinjector 50 mg/0.5 mL SC injection</td>
<td>Humanized IgG1 k mAb TNF inhibitor</td>
</tr>
<tr>
<td>Certolizumab Pegol (CIMZIA) [UCB Inc] (2009)</td>
<td>Lyophilized powder 200 mg/vial SC injection</td>
<td>Humanized Fab fragment TNF inhibitor</td>
</tr>
<tr>
<td>Tocilizumab (ACTEMRA) [Genentech/Roche] (2010)</td>
<td>Vial 20 mg/mL IV infusion</td>
<td>Humanized IgG1 k mAb IL-6 receptor inhibitor</td>
</tr>
<tr>
<td>Tofacitinib (XELJANZ) [Pfizer] (2012)</td>
<td>5mg immediate-release tablets</td>
<td>JAK kinase inhibitor</td>
</tr>
</tbody>
</table>

Year = Year of first approval for RA †ROA = Route of administration §MOA= Mechanism of action
2.3 Availability of Proposed Active Ingredient in the United States

Tofacitinib is currently commercially available in the United States as an IR formulation 5mg BID for the treatment of patients with RA.

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

In the meetings between the applicant and the Agency prior to the current NDA submission, agreements were reached on several aspects of the application, including:

- Initially in development, a phase 3 study was proposed to assess efficacy of the XR formulation compared to placebo with key secondary objectives of comparative assessment between the XR and IR formulations. However, based on the pharmacokinetic profile of the two formulations and the known exposure-response relationships from the IR program, the proposed phase 3 study was not considered to add meaningful information and was determined to not be necessary. (pre-IND Type B meeting, March 22, 2013)

- Subsequently, the agency and the applicant agreed on the proposal to assess tofacitinib XR formulation in a series of clinical pharmacology studies in healthy volunteers characterizing the biopharmaceutical aspects of the new formulation and to establish similarity in key PK exposure parameters for the XR formulation compared to the approved tofacitinib IR formulation.

- Pharmacokinetic (PK) development program with proposed single and multiple-dose PK studies demonstrating comparable exposure and Cmax of the once daily XR formulation to the twice daily IR formulation can be sufficient to support NDA submission for tofacitinib XR 11mg formulation. (pre-NDA meeting, Nov 24, 2014)

- The Agency asked the applicant to submit a PK/PD analysis linking the systemic exposure of tofacitinib to efficacy using data from the previous studies in NDA 203,214. Specifically, agency advised the applicant to identify the most relevant
PK ((pre-NDA meeting, Nov 24, 2014) parameter (e.g. AUC, CMax, or Cmin) for efficacy in order to appropriately bridge the IR efficacy information to the XR formulation. The applicant proposed to use continuous DAS28 in addition to ACR 20, ACR 50 and ACR 70 as efficacy endpoints for PK/PD analysis to bridge between tofacitinib IR and XR formulations. For the PK/PD analysis approach, the Division accepted applicant’s proposal for DAS28. It was at the applicant’s discretion to use adequate PK parameters, with appropriate justification, to bridge the data for the IR to XR formulation. (pre-NDA meeting, Nov 24, 2014)

- Clinical efficacy and safety studies were not conducted in the tofacitinib XR development program for the RA indication. Instead, the applicant will cross-reference all relevant safety and efficacy data from NDA 203,214. (pre-NDA meeting, Nov 24, 2014)

- Submission of one label incorporating the XR information into the current labeling for the immediate release product. (pre-NDA meeting, Nov 24, 2014)

Of note, tofacitinib XR was previously referred to as modified release (MR) tablets per the applicant. However, the USPI will list tofacitinib extended release (XR).

### 2.6 Other Relevant Background Information

#### Issue of Nominal Dosing

Currently approved tofacitinib IR is labeled for oral administration at a dose of 5 mg twice a day for RA. The modified release (XR) formulation was designed as a dose of 11 mg once a day. In the 74-day filing letter, the applicant was notified of a potential review issuer surrounding the differences in nominal dose between the already approved IR formulation (5+5 mg) and the proposed XR formulation (11 mg) instead of 10 mg. The applicant acknowledged that there is a 10% difference in nominal total daily dose between the IR and the XR formulations and further explained the increase in dose was incorporated to match the AUC between the XR and IR formulations. With the 10% increase in dose, the applicant noted a consistent geometric mean AUC ratio (XR/IR) of approximately 100%.

The issue of differences in nominal dosing was further discussed internally within DPARP discussions, in a consult request with Office of Regulatory Policy (September 29, 2015) and with senior management at the New Drug Rounds conference (November 13, 2015). Discussions with both ORP and at the New Drug Rounds while acknowledging a different nominal dose may create confusion at the end-user interface, concluded that there was no regulatory or scientific framework barring approval of the XR formulation despite mismatching of nominal dosing compared to the IR formulation.
3 Ethics and Good Clinical Practices

The applicant 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.

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

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.

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended accepting data without an on-site inspection, noting that OSIS recently inspected the sites and further inspection will be not be necessary at this time. (July 27, 2015).

3.2 Compliance with Good Clinical Practices

The applicant certified that all Studies comprising the tofacitinib XR clinical development program were conducted in accordance with Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, and in compliance with the Food and Drug Administration (FDA) regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations (CFR) 50, 56, and 312.

3.3 Financial Disclosures

The applicant submitted FDA Form 3454 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

Tofacitinib citrate (USAN) is a heterocyclic, small molecule. The citrate salt (CP-690,550-10), and the free base (CP-690,550) of this compound were utilized in nonclinical evaluations, and are also used in clinical studies.

The tofacitinib XR tablet uses ECS (extrudable core system) osmotic delivery technology to modify the release of tofacitinib in a controlled fashion, thereby enabling once-daily administration of tofacitinib.

Tofacitinib 11 mg XR osmotic tablet formulation will be provided as oval, pink film-coated tablets with a drilled hole at one end of the tablet band and “JKI 11” printed on one side of the tablet.

Tofacitinib XR 11 mg tablets contain 17.771 mg of tofacitinib citrate (equivalent to 11 mg of tofacitinib).

4.2 Clinical Microbiology

Not relevant to tofacitinib as an oral tablet.

4.3 Preclinical Pharmacology/Toxicology

No new data submitted in this NDA. Please refer to NDA 203,214 (tofacitinib IR 5mg BID).

4.4 Clinical Pharmacology

Please refer to NDA 203, 214 for detailed clinical pharmacology review of tofacitinib IR formulation.

The core of this NDA submission is comprised of a PK development program that established equivalence of bioavailability between the XR and IR formulations based on
The tofacitinib XR clinical program consisted of 7 Phase 1 healthy volunteer (HV) studies that evaluated the PK of multiple pilot formulations and the proposed commercial XR 11 mg formulation for QD dosing. No new efficacy or safety studies have been conducted in RA patients using the tofacitinib XR formulation in support of this application. The clinical pharmacology and biopharmaceutics studies supporting this NDA and their design features are listed under 5 Sources of Clinical Data and discussed in detail in Dr. Chen’s review.

The tofacitinib XR clinical pharmacology program has demonstrated equivalent AUC and Cmax for the XR 11 mg QD formulation compared to the currently approved tofacitinib (IR 5 mg BID) formulation.

4.4.1 Mechanism of Action

Tofacitinib is 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 common gamma chain mutation, which is in the JAK3 signaling pathway, is also associated with X-linked severe combined immunodeficiency (SCID) phenotype in humans.

4.4.2 Pharmacodynamics

Refer to NDA 203,214.

4.4.3 Pharmacokinetics

Single dose PK

Following administration of tofacitinib XR 11 mg (single oral dose) and tofacitinib IR 10 mg (2 tablets of 5 mg administered approximately 12 hours apart), peak concentrations after the morning dose (Cmax for XR and Cmax1 for IR) were similar. Peak concentrations were reached later for the XR treatment (median T max = 4 hours) than for the IR treatment (median T max,1 = 0.5 hours) and terminal half-life was longer for the XR formulation (mean 5.9 hours) compared to the IR formulation (mean 3.2 hours). Total
plasma tofacitinib exposure based on geometric mean $AUC_{\text{inf}}$ was similar for both treatments (Table 3).

The extent of exposure for a single dose of tofacitinib XR 11 mg was equivalent to the total dose of tofacitinib IR 10 mg administered as two 5 mg doses approximately 12 hours apart, based on the 90% CI for the ratio (XR / IR) of adjusted geometric means for $AUC_{\text{inf}}$ and $C_{\text{max}}$ being wholly within equivalence limits (80% to 125%, Table 3).

Table 3. Statistical Summary of Treatment Comparisons for Plasma Tofacitinib Parameters Following a Single Oral Dose of Tofacitinib XR 11 mg and 2 Separate Oral Dose Administrations of Tofacitinib IR 5 mg (12 hours apart) on Day 1

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Tofacitinib MR</th>
<th>Tofacitinib IR 10 mg</th>
<th>Ratio (Test/Reference) of Adjusted Geometric Means</th>
<th>90% CI for Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{\text{inf}}$ (ng hr/mL)</td>
<td>253.2</td>
<td>243.7</td>
<td>103.92</td>
<td>98.81, 109.28</td>
</tr>
<tr>
<td>$AUC_{\text{last}}$ (ng hr/mL)</td>
<td>250.8</td>
<td>241.4</td>
<td>103.90</td>
<td>98.87, 109.19</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg/mL)</td>
<td>35.98</td>
<td>39.22</td>
<td>91.75</td>
<td>83.27, 101.09</td>
</tr>
</tbody>
</table>

(Source: Dr. Chen’s clinical pharmacology review; MR (modified release) = XR (extended-release))

**Multiple dose PK**

Following administration of tofacitinib XR 11 mg QD and tofacitinib IR 5 mg BID for 5 days, the overall results were consistent with those described above for Day 1 (single dose phase). Total daily plasma tofacitinib exposure based on $AUC_{24}$ was similar for both treatments. Peak concentrations for Day 7 ($C_{\text{max}}$ for XR and $C_{\text{max1}}$ for IR) were also similar with median $T_{\text{max}}$ of 4 hours for XR and median $T_{\text{max1}}$ of 0.5 hours for IR, the same as on Day 1.

Results of the statistical analysis are summarized in Table 4. The 90% CIs for the ratio (XR / IR) of adjusted geometric means for $AUC_{24}$ and $C_{\text{max}}$ values ($C_{\text{max}}$ for XR and $C_{\text{max1}}$ for IR) were within the 80% to 125% interval, demonstrating equivalence of tofacitinib total daily exposure for tofacitinib XR 11 mg QD and tofacitinib IR 5 mg BID.
Exposure-Response

The application of PK/PD modeling approaches demonstrate that Cav is the relevant parameter for efficacy and that the 29% lower Cmin for the XR formulation is not clinically important to the efficacy of tofacitinib. This is supported by the observed lag in the kinetics of clinical response relative to plasma concentrations; the similar clinical efficacy observed with IR 20 mg QD dose compared to IR 10 mg BID despite a large difference in Cmin; and the improved goodness-of-fit characteristics with Cav compared to Cmax or Cmin.

Characteristics of exposure-response relationships for safety
All PK parameters for the XR 11 mg QD dose are equivalent (AUC and Cmax) or slightly lower (29% lower Cmin) as compared to those of the IR 5 mg BID dose.

The expected duration of steady-state plasma concentrations above the in-vitro, whole blood IC50 for JAK 1/3 inhibition (17 ng/mL) is approximately 12-13 hours for both IR and XR formulations over a 24-hour period. The data from 20 mg IR QD in study 1025 suggested that the short term safety profile with once daily sustained inhibition of JAK1/3 for 12-13 hours is comparable to the BID dosing regimen.

5 Sources of Clinical Data
The tofacitinib XR clinical program consisted of 7 Phase 1 healthy volunteer (HV) studies (Table 5) that evaluated the PK of multiple pilot formulations and the proposed commercial XR 11 mg formulation for QD dosing. These studies were designed to characterize the biopharmaceutical aspects of the XR formulation and establish similarity in key PK exposure parameters as compared to the currently approved tofacitinib IR 5 mg BID formulation. These studies included a total of 172 healthy volunteer (HV) subjects in a target age range of 18 to 55 years, inclusive.
No safety or efficacy studies in patients were conducted in the XR program to support the NDA for the RA indication. Instead, safety and efficacy studies from the original NDA 203,214 (Xeljanz (tofacitinib) IR 5mg BID) are cross-referenced to the current submission as agreed upon during the pre-NDA meeting interactions.

Refer to Dr. Chen’s clinical pharmacology review for a detailed review of the clinical pharmacology studies.

5.1 Table of Clinical Studies
# Table 5. Tables of Studies/Clinical Trials

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Objectives</th>
<th>Treatment Groups</th>
<th># of Subjects</th>
<th>Study Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3921113</td>
<td>Feasibility study of XR formulation</td>
<td>Single dose&lt;br&gt;IR 10mg&lt;br&gt;20mg (capsule -)&lt;br&gt;20mg (capsule -)</td>
<td>12</td>
<td>Single Dose</td>
</tr>
<tr>
<td>(Singapore)</td>
<td></td>
<td>Single dose&lt;br&gt;XR 22mg (ECS osmotic tablet); fasted and fed&lt;br&gt;XR 22mg&lt;br&gt;XR 22mg</td>
<td>30</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A3921131</td>
<td>Preliminary relative bioavailability of pilot formulations and food effect</td>
<td>Single dose&lt;br&gt;IR 10mg&lt;br&gt;XR 22mg (ECS osmotic tablet); fasted and fed&lt;br&gt;XR 22mg</td>
<td>20</td>
<td>Single Dose</td>
</tr>
<tr>
<td>(Singapore)</td>
<td></td>
<td>Single Dose&lt;br&gt;XR 22mg (ECS osmotic tablet); fasted&lt;br&gt;XR 11mg (ECS osmotic tablet); fasted</td>
<td>20</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A3921163</td>
<td>Relative BA of initial commercial-scale (osmotic) formulation</td>
<td>IR 10mg, fasted&lt;br&gt;XR 11mg (ECS osmotic tablet); fasted</td>
<td>26</td>
<td>Single Dose</td>
</tr>
<tr>
<td>(Belgium)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3921180</td>
<td>Food Effect on proposed-commercial (Osmotic) formulation</td>
<td>XR 11mg (ECS osmotic tablet); fasted and fed&lt;br&gt;3 formulations – target release, slow release and fast release</td>
<td>24</td>
<td>Single Dose</td>
</tr>
<tr>
<td>(United States)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3921195</td>
<td>In-vitro dissolution with in-vivo plasma drug concentrations (IVIVC study)</td>
<td>IR 5mg, fasted&lt;br&gt;XR 22mg fasted&lt;br&gt;XR 11 mg (ECS osmotic tablet); fasted; 3 formulations – target release, slow release and fast release</td>
<td>36</td>
<td>Single Dose</td>
</tr>
<tr>
<td>(Belgium)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3921212</td>
<td>Bioequivalence of proposed-commercial (Osmotic) formulation</td>
<td>Single dose phase: single dose&lt;br&gt;IR 5mg BID&lt;br&gt;XR 11mg QD&lt;br&gt;Multiple Dose Phase&lt;br&gt;IR 5mg BID&lt;br&gt;XR 11mg QD (ECS osmotic tablet)</td>
<td>24</td>
<td>Single dose phase Multiple dose phase (5 days)</td>
</tr>
</tbody>
</table>

(Source: Table 1, Summary of Clinical Safety)
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. As noted above, the clinical development program for tofacitinib XR 11mg formulation consisted of 7 clinical pharmacology studies (listed in Table 5 above) in healthy volunteers to characterize the biopharmaceutic aspects of the XR formulation and to establish PK bioequivalence between the XR and IR formulations. These studies are reviewed in detail in Dr. Chen’s clinical pharmacology review.

5.3 Discussion of Individual Studies/Clinical Trials

Refer to Dr. Chen’s clinical pharmacology review for a detailed review of the clinical pharmacology studies. The 7 HV studies supporting this NDA include 4 bioavailability (BA) studies (A3921113, A3921131, A3921132 and A3921163) which evaluated PK of the pilot or initial commercial-scale formulations; a food effect (A3921180) and a single- and multiple-dose PK study with the proposed commercial formulation (A3921212, pivotal study); and, an IVIVC study (A3921195) which investigated the relationship between in vitro dissolution and in vivo PK performance of the XR formulations.

Osmotic capsules with different release durations of tofacitinib were evaluated in the initial controlled release feasibility study (A3921113). Subsequently, tablets and Extrudable Core System (ECS) osmotic tablets were evaluated to select the most appropriate controlled release formulation technology platform for further development (A3921131). The ECS osmotic tablet platform was selected for further clinical and commercial development and was used to support subsequent studies (A3921132, A3921163, A3921180, A3921195 and A3921212). Study A3921212 was considered the pivotal study for establishing the equivalence of the proposed commercial tofacitinib XR 11 mg QD formulation to the currently marketed IR 5 mg BID formulation.

Extrinsic factors such as food and alcohol were studied for their effects on the PK of tofacitinib. Intra- and inter-subject variability for Cmax and AUCinfin (area under the plasma concentration-time profile from time-zero extrapolated to infinite time) was examined by study.

6 Review of Efficacy

Efficacy Summary
No new clinical efficacy information was included in this NDA. Please refer to NDA 203,214 tofacitinib IR for a review of efficacy. Pursuant to pre-NDA agreement with the Agency, the applicant cross-referenced efficacy information from NDA 203,214.

**Bridging Efficacy from Tofacitinib IR to Tofacitinib XR** (adapted from Dr. Chen’s clinical pharmacology review)

*Applicant’s rationale*

The PK profile of the XR formulation, demonstrating overall similarity in PK parameters (equivalent AUC and Cmax, and 29% lower Cmin), and evidence from E-R relationships from the tofacitinib IR RA development program support the bridging of efficacy from IR 5 mg BID to XR 11 mg QD.

The analyses primarily focused on improvements in DAS28-3(CRP), as agreed with FDA on 24 November 2014 at the pre-NDA meeting, with additional analyses based on ACR response criteria as well as other relevant biomarker and nonclinical efficacy data from the IR development program.

*Dr. Chen’s review*: A rigorous analysis assessing the relevant PK parameter for tofacitinib efficacy was performed using Emax model, with the primary endpoint ACR 20 and other endpoints such as DAS 28 and ACR 50 and 70. Goodness-of-fit plots based on the applicant’s analyses showed that the model fitted the data reasonably well. Also, the reviewer’s independent analysis of ACR 20 resulted in similar results that Cave is the most relevant PK parameter. Overall, the reviewer concludes that the analysis, and the corresponding conclusions and interpretations, presented by the applicant are reasonable.

**6.1 Indication**

Same as tofacitinib IR 5mg BID: “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**

N/A (see Efficacy Summary above)
6.1.2 Demographics
N/A (see Efficacy Summary above)

6.1.3 Subject Disposition
N/A (see Efficacy Summary above)

6.1.4 Analysis of Primary Endpoint(s)
N/A (see Efficacy Summary above)

6.1.5 Analysis of Secondary Endpoints(s)
N/A (see Efficacy Summary above)

6.1.6 Other Endpoints
N/A (see Efficacy Summary above)

6.1.7 Subpopulations
N/A (see Efficacy Summary above)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations
N/A (see Efficacy Summary above)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects
N/A (see Efficacy Summary above)

6.1.10 Additional Efficacy Issues/Analyses
N/A (see Efficacy Summary above)
7 Review of Safety

Safety Summary

There were no safety studies in the RA indication to support this NDA submission. Pursuant to pre-NDA agreement with the Agency, the applicant cross-referenced safety information from NDA 203,214 (tofacitinib IR 5mg formulation). As such, refer to NDA 203,214 tofacitinib IR for a review of safety.

The 7 clinical-pharmacology phase 1 studies (Table 5) in healthy volunteers conducted to characterize the PK profile of the tofacitinib XR formulation included a total of 172 healthy volunteers (ages 18-55). In this clinical program, tofacitinib XR was overall safe and well-tolerated in healthy volunteers. Majority of adverse events (AE’s) were mild and similar between the XR and IR formulations. There were no clear differences observed between the XR and IR formulations in the frequency and types of AEs reported. There were no clinically important findings in laboratory tests associated with study treatment. No serious adverse events, adverse events of special interest (AESI) or deaths were reported. Finally, no new safety signals were identified.

Bridging Safety from Tofacitinib IR to Tofacitinib XR (adapted from Dr. Chen’s clinical pharmacology review)

With the exception of Phase 1 clinical pharmacology studies, no new safety studies were conducted in RA patients using the tofacitinib XR formulation to support this NDA.

Applicant’s rationale

Bridging of safety from the tofacitinib IR formulation to the XR formulation is supported by the PK profile of the XR formulation and the known exposure-safety relationships from the tofacitinib IR program. The overall safety profile of the XR formulation is expected to be consistent with that of the IR formulation based on the considerations summarized below.

- All PK parameters for the XR 11 mg QD dose are equivalent (AUC and Cmax) or slightly lower (29% lower Cmin) as compared to those of the IR 5 mg BID dose. Inter- and intra-subject variability was comparable across all PK parameters between the XR and IR formulations. Negligible accumulation of systemic exposure (AUC accumulation ratio of 1.12) is seen following repeated dosing of tofacitinib XR. Similar to the IR formulation, more than 95% of tofacitinib XR is eliminated within 24 hours following discontinuation of treatment.
The expected duration of steady-state plasma concentrations above the in-vitro, whole blood IC50 (concentration producing 50% of the maximum inhibition) for JAK 1/3 inhibition (17 ng/mL) is approximately 12-13 hours for both formulations over a 24-hour period. This suggests a similar level of target enzyme inhibition over the dosing interval.

E-R relationships for several safety endpoints in the IR development program, including AEs such as serious infections and changes in laboratory safety outcomes indicate that neither Cmax nor Cmin provides additional predictive value over and above dose or AUC (or Cav) in E-R relationships.

Dr. Chen’s review: The exposure response for safety was reviewed for tofacitinib IR formulation in NDA203214. As the applicant stated, the exposure response is consistent with dose response, and the tofacitinib concentration information did not provide additional explanation for the AEs. For the long term safety events, such as serious infection and malignancy, the AE information was all based on BID dosing regimens, and the PK parameters (Cmax, Cmin and Cave) were highly correlated. Therefore, we cannot identify the most relevant PK parameter for these AEs.

For short term safety measured by laboratory parameters, such as LDL, HDL, serum creatinine, and absolute neutrophil counts, the 20 mg QD dose appears to have better safety profiles as measured by these laboratory parameters, compared to 10 mg BID (study 1025). The data from 20 mg IR QD in study 1025 suggested that the short term safety profile with once daily sustained inhibition of JAK1/3 for 12-13 hours is comparable to the BID dosing regimen.

Anticipated Safety Risks with Tofacitinib

Tofacitinib is a potent, inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome (Karaman et al, 2008). In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2 (Meyer et al, 2010). Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including interleukin (IL)-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, development, homeostasis, proliferation, and function; therefore, inhibition of their signaling may result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and interferon (IFN)y (Murray, 2007; O’Sullivan et al, 2007). At higher exposures,
inhibition of erythropoietin could occur via inhibition of JAK2 signaling (Meyer et al, 2010).

Safety Summary of tofacitinib IR (Adapted from Dr. Nikolov’s clinical review, NDA 203,214)

“Safety data in this NDA (203,214) 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. 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.

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.

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 from the Arthritis Advisory Committee panel.”

Consequently, the USPI for tofacitinib IR includes a boxed warning for serious infections and malignancies. The approval letter for tofacitinib IR (Nov 6, 2012) noted the aforementioned safety risks and required the applicant to conduct a postmarketing study.

“The clinical development program showed that treatment with Xeljanz (tofacitinib) is associated with an increase in cholesterol levels, which raises the concern of an increase in cardiovascular adverse events with Xeljanz (tofacitinib) therapy. An increase in serious infections and malignancy was also noted in the Xeljanz (tofacitinib) clinical development program.

.. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:"

1934-3    Controlled clinical trial to evaluate the long term safety of tofacitinib in patients with rheumatoid arthritis. The trial should include two doses of tofacitinib and an active comparator. The trial should be of sufficient size and duration to evaluate safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy.

Proposed timelines per the applicant:
Final Protocol Submission: March 2013
Trial Completion: December 2019
Final Report Submission: June 2020

7A. Overview of Clinical Safety for Tofacitinib XR in Healthy Volunteers

Table 5 lists the 7 phase 1 studies that comprised the clinical development program for tofacitinib XR. These were Phase 1, open-label, randomized, crossover design studies. In these studies a total of 172 healthy volunteers (HVs) between 18 and 55 years of age, inclusive, were administered tofacitinib (IR and/or XR) as single or multiple doses (up to 5 days).
Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 6. Summary of Treatment Duration across all XR studies

<table>
<thead>
<tr>
<th></th>
<th>IR 5 mg TDD</th>
<th>IR 10 mg TDD</th>
<th>MR 11 mg TDD</th>
<th>MR 22 mg TDD</th>
<th>Other&lt;sup&gt;2, 3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>36</td>
<td>92</td>
<td>129</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td>Duration (Days)</td>
<td>1</td>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>68</td>
<td>106</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td></td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BID = twice daily; IR = immediate release; ISS = integrated summary of safety; mg = milligram; MR = modified release; QD = once daily; TDD = total daily dose.
<sup>a</sup> All doses were administered as a single morning dose except for Study A3921212 where IR 10 mg was administered as 2×5 mg tablets 12 hours apart (single dose phase) or 5 mg BID (multiple dose phase).
<sup>b</sup> Other includes tofacitinib MR 20 mg 6 hour and MR 20 mg 12 hour capsules from Study A3921113; and, tofacitinib MR 22 mg 5 hour (fasted and fed) and MR 22 mg 9 hour (fasted) provisional formulations from Study A3921131. In this document “provisional” and “pilot” are used interchangeably. Healthy volunteers participating in Study A3921212 received doses of tofacitinib (MR or IR) for a total of 6 days. Day 1 and Day 3 through Day 7.
<sup>c</sup> Source: Table 3, Summary of Clinical Safety
MR (modified release) = XR (extended-release)

Table 6 provides the numbers of HVs who received treatment with the tofacitinib XR and IR formulations across the 7 Phase 1 studies. Tofacitinib XR and IR were administered as single or multiple doses (up to 5 days).

Demographic and other characteristics of the study population across all studies are provided in Table 7. A total of 172 HVs between 18 and 55 years of age, inclusive, enrolled in the tofacitinib XR Phase 1 studies. Subjects were primarily male (97%) and of White (48.3%) or Asian (40.7%) race.
Table 7. Demographic Characteristics of Healthy Volunteers

<table>
<thead>
<tr>
<th>Number (% of Subjects)</th>
<th>Male (N=166)</th>
<th>Female (N=6)</th>
<th>Total (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18-44</td>
<td>145 (87.3)</td>
<td>1 (16.7)</td>
<td>146 (84.9)</td>
</tr>
<tr>
<td>45-64</td>
<td>21 (12.7)</td>
<td>5 (33.3)</td>
<td>26 (15.1)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean</td>
<td>32.1</td>
<td>50.2</td>
<td>32.8</td>
</tr>
<tr>
<td>SD</td>
<td>8.7</td>
<td>4.8</td>
<td>9.2</td>
</tr>
<tr>
<td>Range</td>
<td>19-55</td>
<td>41-54</td>
<td>19-55</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>77 (46.4)</td>
<td>6 (100.0)</td>
<td>83 (48.3)</td>
</tr>
<tr>
<td>Black</td>
<td>14 (8.4)</td>
<td>0</td>
<td>14 (8.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>70 (42.2)</td>
<td>0</td>
<td>70 (40.7)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.0)</td>
<td>0</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>Weight (kg):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>75.0</td>
<td>71.1</td>
<td>74.9</td>
</tr>
<tr>
<td>SD</td>
<td>11.7</td>
<td>9.6</td>
<td>11.7</td>
</tr>
<tr>
<td>Range</td>
<td>47.4-108.1</td>
<td>61.0-82.4</td>
<td>47.4-108.1</td>
</tr>
<tr>
<td>BMI (kg/m**2):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>24.4</td>
<td>26.1</td>
<td>24.5</td>
</tr>
<tr>
<td>SD</td>
<td>3.1</td>
<td>3.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Range</td>
<td>17.7-30.5</td>
<td>22.3-29.8</td>
<td>17.7-30.5</td>
</tr>
<tr>
<td>Height (cm):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>175.2</td>
<td>165.2</td>
<td>174.8</td>
</tr>
<tr>
<td>SD</td>
<td>7.0</td>
<td>9.4</td>
<td>7.3</td>
</tr>
<tr>
<td>Range</td>
<td>160-197</td>
<td>150-178</td>
<td>150-197</td>
</tr>
</tbody>
</table>


Body Mass Index (BMI) is calculated as weight/(height*0.01)**2.

cm = centimeter; ISS = integrated summary of safety; kg = kilogram; MR = modified release; QD = once daily; SD = standard deviation; m = meter.

(Source: Table 4, Summary of Clinical Safety)

Adverse Events

Safety assessment is descriptive in these HV clinical-pharmacology studies. Adverse events (AEs) presented in the applicant safety summary were coded using the MedDRA version 17.0.

Table 8 provides a summary of all-cause treatment emergent adverse events (TEAEs) across the XR clinical program. None of the 172 HVs participating in XR studies experienced an SAE (serious adverse event), severe AE, dose reduction, or death.
Table 8. Summary of TEAEs across All XR Studies

<table>
<thead>
<tr>
<th>Number (%) of subjects:</th>
<th>IR 5 mg TDD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IR 10 mg TDD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MR 11 mg TDD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MR 22 mg TDD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Other&lt;sup&gt;ab&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects evaluable for AEs</td>
<td>36</td>
<td>92</td>
<td>129</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td>Number of AEs</td>
<td>15</td>
<td>36</td>
<td>56</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Subjects with AEs</td>
<td>9 (25.0)</td>
<td>24 (26.1)</td>
<td>40 (31.0)</td>
<td>20 (26.3)</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>Subjects with SAEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with Severe AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subjects discontinued due to AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with dose reduced or temporary discontinuation due to AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

All causality TEAEs from the 7 Phase 1 tofacitinib XR studies occurring in 2 or more subjects across the studies are presented by System Organ Class (SOC) in Table 9. The greatest number of AEs experienced by all subjects across all treatment groups occurred in Gastrointestinal Disorders SOC, followed by the Nervous System Disorder SOC. Diarrhea and headaches were the most commonly reported AEs across all studies.
Table 9. TEAEs in ≥2 Subjects across All XR Studies

<table>
<thead>
<tr>
<th></th>
<th>IR 5 mg TDDa</th>
<th>IR 10 mg TDDa</th>
<th>MR QD 11 mg TDDa</th>
<th>MR QD 22 mg TDDa</th>
<th>Otherb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Subjects:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluate for adverse events</td>
<td>36</td>
<td>92</td>
<td>129</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td>With adverse events</td>
<td>9 (25.0)</td>
<td>24 (26.1)</td>
<td>40 (31.0)</td>
<td>20 (26.3)</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>Discontinued due to adverse events</td>
<td>0</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number (%) of Subjects with Adverse Events by:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and High Level Group Term</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and Preferred Term</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GASTROINTESTINAL DISORDERS</td>
<td>2 (5.6)</td>
<td>10 (10.9)</td>
<td>15 (11.6)</td>
<td>3 (3.9)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Gastrointestinal motility and defecation conditions</td>
<td>2 (5.6)</td>
<td>4 (4.3)</td>
<td>8 (6.2)</td>
<td>2 (2.6)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Change of bowel habit</td>
<td>0</td>
<td>2 (2.2)</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (5.6)</td>
<td>3 (3.2)</td>
<td>7 (5.4)</td>
<td>2 (2.6)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Gastrointestinal signs and symptoms</td>
<td>0</td>
<td>7 (7.6)</td>
<td>6 (4.7)</td>
<td>1 (1.3)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>2 (2.2)</td>
<td>1 (0.8)</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2 (2.2)</td>
<td>3 (2.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</td>
<td>0</td>
<td>5 (5.4)</td>
<td>5 (3.9)</td>
<td>1 (1.3)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Administration site reactions</td>
<td>0</td>
<td>4 (4.3)</td>
<td>2 (1.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Puncture site hemorrhage</td>
<td>0</td>
<td>2 (2.2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular puncture site bruise</td>
<td>0</td>
<td>2 (2.2)</td>
<td>2 (1.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General system disorders NEC</td>
<td>0</td>
<td>1 (1.1)</td>
<td>3 (2.3)</td>
<td>1 (1.3)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1 (1.1)</td>
<td>3 (2.3)</td>
<td>1 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>INFECTIONS AND INFESTATIONS</td>
<td>4 (11.1)</td>
<td>3 (3.2)</td>
<td>6 (4.7)</td>
<td>3 (3.9)</td>
<td>0</td>
</tr>
<tr>
<td>Infections – pathogen unspecified</td>
<td>2 (5.6)</td>
<td>2 (2.2)</td>
<td>3 (2.3)</td>
<td>1 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (5.6)</td>
<td>2 (2.2)</td>
<td>1 (1.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Viral infectious disorders</td>
<td>2 (5.6)</td>
<td>0</td>
<td>2 (1.6)</td>
<td>2 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>2 (5.6)</td>
<td>0</td>
<td>2 (1.6)</td>
<td>2 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</td>
<td>0</td>
<td>2 (2.2)</td>
<td>6 (4.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders NEC</td>
<td>0</td>
<td>2 (2.2)</td>
<td>5 (3.9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>0</td>
<td>2 (2.2)</td>
<td>3 (2.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0</td>
<td>0</td>
<td>2 (2.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NERVOUS SYSTEM DISORDERS</td>
<td>5 (13.9)</td>
<td>4 (4.3)</td>
<td>12 (9.3)</td>
<td>6 (7.9)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Headaches</td>
<td>5 (13.9)</td>
<td>2 (2.2)</td>
<td>11 (8.5)</td>
<td>5 (6.6)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (13.9)</td>
<td>2 (2.2)</td>
<td>11 (8.5)</td>
<td>5 (6.6)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Neurological disorders NEC</td>
<td>0</td>
<td>2 (2.2)</td>
<td>1 (0.8)</td>
<td>2 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1 (1.1)</td>
<td>1 (0.8)</td>
<td>2 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</td>
<td>2 (5.6)</td>
<td>4 (4.3)</td>
<td>4 (3.1)</td>
<td>6 (7.9)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Respiratory disorders NEC</td>
<td>2 (5.6)</td>
<td>2 (2.2)</td>
<td>3 (2.3)</td>
<td>5 (6.6)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Oropharyngitis pain</td>
<td>1 (2.8)</td>
<td>0</td>
<td>2 (1.6)</td>
<td>5 (6.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

Includes Protocols: A3921113, A3921131, A3921132, A3921163, A3921180, A3921212

a. All doses were administered as a single morning dose except for Study A3921212 where IR 10 mg was administered as 2x5 mg tablets 12 hours apart (single dose phase) or 5 mg BID (multiple dose phase).

b. Other incl. tofacitinib MR 20 mg 6 hour and MR 20 mg 12 hour

(0) (0) tablets from Study A3921113, and tofacitinib MR 22 mg 5 hour (faster and fed) and MR 25 mg 9 hour (faster) provisional formulations from Study A3921131. In this document ‘provisional’ and ‘plot’ are used interchangeably.

(Source: Table 6, Summary of Clinical Safety; MR (modified release) = XR (extended-release))

Adverse Events of Special Interest, SAE’s, Deaths and Discontinuations

No adverse events of special interest, SAE’s or deaths occurred in the 7 tofacitinib XR studies.

There was 1 discontinuation (Subject 10011012) due to an AE (fungal skin infection) while receiving the tofacitinib IR 10 mg (5 mg BID) treatment in Study A3921212. Onset
of the AE occurred during the washout period between Periods 1 and 2. The investigator described this AE as a superficial infection of the skin located in the groin region. The infection was considered to be moderate in intensity and resolved with nystatin and triamcinolone (Mycolog) topical cream treatment.

Clinical Laboratory Evaluations
There were no patterns of change for laboratory tests associated with drug use identified in the 7 tofacitinib XR studies and no laboratory test abnormalities led to discontinuation. There were no abnormal laboratory tests reported as AEs.

Vital Signs, Physical Findings, and Other Observations Related to Safety
There were no clinically significant findings with regards to vital signs or physical examination; and, there were no other clinically significant observations related to safety in the 7 Phase 1 XR studies.

In summary, tofacitinib XR was well tolerated in these phase 1, clinical pharmacology studies. As noted earlier, these AE’s are descriptive in a healthy volunteer population who received single dose or multiple doses of tofacitinib XR up to 5 days. The safety results thus are not reflective of the target RA population. Instead, safety information should be cross-referenced from the tofacitinib IR program with an established safety profile in the RA population (NDA 203,214).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety
There were no safety studies in the RA indication to support this NDA submission. Pursuant to pre-NDA agreement with the Agency, the applicant cross-referenced safety information from NDA 203,214 (tofacitinib IR 5mg formulation).

7.1.2 Categorization of Adverse Events
N/A

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence
N/A
7.2 Adequacy of Safety Assessments

N/A

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

N/A, See section 7A

7.2.2 Explorations for Dose Response

N/A

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

N/A

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

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

N/A

7.3 Major Safety Results

N/A, See section 7A

7.3.1 Deaths

N/A, See section 7A

7.3.2 Nonfatal Serious Adverse Events

N/A, See section 7A
7.3.3 Dropouts and/or Discontinuations
N/A, See section 7A

7.3.4 Significant Adverse Events
N/A, See section 7A

7.3.5 Submission Specific Primary Safety Concerns
N/A

7.4 Supportive Safety Results
N/A

7.4.1 Common Adverse Events
N/A, See section 7A

7.4.2 Laboratory Findings
N/A, See section 7A

7.4.3 Vital Signs
N/A, See section 7A

7.4.4 Electrocardiograms (ECGs)
N/A, See section 7A

7.4.5 Special Safety Studies/Clinical Trials
N/A, See section 7A

7.4.6 Immunogenicity
N/A, See section 7A

7.5 Other Safety Explorations
N/A, See section 7A
7.5.1 Dose Dependency for Adverse Events
N/A

7.5.2 Time Dependency for Adverse Events
N/A

7.5.3 Drug-Demographic Interactions
N/A

7.5.4 Drug-Disease Interactions
N/A

7.5.5 Drug-Drug Interactions
N/A

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity
N/A

7.6.2 Human Reproduction and Pregnancy Data
N/A

7.6.3 Pediatrics and Assessment of Effects on Growth
N/A

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound
N/A

7.7 Additional Submissions / Safety Issues

120-day safety update for the XR program
Healthy Volunteers
As of the cut-off date for this report, 28 April 2015, there is no new or additional safety information in healthy volunteers.

Per discussion at the pre-NDA meeting on 24 November 2014, the applicant agreed to provide FDA with safety information for the tofacitinib XR formulation from the ongoing Japan Phase 3 clinical study, A3921215, related to deaths, serious adverse events (SAEs), and discontinuations due to adverse events (AEs). These data (as of the cutoff date of 28 April 2015) are provided in this update.

RA Patients in Study A3921215
Study A3921215 is an ongoing, randomized, multicenter, double-blind, Phase 3 study to evaluate the non-inferiority for efficacy of 11 mg XR QD to 5 mg IR BID in Japanese adult active RA subjects who have inadequate response to methotrexate (6 mg/week to 16 mg/week). Subjects receive tofacitinib for 12 weeks with stable background methotrexate.

As of 28 Apr 2015, 10 subjects were administered tofacitinib (11 mg XR QD or 5 mg IR BID) and had post-dosing data available for analysis. Blinded safety data from Study A3921215 as of the 28 April 2015 cutoff date are available. The adverse events reported for this study thus far are consistent with the known safety profile observed in RA clinical trials of tofacitinib IR. No new safety signals for tofacitinib were identified and no new or unique events were associated with the XR formulation. No deaths were reported in the tofacitinib XR program through Day 120. Two (2) subjects reported SAEs (one event each), one case of anemia and one case of femoral neck fracture, each. One subject discontinued participation in the study due to AE of anemia.

8 Postmarket Experience

There is no post marketing experience with tofacitinib XR.
9 Appendices

None

9.1 Literature Review/References

NDA 203, 214; Primary clinical review, Dr. Nikolov, June 2012
NDA 203, 214; Addendum to clinical review, Dr. Nikolov, September 2012

9.2 Labeling Recommendations

Consistent with the pre-submission discussions, the applicant submitted one USPI for both the IR and XR tofacitinib formulations. The proposed label incorporates relevant information and data pertinent to the tofacitinib XR 11mg formulation.

The applicant proposes

The clinical pharmacology team, in their independent assessment, noted

Consequently, the clinical pharmacology team recommends, and I agree, that tofacitinib XR should not be used in this specific patient population and recommend these patients can continue to use tofacitinib IR 5mg QD instead.

The labeling discussions with applicant are ongoing at the time of this review.

9.3 Advisory Committee Meeting

None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUWARIA F WAHEED
01/20/2016

NIKOLAY P NIKOLOV
01/20/2016

I concur.
On initial overview of the NDA application for filing:

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FORMAT/ORGANIZATION/LEGIBILITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Identify the general format that has been used for this application, e.g. electronic CTD.</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. On its face, is the clinical section organized in a manner to allow substantive review to begin?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)?</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>5. Are all documents submitted in English or are English translations provided when necessary?</td>
<td>x</td>
<td></td>
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<tr>
<td>6. Is the clinical section legible so that substantive review can begin?</td>
<td>x</td>
<td></td>
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<tr>
<td><strong>LABELING</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>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?</td>
<td>x</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>SUMMARIES</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>8. Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Has the applicant submitted the integrated summary of safety (ISS)?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Has the applicant submitted the integrated summary of efficacy (ISE)?</td>
<td>x</td>
<td></td>
<td></td>
<td>As discussed at the pre-NDA meeting, clinical efficacy and safety would be cross-referenced from original NDA 203214 for Immediate Release (IR) formulation 5mg BID</td>
</tr>
<tr>
<td>11. Has the applicant submitted a benefit-risk analysis for the product?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Indicate if the Application is a 505(b)(1) or a 505(b)(2).  505(b)(1)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>505(b)(2) Applications</strong></td>
<td></td>
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</tr>
<tr>
<td>13. If appropriate, what is the reference drug?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Describe the scientific bridge (e.g., BA/BE studies)</td>
<td>x</td>
<td></td>
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<tr>
<td><strong>DOSE</strong></td>
<td></td>
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</tr>
<tr>
<td>16. 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)?</td>
<td>x</td>
<td></td>
<td></td>
<td>The applicant is bridging this formulation to IR formulation for which</td>
</tr>
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</table>

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908
<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
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<tr>
<td><strong>Study Title:</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Sample Size:</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Arms:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Location in submission:</strong></td>
<td></td>
<td></td>
<td></td>
<td>dosage and schedule have been explored adequately.</td>
</tr>
</tbody>
</table>

**Efficacy**

17. Do there appear to be the requisite number of adequate and well-controlled studies in the application?  
   Pivotal Study #1  
   Indication:  
   
   Pivotal Study #2  
   Indication:  
   
   x As discussed at the pre-NDA meeting, clinical efficacy and safety would be cross-referenced from original NDA 203214 for Immediate Release (IR) formulation 5mg BID

18. 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 See Comment for #17

19. 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 See Comment for #17

20. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?  
   x See Comment for #17

**Safety**

21. 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 As discussed at the pre-NDA meeting, additional clinical safety data will be cross-referenced from the original NDA 203214 for IR formulation 5mg BID

22. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?  
   x Explored with original application (NDA 203214) for the IR formulation

23. Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?  
   x

24. 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

25. For drugs not chronically administered (intermittent or...  

---

\(^1\) 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.
### Content Parameter

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>short course), have the requisite number of patients been exposed as requested by the Division?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>26. Has the applicant submitted the coding dictionary(^2) used for mapping investigator verbatim terms to preferred terms?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. 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?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?</td>
<td>x</td>
<td></td>
<td>There were no deaths or adverse dropouts and serious adverse events that required narratives</td>
<td></td>
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</table>

### OTHER STUDIES

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>29. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. 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)?</td>
<td>x</td>
<td></td>
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</tr>
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</table>

### PEDIATRIC USE

<table>
<thead>
<tr>
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<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

### ABUSE LIABILITY

<table>
<thead>
<tr>
<th>Content Parameter</th>
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<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>32. If relevant, has the applicant submitted information to assess the abuse liability of the product?</td>
<td>x</td>
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<td></td>
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</tr>
</tbody>
</table>

### FOREIGN STUDIES

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>33. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### DATASETS

<table>
<thead>
<tr>
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<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>34. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35. Has the applicant submitted datasets in the format agreed to previously by the Division?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36. Are all datasets for pivotal efficacy studies available and complete for all indications requested?</td>
<td>x</td>
<td>See comment for #17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37. Are all datasets to support the critical safety analyses available and complete?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?</td>
<td>x</td>
<td></td>
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</tbody>
</table>

### CASE REPORT FORMS

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
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<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>39. Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?</td>
<td>x</td>
<td></td>
<td></td>
<td>There were no deaths, serious adverse events or adverse dropouts and that required Case Report Forms</td>
</tr>
<tr>
<td>40. Has the applicant submitted all additional Case Report</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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\(^2\) 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).
<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FINANCIAL DISCLOSURE**

41. Has the applicant submitted the required Financial Disclosure information? x

**GOOD CLINICAL PRACTICE**

42. 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__ x __

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

Potential review issues, identified at the Filing review pertain to the nominal dose of tofacitinib MR, 11 mg, which is different from the nominal dose of tofacitinib immediate release formulation (5 + 5 mg). Additional potential review issues were identified by the clinical pharmacology review team pertaining to the proposed dosing for special populations of patients with moderate to severe renal impairment. The following comments to be conveyed to the Applicant in the 74-Day letter:

1. The Agency acknowledges its previous agreement with the proposed general plan of PK development to support filing of an NDA for the 11 mg daily MR dose. Upon further consideration however, we are concerned that the differences in nominal dose between the already approved IR formulation (5 + 5 mg) and the proposed MR formulation (11 mg) are not consistent with the regulatory requirements for establishing bioequivalence, as stated in the 21 CFR 320.233. Specifically: “Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.” Thus, the Agency’s expectation is that the MR and IR formulations would have equivalent bioavailability at the same molar/nominal dose.

In absence of bioequivalence, you need to provide acceptable justification. The 21 CFR 320.23 continues, to state that, “Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, and are considered medically insignificant for the particular drug product studied.” If you plan to support your application using this provision of the regulations, you will have to provide an appropriate justification. The adequacy of this justification will be a review issue.

[3](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfcfr/CFRSearch.cfm?fr=320.23)

---

Reference ID: 3783184
CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

2. We acknowledge that the proposed tofacitinib MR 11 mg QD appeared to exhibit comparable Cmax and AUC relative to tofacitinib IR 5 mg BID. However, the Cmin of tofacitinib MR 11 mg QD was about 30% lower than that observed with tofacitinib IR 5 mg BID. We also note that the overall tofacitinib concentration time profile of tofacitinib MR 11 mg QD was not similar to that of tofacitinib IR 5 mg BID. You have to provide appropriate justification that these differences do not inadvertently impact the safety and efficacy profiles of the proposed formulation and the once daily dosing regimen of tofacitinib MR 11 mg QD in comparison to the approved tofacitinib IR 5 mg BID. The adequacy of this justification will be reviewed along with the application.

3. You have proposed ___ you have to ___ provide appropriate justification that this difference does not impact the safety and efficacy of tofacitinib. The adequacy of this justification will be a review issue.

Juwaria Waheed, MD  
June 23, 2015

Reviewing Medical Officer  
Date

Nikolay P. Nikolov, M.D.  
June 23, 2015

Clinical Team Leader  
Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908
Received: April 24 2015
74-Day Letter: July 07, 2015
PDUFA: February 24, 2016

NDA 208,246
Tofacitinib MR for RA

MO: Juwaria Waheed, MD
TL: Nikolay Nikolov, MD
Filing Meeting
June 8, 2015

Executive Summary

- Sponsor: Pfizer
- Product: Tofacitinib (JAK3 inhibitor)
- Dosing: Modified Release (MR) 11 mg QD
- Population: Adults with mod-to-severe active RA
- Labeling: One label incorporating MR formulation into the original label for tofacitinib IR 5mg BID
- Recommendation: Fileable as a Standard NDA
**Xeljanz IR**

Tofacitinib IR 5mg BID was approved in 11/2012 with a boxed warning:

- **Serious infections**
  - including opportunistic infections and TB
- **Malignancies**
  - Lymphoma and other malignancies
  - EBV-associated post-transplant lymphoproliferative disorder in renal transplant patients

**Regulatory History**

- **November 2012**
  - Approval of tofacitinib 5 mg (IR formulation) BID for treatment of RA
- **March 2013, Pre-IND Meeting**
  - Agreed with sponsor’s proposed plan to assess tofacitinib-MR formulation via Clin Pham studies in healthy volunteers characterizing the biophamaceutical aspects of the new formulation.
  - These studies demonstrate similar PK exposure parameters for the MR formulation compared to the immediate-release (IR) formulation
- **August 2013, Teleconference**
  - Agreed PK assessments should compare tofacitinib-MR 11 mg QD to tofacitinib-IR 5 mg BID
- **November 2014, Pre NDA Meeting:**
  - Separate NDA submission for tofacitinib MR formulation with labeling incorporated into the current labeling for the IR formulation
  - Proposed Trade name is Xeljanz-XR
  - Pfizer will cross-reference efficacy and safety data for the IR formulation in the new NDA
Regulatory History (contd.)

- November 2014, Pre NDA Meeting:
  - Agreed that evaluation of single and multiple dose PK of the final MR 11 mg formulation compared to IR 5 mg BID formulation demonstrating the bioequivalence of tofacitinib exposure and Cmax for single and multiple dosing of MR 11 mg QD and IR 5 mg BID are adequate to support the NDA submission.

- April 2015, Agreement to initial PSP
**Tofacitinib MR Clinical Program**

- Consists of 7 phase 1 healthy volunteer (HV) studies:
  - Included a total of 172 HVs
  - Evaluated PK parameters of the proposed MR 11mg formulation for daily dosing
  - Characterized the biopharmaceutical aspects
  - Provided bridging in key PK exposure parameters between MR 11mg and the approved IR 5mg BID formulation
  - ISS includes safety and tolerability data from the 7 phase 1 HV studies

- **Clinical safety & efficacy data:**
  - No safety or efficacy studies in patients were conducted in the MR program to support the NDA for the RA indication
  - Instead, safety and efficacy studies from the original NDA 203,214 (Xeljanz (tofacitinib) IR 5mg BID) are cross-referenced to the current submission

**Clinical Program 7 phase 1 HV PK studies**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Objectives</th>
<th>Treatment Groups</th>
<th># of Subjects</th>
<th>Study Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A391113</td>
<td>Feasibility study of MR formulation</td>
<td>Single dose&lt;br&gt;IR 10 mg&lt;br&gt;MR 22 mg (capsule)&lt;br&gt;MR 22 mg (capsule) (b) (4)</td>
<td>12</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A391131</td>
<td>Preliminary relative bioavailability of tablet form and Food Effect</td>
<td>Single dose&lt;br&gt;IR 10 mg&lt;br&gt;MR 22 mg (ECSS cosmetic tablet); fasted and fed&lt;br&gt;MR 22 mg (b) (4) fasted and fed&lt;br&gt;MR 22 mg (b) (4)</td>
<td>30</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A391132</td>
<td>Dose proportionality</td>
<td>Single Dose&lt;br&gt;MR 22 mg (ECSS cosmetic tablet); fasted&lt;br&gt;MR 11 mg (ECSS cosmetic tablet); fasted</td>
<td>20</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A392163</td>
<td>Relative BA of Initial Commercial-scale formulation</td>
<td>IR 10 mg, fasted&lt;br&gt;MR 11 mg fasted</td>
<td>25</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A391190</td>
<td>Food Effect on proposed-commercial formulation</td>
<td>MR 11 mg, fasted and fed</td>
<td>24</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A391155</td>
<td>In vitro dissolution with in-vivo plasma drug concentrations</td>
<td>IR 5 mg, fasted&lt;br&gt;MR 22 mg fasted, MR 11 mg (3 formulations)</td>
<td>36</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A391112</td>
<td>Bioequivalence of proposed-commercial formulation</td>
<td>IR 5mg BID&lt;br&gt;MR 11mg&lt;br&gt;Multiple Dose Phase&lt;br&gt;IR 5mg BID&lt;br&gt;MR 11mg QD</td>
<td>24</td>
<td>Single dose phase&lt;br&gt;Multiple dose phase (5 days)</td>
</tr>
</tbody>
</table>
Integrated Safety Summary

- Total number of subjects: 172 (166 M, 6 F)
  - MR QD 11mg
  - MR QD 22mg
  - IR QD 5 mg
  - IR QD 10mg
  - Other (includes MR 20mg and MR 22mg formulations)
- Overall, safe and well-tolerated in HV
- Majority of AE’s were mild and similar between IR and MR formulations
- No serious adverse events, AESI, or deaths
- No new safety signals

Pediatric Use

- April 2015 – agreed iPSP, Request:
  - A waiver of PREA for JIA patients < 2 years of age
  - A deferral for conducting any pediatric studies using the MR formulation until completion of Study A3921104 (Sept. 2018)
    - efficacy study in patients of age 2 to <18 years with polyarticular JIA using the IR formulation
Brief Review of Labeling

- One label for both MR and IR formulations
  - Proposed label incorporates language about the MR formulation into the current labeling for the IR formulation
- Updates include information and data pertinent to tofacitinib MR 11mg tablet formulation
  - Dosage and administration, Clinical-pharmacology, Drug handling and storage

Filing and Planning

- Clinical Filing Checklist
  - Complete
- Advisory Committee
  - Not recommended
- OSI Audit
  - Interdisciplinary discussion
- Pediatric Development Plan
  - Agreed iPSP
Conclusions and Mid-Cycle Deliverables

- Application is fileable as standard NDA
- Mid-Cycle Deliverables:
  - Complete review of safety
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUWARIA F WAHEED
06/23/2015

NIKOLAY P NIKOLOV
06/23/2015
I concur.