NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplement, New NDA
Application Number(s)	NDA 203214 S-026 NDA 213082
Priority or Standard	Priority
Submit Date(s)	March 26, 2020
Received Date(s)	March 26, 2020
PDUFA Goal Date	September 26, 2020
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM), Office of Immunology and Inflammation (OII)
Review Completion Date	See electronic stamp date
Established/Proper Name	Tofacitinib
(Proposed) Trade Name	Xeljanz
Pharmacologic Class	Janus kinase (JAK) inhibitor
Code name	
Applicant	Pfizer Inc.
Doseage form	NDA 203214 S-026 Oral Tablet NDA 213082 Oral Solution
Applicant proposed Dosing Regimen	XELJANZ/XELJANZ Oral Solution 5 mg twice daily or weight-based equivalent twice daily
Applicant Proposed Indication(s)/Population(s)	Treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older
Recommended Dosing Regimen	XELJANZ/XELJANZ Oral Solution 5 mg twice daily or weight-based equivalent twice daily

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OPQ=Office of Pharmaceutical Quality; OPDP=Office of Prescription Drug Promotion; DMPP= Division of Medical Policy Programs;OSE= Office of Surveillance and Epidemiology; DEPI= Division of Epidemiology; DMEPA=Division of Medication Error Prevention and Analysis; DPV=Division of Pharmacovigilance; DPMH= Division of Pediatric and Maternal Health; DCOA= Division of Clinical Outcome Assessment

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Tofacitinib (CP-690,550), a selective inhibitor of the Janus kinase (JAK) family of kinases, was approved on 06 November 2012 in the United States (NDA 203214) and is marketed as Xeljanz® at a dose of 5 mg twice daily (BID) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. As part of the approval of the original application, and in line with the Pediatric Research Equity Act (PREA), Pfizer was required to conduct the following post marketing requirements (PMRs):

> 1934-1 A multiple-dose pharmacokinetic trial in children from 2 to less than 18 years of age with juvenile idiopathic arthritis (JIA)
>
> 1934-2 A randomized withdrawal, double-blind, placebo-controlled trial to evaluate the efficacy and safety of tofacitinib in children from 2 to less than 18 years of age with polyarticular-course juvenile idiopathic arthritis.

PMR 1934-1 was fulfilled based on the submission of the clinical study report for study A3921103, an open-label multiple dose study to evaluate the pharmacokinetics, safety and tolerability of CP-690,550 in pediatric patients from to 2 less than 18 years of age with Juvenile Idiopathic Arthritis (JIA).

To fulfill PMR 1934-2, and to seek an indication for tofacitinib for the treatment of polyarticular course juvenile idiopathic arthritis (pcJIA), the Applicant submitted this sNDA 203214 (S-26) & NDA 210382 (Xeljanz 1mg/mL oral solution), the focus of this review.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy of Xeljanz tablets / Xeljanz Oral Solution in pediatric patients 2 to 17 years of age with active pcJIA is supported by evidence from adequate and well-controlled trials in adult RA and a trial in 225 pediatric patients 2 to 17 years of age with active pcJIA (consisting of an 18-week, open label, run-in phase followed by a 26-week double-blind, placebo-controlled, randomized withdrawal phase).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Juvenile idiopathic arthritis (JIA) is defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age, where other diagnoses are excluded; this definition is based on the International League of Associations for Rheumatology (ILAR) classification system, the currently widely accepted classification of arthritis in childrens and adolescents. JIA affects an estimated 294,000 children between the ages of 0 and 17 years in the United States.[1] In the ILAR classificaton, JIA is divided into seven subtypes defined by clinical features during the first 6 months of disease: systemic JIA (sJIA), oligoarticular JIA (oJIA), RF positive polyarticular JIA (pJIA), RF negative pJIA, juvenile psoriatic arthritis (JPsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis.

The goals of therapy are to treat the underlying inflammation and prevent associated complications (e.g., joint damage). Without appropriate treatment, pJIA can lead to significant life-long disability starting in childhood. Although multiple therapies are approved for the pJIA population in the United States, there still remains an unmet need for additional therapeutic options in this population. The classes of therapies for pJIA include NSAIDs, corticosteroids (oral, parenteral, and intra-articular), nonbiologic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) and sulfasalazine, and biologic DMARDs which include the following approved therapies by class: (i) TNF blockers [Enbrel (etanercept) and Humira (adalimumab), both administered subcutaneously (SC)]; (ii) a selective T cell co-stimulation modulator [Orencia (abatacept) approved for both intravenous (IV) and SC administration]; and (iii) an IL-6 receptor antagonist [Actemra (tocilizumab) approved for both IV and SC administration].

The safety and efficacy of tofacitinib for pcJIA was assessed in Study A3921104, a PREA PMR study issued for NDA 203214 in November 2012. The study was, a 44-week, two-part study (consisting of an 18-week, open-label, run-in phase, followed by a 26-week double-blind, placebo-controlled, randomized withdrawal phase) in patients 2 years to 17 years of age with active RF negative polyarthritis, RF positive polyarthritis, extended oligoarthritis, and systemic JIA without systemic manifestations who had an inadequate response or intolerance to at least one DMARD which could have included MTX or biologic agents; the study also included patients ages 2 years to 17 years of age with active juvenile psoriatic arthritis (JPsA) and enthesitis-related arthritis (ERA) who had an inadequate response to NSAIDs. Because the tofacitinib pediatric program included JIA patients with active polyarticular involvement, i.e. not limited to the polyarticular subgroup JIA (pJIA) by the ILAR classification, for this program and in this review, polyarticular course JIA (pcJIA) refers to JIA with polyarticular involvement, rather than pJIA.

[1] M Espinosa and BS Gottlieb, "Juvenile Idiopathic Arthritis," Pediatrics in Review, 2012; 33:303-313

In Study A3921104, patients received tofacitinib (dosed at 5 mg twice daily or body weight-based equivalent twice daily) for 18 weeks (run-in phase) followed by randomization to either tofacitinib (dosed at 5 mg twice daily or body weight-based equivalent twice daily) or placebo for 26 weeks (double-blind phase). Only patients who achieved at least a JIA ACR30 response at the end of the run-in phase were randomized (1:1) to the double-blind phase. Treatment with a stable dose of MTX was permitted but was not required during the study. Concurrent use of biologics or DMARDs other than MTX was not permitted in the study.

A total of 225 JIA patients (56 male and 169 female) with active polyarthritis were enrolled in the run-in phase including RF negative (104), RF positive (39), extended oligoarthritis (28), systemic JIA without systemic manifestations (13), JPsA (20), and ERA (21). Patients had a mean (SD) disease duration of 3.8 ± 3.5 years, and a mean (SD) number of active joints of 12.2 ± 8.1.

Of the 225 patients, 173 (76.9%) patients achieved JIA ACR30 response at Week 18 and were randomized into the double-blind phase to either active XELJANZ/XELJANZ Oral Solution (n=88) or placebo (n=85). At the conclusion of the 18-week, open-label, run-in phase, pediatric ACR 30/50/70 responses were 77%, 70%, and 49%, respectively. In both the run-in and double-blind phases, approximately one-third of the patients were taking concomitant oral corticosteroids, and approximately two-thirds were taking concomitant MTX.

The primary endpoint was the occurrence of disease flare at Week 44 relative to the double-blind phase baseline at Week 18. Disease flare was defined (according to Pediatric Rheumatology Collaborative Study Group (PRCSG) / Pediatric Rheumatology International Trials Organization (PRINTO) Disease Flare criteria) as worsening of ≥ 30% in 3 or more of the 6 JIA core response variables with no more than 1 of the remaining JIA core response variables improving by ≥ 30%.

XELJANZ/XELJANZ Oral Solution treated patients experienced significantly fewer disease flares at Week 44 compared to placebo-treated patients (31% [27/88] vs. 55% [47/85]; difference in proportions -25% [95% CI: -39%, -10%]; p=0.0007).

The total patient exposure (defined as patients who received at least one dose of tofacitinib), was 351 patient-years in the overall pcJIA development program which also included an open-label extension study (Study 3921145).

The safety profile for pcJIA patients was generally similar to that of RA patients.

The most common adverse reactions[2] in the double-blind phase of Study A3921104 were upper respiratory tract infection (tofacitinib 15% vs. placebo 11%) and nasopharyngitis (8% vs. 3.5%).[3] These were also among the most common adverse events (AEs) in the overall pcJIA safety database for tofacitinib (upper respiratory tract infection 26% and nasopharygitis 12%) along with vomiting (10%), headache (12%), and JIA (11%), the latter reflecting underlying disease.[4]

AEs leading to discontinuation in the double-bind phase of Study 3921104 were 18% (tofacitinib) vs. 34% (placebo);[5] the majority of these AEs were due to worsening disease (the combined preferred terms of arthritis, condition aggravated, disease progression, and JIA were 16% (tofacitinib) vs. 32% (placebo).[6] Similarly, in the overall pcJIA safety database for tofacitinib, AEs leading to discontinuation were 23%, and the majority were accounted for by worsening disease (disease progression 6%, JIA 5%, and condition aggravated 3%).[7]

There were no deaths. Serious adverse events (SAEs) in the double-bind phase of Study 3921104 were 1% (tofacitinib) vs. 2% (placebo).[8] In the overall pcJIA safety database for tofacitinib, SAEs were 9%.[9] Specific SAEs were distributed across multiple System Organ Classes (SOCs) and, in general, occurred in only 1 patient.[10]

Of the adverse events of special interest (AESI),[11] herpes zoster occurred in 3 subjects and serious infections occurred in 6 subjects in the overall pcJIA safety database for tofacitinib.

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[2] Adverse reactions were defined as adverse events occurring at a higher rate in the tofacitinib group compared to placebo.
[3] Table 29 of report of Study A3921104 page 186
[4] Table 19 of Summary of Clinical Safety pages 55-57
[5] Table 27 of report of Study A3921104 page 183
[6] Table 35 of report of Study A3921104 page 194
[7] Table 25 of Summary of Clinical Safety pages 73-75
[8] Table 27 of report of Study A3921104 page 183
[9] Table 16 of Summary of Clinical Safety page 52
[10] Table 22 of Sumary of Clinical Safety pages 60-61
[11] AESI included the following: 1 Death, 2 Serious infections, 3 Opportunistic infections (OIs) excluding tuberculosis (TB), 4 TB, 5 Herpes zoster, 6 Malignancy excluding non-melanoma skin cancer (NMSC), 7 NMSC, 8 Lymphoma, 9 Major Adverse Cardiovascular Events (MACE), 10 Thromboembolism (TE), including pulmonary embolism (PE) and deep vein thrombosis, 11 Gastrointestinal perforations, 12 Interstitial Lung Disease

The tofacitinib safety evaluation in pcJIA did not identify any new or unexpected safety signals or serious reactions attributable to treatment in this pediatric population.

Tofacitinib represents a novel mechanism of action and an new oral administration option in the treatment of pcJIA.

In conclusion, the benefit-risk profile for tofacitinib for the treatment of pcJIA is favorable.
However, additional characterization of the long-term safety profile of tofacitinib, as a new class of immunosuppressives for the pediatric population, is required in postmarketing studies. Specifically:

- Recent literature concerning a number of JAK inhibtors and bone growth have raised concerns about the potential for drugs of this class to cause adverse bone or cartilage effects. Thus, there is a theoretical risk of effects on bone development and growth with tofacitinib. Although a cynomolgus monkey study in the tofacitinib nonclinical program assessed bone growth radiographically by length measurements of the tibia and radius and found these to be unaffected at the doses studied, histopathology was not conducted; in addition, long bone was not assessed in a rat study in the tofacitinib nonclinical program. Therefore, a nonclinical juvenile animal toxicity study will be required to assess by histopathological examination effects on bone development and growth.
- Serious risks of serious infections (including opportunistic infections), malignancies, and thrombosis are described in the tofacitinib labeling. Additional long-term data (beyond that provided in the pcJIA development program) are needed to assess these risks in pcJIA patients as well as to assess effects on growth in this population. Therefore, a long-term observational safety study which includes a control group (of pediatric pcJIA patients treated with other pcJIA medications as standard of care) will be required to evaluate for these risks.

The data provided in this submission fulfill the PREA PMR 1934-2 under NDA 203214. The study was also conducted in keeping with the provisions of the pediatric Written Request (WR) and appears to have addressed the relevant parts of the WR.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Juvenile Idiopathic Arthritis (JIA) refers to the following seven subtypes of inflammatory arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age (as defined by the ILAR classification system): systemic JIA, oligoarticular JIA, RF positive polyarticular JIA, RF	pcJIA is a serious disease because of its significant morbidity including pain and disability.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	negative polyarticular JIA, juvenile psoriatic arthritis (JPsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis. • pcJIA refers to JIA with polyarticular involvement including all of these subtypes. • Extraarticular manifestations, such as uveitis, may be present. • The prevalence of JIA in developed countries has been reported to be between 16 and 150/100,000 children.	pcJIA has a significant impact on quality of life for patients and families. Uncontolled disease activity is associated with long-term and life-long disability that starts in childhood.
Current Treatment Options	• Approved treatments for pJIA include NSAIDs, corticosteroids (oral, parenteral, and intra-articular), nonbiologic DMARDs such as methotrexate and sulfasalazine, and biologic DMARDs which include the following approved therapies by class: (i) TNF blockers [Enbrel (etanercept) and Humira (adalimumab), both administered subcutaneously (SC)]; (ii) a selective T cell co-stimulation modulator [Orencia (abatacept) approved for both intravenous (IV) and SC administration]; and (iii) an IL-6 receptor antagonist [Actemra (tocilizumab) approved for both IV and SC administration].	Although there are FDA-approved products with an acceptable risk-benefit profile for treatment of pJIA, there remains a population of patients with uncontrolled disease. Tofacitinib represents a novel mechanism of action and mode of administration in the treatment of pcJIA.
Benefit	• The efficacy of tofacitinib for the treatment of active pcJIA in patients 2 years of age and older has been adequately assessed in this application. • The efficacy of tofacitinib for pcJIA was assessed in Study A3921104, a 44-week, two-part study (consisting of an 18-week, open-label, run-in phase, followed by a 26-week double-blind, placebo-controlled, randomized withdrawal phase) in patients 2 years to 17 years of age with active RF negative polyarthritis, RF positive polyarthritis, extended oligoarthritis, and systemic JIA without systemic manifestations who had an inadequate response or intolerance to at least one DMARD which could have included MTX or biologic agents; the study also included patients ages 2 years to 17	Efficacy of Xeljanz tablets / Xeljanz Oral Solution in pediatric patients 2 to 17 years of age with active pcJIA is supported by evidence from adequate and well-controlled trials in adult RA and a trial in 225 pediatric patients 2 to 17 years of age with active pcJIA (consisting of an 18-week, open label, run-in phase followed by a 26-week double-blind, placebo-controlled, randomized withdrawal phase).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	years of age with activeJPsA and ERA who had an inadequate response to NSAIDs. • In Study A3921104, patients received tofacitinib (dosed at 5 mg twice daily or body weight-based equivalent twice daily) for 18 weeks (run-in phase) followed by randomization to either tofacitinib (dosed at 5 mg twice daily or body weight-based equivalent twice daily) or placebo for 26 weeks (double-blind phase). Only patients who achieved at least a JIA ACR30 response at the end of the run-in phase were randomized (1:1) to the double-blind phase. Treatment with a stable dose of MTX was permitted but was not required during the study. Concurrent use of biologics or DMARDs other than MTX was not permitted in the study. • A total of 225 JIA patients (56 male and 169 female) with active polyarthritis were enrolled in the run-in phase including RF negative (104), RF positive (39), extended oligoarthritis (28), systemic JIA without systemic manifestations (13), JPsA (20), and ERA (21). Patients had a mean (SD) disease duration of 3.8 ± 3.5 years, and a mean (SD) number of active joints of 12.2 ± 8.1. • Of the 225 patients, 173 (76.9%) patients achieved JIA ACR30 response at Week 18 and were randomized into the double-blind phase to either active XELJANZ/XELJANZ Oral Solution (n=88) or placebo (n=85). At the conclusion of the 18-week, open-label, run-in phase, pediatric ACR 30/50/70 responses were 77%, 70%, and 49%, respectively. In both the run-in and double-blind phases, approximately one-third of the patients were taking concomitant oral corticosteroids, and approximately two-thirds were taking concomitant MTX. • The primary endpoint was the occurrence of disease flare at Week 44 relative to the double-blind phase baseline at Week 18. Disease flare was	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	defined (according to Pediatric Rheumatology Collaborative Study Group (PRCSG) / Pediatric Rheumatology International Trials Organization (PRINTO) Disease Flare criteria) as worsening of ≥ 30% in 3 or more of the 6 JIA core response variables with no more than 1 of the remaining JIA core response variables improving by ≥ 30%. • XELJANZ/XELJANZ Oral Solution treated patients experienced significantly fewer disease flares at Week 44 compared to placebo-treated patients (31% [27/88] vs. 55% [47/85]; difference in proportions -25% [95% CI: -39%, -10%]; p=0.0007).	
Risk and Risk Management	• The total patient exposure (defined as patients who received at least one dose of tofacitinib), was 351 patient-years in the overall pcJIA development program which also included an open-label extension study (Study A3921145). • The most common adverse reactions in the double-blind phase of Study A3921104 were upper respiratory tract infection (tofacitinib 15% vs. placebo 11%) and nasopharyngitis (8% vs. 3.5%). These were also among the most common adverse events (AEs) in the overall pcJIA safety database for tofacitinib (upper respiratory tract infection 26% and nasopharygitis 12%) along with vomiting (10%), headache (12%), and JIA (11%), the latter reflecting underlying disease. • AEs leading to discontinuation in the double-bind phase of Study A3921104 were 18% (tofacitinib) vs. 34% (placebo); the majority of these AEs were due to worsening disease (the combined preferred terms of arthritis, condition aggravated, disease progression, and JIA were 16% (tofacitinib) vs. 32% (placebo). Similarly, in the overall pcJIA safety database for tofacitinib, AEs leading to discontinuation were 23%, and the	The safety profile for pcJIA patients was generally similar to that of RA patients. The tofacitinib safety evaluation in pcJIA did not identify any new or unexpected safety signals or serious reactions attributable to treatment in this pediatric population. A REMS is not required for the safe use of tofacitinib in patients aged 2-17 years old. Labeling can adequately explain the risk of tofacitinib in pediatric patients. There are no new identified safety issues where a REMS would be expected to mitigate identified risks. The benefit-risk profile for tofacitinib for the treatment of pcJIA is favorable. However, additional characterization of the safety profile

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	majority were accounted for by worsening disease (disease progression 6%, JIA 5%, and condition aggravated 3%). • There were no deaths. Serious adverse events (SAEs) in the double-bind phase of Study A3921104 were 1% (tofacitinib) vs. 2% (placebo). In the overall pcJIA safety database for tofacitinib, SAEs were 9%. Specific SAEs were distributed across multiple System Organ Classes (SOCs) and, in general, occurred in only 1 patient. • Of the adverse events of special interest (AESI), herpes zoster occurred in 3 subjects and serious infections occurred in 6 subjects in the overall pcJIA safety database for tofacitinib. ▪ Recent literature concerning a number of JAK inhibtors and bone growth have raised concerns about the potential for drugs of this class to cause adverse bone or cartilage effects. Thus, there is a theoretical risk of effects on bone development and growth with tofacitinib. Although a cynomolgus monkey study in the tofacitinib nonclinical program assessed bone growth radiographically by length measurements of the tibia and radius and found these to be unaffected at the doses studied, histopathology was not conducted; in addition, long bone was not assessed in a rat study in the tofacitinib nonclinical program. • Serious risks of serious infections (including opportunistic infections), malignancies, and thrombosis are described in the tofacitinib labeling.	of tofacitinib for the pediatric population is required in postmkarketing studies. A nonclinical juvenile animal toxicity study will be required to assess by histopathological examination effects on bone development and growth. A long-term observational safety study which includes a control group (of pediatric pcJIA patients treated with other pcJIA medications as standard of care) will be required to evaluate for the risks of malignancies, serious infections (including opportunistic infections), thrombosis, and effects on growth.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	□X	Clinical outcome assessment (COA) data, such as		
		□X	Patient reported outcome (PRO)	Section 8.1.2
		□X	Observer reported outcome (ObsRO)	Section 8.1.2
		□X	Clinician reported outcome (ClinRO)	Section 8.1.2
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Historically, the classification to characterize arthritis in children and adolescents used the nomenclature of Juvenile Rheumatoid Arthritis (JRA), as defined by the American College of Rheumatology (ACR). This classification system distinguished categories of disease into pauciarticular, polyarticular, and systemic disease.[12]

Currently, the accepted classification system is the more detailed International League of Associations for Rheumatology (ILAR) classification system.[13] In this system, Juvenile idiopathic arthritis (JIA) is defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age, where other diagnoses (such as infections, malignancy, trauma, reactive arthritis, and specific connective tissue diseases such as systemic lupus erythematosus) have been excluded. JIA affects an estimated 294,000 children between the ages of 0 and 17 years in the United States.[14] In the ILAR classification system (described in the table below), JIA is divided into seven subtypes defined by clinical features during the first 6 months of disease.[15]

The tofacitinib clinical development program under review in this application has targeted a patient population that includes rheumatoid factor (RF) positive polyarticular JIA, RF negative polyarticular JIA, extended oligoarticular JIA, systemic JIA without systemic manifestations, juvenile psoriatic arthritis, and enthesitis-related arthritis. Because the tofacitinib pediatric program included JIA patients with active polyarticular involvement, i.e., not limited to the polyarticular subgroup by the ILAR classification, for this program and in this review, polyarticular course JIA (pcJIA) refers to JIA with polyarticular involvement, rather than pJIA.

Although the ILAR classification is the currently accepted classification system for JIA, it should be noted that recent American College of Rheumatology (ACR) JIA treatment guidelines define polyarthritis as ≥ 5 joints ever involved and include patients across different ILAR categories but exclude patients with systemic arthritis, sacroiliitis, or extraarticular manifestations.[16]

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[12] Brewer EJ, Bass J, Baum J, et al. Current proposed revision of JRA criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1997;20(Suppl)195-9.

[13] Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390–392.

[14] M Espinosa and BS Gottlieb, "Juvenile Idiopathic Arthritis," Pediatrics in Review, 2012; 33:303-313

[15] M Espinosa and BS Gottlieb, "Juvenile Idiopathic Arthritis," Pediatrics in Review, 2012; 33:303-313

[16] Ringold S et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care & Res, 2019, 71: 717-734, 2019

Table 1. International League of Associations for Rheumatology (ILAR) Juvenile Idiopathic Arthritis (JIA) Classification[17]

Category	Definition	Frequency (% of all JIA)	Age of Onset	Sex Ratio	Susceptibility Alleles
Systemic onset juvenile idiopathic arthritis (JIA)	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented as daily ("quotidian") for at least 3 days and accompanied by one or more of the following: (1) rash (evanescent), (2) lymphadenopathy, (3) hepatomegaly or splenomegaly, (4) serositis	4%–17%	Childhood	F=M	HLA-DRB1*11
Oligo JIA	Arthritis affecting one to four joints during the first 6 months of disease	27%–56%	Early childhood; peak at 2–4 years	F>>>M	HLA-DRB1*08 HLA-DRB1*11 HLA-DQA1*04 HLA-DQA1*05 HLA-DQB1*04 HLA-A2 (early onset)
• Persistent	Affects no more than four joints throughout the disease course				
• Extended	Affects more than four joints after the first 6 months of disease				
Polyarthritis (RF-negative)	Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are negative	11%–28%	Biphasic distribution; early peak at 2–4 years and later peak at 6–12 years	F>>M	HLA-DRB1*0801
Polyarthritis (RF-positive)	Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are positive on at least two occasions that are 3 months apart	2%–7%	Late childhood or adolescence	F>>M	HLAB1*04 HLA-DR4
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least two of the following: (1) dactylitis, (2) nail pitting, (3) family history of psoriasis in a first-degree relative	2%–11%	Biphasic distribution; early peak at 2–4 years and later peak at 9–11 years	F>M	HLA-B27 *IL23R*[†](new association)
Enthesitis-related arthritis	Arthritis or enthesitis with at least two of the following: (1) sacroiliac tenderness or lumbosacral pain, (2) presence of HLA-B27 antigen, (3) onset of arthritis in a male >6 years old, (4) acute anterior uveitis, (5) family history in a first-degree relative of HLA-B27–associated disease	3%–11%	Late childhood or adolescence	M>>F	HLA-B27 *ERAP1*[†](new association)
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in two or more of the above categories	11%–21%			

Adapted from Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet.* 2007;369:767–768.
[†]Hinks A, Martin P, Flynn E, et al. Subtype specific genetic associations for JIA: ERAP1 with the enthesitis related arthritis subtype and IL23R with juvenile psoriatic arthritis. *Arthritis Res Ther.* 2011;13: R12. HLA=human lymphocyte antigen; JIA=juvenile idiopathic arthritis; RF=rheumatoid factor.

The table above is taken from: M Espinosa and BS Gottlieb, "Juvenile Idiopathic Arthritis," Pediatrics in Review, 2012; 33:303-313

2.2. Analysis of Current Treatment Options

The classes of therapies for treatment of JIA/JRA include biologic and conventional (non-biologic) disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids (systemic and intra-articular).

Biologic DMARDs approved for JIA/JRA are described in the table below.

[17] M Espinosa and BS Gottlieb, "Juvenile Idiopathic Arthritis," Pediatrics in Review, 2012; 33:303-313

Table 2. Biologic DMARDs Approved for JIA/JRA

Class Product	Route of Admin-istration	First Approval	Approval for JIA/JRA Indication	Current Indication Language
Biologic DMARDs				
TNF Blocker				
Enbrel (etanercept)	SC	1998	1999	"reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 and older"
Humira (adalimumab)	SC	2002	2008*; 2014#	"reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older"
Selective T cell Co-stimulation Modulator				
Orencia (abatacept)	IV	2005	2008	"treatment of patients 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis"
	SC	2011	2017	
IL-6 Receptor Anatagonist				
Actemra (tocilizumab)	IV	2010	2011	"treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older."
	SC	2013	2013	

*2008: Humira approved for > 4 years of age; #2014: Humira approved for 2 to 4 years of age

Conventional (non-biologic) DMARDs approved for JIA/JRA include sulfasalazine (first approval for any indication in 1950) and methotrexate (first approval for any indication in 1953). The current JIA/JRA indication for sulfasalazine is "treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs." The current JIA/JRA indication for methotrexate is "treatment of pediatric patients with polyarticular Juvenile Idiopathic Arthritis (pJIA)."

Agents that may be used off-label for JIA/JRA include anakinra, infliximab, and leflunomide, with first approvals for any indication in 2001, 1998, and 1998, respectively.

In addition to the above, various NSAIDs and corticosteroids are approved for JIA/JRA.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tofacitinib was approved for the treatment of adult subjects with active moderate to severe RA who have had an inadequate response or intolerance to methotrexate (MTX), at a dose of 5 mg BID (IR (immediate release) tablets, (approved on 06 November 2012), and at a dose of 11 mg once daily (XR (extended release) tablets, (approved on 23 February 2016). Tofacitinib is also approved for the treatment of adult patients with psoriatic arthritis and ulcerative colitis in the United States.

As part of the approval of the original application, and in line with the Pediatric Research Equity Act (PREA), Pfizer was required to conduct the following post marketing requirements (PMRs):

> 1934-1 A multiple-dose pharmacokinetic trial in children from 2 to less than 18 years of age with juvenile idiopathic arthritis (JIA)
>
> 1934-2 A randomized withdrawal, double-blind, placebo-controlled trial to evaluate the efficacy and safety of tofacitinib in children from 2 to less than 18 years of age with polyarticular-course juvenile idiopathic arthritis.

3.2. Summary of Presubmission/Submission Regulatory Activity

On 13 February 2013, Pfizer submitted IND 117400 to the Agency which included the clinical study protocol for PMR 1934-1, A3921103 "An Open-Label Multiple Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of CP-690,550 in Pediatric Patients From 2 to Less Than 18 Years of Age with Juvenile Idiopathic Arthritis (JIA)." The subsequent study report was submitted to the Agency on 26 September 2016 (NDA 203214 / Sequence 0287). On 15 February 2017, the Agency acknowledged the PMR as fulfilled.

On 08 April 2015, under IND 117400, the Applicant submitted the clinical study protocol for PMR 1934-2, A3921104 "Efficacy, Safety and Tolerability of Tofacitinib for Treatment of Polyarticular Course Juvenile Idiopathic Arthritis (JIA) in Children and Adolescent Subjects".

In study A3921104, Pfizer proposed to dose pediatric patients of 40 to 80 kg body weight using a nominal 15 mg per day (5 + 10 mg), different from the approved nominal dose of 10 mg/day (5 + 5 mg) in the adult RA program. The Applicant justified the higher nominal dosing based on the supportive rationale that the apparent clearance (CL/F) of tofacitinib in JIA patients was estimated about 75% higher than that in RA subjects which was attributed to a higher degree of systemic inflammation in adult RA subjects as compared to JIA patients, suggesting the exposure-response relationship may differ between RA and JIA patients for tofacitinib. The Division expressed concern related to the dose-dependent toxicity of tofacitinib and noted that

a dose greater than what is currently obtained with the approved dose in adults would not be acceptable in JIA patients.

After subsequent communication, the Division and the Applicant agreed on the following strategy for dosing:

- Dosing in children should not exceed the exposure achieved in adults with 5 mg BID dosing
- Lower the dose for children weighing 40 kg or more to 5 mg BID
- Modify the weight-based dosing scheme for children weighing less than 40 kg to align exposures with those targeted for the 5 mg BID dose in children/adolescents with JIA weighing 40 kg or greater in order to ensure interpretability of safety and efficacy results across the age and weight ranges in study 1104.

Subsequently, on 18 March 2016, Pfizer submitted the protocol amendment to IND 117400 incorporating the aforementioned changes.

On 18 June 2018, Pfizer submitted a Request for Agency Feedback to IND 117400 on its proposal to close enrollment of the sJIA cohort within study A3921104. Pfizer encountered recruitment challenges in enrolling this cohort that would significantly impact Pfizer's ability to meet the mandated PMR timeline for completing the study. On 05 July 2018, the Agency provided agreement to close enrollment for this cohort as Pfizer was conducting a separate clinical study focused on assessing safety and efficacy in patients with sJIA (A3921165), and therefore, the continued recruitment for these patients in A3921104 was no longer necessary.

On 31 July 2019, Pfizer submitted a meeting request to gain agreement on the content and format of an sNDA to support the addition of a polyarticular juvenile idiopathic arthritis indication to the Xeljanz label. On 23 October 2019, in preliminary comments, the Agency provided feedback on the following key areas:

- Nonclinical: The Agency expressed interest in the in the potential long-term risks of tofacitinib on pediatric development due to known adverse effects on cartilage in animal studies with some JAK inhibitors.
- Clinical Safety: The Agency requested that Pfizer include available safety data on pediatric growth and development to address the potential risks of chronic therapy with tofacitinib on potential bone effects in the pediatric population in addition to overall long-term safety. The Agency noted that the proposed safety database may be adequate to support submission and filing of the application, and additional long-term safety data may be needed.
- Statistical Analysis: The FDA provided key feedback on the proposed analysis plans for individual and pooled datasets specifically as it relates to the handling of missing data as defined in the SAP.

On 25 October 2019 and 12 November 2019, Pfizer provided clarifying responses to the

Agency's preliminary comments. The responses were deemed adequate; therefore, the pre-sNDA meeting was cancelled.

Nonclinical Communications

On May 27, 2020, the Division requested additional information for the calculations to determine the acceptance of two impurities at NMT (b) (4)% in the oral tofacitinib solution of NDA 213082. A response was received from the Applicant on June 5, 2020, (NDA 213082 SD-6) that explained the calculations used to support their assessment. This was found satisfactory.

In addition, recent literature has identified concerns about potential adverse effects on bone in non-clinical studies of other JAK inhibitors. Thus, on August 13, 2020 an IR requesting additional nonclinical information concerning the juvenile animal toxicity studies conducted for the initial NDA 203214 approval, based on the following considerations:

1. The team notes that the juvenile animal studies (juvenile rat study 10GR307 and juvenile cynomolgus monkey study 09GR248) submitted with the initial approval of tofacitinib for rheumatoid arthritis in adults lacked complete inventories of histopathology assessments with reference to long bones and joints. Of particular interest for the pediatric indication are evaluations of long bones and joints with respect to assessments for potential effects on growth and development. Histopathology exams was limited to the sternum in the monkey study. Although bone growth was assessed radiographically by length measurements of the tibia and radius and found to be unaffected by the doses of tofacitinib used in the monkey study, histopathology was not conducted. Long bone growth was not assessed in the rat study. Thus, the examination of bone growth and development in juvenile animal studies with tofacitinib was incomplete.

2. Recent literature concerning other JAK inhibitors and bone growth have raised concerns about the potential for drugs of this class to cause adverse bone or cartilage effects. Our internal review indicates that differences do exist within the class of JAK inhibitors on bone histopathology findings and bone development and growth, and prediction cannot be based on JAK inhibitor "class" effects at this time.

Respectively, the Agency requested the following Information:

We request that you address potential concerns for tofacitinib to adversely affect bone development and growth in pediatric patients. This might include examination of bone and joint tissue from the monkey and rat studies (Report 09GR248 and 10GR307, respectively) for histopathological findings if tissues from these studies are still available. Further, examination of secondary tissues (i.e., pituitary, parathyroid, thyroid, and adrenal glands) that were not previously examined, but influence bone development should also be considered for histopathological examination. At this time, provide your assessment of the

adequacy of the two juvenile animal studies with tofacitinib to detect potential adverse effects on bone development and growth and confirm if the tissues from the two studies are still available.

The information request was submitted following a discussion at the PeRC meeting of August 11, 2020, and subsequent Interdivisional discussion.

On August 24, 2020 (SD-1853) the Applicant responded acknowledging that as the bone and joint were not identified as a target organ of toxicity in tofacitinib repeat-dose toxicity studies in adult rats or monkeys, these tissues were not examined microscopically in the juvenile toxicity studies as a target organ of concern. The Applicant confirmed that tissue samples from the original studies were no longer available for histopathological examinations. Of note, the bone growth in the juvenile monkey study, assessed radiographically by length measurements of the tibia and radius, was unaffected at the relevant tofacitinib doses. Further, the histopathology of the sternum did not show abnormalities. However, the examination of bone growth and development in juvenile animal studies with tofacitinib was incomplete due to lack of histopathology of long bone and joints and warrants further characterization as a post-marketing requirement (PMR) study in light of recent literature and internal proprietary information as discussed in Section 13, Postmarketing Requirements and Commitments.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The review of the data did not indicate data integrity issues and OSI inspection was not deemed necessary for this application.

4.2. Product Quality

The Applicant introduced a new formulation of tofacitinib (oral solution) in NDA 213082. The data provided in the application support the conclusion that the proposed control strategy for the new presentation combined with in-process, release, and stability testing ensure process consistency and drug substance, formulated drug substance, and drug product with appropriate quality attributes. The manufacturing facilities are in acceptable current good manufacturing practice compliance to manufacture the proposed drug product. The Office of Pharmaceutical Quality recommends approval of NDA 213082 based on the Integrated Quality Assessment finalized on September 2, 2020.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

There were no new nonclinical studies submitted in either NDAs 203214 or 213082. All pharmacology and toxicology studies were previously reviewed under NDA 203214 (review dated July 3, 2012). Two topics were reviewed for this application.

- Impurity levels and qualification for the pediatric oral solution of NDA 213082.
- Reassessment of potential effects of tofacitinib on bone development and growth in juvenile toxicology studies with rats and monkeys

The conclusions from these evaluations were that the impurities in the pediatric oral solution were appropriately qualified as safe from a toxicological perspective and the specifications acceptable. However, there is some concern with the juvenile animal studies ability to support the safety of toficitnib in the pediatric population due to incomplete (absence of histopathology) bone evaluations from both the rat and monkey juvenile animals studies that were reviewed for the original NDA 203214 (review dated July 3, 2012), which was indicated for use in adults. The inadequacy of nonclinical support for pediatric studies was noted in the review at that time. However, at the IND stage for pediatric development, these concerns were mitigated by the absence of abnormal clinical observations, activity, gait and movement, and growth in those animal studies and the pediatric studies were allowed to proceed. More recent information from non-clinical programs of some JAK inhibitors, already approved for adult use and other drugs still in development, have exhibited adverse effects on bone growth and structure. In addition, recent published scientific literature documents the role of the JAK-STAT pathways in bone growth and development.

Of note for tofacitinib, bone growth in the juvenile monkey study, assessed radiographically by length measurements of the tibia and radius, was unaffected at doses that exceeded the maximum equivalent pediatric doses. Further, the histopathology of the sternum did not show abnormalities. The totality of the available non-clinical information suggests that the effects on bone and growth of tofacitinib are largely a hypothetical concern. Per discussions with the Clinical Team, tofacitinib has demonstrated efficacy in the treatment of pcJIA and the incomplete histopathology evaluation of long bones should not preclude approval. However, this outstanding issue warrants further characterization post-marketing. Respectively, the Applicant has agreed to conduct a post-marketing required (PMR) juvenile animal study to assess the effects of tofacitinib on bone growth and development by histopathological examination. With this additional contextual information, Approval of the submissions is recommended from the Nonclinical Perspective.

5.2. Referenced NDAs, BLAs, DMFs

Not applicable.

5.3. Pharmacology

Refer to the Pharmacology-Toxicology Review of NDA 203214 dated July 3, 2012 for detailed description of tofacitinib's pharmacology, briefly described here.

Tofacitinib is a Janus Kinase (JAK) inhibitor. These enzymes are located on the cytoplasmic face of transmembrane cytokine receptors. JAK inhibitors prevent the cytokine-receptor induced phosphorylation of signal transducers and activator of transcription (STATs) necessary fo cytokine signaling and cellular response. Cells of the immune systems, such as circulating cytotoxic T cells, and NK cells, but not T-helper cells or macrophages/monocytes are particularly susceptible to tofacitinib, exhibiting dose-response reductions in cell counts in toxicity studies. Tofacitinib was shown to suppress the cellular responses to many inflammatory mediators which is the basis for its therapeutic effectiveness.

5.4. ADME/PK

Refer to the Pharmacology-Toxicology Review of NDA 203214 dated July 3, 2012 for detailed descriptions of tofacitinib's ADME characteristics studied in vitro and in vivo.

5.5. Toxicology

5.5.1. General Toxicology

Refer to the Pharmacology-Toxicology Review of NDA 203214 dated July 3, 2012 for detailed descriptions of toxicology studies in rats and monkeys conducted with tofacitinib. Of special interest for the pJIA indication are studies in the juvenile rat (review of Report 10GR307, page 181) and juvenile cynomolgus monkey (review of Report 09GR248, page 251). Those GLP reports focused on immune-associated finding observed in studies of adult animals and therefore lacked a comprehensive and complete evaluation of tissues. Histopathology was conducted for immune tissues and some major organs, but lacked comprehensive assessments, with particular reference to lack of histopathological examinations, of long bones and joints. The inadequacy of nonclinical support for pediatric studies was noted in the 2012 review.

In the juvenile rat study (Report 10GR307), animals were dosed orally by gavage from postnatal day 21 (PND 21) to PND 49 at dose levels of 0 (vehicle), 1, 10 and 100 mg/kg/day. This was followed by a 2-month recovery period and animals were sacrificed on PND 50 (study day 29), just prior to sexual maturity, and PND 111 (study day 91), approximately 30 days after sexual maturity. There was no histopathological examinations of bone in this study. Assessment of long bone or body length were not obtained, although body weight was monitored with modest reductions in body weight that, in females, was not dose dependent (high dose males -

6.5%, mid dose females -8%) and weight gain (high dose males -11%, mid dose females -11.6%) compared to controls.

In the juvenile monkey study (Report 09GR248), juvenile cynomolgus monkeys of 13-14 month of age were dosed orally by gavage at dose levels of 0 (vehicle), 0.25, 1, and 5 mg/kg BID, daily for 39 weeks, followed by a 6-month recovery period. Sternum with bone marrow was evaluated by histopathological examination; however, the evaluation of long bones (radius and tibia) was limited to radiographic examinations. Joints were not examined. Growth in terms of body weights increased without an effect of tofacitinib. There was no assessment of body length, although radius and tibia lengths assessed from radiographs increased during the study with no effects of tofacitinib.

Despite the incomplete evaluation of bone and some other tissues in histopathological assessments, pediatric studies were conducted under the IND since there were no indications that movement, gait, activity or other behaviors were affected, and the clinical studies were initiated with older adolescents, gradually including younger subjects. Adverse effects of approved JAK inhibitors on bone development and growth were not reported until 2019. Recent literature concerning a number of JAK inhibitors and bone growth have raised concerns about the potential for drugs of this class to cause adverse bone or cartilage effects. Our internal review indicates that differences do exist within the class of JAK inhibitors on bone histopathology findings and bone development and growth, and prediction cannot be based on JAK inhibitor “class” effects. In addition, the bone growth in the tofacitinib juvenile monkey study, assessed radiographically by length measurements of the tibia and radius, was unaffected at the relevant tofacitinib doses. Further, the histopathology of the sternum did not show abnormalities.

Juvenile rat studies have been conducted for other JAK inhibitors, both approved and in development. Results have been mixed ranging from arrested or reduced bone growth and presence of abnormal histopathological findings to no abnormal findings. Pharmacological differences between the drugs and tofacitinib as well as differences in the presence of certain chemical moieties may explain the variations in findings. Recent medical literature concerning a number of JAK inhibitors and bone growth have also raised concerns about the potential for drugs of this class to cause adverse bone or cartilage effects. However, with so few drugs that have conducted juvenile animal studies, and even fewer that have some commonalities among chemical structure or pharmacology, no conclusion can be made about potential class effects. The lack of appropriate histopathology examinations of structural bone tissue in the juvenile studies with tofacitinib provides an incomplete safety characterization of the drug for the pediatric population. This hinders the ability to clearly identify if effects are limited to a few drugs or if there is a class effect.

The Applicant will be required into conduct a juvenile animal study to assess the effects of tofacitinib on bone growth and development by histopathological examination, as detailed in Section 13, Postmarketing Requirements and Commitments.

5.5.2. Genetic Toxicology

Refer to the Pharmacology-Toxicology Review of NDA 203214 dated July 3, 2012 for detailed descriptions of Genetic Toxicology studies.

5.5.3. Carcinogenicity

Refer to the Pharmacology-Toxicology Review of NDA 203214 dated July 3, 2012 for detailed descriptions of the Carcinogenicity studies.

5.5.4. Reproductive and Developmental Toxicology

Refer to the Pharmacology-Toxicology Review of NDA 203214 dated July 3, 2012 for detailed descriptions of Reproductive and Developmental Toxicology studies.

5.5.5. Other Toxicology Studies

Refer to the Pharmacology-Toxicology Review of NDA 203214 dated July 3, 2012 for detailed descriptions of Other Toxicology studies.

Impurities

During review of the oral solution of tofacitinib (NDA 214082) to be used in the younger pediatric population, two impurities, identified (b) (4) required toxicological evaluation for qualification and acceptance of the proposed specifications. Other impurities in the oral solution were qualified previously in the original Pharmacology Toxicology review of July 3, 2012. A formal consult was not requested, so this assessment is presented in Section 19.3 Nonclinical Appendix. The impurity specifications of not more than (b) (4) % for each were acceptable based on currently recommended Quantitative Structure Analysis Relationships (QSAR) analyses and levels found in ADME studies ((b) (4) was identified as a metabolite) and as assessed in toxicity studies.

6 Clinical Pharmacology

6.1. Executive Summary

Tofacitinib is a Janus kinase (JAK) inhibitor. XELJANZ (tofacitinib) (immediate-release (IR) film-coated tablet, 5 and 10 mg), has been approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis (PsA), and moderately to severely active ulcerative colitis (UC) with the approved dosing regimen as below:

- RA or PsA: 5 mg twice daily (BID)
- UC: 10 mg BID for 8 weeks (up to a maximum of 16 weeks), followed by 5 mg BID for maintenance dosing

On March 26, 2020, Pfizer submitted NDA 203214 Supplement-26 for XELJANZ (tofacitinib) IR tablet (5 mg) and NDA 213082 for tofacitinib oral solution (1 mg/mL) seeking the marketing approval for tofacitinib for the treatment of polyarticular course juvenile idiopathic arthritis (pcJIA). The proposed body weight-based dosing regimen is as below:

- 10 to <20 kg: 3.2 mg (3.2 mL oral solution) BID
- 20 to <40 kg: 4 mg (4 mL oral solution) BID
- ≥ 40 kg: 5 mg (one 5 mg IR tablet or 5 mL oral solution) BID

NDA 203214 Supplement-26 and NDA 213082 applications consist of four clinical studies, including one phase 1 PK study (Study A3921103, n=26), one phase 3 efficacy study (Study A3921104, n=225), one long-term extension study (Study A3921145, n=225) in patients with pcJIA, and one relative bioavailability study (Study A3921354, n=11) in healthy subjects. In addition, one population PK analysis report and one longitudinal PK/PD modeling report were also submitted.

Summary of Clinical Pharmacology Assessment
The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM) have reviewed the clinical pharmacology data submitted under NDA203214-S026 and NDA213082. Both submissions are recommended for approval from a clinical pharmacology perspective for the treatment of patients with pcJIA.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

XELJANZ (tofacitinib) is a JAK inhibitor and has been approved for the treatment of adult patients with moderately to severely active RA, active PsA, and moderately to severely active UC. Of note, the majority of the clinical pharmacology information for tofacitinib was reviewed

with the original application (NDA 203214 by Dr. Lokesh Jain, DARRTs date 06/25/2012). The major findings for this Clinical Pharmacology review are as follows:

- Results from the relative bioavailability study (Study A3921354) indicated that XELJANZ oral solution (1 mg/mL) had a similar bioavailability as the 5 mg IR tablet under fasting condition in adult subjects. The effect of food on tofacitinib absorption is expected to be similar for XELJANZ solution and the 5 mg IR tablet formulation.

- In population PK analysis, body weight was identified as a significant covariate for tofacitinib exposure, supporting the body weight-based dosing regimen in pcJIA subjects. Based on population PK analysis, following the proposed dosing regimen, patients 2 to <18 years of are predicted to have similar exposure as in the pcJIA phase 3 study (A3921104). Comparable steady state concentrations across weight tiers were achieved following the body-weight-based dosing regimen.

- Population PK anslysis showed that none of the other evaluated covariates such as age, race, gender, baseline disease severity, or JIA categories require dose adjustment.

- The tofacitinib exposure (average steady state concentrations, Cavg,ss) in pediatric patients 2 to <18 years of age (range: 13.4-16.73 mg/mL) is approximately 36% lower than the median Cavg,ss (21 mg/mL) in adult RA patients.

  Tofacitinib PK has been characterized in patients with pcJIA in Study A3921103. Results indicated that tofacitinib CL/F values in subjects with pcJIA increase with body weight and were 52.7%, 38.5% and 11.6% higher in the 12 to <18 years (n=8), 6 to <12 years (n=9) and 2 to <6 years (n=9) age groups, respectively, as compared to the reported CL/F in adult RA subjects with 5 mg BID dosing (18.4 L/h). In population PK analysis, the estimated CL/F of tofacitinib in a pcJIA subject with a typical body weight of 46 kg (26.1 L/h) was approximately 42% higher than in RA (18.4 L/h).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen for pediatric subjects with pcJIA is body-weight based dosing regimen:

- 10 to <20 kg: 3.2 mg (3.2 mL oral solution) BID
- 20 to <40 kg: 4 mg (4 mL oral solution) BID
- ≥ 40 kg: 5 mg (one 5 mg IR tablet or 5 mL oral solution) BID

Therapeutic Individualization

The proposed dosing adjustments regarding intrinsic and extrinsic factors are consistent with the approved recommendations for RA.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

XELJANZ (tofacitinib) is a JAK inhibitor and has been approved for the treatment of adult patients with moderately to severely active RA, active PsA, and moderately to severely active UC. Refer to the approved labeling of XELJANZ regarding tofacitinib PK characteristics in subjects with RA, PsA and UC.

Tofacitinib PK in pcJIA

Tofacitinib PK has been characterized in patients with pcJIA in Study A3921103. It is an open-label, non-randomized, multi-center, multiple-dose study in pediatric subjects with pcJIA aged from 2 to <18 years. Patients were enrolled in a staggered approach beginning with older children followed by younger children into 3 cohorts (Cohort 1: 12 to <18 years; Cohort 2: 6 to <12 years; Cohort 3: 2 to <6 years). Tofacitinib was administered orally BID for 5 days based on age and body weight as shown in Table 3 and Table 4. For children who receive 5 mg dose, either tofacitinib IR tablets (5 mg) or oral solution (1 mg/mL) were administered; otherwise, only tofacitinib oral solution was administered. PK samples were collected on Day 5 at pre-dose (0 hours) and 0.5, 1, 2, 4, and 8 hours post-dose and tofacitinib plasma concentrations were measured using a validated HPLC-MS/MS assay (refer to the summary of bioanalytical assays in Appendix for detailed information).

Tofacitinib PK was analyzed using non-compartmental analysis and the PK parameters are summarized in Table 5. Results showed that tofacitinib CL/F values in subjects with pcJIA increase with body weight and were 52.7%, 38.5% and 11.6% higher in the 12 to <18 years, 6 to <12 years and 2 to <6 years age groups, respectively, compared to that reported in adult RA subjects with 5 mg BID dosing (18.4 L/h).

In population PK analysis with pooled PK data from 248 pcJIA subjects from PK study A3921103, study A3921104, and the LTE study A3921145, body weight was identified as a significant covariate for tofacitinib exposure, supporting the body weight-based dosing regimen in pcJIA subjects. The estimated CL/F of tofacitinib in a pcJIA subject with a typical body weight of 46 kg (26.1 L/h) was approximately 42% higher than in RA (18.4 L/h). This conclusion based on pooled data is consistent with the non-compartmental analysis in Study A3921103. Refer to the Pharmacometrics Review in Appendix for detailed information.

While tofacitinib exposure in pcJIA subjects is lower than RA with the approved dose in adults (i.e. 5 mg BID), the use of doses higher than the approved adult dose in pcJIA patients would not be acceptable due to dose-dependent toxicities with tofacitinib.[18] In addition, it is unclear whether other unknown factors may contribute to the differences in clearance and exposure between adults with RA and pcJIA patients. Based on the communication with the Division, the phase 3 protocol maintained 5 mg BID for children weighing 40 kg or more, and had the weight-based dosing scheme for children weighing less than 40 kg to align exposures with those targeted for the 5 mg BID dose in children/adolescents with pcJIA weighing 40 kg or greater. For details of the consideration for pediatric dose selection, refer to Section 3.1 Summary of Presubmission/Submission Regulatory Activity and the Clinical Review for NDA203214/IND 117400 by Dr. Juwaria Waheed dated January 12, 2016.

Table 3. The body-weight based dosing regimen in Study A3921103

Body Weight (kg)	Dose (mg)	Volume (mL)
Dosing scheme for age 6 to <18 years		
5-11	1	1
12-18	1.5	1.5
19-24	2	2
25-31	2.5	2.5
32-39	3	3
≥40	5	5
Dosing scheme for age 2 to <6 years		
5-6	1	1
7-9	1.5	1.5
10-12	2	2
13-15	2.5	2.5
16-19	3	3
20-22	3.5	3.5
23-26	4	4
27-29	4.5	4.5
≥30	5	5

Source: Table 2 of Study A3921103 CSR

[18] FDA-approved tofacitinib labeling

Table 4. Drug administration details in Study A3921103

	Cohort 1, 12 to < 18 Years (N = 8)	Cohort 2, 6 to < 12 Years (N = 9)	Cohort 3, 2 to < 6 Years (N = 9)
Mean weight (kg)	54.0	32.4	17.3
Median dose (mg, BID)	5.0	2.5	3.0
Individual subjects dosed (n):			
5 mg BID (tablet)	6	2	-
3.5 mg BID (solution)	-	-	1
3 mg BID (solution)	2	2	6
2.5 mg BID (solution)	-	3	2
2 mg BID (solution)	-	2	-

Source: Table 12 of Study A3921103 CSR

Table 5. Summary of tofacitinib PK parameters by age group in pcJIA in Study A3921103

Parameter, Units	Parameter Summary Statistics[a] Cohort 1 12 to < 18 Years	Cohort 2 6 to < 12 Years	Cohort 3 2 to < 6 Years	All Cohorts
N	8[b]	9[c]	9	26[d]
Dose, mg (BID)	5.0 (3.0-5.0)	2.5 (2.0-5.0)	3.0 (2.5-3.5)	3.0 (2.0-5.0)
AUC_{tau} ng•h/mL	156.58 (25)	118.81 (27)	142.51 (32)	138.56 (30)
C_{max}, ng/mL	46.97 (40)	41.67 (29)	66.15 (28)	50.74 (38)
T_{max}, h	0.75 (0.50-6.90)	1.00 (0.50-2.05)	0.50 (0.50-1.92)	0.91 (0.50-6.90)
C_{trough}, ng/mL	2.659 (100)	0.757 (127)	0.756 (119)	1.114 (145)
C_{min}, ng/mL	2.503 (86)	0.816 (95)	0.698 (103)	1.104 (123)
t½, h	2.616 ± 0.453	1.949 ± 0.294	1.771 ± 0.406	2.077 ± 0.518
CL/F, L/h	28.09 (22)	25.48 (40)	20.53 (33)	24.32 (34)
V_z/F, L	104.93 (35)	71.00 (40)	51.44 (34)	70.51 (47)

Parameters are defined in Table 4.
Abbreviation: %CV =percent coefficient of variance; BID=twice daily; N=number of subjects; PK=pharmacokinetic; SD=standard deviation.
a. Geometric mean (geometric %CV) for all except: median (range) for Dose and Tmax; arithmetic mean ±SD for t½.
b. N=7 for t½ and Vz/F due to lack of a well-characterized terminal phase in 1 subject.
c. N=8 for t½, Vz/F, CL/F, Cmin, and AUCtau due to incomplete PK sampling for 1 subject.
d. N=24 for t½ and Vz/F and N=25 for Cmin and AUCtau due to the exceptions noted above.

Source: Table 13 of Study A3921103 CSR

XELJANZ (tofacitinib) IR tablets (5 mg) vs. tofacitinib oral solution (1 mg/mL)

XELJANZ (tofacitinib) IR tablets (5 mg) and tofacitinib oral solution (1 mg/mL) were compared in a relative bioavailability study (Study A3921354). It is a Phase 1, randomized, open-label, 2-period, 2-sequence, cross-over (48-hour washout period), single-dose study in 12 healthy subjects. Participants received a single dose of tofacitinib 5 mg IR tablets or tofacitinib 5 mL oral solution (1 mg/mL) following an overnight fast for at least 10 hours. Results of PK analysis indicated that following a single dose of 5 mg tofacitinib with XELJANZ IR tablets (5 mg) or oral

solution (1mg/mL), the systemic exposure of tofacitinib (Cmax, AUC0-t, and AUC0-inf) are comparable (Table 6 and Table 7).

Table 6. Summary of plasma tofacitinib PK parameters (Study A3921354)

Parameter (Units)[a]	Tofacitinib 5 mg Tablet (N=11)	Tofacitinib 5 mg Oral Solution (N=12)
N1,N2	11, 11	12, 12
AUC_{inf} (ng.hr/mL)	126.8 (13)	132.4 (12)
AUC_{last} (ng.hr/mL)	125.7 (14)	131.3 (12)
C_{max} (ng/mL)	34.54 (21)	38.01 (20)
T_{max} (hr)	1.00 (0.500, 1.03)	0.509 (0.500, 1.02)
$t_{1/2}$ (hr)	3.277 ± 0.50048	3.335 ± 0.41910

Source: Table 14.4.5.1
N=Number of subjects in the treatment group
N1=Number of subjects contributing to the summary statistics
N2=Number of subjects where AUC_{inf} and $t_{1/2}$ were determined
a. Geometric mean (%CV) for all except: median (range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$
Note: One participant discontinued after completing Period 1 treatment of tofacitinib 5 mg oral solution due to family emergency.

Source: Table 7 of Study A3921354 CSR

Table 7. Tofacitinib PK comparison after oral administration of tofacitinib 5 mg IR tablets and 5 mL oral solution (1 mg/mL) (Study A3921354)

Parameter (Units)	Adjusted Geometric Means: Tofacitinib 5 mg Oral Solution (Test)	Adjusted Geometric Means: Tofacitinib 5 mg Tablet (Reference)	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio[a]
AUC_{inf} (ng.hr/mL)	132.4	126.8	104.38	(99.99, 108.97)
AUC_{last} (ng.hr/mL)	131.3	125.7	104.48	(100.16, 108.99)
C_{max} (ng/mL)	38.01	34.56	110.00	(99.90, 121.13)

Source: Table 14.4.5.3
Values had been back-transformed from the log scale.
The model was a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect.
a.The ratios (and 90% CIs) were expressed as percentages.

Source: Table 8 of Study A3921354 CSR

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of tofacitinib in patients with pJIA were evaluated in the pivotal Phase 3 study A3921104 and the LTE study A3921145 with the treatment dosing regimen as shown in Table 8. Refer to Sections 7 and 8 for more detailed assessment for effectiveness.

The proposed dosing regimen has been modified from the treatment dosing regimen with fewer weight subgroups as shown in Table 9. Comparison of the estimated tofacitinib Cave, Cmax and Cmin values indicated that, following the administration of tofacitinib with proposed dosing regimen or the treatment dosing regimen in Phase 3 study, the differences in tofacitinib systemic exposure were within 15% across all body weight subgroups (Table 10). Therefore, the proposed dosing regimen (Table 9) is acceptable.

Table 8. The treatment dosing regimen in Studies A3921104 and A3921145

Body Weight (kg)	Dosage Regimen (Run-In Phase: Tofacitinib, Double-Blind Phase: Tofacitinib/Placebo)
5 to <7	2 mg (2 mL oral solution) BID
7 to <10	2.5 mg (2.5 mL oral solution) BID
10 to <15	3 mg (3 mL oral solution) BID
15 to <25	3.5 mg (3.5 mL oral solution) BID
25 to <40	4 mg (4 mL oral solution) BID
≥40	5 mg (one 5 mg tablet or 5 mL oral solution) BID

Source: Table 3 of Study A3921104 CSR

Table 9. The porposed tofacitinib dosing regimen for pediatric subjects with pJIA

Body Weight (kg)	Dosage Regimen
10 to <20	3.2 mg (3.2 mL oral solution) BID
20 to <40	4 mg (4 mL oral solution) BID
≥40	5 mg (one 5 mg tablet or 5 mL oral solution) BID
	(b) (4)

Source: Table 6 of Summary of Clinical Pharmaoclogy

Table 10. Comparison of tofacitinib systemic exposure between the treatment dosing regimen in Phase 3 study and the porposed dosing regimen

		Proposed Dosing Regimen				Treatment Dosing Regimen				Ratio of Proposed/Treatment		
Body Weight Range (kg)	Body Weight (kg)	Dose (mg BID)	Cave (ng/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Dose (mg BID)	Cave (ng/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Cave	Cmax	Cmin
10 - < 15	10	3.2	16.45	69.28	0.61	3	15.42	64.95	0.57	1.07	1.07	1.07
	14.9	3.2	14.54	56.76	0.75	3	13.63	53.21	0.71	1.07	1.07	1.06
15 - < 20	15	3.2	14.51	56.57	0.76	3.5	15.87	61.87	0.83	0.91	0.91	0.92
	19.9	3.2	13.29	49.14	0.86	3.5	14.54	53.75	0.94	0.91	0.91	0.91
20 - < 25	20	4	16.59	61.27	1.08	3.5	14.52	53.61	0.95	1.14	1.14	1.14
	24.9	4	15.5	54.96	1.18	3.5	13.57	48.09	1.03	1.14	1.14	1.15
25 - < 40	25	4	15.48	54.85	1.18	4	15.48	54.85	1.18	1	1	1
	39.9	4	13.4	43.56	1.39	4	13.4	43.56	1.39	1	1	1
>= 40	40	5	16.73	47.68	1.87	5	16.73	47.68	1.87	1	1	1

Source: IR response dated 04/28/2020

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

In population PK analysis, body weight was identified as a significant covariate for tofacitinib exposure, supporting the proposed body weight-based dosing regimen in pJIA subjects. The efficacy of tofacitinib in patients with pJIA were evaluated in the pivotal Phase 3 study A3921104 and the LTE study A3921145. Refer to Sections 7 and 8 for more detailed assessment for effectiveness.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

For subjects with renal and hepatic impairment, the proposed dosing adjustment for pJIA is consistent with the approved recommendations for RA subjects, which is reasonable.

- For patients with moderate or severe renal impairment, or patients with moderate hepatic impairment:
  - If taking 3.2 mg BID, reduce to 3.2 mg once daily (QD)
  - If taking 4 mg BID, reduce to 4 mg QD
  - If taking 5 mg BID, reduce to 5 mg QD
  - For patients undergoing hemodialysis, dose should be administered after the dialysis session on dialysis days. If a dose was taken before the dialysis procedure, supplemental doses are not recommended in patients after dialysis.
- Use in patients with severe hepatic impairment is not recommended.

Population PK analysis showed that none of the other evaluated covariates such as age, race, gender, baseline disease severity, or JIA categories require dose adjustment.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

XELJANZ IR tablets (5 mg) have been approved to be administered with or without food. Under fasted condition, 5 mg tofacitinib oral solution (1 mg/mL) produces comparable systemic exposure of tofacitinib as compared to 5 mg IR tablets (Study A3921354). In all clinical studies in pJIA, including the PK study A3921103, Phase 3 study A3921104, and the LTE study A3921145, both XELJANZ IR tablets and tofacitinib oral solution have been given regardless of food. Therefore, the proposed dose administration for tofacitinib oral solution (1 mg/mL) with or without food is acceptable.

For drug-drug interactions, the proposed dosing adjustment for pJIA is consistent with the approved recommendations for RA subjects, which is reasonable.

- Patients receiving strong CYP3A4 inhibitors (e.g., ketoconazole), or a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole):
    - If taking 3.2 mg BID, reduce to 3.2 mg QD
    - If taking 4 mg BID, reduce to 4 mg QD
    - If taking 5 mg BID, reduce to 5 mg QD

Question on clinically relevant specifications (TBD)?

None

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 11. Clinical Development Program for pcJIA

Study A392	Population	Primary EP/ Key Secondary EPs	Treatment Arms
1103 OL, multiple-dose study, 5-day, PK study	Active JIA + sJIA without active systemic features Cohort 1: 12 to <18 years; N=8 Cohort 2: 6 to <12 years; N=9 Cohort 3: 2 to <6 years; N=9	To characterize PK, safety and tolerability Oral clearance (CL/F) on day 5	Tofacitinib 5 mg BID or weight-based equivalent
1104 OL run-in phase followed by DB, PC, RW	Active JIA, 2 to <18 years N=225 R in DB, N=173 Tofa 88; PBO 85	Occurrence of disease flare (PRCSG/PRINTO criteria) at Week 44	Tofacitinib 5 mg PO BID or oral solution 1mg/ML PO BID (weight-based equivalent)
1145 OL, LTE	pJIA and sJIA patients from prior studies Enrolled from Studies A392 1103; N=26 1104; N=197 1165; N=2*	Long term safety	OL Tofacitinib 5 mg BID or weight-based equivalent
1354 R, OL, 2 period, cross-over, single dose study	Healthy Population N=5 N=6	PK bridging between tablet and oral solution formulation To demonstrate the equivalence of the extent of exposure between a single dose of tofacitinib 5 mL oral solution (1 mg/mL) relative to 5 mg tablet; EP: AUCinf, AUClast	Study 1354 was not included in safety or efficacy analyses

Source: Reviewer. NDA 203214 S-26 Clinical Overview
OL:open-label; PK:pharmacokineticis; DB:double-blind; PC:placebo-controlled; RW:randomized withdrawal
*Study 1165 is an ongoing tofacitinib study in patients with systemic JIA (sJIA). Two patients from study 1165 were enrolled in the LTE Study 1145, however these sJIA patients were not included in the safety or efficacy analyses for pcJIA

7.2. Review Strategy

The strategy for the evaluation of efficacy endpoints will be first to consider the results using data only from the main study (A3921104). However, the design and conduct of the study was that when a patient discontinued treatment and withdrew from the main study early, they would enroll into the extension study (A3921145), and either continue or re-initiate tofacitinib. Since the Applicant's pre-specified analyses was for the purpose of making comparisons between tofacitinib and placebo at week 44 for the secondary endpoints of ACR and CHAQ-DI, it is not consistent with the design and conduct of the study. Therefore, we found it appropriate to consider the use of extension data since the results from these data is reflective of the design and conduct of the study.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study A3921104

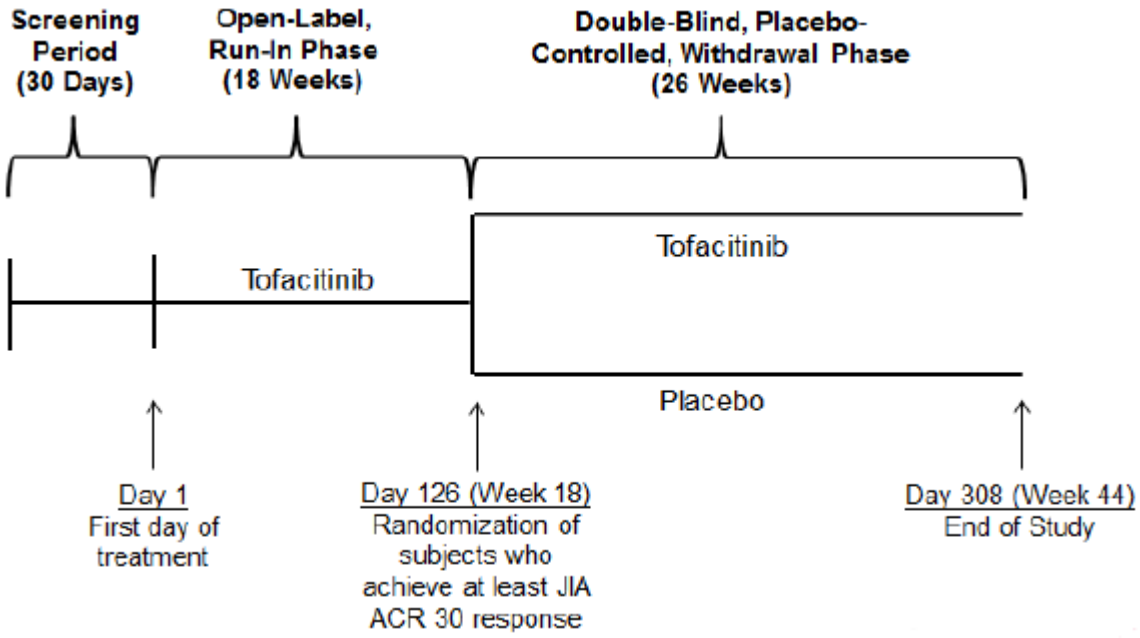
Data Quality and Integrity

There were no issues concerning the submission of data sets and files.

Trial Design

Study A3921104 was a multi-center, randomized withdrawal, double-blind, placebo-controlled, parallel group study. The run-in phase was an 18-week open-label period, where all subjects initiated tofacitinib. Following the run-in phase, subjects who achieved at least a JIA ACR 30 response were randomized with a 1:1 ratio to either placebo or tofacitinib for the 26-week double-blind phase. A schematic of the study design is shown in Figure 1 below:

Figure 1: Study Design



Source: CSR Page 61

Reviewer's comments:

- For the remainder of this section, I will refer to randomization at Week 18 as double-blind baseline.

- It was pre-planned that subjects who discontinued therapy would withdraw from the study but enter into a long-term open label extension study (A3921145), where all subjects would receive tofacitinib.

Study Endpoints

Primary Endpoint: The occurrence of disease flare by Week 44 from double-blind baseline

Secondary Endpoints: Secondary endpoints included in the sequential testing procedure are:

- Achieving JIA ACR 50, 30, 70 response at Week 44 (from open-label baseline)
- Change in CHAQ - Disability Index (DI) at Week 44 from double-blind baseline

Statistical Analysis Plan

There were 4 versions of the Statistical Analysis Plan (SAP), with the final version being finalized in April 2019. In general, the sponsor implemented most of our suggestions and we agreed to most changes. The issue of subjects discontinuing the study after occurrence of disease flare and the concern that it would create a large amount of missing data was discussed and that the use of extension data may not be of clinical relevance. The Applicant was encouraged to follow all subjects throughout Week 44, regardless of occurrence of disease flare.

Protocol Amendments

There were 6 amendments with the last amendment finalized in July 2018. There were no statistical changes that compromised the integrity and conduct of the study.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant certified that all clinical investigations in the supplemental BLA were conducted according to all applicable laws and regulations including, but not limited to, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origin in the Declaration of Helsinki, and applicable privacy laws and Pfizer SOPS in place at that time.

Financial Disclosure

The applicant submitted FDA Form 3454 (v.10/09) certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified.

Patient Disposition

From Table 10 below, a total of 225 subjects entered into the open-label run-in phase. Of these 185 (82%) completed the phase.

Table 12: Open-Label Phase Completion

Open Label Phase	Tofacitinib (N=225)
Entered [n(%)]	225 (100)
Completed [n(%)]	185 (82.22)

Source: CSR (Page 79) and Statistical Reviewer's Analysis

Table 11 below presents the disposition of subjects in the double-blind phase. A total of 173 subjects were randomized. Of these subjects, 69% in the tofacitinib group and 45% in the placebo group completed the double-blind phase. The primary reason for study discontinuation was insufficient clinical response, which was associated with occurrence of disease flare. Except for a few cases, disease flare occurred in subjects who experienced insufficient clinical response.

Table 13: Randomization, Completion, and Discontinuation of the Double-Blind Phase

	Tofacitinib (N=88)	Placebo (N=85)	Total (N=173)
Randomized to DB Phase [n(%)]	88 (100)	85 (100)	173 (100)
Completed DB Phase [n(%)]	61 (69.32)	38 (44.71)	99 (57.23)
Discontinued DB Phase [n(%)]	27 (30.68)	47 (55.29)	74 (42.77)
Insufficient Clinical Response [n]	22	44	66
Occurrence of Disease [n]	21	42	63
No Occurrence of Disease [n]	1	2	3
Adverse Event [n]	2	2	4
Other [n]	3	1	4

Source: CSR (Page 79) and Statistical Reviewer's Analysis

Protocol Violations/Deviations

There were 4 patients on placebo with key protocol deviations, one of whom led to discontinuation of treatment and subsequently early study withdrawal and three who remained in the study but eventually had occurrence of disease flare. There were no patients on tofacitinib with key protocol deviations that led to discontinuation of treatment. The small number of protocol deviations do not significantly impact the study results or the overall conclusions from the study.

Table(s) of Demographic Characteristics

To help describe baseline demographic and disease characteristics, the following analysis populations are defined as follows:

- Open-Label Full Analysis Set (OLFAS): Subjects enrolled and who received at least 1 dose of study medication in the open-label phase
- Double-Blind Full Analysis Set (DBFAS): Subjects randomized to the double-blind phase who received at least 1 dose of study medication
- Double-Blind Polyarticular Course JIA Analysis Set (DBJAS): pJIA subjects in DBFAS (i.e., excluding subjects in Enthesitis Related Arthritis (ERA) and Juvenile Psoriatic Arthritis (jPsA) categories)

Table 12 below displays demographic characteristics for the OLFAS. Among the 225 subjects, 75% who entered the open-label phase were female, the majority were white (87%) and 43% were from North America.

Table 14: Baseline Demographic Characteristics in the OLFAS

	Tofacitinib (N=225)
Sex [n(%)]	
Male	56 (24.89)
Female	169 (75.11)
Age (years)	
Mean (SD)	11.92 (4.06)
Age Group [n(%)]	
2 - < 12	86 (38.22)
12 - < 18	139 (61.78)
Race [n(%)]	
White	196 (87.11)
Black or African American	5 (2.22)
Other	24 (10.67)
Geographical Region [n(%)]	
North America	96 (42.67)
South or Central America	47 (20.89)
Europe	6 (2.67)
All Other	76 (33.78)

Source: CSR (Page 97-98) and Statistical Reviewer's Analysis

Table 13 below displays demographic characteristics for the DBFAS. The demographics are similar to the open-label phase. Furthermore, demographics were generally balanced between treatment arms.

Table 15: Baseline Demographic Characteristics in the DBFAS

	Tofacitinib (N=88)	Placebo (N=85)	Total (N=173)
Sex [n(%)]			
Male	22 (25.00)	21 (24.71)	43 (24.86)
Female	66 (75.00)	64 (75.29)	130 (75.14)
Age (years)			
Mean (SD)	11.88 (4.34)	11.87 (4.06)	11.87 (4.19)
Age Group [n(%)]			
2 - < 12	33 (37.50)	32 (37.65)	65 (37.57)
12 - < 18	55 (62.50)	53 (62.35)	108 (62.43)
Race [n(%)]			
White	76 (86.36)	74 (87.06)	150 (86.71)
Black or African American	4 (4.55)	1 (1.18)	5 (2.89)
Other	8 (9.09)	10 (11.76)	18 (10.40)
Geographical Region [n(%)]			
North America	31 (35.23)	41 (48.24)	72 (41.62)
South or Central America	22 (25.00)	15 (17.65)	37 (21.39)
Europe	5 (5.68)	1 (1.18)	6 (3.47)
All Other	30 (34.09)	28 (32.94)	58 (33.53)

Source: CSR (Page 103-104) and Statistical Reviewer's Analysis

Other Baseline Characteristics

Tables 14-15 below display disease characteristics at open-label baseline for the OLFAS and DBFAS, respectively, and Table 16 at double-blind baseline for the DBFAS. The characteristics presented are the 6 components in determining occurrence of disease and JIA ACR response. It appears that characteristics were generally balanced between the treatment arms. Furthermore, comparing Tables 15-16, we note the improvement in component scores in the DBFAS. This is a result of initiating tofacitinib during the open-label phase.

Table 16: Disease Characteristics at Open-Label Baseline in the OLFAS

	Tofacitinib (N=225)
Sum of LOM Joints	
Mean (SD)	7.52 (6.89)
Sum of Active Joints with Swelling / Pain	
Mean (SD)	12.23 (8.11)
Global Assessment of Disease Activity	
Mean (SD)	6.18 (1.88)
CHAQ - Disability Index Score	
Mean (SD)	0.96 (0.72)
Overall Well-Being	
Mean (SD)	4.87 (2.53)
Erythrocyte Sedimentation Rate (mm/h)	
Mean (SD)	25.34 (24.76)

Source: CSR (Page 101-102) and Statistical Reviewer's Analysis

Table 17: Disease Characteristics at Open-Label Baseline in the DBFAS

	Tofacitinib (N=88)	Placebo (N=85)	Total (N=173)
Sum of LOM Joints			
Mean (SD)	8.59 (7.67)	6.45 (5.31)	7.54 (6.69)
Sum of Active Joints with Swelling / Pain			
Mean (SD)	12.33 (7.07)	11.36 (7.75)	11.86 (7.41)
Global Assessment of Disease Activity			
Mean (SD)	6.13 (1.90)	6.04 (1.88)	6.08 (1.88)
CHAQ - Disability Index Score			
Mean (SD)	0.92 (0.69)	0.95 (0.74)	0.93 (0.71)
Overall Well-Being			
Mean (SD)	4.72 (2.49)	4.75 (2.57)	4.73 (2.52)
Erythrocyte Sedimentation Rate (mm/h)			
Mean (SD)	24.79 (22.47)	26.44 (26.32)	25.60 (24.38)

Source: CSR (Page 107-108) and Statistical Reviewer's Analysis

Table 18: Disease Characteristics at Double-Blind Baseline in the DBFAS

	Tofacitinib (N=88)	Placebo (N=85)	Total (N=173)
Sum of LOM Joints			
Mean (SD)	1.91 (4.51)	1.45 (2.33)	1.68 (3.61)
Sum of Active Joints with Swelling / Pain			
Mean (SD)	1.41 (2.27)	1.61 (2.74)	1.51 (2.51)
Global Assessment of Disease Activity			
Mean (SD)	1.61 (1.64)	1.39 (1.46)	1.50 (1.55)
CHAQ - Disability Index Score			
Mean (SD)	0.44 (0.51)	0.44 (0.58)	0.44 (0.55)
Overall Well-Being			
Mean (SD)	2.01 (1.89)	1.91 (1.91)	1.96 (1.89)
Erythrocyte Sedimentation Rate (mm/h)			
Mean (SD)	13.39 (13.42)	13.79 (11.94)	13.58 (12.68)

Source: CSR (Page 107-108) and Statistical Reviewer's Analysis

Tables 17-18 below summarize the JIA categories in the OLFAS and DBFAS. In the DBFAS, the proportion of subjects in each JIA category is generally similar in both treatment groups.

Table 19: JIA Categories: OLFAS

	Tofacitinib (N=225)
JIA Category [n(%)]	
Enthesitis Related Arthritis	21 (9.33)
Extended Oligoarthritis	28 (12.44)
Juvenile Psoriatic Arthritis	20 (8.89)
RF+ Polyarthritis	39 (17.33)
RF- Polyarthritis	104 (46.22)
Systemic JIA with active arthritis but without active systemic features	13 (5.78)

Source: Statistical Reviewer's Analysis

Table 20: JIA Categories: DBFAS

	Tofacitinib (N=88)	Placebo (N=85)	Total (N=173)
JIA Category [n(%)]			
Enthesitis Related Arthritis	9 (10.23)	7 (8.24)	16 (9.25)
Extended Oligoarthritis	8 (9.09)	10 (11.76)	18 (10.40)
Juvenile Psoriatic Arthritis	7 (7.95)	8 (9.41)	15 (8.67)
RF+ Polyarthritis	14 (15.91)	14 (16.47)	28 (16.18)
RF- Polyarthritis	45 (51.14)	42 (49.41)	87 (50.29)
Systemic JIA with active arthritis but without active systemic features	5 (5.68)	4 (4.71)	9 (5.20)

Source: Statistical Reviewer's Analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was assessed at each visit during the study and was verified by interviewing subjects and through accounting of returned containers and trial medication at each visit. Subjects who were less than 80% or >110% compliant with the regimen were documented in the appropriate CRF. In subjects who demonstrated noncompliance between visit intervals, both the subject and parent/legal guardian were counseled by study staff to address reasons for noncompliance. If after counseling the subject continued to exhibit noncompliance over 2 consecutive study visits, the subject was to be withdrawn from the study.

During the open-label phase, the number of subjects with any prior medication was 224 (99.6%). Of these, there were 160 (71.1%) who used prior analgesic medication, 159 (70.7%) who used prior NSAIDs, 20 (8.9%) who used prior non-anti-inflammatory analgesic, and 3 (1.3%) with prior opioid use.

There were 216 (96%) of subjects with prior DMARD, corticosteroid, and immunosuppressant use. Of these, 85 subjects (37.8%) used biological disease-modifying antirheumatic drugs (bDMARDs) and 206 (91.6%) subjects used conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). The most frequently used bDMARD was etanercept (52 [23.1%] subjects). MTX was the most frequently used csDMARD (204 [90.7%] subjects), with folate being used by 164 (72.9%) of subjects. Further, corticosteroids were used by 111 (49.3%) subjects, with the most common being prednisone (61 [27.1%]).

During the open-label run-in phase, there were 171 (76.0%) of subjects who used DMARD, corticosteroid, and/or immunosuppressant medications. Of these, csDMARDs were used concomitantly by 149 (66.2%) subjects, while MTX and folate were taken concomitantly by 148

(65.8%) subjects and 145 (64.4%), respectively. Corticosteroids were used concomitantly by 75 (33.3 %) subjects. One patient was taking hydroxychloroquine, and another subject was taking sulfasalazine during the screening period. Concomitant use of bDMARDs was prohibited during the study.

During the double-blind phase, there were a total of 69 (78.4%) and 63 (74.1%) subjects in the tofacitinib and placebo groups, respectively, that used DMARD, and/or corticosteroid concomitant medications.

Of these, csDMARDs (MTX) were used concomitantly by 58 (65.9%) subjects in the tofacitinib group and 58 (68.2%) subjects in the placebo group. Corticosteroids were used concomitantly by a numerically higher number of patients in the tofacitinib 5 mg BID group 35 (40%) compared to subjects in the placebo group 23 (27%) subjects. Folate was used concomitantly by 57 (64.8%) subjects in the tofacitinib group and 57 (67.1%) subjects in the placebo group. In general, concomitant medication use was similar between the tofacitinib and placebo groups.

Rescue medications were administered as specified by the protocol.

Protocol Specified Control of Type-I Error: The primary and secondary endpoints were tested sequentially as follows:

1. Occurrence of disease flare
2. JIA ACR 50
3. JIA ACR 30
4. JIA ACR 70
5. CHAQ - DI

Efficacy Results – Primary Endpoint

- **Protocol Specifed Primary Analysis**
  - Primary Estimand:
    1. Population: DBJAS
    2. Variable: Occurrence of disease flare by week 44

3. Handling of intercurrent events: Subjects who discontinued treatment were considered as having occurrence of disease. The exception were subjects who met JIA ACR defined clinical remission criteria (i.e., inactive disease for at least 24 weeks) at the time of discontinuation, who were then considered as not having occurrence of disease.

4. Population-level summary for the variable: Difference in proportion of subjects experiencing occurrence of disease flare between tofacitinib and placebo

Reviewer's comment: It appears that a composite variable strategy was used to address intercurrent events due to discontinued treatment. The intercurrent event is considered in itself to be informative about the subjects outcome for the primary endpoint and is therefore incorporated into the definition of the variable.

- Primary Analysis Model: Normal approximation (Wald) to the difference in binomial proportions.

- **Data capture for the primary endpoint**

Tables 19 and 20 below summarize data capture for the primary endpoint in the DBJAS and DBFAS, respectively. We see the occurrence of disease is a composite of either known event or imputed event due to pre-mature treatment discontinuation. There were 10 and 11 subjects who discontinued treatment and withdrew from the study early and were considered as having occurrence of disease in the DBJAS and DBFAS, respectively.

Table 21: Data Capture for the Primary Endpoint for Study A3921104: DBJAS

	Tofacitinib (N=72)	**Placebo (N=70)**	**Total (N=142)**
No Occurrence of Disease [n(%)]	51 (70.83)	33 (47.14)	84 (59.15)
Occurrence of Disease [n(%)]	21 (29.17)	37 (52.86)	58 (40.85)
Known[n]	15	33	48
Imputed [n]	6	4	10

Statistical Reviewer's Analysis

Table 22: Data Capture for the Primary Endpoint for Study A3921104: DBFAS

	Tofacitinib (N=88)	Placebo (N=85)	Total (N=173)
No Occurrence of Disease [n(%)]	61 (69.32)	38 (44.71)	99 (57.23)
Occurrence of Disease [n(%)]	27 (30.68)	47 (55.29)	74 (42.77)
Known[n]	21	42	63
Imputed [n]	6	5	11

Statistical Reviewer's Analysis

- **Results and Conclusions**

Table 21 below displays the results of the Applicant's pre-specified analysis of the primary endpoint in the DBJAS. The difference in the proportion of subjects experiencing occurrence of disease is -23.7%. Since the upper bound of the 95% confidence interval is -8.0%, we conclude that tofacitinib is effective in reducing the rate of disease compared to placebo among subjects who had previously initiated tofacitinib for 18 weeks and had at least a JIA ACR 30 response.

Table 23: Applicant's Analysis Results on the Occurrence of Disease Flare: DBJAS

	Occurrence of Disease		Tofacitinib - Placebo		
Treatment	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	72	21 (29.17%)	-23.69%	(-39.41%, -7.97%)	0.0031
Placebo	70	37 (52.86%)			

Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: CSR (Page 111) and Statistical Reviewer's Analysis

Table 22 below displays the results using the same methods of analysis using the DBFAS. The difference in the proportion of subjects experiencing occurrence of disease is -24.6%, and the upper bound of the 95% confidence interval is -10.3%. Hence, the conclusion remains the same as in the DBJAS.

Table 24: Analysis Results on the Occurrence of Disease Flare: DBFAS

	Occurrence of Disease		Tofacitinib - Placebo		
Treatment	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	88	27 (30.68%)	-24.61%	(-38.91%, -10.31%)	0.0007
Placebo	85	47 (55.29%)			

Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: Statistical Reviewer's Analysis

- **Sensitivity Analysis**

Due to considering subjects who discontinued treatment before occurrence of disease as then having occurrence of disease, as a sensitivity analysis, we consider a worst case scenario, where only subjects on tofacitinib with unknown status are considered as having occurrence of disease flare and placebo subjects with unknown status are not. Hence, from Tables 19 and 20 above, we consider the 4 placebo subjects in the DBJAS with unknown status and 5 placebo subjects with unknown status in the DBFAS as not having experienced occurrence of disease flare. Tables 23 and 24 below display the results. In both analyses, the results are still significant. Thus, even under a worst case scenario, the conclusion concerning the treatment effect of tofacitinib in the primary endpoint do not change and we remain confident that tofacitinib reduces the rate of occurrence of disease.

Table 25: Analysis Results on the Occurrence of Disease Flare (Worst Case Scenario): DBJAS

	Occurrence of Disease		Tofacitinib - Placebo		
Treatment	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	72	21 (29.17%)	-17.98%	(-33.69%, -2.26%)	0.025
Placebo	70	33 (47.14%)			

Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: Statistical Reviewer's Analysis

Table 26: Analysis Results on the Occurrence of Disease Flare (Worst Case Scenario): DBFAS

	Occurrence of Disease		Tofacitinib - Placebo		
Treatment	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	88	27 (30.68%)	-18.73%	(-33.08%, -4.38%)	0.0105
Placebo	85	42 (49.41%)			

Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: Statistical Reviewer's Analysis

- **Supplementary Analyses using Extension Data**

As stated above, subjects who discontinued therapy and subsequently withdrew from the study entered into a long-term open label extension study, where all subjects received tofacitinib. Of the 58 subjects in the DBJAS who withdrew from the study, 55 continued into the long term extension study. Likewise, of the 74 subjects in DBFAS who withdrew from the study, 71 continued into the long term extension study. Therefore, we can utilize the available data from the extension study to capture "equivalent" week 44 data. However, we note that a limitation of using data from the extension study is that data was collected at baseline and at month 1, 3, and 6. Therefore, to capture "equivalent" week 44 data, the analysis window needed to be enlarged from the pre-specified window of the main study.

Tables 25 and 26 below display the results of the primary endpoint using the extension study data in DBJAS and DBFAS. We see that the results and conclusions are consistent with the results in Tables 21-24.

Table 27: Analysis Results on the Occurrence of Disease Flare using Extension Data: DBJAS

	Occurrence of Disease		Tofacitinib - Placebo		
Treatment	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	72	17 (23.61%)	-24.96%	(-40.24%, -9.69%)	0.0014
Placebo	70	34 (48.57%)			

Subjects with missing data are considered as having occurrence of disease
Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: Summary of Clinical Efficacy (Page 53) and Statistical Reviewer's Analysis

Table 28: Analysis Results on the Occurrence of Disease Flare using Extension Data: DBFAS

	Occurrence of Disease		Tofacitinib - Placebo		
Treatment	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	88	23 (26.14%)	-25.63%	(-39.67%, -11.59%)	0.0003
Placebo	85	44 (51.76%)			

Subjects with missing data are considered as having occurrence of disease
Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: Response to July 1, 2020 Information Request (Page 1) and Statistical Reviewer's Analysis

Efficacy Results – Secondary Endpoints

- JIA ACR 50-30-70

Tables 27 and 28 below describe the disposition of data capture for the secondary endpoints of JIA ACR for the DBJAS and DBFAS during study A3921104. The amount of missing data is large (~40 and 43%), for which the primary reason is due to occurrence of disease flare. This is explained because it was pre-planned that once a subject experiences disease flare, they would discontinue from the main study and enroll into the long-term extension study.

Table 29: Data Capture for ACR at Week 44 for Study A3921104: DBJAS

	Tofacitinib (N=72)	Placebo (N=70)	Total (N=142)
# Subjects with captured ACR [n(%)]	51 (70.83)	33 (47.14)	84 (59.15)
# Subjects with missing ACR [n(%)]	21 (29.17)	37 (52.86)	58 (40.85)
Insufficient Clinical Response [n]	16	34	50
Occurrence of Disease [n]	15	33	48
No Occurrence of Disease [n]	1	1	2
Adverse Event [n]	2	2	4
Other [n]	3	1	4

Source: Statistical Reviewer's Analysis

Table 30: Data Capture for ACR at Week 44 for Study A3921104: DBFAS

	Tofacitinib (N=88)	Placebo (N=85)	Total (N=173)
# Subjects with captured ACR [n(%)]	61 (69.32)	38 (44.71)	99 (57.23)
# Subjects with missing ACR [n(%)]	27 (30.68)	47 (55.29)	74 (42.77)
Insufficient Clinical Response [n]	22	44	66
Occurrence of Disease [n]	21	42	63
No Occurrence of Disease [n]	1	2	3
Adverse Event [n]	2	2	4
Other [n]	3	1	4

Source: Statistical Reviewer's Analysis

Tables 29 and 30 below are the results of the Applicant's pre-specified analyses for the DBJAS and DBFAS. We see that tofacitinib significantly improves the response rate for ACR 50-30-70 in both the DBJAS and DBFAS, however, subjects with missing ACR data at week 44 were considered to be non-responders.

Table 31: Applicant's Analysis Results on ACR 50-30-70 at Week 44: DBJAS

			Response	Tofacitinib - Placebo		
ACR Response	**Treatment**	**N**	**n(%)**	**Diff**	**95% CI**	**P-value**
ACR 50	Tofacitinib	72	48 (66.67)	19.52%	(3.55%, 35.50%)	0.0166
	Placebo	70	33 (47.14)			
ACR 30	Tofacitinib	72	51 (70.83)	23.69%	(7.97%, 39.41%)	0.0031
	Placebo	70	33 (47.14)			
ACR 70	Tofacitinib	72	39 (54.17)	17.02%	(0.88%, 33.17%)	0.0387
	Placebo	70	26 (37.14)			

Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: CSR (Page 114) and Statistical Reviewer's Analysis

Table 32: Analysis Results on ACR 50-30-70 at Week 44: DBFAS

			Response	Tofacitinib - Placebo		
ACR Response	**Treatment**	**N**	**n(%)**	**Diff**	**95% CI**	**P-value**
ACR 50	Tofacitinib	88	58 (65.91)	22.38%	(7.92%, 36.84%)	0.0024
	Placebo	85	37 (43.53)			
ACR 30	Tofacitinib	88	61 (69.32)	25.79%	(11.51%, 40.07%)	0.004
	Placebo	85	37 (43.53)			
ACR 70	Tofacitinib	88	47 (53.41)	19.29%	(4.79%, 33.79%)	0.0091
	Placebo	85	29 (34.12)			

Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: Statistical Reviewer's Analysis

From Tables 27 and 28 above, there are 58 and 74 subjects with missing week 44 ACR data in the DBJAS and DBFAS, respectively, and that the primary reason is due to occurrence of disease. So to consider these subjects to be non-responders is not appropriate because it primarily assumes that subjects who experience disease flare cannot attain ACR response at a future time. This assumption was not supported by the data and shown to be false, since analyses utilizing data from the extension study demonstrated that subjects (at least who were randomized to tofacitinib) who discontinued therapy due to experience of disease flare did attain ACR response at week 44 (see the supplementary analysis section below).

- **Supplementary Analysis using Extension Data**

Tables 31 and 32 display the ACR results utilizing the extension data for the DBJAS and DBFAS. We note that occurrence of disease (the primary endpoint) and re-initiation of tofacitinib are considered intercurrent events.

Table 33: Analysis Results on ACR 50-30-70 at Week 44 using Extension Data: DBJAS

			Response	Tofacitinib - Placebo		
ACR Response	**Treatment**	**N**	**n(%)**	**Diff**	**95% CI**	**P-value**
ACR 50	Tofacitinib	72	63 (87.50)	-1.07%	(-11.74%, 9.60%)	0.844
	Placebo	70	62 (88.57)			
ACR 30	Tofacitinib	72	67 (93.06)	-1.23%	(-9.23%, 6.77%)	0.7632
	Placebo	70	66 (94.29)			
ACR 70	Tofacitinib	72	51 (70.83)	2.26%	(-12.85%, 17.38%)	0.7693
	Placebo	70	48 (68.57)			

Subjects with missing data are considered non-responders
Source: Summary of Clinical Efficacy (Page 56) and Statistical Reviewer's Analysis

Table 34: Analysis Results on ACR 50-30-70 at Week 44 using Extension Data: DBFAS

			Response	Tofacitinib - Placebo		
ACR Response	**Treatment**	**N**	**n(%)**	**Diff**	**95% CI**	**P-value**
ACR 50	Tofacitinib	88	77 (87.50)	-0.74%	(-10.46%, 8.99%)	0.8822
	Placebo	85	75 (88.24)			
ACR 30	Tofacitinib	88	82 (93.18)	0.24%	(-7.33%, 7.82%)	0.9504
	Placebo	85	79 (92.94)			
ACR 70	Tofacitinib	88	62 (70.45)	4.57%	(-9.30%, 18.45%)	0.5183
	Placebo	85	56 (65.88)			

Subjects with missing data are considered non-responders
Source: Response to July 1, 2020 Information Request (Page 2) and Statistical Reviewer's Analysis

Tables 33 and 34 below display the confirmed ACR responders at week 44 between the main and extension studies in the DBJAS and DBFAS. We see that a large portion of subjects who were randomized to tofacitinib who withdrew from the main study early still attained an ACR response. Therefore, we conclude that the the Applicant's method of considering subjects who discontinued therapy as non-responders is inappropriate.

Table 35: Confirmed ACR Responders at Week 44: DBJAS

ACR Response	Treatment	Main n/N_1	Extension n/N_2	Missing n/N_3	Total n/N
ACR 50	**Tofacitinib**	48/51	15/19	0/2	63/72
	Placebo	33/33	29/36	0/1	62/70
ACR 30	**Tofacitinib**	51/51	16/19	0/2	67/72
	Placebo	33/33	33/36	0/1	66/70
ACR 70	**Tofacitinib**	39/51	12/19	0/2	51/72
	Placebo	26/33	22/36	0/1	48/70

Source: Statistical Reviewer's Analysis
N_1: Number of subjects who completed Study A3921104
N_2: Number of subjects who discontinued Study A3921104 early and continued into Study A3921145
N_3: Number of subjects who discontinued Study A3921104 and did not continue into Study A3921145

Table 36: Confirmed ACR Responders at Week 44: DBFAS

ACR Response	Treatment	Main n/N_1	Extension n/N_2	Missing n/N_3	Total n/N
ACR 50	**Tofacitinib**	58/61	19/25	0/2	77/88
	Placebo	37/38	38/46	0/1	75/85
ACR 30	**Tofacitinib**	61/61	21/25	0/2	82/88
	Placebo	37/38	42/46	0/1	79/85
ACR 70	**Tofacitinib**	47/61	15/25	0/2	62/88
	Placebo	29/38	27/46	0/1	56/85

Source: Statistical Reviewer's Analysis
N_1: Number of subjects who completed Study A3921104
N_2: Number of subjects who discontinued Study A3921104 early and continued into Study A3921145
N_3: Number of subjects who discontinued Study A3921104 and did not continue into Study A3921145

- **CHAQ-DI**

Table 35 below display the results for the change in CHAQ-DI from double-blind baseline. The Applicant's pre-specified analysis in the DBJAS is significant, however, similar to the ACR endpoint, due to study withdrawal after occurrence of disease, there is a large amount of missing data. The analysis model used was the mixed model repeated measurement (MMRM),

which assumes data that is missing to be missing at random, i.e., it assumes that measurements for subjects with missing data are similar to those on the same arm with captured data. Hence, since the primary reason of study withdrawal was due to occurrence of disease, missing CHAQ-DI scores for subjects who experienced occurrence of disease are modelled after subjects who did not experience occurrence of disease, which may not be an appropriate assumption.

Table 37: Applicant's Analysis Results for Change in CHAQ-DI at Week 44 from Double-Blind Baseline: DBJAS

	Tofacitinib	Placebo
N	72	70
Change from baseline		
LS Mean (SE)	-0.09 (0.04)	0.03 (0.04)
Comparison to Placebo		
LS Mean (SE)	-0.12 (0.05)	
95% C.I.	(-0.22, -0.01)	
P-value	0.0292	

Estimates is based on Mixed Model for Repeated Measurements (MMRM) with double-blind baseline CHAQ-DI scores as a covariate and treatment, visit, JIA category, open-label C-reactive protein and treatment-by-visit interaction as fixed effects
Source: CSR (Page 118) and Statistical Reviewer's Analysis

Table 36 below displays the results in the DBFAS. Here, we see that the results are not significant since the p-value > 0.05. Therefore, though the pre-specified analysis in the pre-specified population (DBJAS) attained a significant result, we are not confident that tofacitinib reduces CHAQ-DI from double-blind baseline.

Table 38: Analysis Results for Change in CHAQ-DI at Week 44 from Double-Blind Baseline: DBFAS

	Tofacitinib	Placebo
N	88	85
Change from baseline		
LS Mean (SE)	-0.06 (0.04)	0.04 (0.04)
Comparison to Placebo		
LS Mean (SE)	-0.10 (0.05)	
95% C.I.	(-0.20, 0.01)	
P-value	0.063	

Estimates is based on Mixed Model for Repeated Measurements (MMRM) with double-blind baseline CHAQ-DI scores as a covariate and treatment, visit, JIA category, open-label C-reactive protein and treatment-by-visit interaction as fixed effects
Source: Statistical Reviewer's Analysis

- **Supplementary Analysis using Extension Data**

Similar to occurrence of disease and ACR, we utilized the extension data. Tables 37 and 38 display the results.

Table 39: Results for change in CHAQ-DI at Week 44 from Double Blind Baseline using Extension Data: DBJAS

	Tofacitinib	Placebo
N	72	70
Change from baseline		
LS Mean (SE)	-0.07 (0.03)	-0.02 (0.04)
Comparison to Placebo		
LS Mean (SE)	-0.04 (0.04)	
95% C.I.	(-0.13, 0.04)	
P-value	0.3054	

Estimates is based on Mixed Model for Repeated Measurements (MMRM) with double-blind baseline CHAQ-DI scores as a covariate and treatment, visit, JIA category, open-label C-reactive protein and treatment-by-visit interaction as fixed effects
Source: Response to July 1, 2020 Information Request (Page 3) and Statistical Reviewer's Analysis

Table 40: Results for change in CHAQ-DI at Week 44 from Double Blind Baseline using Extension Data: DBFAS

	Tofacitinib	Placebo
N	88	85
Change from baseline		
LS Mean (SE)	-0.06 (0.03)	-0.04 (0.03)
Comparison to Placebo		
LS Mean (SE)	-0.02 (0.04)	
95% C.I.	(-0.10, 0.06)	
P-value	0.5736	

Estimates is based on Mixed Model for Repeated Measurements (MMRM) with double-blind baseline CHAQ-DI scores as a covariate and treatment, visit, JIA category, open-label C-reactive protein and treatment-by-visit interaction as fixed effects
Source: Response to July 1, 2020 Information Request (Page 3) and Statistical Reviewer's Analysis

Subgroup Analyses

This section summarizes results from the analyses of the primary endpoint within subgroup

levels. The subgroup levels explored are:

- Sex (Male; Female)
- Age (<12 ; ≥12)
- Race (White; Non-White)
- Region (North America; Not North America)

Tables 39-42 display the results of the subgroup analyses for sex, age, race and region in the DBFAS. There are significant treatment effects among females, among subjects less than 12 and at least 12, among whites, and among subjects who are outside of North America. Non-significant treatment effects are likely due to small sample sizes.

Table 41: Subgroup Analysis of the Primary Endpoint: Sex: DBFAS

	Occurrence of Disease		Tofacitinib - Placebo[a]		
Males	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	22	8 (36.36%)	-16.02%	(-42.82%, 13.47%)	0.3068
Placebo	21	11 (52.38%)			
	Occurrence of Disease		**Tofacitinib - Placebo**		
Females	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	66	19 (28.79%)	-27.46%	(-43.80%, -11.12%)	0.001
Placebo	64	36 (56.25%)			

a Due to the small sample sizes, to improve coverage probability, the Agresti-Caffo correction of adding 1 response and 1 non-response to tofacitinib and placebo was used
Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: Statistical Reviewer's Analysis

Table 42: Subgroup Analysis of the Primary Endpoint: Age: DBFAS

	Occurrence of Disease		Tofacitinib - Placebo		
<12	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	33	9 (27.27%)	-28.98%	(-51.92%, -6.04%)	0.0133
Placebo	32	18 (56.25%)			
	Occurrence of Disease		**Tofacitinib - Placebo**		
≥12	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	55	18 (32.73%)	-21.99%	(-40.25%, -3.73%)	0.0182
Placebo	53	29 (54.72%)			

Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: Statistical Reviewer's Analysis

Table 43: Subgroup Analysis of the Primary Endpoint: Race: DBFAS

	Occurrence of Disease		Tofacitinib - Placebo		
White	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	76	24 (31.58%)	-22.48%	(-37.91%, -7.04%)	0.0043
Placebo	74	40 (54.05%)			
	Occurrence of Disease		**Tofacitinib - Placebo[a]**		
Non-White	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	12	3 (25.00%)	-38.64%	(-68.46%, 2.52%)	0.0686
Placebo	11	7 (63.64%)			

a Due to the small sample sizes, to improve coverage probability, the Agresti-Caffo correction of adding 1 response and 1 non-response to tofacitinib and placebo was used
Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: Statistical Reviewer's Analysis

Table 44: Subgroup Analysis of the Primary Endpoint: Region: DBFAS

	Occurrence of Disease		Tofacitinib - Placebo		
North America	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	31	14 (45.16%)	-10.94%	(-34.12%, 12.25%)	0.3553
Placebo	41	23 (56.10%)			
	Occurrence of Disease		**Tofacitinib - Placebo**		
Not North America	**N**	**n (%)**	**Diff**	**95% CI**	**P-value**
Tofacitinib	57	13 (22.81%)	-31.74%	(-50.04%, -13.43%)	0.0007
Placebo	44	24 (54.55%)			

Confidence intervals and p-values computed using Normal approximation (Wald) to the difference in Binomial proportions
Source: Statistical Reviewer's Analysis

- **Shrinkage Analyses Results**

Shrinkage analyses for sex, age, race, and region was performed. Bayesian hierarchical modeling produces shrinkage estimates of the individual study treatment effects by removing the within study variability. Further, treatment effects are regarded as exchangeable, which allows them to be different but related. Therefore, shrinkage estimates tend to be more precise and provide narrower confidence/credible intervals. For computational purposes, the odds ratio is used rather than difference in proportions. Below is the model used in the analysis for age, sex, race, and region:

$$Y_i = \log OR \sim N(\mu_i, \sigma_i^2), i = 1, 2$$

$$\mu_i \sim N(\mu, \tau^2), i = 1, 2$$

$$\mu \sim \mathrm{N}(0, 32), \quad \tau^{-2} \sim Gamma(0.001, 0.001)$$

We assume that before seeing data, the log odds ratio is 0 (equivalent to the odds ratio is 1) and we further place one-eighth of a response (occurrence of disease) and one-eighth of a non-response (non occurrence of disease) on tofacitinib and placebo. Thus,

$$Var(\log OR) \approx \frac{1}{\frac{1}{8}} + \frac{1}{\frac{1}{8}} + \frac{1}{\frac{1}{8}} + \frac{1}{\frac{1}{8}} = 32$$

Tables 43-46 below are the results of the shrinkage analyses. We note that when analyzing non-whites in isolation, the treatment effect was not significant. However, after performing the shrinkage analyses, we obtain a nominally significant result (Table 45).

Table 45: Shrinkage Analysis: Sex

	Before Shrinkage Estimates		After Shrinkage Estimates	
Males[a]	**Log OR (SE)**	**OR (95% CI)**	**Log OR (SE)**	**OR (95% CI)**
Tofacitinib vs. Placebo	-0.598 (0.593)	0.550; (0.172, 1.760)	-0.867 (0.456)	0.420; (0.186, 1.176)
Females	**Log OR (SE)**	**OR (95% CI)**	**Log OR (SE)**	**OR (95% CI)**
Tofacitinib vs. Placebo	-1.157 (0.371)	0.314; (0.152, 0.650)	-1.056 (0.337)	0.348; (0.179, 0.673)

a Includes additional 1 response and 1 non-response to tofacitinib and placebo
Estimates are unadjusted
Source: Statistical Reviewer's Analysis

Table 46: Shrinkage Analysis: Age

	Before Shrinkage Estimates		After Shrinkage Estimates	
< 12	**Log OR (SE)**	**OR (95% CI)**	**Log OR (SE)**	**OR (95% CI)**
Tofacitinib vs. Placebo	-1.232 (0.529)	0.292; (0.103, 0.822)	-1.097 (0.416)	0.334; (0.142, 0.740)
≥ 12	**Log OR (SE)**	**OR (95% CI)**	**Log OR (SE)**	**OR (95% CI)**
Tofacitinib vs. Placebo	-0.910 (0.398)	0.403; (0.184, 0.879)	-0.990 (0.349)	0.372; (0.192, 0.745)

Estimates are unadjusted
Source: Statistical Reviewer's Analysis

Table 47: Shrinkage Analysis: Race

	Before Shrinkage Estimates		After Shrinkage Estimates	
White	**Log OR (SE)**	**OR (95% CI)**	**Log OR (SE)**	**OR (95% CI)**
Tofacitinib vs. Placebo	-0.936 (0.340)	0.392; (0.202, 0.763)	-0.975 (0.321)	0.377; (0.202, 0.710)
Non-White[a]	**Log OR (SE)**	**OR (95% CI)**	**Log OR (SE)**	**OR (95% CI)**
Tofacitinib vs. Placebo	-1.386 (0.822)	0.250; (0.050, 1.251)	-1.100 (0.521)	0.333; (0.1, 0.850)

a Includes additional 1 response and 1 non-response to tofacitinib and placebo
Estimates are unadjusted
Source: Statistical Reviewer's Analysis

Table 48: Shrinkage Analysis: Region

	Before Shrinkage Estimates		After Shrinkage Estimates	
North America	**Log OR (SE)**	**OR (95% CI)**	**Log OR (SE)**	**OR (95% CI)**
Tofacitinib vs. Placebo	-0.439 (0.479)	0.645; (0.252, 1.647)	-0.735 (0.441)	0.479; (0.220, 1.242)
Not North America	**Log OR (SE)**	**OR (95% CI)**	**Log OR (SE)**	**OR (95% CI)**
Tofacitinib vs. Placebo	-1.402 (0.437)	0.246; (0.104, 0.580)	-1.157 (0.404)	0.314; (0.136, 0.660)

Estimates are unadjusted
Source: Statistical Reviewer's Analysis

Efficacy Results and Conclusions

- The primary analysis of the primary endpoint demonstrated the superiority of tofacitinib to placebo in the study population with no concern of missing data.

- The secondary endpoint of ACR responses supported the superiority of tofacitinib to placebo with the Applicant's pre-specified analyses; however, there is a concern in the interpretation of the analyses results of the secondary endpoints, due to the large number of subjects who were considered non-responders. Since subjects randomized to placebo who withdrew early from the main study re-initiated tofacitinib, a direct comparison to placebo, (b) (4) cannot be made.

- In the analysis of CHAQ-DI from double-blind baseline, while the p-value of the Applicant's pre-specified analysis in the DBJAS is 0.03, the p-value of the analysis in the DBFAS is 0.06. Importantly, the results rely on the strong missing at random assumption. In addition, since subjects randomized to placebo who withdrew early from the main study re-initiated tofacitinib, a direct comparison to placebo, (b) (4) cannot be made.

- Taking these points into consideration, the Division of Biometrics II recommends inclusion of only the primary endpoint in the product labeling. Results based off the DBFAS would be preferred for product labelling since it should provide a more precise estimate of the treatment effect. However, since the product is not indicated for subjects with ESA and jPsA, the decision should also be made based on clinical considerations.

  In regard to ACR response rates, there is difficulty in interpreting the pre-specified results due to the large amount of subjects who discontinued placebo and re-initiated tofacitinib. (b) (4)

(b) (4)

Dose/Dose Response

N / A

Durability of Response

N / A

Persistence of Effect

N / A

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

N / A

Additional Analyses Conducted on the Individual Trial

See section on subgroup and shrinkage analysis.

Integrated Review of Effectiveness

N / A

8.1.3. Assessment of Efficacy Across Trials

N / A

8.1.4. Integrated Assessment of Effectiveness

Efficacy of Xeljanz tablets / Xeljanz Oral Solution in pediatric patients 2 to 17 years of age with active pcJIA is supported by evidence from adequate and well-controlled trials in adult RA and the results of Study A3921104 (as described in Section 8.1.2 above).

8.2. Review of Safety

8.2.1. Safety Review Approach

Table 50 provides an overview of the safety populations used for the analysis of safety of tofacitinib in the pcJIA program.

Table 49. Safety Analysis Populations in the Tofacitinib pcJIA program

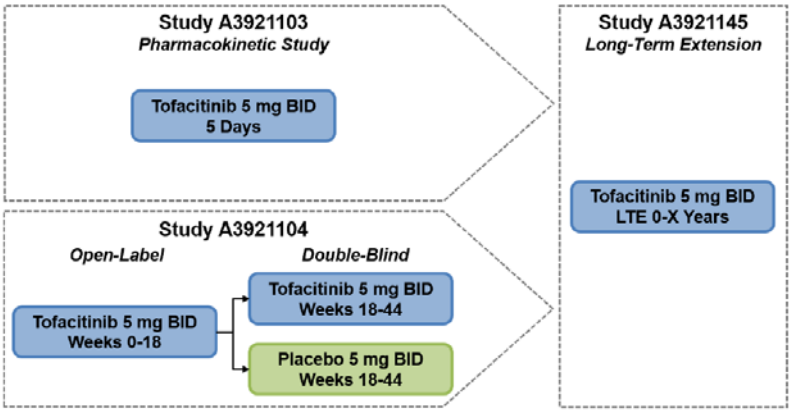
Safety analysis Population	Description	Purpose of Safety Analysis
Study A3921104 Population		
Open-label, Run-in phase	Subjects enrolled, received at least one dose of tofacitinib in open-label, run-in phase	Assess safety after initial treatment
Double-blind phase	Subjects received at least one dose of tofacitinib or placebo in double-blind phase, reported under received treatment	Compare safety of tofacitinib 5 mg BID with placebo
Entire Study Period (OL + DB)	Subjects enrolled and received at least one dose of tofacitinib in Study A3921104. The period of exposure to tofacitinib in the open-label Run-in phase and in the double-blind phase was included. The placebo exposure period for the subjects in the placebo group was excluded.	Assess safety of exposure to tofacitinib in the setting of the entire study
Integrated Safety Analysis		
Integrated Safety Analysis Population (ISAP)	All subjects that received at least 1 dose of tofacitinib in any of the 3 studies (A3921103, A3921104, and A3921145).	All the integrated safety analyses are based on the ISAP, except otherwise indicated
Source: Reviewer; Summary of Clinical Safety, Section 2.7.4		

The safety assessment of tofacitinib in patients with pcJIA is primarily based on safety findings from study A3921104 (also referred to as study 1104 in this review) which enrolled 225 patients. As outlined above, study 1104 is a 44-week, two-part study (consisting of an 18-week, open-label, run-in phase, followed by a 26-week double-blind, placebo-controlled, randomized withdrawal phase) in patients 2 years to 17 years of age with pcJIA. Safety for this study is presented as adverse events occurring in the double-blind phase where tofacitinib treatment is

compared to placebo, and over the entire study period which includes both the open-label phase and double-blind phase.

In addition to Study 1104, an integrated safety analysis was used to pool safety data from studies 1003, 1104 and 1145 to allow for longer-term evaluation of adverse events in JIA patients treated with tofacitinib 5 mg BID, see Figure 2. A total of 251 subjects from the 3 studies were included in the integrated safety analysis population (ISAP). Pooling of studies 1103 and 1104 was considered appropriate because of their homogeneous subject populations (i.e., pediatric subjects with JIA aged from 2 to 17 years) and treatment dosing regimen.

Figure 2. Pooled JIA Safety Studies for Integrated Safety Assessment of Tofacitinib 5mg BID



Source: Summary of Clinical Safety, Figure 1.

In the integrated analysis, exposure data were evaluated from the first dosing in the qualifying studies 1103 and 1104 through the end of tofacitinib use, which occurred either in the qualifying studies or the LTE study 1145, or until the cutoff date (June 4, 2019) in study 1145 (if subjects were still continuing in the LTE phase). Due to the randomized withdrawal design of the study, some patients had an interruption of tofacitinib regimen while randomized to placebo withdrawal. For subjects randomized to placebo in study 1104, the double-blind phase placebo exposure, and events occurring therein, were excluded from the pooled analysis, except for the first 28 days of placebo exposure which were associated with and included in the risk period of tofacitinib received in the open-label phase of study 1104. Likewise, the placebo subjects' tofacitinib exposure from the qualifying open-label phase and the LTE as well as the events occurring during this time were included in the integrated safety dataset.

The 90 Day Safety Update contained clinical safety data on cumulative safety from the open-label extension in study 1145 up to January 21, 2020.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 225 subjects were exposed to tofacitinib 5 mg BID during study 1104. Table 50

provides details of exposure during the open-label run-in phase, the double-blind phase and over the entire study

Table 50. Study 1104 - Tofacitinib Exposure in Open-label, Double-blind and Total Study Periods

	OLFAS	DBSAS		Total (Entire)
	Tofacitinib 5mg BID	Tofacitinib 5mg BID	Placebo	Tofacitinib 5mg BID
Duration of Treatment (Days)[1]				
n	225	88	85	225
Mean	115.16	143.68	114.36	171.36
Std Dev	126.00	180.00	68.53	127.00
Median	27.56	61.60	129	91.64
Range (min,max)	(4.00, 153.00)	(14.00, 202.00)	(8.00, 193.00)	(4.00, 325.00)
Subject-Year	70.94	34.62	26.61	105.56
Category (Days)				
<28	5 (2.2)	8 (9.1)	11 (12.9)	5 (2.2)
28-56	14 (6.2)	7 (8.0)	17 (20.0)	14 (6.2)
57-84	12 (5.3)	4 (4.5)	7 (8.2)	12 (5.3)
85-112	6 (2.7)	4 (4.5)	6 (7.1)	5 (2.2)
113-140	186 (82.7)	4 (4.5)	2 (2.40)	101 (44.9)
141-168	2 (0.9)	2 (2.3)	4 (4.7)	13 (5.8)
>168	0	59 (67.0)	38 (44.7)	75 (33.3)

Source: NDA 203214, Summary of Clinical Safety, Table 6.
OLFAS: open-label full analysis set (18-weeks); DBSAS: double-blind safety analysis set (26-weeks); Subject-Year = Patient Year (PY); The total subject-year is the sum of the durations of treatment (actual tofacitinib dosing days) across all the subjects divided by 365.25

A total of 251 subjects were exposed to the tofacitinib 5 mg BID dose in the JIA ISAP safety database. Among the exposed subjects in the ISAP, the overall exposure was 351 PY and the mean duration of exposure was 511 days (median duration 485 days). Table 51 provides the exposure duration for the integrated safety population.

Table 51. Tofacitinib Exposure - Integrated Safety Analysis Population (ISAP)

	Tofacitinib 5 mg BID (N=251)
Duration	
<=1 Week	1 (0.4)
>1 week - 1 month	2 (0.8)
>1 month - 2 months	7 (2.8)
>2 months - 3 months	6 (2.4)
>3 months - 6 months	20 (8.0)
>6 months - 12 months	42 (16.7)
>12 months - 18 months	63 (25.1)
>18 months - 24 months	53 (21.1)
>24 months - 30 months	33 (13.1)
>30 months - 36 months	10 (4.0)
>36 months - 42 months	0
>42 months - 48 months	5 (2.0)
>48 months	9 (3.6)
Mean Duration (Days)	511.36
Median Duration (Days)	485
Range (Days)	(4, 1987)
Total Drug Exposure (PY)	351.39

Source: NDA 203214, Summary of Clinical Safety, Table 7, Section 2.7.4.1.2.

Adequacy of the safety database

Baseline demographics and disease activity suggest that the study enrolled patients representative of those seen in clinical practice with JIA including a proportion of patients who were on concomitant background DMARD therapy e.g. methotrexate, corticosteroids, and NSAIDs. Consequently, this study allows for a reasonable assessment of tofacitinib as it is likely to be used in clinical practice.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

None.

Categorization of Adverse Events

Adverse events were coded by using the MedDRA version 22.0. SAEs were defined as any event

that resulted in death, was life-threatening, resulted in a persistent or significant disability or incapacity, required in-patient hospitalization or prolongation of existing hospitalization, or resulted in a congenital anomaly or birth defect. In addition, other important medical events were considered SAEs if they jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed in this definition.

Routine Clinical Tests

The type and frequency of the routine clinical testing in the confirmatory study 1104 and the supporting extension study 1145 were generally acceptable.

8.2.4. Safety Results

Summary of Safety

The safety of tofacitinib is well-characterized in numerous clinical studies across various indications, including in adult patients with RA. In this pcJIA clinical program, no new safety signals were identified in the pediatric patients compared to the known adverse event profile of Xeljanz in adult patients.[1] The safety profile of using tofacitinib in children with pcJIA was consistent with the known safety profile of tofacitinib. See Section 8.2.12 Integrated Assessment of Safety and Safety Summary.

8.2.4.1. Adverse Events

An overview of adverse events (AEs) in study 1104 and in the integrated safety analysis population is presented in Table 52 below.

[1] FDA-approved tofacitinib labeling

Table 52. Overview of Adverse Events in Study 1104 and in Integrated Safety Analysis (ISAP)

	Study 1104			Integrated Safety Analysis (ISAP)
Event Type	Entire Tofa exposure period Tofa 5 mg BID N=225	Double-blind phase		Tofa 5 mg BID N=251
		Tofa 5 BID (N=88)	PBO (N=85)	
Patients with ≥1 TEAE	176(78)	68(77)	63(74)	227(90)
Patients with ≥1 SAE	8(4)	1(1)	2(2)	24(10)
Discontinuation due to AE	42(19)	16(18)	29(34)	58(23)
Dose reduced or temporary DC due to AE	25(11)	9(10)	8(9)	58(23)
AESI – Herpes Zoster	2	0	0	1
AESI – Serious Infections	3	0	0	6
Deaths	0	0	0	0

Source: Reviewer; Summary of Clinical Safety Section 2.7.4.2, CSRA3921104
AESI: Adverse Events of Special Interest; DC: discontinuation; TEAE: treatment emergent adverse event; SAE: serious adverse event

In study 1104, 176 (78%) subjects exposed to tofacitinib 5 mg BID experienced 554 TEAEs, with SAEs reported for 8 (4%) subjects receiving tofacitinib. Most TEAEs were mild to moderate in severity, and severe adverse events were reported for 5 (2%) subjects. In the open-label, run-in phase , there were 411 TEAEs experienced by 153 (68.0%) subject; with SAEs reported for 7 (3.1%) subjects. In the double-blind phase, the rates of AEs were similar between tofacitinib 5 mg BID and placebo, with 160 and 166 TEAEs experienced by 68 (77%) and 63 (74%) subjects, respectively. There was 1 case of SAE in the tofacitinib group compared to 2 cases to SAEs in the PBO group.

During the entire tofacitinib exposure period for study 1104, the most common AEs that led to discontinuation were related to disease progression. The proportion of subjects who discontinued due to an AE was higher in the placebo (29 [34%]) compared to tofacitinib 5 mg BID (16 [18%]). Among the selected adverse events of special interest for tofacitinib, herpes zoster (n=2) and serious infections (n=3) were reported in the open-label portion of study 1104. There were no other AESI reported for study 1104.

In the integrated safety analysis population (ISAP), 227 (90%) subjects experienced 1132 TEAEs, with SAEs reported for 23 (9%) of subjects in the tofacitinib pcJIA clinical program. Most AEs were of mild to moderate severity, and sever AEs were reported for 15 (6%) of pcJIA patients. As in study 1104, the most common AEs that led to treatment discontinuation in the ISAP were also related to disease progression. Among the AESI, herpes zoster and serious infections were also the only AESI reported in ISAP.

Details of the safety results are discussed below.

8.2.4.1.1. Deaths

There were no deaths reported in the tofacitinib pcJIA clinical program, including the pivotal study 1104, LTE study 1145 and the PK study 1103.

8.2.4.1.2. Serious Adverse Events

Of the total 10 SAEs in study 1104, 7 SAEs were reported during the open-label period, and 3 during the double-blind phase. All SAEs were reported in 1 subject each. Three subjects were hospitalized for serious infections during open-label treatment with tofacitinib: 1 subject with pneumonia, 1 subject with appendicitis and 1 subject with a history of craniosynostosis repair was hospitalized for epidural empyema, sinusitis and subperiosteal abscess. Other SAEs included Crohn's disease (n=1), diarrhea and vomiting (n=1), JIA (n=1), and condition aggravated under SOC of general disorders and administration site conditions (n=1).

In the double-blind phase, 1 SAE of pilonidal cyst was reported by 1 subject in the tofacitinib 5 mg BID group and a total of 2 SAEs were reported by 2 subjects in the placebo group: 1 case of appendicitis and intussusception in the same patient and 1 case of JIA.

In the integrated safety analysis population, serious adverse events were reported in 24 patients (9.6%), corresponding to an incidence rate of 6.18 (3.87, 9.36) subjects with SAEs/100 PYs. **Table 53** presents the SAEs in the pcJIA clinical program. Most common SAEs were reported under the SOC of infections and infections occurring in 9 patients (3.6%) followed by musculoskeletal disorders, reported in 5 patients (2%). SAEs under the Psychiatric disorders SOC were reported for 3 patients (1.2%) including 1 case each of suicidal ideation, suicide attempt and homicidal ideation. AEs related to suicidal ideation are discussed further under the section of significant AEs and Section 10 Pediatrics

Table 53. Serious Adverse Events - ISAP

Number (%) of Patients with SAEs: by SOC and PT	Tofacitinib 5 mg twice daily – ISAP (N=251) N (%)
Total Number of Subjects with Serious Adverse Events	24 (9.6)
Gastrointestinal disorders	3 (1.2)
Abdominal pain	1 (0.4)
Crohn's disease	1 (0.4)
Diarrhea	1 (0.4)
Vomiting	1 (0.4)
General disorders and administration site conditions	2 (0.8)
Condition aggravated	1 (0.4)
Disease progression	1 (0.4)

Infections and infestations	9 (3.6)
Abscess limb	1 (0.4)
Appendicitis	1 (0.4)
Epidural empyema	1 (0.4)
Herpes zoster	1 (0.4)
Influenza	1 (0.4)
Pilonidal cyst	1 (0.4)
Pneumonia	1 (0.4)
Pyelonephritis acute	1 (0.4)
Sinusitis	1 (0.4)
Subperiosteal abscess	1 (0.4)
Urinary tract infection	1 (0.4)
Injury, poisoning and procedural complications	1(0.4)
Forearm fracture	1 (0.4)
Musculoskeletal and connective tissue disorders	5 (2.0)
Joint effusion	1 (0.4)
Juvenile idiopathic arthritis	3 (1.2)
Muscle spasms	1 (0.4)
Nervous system disorders	2 (0.8)
Headache	1 (0.4)
Migraine	1 (0.4)
Psychiatric disorders	3 (1.2)
Major depression	1 (0.4)
Suicidal ideation	1 (0.4)
Suicide attempt	1 (0.4)
Homicidal ideation	1 (0.4)
Source: Reviewer; Summary of clinical safety, Tables 22, 23; 3 month safety update Section 1.2 For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.	

In the 90-day safety update, seven more SAEs were reported in 7 patients since the initial submission. Cumulatively, SAEs were experienced by 31 subjects (12.4%) exposed to tofacitinib in the pcJIA clinical program, corresponding to an incidence rate of 6.64 (4.48, 9.47) subjects with SAE/100 PYs, which is consistent with the initial submission. Five out of the 7 SAEs were related to hospitalizations for infections, including a wound infection, gastritis, appendicitis, peritonsillar abscess and herpes zoster. In addition, 1 subject had a spontaneous abortion which was considered a medically important SAE, and 1 subject was hospitalized due to pyrexia.

8.2.4.1.3. Dropouts and/or Discontinuations Due to Adverse Effects

During the entire tofacitinib exposure period for study 1104, 42 (18.7%) patients discontinued from the study because of an AE. In the open-label, run-in phase, 26 (11.6%) subjects discontinued from the study because of an AE. The most common TEAE by Preferred Term (PT) that led to discontinuation were JIA (6 [2.7%]), Disease Progression (5 [2.2%]), and Condition Aggravated (3 [1.3%])

During the double-blind phase of study 1104, fewer patients in the tofacitinib treatment group discontinued due to an AE compared to the placebo treatment group. There were 16 [18.2%] subjects in the tofacitinib 5 mg BID group and 29 [34.1%] subjects in the placebo group that discontinued the study because of an AE. The most frequently reported PTs for the tofacitinib 5 mg BID and placebo groups were Disease progression (8 [9.1%] and 10 [11.8%] subjects, respectively), and Juvenile idiopathic arthritis (3 [3.4%] and 12 [14.1%] subjects, respectively).

There were 20 (8.9%) subjects with dose reduced or temporarily discontinued because of an AE in the open-label run-in phase. During the double-blind phase, there were 9 (10.2%) subjects in the tofacitinib 5 mg BID group and 8 (9.4%) subjects in the placebo group with dose reduced or temporarily discontinued because of an AE. One case of infection each in the treatment (pilonidal cyst repair (n=1)) and placebo (appendicitis, n=1) treatment groups, respectively, resulted in discontinuation.

In study 1104, any subject who did not have a disease improvement of JIA ACR30 in the open-label phase, or any subject who experienced disease worsening throughout the study had to be discontinued. In many instances, lack of efficacy was recorded as an AE (flare, disease worsening) which helps explain the high rates of discontinuations due to AEs in this study.
.
In the integrated safety analysis population, 58 patients (23.1%) discontinued from the study due to an AE. The most frequently reported AEs by PT leading to discontinuation in the integrated analysis were Disease progression (16 [6.4%]), JIA (13 [5.2%]), and Condition aggravated (8 [3.2%]). Infections resulting in treatment discontinuation were reported in 6 patients (2.4%).

8.2.4.2. Significant Adverse Events

8.2.4.2.1. Adverse Events of Special Interest (AESI)

The following safety signals, AEs of special interest, were selected based on the clinical experience with tofacitinib in adult RA subjects: death, serious infections, opportunistic infections excluding TB, Tuberculosis (TB), Herpes Zoster, thromboembolism, malignancy (excluding NMSC), NMSC (non-melanoma skin cancer), lymphoma, major adverse cardiovascular events (MACE), gastrointestinal perforations, interstitial lung disease (ILD), and macrophage activation syndrome (MAS).

Of the AESI for tofacitinib pcJIA program, serious infections and herpes zoster were the only reported adverse events of special interest (AESI) in the pcJIA program.

8.2.4.2.1.1. Serious Infections

Overall, there were 6 subjects with serious infections in the integrated safety population of the pcJIA program, representing an incidence rate of 1.64 events/100 PY (0.60,3.57). With the 90 day safety update, there were 4 additional cases of serious infections. Cumulatively, there were 10 subjects with serious infections, representing an incidence rate of 2.14 events/100 PY (1.03, 3.94). Of note, one case of serious infection (pilonidal cyst requiring hospitalization/wound vac) was incorrectly coded and was therefore, not included in the above incidence rate calculations.

Of these subjects, all but one subject recovered from the infection. None of the serious infections were considered to be opportunistic by an independent adjudication committee

Four subjects experienced serious infections in study 1104: 3 during the open-label run-in phase (1 subject with pneumonia, 1 subject with epidural empyema, pan sinusitis and subperiosteal abscess with a history of craniosynostosis repair, and 1 subject with appendicitis).

One SAE/infection in the tofacitinib treatment group in the double-blind phase, pilonidal sinus repair, was erroneously coded to the SOC Surgical and medical procedures instead of Infections even though the subject was admitted to the hospital after surgery to treat a pilonidal cyst because of the infection, large incision site, and the need for wound vac placement. This event was inadvertently not captured in the programmed list of serious infection events. It was adjudicated as not meeting opportunistic infection criteria. Of the AESI, a total of 1 AE of serious infection (appendicitis) occurred in 1 (1.2%) subject in the placebo group.

Three subjects had serious infections in LTE study 1145: acute pyelonephritis, abscess limb (buttocks) and UTI. The subject with UTI discontinued before the infection was resolved 70 days after onset or UTI.

There were two subjects outside of the 28-day risk period who were hospitalized for serious infections (influenza, herpes zoster) in LTE study 1145, 33 and 40 days after the last dose of tofacitinib 5 mg BID (5 days and 12 days outside of risk period). These events are not included in the calculation of the incidence rate for serious infections in the safety population (ISAP).

In the 90-day safety update (since the initial submission), there were 4 subjects with serious infections within the risk period after the initial submission and hence included in the updated calculation of the incidence rate. There was one case each of wound infection, appendicitis, severe multi-dermatomal herpes zoster, and influenza.

There was one subject outside of the risk period who was hospitalized for serious infection (abscess); this event was not included in the incidence rate for serious infections as it was outside of the risk period.

8.2.4.2.1.2. Herpes Zoster

Overall, there were 3 subjects with herpes zoster (HZ) reported in integrated safety analysis set for pcJIA, representing an incidence rate of 0.82 (0.17, 2.4) events/100 PY. With the 90-day safety update, there was one more case of HZ; cumulatively, there were 4 subjects with herpes zoster within the risk period, resulting in an incidence rate of 0.86 (0.23, 2.20) events/100 PY for the ISAP.

All 3 reported HZ cases in the initial submission were mild to moderate and monodermatomal. There were 2 cases of herpes zoster (HZ) adjudicated during the open-label run-in phase; both events were in a single dermatome and did not meet the criteria for being considered an opportunistic infection.

Two subjects, aged 5 and 8 years, experienced a single episode of mild, monodermatomal HZ during study 1104, the events occurring in the open-label phase after 98 days and 19 days of treatment, respectively, with tofacitinib 5 mg BID. Both subjects received concomitant treatment with MTX and CS. Both episodes resolved after treatment with antiviral drugs and temporary, or permanent discontinuation of study drug.

One subject, aged 11 years, experienced an episode of moderate, monodermatomal herpes zoster in the LTE study 1145 after 417 days of treatment with tofacitinib 5 mg BID. This subject temporarily discontinued treatment with tofacitinib 5 mg BID and recovered after antiviral treatment.

In the period covered by the 90-day safety update, one subject, aged 8 years, was hospitalized for severe multi-dermatomal HZ in the LTE study 1145 after 357 days of treatment with tofacitinib. The investigator considered this event related to study drug. The subject received antiviral treatment, recovered after 19 days and was permanently discontinued from the study as a result of this event. This event was still under review by the adjudication committee for Opportunistic Infections at the time of the data cutoff (21 Jan 2020) for the safety update.

8.2.4.2.1.3. Other AESI

There were no cases of deaths, gastrointestinal perforation, interstitial lung disease, major adverse cardiovascular events, malignancy, macrophage activation syndrome, opportunistic infection, thromboembolic events (deep vein thrombosis, pulmonary embolus, or arterial or

venous thromboembolism), or active tuberculosis in the initial submission or in the period covered by the 90-day safety update. Given the long-latency of malignancies and cardiovascular events, limited conclusions can be drawn from the observation that there were no events reported during an overall exposure of 351 PYs to tofacitinib 5 mg BID in the pcJIA integrated safety population.

There were 3 events adjudicated as possible or probable drug induced liver injury (DILI) during the open-label run-in phase; 2 were mild and 1 was moderate. All 3 hepatic events occurred in the first 4 to 8 weeks of treatment with tofacitinib 5 mg BID in study 1104 and all 3 subjects were receiving background MTX. None met Hy's Law criteria. No drug induced liver injury events were adjudicated during the double-blind phase. In the 90-day safety update, there were no AEs adjudicated for DILI.

8.2.4.3. Psychiatric Events

Psychiatric disorders were reported in 10 patients on tofacitinib 5 mg BID in the ISAP, corresponding to an incidence rate of 2.80 (1.34, 5.15) subjects with events/100 PYs. After the cutoff date for the initial submission (04 June 2019), 3 additional subjects with psychiatric disorders were reported in the safety database, for a total of 13 patients who experienced psychiatric AEs, the cumulative incidence rate was 2.86 (1.52, 4.90) subjects with events /100 PYs.

Within the psychiatric disorders, adverse events were notable for depression, suicidal ideation and self-injurious behaviors. The incidence rate for suicidal and self-injurious behaviors for the initial submission was 0.82 (0.17, 2.39) subjects with events/100 PYs), which is consistent with the incidence rate of 0.86 (0.23, 2.19) subjects with events/100 PYs in the 90-day safety update.

There were 5 cases of suicidal ideation/attempt in the integrated safety analysis. There was one case of aggressive behavior, and one case of major depressive disorder (MDD) and homicidal ideation in the same patient. Narratives for these cases are summarized below from review of the case narratives from Studies 1104 and 1105, including the 90-day safety update and from the DPMH consult review.

1. *Patient* (b) (6) *– LTE Study ID (ID* (b) (6) *in Study 1104) 13yo WF , USA – SAE of Suicide ideation.*
   13 yo WF who experienced SAE of suicidal ideation, Day 32. Past medical history of bereavement, ADHD, MDD, autism spectrum disorder, bipolar I disorder, anxiety disorder, chronic abdominal pain. She also had a past medical history for suicidal ideation leading to four hospitalizations. Day 35 - she was cleared for discharge by a psychiatrist. Day – 35 she was withdrawn from the study. Subject was reported to have stress and bereavement on the passing of her Mother.

2. *Patient* (b) (6) *(ID* (b) (6) *in Study 1104) 15yo WF, Turkey – SAE of Suicide Attempt.*
15 yo WF, Day 403, she experienced a SAE of suicide attempt requiring hospitalization. She had ingested 4 tofacitinib tabs (10 mg ea) and 10 x 10 mg tabs of prednisolone. Stomach irrigation, remained in-patient for one night, and was discharged the following day, stable. She restarted tofacitinib on Day 404 through Day 417 without consulting the clinical investigator. She was withdrawn from the study on Day 417. The clinical investigator did not conclude there was a reasonable possibility that the suicide event could be attributed to tofacitinib.

No past medical history besides RF- polyarthritis. On prednisolone 10 mg PO daily and Ibuprofen 800 mg PO prn. Started in OL LTE (b) (6) (Study Day 417). From (b) (6) (Study day 240) also started taking Metoject.

3. *Patient* (b) (6) *(ID* (b) (6) *in Study 1104) 14yoWF, USA – SAE of Tylenol overdose*
14 yo WF, enrolled in LT E, OL study taking tofacitinib 5 mg BID. On Day 26, experienced a non-serious event of AMPS (amplified musculoskeletal pain syndrome), mild severity. On Day 621, she experienced a SAE of Tylenol overdose (paracetamol, 9 x 500 mg tabs on (b) (6) and then, 10 x 500 mg tabs on (b) (6)), considered mild severity and was hospitalized with the diagnosis of suicidal ideation. She denied wanting to hurt herself or being in excessive pain. During hospitalization, she was diagnosed with mild depression. She was discharged on Day 622 stable. She had feelings of feeling down and expressed disagreement with the diagnosis of suicidal ideation. She was also taking paracetamol at a higher than recommended dose. On follow-up, she was not doing well with her JIA and AMPS. She denied feeling suicidal and claimed to be in more pain, felt down, and anxious. The teen claimed that she did not realize she had taken so much paracetamol.

4. *Patient* (b) (6) *, (Same ID for Study 1104) 15yo WF, USA – AE of Intermittent Suicide Ideation.*
15 yo WF, OLE, with psoriatic arthritis x 5 years and past medical history of suicidal behavior, depression and insomnia. Received placebo in Study 1104 and rolled over into LTE study 1145. On (b) (6) (Study Day 178), reported to have intermittent suicidal ideation of mild severity. She was treated with sertraline HCl and she recovered from the suicidal ideation and continued on study treatment without additional suicidal ideation events.

5. *Patient* (b) (6) *(Ext Study), (ID* (b) (6) *in Study 1104) 8yo WM (Brazil) – AE of worsening of behavior alteration (aggressiveness).*
8 yo M (Brazilian) with enthesitis related arthritis. His past medical history included behavior disorder, learning deficit, aggressivity, psychiatric spectrum. He was not taking any psychotropic medications at the time of study enrolment. He was taking 4 ml BID

of tofacitinib oral solution. On Day 188, he was reported to have worsening behavior (aggressiveness). He was under treatment with risperidone (0.5 mg once daily) for behavior alteration (Day 55 to Day 86). On Day 188, he was restarted on risperidone at a higher dose (2 mg BID) for this event of worsening aggressiveness. He was permanently withdrawn from study due to withdrawal by parent/guardian on (b) (6) (b) (6) (day of event, Study Day 188).
Concomitant medications: Muvinlax (abdomen pain); omeprazole (abdominal pain, nausea, and epigastric pain); ondansetron (vomiting); paracetamol (pain and upper respiratory tract infection); and dipyrone and amoxicillin/clavulanate (upper respiratory tract infection)

The investigator considered the event of worsening of behavior alteration (aggressiveness) as related to study drug.

6. *Patient* (b) (6) *(ID* (b) (6) *in Study 1004) 17yo WF, USA – AEs of Suicidal ideation/intentional self-injury, and Non-suicidal self-injury.*
Started treatment in OL LTE on Study Day 1 (b) (6)). Before start of LTE study, on (b) (6) (Day -34), reported to have a non-serious AE of suicidal ideation, considered severe by investigator. She was referred to the emergency room by the school guidance counselor. No medications were prescribed for this event. No action was taken with tofacitinib. Recovered from event on (b) (6) (Day -32). Investigator considered the event of suicidal ideation due to psychological trauma related to recent suicide of her classmate. On (b) (6) (Study Day 29), reported non-serious AE of non-suicidal self-injury, of mild severity. No treatment given for the vent. No action taken for study drug due to event. Investigator considered depression as cause. Details of intentional self-injury were not provided.
PMH: RF- polyarthritis for 10 years, 7 months, dyspnea, TMJ syndrome, allergies seasonal. No prior history of psychiatric disorders. Concomitant medications: loratadine, clotrimazole

7. *Case ID* (b) (6) *(ID* (b) (6) *in Study 1104), 11yo WF, USA – SAE of Major depressive disorder and Homicidal ideation.* Event onset day 571 – event stop date 578. Dose remained unchanged. Treatment was discontinued on day 738. Tthe case narrative of the homicide/MDD episode is not included in Study 1104 CSR, or the 90-day safety update narratives of LTE.

After the cutoff date for the initial submission (04 June 2019), 3 additional subjects with psychiatric disorders were reported in the safety database: one 10-yr old subject had mild depressed mood after 659 days of tofacitinib treatment for 1 day; one 15-yr old subject had mild intermittent suicidal ideation after 346 days for 476 days, and one 4-yr old subject had mild attention deficit/ hyperactivity disorder after 1073 days of tofacitinib treatment for 456 days. All subjects recovered from the event.

Given the unique safety signal for tofacitinib, the Division consulted the Division of Pediatric and Maternal Health (DPMH) to further assess a potential safety signal of suicidal behavior in pcJIA patients treated with tofacitinib. DPMH upon review of the psychiatric AE data, and supporting literature concluded that there was insufficient evidence to causally attribute these AE's to tofacitinib use. Most of the cases were confounded by medical history and/or circumstances of stress during tofacitinib exposure. Further, pediatric rheumatology literature reports that the relationship between physical activity level, anxiety, depression, and functional ability in children and adolescents with juvenile idiopathic arthritis are correlated with disease activity, similarly as in adults.[1] The authors emphasized the need for clinical evaluation of the emotional state of children who report pain and that the incidence of psychiatric disorders such as depression and anxiety scores in JIA correlate with physical disability. See Section 10 Pediatrics for additional details.

The Division also consulted The Division of Pharmacovigilance I (DPV-I) who analyzed reports of psychiatric disorders, with a focus on suicide or self-harm behaviors, associated with tofacitinib use in the FDA Adverse Event Reporting System (FAERS) database. The following is an excerpt from DPV-I memo dated September 11, 2020: As of August 24, 2020, the FAERS database contained over 7,000 reports with tofacitinib containing Preferred Terms (PTs) in the System Organ Class Psychiatric disorders. Of these, 131 reports were isolated with the Standardized MedDRA Query Suicide and self-injury; hands-on review of these reports revealed 101 unique reports, of which 89 contained serious outcomes including 6 completed suicides. Of the 101 reports, a single non-fatal pediatric report was identified in the search strategy. Review of the 101 reports revealed several common themes which limited the ability to assess causality between tofacitinib and the events. Most reports either contained limited information (e.g., time to onset, psychiatric history or ongoing psychiatric disorders, concomitant medications) or described confounding or contributing factors (e.g., concomitant medications labeled for behavioral disturbances, underlying psychiatric illness, poor rheumatic disease control). DPV-I noted the presence of reports coding patient statements as suicidal ideation, although additional evidence to support self-harm behaviors were lacking.

The six completed suicide reports generally contained limited information or other contributors (high dose steroids, underlying psychiatric disease, significant rheumatic disease burden) which made assessment of tofacitinib's role in the events difficult. Three reports described abatement of psychiatric symptoms including suicidal ideation following discontinuation of tofacitinib. These reports were notable due to the presence of positive dechallenge, however, contained limited information for assessment.

[1] Aasland A et al. Psychological outcome in juvenile chronic arthritis: a nine-year follow-up. Clin Exp Rheumatol 1997; 15:561-8.

A single pediatric report occurring in a 16-year-old female enrolled in a long-term open-label juvenile idiopathic arthritis study was isolated in the search strategy. She was treated with tofacitinib for approximately 2 years and then experienced suicidal ideation following titration of her anti-depressant medications for underlying depression. She was hospitalized for a week for treatment and tofacitinib was discontinued. Tofacitinib was resumed following hospital discharge.

DPV-I, in conclusion, did not identify any discernable patterns or trends within the FAERS reports of suicide or self-harm events associated with tofacitinib use. It was difficult to assess the contribution of tofacitinib to the suicide or self-harm events due to the limitations of the FAERS database and issues as outlined above.

In summary, there were 13 cases of psychiatric disorders, including 5 cases of suicidal ideation and 1 case of homicidal ideation and MDD in the tofacitinib pcJIA clinical program. There were no reported cases of completed suicides, injury to others or homicides. Literature, as noted above, reports a relationship between mental health issues including anxiety and depression in pediatric pcJIA patients and disease severity; as well as higher rates of depression in the JIA population compared to their healthy peers. No adverse drug reactions related to depression or suicidality have been identified in the adult tofacitinib program.

In this review team's assessment, the tofacitinib pcJIA clinical program, is notable for psychiatric disorders, specifically AEs of anxiety, depression and suicidal ideation. However, given the few number of cases and limitations as discussed above, including confounding by disease severity, medical history, external stressors, a causal association between tofacitinib use and psychiatric disorders including depression, anxiety and suicidal ideation cannot be determined. Data is limited to support a labeling change, or warrant inclusion of these specific AEs in the PMR study.

It is worth noting that although a separate drug class from JAK-inhibitors, several monoclonal antibodies (particularly mAbs used for treating autoimmune diseases that suppress the immune system) have been linked to neuropsychiatric adverse effects in patients including depression and suicidal ideation and behavior Minnema LA et al. (2019) [1].

8.2.4.4. Effects on growth

Height and weight were assessed during study visits throughout subject participation in the index and LTE studies. Height and weight were compared with data from standard growth charts and summarized using Z-scores. Z-scores are standard deviation scores used to compare

[1] Minnema LA et al. Exploring the Association between Monoclonal Antibodies and Depression and Suicidal Ideation and Behavior: a VigiBase Study. Drug Safety (2019) 42:887-895.

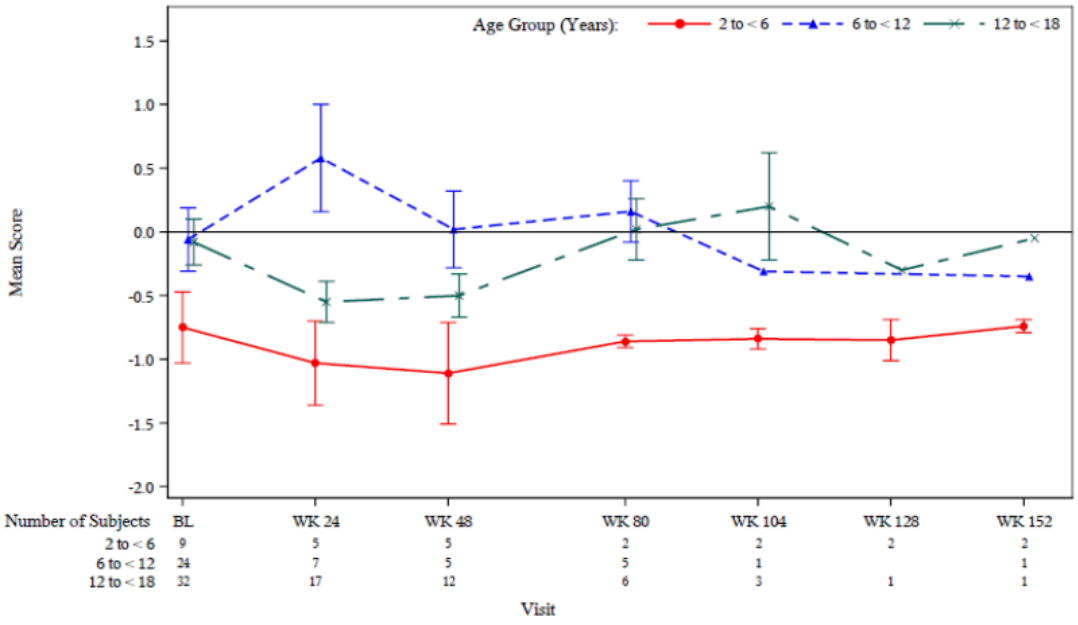
the height or weight of JIA subjects to that of healthy children of the same age. A Z-score < 0 indicates a shorter stature compared to a healthy child of the same age. Growth profiles were assessed via evaluation of the mean Height Z-score over time.

Body Height

No meaningful changes from baseline in Height Z-score were seen in pcJIA subjects by age and by gender in the Continuous Integrated Safety Analysis Population (CISAP). CISAP included all patients in the safety database without any interruption in tofacitinib treatment exceeding 14 day. However, data is limited to 27 patients (6 males, 21 females) who were followed continuously for ≥2 years.

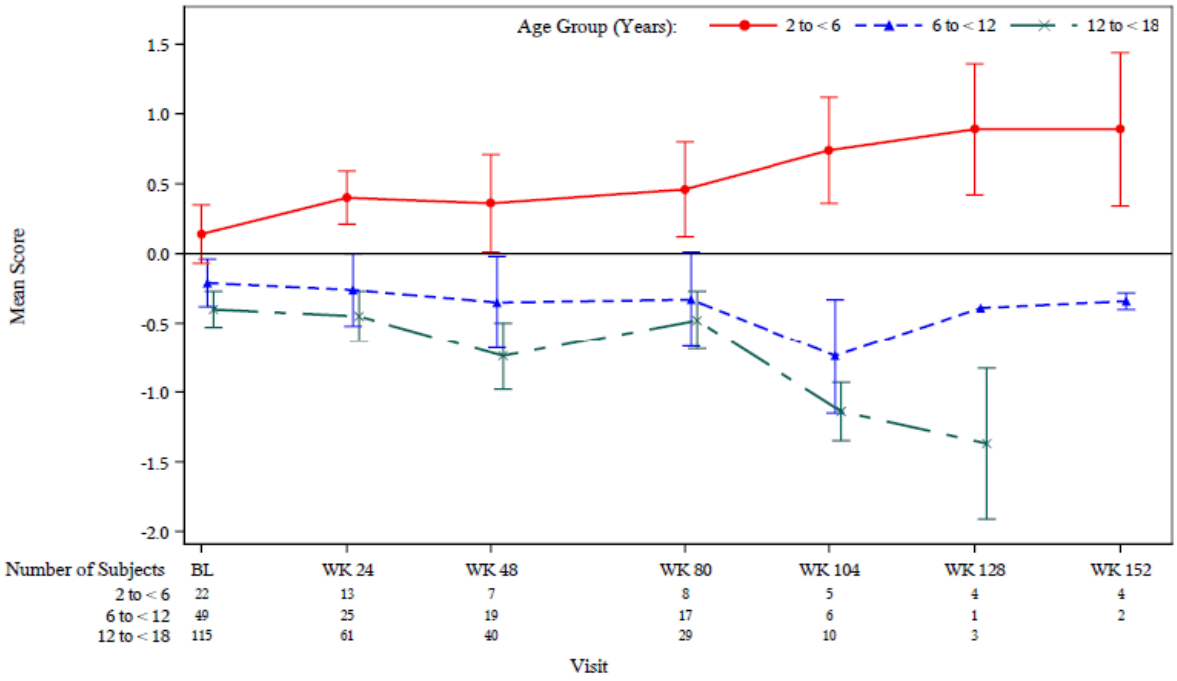
Figure 3 and Figure 4 present the growth/height profiles of pcJIA subjects treated with tofacitinib through 2 years in the CISAP, by age and by gender.

Figure 3. Mean Height Z-score (+/- SE) Over Time in Males - CISAP



Source: SCS Section 2.7.4.4.3.2, Figure 15

Figure 4. Mean Height Z-score (+/- SE) Over Time in Females – CISAP



Source: SCS Section 2.7.4.4.3.2, Figure 16

The youngest age cohort of male pcJIA subjects of 2 to < 6 years consistently had Z-scores between – 0.5 and -1.0, indicating a shorter stature compared to healthy children of the same age. Male pcJIA subjects between 6 and < 18 years had consistently Z- scores between -0.5 to +0.5, indicating similar stature than normal adolescents of the same age . In the female cohort pcJIA subjects between 6 and < 18 years had consistently Z-scores between -0.2 to -1.2 S.D. indicating shorter stature than normal adolescents of the same age. The youngest age cohort of female pcJIA subjects consistently had positive mean Z-scores indicating no impact on their height compared to healthy children of the same age.

Limited conclusions can be drawn from the data collected on growth as height was assessed continuously for ≥2 years in extremely few pcJIA subjects in the CISAP. Additionally, other factors can impact growth in the pcJIA population including chronic inflammatory disease, and corticosteroid use. The data from the tofacitinib pcJIA clinical program are limited to inform treatment related impact on growth.

The study was not designed to evaluate the effect of tofacitinib on bone growth and development which would potentially entail detailed assessments of impact on bone growth, for a reasonable duration of time.

Body Weight

Body weight profiles were assessed via change from baseline in Weight Z-score. There were no significant changes from baseline in weight of subjects Z-scores over time of pcJIA subjects continuously evaluated over 2 years in the CISAP. Similar to considerations for height, limited conclusions can be drawn from the data collected on growth as weight was assessed continuously for ≥2 years in extremely few pcJIA subjects in the CISAP

8.2.4.5. pcJIA-specific Adverse Events

Uveitis

There was one case (1.2%) of uveitis in the pcJIA program that occurred in a placebo-treated patient at Week 24 in study 1104. One other subject reported uveitis symptoms after 639 days of exposure to tofacitinib, but these symptoms were not recorded as an adverse event as the symptoms were not considered consistent with active uveitis. There were no new cases of uveitis reported in the period covered by the 90-day safety update.

Fractures

Cumulatively, 8 non-vertebral fractures of mild to moderate severity have been reported in 8 subjects the pcJIA clinical program, resulting in an incidence rate of 2.40 subjects with events/100 PYs for overall fractures in the pcJIA clinical program. One of these fractures was reported as an SAE (Table 53).

Macrophage Activation Syndrome

As noted above in AESI, there were no cases of MAS reported in the cumulative JIA ISAP. MAS more commonly occurs in systemic JIA patients (a subgroup of JIA) who were not evaluated in this pcJIA clinical program.

8.2.5. *Treatment Emergent Adverse Events and Adverse Reactions*

In study 1104, 176 (78%) subjects exposed to tofacitinib 5 mg BID experienced 554 TEAEs. Most TEAEs were mild to moderate in severity, and severe adverse events were reported for 5 (2%) subjects. In the open-label, run-in phase, 411 TEAEs were experienced by 153 (68%) subjects. In the double-blind phase, the rates of AEs were similar between tofacitinib 5 mg BID and placebo, with 160 and 166 TEAEs experienced by 68 (77%) and 63 (74%) subjects, respectively. In the integrated safety analysis population (ISAP), 227 (90%) subjects experienced 1132 TEAS.

The most frequently reported PTs with ≥2% occurrence in the open-label run-in phase were

upper respiratory tract infection (10.7), headache (7.1%), nausea (5.8%), and vomiting (5.8%). The most frequently reported PTs in the double-blind phase with ≥2% occurrence were as follows:

- Tofacitinib 5 mg BID group: upper respiratory tract Infection (14.8%), disease progression (9.1%), and nasopharyngitis (8.0%).
- Placebo group: disease progression (15.3% subjects), juvenile idiopathic arthritis (14.1%), and upper respiratory tract infection (10.6%).

The most frequently reported AEs in the double-blind phase of study 1104 with a ≥ 10% occurrence in tofacitinib, or placebo treatment group were, upper respiratory tract infection (tofacitinib: 14.8 %, placebo: 10.6% %), juvenile idiopathic arthritis (tofacitinib: 3.4%; placebo: 14.1%), and disease progression (tofacitinib: 9.1%; placebo: 15.3%).

There were no clinically meaningful differences, with the exception of disease progression, and JIA (exacerbation) which were reported more commonly in the placebo group, between the tofacitinib and the placebo groups.

Table 54 presents the common AEs (with ≥2% occurrence) in the integrated safety population. The most common AEs occurring with ≥10% for tofacitinib treatment reported in the integrated safety population, by PT, were upper respiratory tract infection (25.9%) and nasopharyngitis (11.6%), headache (12.4%), JIA (10.8%), and vomiting (10.0%). No unique safety signals were identified in the integrated safety analysis population. The 90-day safety update results were also consistent with study 1104 and ISAP results.

Table 54. Summary of TEAEs by SOC and PT ≥2% - ISAP

Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	Tofacitinib 5 mg BID (N=251)
Blood And Lymphatic System Disorders	23 (9.2)
Anaemia	8 (3.2)
Leukopenia	6 (2.4)
Gastrointestinal Disorders	81 (32.3)
Abdominal discomfort	5 (2.0)
Abdominal pain	18 (7.2)
Abdominal pain upper	11 (4.4)
Constipation	9 (3.6)
Diarrhoea	13 (5.2)
Dyspepsia	6 (2.4)
Nausea	23 (9.2)
Vomiting	25 (10.0)
General Disorders And Administration Site Conditions	68 (27.1)
Condition aggravated	12 (4.8)
Disease progression	23 (9.2)
Fatigue	5 (2.0)
Non-cardiac chest pain	5 (2.0)
Pyrexia	22 (8.8)
Infections And Infestations	158 (62.9)
Bronchitis	10 (4.0)
Conjunctivitis	6 (2.4)
Ear infection	11 (4.4)
Gastroenteritis	12 (4.8)
Gastroenteritis viral	5 (2.0)
Influenza	20 (8.0)
Nasopharyngitis	29 (11.6)
Pharyngitis	16 (6.4)
Pharyngitis streptococcal	9 (3.6)
Pneumonia	5 (2.0)
Respiratory tract infection	9 (3.6)
Sinusitis	18 (7.2)
Tinea pedis	5 (2.0)
Upper respiratory tract infection	65 (25.9)
Urinary tract infection	14 (5.6)
Viral infection	19 (7.6)
Viral upper respiratory tract infection	7 (2.8)
Injury, Poisoning And Procedural Complications	49 (19.5)
Contusion	6 (2.4)
Ligament sprain	7 (2.8)

Limb injury	6 (2.4)
Skin abrasion	6 (2.4)
Investigations	53 (21.1)
Alanine aminotransferase increased	13 (5.2)
Aspartate aminotransferase increased	13 (5.2)
Blood creatine phosphokinase increased	12 (4.8)
Blood triglycerides increased	6 (2.4)
C-reactive protein increased	6 (2.4)
Haemoglobin decreased	7 (2.8)
Metabolism And Nutrition Disorders	14 (5.6)
Decreased appetite	7 (2.8)
Musculoskeletal And Connective Tissue Disorders	78 (31.1)
Arthralgia	20 (8.0)
Arthritis	7 (2.8)
Back pain	8 (3.2)
Juvenile idiopathic arthritis	27 (10.8)
Pain in extremity	9 (3.6)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	8 (3.2)
Skin papilloma	8 (3.2)
Nervous System Disorders	41 (16.3)
Headache	31 (12.4)
Respiratory, Thoracic And Mediastinal Disorders	51 (20.3)
Cough	17 (6.8)
Epistaxis	10 (4.0)
Oropharyngeal pain	13 (5.2)
Rhinitis allergic	5 (2.0)
Skin And Subcutaneous Tissue Disorders	37 (14.7)
Acne	6 (2.4)
Rash	7 (2.8)
Urticaria	5 (2.0)

Source: Summary of clinical safety, Section 2.7.4.2.1.1, Table 19

In summary, the most frequently reported AEs with ≥2% occurrence in the tofacitinib pcJIA clinical program were infections, followed by disease progression (captured by a combination of various PTs including JIA, disease progression, condition aggravated), and gastrointestinal AEs of nausea and vomiting.

Laboratory Findings

Changes in selected hematology parameters, liver enzymes, creatinine and creatine kinase (CK) and lipid profiles, as well as in lipid profiles were observed. The laboratory changes observed in the pcJIA program were consistent with those seen in the RA population. Overall, 21 subjects (8.4%) in the integrated analysis (ISAP) had to be retested for a single hemoglobin (Hb) decrease that fell ≥2 g/dL below baseline. There was no evidence of Hb decreases over time in the pcJIA program. There were 10 subjects (4%) who had a single AST and/or ALT with a value >3X the ULN (upper limit of normal). One subject was required to be discontinued due to 2 sequential AST or ALT elevations >5 x ULN. There were 3 events adjudicated as possible or

probable drug induced liver injury (DILI) during the pcJIA program; 2 were mild and 1 was moderate. All 3 hepatic events occurred in the first 4 to 8 weeks of treatment with tofacitinib 5 mg BID in study 1104 and all 3 subjects were receiving background MTX. None met Hy's Law criteria.

Vital Signs

Vital signs were assessed at all visits and no clinically relevant changes in vital sign parameters were observed.

Electrocardiograms (ECGs)

ECGs were not assessed in study 1104.

Immunogenicity

Not applicable.

8.2.6. Analysis of Submission-Specific Safety Issues

See Section 8.2.4 Safety Results.

8.2.7. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not Applicable.

8.2.8. Safety Analyses by Demographic Subgroups

No clinically meaningful differences in safety were observed across the 3 age groups studied, or across genders, or JIA subtypes.

The two drug formulations (5 mg IR tablet and 1mg/mL oral solution) had similar incidence rates of TEAEs, SAEs and AEs leading to DC. Overall, there was no significant difference in the safety profile observed between the two formulations.

8.2.9. Specific Safety Studies/Clinical Trials

Not Applicable.

8.2.10. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No specific trials were conducted to assess for carcinogenicity in humans.

Human Reproduction and Pregnancy

There was 1 event of paternal exposure in study 1104. A subject's partner was reported to be 11 weeks pregnant at the time of reporting. The outcome was a full-term (36 weeks), normal, male baby born weighing 2930 grams.

There was one case of spontaneous abortion in the 90-day safety update. A 14yo F, on Day 358 of tofacitinib treatment in the LTE study, had an SAE of pregnancy. The drug was permanently withdrawn on Day 357, and the subject was withdrawn from the study on Day 358 due to AE of pregnancy. On Day 364, the subject was confirmed to have a spontaneous abortion.

Pediatrics and Assessment of Effects on Growth

There were no dedicated studies to asses the impact of tofacitinib on growth in the pcJIA population. Specific bone monitoring (such as imaging via MRI or X-ray) to evaluate the impact on growth plates was not conducted in the tofacitinib pcJIA clinical program. Height and weight were assessed during study visits throughout subject participation in the index and LTE studies. Height and weight were compared with data from standard growth charts and summarized using Z-scores. No clinically meaningful changes from baseline in height and weight Z-scores over time of pcJIA subjects continuously evaluated over 2 years, although the low number of patients followed over time limit the conclusions that can be drawn. See *Effects on growth* for additional details.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Drug overdose was reported infrequently in the pcJIA program with no AEs associated with the higher doses. In study 1104, one subject received a 50% higher dose than prescribed (3 doses daily instead of 2) in the first 4 weeks of treatment with tofacitinib, after which this subject was permanently discontinued.

In study 1145, overdoses were reported 6 subjects. There was one case of intentional overdose in the pcJIA safety database. One subject took 4 pills of tofacitinib (20 mg/day) and 10 pills of prednisolone in a suicide attempt. She did not have a medical history of depression, suicidal attempts, or any psychiatric disorders. See Psychiatric Events for case narrative. There were no cases of overdose of tofacitinib in study 1103.

No cases of drug abuse, withdrawal or rebound have been reported in the pcJIA program.

8.2.11. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Tofacitinib has been on the US market since 2012, approved for the treatment of adult subjects

with active moderate to severe RA who have had an inadequate response or intolerance to methotrexate (MTX), for psoriatic arthritis, and for ulcerative colitis in 2019. No new safety signals have been identified in the postmarketing setting that would affect the risk-benefit assessment for these indications.

Expectations on Safety in the Postmarket Setting

The studied patient population is similar to the target population. Given the postmarketing experience with tofacitinib in patients with RA, no substantial differences in safety are expected from the known safety profile of tofacitinib.

8.2.12. Integrated Assessment of Safety and Safety Summary

The safety assessment of tofacitinib in patients with pcJIA is primarily based on safety findings from Study 1104 which enrolled 225 patients. The integrated safety analysis population (ISAP) provides additional evidence of supportive safety by pooling safety data from 251 patients exposed to tofacitinib 5 mg BID in the pivotal study 1104, LTE study 1145 and PK study 1103, as described earlier in section 8.2. The safety database size and duration of follow up are adequate to provide a reasonable assessment of benefit-risk of tofacitinib in pcJIA.

The review of the clinical safety data indicates that the main areas of safety remain consistent with the previously defined safety profile of tofacitinib.

- No new safety signals were identified in the pcJIA program.
- The types of AEs and SAEs are expected for the underlying patient population and consistent with findings in adults with RA.
- The most frequently reported AEs in the tofacitinib pcJIA clinical program were infections, followed by disease progression (captured by a combination of various PTs including JIA, disease progression, condition aggravated), and gastrointestinal AEs of nausea and vomiting.
- Infections were the most frequently reported SAEs, consistent with the known safety profile of tofacitinib.
- Of the AESI identified for tofacitinib, serious infections and herpes zoster were the only reported AESIs in the pcJIA program.
- No opportunistic infections were reported.
- Of the significant adverse events reported, psychiatric disorders including depression, anxiety, and suicidal ideation were notable in the pcJIA program. However, given the confounding by disease severity, medical and psychiatric history, external stressors, a causal association between tofacitinib use and psychiatric disorders cannot be concluded.
- No deaths were reported in the tofacitinib pcJIA program.

To assess long-term safety in the pediatric population, a PMR study has been agreed upon with the applicant. See Sections 1.3 Benefit-Risk Assessment and Section 13 Postmarketing Requirements and Commitment for details. Considerations for issuing a clinical PMR included:

- Tofacitinib is a first-in-class drug for this pediatric indication
- Immunosuppressive nature of the drug Limited long-term assessment of safety in the pediatric population
- Labeled risks of tofacitinib
- Potential risk of bone toxicity affecting growth from non-clinical studies of JAK-inhibitors

Therefore, to ensure the long-term risk-benefit profile of tofacitinib in pcJIA remains favorable, safety should be further assessed in a long term safety study with inclusion of a reference group (of pediatric pcJIA patients treated with other pcJIA medications as standard of care), to assess risk of malignancies (including lymphoma), serious infections (including opportunistic infections), thrombosis and effects on growth and development.

8.3. Statistical Issues

The statistical issues are summarized as follows:

- The Applicant's analyses for ACR and CHAQ-DI at week 44 comparing tofacitinib and placebo is not consistent with the design and conduct of the study since subjects who discontinued treatment and withdrew from the study early continued into the extension study where they either continued or re-initiated tofacitinib. The Applicant considered subjects who discontinued treatment early as missing, which amounted to a total of 43% (55% on placebo) in the DBFAS.

- In the analyses of ACR, the Applicant considered subjects with missing data as non-responders. Since the primary reason for study withdrawal was occurrence of disease flare, this assumes that subjects who experience disease flare cannot see improvement in ACR at a future time point. This assumption is not supported when considering the use of extension data.

- In the analysis of CHAQ-DI from double-blind baseline, the Applicant used the MMRM, which assumes missing data to be missing at random, i.e., it assumes that measurements for subjects with missing data are similar to those on the same arm with captured data, i.e., missing CHAQ-DI scores for subjects who experienced occurrence of disease are modelled after subjects who did not experience occurrence of disease.

Resolution and discussion of statistical issues:

- To reflect the design and conduct of the study, extension data were utilized. However, a limitation is that since analysis visits were more spread out than in the main study, the analysis window needed to be enlarged to capture "equivalent" Week 44 data.

- In regard to ACR responses and CHAQ-DI endpoints, there is no simple resolution in quantifying the treatment effect size of staying on tofacitinib compared to initiating placebo for an additional 26 weeks in attaining ACR response or lowering CHAQ-DI, since subjects randomized to placebo who withdrew from the study early re-initiated tofacitinib in the extension study.

The statistical issues that arose during the review (b) (4) (b) (4) do not impact the approvability of tofacitinib in the study population.

8.4. Conclusions and Recommendations

The efficacy of tofacitinib for pcJIA was assessed in a single study, Study pcJIA-I (NCT02592434), a 44-week, two-part study (consisting of an 18-week, open-label, run-in phase, followed by a 26-week double-blind, placebo-controlled, randomized withdrawal phase) in pcJIA patients 2 years to 17 years of age with active polyarthritis. Patient subtypes included RF negative polyarthritis, RF positive polyarthritis, extended oligoarthritis, and systemic JIA without systemic manifestations who had an inadequate response or intolerance to at least one DMARD which could have included MTX or biologic agents; the study also included patients ages 2 years to 17 years of age with active juvenile psoriatic arthritis (JPsA) and enthesitis-related arthritis (ERA) who had an inadequate response to NSAIDs.

Of the 225 patients enrolled, 173 (76.9%) patients achieved JIA ACR30 response at Week 18 and were randomized into the double-blind phase to either tofacitinib treatment (n=88) or placebo (n=85). At the end of the 18-week, open-label, run-in phase, pediatric ACR 30/50/70 responses were 77%, 70%, and 49%, respectively.

The primary endpoint was the occurrence of disease flare at week 44 relative to the double-blind phase baseline at Week 18. The study met its primary endpoint at week 44 with tofacitinib treated patients experiencing significantly fewer disease flares compared to placebo-treated patients (31% [27/88] vs. 55% [47/85]; difference in proportions -25% [95% CI: -39%, -10%]; p=0.0007). The clinical efficacy results from the primary analysis demonstrate a statistically significant and clinically meaningful difference between the two groups providing evidence of efficacy of tofacitinib in treating patients with active polyarticular-course JIA.

The safety of tofacitinib is well-characterized in numerous clinical studies across various indications, including in adult patients with RA. In this pcJIA clinical program, no new safety signals were identified in the pediatric patients compared to the known adverse event profile of tofacitinib in adult patients [1]. The safety profile of using tofacitinib in children with pcJIA was consistent with the known safety profile of tofacitinib.

[1] FDA-approved tofacitinib labeling

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was convened for NDA 203214/S-026 and NDA 213082. No issues were identified warranting Advisory Committee input, as the efficacy of tofacitinib was clear, with an acceptable safety profile that was consistent with the known safety profile of tofacitinib.

10 Pediatrics

The sNDA 203214/S-026 for Xeljanz (tofacitinib) oral tablet, 5 mg, and the original NDA 213082 for Xeljanz (tofacitinib) oral solution, 1 mg/mL, for once daily dosing, propose a new dosing form and new indication in polyarticular-course juvenile idiopathic arthritis (pcJIA).

In the Approval Letter for tofacitinib (dated November 6, 2012) for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate, FDA agreed to waive the pediatric study requirement for birth to less than 2 years of age because necessary studies are impossible or highly impracticable as pcJIA is not diagnosed in children less than 2 years of age. FDA also deferred submission of a pediatric assessment for ages 2 years through 17 years of age because the product is ready for approval for use in adults and the pediatric studies had not been completed at that time. The deferred pediatric studies required by section 505B(a) of the Food Drug Cosmetic Act (FDCA) are required postmarketing studies. Currently, there are no approved indications for tofacitinib in any pediatric patient population although tofacitinib has a PREA postmarketing requirement (PMR) for Ulcerative Colitis (UC).

Section 8.4 (Pediatric Use) will state that safety and effectiveness of XELJANZ/XELJANZ Oral Solution for the treatment of active pcJIA have been established in pediatric patients from 2 years to 17 years of age. Use of XELJANZ/XELJANZ Oral Solution in this age group is supported by evidence from adequate and well-controlled studies of XELJANZ in adults with additional data from a clinical study of XELJANZ/XELJANZ Oral Solution in (b) (4) pediatric patients (2 years to 17 years of age) with active pcJIA consisting of an 18-week open label run-in period followed by a randomized, (b) (4) 26-week placebo-controlled period.

The data submitted in this application, fulfils the PREA PMR 1934-2 under NDA 203214.

The pediatric assessment was discussed at PeRC on August 11, 2020. PeRC agreed with the Division's recommendation that the pediatric assessment for pcJIA was complete.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The most notable revisions to the Prescribing Information are summarized below.

- Indications and Usage (Section 1 of Label):
  - The indication reads: XELJANZ/XELJANZ Oral Solution is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older. We note that this indication and the description of the population refer to polyarticular *course* JIA which is slightly different than the reference to pJIA in all of the previously approved products for this indication. The review team believes that this description is a more accurate representation of the population studied. Specifically, the tofacitinib pediatric program included JIA patients with active polyarticular involvement, i.e. not limited to the polyarticular subgroup JIA (pJIA) by the ILAR classification.
  - The sentence (b) (4) (b) (4) from the RA indication statement (originally approved language) was removed to reflect a current labeling practice, as this statement does not provide information for the safe or effective use of the product, and this sentence does not provide useful information to prescribers.

- Dosage and Administration (Section 2 of Label)
  - Important Administration Instructions (Section 2.1 of Label)
    - A bulleted sentence "XELJANZ XR (tofacitinib extended-release tablets) is not interchangeable or substitutable with XELJANZ Oral Solution." was added because there is the potential for medication errors where users receive the immediate release oral solution to achieve an 11 mL XR dose (as the solution is 1 mg/mL). For example, if a healthcare professional intended to prescribe "Xeljanz XR 11 mg once daily" and the modifier "XR" was omitted or overlooked, the prescription would be interpreted as "Xeljanz 11 mg once daily." In such a case, the immediate release tablets would not be dispensed because, with the strengths available, it would not be possible to achieve 11 mg. However, the oral solution could be dispensed with the understanding that the patient would take 11 mL once daily (1 mg/mL solution).
    - A bulleted sentence "Changes between XELJANZ and XELJANZ XR should be made under the supervision of the healthcare provider *[see Dosage and Administration (2.2)]*." was added to clarify that healthcare providers may switch between the immediate release tablets and extended release tablets (as described at the end of Section 2.2).

- Throughout Section 2 of Label
  - Throughout Section 2 Dosage and Administration, "tablets" was added after XELJANZ and "extended-release tablets" was added after XELJANZ XR to minimize risk of confusion between formulations.
- Recommended Dosage in Polyarticular Course Juvenile Idiopathic Arthritis (Section 2.4 of Label)
  - The sentence (b) (4) (b) (4) was removed because the current practice is not to include information in the Dosage and Administration section unless necessary for safe or effective use of the product, and this sentence does not provide useful information to prescribers.

- Adverse Reactions – Clinical Trials Experience (Section 6.1 of Label) - Polyarticular Course Juvenile Idiopathic Arthritis sub-section
  - The total patient exposure was added.
  - The sentence "In general, the types of adverse drug reactions in patients with pJIA were consistent with those seen in RA patients *[see Adverse Reactions (6.1)]*." was added.
  - A sentence describing particular adverse reactions was removed because these adverse reactions were already described elsewhere in the Clinical Trials Experience section

- Clinical Studies – Polyarticular Course Juvenile Idiopathic Arthritis (Section 14.4 of Label)
  - The original presentation of results proposed by the Applicant (only for the polyarticular JIA population; as defined by ILAR criteria) was revised to also include the results from the population studied because presentation of the entire study population more accurately supports the proposed indication of patients with polyarticular course JIA and is consistent with the regulatory precedent.
  - (b) (4)
  -

(b) (4)

The Applicant's proposed statement (b) (4) (b) (4) was replaced with the more factual statement presenting JIA ACR 30/50/70 results at the end of the open label phase (Week 18) to contextualize the interpretation of the primary endpoint.

Other Prescription Drug Labeling

The Applicant submitted patient labeling for Xeljanz (tofacitinib) tablets / Xeljanz (tofacitinib) Oral Solution. The Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the patient labeling. The final labeling will reflect their recommendations. Refer to the OPDP/DMPP Patient Labeling Review in DARRTs (August 26, 2020). In summary, in the collaborative review of the patient labeling, the Division did the following: simplified wording and clarified concepts where possible; ensured that the Medication Guide (MG) and Instructions for Use (IFU) is consistent with the Prescribing Information (PI); removed unnecessary or redundant information; ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language; ensured that the MG meets the Regulations as specified in 21 CFR 208.20; ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

All labeling changes were agreed upon with the Applicant.

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not required for the safe use of tofacitinib in patients aged 2-17 years old. Labeling can adequately explain the risk of tofacitinib in pediatric patients. There are no new identified safety issues where a REMS would be expected to mitigate identified risks.

13 Postmarketing Requirements and Commitments

Clinical postmarketing requirement (PMR)

In considering whether a postmarketing requirement for safety should be enacted, the review team considered the following factors:

- Tofacitinib would be the first JAK inhibitor approved for pcJIA
- The application contains limited data on the long-term safety of tofacitinib in patients with pcJIA
- There are a number of effective therapeutic options for this patient population
- JAKs have physiological functions in immune system development
- Recent evidence from non-clinical studies with other JAK inhibitors suggests effects on skeletal system and bone ossification.

Therefore, to ensure the long-term benefit-risk profile of tofacitinib in pcJIA remains favorable, the team concluded that safety should be further assessed by a long-term safety study with inclusion of a control group, to evaluate for malignancies, serious infections, thrombosis, and effects on growth. The Office of Surveillance and Epidemiology (OSE) review team has determined that these potential toxicities cannot be adequately assessed using the Active Risk Identification Analysis (ARIA). Consequently, the safety PMR is:

> Conduct a long-term observational safety study in pediatric patients 2-17 years of age with polyarticular-course JIA (pcJIA) treated with tofacitinib to evaluate for the risk of malignancies, serious infections (including opportunistic infections), thrombosis, and effects on growth. The study should include a control group of pediatric pcJIA patients treated with other pcJIA medications as standard of care. Patients should be followed for 5 years.
>
> | | |
> |---|---|
> | Draft Protocol Submission: | 03/2021 |
> | Final Protocol Submission: | 07/2021 |
> | Trial Completion: | 02/2030 |
> | Final Report Submission: | 09/2030 |

The review team also acknowledges the recommendation by the OSE consult team who suggested revisions to the PMR language, specifically the following: (1) revising the follow up duration from 5 years to 7 years; (2) replacing the statement that the control group must be receiving “standard of care” medications for pcJIA with a statement specifying particular medications for pcJIA (“tocilizumab, “adalimumab”, etanercept”, and “abatacept”), and addition of a statement that adjustment for disease severity must be done since these medications may be used in patients with less severe disease than those initiating tofacitinib. In considering these recommended changes to the PMR language, the Division review team

noted that the 5-year follow up period falls within the 3 to 7 year period defined by DEPI for malignancies, and that since many patients will likely change therapy over time, a longer duration will likely result in more missing data which would negatively impact the interpretability of the results. The Division noted that having active polyarticular disease is an indicator of burden of disease and the statement "standard of care" helps to ensure that the control group will be appropriately matched.

Nonclincal PMR

As discussed in Section 5, 5 Nonclinical Pharmacology/Toxicology, the examination of bone growth and development in juvenile animal studies with tofacitinib was incomplete. Given the recent information on bone toxicity in animal studies with other JAK inhibitors, assessment of the potential for tofacitinib to adversely affect bone development and growth is warranted. Based on review of the data in this submission, the following postmarketing requirement (PMR) was conveyed to the applicant:

> Conduct a nonclinical juvenile animal toxicity study to address the potential for tofacitinib to adversely affect bone development and growth. Effects on bone development and growth should be assessed by histopathological examination. Other appropriate methods might be included to follow up on any findings as deemed necessary. The study should include a recovery period to address if any observed adverse findings are reversible.
>
> Draft Protocol Submission: 11/2020
> Final Protocol Submission: 01/2021
> Trial Completion: 07/2021
> Final Report Submission: 10/2021

14 Division Director (Clinical)/Signatory Comments

On March 26, 2020, Pfizer submitted the present NDA 203214 Supplement-26 for XELJANZ (tofacitinib) immediate release (IR) tablet (5 mg) and NDA 213082 for tofacitinib oral solution (1 mg/mL) seeking the approval of tofacitinib for the treatment of polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older.

The primary data in support of this application are derived from two studies (1934-1 and 1934-2) which were required under PREA and were issued at the time of the original NDA approval for adult RA indication on November 06, 2012.

- Study 1934-1 (also referred to as A3921103 in this document) was a multiple-dose pharmacokinetic trial in children from 2 to less than 18 years of age with juvenile idiopathic arthritis. This PMR was fulfilled on February 15, 2017.

- Study 1934-2 (also referred to as A3921104 in this document) was a randomized withdrawal, double-blind, placebo-controlled trial to evaluate the efficacy and safety of tofacitinib in children from 2 to less than 18 years of age with polyarticular-course juvenile idiopathic arthritis.

These studies were also included in a pediatric Written Request (Study 1 and Study 2) issued for tofacitinib on August 12, 2015, and amended on July 12, 2016 and October 03, 2019.

This application was reviewed on a Priority review clock.

New Dosage Form

With this submission, the Applicant also proposed a new age-appropriate formulation of tofacitinib (oral solution) in NDA 213082. The Office of Pharmaceutical Quality recommends approval of NDA 213082 based on the Integrated Quality Assessment. I agree with this recommendation.

Dosing

The dosing of tofacitinib in the pcJIA study was selected based on data from study A3921103 not to exceed the exposures of 5 mg twice daily dosing in adults with RA, in light of the dose-dependent toxicities, including serious and opportunistic infections, malignancy, thrombosis, and mortality, observed with the higher 10 mg twice daily dosing.[1]

[1] FDA-approved tofacitinib labeling

The proposed body weight-based dosing regimen is:

- 10 to <20 kg: 3.2 mg (3.2 mL oral solution) BID
- 20 to <40 kg: 4 mg (4 mL oral solution) BID
- ≥ 40 kg: 5 mg (one 5 mg IR tablet or 5 mL oral solution) BID

The proposed dosing regimen has been modified from the phase 3 dosing regimen with fewer weight subgroups. The clinical pharmacology review team concluded that following the proposed dosing regimen, patients 2 to <18 years of are predicted to have similar PK exposure as in the phase 3 study.

The clinical pharmacology review team concluded that the new dosage form of tofacitinib, oral solution (1 mg/mL), had a similar bioavailability as the 5 mg immediate release tablet and that the proposed dosing adjustments regarding intrinsic and extrinsic factors are consistent with the approved recommendations for RA.

The Office of Clinical Pharmacology (OCP), Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM), recommended approval of this submission for the treatment of patients with active pcJIA 2 years of age and older. I agree with the OCP assessment and recommendation.

Clinical Program

Data from PK study (A3921103) informed the dosing for study A3921104, as detailed in the Clinical Pharmacology section above.

The confirmatory efficacy study A3921104 was a multi-center, randomized withdrawal, double-blind, placebo-controlled, parallel group study. The run-in phase was an 18-week open-label period, where all subjects initiated tofacitinib. Following the run-in phase, subjects who achieved at least a JIA ACR 30 response were randomized with a 1:1 ratio to either placebo or tofacitinib for the 26-week double-blind phase.

The study was conducted as planned. Of the 225 patients with active polyarticular course JIA enrolled in the open-label phase, 173 (77%) achieved JIA ACR30 response at Week 18 and were randomized into the double-blind randomized withdrawal phase. The primary endpoint was the occurrence of disease flare at Week 44 relative to the double-blind phase baseline at Week 18. Disease flare was defined as worsening of ≥30% in 3 or more of the 6 JIA core response variables with no more than 1 of the remaining JIA core response variables improving by ≥30%.

Tofacitinib-treated patients experienced significantly fewer disease flares at Week 44 compared to placebo-treated patients (31% [27/88] vs. 55% [47/85]; difference in proportions -25% [95%

CI: -39%, -10%]; p=0.0007). These results were supported by sensitivity analyses. These results are statistically robust and clinically meaningful to establish the efficacy of tofacitinib in pcJIA.

The safety was derived primarily from the confirmatory phase 3 study A3921104 with supportive data from the PK study A3921103 and the long-term extension study A3921145 in a total of 251 pcJIA patients with a mean duration of exposure of 511 days. The size and duration of the safety database is adequate to provide a reasonable benefit risk assessment in this population.

No deaths occurred in the program. Infections were the most frequently reported SAEs, consistent with the known safety profile of tofacitinib. Of the AESI identified for tofacitinib, serious infections and herpes zoster were the only reported adverse events of special interest (AESI) in the pcJIA program. There were no cases of thrombosis. The most frequently reported AEs were infections, followed by disease progression, and gastrointestinal AEs of nausea and vomiting. While psychiatric events were reported in the pcJIA clinical program, including cases of suicidal ideation/attempt, the review team concluded that there was insufficient evidence to causally attribute these adverse events to tofacitinib use. This assessment was based on review of the case narratives and analysis of the FDA Adverse Event Reporting System (FAERS) database by Division of Pharmacovigilance I, as detailed in the review of safety in this document.

In summary, the team concluded, and I agree, that adverse reactions observed in pediatric program were consistent with those reported in RA patients.

Benefit-risk Assessment

The benefit-risk profile of tofacitinib in pcJIA is favorable. The efficacy of tofacitinib in patients with pcJIA ages 2 to 17 years of age has been demonstrated in study A3921104, based on the statistically robust and clinically meaningful results from the controlled randomized withdrawal comparisons, as detailed in this review. The oral route of administration and the age-appropriate oral solution formulation provide additional benefit of a convenient dosage form to this patient population for which most of the available therapies are injectables.

The risks of tofacitinib treatment in this patient population appear to be qualitatively similar as those seen in adults with RA and the known safety profile of tofacitinib; with the primary serious risk being an increased risk of infection. However, the risks of tofacitinib are not minimal, and JAKs have physiological functions in immune and potentially in the skeletal system development. Therefore, to ensure the long-term benefit-risk profile of tofacitinib in pcJIA remains favorable, the team concluded, and I agree, that safety should be further assessed by a long-term safety study with inclusion of a control group, to evaluate for malignancies, serious infections, thrombosis, and effects on growth, as outlined in Section 13, Postmarketing Requirements and Commitments.

In addition, recent literature and other data have identified concerns about potential adverse effects on bone in non-clinical studies of other JAK inhibitors. However, the juvenile animal studies from the tofacitinib original non-clinical program, did not have a complete full panel of histopathology evaluations of long bones to specifically assess for potential effects on growth. Histopathological exams of the previously submitted juvenile animal studies were limited to the sternum in the monkey study and bone marrow in the rat study. Therefore, examination of bone growth and development in juvenile animal studies with tofacitinib was incomplete due to lack of histopathology of long bone and joints and warrants further characterization as a post-marketing requirement, as outlined in Section 13, Postmarketing Requirements and Commitments.

Of note, the bone growth in the juvenile monkey study, assessed radiographically by length measurements of the tibia and radius, was unaffected at doses that exceeded the maximum equivalent pediatric doses. Further, the histopathology of the sternum did not show abnormalities. The totality of the available non-clinical information suggests that the effects on bone and growth of tofacitinib are largely a hypothetical concern and do not impact the benefit-risk that would preclude approval. The meaningful longitudinal clinical assessment of growth in the pcJIA clinical program was limited to a small number of patients who were exposed to at least two years. Thus, to further address tofacitinib's potential to adversely impact bone ossification and growth, additional clinical and non-clinical post-marketing studies, as described above, will be required.

Regulatory Action

The regulatory action for this submission is Approval with labeling changes agreed upon with the Applicant. A clinical and a non-clinical PMR studies are required as detailed above.

The data provided in this submission fulfil the PREA PMR 1934-2 under NDA 203214. The study was also conducted in keeping with the provisions of the pediatric WR and appears to have addressed the relevant parts of the WR.

15 Appendices

15.1. References

See footnotes.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Studies A3921103, A3921104, A3921145

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 638 of 661 investigators[1]		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13 of 661 investigators had financial information to disclose		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 7 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)

[1] The applicant notes that this number represents all the investigators listed on the form and is not unique. Some investigators may have participated in more than one study and multiple financial disclosure forms may have been collected for a single investigator.

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 10		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Impurity Assessment

In the oral solution formulation, there are two impurities identified (b) (4) (b) (4) that required toxicological assessments for qualification at the proposed specifications of NMT (b) (4)%. For the first approval of NDA 203214 as a tablet formulation of tofacitinib, (b) (4) had a specification of ≤(b) (4)%, and (b) (4) was not an impurity.

(b) (4)

(b) (4) is the (b) (4) in the tofacitinib citrate drug substance (b) (4). In the oral solution, it is also a a degradant (b) (4) of tofacitinib that has the potential to increase during drug product stability. QSAR analysis using DEREK and SARAH programs resulted in a non mutagenic classification (Class 5).

In toxicity studies, (b) (4) was present at (b) (4)% in tofacitinib citrate lot 43798-2-1H used in the 6-week rat study and at (b) (4)% in lot E01001098 used in the 39-week juvenile monkey study (refer to the Pharmacology Toxicology review of July 3, 2012 for details of all studies mentioned in this section). In the 6-week rat study (Report 01-2063-06) at the NOAEL of 100 mg/kg/day, rats were dosed with 100 µg/kg/day of (b) (4) ((b) (4)% x 100 mg/kg/day). The Applicant also supported the safety of this impurity with the juvenile monkey study Report 09GR248, but that study lacked histopatholgical assessments for a full panel of organs and tissues and could only be considered partially supportive of the impurity qualification. Although the juvenile monkey study provided a 1.3 fold safety factor for assessments that were conducted, the study was not used to support this impurity. Comparing these amounts with the maximum anticipated pediatric level of (b) (4) µg/kg/day ((b) (4)% x 2 mg x 2/day per 5 kg child) indicates that the daily human pediatric dose is 2-fold less than the safe level determined from the rat study on a mg/m^2 basis. In most cases, a toxicology study with a minimum duration of 13 weeks is required for qualification of an

impurity in a chronically used drug impurity; however, the 6-week rat study with support from the 39-week juvenile monkey study was considered acceptable.

- The NMT (b) (4)% specification level is acceptable for impurity (b) (4).

(b) (4) is an (b) (4) degradation product in photo, thermal stability studies and importantly has the (b) (4) as metabolite (b) (4). The metabolite is formed in human, monkey and rat and is detectable in the plasma. QSAR analysis using DEREK and SARAH programs resulted in a non mutagenic classification (Class 5).

In mass balance studies in rats, monkeys, and humans, radioactive metabolite (b) (4) of radioactive labeled tofacitinib was measure in plasma. The levels in plasma were rat (b) (4)% over 0-8 hr postdose (10 mg/kg, oral; Report DM2005-690550-055), monkey (b) (4)% 0-2 hr, (b) (4)% 0-24 hr postdose (5 mg/kg, oral; Report DM2004-690550-052), and human (b) (4)% 0-8 hr postdose (50 mg/kg; label dosage 5 or 10 mg BID; Report DM2004-690550-049). The values for the rat and monkey were extrapolated to provide body burden dose, in µg/day, (refer to the tables below) based on rat and monkey repeated dosing studies at NOAELs assuming no metabolism or elimination. The calculated body burden of (b) (4) at the high dose in rats was (b) (4) µg/kg/day, or (b) (4) µg/m^2/day. The maximum exposure in a 2 year old child was calculated to be (b) (4) ug/kg/day or (b) (4) ug/m^2/day. At the (b) (4)% impurity specification level, the body burden would increase slightly to (b) (4) µg/kg/day, just above the calculated (b) (4) µg/kg/day value. The expected level in a 2 year old child would be 16-fold less than that calculated to occur in the rat at the NOAEL dose extrapolated from empirical data. This was considered acceptable to qualify (b) (4) at a specification of (b) (4)%.

- The NMT (b) (4)% specification level is acceptable for impurity (b) (4).

Table 2. (b) (4) Abundance as % of Dose from Mass Balance Studies in Human, Rat, and Monkey

Excreta	Human	Male Rat	Female Rat	Monkey
Urine	(b) (4)			
Feces				
Total				

ND = Not detected.
Source Documents: Human mass balance Study DM2004-690550-049 (Table 7/8); Rat mass balance Study DM2005-690550-055 (Table 6); Monkey mass balance Study DM2004-690550-052 (Table 10).

Table 3. Calculated Body Burden of Metabolite (b) (4) of Tofacitinib in Rats Based on 6-Month Chronic Toxicology Doses

Tofacitinib Dose (mg/kg/day)	Sex	Tofacitinib Dose (µg/kg/day)	(b) (4) Metabolite[a]	
			(µg/kg/day)	(µg/m²/day[b])
1	Male	1000	(b) (4)	
1	Female	1000		
10	Male	10000		
10	Female	10000		
100	Male	100000		
100	Female	100000		

a (b) (4)% for males and (b) (4)% for females by mass balance multiplied by tofacitinib daily dose.
b. Conversion factor = 6 (Nair & Jacob, 2016).

Table 4. Calculated Body Burden of Metabolite (b) (4) of Tofacitinib in Monkeys Based on 9-Month Chronic Toxicology Doses

Tofacitinib Dose (mg/kg/day)	Tofacitinib Dose (µg/kg/day)	(b) (4) Metabolite[a]	
		(µg/kg/day)	(µg/m²/day)[b]
0.5	500	(b) (4)	
2	2000		
10	10000		

a. (b) (4)% by mass balance multiplied by tofacitinib daily dose.
b. Conversion factor = 12 (Nair & Jacob, 2016).

Table 5. Calculated Body Burden of Metabolite (b) (4) of Tofacitinib in Human Pediatric Subjects Based on Body Weight Doses

Tofacitinib Dose	Body Weight (kg)	Tofacitinib Dose (µg/kg/day)[a]	(b) (4) Metabolite[b]		(b) (4) Metabolite with (b) (4)% Impurity	
			(µg/kg/day)	(µg/m²/day)[c]	(µg/kg/day)	(µg/m²/day)[c]
5 mg BID						
2	5 to <7	800	(b) (4)			
2.5	7 to <10	714				
3	10 to <15	600				
3.5	15 to <25	467				
4	25 to <40	320				
5	≥40	250				

BID = Twice daily.
a. Tofacitinib dose based on the lower limit of body weight range.
b. (b) (4)% by mass balance multiplied by tofacitinib daily dose.
c. Conversion factor = 25 (Nair & Jacob, 2016).

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

15.4.1 Summary of Bioanalytical Assays

Tofacitinib in human plasma has been measured using solid phase extraction followed by high-performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS) as listed in

Table 55. The HPLC-MS/MS method (Pfizer Validation A3929023) was initially developed and validated at (b) (4) (Table 56) and then transferred to (b) (4) (b) (4) and validated (Pfizer Validation A3929032) (Table 57). The bioanalytical assays were cross validated between (b) (4). All clinical samples were analyzed within the established stability period.

Table 55. Summary of the bioanalytical methods for tofacitinib measurement in human plasma

Clinical Study	Assay Laboratory	Pfizer Validation No.	Compound Analyzed	Matrix	Inter-run Precision %CV[a]	Inter-run Accuracy %RE	ISR
A3921103	(b) (4)	A3929023	Tofacitinib	Plasma	≤5.9%	-1.5% to 1.7%	Yes
A3921104		A3929023	Tofacitinib	Plasma	≤28.9%[b]	0.8% to 7.3%	Yes
A3921104		A3929032	Tofacitinib	Plasma	≤5.85%	-2.55% to 0.297%	Yes
A3921145		A3929023	Tofacitinib	Plasma	≤7.9%	0.3% to 4.0%	Yes
A3921145		A3929032	Tofacitinib	Plasma	≤20.5%[c] ≤3.65%[d]	-5.24% to -0.731%[c] -2.33% to -0.731%[d]	Yes
A3921354		A3929032	Tofacitinib	Plasma	1.61% to 5.97%	-2.65% to -1.32%	Yes

%CV = percentage coefficient of variation; %RE = percentage relative error; ISR = incurred sample reanalysis; HPLC-MS/MS = High Performance Liquid Chromatography and Tandem Mass Spectrometry SOP = standard operating procedure; QC = quality control; QCL = low quality control samples; (b) (4)

a. Statistics (%RE and %CV) based on mean assay performance of low, mid-low, mid-high, high and dilution (if applicable) QC samples from all analytical batches meeting acceptance criteria.

b. Overall %CV at QCL was >15% due to the abnormally high RE% for one QCL sample in Run 24 from Study A3921104. Upon examination of sample preparation record and HPLC-MS/MS data of this QCL sample, there was no obvious analytical reason and preparation error or contamination. Therefore, this QC was included in overall QC statistical calculation. Run 24 met acceptance criteria defined in bioanalytical study plan and the SOPs of Pfizer and (b) (4). It is concluded that the high %CV of QCL has no impact to sample results.

c. Includes one statistical outlier. Outlier assessment was based on laboratory SOP.

d. Excludes statistical outlier. Outlier assessment was based on laboratory SOP.

Source: Table 7 of Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 56. Summary of the bioanalytical method validation for the determination of tofacitinib in human plasma (Validation report A3929023)

Report Title	The Validation of an HPLC-MS/MS Assay Method for the Determination of CP-690550 in Human Lithium Heparin Plasma Addendum 01
Pfizer Validation Plan Number	A3929023
Pfizer Sponsor Location	Groton, USA
Pfizer Principal Contact	Haihong Shi
Bioanalytical Laboratory	(b) (4)
Bioanalytical Laboratory Project Reference	12BAS0395
Bioanalytical Laboratory Method Number	11BASM165V1
Principal Bioanalytical Investigator	(b) (4)
Method Description	
Reference Standard(s)	CP-690550, Lot 65806-24-5QS
Internal Standard	PF-4994438-10, Lot 00116516-0151-KTG00A
Matrix	Human Plasma
Anticoagulant	Lithium Heparin, Cross with Sodium Heparin
Source of Control Matrix	(b) (4)
Sample Storage Temperature	-20±5°C
Extraction Method	Solid Phase Extraction
Detection Method	HPLC-MS/MS
Sample Aliquot Volume	50 µL
Regression, Weighting	Quadratic, 1/conc. squared
Quantification	Peak Area Ratios
Calibration Range	0.100 to 350 ng/mL
ULOQ	350 ng/mL
LLOQ	0.100 ng/mL
Validation (VQC) Sample Concentrations	0.100, 0.300, 4.00, 40.0, 280 and 700 (dilution VQC) ng/mL
Assay Performance	
Intra-Assay Validation (VQC) Sample Statistics	Precision (%CV) ≤ 12.4%; Accuracy (%RE) -8.0% to 2.5%
Inter-Assay Validation (VQC) Sample Statistics	Precision (%CV) ≤ 9.9%; Accuracy (%RE) -3.8% to 7.0%
Dilution Factors	10-fold

Selectivity	
Matrix	6 out of 6 Human Lithium Heparin Plasma Lots Passed
Analyte Carryover	≤12.3%
Internal Standard Carryover	≤0.3%
Stability	
Ambient Temperature Matrix Stability	25.5 hours at 25±5°C in human lithium heparin plasma
Frozen Storage Matrix Stability	35, 103 days in human lithium heparin plasma at -20±5°C and -80±10°C
Freeze/Thaw Matrix Stability	5 Cycles at -20±5°C and -80±10°C in human lithium heparin plasma
Extract Stability	122.5 hours at room temperature in 50% MeOH
Re-injection Reproducibility Stability	86hours at room temperature in 50% MeOH

Note that the long term stability has been updated to be 943 days in Addendum 05.

Source: Validation summary from Bioanalytical Metgod Validation Report A3929023 Addendum 01

Table 57. Summary of the bioanalytical method validation for the determination of tofacitinib in human plasma (Validation report A3929032)

Report Title	The Validation of an LC-MS/MS Method for the Determination of CP-690,550 in Lithium Heparin Human Plasma
Pfizer Validation Plan Number	A3929032
Pfizer Sponsor Location	Groton, CT, USA
Pfizer Principal Contact	Penelope Crownover
Bioanalytical Laboratory	(b) (4)
Bioanalytical Laboratory Project Reference	RGTF2
Bioanalytical Laboratory Method Number	LCMSD 826
Principal Bioanalytical Investigator	(b) (4)
Method Description	
Reference Standard	CP-690,550 (Tofacitinib Citrate), Lot 120278-QCS
Internal Standard	PF-04994438-10 ([$^{13}C_3$, ^{15}N]CP-690,550-10), Lot 00116516-0151-KTG00A
Biological Matrix	Human Plasma
Anticoagulant	Lithium Heparin
Matrix Modification	None
Source of Control Matrix	(b) (4)
Sample Storage Temperature	-25 ± 5 °C
Extraction Method	Solid Phase Extraction
Detection Method	LC-MS/MS
Sample Aliquot Volume	50 µL
Regression, Weighting	Linear, 1/concentration^2
Quantification	Peak Area Ratios
Calibration Range	0.100 to 100 ng/mL
ULOQ	100 ng/mL
LLOQ	0.100 ng/mL
Validation Sample Concentrations	0.100, 0.300, 10.0, 40.0, 75.0, and 200 (dilution) ng/mL
Assay Performance	
Intra-Assay Validation Sample Statistics	Precision (%CV) ≤ 4.90%; Accuracy (%RE) -4.73% to 5.55%
Inter-Assay Validation Sample Statistics	Precision (%CV) ≤ 4.88%; Accuracy (%RE) -2.04% to 1.31%
Dilution Factors	10-fold
Analyte Recovery	79.1%
Internal Standard Recovery	76.2%

Selectivity			
ULOQ Selectivity	No peaks detected at the mass transitions or expected retention time of the unfortified internal standard		
Matrix Effects	10 out of 10 individual human lots fortified with 0.300 ng/mL and 75.0 ng/mL CP-690,550 met acceptance criteria		
Analyte Interference Check	No effect on the quantitation of CP-690,550 in human plasma		
Selectivity Check for Co-Administered Medications	No effect on the quantitation of CP-690,550 in human plasma		
	Medication	Lot	Concentration
	Nicotine	R02011	0.1 µg/mL
	Acetylsalicylic Acid	SLBH3575V	10 µg/mL
	Theophylline	J1H052	25 µg/mL
	Cotinine	FN10221506	0.5 µg/mL
	Caffeine	K0K210	20 µg/mL
	Ibuprofen	R024X0	50 µg/mL
	Dextromethorphan	FN070912-02	0.05 µg/mL
	Dextrorphan	070m4616v	0.8 µg/mL
	Acetaminophen	K01244	50 µg/mL
Analyte Carryover	≤ 20%		
Internal Standard Carryover	≤ 5%		
Stability			
Stock Solution	29 days at 2 to 8 °C for 100 µg/mL in acetonitrile/water (50:50, v/v) 29 days at 2 to 8 °C for 10.0 µg/mL in acetonitrile/water (50:50, v/v) 6 hours at room temperature for 100 µg/mL in acetonitrile/water (50:50, v/v) 6 hours at room temperature for 10.0 µg/mL in acetonitrile/water (50:50, v/v)		
Internal Standard Stock Solution	29 days at 2 to 8 °C for 100 µg/mL in acetonitrile/water (50:50, v/v) 6 hours at room temperature for 10.0 µg/mL in acetonitrile/water (50:50, v/v)		
Working IS Solution	26 days at 2 to 8 °C for 10.0 ng/mL in acetonitrile/water (50:50, v/v)		
Ambient Temperature Matrix Stability*	23 hours at room temperature		
Frozen Storage Matrix Stability*	12 days at -25 ± 5 °C and -80 ± 10 °C		
Freeze/Thaw Matrix Stability*	5 cycles at -25 ± 5 °C 5 cycles at -80 ± 10 °C		
Re-injection Reproducibility Stability	63.9 hours at 2 to 8 °C		
Extract Stability	123 hours at 2 to 8 °C		
Whole Blood Stability	2 hours on ice and at room temperature with either a room temperature or refrigerated centrifuge		

* Time 0 was analyzed and additional timepoints will be run and added to the report as an addendum.

Note that the long term stability has been updated to be 973 days in Addendum 03.

Source: Validation summary from Bioanalytical Metgod Validation Report A3929032

15.4.2 Pharmacometrics Review

Report title
Population PK analysis of tofacitinib (CP-690,550) in polyarticular juvenile idiopathic arthritis (pJIA) patients

Objectives

- To describe the PK of CP-690,550 in pediatric patients from 2 to less than 18 years of age with pJIA
- To Identify potential covariates in the study population(s) which account for the variability in CP-690,550 exposure

Software
The population PK model was conducted out using the nonlinear mixed effects modeling approach. The software package NONMEMR (ICON Development Solutions, Hanover, MD) version 7.4.1 and Perl-speaks-NONMEM (PsN) version 4.8.0 as supporting software for the execution of NONMEM were used. R version 3.4.1 was used for data handling, exploratory data analysis and creation of graphs for presentations and reports. R package, Xpose4 version 4.6.1 was used to export PK parameter. mrgsolve R package version 0.8.10 was used for simulation. The estimation method was the first order conditional with interaction (FOCEI).

Data Source
Tofacitinib population PK analysis in pcJIA patients includes data from a Phase 1 PK study (A3921103), a pivotal phase 3 study (A3921104), and an ongoing long term extension (LTE) Study (A3921145), in which patients from Studies A3921103 and A3921104 were furthermore enrolled for long-term safety assessment. A total of 1392 plasma concentration records of 246 subjects were included in the final analysis. The study design of the three clinical studies are summarized in Table 58. Tofacitinib was orally administered twice daily based on age and/or body weight (refer to the Clinical Pharmacology Review in Section 6 for more details). The key baseline continuous and categorical demographics are summarized in Table 59 and Table 60, respectively.

Table 58. Summary of studies included in the population PK analysis

Protocol	Phase	Protocol Design	Population	n	Plasma Sampling Schedule for PK
A3921103	1	A open-label, non-randomized, multi-center, multiple-dose (for 5 days) study to characterize the PK and safety of CP-690,550	Pediatric subjects with active JIA from 2 to <18 years of age	26	0 (pre-dose), 0.5, 1, 4, and 8 hours post morning dose on Day 5 (approximately 11-13 hour postdose since the evening dose on Day 4)
A3921104	3	A randomized withdrawal (18 weeks open-label phase) then double-blind, placebo controlled study (26 weeks double-blind phase) to compare the efficacy of CP-690,550 versus placebo for the treatment of signs and symptoms of JIA	Pediatric subjects with active JIA from 2 to <18 years old	225	In the first 40 subjects[a] enrolled : 0.25, 0.75, 3 hours post dose on Day 1. For all subsequent subjects[a] enrolled, 0 (pre-dose), 0.75 and 3 hours post dose on Day 14 (or Day 28). For all subjects, 0 (pre-dose) and 0.75 hours post dose on Day 84 (or later visit up to Day 126).
A3921145[b]	2/3	A long-term, open label, follow-up study to characterize long-term safety and tolerability of CP-690,550 for the treatment of JIA. Planned to run until the first global marketing approval of CP-690,550 for the treatment of JIA	Pediatric subjects who previously participated in qualifying/index studies A3921103 and A3921104	230	0 (pre-dose), 0.5 and 2 hours post dose at Month 12, Month 24, Month 36 visits, and/or at Early Termination (if feasible) up to Month 36.

Source: Table 3 of Population PK Report

Table 59. Key continuous demographic and baseline characteristics by treatment

Covariate	Statistic	2 mg	2.5 mg	3 mg	3.5 mg	4 mg	5 mg	10 mg	Total
Age (yrs)	Mean	7	7.6	4.89	5.97	10.5	14.2	13	11.6
	Median	7	9	4	6	10	15	12	12
	Min	6	3	2	2	7	8	10	2
	Max	8	11	12	10	16	17	17	17
	SD	1.41	3.85	3.38	1.61	2.28	2.14	3.61	4.2
Body Weight (kg)	Mean	22.4	22.3	19.8	20.9	32.6	57.7	54.7	44.8
	Median	22.4	27.2	17	20.7	34	55.8	58.6	46.3
	Min	20.3	13.9	11.1	15	25.3	38	42.9	11.1
	Max	24.5	28	38.4	24.9	38.5	122	62.5	122

Covariate	Statistic	2 mg	2.5 mg	3 mg	3.5 mg	4 mg	5 mg	10 mg	Total
	SD	2.97	7.5	9.68	2.61	4.07	12.6	10.4	19.2
Height (cm)	Mean	118	121	109	116	140	160	158	146
	Median	118	130	102	116	142	159	160	152
	Min	111	99	85	93	123	136	144	85
	Max	124	142	155	134	152	186	168	186
	SD	8.91	20.3	21.4	9.24	8.52	9.61	12.3	22.1
Body mass index (kg/m^2)	Mean	16.1	14.8	15.8	15.6	16.7	22.5	21.9	19.9
	Median	16.1	14.3	15.6	15.8	16.4	22	22.1	19.5
	Min	15.9	13.6	12	13.2	13.7	16.1	20.7	12
	Max	16.4	16.6	20.5	19.9	20.8	43.9	22.8	43.9
	SD	0.304	1.21	2.16	1.49	1.81	4.06	1.06	4.58
Body surface area (m^2)	Mean	0.854	0.869	0.766	0.819	1.13	1.59	1.54	1.33
	Median	0.854	1.01	0.64	0.822	1.17	1.57	1.61	1.4
	Min	0.787	0.615	0.517	0.609	0.953	1.24	1.3	0.517
	Max	0.921	1.06	1.31	0.971	1.28	2.26	1.71	2.26
	SD	0.0948	0.229	0.265	0.0856	0.101	0.187	0.212	0.377
Creatinine clearance (mL/min)	Mean	170	160	185	170	172	153	141	161
	Median	170	156	170	164	161	143	147	155
	Min	136	136	123	92.7	72.2	81.7	119	72.2
	Max	204	183	275	239	269	407	158	407
	SD	48	19.8	46.5	32	42.9	42.5	20.5	42.2
Serum creatinine (mg/dL)	Mean	0.4	0.42	0.353	0.388	0.444	0.603	0.667	0.525
	Median	0.4	0.4	0.3	0.4	0.4	0.6	0.6	0.5
	Min	0.3	0.3	0.2	0.3	0.3	0.3	0.5	0.2
	Max	0.5	0.5	0.6	0.7	0.7	1.2	0.9	1.2
	SD	0.141	0.0837	0.135	0.0857	0.102	0.13	0.208	0.157
C-reactive protein (mg/dL)	Mean	0.125	0.988	1.94	1.36	1.35	0.91	0.97	1.12
	Median	0.125	0.52	0.19	0.24	0.36	0.17	0.02	0.21
	Min	0.02	0.03	0.02	0.02	0.02	0.02	0.02	0.02
	Max	0.23	2.53	10.8	8.66	8.69	12.5	2.87	12.5
	SD	0.148	1.11	3.34	2.21	2.2	1.91	1.65	2.12
Albumin (g/dL)	Mean	4.35	4.26	4.21	4.25	4.12	4.32	4.1	4.27
	Median	4.35	4.2	4.2	4.3	4.1	4.3	3.9	4.3
	Min	4.1	4	3.6	3.4	3.3	3.4	3.9	3.3
	Max	4.6	4.5	4.9	4.9	5.1	5.5	4.5	5.5
	SD	0.354	0.195	0.363	0.298	0.407	0.354	0.346	0.358
Alanine transaminase	Mean	20.5	19.4	14.3	12	12.5	17.4	18	15.7

Covariate	Statistic	2 mg	2.5 mg	3 mg	3.5 mg	4 mg	5 mg	10 mg	Total
(U/L)	Median	20.5	15	15	12	11	14	17	13
	Min	13	8	7	5	5	5	15	5
	Max	28	38	23	23	28	139	22	139
	SD	10.6	11.9	5.06	3.72	5.34	14.2	3.61	11.6
Alkaline phosphatase	Mean	179	194	205	171	192	132	112	154
(U/L)	Median	179	213	195	184	178	108	126	140
	Min	139	88	106	48	72	27	75	27
	Max	219	251	311	258	481	423	136	481
	SD	56.6	62.3	54.5	52.1	78.8	72.7	32.7	74.4
Aspartate transaminase	Mean	28.5	33.2	27.3	24.4	21.7	20	25	21.8
(U/L)	Median	28.5	29	31	25	21	19	25	20
	Min	19	23	19	13	11	9	24	9
	Max	38	53	34	34	35	79	26	79
	SD	13.4	12.4	6.11	5.33	5.44	7.5	1	7.46
PGA score	Mean	7.5	7.4	7	6.3	6.67	6.32	7.33	6.47
	Median	7.5	8	7	7	7	6	8	7
	Min	6	5	3	2	2	2	6	2
	Max	9	9	10	9	10	10	8	10
	SD	2.12	1.82	1.53	2.02	1.95	1.92	1.15	1.9
CHAQ score	Mean	2	1	1.13	1.09	1.03	0.978	0.667	1.01
	Median	2	1	1	1	1	1	0	1
	Min	2	0	0	0	0	0	0	0
	Max	2	2	3	3	3	3	2	3
	SD	0	1	0.99	0.914	0.843	0.781	1.15	0.826
BJADAC score	Mean			21.1	21	23.8	21	23.3	21.5
	Median			18	19.5	24	20	24	20
	Min			12	9	8	6	16	6
	Max			38	38	52	41	30	52
	SD			7.94	8.36	9.66	7.03	7.02	7.79
BJADAE score	Mean			19.7	20.9	24	20.8	23	21.3
	Median			17	21	21	20	24	20
	Min			12	9	10	5	16	5
	Max			37	38	52	40	29	52
	SD			7.07	8.1	10	7.07	6.56	7.85

BJADAC and BJADAE scores are not available for 2-2.5 mg dose groups since these dose groups exist only in Study A3921103, which did not collect any efficacy endpoints. Abbreviations: Baseline values for BAGE: age; BWT: weight; BHT: height; BBMI: body mass index; BCCL: creatinine clearance; BCRP: C-reactive protein; BALB: albumin; BALK: alkaline phosphatase; BALT: alanine transaminase; BAST: aspartate transaminase; BBSA: body surface area; CHAQ:Childhood Health Assessment Questionnaire; BJADAC: Juvenile Arthritis Disease Activity Score with C-Reactive Protein; BJADAE:Juvenile Arthritis Disease Activity Score with Erythrocyte Sedimentation Rate.

Source: Table 5 of Population PK Report

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Table 60. Key categorical demographic and baseline characteristics by treatment

Covariate	Level	2 mg	2.5 mg	3 mg	3.5 mg	4 mg	5 mg	10 mg	Total
Total		2 (0.8)	5 (2)	19 (7.7)	33 (13.4)	39 (15.9)	145 (58.9)	3 (1.2)	246 (100)
PROTOCOL*	A3921103	2 (100)	5 (100)	10 (52.6)	1 (3)	0	8 (5.5)	0	26 (10.6)
	A3921104	0	0	9 (47.4)	32 (97)	39 (100)	137 (94.5)	3 (100)	220 (89.4)
SEX	Female	0	3 (60)	14 (73.7)	24 (72.7)	29 (74.4)	110 (75.9)	2 (66.7)	182 (74)
	Male	2 (100)	2 (40)	5 (26.3)	9 (27.3)	10 (25.6)	35 (24.1)	1 (33.3)	64 (26)
RACE	Black	0	0	0	0	1 (2.6)	4 (2.8)	0	5 (2)
	Other	0	0	1 (5.3)	4 (12.1)	6 (15.4)	14 (9.7)	0	25 (10.2)
	White	2 (100)	5 (100)	18 (94.7)	29 (87.9)	32 (82.1)	127 (87.6)	3 (100)	216 (87.8)
ETHNICITY	Hispanic or Latino	0	0	1 (5.3)	9 (27.3)	14 (35.9)	38 (26.2)	0	62 (25.2)
	Not Hispanic or Latino	0	0	8 (42.1)	23 (69.7)	25 (64.1)	99 (68.3)	3 (100)	158 (64.2)
	Unknown	2 (100)	5 (100)	10 (52.6)	1 (3)	0	8 (5.5)	0	26 (10.6)
FORMULATION*	Solution	2 (100)	5 (100)	19 (100)	33 (100)	39 (100)	2 (1.4)	0	100 (40.7)
	Tablet	0	0	0	0	0	143 (98.6)	3 (100)	146 (59.3)
TNF-ALPHA	TNF experienced	0	0	1 (5.3)	8 (24.2)	16 (41)	45 (31)	3 (100)	73 (29.7)
	TNF naive	2 (100)	5 (100)	18 (94.7)	25 (75.8)	23 (59)	100 (69)	0	173 (70.3)
ORAL STEROIDS	Concomitant use	0	0	1 (5.3) (10.5)	8 (24.2) (3)	16 (41) (5.1)	45 (31) (4.8)	2 (100) (33.3)	13 (5.3)

Covariate	Level	2 mg	2.5 mg	3 mg	3.5 mg	4 mg	5 mg	10 mg	Total
	No concomitant use	2 (100) (100)	5 (100) (100)	18 (94.7) (89.5)	25 (75.8) (97)	23 (59) (94.9)	100 (69) (95.2)	3 (100) (66.7)	233 (94.7)
METHOTREXATE	Concomitant use	0	5 (100)	10 (52.6)	3 (9.1)	3 (7.7)	17 (11.7)	0	38 (15.4)
	No concomitant use	2 (100)	0	9 (47.4)	30 (90.9)	36 (92.3)	128 (88.3)	3 (100)	208 (84.6)
NSAID/COX-2	Concomitant use	1 (50)	3 (60)	6 (31.6)	4 (12.1)	6 (15.4)	20 (13.8)	0	40 (16.3)
	No concomitant use	1 (50)	2 (40)	13 (68.4)	29 (87.9)	33 (84.6)	125 (86.2)	3 (100)	206 (83.7)
NUMBER DMARD FAILURES	0	2 (100)	0	1 (5.3)	2 (6.1)	0	12 (8.3)	0	17 (6.9)
	1	0	3 (60)	13 (68.4)	17 (51.5)	17 (43.6)	62 (42.8)	0	112 (45.5)
	2	0	1 (20)	5 (26.3)	8 (24.2)	10 (25.6)	39 (26.9)	1 (33.3)	64 (26)
	3	0	1 (20)	0	6 (18.2)	12 (30.8)	32 (22.1)	2 (66.7)	53 (21.5)
JIA CATEGORY	Patient extended oligoarthritis	0	0	5 (26.3)	8 (24.2)	3 (7.7)	14 (9.7)	1 (33.3)	31 (12.6)
	Patient polyarthritis RF+	0	0	0	2 (6.1)	7 (17.9)	29 (20)	0	38 (15.4)
	Patient polyarthritis RF-	1 (50)	5 (100)	13 (68.4)	16 (48.5)	21 (53.8)	64 (44.1)	0	120 (48.8)
	Patient psoriatic arthritis	1 (50)	0	0	1 (3)	1 (2.6)	18 (12.4)	1 (33.3)	22 (8.9)
	Patient systemic JIA with active arthritis but without active systemic features	0	0	1 (5.3)	4 (12.1)	3 (7.7)	4 (2.8)	0	12 (4.9)
	Patient with enthesitis related arthritis	0	0	0	2 (6.1)	4 (10.3)	16 (11)	1 (33.3)	23 (9.3)

Source: Table 6 of Population PK Report

Population PK Model Development:
The analyses were conducted in the following steps: 1) Base structural model development 2) Random effects model development 3) Covariate model development 4) Final model development 5) Assessment of Model Predictive Performance (Validation)

In brief, a population PK model was developed using the nonlinear mixed effects modeling approach to characterize the population PK of tofacitinib in subjects with pcJIA. A prior population PK model with only data from PK Study A3921103 was used as a base one-compartment model with first-order absorption. A priori allometric weight scaling was inherently built into all disposition parameters with exponent coefficients, to be estimated. A stepwise covariate testing approach was used to identify a final model with significant covariates. Covariates evaluated in the POPPK analysis are summarized in Table 61. Continuous covariates were included in the model as a power function referenced to the median of the observed data. Categorical covariates were entered into the model as a single coefficient, with a separate dichotomous (0, 1) variable serving as an indicator for each category. P-values of 0.05 and 0.001 were chosen for inclusion (forward) and exclusion (backward) of an additional covariate to find a parsimonious final model, respectively. The final model was evaluated based on goodness-of-fit plots, nonparametric bootstrap, and visual predictive checks.

Table 61. Potential covariate relationships for assessment

Population Parameter	Covariates
CL/F	Sex, age, race, patient type (JIA categories: extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, systemic JIA with active arthritis but without active systemic features, psoriatic and enthesitis related arthritis), extent of disease (baseline PGA, JADAS-27, CHAQ), region, baseline renal function, baseline C-reactive protein, baseline Albumine, baseline Alanine transaminase, baseline Aspartate transaminase, baseline Alkaline phosphatase, concomitant medication (steroids, methotrexate, DMARDs, etc.)
Vc/F	Sex, age, race, patient type (JIA categories)
k_a	Formulation (oral solution, tablet)
F	Formulation (oral solution, tablet)

Source: Table 4 of Population PK Report

Results
A one compartment disposition model with first order absorption and a lag time was retained as the final model to adequately describe tofacitinib plasma concentration-time profiles in pcJIA. The allometric model was used to describe the effect of body weight over time on these PK parameters. Formulation was identified as a significant covariate on ka, where oral solution is associated with 1.64-fold more rapid absorption than tablet.

Visual predictive check indicated that the final model described the central tendency and variability of the data well. The estimated pharmacokinetic parameter values based on the original dataset were in good agreement with the medians of the parameter values estimated from the bootstrap replicates. The fixed and random effects parameter estimates for the final population pharmacokinetic model are listed in Table 62. The goodness-of-fit plots for the final model for all data are shown in Figure 5. The Visual Predictive Check plot for the final model as tims after dose and by baseline body weight are shown in Figure 6 and Figure 7.

Table 62. Parameter estimates for final model

Parameter	Estimate	RSE(%)	95% CI	SIR Estimate	SIR 95% CI
$\theta_{CL/F}(L/hr)$	26.053	2.30	(24.880 - 27.226)	26.069	(25.200, 27.127)
$\theta_{V}(L)$	89.217	2.55	(84.755 - 93.679)	89.316	(86.117, 92.905)
$\theta_{Ka}(hr^{-1})$	2.779	12.04	(2.123 - 3.435)	2.768	(2.292, 3.440)
$\theta_{\text{Exponent on CL/F}}$	0.310	13.40	(0.228 - 0.391)	0.310	(0.248, 0.372)
$\theta_{\text{Exponent on V/F}}$	0.537	9.57	(0.436 - 0.637)	0.537	(0.475, 0.598)
$\theta_{\text{Covariance between CL/F and V/F}}$	0.273	38.91	(0.065 - 0.481)	0.271	(0.136, 0.414)
$\theta_{\text{Error}}(\%)$	40.98	5.95	(36.20 - 45.76)	41.00	(37.84, 44.46)
$\theta_{\text{Lag time}}(hr)$	0.186	5.02	(0.167 - 0.204)	0.18	(0.172, 0.195)
$\theta_{\text{Error before TAD=1.08hr}}(\%)$	67.96	6.17	(59.74 - 76.18)	67.991	(62.99, 73.44)
$\theta_{\text{Formulation Effect}}$	1.641	38.37	(0.407 - 2.875)	1.61	(0.947, 2.677)
$\omega_{CL/F}$	0.055	18.27	(0.036 - 0.075)	0.056	(0.043, 0.070)
$\omega_{\text{CL/F-Ka}}$*	-0.099	-33.97	(-0.166 - -0.033)	-0.097	(-0.148, -0.051)
ω_{Ka}	1.461	16.31	(0.994 - 1.928)	1.478	(1.133, 1.902)
$\omega_{\text{CL/F-Error}}$*	0.074	24.09	(0.039 - 0.109)	0.072	(0.053, 0.095)
$\omega_{\text{Ka-Error}}$*	-0.567	-11.47	(-0.695 - -0.440)	-0.555	(-0.679, -0.440)
ω_{Error}	0.247	13.61	(0.181 - 0.313)	0.245	(0.198, 0.309)

Repository artifact ID FI-197280. Line 1 substituted.
*ω represents the off-diagonal elements of the omega block; CI=Confidence Interval; RSE=Relative standard error; SIR=Sampling Importance Re-sampling; TAD=Time After Dose.

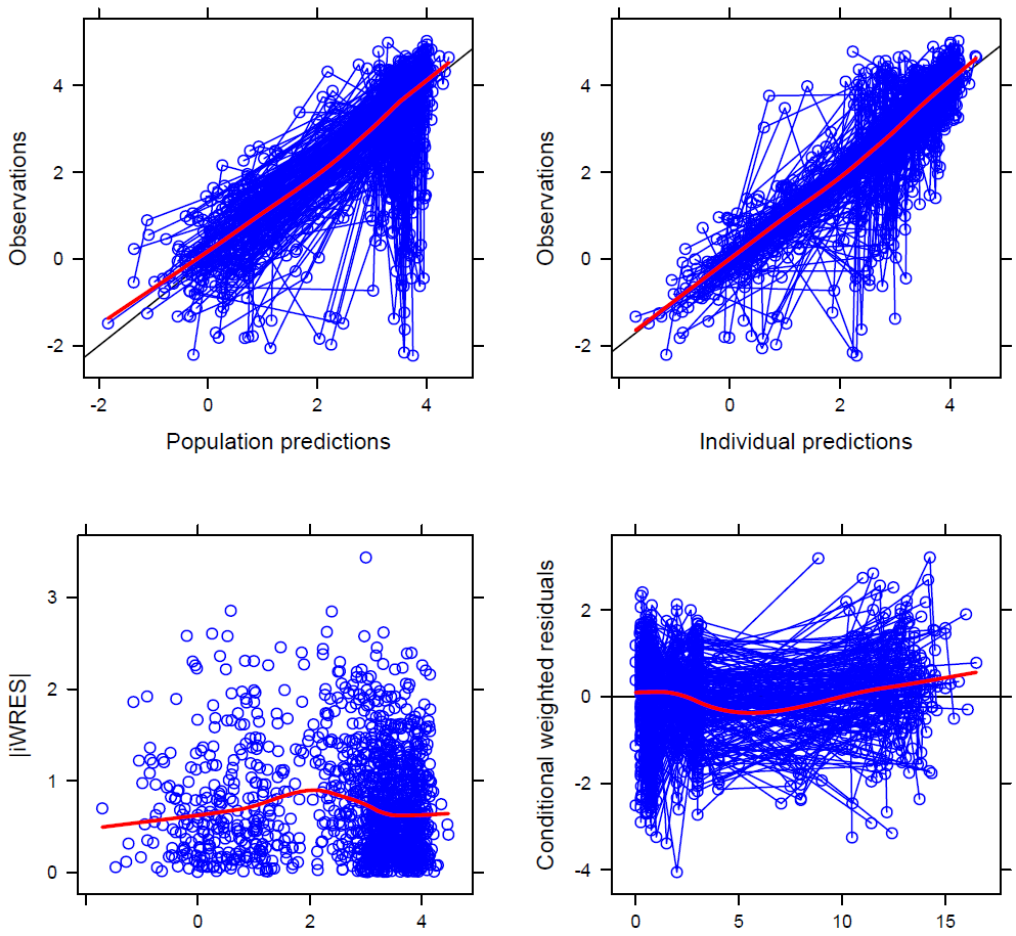
The inclusion of such characteristics is described in Equation 1:

$$TVCL_i = \theta_{TVCL} \cdot \left(\frac{WT_i}{70}\right)^{\theta_1} \quad TVV_{ci} = \theta_{TVV_c} \cdot \left(\frac{WT_i}{70}\right)^{\theta_2} \qquad (1)$$

Where $TVCL_i$ and TVV_{ci} are population typical values for CL and V_c for the i^{th} individual with weight, WT, kg and θ_1 and θ_2 are the allometric exponent estimates for CL/F and V/F, respectively.

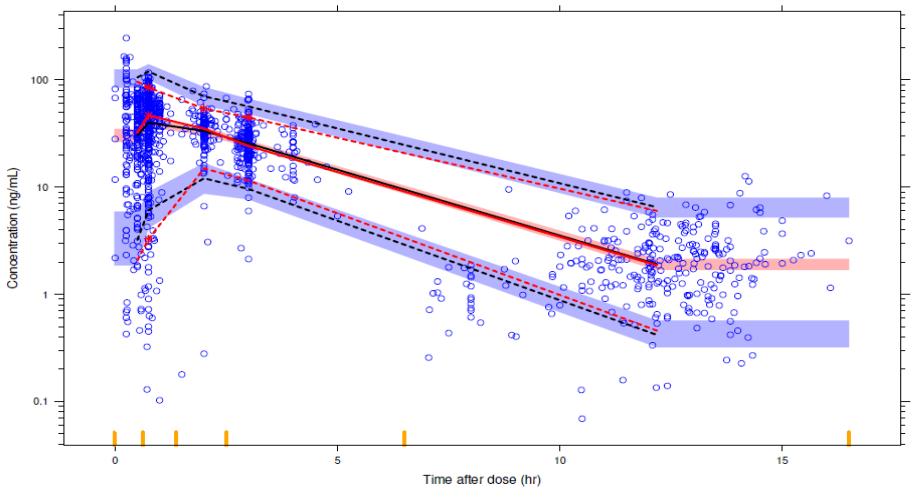
Source: Adapted from Table 9 of Population PK Report

Figure 5. Goodness-of-fit plots for the final model



Source: Figure 6 of Population PK Report

Figure 6. Prediction corrected visual predictive check for final PK model as time after dose

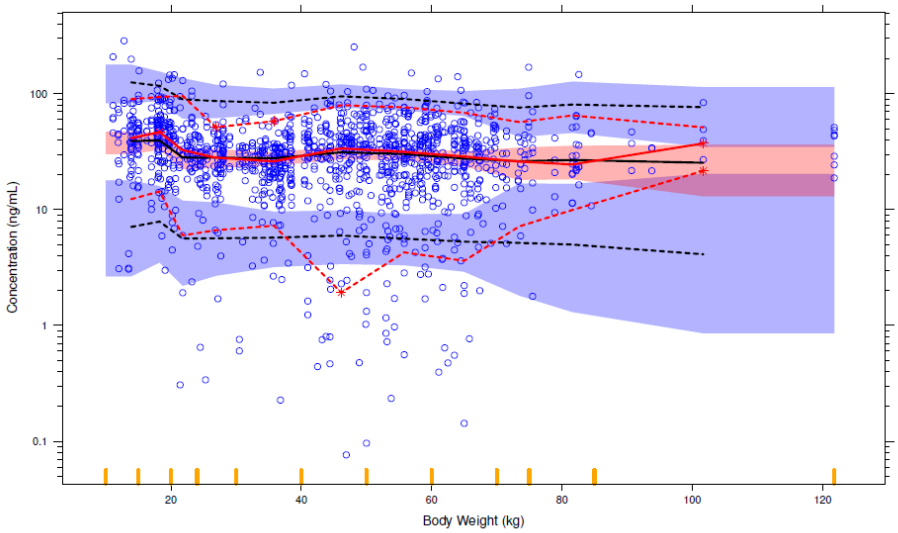


Repository artifact ID FI-484833.

Red dashed lines represent 90% confidence interval (95% upper limit and 5% lower limit) of observed data. Red solid line is median (50%) of observed data. Black dashed lines represent 90% predictive interval (95% upper limit and 5% lower limit) based on simulations. Black solid line represents median based on simulations. Shaded area is predicted 95% confidence interval of upper limit, lower limit or median (50%) based on simulations.

Source: Figure 9 of Population PK Report

Figure 7. Prediction corrected visual predictive check for final PK model vs. baseline body weight



Repository artifact ID FI-484836.
Red dashed lines represent 90% confidence interval (95% upper limit and 5% lower limit) of observed data. Red solid line is median (50%) of observed data. Black dashed lines represent 90% predictive interval (95% upper limit and 5% lower limit) based on simulations. Black solid line represents median based on simulations. Shaded area is predicted 95% confidence interval of upper limit, lower limit or median (50%) based on simulations.

Source: Figure 11 of Population PK Report

Reviewer's comments: *The applicant's population PK analysis is acceptable.*

- *The goodness-of-fit plots and the visual predictive check indicate that the developed population PK model with pooled PK data from the Phase 1 PK study (A3921103), pivotal phase 3 study (A3921104) and an ongoing LTE study (A3921145) adequately characterize the PK profiles of tofacitinib in patients with pcJIA.*
- *Body weight was identified to significantly impact the systemic exposure of tofacitinib, supporting the proposed weight-based dosing regimen in pcJIA subjects.*
- *Although formulation was identified as a significant covariant on Ka, suggesting 1.6-fold more rapid absorption of oral solution than tablet, results from a relative bioavailability study (A3921354) showed that following a single dose of 5 mg tofacitinib using XELJANZ IR tablets (5 mg) or oral solution (1mg/mL), the systemic exposure of tofacitinib (Cmax, AUC0-t, and AUC0-inf) are comparable. Refer to the Clinical Pharmacology Review in Section 7 for more detailed information.*
- *None of the other evaluated covariates such as age, race, gender, baseline disease severity, or JIA categories require dose adjustment.*

15.5. Additional Clinical Outcome Assessment Analyses

The Division sought input from the Division of Clinical Outcome Assessment (DCOA) on the adequacy of the CHAQ Disability Index (b) (4). Excerpt from the COA consult review dated Sep 1, 2020, is included below:

The Applicant administered the Childhood Health Assessment Questionnaire (CHAQ) caregiver-reported version to both caregivers and patients aged ≥ 14 years in Study A3921104 and seeks (b) (4) an assessment of ability to perform daily functional activities.

Based on information provided in this submission, the COA review concluded the following:

1. There is insufficient evidence to demonstrate that the CHAQ Disability Index caregiver-reported version is fit-for-purpose (b) (4) as the Applicant did not submit information to support content validity of the CHAQ Disability Index from the perspective of patients with JIA and their caregivers. In the absence of this information, in this submission, it is unclear if the CHAQ Disability Index measures functional activities that are relevant to (and age-appropriate for) patients and caregivers, and whether the instrument's instructions, items, and response options are appropriate and understandable to patients and caregivers as intended.
2. It is unclear whether the demonstrated change in CHAQ Disability Index score is clinically meaningful. Anchor-based analyses are our preferred method for determining clinically meaningful change thresholds for COA scores, but the Applicant did not include anchor scales in Study A3921104, so anchor-based analyses were not conducted. The Applicant cites published literature[1] that describes minimal clinically important differences (MCIDs) in CHAQ Disability Index scores of -0.188 for improvement and +0.125 for deterioration (on a scale of 0-3, where "0" indicates no difficulty performing functional activities and "3" indicates inability to conduct functional activities), but the authors of the publication noted that these differences were small and concluded that "the CHAQ in its current form may be too insensitive to determine important short term changes in health and disease for a given patient."

In summary, the DCOA consult team determined that there is limited information provided in this submission, to support the content validity of the CHAQ Disability Index from the perspective of patients with JIA and their caregivers, (b) (4) (b) (4). Additionally, the Applicant did not provide evidence to support a clinically meaningful within-patient change in the CHAQ Disability Index score.

[1] H I Brunner, M S Klein-Gitelman, M J Miller, A Barron, N Baldwin, M Trombley, A L Johnson, A Kress, D J Lovell, E H Giannini. *Minimal clinically important differences of the childhood health assessment questionnaire*. J Rheumatol. 2005 Jan;32(1):150-61.

15.6. Division of Pediatric and Maternal Health (DPMH) Consult Review

The Division sought input from DPMH for these tofacitinib submissions seeking a pediatric indication.

The sNDA 203214/S-026 for Xeljanz (tofacitinib) oral tablet, 5 mg, and the original NDA 213082 for Xeljanz (tofacitinib) oral solution, 1 mg/mL, for once daily dosing, propose a new dosing form and new indication in polyarticular-course juvenile idiopathic arthritis (pcJIA).

In the Approval Letter for XELJANZ (dated November 6, 2012) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate, FDA agreed to waive the pediatric study requirement for birth to less than 2 years of age because necessary studies are impossible or highly impracticable as pcJIA is not diagnosed in children less than 2 years of age. FDA also deferred submission of a pediatric study for ages 2 years through 17 years of age because the product is ready for approval for use in adults and the pediatric studies had not been completed at that time. The deferred pediatric studies required by section 505B(a) of the Food Drug Cosmetic Act (FDCA) are required postmarketing studies. Currently, there are no approved indications for XELJANZ (tofacitinib) in any pediatric patient population although Xeljanz has a PREA postmarketing requirement (PMR) for Ulcerative Colitis (UC). The PREA PMRs for pcJIA are summarized in this Unireview and have been determined to fulfill the PREA PMR requirements for this indication.

Section 8.4 (Pediatric Use) will state that safety and effectiveness of XELJANZ/XELJANZ Oral Solution for the treatment of active pcJIA have been established in pediatric patients from 2 years to 17 years of age. Use of XELJANZ/XELJANZ Oral Solution in this age group is supported by evidence from adequate and well-controlled studies of XELJANZ in adults with additional data from a clinical study of XELJANZ/XELJANZ Oral Solution in (b) (4) pediatric patients (2 years to 17 years of age) with active pcJIA consisting of an 18-week open label run-in period followed by a randomized, (b) (4) 26-week placebo-controlled period.

DPMH consult team assessment of the reported events of psychiatric disorders in the pcJIA clinical program:

Psychiatric Disorder events are reported in the pcJIA clinical study and the long-term extension study including depression, aggression, anxiety, anxiety disorder (mood), major depression, suicide disorder, suicide attempt, suicidal ideation, intentional self-injury, homicidal ideation, and intentional self-injury. The majority of these reported events do not appear to be causally attributed to tofacitinib exposure and are confounded by pre-existing medical history and/or temporally related to events of stress concurrently during exposure to tofacitinib. See the Unireview, Section 8.2 Review of Safety, for details on individual narratives with reported psychiatric disorders. Published literature in pediatric rheumatology reports that the

relationship between physical activity level, anxiety, depression, and functional ability in children and adolescents with juvenile idiopathic arthritis are correlated with disease activity, similarly as in adults.[1] The authors emphasized the need for clinical evaluation of the emotional state of children who report pain and that the incidence of psychiatric disorders such as depression and anxiety scores in JIA correlate with physical disability. Margetic B et al (2005) cite that pain perception was significantly correlated with depression scores.[2, 3]

As described in Xeljanz labeling, "JAK inhibitors are (b) (4) intracellular enzymes which transmit signals from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. (b) (4) (b) (4).[4] At this time, there does not appear to be a pathophysiologic plausible mechanism of action for attribution of causality to tofacitinib to affect psychiatric events via crossing into the blood brain barrier. However, published literature, Minnema LA et al. (2019)[5], report that several monoclonal antibodies, though different from the class of JAK inhibitors, have been linked to neuropsychiatric adverse effects in patients including depression and suicidal ideation and behavior.

[1] Aasland A et al. Psychological outcome in juvenile chronic arthritis: a nine-year follow-up. Clin Exp Rheumatol 1997; 15:561-8.
[2] Margetic B et al. Depression, Anxiety, and Pain in Children with JIA. 2005; Eur Psychiatry, 20(3): 274-276
[3] Rapoff MA, Lindsley CB, Karlson C. Medical and psychological aspects of juvenile rheumatoid arthritis in Roberts MC (Edition) Handbook of Pediatric Psychology, 4th ed, 2009, Guilford, New York, pages 366-380.
[4] sNDA 203214/s-026 XELJANZ (tofacitinib) oral tablet, 5 mg, and original NDA 213082 XELJANZ Oral Solution, labeling, Section 11 and 12, dated 9-9-20.
[5] Minnema LA et al. Exploring the Association between Monoclonal Antibodies and Depression and Suicidal Ideation and Behavior: a VigiBase Study. Drug Safety (2019) 42:887-895.

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