NDA 203214 S-038, NDA 208246 S-025, NDA 213082 S-010 Multi-Disciplinary Review Memorandum
Xeljanz, Xeljanz XR (tofacitinib)

sNDA Post-Approval Labeling Supplement Multi-Disciplinary Review Memorandum

Application Type	Post Approval Labeling Supplement with clinical data
Application Number(s)	NDA 203214 S-038; NDA 208246 S-025; NDA 213082 S-010
Priority or Standard	Priority
Submit Date(s)	August 23, 2024
Received Date(s)	August 23, 2024
PDUFA Goal Date	February 23, 2025
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 and tofacitinib XR
(Proposed) Trade Name	Xeljanz and Xeljanz XR
Pharmacologic Class	Janus kinase (JAK) inhibitor
Code name	CP-690,550
Applicant	Pfizer, Inc.
Dosage form	NDA 203214 S-038 Immediate-release oral tablet NDA 208246 S-025 Extended-release oral tablet NDA 213082, S-010 Oral Solution
Applicant proposed Dosing Regimen	Xeljanz: 5 mg twice daily; 1 mg/mL oral solution
Applicant Proposed Indication(s)/Population(s)	None
Recommendation on Regulatory Action	Approval of labeling changes

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Javonna Stevens, Pharm.D.
Office of Clinical Pharmacology Reviewer(s)	Lei He, Ph.D.
Office of Clinical Pharmacology Team Leader(s)	Jianmeng Chen, M.D., Ph.D.
Clinical Reviewer	Stefanie Freeman, M.D.
Clinical Team Leader	Eric J. Gapud, M.D., Ph.D.
Statistical Reviewer	Rabab Elnaiem, Ph.D.
Statistical Team Leader	Dong-Hyun Ahn, Ph.D.
Deputy Division Director	Ozlem Belen, M.D., M.P.H.

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
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
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
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Tofacitinib (CP-690,550, Xeljanz, Xeljanz XR) is an oral inhibitor of the Janus kinase (JAK) family of kinases. JAKs are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcriptions (STAT) which modulate intracellular activity including gene expression. Tofacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.

Tofacitinib was initially approved for the treatment of adult patients with rheumatoid arthritis (RA) on November 6, 2012 (new drug application [NDA] 203214). Tofacitinib Xeljanz/Xeljanz XR is currently approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more TNF blockers, treatment of adult patients with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to one or more TNF blockers, adult patients with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to one or more TNF blockers at a dose of 5 mg twice daily (Xeljanz immediate release [IR] tablets, NDA 203214), and at a dose of 11 mg once daily (Xeljanz XR modified release [MR] tablets, NDA 208246). Tofacitinib is also approved for treatment adult patients with moderately to severely active ulcerative colitis (UC), who have an inadequate response or who are intolerant to one or more TNF blockers (IR tablets, NDA 203214, and MR tablets, NDA 208246). Xeljanz/Xeljanz Oral Solution is approved for the indication of treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blockers (Xeljanz/Xeljanz Oral Solution, NDA 213082).

Pfizer, Inc., referred to as Pfizer or the Applicant, has submitted a prior approval supplement with clinical data on August 23, 2024 for tofacitinib to NDAs 203214 (IR tablets), 208246 (MR tablets), and 213082 (oral solution). These submissions include labeling updates for inclusion of information regarding treatment of patient with systemic juvenile idiopathic arthritis (sJIA). Although the supplement has been submitted to NDA 208246, only information for the 5 mg oral tablets (NDA 203214) and the 1mg/mL oral solution (NDA 213082) has been included.

No new indications are being sought in the current Application.

The Applicant has also included the required remaining study reports to meet the terms of the Pediatric Written Request (PWR)-Amendment 3 for the review of the Pediatric Exclusivity Determination and to propose updates to the United States Package Insert (USPI).

1.2. Conclusions

On August 23, 2024, Pfizer submitted the NDA 203214 Supplement 38 (S-038) for XELJANZ (tofacitinib) immediate release (IR) tablet (5 mg), NDA 208246 Supplement 25 (S-025) and NDA 213082 Supplement 10 (S-010) for tofacitinib oral solution (1 mg/mL) seeking a post-approval labeling update to include information for tofacitinib for the treatment of sJIA in patients 2 years of age and older.

No new indication is being sought in the current submission.

In this submission, the Applicant submitted final clinical study reports (CSRs) for Study A3921165, a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability and pharmacokinetics of tofacitinib in children 2 to <18 year of age with active sJIA, and the second interim study report from Study A3921145.

Study A3921165 was conducted to evaluate the efficacy and safety of tofacitinib for the treatment of sJIA. Study A3921165 enrolled 100 subjects in the open-label (OL) phase of the study with active sJIA ages 2 to <18 years. Fifty-nine (59) subjects who met the study responder criteria in the OL phase continued into a double-blind (DB) randomized withdrawal phase (28 subjects received tofacitinib 5mg BID or a weight-based equivalent in patients <40 kg, and 31 subjects received placebo) for up to an additional 24 weeks. The primary efficacy endpoint of time to disease flare in the randomized double-blind withdrawal period of the study was not met. The Applicant specified two (2) study analyses with the first study analysis conducted after 28 subjects reported flare in the DB phase and a final analysis to be conducted if the study did not stop for efficacy or futility and when 37 subjects reported flare in the DB phase. The primary endpoint (time to sJIA disease flare in the DB phase) met the pre-specified criteria for futility in the first study analysis. There was no statistically significant difference in the time to sJIA disease flare between the tofacitinib 5 mg BID and placebo groups in the DB phase of the study, and the study was stopped for futility. Although the study did not meet the primary endpoint, the study provided safety data for treatment of sJIA patients with 5 mg BID tofacitinib or a weight-based equivalent in patients <40 kg.

The Applicant also submitted the second interim CSR for Study A3921145, a long-term extension (LTE) study in patients with JIA who participated in three initial index studies (A3921104, A3921103, A3921165). The LTE study enrolled a total of 280 patients. The index studies provided support for the prior approval of tofacitinib in pcJIA (NDA 203214 S-026) and included patients with sJIA patients who participated in study A3921165.

Along with the available safety data from other tofacitinib clinical programs in adults and

pediatric patients, Study A3921165 provides adequate exposure to evaluate the safety of tofacitinib in patients with sJIA. Reported SAEs and AEs were generally consistent with events expected based on the underlying disease and also consistent with the known tofacitinib safety profile reported in RA patients and observed in the pcJIA studies. The safety observed in Study A3921165 demonstrated the most frequently reported adverse events were AEs related to infections and disease activity. No new safety signals were identified. Safety data from the ongoing LTE study A3921145 second interim report were also consistent with the safety observed in the index JIA studies, including Study A3921165, and the prior first interim report for the LTE study A3921145.

As study A3921165 did not meet its primary endpoint for the sJIA indication, the Applicant has provided a post-approval labeling supplement with clinical data to include information from the sJIA population in Section 8.4, Pediatric Use, of the United States Prescribing Information (USPI).

The recommended regulatory action is Approval of the labeling changes agreed upon with the Applicant in Section 8.4 of the USPI, which includes information on the study conducted in patients with sJIA (Study A3921165).

2 Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

Tofacitinib (new drug application [NDA] 203214) was initially approved on November 6, 2012, for the treatment of adult patients with moderate to severely active RA who have had an inadequate response or intolerance to methotrexate.

The indications for which tofacitinib is currently approved are as follows:

- For the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more TNF blockers.
- For the treatment of adult patients with active PsA who have had an inadequate response or intolerance to one or more TNF blockers.
- For the treatment of adult patients with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers.
- For the treatment of adult patients with moderately to severely active UC, who have an inadequate response or who are intolerant to one or more TNF blockers.
- For the treatment of active polyarticular course juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blockers.

The safety and tolerability of tofacitinib was initially established in adults. Tofacitinib is potent immunosuppressant and warning and precautions for tofacitinib include serious infections including opportunistic infections, tuberculosis, and viral reactivation (e.g., herpes zoster), gastrointestinal perforations, major adverse cardiac events (MACE), thrombosis, hypersensitivity, lymphomas and other malignancies. An increased risk of all-cause mortality for patients receiving tofacitinib compared to TNF blockers was seen in a safety study conducted in rheumatoid arthritis patients over 50 years of age with at least one cardiovascular risk factor. Treatment with tofacitinib has also been associated with laboratory abnormalities (e.g., decreases in lymphocytes and neutrophils, elevations in lipids, liver enzymes) and patients receiving tofacitinib should not receive live vaccinations.

Pediatric Development

As part of the approval of the original application, consistent 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.

In addition, the Sponsor submitted a Proposed Pediatric Study Request on April 20, 2015, to NDA 203214 to investigate the potential use of tofacitinib and evaluate the safety and efficacy of tofacitinib in the treatment of Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Systemic Juvenile Idiopathic Arthritis (sJIA) in patients 2 years or older.

On August 12, 2015, the Agency issued a Pediatric Written Request (PWR) for NDA 203214 in treatment of polyarticular juvenile idiopathic arthritis (pJIA) and systemic juvenile idiopathic arthritis (sJIA). The PWR included four clinical studies. Study 1 (A3921103) was a multiple-dose pharmacokinetic study in pJIA patients 2 to <18 years which was to be completed before the efficacy trials. Study 2 (A3921104) was a randomized withdrawal, double-blind, placebo-controlled efficacy study in pJIA patients 2 to <18 years of age. Study 3 (A3921165) was a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy, safety and pharmacokinetics of tofacitinib in children 2 to <18 year of age with active sJIA. Study 4 (A3921145) was an open-label long-term follow-up study in JIA patient 2 to <18 years who have previously participated in studies 1 through 3. The PWR was revised on July 12, 2016 (Amendment 1), October 3, 2019 (Amendment 2), and February 2, 2024 (Amendment 3).

On February 13, 2013, Pfizer submitted IND 117400 to the Agency, which included the clinical study protocol for PMR 1934-1, Study A3921103 (Study 1), "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 September 26, 2016 (NDA 203214 / Sequence 0287). On February 15, 2017, the Agency acknowledged the PMR as fulfilled.

On April 8, 2015, under IND 117400, the Sponsor submitted the clinical study protocol for Study A3921104 (Study 2), "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 Sponsor justified the higher nominal dosing based on the supportive rationale that the apparent clearance (CL/F) of tofacitinib in JIA patients was estimated to be about 75% higher than in RA subjects, attributed to a higher degree of systemic inflammation in adult RA subjects as compared to JIA patients. This suggested that the exposure-response relationship for tofacitinib may differ between RA and JIA patients. The Division expressed concern related to the dose-dependent toxicity of tofacitinib and noted that a higher dose than what is currently approved in adults may lead to increased exposure and

would not be acceptable in JIA patients. After subsequent communication, the Division and the Sponsor 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.

On March 18, 2016, Pfizer submitted the protocol amendment to IND 117400 incorporating the dosing changes.

On June 18, 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. On July 5, 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, Study 3), and therefore, the continued recruitment for these patients in A3921104 was no longer necessary.

On July 31, 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 October 23, 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.

Pfizer submitted the NDA 213082 and NDA 203214 Supplement 26 on March 26, 2020, for an indication of active pcJIA. On September 25, 2020, tofacitinib was approved for the treatment of pcJIA in patients 2 years of age and older (NDA 203214 Supplement 26 and NDA 213082). The PREA PMRs for RA were considered fulfilled.

During review of the original NDA submission, the juvenile animal studies in rats and cynomolgus monkey lacked histologic evaluation of long bone and joints following tofacitinib treatment. This missing histopathology evaluation in juvenile animal toxicity studies left unaddressed potential safety concerns for the pediatric population since similarly acting JAK inhibitors resulted in abnormal bone development in juvenile animal toxicity studies. Therefore, a Postmarketing Requirement (PMR) was issued at the time of approval for the pcJIA indication to conduct a study of bone and joint histology in juvenile rats.

> PMR 3944-2: 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.

The Applicant completed the nonclinical PMR study and submitted the final report on October 29, 2021. The PMR study was considered acceptable to support the safety of tofacitinib in the pediatric indications for bone and joint safety (see nonclinical PMR review dated December 21, 2021). The PMR was considered fulfilled.

Also at the time of approval for the pcJIA indication, another PMR (PMR 3944-1) was issued to 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. This study may provide additional pediatric safety information relevant to pediatric safety for the pcJIA indication. However, there is currently no available data from this study.

In the current submission, the Applicant has included the remaining outstanding requirements of the PWR which include the final study report for SJIA study A3921165 (Study 3) and the interim CSR for JIA Study A3921145 (Study 4) which enrolled 280 patients as of the data cutoff (February 26, 2024).

2.2. Summary of Presubmission/Submission Regulatory Activity

A description of meetings relevant to the current submission are described below:

On December 30, 2022, the Sponsor submitted a Type C meeting request, and written responses were provided to discuss the status of ongoing clinical sJIA study A3921165 (Study 3): "Efficacy, Safety, Tolerability and Pharmacokinetics of Tofacitinib for Treatment of Systemic Juvenile Idiopathic arthritis (sJIA) with Active Systemic features in Children and Adolescent Subjects." This meeting request included a plan to defer submission of the supplement to

September 29, 2024, based on current study enrollment status and study timelines. The Agency acknowledged the recruitment issues and efforts to increase enrollment, however the submission of the final study reports would need to be less than 15 months before the patent or exclusivity is due to expire. It was noted that in order to meet the timeline the submission of pediatric study reports to request Pediatric Exclusivity would need to be submitted by September 7, 2024 and the Applicant would need to amend the Written Request with the new proposed date. The Sponsor also planned to update the study design and the statistical analysis plan (SAP) to reflect the interim efficacy analysis.

On April 12, 2024, Pfizer submitted a Type D meeting request (IND 117400, SN0893) to discuss and gain agreement on the format and content of the submission to fulfill PWR -Amendment 3. The meeting request was granted on April 25, 2024, as Written Responses Only (WRO). On May 31, 2024, the Agency issued the Type D WRO which included that it would be appropriate to submit the proposed labeling updates as part of a Prior Approval Supplement (PAS) –Labeling supplement with Clinical Data. The data provided appear most appropriate as a labeling update for Section 8.4 Pediatric Use, as Study A3921165 (Study 3 of PWR) did not meet its primary efficacy objective to support an sJIA indication. Additionally, the Agency stated that the Applicant's proposal to submit the required PWR sJIA reports and Prior Approval Efficacy Supplement in one dossier was acceptable.

3 Nonclinical Pharmacology/Toxicology

3.1. Executive Summary

No new nonclinical data was submitted nor required for this supplemental Application. The relevant information was previously reviewed.

4 Clinical Pharmacology

4.1. Summary of Clinical Pharmacology Assessment

In these applications, no new clinical pharmacology studies were submitted, and no new indication or labeling updates in clinical pharmacology sections were proposed. While the Applicant submitted one population modeling analysis report (PMAR-EQDD-A392I-sNDA-1703), the PK conclusion is consistent with prior population PK findings (Refer to NDA 203214 S-026/ NDA 213082 Unireview dated September 25, 2020, and NDA 203214 S-038/NDA 208246 S-025/NDA 213082 S-010 Clinical Pharmacology Review by Dr. Lei He dated November 1, 2024). In addition, the PWR is considered fulfilled from a clinical pharmacology perspective. For the full detailed clinical pharmacology assessment, refer to the NDA 203214 S-038/NDA208246 S-025/NDA213082 S-010 Clinical Pharmacology Review by Dr. Lei He dated December 13, 2024.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 1. Clinical Trials Relevant to the sNDA

Trial Identity	NCT Number	Trial Design	Treatment Arms (# of Patients)	Primary Efficacy Endpoint	Treatment Duration/	Number of Patients Randomized	Study Population	Number of Sites and Countries
Controlled studies in SJIA patients to support efficacy and safety								
A3921165	NCT03000439	MC, R, withdrawal design. 2-part OL phase followed by R, DB, PC, withdrawal phase to assess efficacy and safety study in patients with active SJIA	OL phase: 100 patients R, withdrawal DB phase: 59 Tofacitinib: 28 Placebo: 31	Time to sJIA disease flare in the DB randomized withdrawal phase	BID tofacitinib; 5 mg tablet in subjects ≥40 kg or weight adjusted oral solution in subjects <40 kg/Up to 52 weeks	N=100	Pediatric patients 2 to <18 years with active SJIA	101 sites in the following countries: United States, Argentina, Belgium, Brazil, Canada, China, Germany, India, Israel, Mexico, Poland Russian Federation, South Africa, Spain Turkey, Ukraine
Long Term Extension Study to support Safety in JIA patients								
A3921145	NCT01500551	Phase 2/3, LT, OL, follow-up study	Tofacitinib 5 mg BID (n=134) Placebo (n=136)	Safety Study	OL; BID tofacitinib; 5 mg tablet in subjects ≥40 kg or weight adjusted oral solution in subjects <40 kg	N=280 Study A3921103:26 Study A3921103:199 Study A3921165:55	JIA patients who previously participated in qualifying study	67 study sites: 16 countries

Source: Reviewer
Abbreviations:; BID, twice daily; DB, double-blind; MC, multicenter; NCT, National Clinical Trial; OL, open label; LT, long-term; PC, placebo-controlled; PG, parallel-group; R, randomized

5.2. Review Strategy

The two (2) clinical studies included in the current submission are:

- Study A3921165 evaluated tofacitinib therapy in patients with sJIA with active systemic features. The study was a randomized withdrawal design and evaluated the efficacy, safety and pharmacokinetics of tofacitinib 5 mg BID, or a weight-based dose solution of 1 mg/mL in children from 2 to <18 years of age with sJIA with active systemic features.
- Study A3921145 was an OL long-term follow-up trial which includes patients with both pcJIA and sJIA aged 2 to <18 years who have previously participated in Studies A3921103, A3921104 and A3921165, and is intended to inform on long-term safety. This study is ongoing. The Applicant has submitted an interim CSR with a data cutoff date of February 26, 2024.

Information from Studies A3921103 and A3921104 and the first interim analysis from the long-term extension study A3921145 provided support for approval of the pcJIA indication and were previously reviewed under NDA 203214 S-026.

The studies were conducted in pediatric patients with JIA using two (2) formulations of tofacitinib: an oral immediate release (IR) tablet and oral solution. These formulations allowed for dosing based on the patient's weight. Weight-based dosing was used to ensure consistent exposure among different weight groups.

Study A3921165 was the primary study to evaluate safety and efficacy of tofacitinib in sJIA and will be the primary focus of this review. Study A3921145 contributes additional long-term safety data in patients with JIA, including patients with sJIA and pcJIA, and will be discussed further in the Review of Safety in Section 6.3.

6 Statistical and Clinical and Evaluation

6.1. Review of Relevant Individual Trials in The Submission

6.1.1. Study A3921165

Protocol Title: Efficacy, Safety, Tolerability and Pharmacokinetics of Tofacitinib for Treatment of Systemic Juvenile Idiopathic Arthritis (sJIA) With Active Systemic Features in Children and Adolescent Subjects

Trial Design

This study consisted of a two-part open-label (OL) phase and a double-blind (DB) randomized withdrawal phase. Only subjects who were responders based on meeting JIA ACR30 response criteria in the OL phase of the study were randomized into the randomized withdrawal period.

Subjects were enrolled into an OL phase during which they received tofacitinib 5 mg twice daily (BID) oral tablets, or an equivalent weight-based lower dose of tofacitinib oral solution (1 mg/mL) BID for subjects <40 kg (both dosing regimens will be referred to as tofacitinib 5 mg BID throughout this document). The OL phase was divided into two parts (Part 1 and 2).

All subjects in Part 1 were set to achieve and maintain a minimum level of clinical response for at least 4 weeks:

- Subjects who were not taking corticosteroids (CS) or were not required to taper CS dosing (taking doses of CS ≤0.2 mg/kg/day) had to maintain an Adapted JIA ACR 30 response (see definition of a response below) for at least 4 weeks in Part 1 to be eligible for the DB withdrawal phase.
- Subjects who were treated with stable oral prednisone (or equivalent) doses ≤0.2 mg/kg/day and were able to maintain an Adapted JIA ACR 30 response for 4 weeks in Part 1 were allowed to skip Part 2 and be randomized in the DB withdrawal phase.

In Part 2, subjects who were treated with background CS >0.2 mg/kg/day oral prednisone (or equivalent) must taper their CS dose to a target range. CS tapering could continue as long as an Adapted JIA ACR 50 response was maintained. Subjects who successfully tapered their CS dose while maintaining the defined clinical response (adapted JIA ACR 50 response), were eligible for the DB withdrawal Phase. Subjects taking CS doses >0.2 mg/kg/day who failed to achieve an Adapted ACR 50 response during Part 2 were not randomized into the DB phase of the study.

The minimum total duration of treatment with a stable dose of tofacitinib for subjects completing Parts 1 and 2 was set to be at least 12 weeks to qualify to enter the DB randomized withdrawal phase of the study.

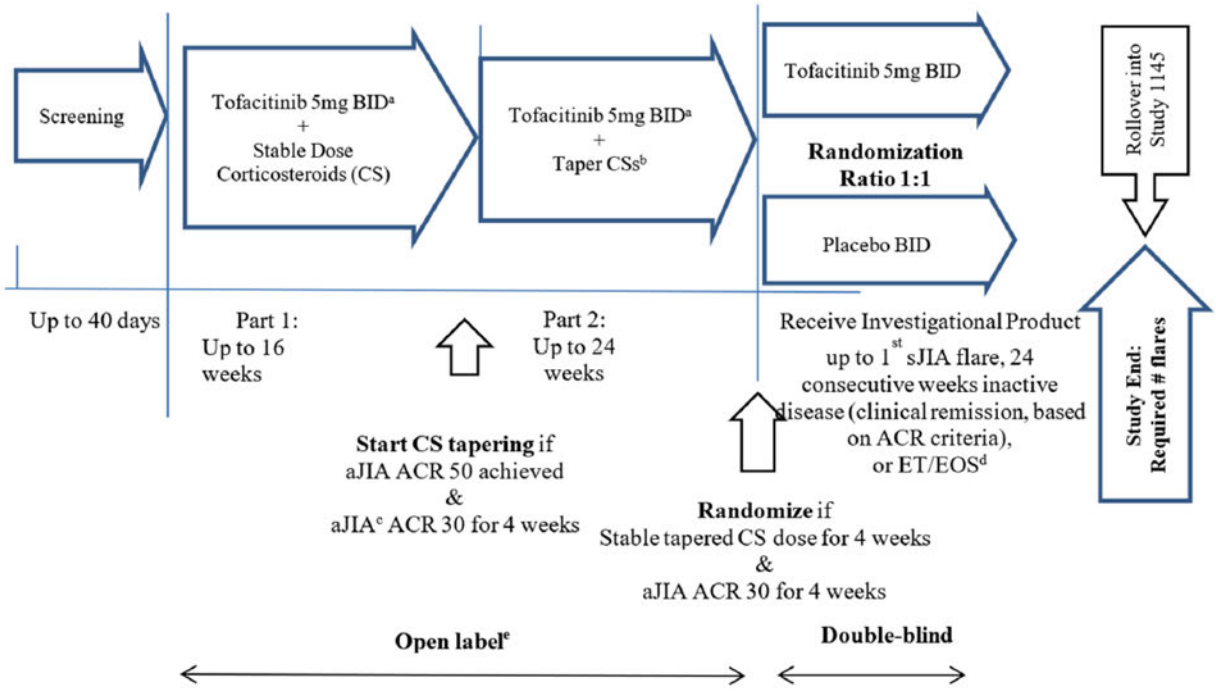
At the start of the DB randomized withdrawal phase, "responders" from the OL phase were randomized into 2 sequences: 5 mg BID tofacitinib or placebo (withdrawal of tofacitinib). Subjects were to continue in the DB phase of the study until one of the following events occur:

- The subject experiences an sJIA flare during the double-blind phase
- The subject experiences 24 consecutive weeks of inactive disease as assessed using JIA ACR (clinical remission)

All subjects participating in this study, including those who discontinued Investigational Product (IP) at the any phase of the study, had the option, if eligible, of enrolling in the tofacitinib long-term extension study (A3921145). Subjects who discontinued IP in the DB phase and who do not enter A3921145 were required to perform all scheduled visits until Week 52 after randomization or until the study concludes, whichever comes first. Subjects who discontinued the study in the OL phase and did not enter A3921145, were required to perform a follow-up visit 28 days after the last dose of study treatment.

Figure 1 presents the study schema for Study A3921165.

Figure 1: Study Schema (Study A3921165)



Source: Protocol, amendment 8, page 16.
a Subjects <40 kg will receive an equivalent weight-based lower dose of tofacitinib 5 mg BID.
b CS Tapering is only required for subjects treated with CS >0.2 mg/kg/day oral prednisone (or equivalent). During the active CS tapering period in Part 2 subjects must maintain an Adapted JIA ACR 50 response.

c aJIA: Adapted JIA.
d Subjects who discontinue Investigational Product in the randomized withdrawal phase continue in study until week 52 after randomization or until the study concludes, whichever comes first.
e Subjects who discontinue the study in the open-label phase and do not enter A3921145 within 4 weeks, will be required to perform a follow-up visit 28 days after the last dose of Investigational Product.

Protocol Descriptions:

sJIA Flare:
Flare was defined as at least one of the following:

- Recurrence of fever [(>38° C/100.4° F) on 2 or more consecutive days] considered to be due to sJIA activity.
- Worsening of 30% or more in three or more of the six variables of the JIA core set with no more than one variable of the JIA core set improving by 30% compared to the day of randomization into the withdrawal phase.

Adapted Juvenile Idiopathic Arthritis American College of Rheumatology (Adapted JIA ACR) 30/50 Response:
Response was defined as absence of fever due to sJIA (temperature ≤38° C/100.4° F) in the preceding 7 days along with an improvement of at least 30% / 50% from baseline (Day 1 of study drug before first tofacitinib administration) in at least 3 of the 6 JIA core components, with worsening of ≥30% / ≥50% in no more than 1 of the remaining components, which include:

- Number of joints with active arthritis.
- Number of joints with limited range of motion.
- Physician global evaluation of disease activity (21 circle VAS).
- Parent/legal guardian/Child evaluation of overall well-being (21 circle VAS).
- Functional ability (Childhood Health Assessment Questionnaire [C-HAQ]) without aids and devices.
- Erythrocyte Sedimentation Rate (ESR).

Key Entry Criteria

Key inclusion criteria in brief were as follows:

1. Male or female aged 2 to <18 years
2. Diagnosed with sJIA according to International League Against Rheumatism (ILAR) criteria, and, in the opinion of the investigator, have active disease prior to screening
3. Treatment with stable doses of methotrexate (MTX) and/or oral CSs is permitted
4. No evidence or history of untreated or inadequately treated active or latent tuberculosis (TB) infection

Key exclusion criteria:

1. Previous JIA treatment with tofacitinib
2. Current symptoms or findings of myocarditis, endocarditis or more than minimal

pericardial effusion associated with sJIA
3. Current symptoms or findings of more than minimal pleuritis with sJIA
4. Subjects who are still within the washout periods for disallowed nonbiological and biological disease modifying antirheumatic drugs (bDMARDs)
5. Infections:
    a. Chronic infections
    b. Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to be opportunistic by the investigator within the 3 months prior to the first dose of study intervention
    c. Any treated infections within 2 weeks of baseline
    d. A subject known to be infected with Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C
    e. History of infected joint prosthesis with prosthesis still in situ
6. History of recurrent (more than one episode) herpes zoster or disseminated (at least one episode) herpes zoster, or disseminated (at least one episode) herpes simplex
7. Diagnosis of active Macrophage Activation Syndrome (MAS) within 3 months prior to the first dose of study intervention
8. Blood dyscrasias, including:
    a. Hemoglobin <9 g/dL
    b. White Blood Cell count $<3.0 \times 10^9$/L;
    c. Absolute Neutrophil count $<1.2 \times 10^9$/L;
    d. Platelet count $<100 \times 10^9$/L;
    e. Absolute Lymphocyte count $<0.75 \times 10^9$/L.
9. Estimated glomerular filtration rate [eGFR] <40 mL/min/1.73 m^2 at Screening. The eGFR will be calculated by the central lab using the bedside Schwartz formula.
10. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥1.5 times the upper limit of normal or any other clinically significant laboratory abnormality

Discontinuation and Withdrawal Criteria

Reasons for permanent discontinuation of study intervention include the following;

- Insufficient clinical response
- Adverse events
- Medication error without associated adverse event
- Subject died
- Protocol violation
- Lost to-follow up
- Does not meet entrance criteria
- No longer willing to participate in study
- Pregnancy
- Study terminated by sponsor

Subjects will have the option, if eligible (based on inclusion and exclusion criteria), of enrolling in the tofacitinib JIA long term extension study (A3921145) after completion of this study.

A subject may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include;

- Lost to follow-up
- No longer willing to participate in study
- Study terminated by Sponsor
- Subject died

Additional criteria for discontinuation and withdrawal due to safety events or laboratory findings are described in the safety section of this review.

Study Endpoints

The Applicant pre-specified the primary endpoint to be time to sJIA disease flare in the DB randomized withdrawal phase. In addition, multiple secondary endpoints were pre-specified, including adapted JIA ACR 30/50/70/90/100 responses at every visit from Day 7 onward in the OL and the DB phases.

Statistical Analysis Plan

The Applicant specified the following analysis sets:

- Open-Label Part 1 Set: All subjects who were enrolled into the OL part 1 phase of the study and received at least one dose of investigational product in part 1.
- Open-Label Part 2 Set: All subjects who were enrolled into the OL part 2 phase of the study and received at least one dose of investigational product in part 2.
- Double-Blind Full Set: All randomized subjects who have received at least one dose of investigational product in the DB phase.

The primary endpoint of time to flare in the DB phase was used to assess superiority of tofacitinib to placebo through the Kaplan-Meier methods. The difference in time to flare between the two treatment groups (tofacitinib vs. placebo) was assessed using an unstratified log-rank test. Hazard ratios (tofacitinib/placebo) and 95% CIs were obtained from a Cox proportional hazards model with treatment group as covariate.

The primary analysis was based on a pre-specified composite estimand:

- Population: sJIA patients, as defined by the inclusion criteria for the DB phase, who are randomized.
- Treatment: tofacitinib 5 mg BID, placebo.

- Variable: time to sJIA disease flare in the DB phase.
- Intercurrent event (ICE) handling: investigational product discontinuation was defined as the intercurrent event (a composite strategy was used for this ICE).
- Population-level summary: hazard ratio of disease flare for those assigned to tofacitinib at randomization versus those assigned to placebo at randomization in the DB phase.

At least 100 subjects were to be enrolled in the OL run-in phase of the study. Of these subjects, least 12 subjects were targeted to be enrolled in each of the following age groups: from 12 to <18 years, from 6 to <12 years, and from 2 to <6 years. It was estimated that approximately 55 percent of subjects was to enter the randomized withdrawal period of the study.

The statistical analysis plan (SAP) specified two planned analyses:

- The First Analysis was to be performed after 28 subjects have reported flare in the DB phase.
- If the study did not end for efficacy or futility at the First Analysis, a total of 37 subjects with flares were required for the Final Analysis.

To protect the integrity of the study and to preserve the type I error rate at 0.025 (1-sided test) and the overall study power maintained at 80% (type II error rate β=0.2), the Applicant specified spending a fraction of α for efficacy and a fraction of β for futility at the First Analysis, so it was accounted for in the overall type I error rate and type II error rate, respectively.

A formal efficacy boundary for rejecting the null hypothesis was pre-specified and constructed by using the spending function methodology of the gamma family design with γ= 4. Similarly, a formal futility boundary for not rejecting the null hypothesis was pre-specified and constructed by using the spending function methodology of the gamma family design with γ= -4. Boundaries with 28 flares at the First Analysis were pre-specified as follows:

- If the value of the test-statistic at the First Analysis crosses the efficacy boundary ($z \leq -1.973$, 1-sided $p \leq 0.0242$), the trial was to be stopped for efficacy
- If the value of the test-statistic at the First Analysis crosses the futility boundary ($z \geq -1.240$, 1-sided $p \geq 0.1074$), the trial was to be stopped for futility.
- Otherwise, the trial was to continue as planned. The Final Analysis was to be performed after flares had been reported in 37 subjects.

Protocol Amendments

The original protocol version date was March 15, 2017. There was a total of 8 protocol amendments with the last being Amendment 8, dated September 1, 2023. There were no protocol changes that compromised the integrity of the study results. Key changes in each of the protocol amendments are described below.

Amendment 1: Included clarification to schedule of study activities, and entry criteria. Added exclusion criteria for subjects without documented evidence of VZV prior exposure, corrected washout periods for prior medications, added immunoglobulin IV to prohibited medications list, added telephone contact at Week 11 for patients who had a dose increase at Day 14, clarified analyses to be conducted at study visits and updated Tanner assessment from Day 1 to screening visit and updated PK sampling.

Amendment 2 and 3: In response to a Special Safety Concern of pulmonary embolism identified in an adult RA study, screening was stopped, administration of the 10 mg BID dose was discontinued, and examination of subjects at each visit to identify potential risks for VTE was implemented. The original protocol design included the 10 mg BID dose since it was anticipated that, due to the underlying pathophysiology of sJIA, subjects may require a higher dose to achieve efficacy than that needed for pcJIA. Amendment 3 included the addition of risk factor checks for VTEs.

Temporary measures for study visits during public emergencies were implemented in Amendments 3, as well as Amendments 5, 6 and 7, due to the COVID-19 pandemic. These alternative measures were put in place to enable continued collection of data and safety monitoring. This included the addition of remote visits and use of local labs. As a result of the conflict in Ukraine and Russia, screening and enrollment were halted in these countries and the temporary measures for study visits during public emergencies were implemented.

Amendment 4: Changes were made to the inclusion criteria #2 that subjects must have active disease at the time of screening and enrollment but no longer required 6 weeks of active disease before screening. This change was made to minimize the length of time that sJIA patients with active disease would go without treatment. Creatinine monitoring and discontinuation criteria were updated.

Amendment 5: Changes were made to facilitate enrollment of sJIA patients who were previously treated with bDMARDs or JAK inhibitors. The washout period for bDMARDs was shortened from 5 half-lives to 2 half-lives. To minimize the length of time that sJIA patients with active disease may not have adequate treatment. The exclusion criteria #1 was also amended to allow patients who were previously treated with JAK inhibitors other than tofacitinib to enroll.

Amendment 6: The secondary efficacy endpoint was updated to Occurrence of inactive disease status at every visit from Day 7 onward (JIA ACR) in the open label phase and the double-blind phase and assessment of clinical remission in the double-blind phase as clinical remission is not evaluated in the OL phase. The statistical analysis was updated to: Difference in time to flare between the two treatment groups (tofacitinib 5 mg BID vs. placebo) will be assessed using a stratified log rank test if enough events are observed in each stratum. Otherwise, the

unstratified log-rank test will be used. The protocol exclusion criteria requiring a positive VZV serology test was eliminated as most children with sJIA screened for the study had not received varicella vaccination nor were they previously exposed to varicella. Additional weekly screening of subjects by their caregiver was implemented to identify potential varicella rash.

Amendment 7: Key changes included updates for follow-up information collection in that subjects who discontinue the Investigational product in the double-blind phase and who do not enter study A3921145 will continue in study A3921165 for follow up of efficacy and safety endpoints. Subjects will be required to perform all scheduled visits until Week 52 after randomization or until the study concludes, whichever comes first. Subjects should receive standard-of-care treatment in accordance with local treatment guidelines. Additional clarification was provided that subjects in randomized withdrawal phase will receive Investigational Product up to 1st sJIA flare, 24 consecutive weeks inactive disease or early termination (ET)/end of study (EOS) visit. The JIA CAR Clinical Inactive Disease and Clinical Remission Criteria was updated to include that clinical inactive disease will be defined only using ESR and not CRP.

Amendment 8: Key changes included changes to the statistical analysis to allow for two planned analyses. The first analysis to be performed after at least 20 subjects have reported flare in the double-blind phase (approximately 50% of the total flares expected). The purpose of this analysis is to allow early stopping of the study for efficacy or futility, and to assess safety of tofacitinib. The final analysis was to be performed after flares have been reported in approximately 40 subjects.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestations that the studies were conducted in accordance with the principles set forth in the International Ethics Guidelines for Biomedical Research Involving Human Subjects, Council for International Organizations of Medical Sciences, the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice Guideline [E6] and applicable laws and regulations.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators. No potentially conflicting financial interests were identified.

Patient Disposition

The study enrolled a total of 100 subjects into Part 1 of the OL phase (OLP1), out of which 54 (54%) subjects taking corticosteroids >0.2 mg/kg/day at baseline entered into Part 2 of the OL phase (OLP2). Of the total subjects, 59 (59%) subjects who achieved the defined clinical response (CS tapering and adapted JIA ACR 50 response) were randomized into the double-blind withdrawal Phase (DB). There were 28 (20%) and 31 (31%) subjects randomized Tofacitinib 5 mg BID and placebo, respectively. The study was conducted at 101 sites in 23 countries.

Table 2. Study A3921165 Analysis Sets

	Tofacitinib 5 mg BID n (%)	Placebo n (%)
Open-Label Part 1 Analysis Set (OLPT1)	100 (100)	-
Open-Label Part 2 Analysis Set (OLPT2)	54 (54.0)	-
Double-Blind Full Analysis Set (DBFAS)	28 (20.0)	31 (31.0)

Source: Reviewer's Analysis

Subject disposition for OLP1 is summarized in Table 3. Among the 100 subjects enrolled and treated with Tofacitinib 5mg BID, the treatment discontinuation rate was 24%. The primary reasons for discontinuation were "adverse event" (6%) and "insufficient clinical response" (17%).

Table 3. Study A3921165 Subject Disposition – Open-Label Phase Part 1 (OLPT1)

	Tofacitinib 5mg BID (N = 100) n (%)	Placebo n (%)
Enrolled/Treated	100	-
Treatment Completed	76 (76.0)	-
Treatment Discontinued	24 (24.0)	-
Reasons for permanent discontinuation of study treatment		
Adverse Event	6 (6.0)	-
Insufficient clinical response	17 (17.0)	-
Entrance criteria	0	-
Lost to Follow up	0	-
Withdrawal by parent/guardian	0	-
Other	1 (1.0)	-

Source: Reviewer's Analysis
Abbreviations: N = number of subjects in analysis populations, n = number of subjects within category, OLPT1 = Open-Label Part 1 Analysis Set

Subject disposition for Part 2 of the OL phase (OLP2) is summarized in Table 4. Among the 54 subjects enrolled and treated with Tofacitinib 5mg BID, the treatment discontinuation rate was 29.6%. The primary reason for discontinuation was "insufficient clinical response" (20.4%).

Table 4. Study A3921165 Subject Disposition – Open-Label Phase Part 2 (OLPT2)

	Tofacitinib 5mg BID (N = 54) n (%)	Placebo n (%)
Enrolled /Treated	54 (54.0)	-
Treatment Completed	38 (70.4)	-
Treatment Discontinued	16 (29.6)	-
Reasons for permanent discontinuation of study treatment		
Adverse Event	0	-
Insufficient clinical response	11 (20.4)	-
Entrance criteria	0	-
Lost to Follow up	0	-
Withdrawal by parent/guardian	0	-
Other	5 (9.3)	-

Source: Reviewer's Analysis
Abbreviations: N = number of subjects in analysis populations, n = number of subjects within category, OLPT2 = Open-Label Part 2 Analysis Set

Subject disposition for the DB randomized Phase (DBFAS) is summarized in

Table 5, 59 subjects were in enrolled in the DB Phase (28 subjects were randomized to receive Tofacitinib 5mg BID and 31 subjects were randomized to receive placebo). In the Tofacitinib group, treatment discontinuation rate was 82.1%, with the primary reasons for discontinuation "other" (35.7%) and "insufficient clinical response" (32.1%). In the placebo group, treatment discontinuation rate was 90.3%, with the primary reasons for discontinuation "other" (35.5%) and "insufficient clinical response" (51.6%)

Table 5. Study A3921165 Subject Disposition – Double-Blind Phase (DBFAS)

	Tofacitinib 5mg BID (N = 28) n (%)	Placebo (N = 31) n (%)
Randomized/Treated	28 (28.0)	31 (31.0)
Treatment Discontinued	23 (82.1)	28 (90.3)
Reasons for permanent discontinuation of study treatment		

Adverse Event	2 (7.1)	1 (3.2)
Insufficient clinical response	9 (32.1)	16 (51.6)
Entrance criteria	0	0
Lost to Follow up	0	0
Withdrawal by parent/guardian	2 (7.1)	0
Other	10 (35.7)	11 (35.5)

Source: Reviewer's Analysis
Abbreviations: N = number of subjects in analysis populations, n = number of subjects within category, DBFAS = Double-Blind Full Analysis Set

Protocol Violations/Deviations

Study A3921165

The most frequently reported important protocol deviations, both in the OL and DB phases, were related to sample collection and analysis.

During open-label period 1 (OLPT1), 61.0% of subjects had a protocol deviation considered important by the Applicant. The most frequently reported important protocol deviations in the OLPT1 and open label period 2 (OLPT2) analysis set were related to laboratory or investigational product issue. The most frequently reported important protocol deviations (≥10% of reported deviations) in OLPT1 and OLPT2 were 'PK samples not properly collected, stored or handled', 'lab not done', 'Specimen not analyzed and retest not performed' and 'study drug compliance not calculated'. In the DB analysis set, 15 (53.6%) subjects in the tofacitinib arm and 15 (48.4%) in the placebo arm had important protocol deviations identified. The most frequently reported important protocol deviations in both treatment arms was 'specimen could not be analyzed and retest not performed' (tofacitinib [n=7] and placebo [n=6]). Overall the most common important protocol deviations in the DB period were related to laboratory or investigation product issues.

Table of Demographic Characteristics

Table 6. Study A3921165 Baseline Demographics Characteristics

	OLPT1	OLPT2	DBFAS	
	Tofacitinib 5mg BID N=100	Tofacitinib 5mg BID N=54	Tofacitinib 5mg BID N=28	Placebo N=31
Age, years				
Mean (SD)	9.97 (4.1)	9.9 (4.3)	10.36 (4.3)	10.35 (4.6)
Median	10.0	10.0	10.5	11.0
Range	2.0, 17.0	2.0, 17.0	3.0, 17.0	2.0, 17.0
Age group (years), n (%)				
2 to < 6	17 (17.0)	10 (18.5)	3 (10.7)	6 (19.3)
6 to < 12	43 (43.0)	21 (38.9)	12 (42.9)	11 (35.5)
12 to < 18	40 (40.0)	23 (42.6)	13 (46.4)	14 (45.2)
Sex, n (%)				
Male	56 (56.0)	33 (61.1)	16 (57.1)	22 (71.0)
Female	44 (44.0)	21 (38.9)	12 (42.9)	9 (29.0)
Race, n (%)				
American Indian/Alaskan	0	0	0	0
Asian	49 (49.0)	23 (42.6)	13 (46.4)	14 (45.2)
Black	7 (7.0)	4 (7.4)	3 (10.7)	2 (6.5)
Native Hawaiian	0	0	0	0
White	39 (39.0)	23 (42.6)	11 (39.3)	13 (41.9)
Other/mixed	5 (5.0)	4 (7.4)	1 (3.6)	2 (6.5)
Ethnicity, n (%)				
Hispanic or Latino	14 (14.0)	11 (20.4)	3 (10.7)	4 (12.9)
Not Hispanic or Latino	86 (86.0)	43 (79.6)	25 (89.3)	27 (87.1)
Geographic region, n (%)				
North America	8 (8.0)	6 (11.1)	1 (3.6)	2 (6.5)
South and Central America	9 (9.0)	9 (16.7)	3 (10.7)	3 (9.7)
Europe	8 (8.0)	4 (7.4)	2 (7.1)	1 (3.2)
Asia	48 (48.0)	22 (40.7)	13 (46.4)	14 (45.2)
Other	27 (27.0)	13 (24.1)	9 (32.1)	11 (35.5)

Source: Reviewer's Analysis

Abbreviations: OLPT1 = Open-Label Part 1 Analysis Set, OLPT2 = Open-Label Part 2 Analysis Set, DBFAS = Double-Blind Full Analysis Set

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 7. Study A3921165 Baseline Disease Characteristics

	OLPT1	OLPT2	DBFAS	
	Tofacitinib 5mg BID N=100	Tofacitinib 5mg BID N=54	Tofacitinib 5mg BID N=28	Placebo N=31
Number of Joints with Active Arthritis				
Mean (SD)	10.6 (10.0)	10.5 (9.6)	8.3 (7.0)	8.6 (7.4)
Median	6.0	6.0	6.0	6.0
Range	2.0, 63.0	2.0, 40.0	2.0, 32.0	2.0, 30.0
Number of Joints with Limitation of Motion				
Mean (SD)	6.4 (9.9)	6.0 (8.8)	4.9 (7.3)	4.4 (7.0)
Median	2.0	2.0	1.5	2.0
Range	0.0, 65.0	0.0, 32.0	0.0, 29.0	0.0, 33.0
Number of Swollen Joints				
Mean (SD)	9.6 (9.4)	9.6 (9.2)	7.5 (6.6)	7.7 (7.2)
Median	6.0	6.0	5.5	5.0
Range	0.0, 58.0	0.0, 36.0	1.0, 32.0	0.0, 30.0
Number of Painful/Tender Joints				
Mean (SD)	9.8 (11.3)	9.7 (10.8)	10.0 (9.9)	8.3 (9.6)
Median	6.0	5.5	7.5	6.0
Range	0.0, 67.0	0.0, 44.0	0.0, 44.0	0.0, 41.0
Fever, n (%)				
Yes	23 (23.0)	11 (20.4)	9 (32.1)	9 (29.0)
No	77 (77.0)	43 (79.6)	19 (67.9)	22 (71.0)
Physician Global Evaluation of Overall Disease Activity				
Mean (SD)	6.9 (1.9)	6.8 (1.8)	6.9 (1.9)	6.5 (2.0)
Median	7.5	7.0	7.5	7.0
Range	1.0, 10.0	1.0, 10.0	1.0, 9.0	2.0, 9.5
C-reactive protein (CRP) (mg/dL)				
Mean (SD)	4.9 (5.2)	4.9 (4.5)	3.4 (4.4)	2.6 (3.6)
Median	2.9	3.3	1.5	1.4
Range	0.0, 24.6	0.0, 18.1	0.0, 18.5	0.0, 13.9
C Reactive Protein Category, n (%)				
Normal	15 (15.0)	7 (13.0)	7 (25.0)	7 (22.6)
Above Normal	85 (85.0)	47 (87.0)	21 (75.0)	24 (77.4)

Source: Reviewer's Analysis
Abbreviations: OLPT1 = Open-Label Part 1 Analysis Set, OLPT2 = Open-Label Part 2 Analysis Set, DBFAS = Double-Blind Full Analysis Set

Efficacy Results – Primary Endpoint

The First Analysis of the primary endpoint (time to sJIA disease flare in the DB phase) was conducted on the data as of the cutoff date of 03 Jan 2024 (snapshot date of 02 Feb 2024). The tofacitinib 5 mg BID group did not show statistical superiority over the placebo group in the DB phase (HR 0.63 [0.30, 1.35]; p=0.1171); the p-value (1-sided) of 0.1171 from the primary endpoint analysis exceeded the First Analysis Futility Stopping Boundary of p-value (1-sided) of 0.1074. Therefore, the outcome of the First Analysis met the pre-specified criteria for futility.

Table 8. Study A3921165 Time to sJIA Disease Flare in Double-Blind Phase (DBFAS) - First Analysis

	Tofacitinib 5 mg BID (N=28)	Placebo (N=31)
Number of Subjects with Event	11 (39.3%)	17 (54.8%)
Types of Event		
Experienced Disease Flare	7 (25.0%)	13 (41.9%)
Discontinued Investigational Product due to Other Reasons	4 (14.3%)	4 (12.9%)
Number of Censored Subjects	17 (60.7%)	14 (45.2%)
Reasons for Censoring		
Subject Remained Flare-Free through Data cut-off date*	14 (50.0%)	11 (35.5%)
Completed Study Participation after achieving Clinical Remission	3 (10.7%)	3 (9.7%)
Hazard Ratio (Tofacitinib vs Placebo) [95% CI] **	0.63 [0.30, 1.35]	
p-value***	0.1171	

Source: Reviewer's Analysis
Note: The First Analysis was conducted based on the data as of the cutoff date of 03 Jan 2024 (snapshot date of 02 Feb 2024) with 28 flares. Double-Blind Full Set was defined as all randomized subjects who have received at least one dose of investigational product in the DB phase.
*Two subjects who were assessed as clinical remission by CCC and completed study participation are included in this category, due to discrepancies between CCC assessment and programmatically derived remission status.
*Hazard ratio based on Cox proportional hazards model with treatment group as covariate; under proportional hazards, hazard ratio <1 indicates a reduction in hazard ratio in favor of Tofacitinib 5 mg BID to Placebo.
***P-value from unstratified Log-rank test.

6.2. Statistical Summary and Conclusion

The Applicant conducted a randomized withdrawal study to evaluate efficacy, safety and tolerability, and pharmacokinetics of tofacitinib as a treatment for sJIA. The study enrolled 100 subjects into the OL phase, and 59 subjects met the response criteria and were randomized into the DB phase (28 subjects received Tofacitinib 5mg BID and 31 subjects received placebo).

The Applicant specified two (2) analyses. The First analysis was conducted after 28 subjects reported flare in the DB phase. The Final analysis was to be conducted if the study did not stop for efficacy or futility and when 37 subjects reported flare in the DB phase. The primary endpoint (time to sJIA disease flare in the DB phase) met the pre-specified criteria for futility at the First Analysis (a p-value of 0.1171 exceeding the Futility Stopping Boundary of 0.1074). There was no statistically significant difference in the time to sJIA disease flare between the tofacitinib 5 mg BID and placebo groups in the DB phase of the study, and the study was stopped for futility.

6.3. Review of Safety

6.3.1. Safety Review Approach

Safety in the sJIA patient population was evaluated in Study A3921165. Study A3921165 was conducted as a phase 3 randomized withdrawal design study in subjects from 2 to <18 years of age with active sJIA. The assessment presented in this review is based on all available safety data from the CSR. See Section 6.1.1 for a full discussion of the design of Study A3921165 and Figure 1.

Additional supporting safety data were reviewed from Study A3921145, an ongoing open-label LTE study that includes patients with JIA who had previously completed other studies (A3921103, A3921104 or A3921165) in the JIA program. Patients who potentially benefited from treatment in a qualifying index study could continue to receive tofacitinib at the same dose. The data cut-off date for the interim analysis provided in the second interim CSR was February 26, 2024. See Section 6.3.5 for a full discussion of the design of Study A3921145.

All subjects in Study A3921165, including those who discontinued in the OL or DB phase, had the option, if eligible (based on inclusion and exclusion criteria), of enrolling in Study A3921145 after completion of Study A3921165 to receive open-label tofacitinib. Subjects who discontinued Investigational Product in the DB phase of Study A3921165 and who did not enter Study A3921145 continued follow up within Study A3921165.

The safety observed in the clinical studies conducted in sJIA patients was also evaluated in the context of the known safety profile for tofacitinib established in adults and for pediatric patients with pcJIA.

6.3.2. Review of the Safety Database

Overall Exposure

Study A3921165

In Study A3921165, the overall study exposure included both the OL and DB phases of the study. A total of 100 subjects were enrolled in the OL phase and 59 subjects continued into the DB phase. For the OL phase, the mean duration of tofacitinib treatment was 90.6 days in OLPT1 and 84.4 days in OLPT2. The median (range) duration of treatment in OLPT1 was 85 (1, 167) days and in the OLPT2 was 82 (1, 167) days. The total drug exposure in Part 1 OLPT1 was 25 patient-years (PY), and the total drug exposure in Part 2 OLPT2 was 12 PY. For the DB withdrawal phase, the mean and median duration of treatment was greater for the tofacitinib group than for the placebo group. During the DB phase the mean duration of treatment was 244.5 days for the placebo group and 385.5 days for the tofacitinib 5 mg BID group. The median (range) duration of treatment was 169 (15, 1484) days in the placebo group and 283 (10, 1841) days in the tofacitinib 5 mg BID group (Table 9).

Table 9. Exposure Duration Study A3921165 Double-Blind Phase

Exposure Duration	**Tofa 5 mg BID or weight based N=28**	**Placebo N=31**	**Total N=59**
Total Drug exposure			
Patient-years of exposure	30	21	50
Duration of treatment (days)			
N	28	31	59
Mean (SD)	385.5	244.5	311.4
Median (range)	283 (10, 1841)	169 (15, 1484)	231 (10, 1841)

Source: Adapted from Applicant's Clinical Overview Table 3
Abbreviations: BID, twice daily; Tofa, tofacitinib

As discussed in Protocol Amendments under Section 6.1.1, the protocol was revised in Protocol Amendment 2 to remove an initially planned 10 mg BID tofacitinib dose due to safety concerns identified in a safety study in the adult RA population. At the time Protocol Amendment 2 went into effect, only Cohort 1 had completed, and Cohort 2 was ongoing. Two subjects had required a dose escalation to 10 mg BID after Day 14 due to an uncontrolled fever. One of the two subjects discontinued 4 days after the dose increase due to an sJIA exacerbation and 1 subject had their dose decreased to tofacitinib 5 mg BID.

Adequacy of the safety database:

Safety data for tofacitinib is available from other clinical programs in rheumatologic indications including adults with RA, PsA, and AS and for pediatric patients with pcJIA. Given the available

safety data from other tofacitinib clinical programs in adults and pediatrics these studies provide adequate exposure to evaluate the safety of tofacitinib in patients with sJIA.

6.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

None.

Categorization of Adverse Events

Overall, the Applicant's process for recording, coding and categorizing AEs was acceptable.

AEs were defined as any untoward medical occurrence in a study subject administered a product or a medical device; the event need not necessarily have a causal relationship with the treatment. AEs were considered treatment-emergent adverse events (TEAEs) if the event had an onset during the treatment phase of interest. Serious adverse events (SAEs) were defined as any untoward medical occurrence at any dose that: results in death; is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; results in congenital anomaly/birth defect or is considered to be an important medical event.

Severity assessment was made by the investigators using the following scale:

- Mild: events that do not interfere with the subject's usual function
- Moderate: events that interfere to some extent with usual function
- Severe: events that interfere significantly with the subject's usual function

The Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 was used for coding of AEs in Study A3921165 and Study A3921145.

While the protocol did not define specific adverse event of special interest (AESI), the protocol did include specific events for which additional information, monitoring or discontinuation would be required. Analysis of adverse events of special interest (AESIs) based on the tofacitinib clinical development program was conducted. Adjudication committees, independent and external to the Applicant were established for reviews of the following potential AEs:

- Opportunistic infections [OI]
- Malignancies
- Cardiovascular events (major adverse cardiac events [MACEs]
- Deep vein thrombosis [DVT]
- Pulmonary embolism [PE]
- Arterial thrombotic events [ATE])
- Hepatic events (drug-induced liver injury [DILI])
- Gastrointestinal (GI) perforations

- Macrophage activation syndrome (MAS)
- Interstitial lung disease (ILD) - evaluated by an independent internal review committee

Routine Clinical Tests

Safety assessments in Study A3921165 included physical examinations, weight, height, vital signs, clinical laboratories (screening, baseline, every 4 weeks during OLP1, OLP2 and DB), fasting lipid panel (baseline, every 4 weeks during OLTP1, OLPT2 and DB), and Tanner stages (screening and end of study) to assess growth and physical development.

6.3.4. Safety Results

Overview of AEs in Study A3921165
The OL run in phase of Study A3921165 was divided into two parts referred to as OLPT1 and OLPT2 as described in Section 6.1.1. During OLPT1, there were 113 TEAEs in 55 (55%) subjects. During OLPT2, there were a total of 52 TEAEs in 24 (44%) subjects (Table 10).

During the DB phase of the study a similar proportion of patients in both treatment arms had TEAEs. In the tofacitinib arm, there were a total of 62 TEAEs in 23 (82.1%) subjects, and, in the placebo arm, there were a total of 73 TEAEs in 25 (80.6%) subjects (Table 11).

Table 10. Study A3921165 Overview of Adverse Events in Open-Label Treatment Phase

Number (%) of Subjects	**Tofa 5 mg BID/wt. based equivalent**
Open label part 1 (OLPT1)	**N=100**
Number of adverse events	113
Subjects with adverse events	55 (55)
Subjects with serious adverse events	7 (7.0)
Subjects with severe adverse events	3 (3.0)
Subjects discontinued from study due to adverse events	6 (6.0)
Subjects who discontinued study drug due to adverse events	6 (6.0)
Subjects with interruption due to adverse events	7 (7.0)
Deaths	0
Open label part 2 (OLPT2)	**N=54**
Number of adverse events	52
Subjects with adverse events	24 (44.4)
Subjects with serious adverse events	0
Subjects with severe adverse events	0
Subjects discontinued from study due to adverse events	0
Subjects who discontinued study drug due to adverse events	0
Subjects with interruption due to adverse events	2 (3.7)
Deaths	0

Source: Adapted from Applicant's CSR Tables 20 and 21

Open-Label Phase Part 1 is from Day 1 up to 16 weeks. Open-Label Phase Part 2 is from end of Open-Label Phase Part 1 and takes up to 24 weeks for subjects who started corticosteroid tapering.
Abbreviations: tofa=tofacitinib, wt= weight

Table 11. Study A3921165 Overview of Adverse Events in Double-Blind Treatment Phase

Number (%) of Subjects	**Tofa 5 mg BID/wt. based equivalent N=28**	**Placebo N=31**
Number of adverse events	62	73
Subjects with adverse events	23 (82.1)	25 (80.6)
Subjects with serious adverse events	0	2 (6.5)
Subjects with severe adverse events	0	2 (6.5)
Subjects discontinued from study due to adverse events	10 (35.7)	16 (51.6)
Subjects who discontinued study drug due to adverse events	11 (39.3)	16 (51.6)
Subjects with temporary interruption due to adverse events	0	4 (12.9)
Subjects with dose reduction due to adverse events	0	0
Deaths	0	0

Source: Adapted from Applicant's Clinical Overview Table 4.
Abbreviations: BID= twice daily, Tofa= tofacitinib, wt=weight

Deaths

No deaths were reported in Study A3921165. However, one (1) death was reported in a 16-year-old female subject in South Africa who completed Study A39211165 and then entered into the LTE study A3921145.

The subject ([(b) (6)]) began treatment in the LTE study in [(b) (6)] and received tofacitinib 5 mg BID until she experienced an event of weight loss in [(b) (6)] (~11 months after starting treatment in the open-label study). She reported a 4 kg weight loss (over 3 months from [(b) (6)]), and night fevers. Her concomitant medications included ibuprofen, prednisone, isoniazid for latent TB (the subject's mother had been diagnosed with TB meningitis around the same time), medroxyprogesterone, and pyridoxine. The subject was reportedly weak with arthritis flares in ankles. Isoniazid was started for TB prophylaxis, and she was referred to TB clinic for testing. A chest X-ray was normal. The study drug was stopped with the last dose received on [(b) (6)] (Study Day 336). She was seen by a local general practitioner and referred to hospital on [(b) (6)]. She received a blood transfusion for anemia and was discharged on [(b) (6)]. She was also switched to 4 drug treatment for TB on [(b) (6)], which included ethambutol, isoniazid, pyrazinamide and rifampin. She continued to have fevers and experienced and additional 10 kg weight loss between [(b) (6)] and [(b) (6)]. On [(b) (6)] she was admitted to local hospital with diarrhea, dehydration, and treated with antibiotics. At the time of admission, she was severely weak, with new onset pleural effusion, and could not walk. She had tachycardia, severe ankle edema, and ongoing diarrhea. Possible sepsis and possible MAS were considered. She died on [(b) (6)]. An autopsy was not conducted.

Serious Adverse Events

During the OL phase for Study A3921165, seven subjects (7%) reported 8 SAEs, all in OLPT1. The only SAE term reported in more than one subject was Still's disease (3 [3.0%]). One (1) subject had two serious events during OLPT1, which were events of depression and overdose (sertraline). The other SAEs reported during OLPT1 included events of hemophagocytic lymphohistiocytosis, histiocytic necrotizing lymphadenitis, and Hodgkin's disease with each of these events reported in single subjects (Table 12).

Table 12. Study A3921165 Serious Adverse Events during Open-Label Phase 1 by MedDRA Preferred Term

	Tofacitinib (N=100) n (%)
Subjects with at least 1 Treatment-Emergent SAE	7 (7)
Still's Disease	3 (3)
Depression	1 (1)
Hemophagocytic lymphohistiocytosis	1 (1)
Histiocytic necrotizing lymphadenitis	1 (1)
Hodgkin's disease	1 (1)
Overdose	1 (1)

Source: Adapted from Applicant's CSR Table 26.

During the DB phase, 2 (6.5%) subjects had SAEs. Both subjects were in the placebo group and had serious events of Bronchitis and Nephrolithiasis. No SAEs were reported in the tofacitinib arm during the double-blind phase.

SAEs considered events of interest reported in the OLTP1 are described in detail as follows:

- An event of histiocytic necrotizing lymphadenitis occurred in a 13-year-old male ([(b) (6)]) subject who weighed 50 kg. His concomitant medications included oral prednisone, bicyclol, ibuprofen, cetirizine hydrochloride, ornithine aspartate and diclofenac sodium. At the OL Week 4 visit, he presented with a 4-day history of fever along with neck and axillary lymph node enlargement. He also reported a prior upper respiratory tract infection. On Study Day 30 of the OL period, he was hospitalized and underwent a lymph node biopsy. He was diagnosed with subacute necrotizing lymphadenitis (MedDRA preferred term: histiocytic necrotizing lymphadenitis). During the hospitalization he underwent a chest and head CT, joint ultrasound, and a bone marrow biopsy. On Study Day 39, both alanine aminotransferase and aspartate aminotransferase were elevated >3 × ULN and >6 × ULN, respectively. He was treated with calcium carbonate/cholecalciferol, etamsilate, alfacalcidol, glucurolactone, cysteine/glycine/glycyrrhizic

acid/ammonium salt, glutathione, ibuprofen, and immunoglobulin. He was discontinued from the OL phase on Study Day 39 due to the event of histiocytic necrotizing lymphadenitis with the last dose of tofacitinib 5 mg oral tablet BID taken on Study Day 29. He recovered from the event of histiocytic necrotizing lymphadenitis on Study Day 45 and was discharged from hospital on the same day. An event of "hepatic lesion" was reported on Study Day 30, which was considered mild in severity and resolved on Study Day 72. The subject had a prior history of liver impairment with abnormal liver enzymes on initial screening visit but were normal at retest and baseline. Evaluation of his elevations of liver enzymes was conducted during the study to rule out EBV and demonstrated negative EBV-CA-IgM and EBV-EA-IgA but positive EBV-NA-IgG and EBV-CA-IgG, suggesting possible reactivation of EBV.

The event of histiocytic necrotizing lymphadenitis was considered an event of special interest and was reviewed by the macrophage activation syndrome (MAS) adjudication committee. The MAS adjudication committee assessed the event of histiocytic necrotizing lymphadenitis as probable MAS with >50% to 95% certainty. The committee commented that this could be consistent with possible MAS. However, an unusual feature of this event was the resolution with minimal therapy. It was noted that clinical labs were suggestive of macrophage activation syndrome including low WBC, and platelets and elevated ferritin, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase.

The hepatic event review committee evaluated the elevated laboratories (verbatim term "liver lesion") on Study Day 39 as viral hepatitis and unlikely for drug-induced liver injury. The evaluators reported that this hepatocellular injury pattern was possibly due to reactivation of Epstein-Barr virus. The event did not meet Hy's law criteria and was considered mild in severity.

- SAEs of depression and overdose were reported in a 10-year-old female ((b) (6)) who weighted 56.4 kg during the OL phase. On Study Day 3, the subject had a non-serious event of depression and was treated with sertraline hydrochloride. On Study Day 16, a drug overdose with sertraline was reported. The subject was admitted to the outpatient department and received gastric lavage. Other reported AEs during the hospitalization included a report of myocardial injury with elevation of creatine kinase which was considered non-serious. On Study Day 19, she recovered from the overdose event and was discharged from the hospital. The treatment with sertraline hydrochloride was stopped. On Study Day 23, the intensity of the event of depression worsened to severe which led to hospitalization. She underwent treatment with biofeedback therapy and transcranial magnetic stimulation. She was treated with quetiapine fumarate, fluoxetine hydrochloride, magnesium valproate, alprazolam, and propranolol. No changes were made to the study intervention due

to the events. On Study Day 30, she discontinued study treatment. The event was reported as recovered on Study Day 55, and she was discharged from the hospital. She was withdrawn from the study at her request. The Investigator and Applicant assessed the causality of depression as not related to the study. A discharge summary indicated that depression was present prior to participation in the study. However, a history of depression and prior suicidality was not able to be confirmed by the Applicant or the Investigator.

- An SAE of Hodgkin's disease was reported in a 15-year-old female ((b) (6)) during the OL phase of the study. She initially presented with lymphadenopathy on Study Day 78. Her sJIA was initially diagnosed shortly before study inclusion (~2 months prior). Prior to screening, the subject had at least 6 weeks of active disease with fever, evanescent salmon colored rash, high C-reactive protein (CRP) (19.4 mg/dl) and Erythrocyte Sedimentation Rate (ESR) (123 mm/hr), and three active joints. She had received one dose of intramuscular (IM) 40 mg of methylprednisolone acetate 9 days before enrollment. At enrollment/baseline, she was treated with nonsteroidal anti-inflammatory drugs (NSAIDs) only. In the study she had initial improvement but with worsening of disease noted at Week 10. She developed supraclavicular lymphadenopathy and a diagnosis of Hodgkin's disease was made on biopsy. According to the Investigators, the haemato-oncologists believed that the symptoms and signs of Hodgkin's disease mimicked sJIA and preceded her enrollment in the study. The events of Lymphadenopathy and Hodgkin's disease were adjudicated by the malignancy adjudication committee.

- An SAE of hemophagocytic lymphohistiocytosis/macrophage activation syndrome occurred in a 15-year-old female ((b) (6)) subject on Study Day 70. She had a medical history of celiac disease and sJIA. Concomitant medications included naproxen, famotidine, cholecalciferol and ferrous sulfate. She initially developed fatigue and myalgia with fever (maximum temperature of 101°F). She went to the emergency room (ER) for chest tightness; assessment and laboratory tests were performed. She had some improvement with naproxen and ketorolac in the ER, however, she developed worsening fatigue and achiness. Her laboratory tests showed worsening leukopenia and neutropenia; elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), ferritin and LDH. Due to concern of possible medication side effects of leukopenia, neutropenia and elevated liver enzyme tests, the study drug was withheld. She had recurrent fevers of 102°F and 101°F. She also reported new congestion and sinus pressure. Levofloxacin was started due to a concern for sinus infection (sinusitis) along with a steroid taper of oral prednisone due to concern for evolving MAS with sJIA. She was discontinued from the study. The event of hemophagocytic lymphohistiocytosis was adjudicated by the macrophage activation syndrome as definite: >95% certainty. The committee

considered the event as most likely MAS in the setting of sinus infection in known sJIA.

The SAEs observed in Study A3921165, including events of disease flare and MAS, are consistent with serious events anticipated in an sJIA patient population. Events of depression and suicidality were also noted and assessed in the prior review of the JIA clinical studies with tofacitinib (see review NDA 203214 S-026).

Dropouts and/or Discontinuations Due to Adverse Effects

In the OL run-in phase, 6 subjects in OLPT1 discontinued the study due to AE. Four (4) of the 6 subjects discontinued the study discontinued due to an SAE. The SAEs leading to discontinuation were events of hemophagocytic lymphohistiocytosis (resolved), histiocytic necrotizing lymphadenitis (resolved), Hodgkin's disease (not resolved), and Still's disease (resolved) as described above (see "Serious Adverse Events"). Nonserious AEs leading to discontinuation were due to Still's disease, and Helicobacter infection. No subjects discontinued the study due to AE during the OLPT2.

During the DB phase, 27 subjects permanently discontinued study drug due to AEs. Among the 27 subjects, 11 (39.3%) were in the tofacitinib group, and 16 (51.6%) were in the placebo group. Most discontinuations in the DB phase were due to sJIA flare (MedDRA PT of Still's disease) with 8 [28.6%] subjects in the tofacitinib group and 14 [45.2%] subjects in the placebo group. Two (2) subjects in the tofacitinib group (7.1%) discontinued study treatment due to events of hemoglobin decreased.

The protocol also allowed for dose modifications or temporary discontinuations. Seven (7) subjects (7%) had a temporary discontinuation due to AE in the OLPT1, and 2 subjects (3.7%) had temporary discontinuations due to an AE in OLPT2. No subjects had dose reductions during the OL run-in phase. During the DB phase, four (4) subjects had a temporary interruption in study drug, all of whom were in the placebo arm.

Treatment Emergent Adverse Events and Adverse Reactions

During the OL run-in portion of the study, TEAEs were most frequently reported in the SOC of Infections and Infestations. In the DB phase of the study, TEAEs were most frequently reported in the SOC of Musculoskeletal and Connective Tissue Disorders with the most frequently reported preferred term in both treatment arms of sJIA flare (Still's disease). Reported TEAEs by MedDRA SOC for both the OL and DB treatment periods are shown in Table 13.

The SOCs in which TEAEs were most frequently reported (≥10% of subjects) in the DB phase were:

- Placebo: Musculoskeletal and Connective Tissue Disorders (54.8%), Infections and Infestations (45.2%), and Investigations (12.9%).
- Tofacitinib 5 mg BID: Musculoskeletal and Connective Tissue Disorders (35.7%), General Disorders and Administration Site Conditions, Infections and Infestations, Investigations (21.4% each), Gastrointestinal Disorders, Injury, Poisoning and Procedural Complications (14.3% each), and Metabolism and Nutrition Disorders (10.7%).

Table 13. Study A3921165 MedDRA System Organ Class for Reported TEAE for Open-Label Phase (OLPT1 and OLPT2) and Double-Blind Withdrawal Treatment Phase

	OLTP1	OLTP2	Double Blind	
	Tofacitinib (N=100) n (%)	Tofacitinib (N=24) n (%)	Tofacitinib (N=28) n (%)	Placebo (N=31) n (%)
Any Adverse event	40 (40.0)	24 (44.4)	23 (82.1)	25 (80.6)
Blood and lymphatic system disorders	2 (2.0)	4 (7.4)	1 (3.6)	2 (6.5)
Cardiac disorders	3 (3.0)	0	0	0
Ear and labyrinth disorders	2 (2.0)	0	0	0
Endocrine disorders	1 (1.0)	1 (1.9)	0	0
Eye disorders	5 (5.0)	1 (1.9)	0	1 (3.2)
Gastrointestinal disorders	11 (11.0)	4 (7.4)	4 (14.3)	2 (6.5)
General disorders and administration site conditions	9 (9.0)	2 (3.7)	6 (21.4)	1 (3.2)
Hepatobiliary disorders	2 (2.0)	1 (1.9)	2 (7.1)	0
Immune system disorders	1 (1.0)	0	0	0
Infections and infestations	31 (31.0)	14 (25.9)	6 (21.4)	14 (45.2)
Injury, poisoning and procedural complications	3 (3.0)	2 (3.7)	4 (14.3)	1 (3.2)
Investigations	3 (3.0)	3 (5.6)	6 (21.4)	4 (12.9)
Metabolism and nutritional disorders	0	1 (1.9)	3 (10.7)	1 (3.2)
Musculoskeletal and connective tissue disorders	8 (8.0)	3 (5.6)	10 (35.7)	17 (54.8)
Neoplasms benign, malignant and unspecified	3 (3.0)	1 (1.9)	1 (3.6)	0

Nervous system disorders	1 (1.0)	1 (1.9)	1 (3.6)	2 (6.5)
Psychiatric disorders	2 (2.0)	0	1 (3.6)	1 (3.2)
Reproductive system and breast disorders	1 (1.0)	1 (1.9)	0	0
Renal and urinary disorders	0	0	0	1 (3.2)
Respiratory, thoracic and mediastinal disorders	5 (5.0)	0	2 (7.1)	2 (6.5)
Skin and subcutaneous tissue disorders	5 (5.0)	3 (5.6)	0	1 (3.2)
Surgical and medical procedures	0	1 (1.9)	0	0

Abbreviations: OLPT1: open-label treatment period 1, OLPT2: open-label treatment period 2, n=number of subjects with the event.
Source: Adapted from Applicant's CSR Tables 14.3.1.2.2.1, 14.3.1.2.2.2 and 14.3.1.2.2.3

During the OL phase, the most frequently reported AE terms (MedDRA PTs) in OLTP1 were upper respiratory tract infection (10 [10.0%]), nasopharyngitis (6 [6.0%]), pyrexia (6 [6.0%], and Still's disease 4 [4%]). TEAEs of cough, influenza, nausea, vomiting, rash, and urinary tract infection were each reported in 3 (3%) subjects during OLPT1. In OLPT2, the most frequently reported AE terms were upper respiratory tract infection (7 [13.0%]), COVID-19 (5 [9.3%]) and Still's disease (3 [5.6]). The most frequently reported TEAEs during the OL phase are shown below in Table 14.

Table 14. Study A3921165 Treatment-Emergent Adverse Events Reported in ≥3% of subjects in the Open-Label Phase of the Study

Number (%) of Subjects by MedDRA Preferred Term	OLPT1 -Tofacitinib N=100 n (%)	OLPT2- Tofacitinib N=54 n (%)
Any Adverse Event	55 (55)	24 (44)
Upper Respiratory Tract Infection	10 (10)	7 (13)
Nasopharyngitis	6 (6)	1 (1.9)
Pyrexia	6 (6)	2 (3.7)
Still's Disease	4 (4)	3 (5.6)
Cough	3 (3)	0
Influenza	3 (3)	0
Nausea	3 (3)	0
Rash	3 (3)	1 (1.9)
Urinary tract infection	3 (3)	1 (1.9)
Vomiting	3 (3)	1 (1.9)
Abdominal pain upper	0	2 (3.7)
COVID-19	0	5 (9.3)
Contusion	1 (1.0)	2 (3.7)

Open-Label Phase Part 1 (OLPT1) is from Day 1 up to 16 weeks. Open-Label Phase Part 2 (OLPT2) is from end of Open-Label Phase Part 1 and up to 24 weeks for subjects who started corticosteroid tapering.
Source: Adapted from Applicant's CSR Table 23, 24 and Tables 14.3.1.2.2.1, 14.3.1.2.2.2.

In the placebo arm during the DB phase, the most frequently reported AE terms were Still's disease (14 [45.2%]), upper respiratory tract infection (5 [16.1%]), bronchitis, urinary tract infection (3 [9.7%] each), COVID-19, diarrhea, myalgia, and pharyngitis (2 [6.5%] each). In the tofacitinib arm the most frequently reported terms were Still's disease (8 [28.6%]), pyrexia (4 [14.3%]) upper respiratory tract infection, vomiting (3 [10.7%]), fall, hemoglobin decreased, hypertransaminasaemia, hypertriglyceridaemia, and nasopharyngitis (2 [7.1%] each). The most frequently reported TEAEs in the DB phase are shown in Table 15.

Table 15. Study A3921165 Treatment Emergent Adverse Events Reported in ≥5% of Subjects (either study arm) in the Double-Blind Phase

Number (%) of Subjects by MedDRA Preferred Term	Tofacitinib (N=28) n (%)	Placebo (N=31) n (%)
Any Adverse Event	23 (82.1)	25 (80.6)
Still's disease	8 (28.6)	14 (45.2)
Pyrexia	4 (14.3)	1 (3.2)
Upper respiratory tract infection	3 (10.7)	5 (16.1)
Vomiting	3 (10.7)	1 (3.2)
Nasopharyngitis	2 (7.1)	1 (3.2)
Fall	2 (7.1)	0
Hemoglobin decreased	2 (7.1)	0
Hypertransaminasemia	2 (7.1)	0
Hypertriglyceridemia	2 (7.1)	0
Diarrhea	1 (3.6)	2 (6.5)
Urinary tract infection	0	3 (9.7)
Bronchitis	0	3 (9.7)
COVID-19	0	2 (6.5)
Myalgia	0	2 (6.5)
Pharyngitis	0	2 (6.5)

Source: Adapted from Applicant's CSR Table 25 and Table 14.3.1.2.2.3.

Most TEAEs were mild to moderate in severity. Three (3) severe events were reported during OLPT1 and included events of lymphadenopathy, hemophagocytic lymphohistiocytosis, and Hodgkin's disease. No severe events were reported during OLPT2. Severe events reported during the DB withdrawal treatment period included a single event of hepatic enzyme increased and two severe events of Still's disease. The three (3) events were reported in two (2) subjects, both in the placebo arm.

The reported TEAEs in both study periods were generally consistent with events anticipated in an sJIA patient population. Events were also consistent with the known safety profile for tofacitinib, and no new safety signals were identified. TEAEs were also generally similar between the placebo and tofacitinib arms during the double-blind period of the study although some numerical differences are noted.

Significant Adverse Events

Tofacitinib is a member of the JAK inhibitor class, which are potent immunosuppressants. Tofacitinib has also been studied in other patient populations and AEs of special interest (AESI) have been identified for additional analysis which include events of serious infections, viral reactivation, malignancies, thromboembolic events, MACE, GI perforations, and laboratory abnormalities. Safety endpoints including potential events of opportunistic infections, tuberculosis, malignancy, GI perforations, MACE, and thromboembolic events were to be adjudicated. A serious complication of sJIA include events of MAS. Any potential events of MAS in the sJIA clinical studies were also considered AESI and were adjudicated.

Adjudication committees described in the study protocols included a Cardiovascular Endpoint Adjudication Committee (CV EAC), Malignancy Adjudication Committee (MAC), Opportunistic Infection Review Committee (OIRC), Hepatic Event Review Committee (HERC), Gastrointestinal Perforation Review Committee (GIPRC), and Macrophage Activation Syndrome (MAS) Review Committee. Members of the external adjudication committees were to be blinded to the study treatment assignments. The Applicant provided the adjudication charters for each of the committees. The protocol also included that an internal committee of medically qualified personnel with expertise in the assessment and diagnosis of respiratory disease would review and categorize potential events of interstitial lung disease (ILD).

In Study A3921165, there were no cases of GI perforation, ILD, MACE, opportunistic infection, TB infections, thromboembolism (including PE or DVT), or uveitis reported.

During the OL phase of Study A3921165, there were 6 AESIs reported. During the DB phase there were 2 AESIs reported.

The 6 events reported in the OL phase included 2 events of MAS. During the OL phase, one event of malignancy excluding non-melanoma skin cancer (NMSC) was confirmed by adjudication (Hodgkin's disease). Three (3) hepatic events considered AESIs were also reported during the OL phase which were adjudicated. One (1) event (haemophagocytic lymphohistiocytosis) was assessed as possible DILI. Two (2) other adjudicated events (hepatic lesion, hepatic steatosis) were assessed as unlikely DILI.

In the DB phase, one serious infection was reported in the placebo arm. No events of herpes zoster, herpes simplex, varicella or opportunistic infections were reported. No events of MAS were reported in DB phase. There were also no events of malignancy, or cardiovascular events that were adjudicated during this study phase. A hepatic event in a subject in the placebo arm who also experience a concurrent sJIA flare was classified as an AESI.

Exposure estimates and incidence rates (IRs) (per 100 PY) were summarized for TEAEs, SAEs, and each AESI in the DB phase (excluding hepatic events). Incidence rates were provided for the following AESI during the DB treatment period as follows:

- Non-adjudicated: Serious infection events including tuberculosis, varicella and herpes zoster.
- Adjudicated: cardiovascular events, gastrointestinal perforation events, MAS events, malignancy events, and opportunistic infections.

Based on the Applicant's analysis, the proportion of subjects reporting TEAEs and their respective incidence rates were similar between the tofacitinib and placebo group.

Overall, few AESIs were reported in Study A3921165, and the reported events were consistent with the known safety profile for tofacitinib. Specific AESIs are discussed in more detail in the following sections.

Serious Infections

Serious infections including tuberculosis, varicella and herpes zoster were considered AESI. Opportunistic infections were to be adjudicated. One serious infection was reported during the study. During the DB phase one serious infection (bronchitis) was reported in a subject in the placebo group. No events of tuberculosis, herpes zoster or varicella were reported in the DB phase or OL phase of the study. No opportunistic infections were reported.

Major Adverse Cardiac Events

Cardiovascular events were reviewed by an independent review committee. Events to be adjudicated included any events of death (coronary and noncoronary), myocardial infarction (non-fatal), coronary revascularization events, unstable angina (ischemic heart disease, standardized MedDRA query [SMQ]), stroke (fatal and non-fatal, CNS hemorrhages and cerebrovascular conditions SMQ), transient ischemic attack (ischemic central nervous system, vascular conditions SMQ), congestive heart failure (cardiac failure SMQ), peripheral arterial vascular disease (embolic and thrombotic events SMQ), pulmonary embolism, deep vein thrombosis, dyspnea, chest pain and events of leg edema and swelling.
No cardiovascular events were identified for adjudication.

Malignancy

One event of malignancy (excluding non-melanoma skin cancers) was reported in Study A3921165 (see narrative in SAE for more details). The event of Hodgkin's disease occurred during the OL phase. The Investigator considered the event to be present prior to enrollment in the study and considered that the event resulted in a misdiagnosis of sJIA. Events to be adjudicated were identified by any AEs in the malignant tumors MedDRA SMQ.

Hepatic Events

Treatment with tofacitinib is associated with increased incidence of liver enzyme elevations. Subjects with elevation in ALT or AST ≥1.5× the upper limit of normal were excluded from enrollment in the clinical studies.

In Study A3921165, four (4) hepatic events were identified and adjudicated for possible drug induced liver injury (DILI). Events for adjudication could be identified from the Investigator or Sponsor and included events considered potential Hy's Law cases, AST or ALT elevation ≥5x ULN, events meeting hepatic discontinuation criteria outlined in the protocol, serious adverse events in the MedDRA Hepatobiliary SOC, serious and nonserious adverse events coding to the MedDRA liver infections or infectious biliary disorders SMQ, events of DILI, or any death in a subject with ALT or AST ≥3 x ULN, bilirubin≥2 x ULN or a report of jaundice. Three (3) hepatic events were identified during the OL phase and one (1) event was identified in the DB period. Two (2) of the four (4) events were adjudicated and assessed as possible DILI:

- Hemophagocytic lymphohistiocytosis occurred in the OL phase in a subject receiving concomitant diclofenac and experiencing MAS concurrently.
- Hepatic enzyme increased occurred in the DB phase in a subject receiving placebo who experienced a concurrent sJIA flare.

Two (2) events were adjudicated and assessed as unlikely to be DILI:

- Reported event of "hepatic lesion" which occurred in a subject with histiocytic necrotizing lymphadenitis in the OL phase and was thought to be related to possible reactivation by EBV. The subject presented with elevation in AST and GGT (ALT, bilirubin and alkaline phosphatase were normal).
- Hepatic steatosis which occurred in a subject in the OL phase

No subjects met laboratory criteria for discontinuation of the study due to elevated AST or ALT levels during the study. Discontinuation criteria related to hepatic laboratory criteria defined in the protocol was 2 sequential AST or ALT elevations of ≥3 × ULN with either at least 1 total bilirubin value >2 × ULN, accompanied by elevated INR, or accompanied by symptoms consistent with hepatic injury, or 2 sequential AST or ALT elevations >5 × ULN regardless of total bilirubin.

Laboratory criteria for monitoring of liver enzymes (any single AST and/or ALT elevation of ≥3x ULN regardless of total bilirubin) were met by 3 subjects in OLP1, 1 subject in OLP2, and 4 subjects in the DB phase (2 subjects in each study arm).

Mean changes from baseline in ALT, AST and bilirubin values were evaluated. Overall increases in mean change from baseline for AST and ALT were noted in OLPT1 through Week 12 with values near OL baseline by Week 16. During the DB phase, variability was noted in the mean AST and ALT values, with mean values higher in the tofacitinib arm compared to the placebo at several study timepoints.

The highest post-baseline AST elevations of ≥10xULN, and ≥5x ULN each occurred in one (1) subject in OLPT1. One (1) subject had a post-baseline ALT elevation of ≥ 5xULN. Additionally, one (1) subject had an AST elevation ≥3x ULN, and 2 subjects had ALT elevation ≥3x ULN in OLTP1. In OLPT2, one (1) subject had a post-dose ALT elevation ≥3x ULN. Two (2) subjects in the placebo arm and one (1) subject in the tofacitinib arm had elevations of AST ≥3x ULN in the DB period, and (1) one subject in the placebo arm and 2 subjects in the tofacitinib arm had ALT elevations of ≥3x ULN in the DB period. One (1) subject in the placebo arm also had an ALT elevation of ≥10x ULN in the DB portion of the study.

Macrophage Activation Syndrome (MAS)

Four (4) potential cases of MAS were identified during the clinical study. All 4 cases were identified in OLPT1. Potential cases of MAS could be identified by the Investigator or the Applicant during the ongoing review of the clinical database. The protocol also included MAS laboratory criteria for identification of a MAS event. Per the protocol, a subject was classified as having MAS based on the 2016 ACR/EULAR/PRINTO Criteria if they experienced a fever at a visit plus ferritin >684 ng/mL, and at least 2 of the following 4 laboratory variables: platelets ≤181 $x10^9$/L, AST >48 U/L, triglycerides > 156 mg/dL, fibrinogen ≤360 mg/dL.

Three (3) of the four identified potential cases of MAS were reviewed by the MAS adjudication committee. One (1) of the identified cases was not reviewed by the MAS adjudication committee. This subject ((b) (6)) met the laboratory criteria on Study Day 14. However, all laboratory abnormalities resolved by the following visit; the fever resolved with paracetamol; and the symptoms of sJIA remained unchanged, and, therefore, the case was determined to not meet the adjudication criteria for a MAS event. Of the 3 cases evaluated by the MAS adjudication committee, 2 cases were considered to be either definite or probable MAS by adjudication (described below). One case was considered unlikely to be MAS. This subject ((b) (6)) had an elevation in AST which presented prior to an sJIA flare and did not meet other laboratory criteria.

The 2 cases considered to meet the MAS criteria following adjudication were also SAEs:

- Subject (b) (6) had an event reported as MedDRA PT: Hemophagocytic lymphohistiocytosis) that was adjudicated as a definite event of MAS. The subject had a fever and met laboratory criteria for MAS (ferritin = 3156 ng/ml, platelets = 151 x 103/mm3, and AST = 618 IU/L). However, the fever and laboratory abnormalities did not occur on the same day with the fever preceding the laboratory abnormalities.

- Subject (b) (6) had an event reported as the MedDRA PT: Histiocytic necrotizing lymphadenitis) that was adjudicated as probable MAS (>50% to 95%). Fever and laboratory criteria were met [AST = 57.5 U/L and platelets = 121 x 109/L; ferritin = 902.6 ng/ml ((b) (6))], although occurring on different days with the fever preceded the laboratory abnormalities.

No potential MAS events were identified during the OLPT2 or DB phases of Study A3921165.

Laboratory Findings

In Study A3921165, the observed laboratory changes were consistent with the observed changes for tofacitinib in the RA population.

The protocol for Study A3921165 included guidelines for safety monitoring and discontinuation criteria for laboratory abnormalities. The guidelines regarding monitoring (laboratory re-testing), temporary holding, and discontinuation of the study drug for laboratory findings were included in the protocol were as follows.

The following laboratory abnormalities required prompt re-testing, ideally within 3-5 days:

- Lymphocyte counts <500 lymphocytes/mm^3
- Neutrophil counts <1000 neutrophils/mm^3
- Platelet counts <100,000 platelets/mm^3
- Any single hemoglobin value <8.0 g/dL
- Any single hemoglobin value that is ≥2 gm/dL below the baseline
- Any single AST and/or ALT elevation >3 times the upper limit of normal, regardless of the total Bilirubin (repeat laboratory testing must include CK, Total Bilirubin, Direct and Indirect Bilirubin, GGT, INR and alkaline phosphatase)
- Any single serum creatinine increase >50% over the average of screening (most recent value prior to baseline) and baseline values OR an absolute increase in serum creatinine ≥0.5 mg/dL (≥44.2 µmol/L) AND any single CrCl decrease of >30% over the average of screening (most recent value prior to baseline) and baseline values
- Increased lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) should be monitored and treated according to local guidance (e.g., diet and behavior modification, statin therapy).

Investigational Product was discontinued for:

- Two (2) sequential lymphocyte counts <500 lymphocytes/mm^3;
- Two (2) sequential neutrophil counts <500 neutrophils/mm^3
- Two (2) sequential platelet counts <75,000 platelets/mm^3
- Two (2) sequential hemoglobin <8.0 g/dL or a decrease of more than 30% from baseline value
- Two (2) sequential AST or ALT elevations >3 times the upper limit of normal with at least one Total Bilirubin value >2 times the upper limit of normal
- Two (2) sequential AST or ALT elevations >3 times the upper limit of normal with an abnormal INR
- Two (2) sequential AST or ALT elevations >3 times the upper limit of normal accompanied by symptoms consistent with hepatic injury

- Two (2) sequential AST or ALT elevations >5 times the upper limit of normal, regardless of Total Bilirubin or accompanying symptoms
- Two (2) sequential increases in serum creatinine >50% over the average of screening and baseline values OR an absolute increase in serum creatinine ≥0.5 mg/dL (≥44.2 µmol/L) over the average of screening and baseline values AND a confirmed (two sequential) CrCl decrease of >30% over the average of screening and baseline CrCl values. If the serum creatinine increase and the CrCl decrease had an identifiable and reversable reason (e.g., concomitant medication), then an additional retest could be considered after discussion with the Sponsor study clinician or medical monitor. After retest, a decision for the subject to continue in the study could be made after discussion with the Sponsor study clinician or medical monitor;
- A single positive HBc Ab and a negative HBs Ab.

In the OL phase of the study, there were 20 events identified in OLPT1 and 6 events in OLPT2 that met the protocol criteria for monitoring. The most frequent criteria met were hemoglobin value <8 g/dL or one that drops ≥2 g/dL below open-label baseline in OLPT1. This event was met in 8 (8%) subjects during OLPT1. This criterion was met by one (1.9%) subject in OLPT2. The criteria for any single increase in serum creatinine >50% over the average of screening and open-label baseline values OR and absolute increase in serum creatinine ≥0.5 mg/dl (≥44.2 µmol/L) over the average of the screening and open-label baseline values, AND any single creatinine clearance decrease of >30% over the average of screening and open-label baseline values was met by 6 (6%) subjects in OLPT1 and by 3 (5.6%) subjects in OLPT2. Criteria for ALT/AST elevations >3x ULN were met by 3 (3%) subjects in OLPT1 and one (1.9%) subject in OLPT2. One subject met the monitoring criteria for lymphocyte counts in OLTP1 and OLTP2 and 2 subjects met criteria related to monitoring for platelet counts during OLTP1.

No subjects met the laboratory study drug discontinuation criteria in OLPT1. Two (2) out of the 54 subjects (3.7%) met the laboratory criteria for study drug discontinuation in OLPT2. Both subjects met the following criteria for laboratory discontinuation: Two (2) sequential increases in serum creatinine >50% over the average of screening and open-label baseline values OR an absolute increase in serum creatinine ≥0.5 mg/dl (≥44.2 µmol/L) over the average of the screening and open-label baseline values, AND any single creatinine clearance decrease of >30% over the average of screening and open-label baseline values. For these findings in serum creatinine, however the protocol allowed for subjects to be continued after a retest and a discussion with the medical monitor to determine any identifiable and reversible reason for the renal findings.

During the DB randomized withdrawal phase, there were 12 laboratory criteria events in the tofacitinib arm and 10 events in the placebo arm that met the criteria for monitoring. The criteria most commonly met criteria for the tofacitinib arm in this period was related to elevation in serum creatinine (4/28 [14.3%] subjects). The criteria most commonly met for the placebo arm were decreases in hemoglobin (6/31 [19.4%] subjects).

No subjects were discontinued due to decreases in lymphocytes, neutrophil or platelet counts as defined by the protocol. No subjects were discontinued in either the DB phase or OL phase who had elevations of either AST or ALT that met criteria for monitoring.

Six (6) subjects in the DB phase met the protocol defined criteria for discontinuation due to changes in hemoglobin or creatinine levels. Five (5) of these subjects were in the tofacitinib group and 1 subject was in the placebo group. In the tofacitinib arm, the laboratory criteria met included increased serum creatinine in 3 subjects (one permanently discontinued) and decreases in hemoglobin in 2 subjects (both discontinued). In the placebo arm, a single subject met the laboratory discontinuation criteria for increases in serum creatinine.

Mean and median changes in laboratory parameters were evaluated, and the observed changes in laboratory parameters were consistent with the known safety profile for tofacitinib.

Vital Signs

Vital signs evaluated during the study included heart rate, blood pressure, body weight, height, BMI and temperature. Overall, no clinically relevant changes were observed in vital sign parameters.

Development and Growth

Tanner Stage of Development data in the OL and DB phases were assessed, and the Applicant evaluated and summarized findings by gender and age group. At the last assessment of the study, it was expected that there would be little if any changes in subjects <12 years of age across the Tanner Stage of Development, and changes in distribution for those ≥12 years were generally consistent with expected increases by age and stage of development.

Changes from baseline in weight and height Z-scores in the OL and DB phases were also evaluated. Both male and female subjects in the study were smaller than average for their age. This finding would be anticipated for patients with sJIA. No clear trends in changes in Z-scores were identified between treatment arms during the DB phase. The small number of subjects with data available for each age group and at each timepoint and during the DB period, limits the interpretability of the available data.

Summary

In Study A3921165, the most frequently reported adverse events were AEs for infection and disease activity. Reported SAEs and AEs were generally consistent with events expected based

on the underlying disease and also consistent with the known tofacitinib safety profile reported in RA patients and observed in the pcJIA studies. No deaths occurred during study A3921165.

6.3.5. Studies Providing Additional Safety Support

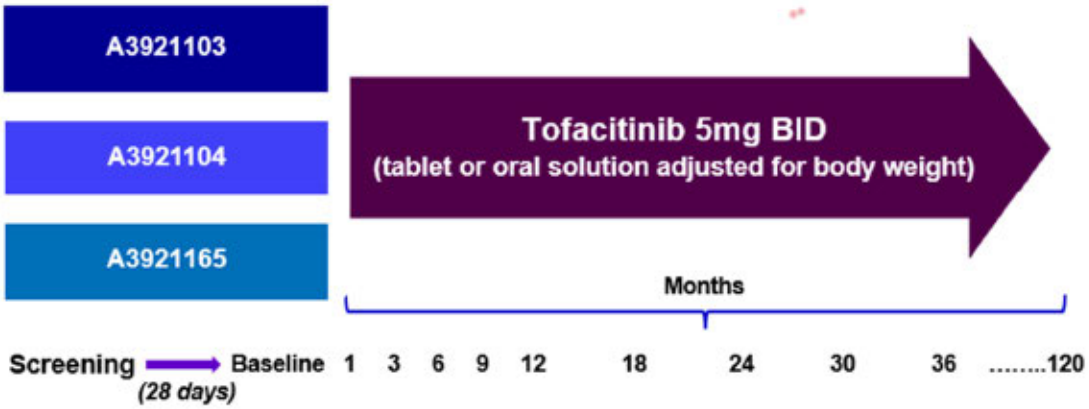
Study A3921145

Study A3921145 was an open-label LTE study which included patients with JIA ages 2 years and older who had previously completed other studies (A3921103, A3921104 or A3921165) in the JIA program. Subjects who potentially benefited from treatment in the index studies could continue receiving tofacitinib at the same dose in the open-label LTE study. The study is ongoing, but safety information based on an interim data-cut of February 26, 2024, was provided. The primary objective of the study was to characterize long-term safety and tolerability of tofacitinib for the treatment of JIA. Secondary study objectives include evaluation of the persistence of efficacy of tofacitinib for the treatment of the signs and symptoms of JIA. Approximately 340 patients were projected to enroll into the open-label LTE study after completing one of the 3 qualifying index studies (A3921103, A3921104 or A3921165) in the JIA program.

Study visits occurred at baseline, Month 1, Month 3 and every 3 months thereafter while in the study. For subjects who entered this study from the A3921103 and A3921104 index studies, their participation in this study ended after the first marketing approval of tofacitinib for the treatment of pcJIA in any country. This study will end once the last subject, and all other subjects, who entered from Study A3921165 have completed approximately 1 year in this study or after the first marketing approval of tofacitinib for the treatment of sJIA, whichever comes first.

In Study A3921145, safety assessment included assessment of signs and symptoms of sJIA, physical examinations, vital signs (BP, HR and body temperature), clinical laboratories (baseline, and every 3 months), and fasting lipid panels (baseline and approximately every 6 months through year 5 and then annually). Assessments for growth and physical development also included weight, height, and Tanner stages. Tanner stages were assessed at study baseline and the end of study as well as annually. The study design is shown in Error! Reference source not found..

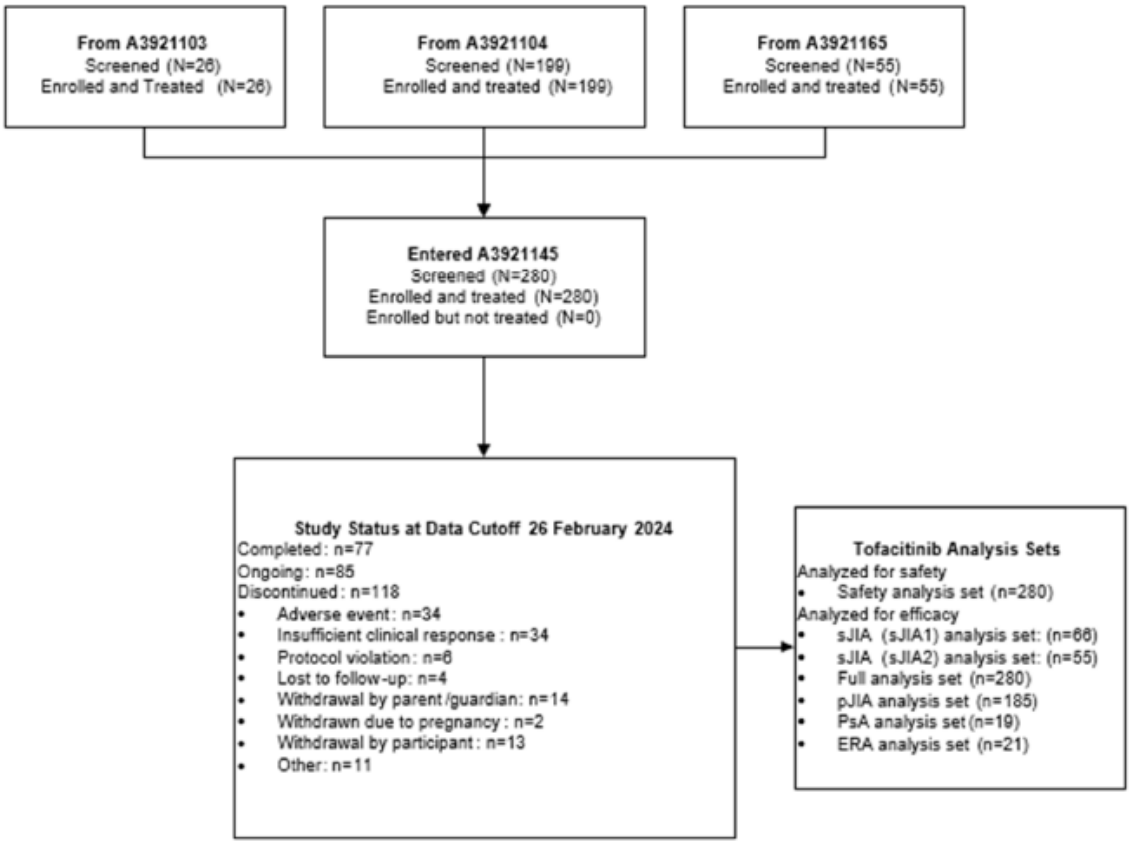
Figure 2. Study A3921145 Study Design



Source: Applicant's CSR for Study A3921145

In Study A3921145, a total of 280 subjects were enrolled. The study was conducted at 67 sites in 16 countries. At the time of the data cut-off for the interim analysis, 85 subjects were ongoing in the trial. The majority (199) of subjects were enrolled from Study A3921104; 55 subjects were enrolled from Study A3921165; and 26 subjects from Study A3921103. Figure 3 summarizes the disposition as well as the data analysis sets for Study A3921145.

Figure 3. Study A3921145 Disposition and Analysis Set



Source: Applicant's Clinical Safety Report Figure 2.

The most common reasons for study discontinuations were adverse events (34 [12%]) and insufficient clinical response (34 [12%]).

The mean (standard deviation [SD]) study exposure for all subjects participating in Study A3921145 is 35.8 (26.2) month with a median exposure of 37 months and range of 0 to 117 months. For the 55 subjects who continued into Study A3921145 from the 165 study with active sJIA the mean (SD) duration of treatment was 12.7 (12.8) months with a median exposure of 8.7 months and a range of 0 to 63 months.

Of the 55 subjects who participated in Study A3921165 and were included in the A3921145 dataset, 26 participated in only the OL phase of Study A3921165 and were not randomized in the DB period. Eighteen (18) subjects were in the DB tofacitinib arm, and 11 were randomized to the placebo arm of the DB phase of the study.

Study A3921145 Interim Safety

The safety data from the long-term open-label LTE study A3921145 in subjects with JIA were consistent with the known safety profile for tofacitinib and with the safety observed in the respective index studies. The Applicant provided additional safety data in the interim clinical safety report for all JIA patients in the study as well as the subset of sJIA patients who participated in Study A3921165 (SJIA2). The summary of safety from the second interim cut of Study A3921145 is shown in Table 16. A total of 1389 TEAEs were reported in 249 subjects.

Table 16. Study A3921145 Summary of Treatment Emergent Adverse Events- Full Safety Analysis Set

Number (%) of subjects	Tofacitinib N=280 n (%)
Adverse Events	249 (88.9)
Serious Adverse Events	43 (15.4)
Severe Adverse Events	25 (8.9)
Discontinued from study due to Adverse Events	35 (12.5)
Discontinued from study drug due to AE and continued in Study	1 (0.4)
Dose Reduced or Temporary discontinuation due to AE	89 (31.8)

Source: Adapted from Applicant's interim CSR Table 11.
Includes data up to 365 days after last dose of study drug.

In the overall study population, TEAEs were most frequently reported in the SOCs of Infection and Infestations (187 [66.8%] subjects), Musculoskeletal and Connective Tissue Disorders (101/280 [36.1%] subjects), and GI Disorders (81/280 [28.9%] subjects). Most AEs were mild (115/280 [41.1%]) or moderate (109/280 [38.9%]) in severity. Severe AEs were reported in 25 (8.9%) subjects. The most frequent severe AEs were reported in the Musculoskeletal and Connective Tissue Disorders SOC and in Psychiatric Disorders SOC in 5 subjects (1.8%) each, and in General disorders and Administration Site Conditions SOC in 4 (1.4%) subjects. The most frequent severe AEs by PT were pyrexia and herpes zoster, both in 3 subjects (1.1%). Other severe events included appendicitis, diarrhea, disease progression, chronic cholecystitis, hypertransaminasemia, limb abscess, peritonsillar abscess, femur fracture, hepatic enzyme increased, joint stiffness, muscle spasms, osteoarthritis, osteonecrosis, sacral pain, Still's disease, temporomandibular joint syndrome, skin papilloma, pregnancy, homicidal ideation, major depression, suicidal ideation (2 subjects), suicide attempt (2 subjects), ureterolithiasis, ovarian cyst, dyspnea, acne, pigmentation disorder.

TEAEs for subjects in Study A3921145 who had previously participated in study A3921165 corresponding to dataset SJIA2 occurred in 43/55 subjects (78.2%). A total of 109 TEAEs were reported. TEAEs occurring in the sJIA subjects in study A3921145 who previously participated in study A3921165 are shown in Table 17.

Table 17. Summary of TEAEs in SJIA subjects from Study A3921165 who participated in A3921145 (SJIA2)

Number (%) of subjects with any	Tofacitinib N=55 n (%)
Adverse events	43 (78.2)
Serious adverse events	7 (12.5)
Severe adverse events	3 (5.5)
Discontinued from study due to adverse events	6 (10.9)
Discontinued study drug due to AE and continue Study	1 (1.8)
Dose reduced or temporary discontinuation due to adverse events	8 (14.5)

Source: Adapted from Applicant's CSR Table 14.3.1.2.1.2

Deaths

No deaths were reported through the data cut date of February 26, 2024, for the interim submission of the CSR. However, one (1) death occurred after the cut-off date in a subject that previously participated in Study A3921165. This event was previously described in the discussion of safety data for Study A3921165.

Serious Adverse Events

There were 43 subjects (15.4%) in Study A3921145 with at least one (1) treatment-emergent SAE. The most commonly reported SAEs were suicidal ideation (5 subjects), herpes zoster (4 subjects), and Still's disease (4 subjects). SAEs that occurred in more than one (1) subject are shown in Table 18. All other preferred terms for SAEs were reported in single subjects.

Table 18. Study A3921145 Serious Adverse Events Reported in >1 Subject by MedDRA Preferred Term (PT)

Number (%) of subjects by Preferred Term:	Tofacitinib (N=280) n (%)
Subjects with at least 1 treatment emergent SAE	43 (15.4)
Suicidal ideation	5 (1.8)
Herpes zoster	4 (1.4)
Still's disease	4 (1.4)
Abortion spontaneous	2 (0.7)
Appendicitis noninfective	2 (0.7)
Juvenile idiopathic arthritis	2 (0.7)
Pyrexia	2 (0.7)
Suicide attempt	2 (0.7)

Source: Adapted from Applicant's CSR Table 13.

Of the two (2) events of suicide attempt noted in the current interim report for Study A3921145, one (1) was previously reported and discussed in the prior interim study review and in the prior JIA studies (see the Review for NDA 203214 S-026). The other event is new since the previous interim data cut date. The new event occurred in a 13-year-old female subject ([redacted]) who previously participated in the index study A3921104. She was initially receiving weight adjusted dose of tofacitinib 4 mL oral solution BID for 266 days. Her dose was adjusted to 5 mL oral solution and subsequently to oral tablets (5 mg BID). She was dosed through Study Day 812. On Study Day 814 she took alprazolam and amitriptyline tablets belonging to another family member. She was hospitalized and treated with gastric lavage and subsequently started on clonazepam. Tofacitinib was stopped and she was discharged from the hospital on Study Day 822. The Investigator assessed the event causality as not related to the study intervention and noted that the subject also had additional family stressors.

Four new cases of suicidal ideation were reported Study A3921145 as of the second interim data cut date.

Pediatric rheumatology literature reports that patients with JIA are diagnosed with mental and behavioral disorders more often than controls.[1,2] Cases of suicidal behavior were also noted in the prior interim study report for Study A3921145 and in the integrated safety data in the submission for the initial JIA index studies. Psychiatric events identified in the initial review included events of depression, suicide attempt, suicide ideation and self-injurious behaviors. In the prior review for NDA 203214 S-026, the potential signal of suicidal behavior was reviewed and the Division of Pediatric and Maternal Health (DPMH) and the Division of Pharmacovigilance I (DPV-I) was consulted 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 AEs to tofacitinib use. Most of the cases were confounded by medical history and/or circumstances of stress during tofacitinib exposure. DPV-I analyzed reports of psychiatric disorders with a focus on suicide or self-harm behaviors associated with tofacitinib in the FDA Adverse Event reporting System (FAERS) database. 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 and noted it was difficult to assess the contribution of tofacitinib to the suicide or self-harm events. See the NDA 203214 S-026 review for further discussion.

In the current submission some additional cases of suicidal behavior have been identified. The cases in the current interim report for the LTE study A3921145 and in Study A3921165 are consistent with those noted in the prior review. Based on the limited numbers of new cases, no

---

[1] Kyllönen et al. Pediatric Rheumatology (2021) 19:105. https://doi.org/10.1186/s12969-021-00599-x
[2] McHugh, A. et al. JRheum. (2022). doi: 10.3899.
http://www.jrheum.org/content/jrheum/early/2022/03/10/jrheum.210489.full.pdf

new signal is identified. Consistent with the prior review, the data are not sufficient to support a labeling change at this time.

Overall, SAEs as of the second interim data cut for Study A3921145 were consistent with the safety observed in pcJIA population as described in the prior review for NDA 203214 S-026. No new safety signals were observed.

Discontinuations

The number of subjects who permanently discontinued from the study due to an AE was 35 (12.5%). One (1) subject discontinued study drug due to an AE but remained in the study. The most common causes of study discontinuation were related to Infections and infestations (SOC) and Musculoskeletal and Connective Tissues Disorders (SOC) (8 subjects [2.9%] each, respectively). The most commonly reported MedDRA PTs leading to discontinuation were Herpes zoster, Still's disease (sJIA disease flare), and Interferon gamma release assay positive (3 subjects [1.1%] each, respectively).

Dose reductions or temporary discontinuations due to an AE occurred in 89 subjects (31.8%). The most common reasons for dose reductions or temporary discontinuations were due to AEs of Infections and infestations (SOC) (61 [21.8%]).

Adverse Events of Special Interest

Adverse events of Special Interest (AESI) in this study were based on the known safety profile of tofacitinib and on events relevant to JIA patients. Adjudication for potential AESIs in Study A3921145 included events of MACE, malignancy, GI perforation, hepatic events, interstitial lung disease, opportunistic and other special interest infections, and MAS.

No subjects met adjudication criteria for MACE, malignancy (excluding non-melanoma skin cancer), TB, GI perforations, drug induced liver injury and other hepatic events, or interstitial lung disease. There were no events of pulmonary embolism or deep vein thrombosis.

A single subject had an adjudicated event of MAS (Still's disease).

As of the second interim data cut, there were 3 cases of uveitis reported with 2 cases which were mild in severity and one case was moderate in severity.

Thirteen subjects (4.6%) had serious infections and 6 (2.1%) had events herpes zoster. One subject with a varicella infection was reported as a herpes zoster infection. Two cases of herpes zoster were adjudicated as multidermatomal (nonadjacent or >2 adjacent dermatomes) and met the criteria for being considered an opportunistic infection. The Incidence rate (IR) for serious infections was 1.52 per 100 patient-years with a 95% confidence interval of 0.81 to 2.6. The incidence rate for herpes zoster infections was 0.7 per 100 patient-years with a 95% CI of 0.26 to 1.53.

To further characterize expected rates for AESIs, the Applicant conducted a comparison of IRs for each safety event of interest for adults in the RA clinical development program for tofacitinib with IRs observed in the JIA LTE study. The IRs for AESIs observed in the JIA LTE study were generally consistent with rates of events observed in the RA studies in adults. The Applicant also compared the observed rates with available published rates for safety events of interest in JIA patients treated with bDMARDs, and noted the incidence rates for the safety events of interest were generally similar to rates for published clinical trials (including observational and randomized controlled) trials for bDMARDs.

Clinical Laboratories, Vital Signs, Pediatric Growth and Development

Laboratory changes were evaluated from baseline in the LTE study. Changes in laboratories were consistent with expected changes based on the known safety profile for tofacitinib and with changes observed in the index studies.

No clinically meaningful changes in vital signs were identified.

Weight and height z-scores were also reviewed. Through the data cut-off period, no clinically meaningful changes from baseline were identified. Weight was noted to be variable and slightly above median for most age groups except for ages 2 to <6 years and height was noted to be slightly below median for all age groups. One AE of growth retardation was reported and considered likely due to corticosteroid use and disease under study. Tanner stages of development were also collected. However, there is limited information available for analysis.

Summary

Safety data from the ongoing LTE study A3921145 second interim were supportive of the safety observed in the index JIA studies and prior interim review. Infections and disease activity were the most frequently report AEs. The type of AEs and SAEs observed were expected for the patient population and consistent with findings in adults with RA. No new safety signals were identified.

6.3.6. Safety in the Postmarket Setting

Safety in Postmarket Setting

Tofacitinib was first approved for RA in the United States on November 6, 2012. It is has received marketing authorization in 105 countries. The Applicant has included the Periodic Safety Update Report for the reporting period of November 6, 2023, through May 5, 2024 in the current submission. The report includes that as of the data lock point 23,820 subjects have participated in tofacitinib Sponsor-initiated clinical trials worldwide, with 18,001 subjects exposed to tofacitinib. The report includes that cumulatively, there have been approximately

868,959 patient-years of exposure to tofacitinib from marketing experience. No new safety risks have been identified during the reporting period.

6.4. Safety Conclusions and Recommendations

The Applicant submitted data from Study A3921165 to evaluate the treatment of sJIA with tofacitinib. Study A3921165 enrolled 100 subjects (2 to <18 years) with active sJIA. Fifty-nine (59) subjects who met the study responder criteria in the OL phase continued into a DB randomized withdrawal phase for up to an additional 24 weeks. Although the primary efficacy endpoint was not met, the study provided safety data for treatment of sJIA patients with 5 mg BID tofacitinib or a weight-based equivalent in patients <40 kg. The most frequently reported adverse events in Study A3921165 were AEs related to infections and disease progression.

Additional safety data for subjects with JIA, including sJIA patients who participated in the index Study A3911165, are provided form the LTE study A3921145. Safety data from the ongoing LTE Study A3921145 through second interim data cut date, were consistent with the safety observed in the index JIA studies, including 55 patients with sJIA previously enrolled in Study A3921165, as well as the previous interim review of safety data from Study A3921145 through the first interim cut date.

Along with the available safety data from other tofacitinib clinical programs in adults and pediatrics, Studies A3921165 and A3921145 up to the second interim data cut date provide adequate exposure to evaluate the safety of tofacitinib in patients with sJIA. The overall safety profile in the sJIA population observed in Studies A3921165 and A3921145 is consistent with the known safety profile of tofacitinib and as well as the observed safety profile in pcJIA, the sole pediatric population for which tofacitinib is currently approved. No new safety signals were identified.

No new indications are sought with the current supplement. The Applicant has provided a post-approval labeling supplement to include safety data from the sJIA population in Section 8.4 of the USPI.

7 Advisory Committee Meeting and Other External Consultations

An advisory committee (AC) meeting was not recommended for this post-approval labeling supplement.

8 Pediatrics

The current submission includes the final study reports for study A3921165 and the second interim report for study A3921145. Study A3921165 fulfills the requirements for Study 3 of the Pediatric Written Request, issued to Pfizer on August 12, 2015, and amended on July 12, 2016, October 3, 2019 and February 2, 2024. The study design, objective, patients to be studied, endpoints, and timeline are consistent with the requirements outlined for Study 3 of the Pediatric WR. Thus, this portion of the WR should be considered fulfilled.

The requirements for Studies 1 and 2 were fulfilled previously with the submission of NDA 213082 and NDA 203214/S-026 on March 26, 2020. The first interim report from LTE study A3921145 was also included in this previous submission. Thus, with the submission of the current supplement, the Applicant has met the timeframe for completion of the Pediatric WR on or before September 7, 2024.

The Pediatric WR and the Applicant's submissions were reviewed by the Pediatric Exclusivity Board on January 22, 2025. The exclusivity board agreed with the Division that the terms of the Pediatric WR were fulfilled and that tofacitinib should be granted pediatric exclusivity.

A PeRC meeting was also held on February 18, 2025, to discuss the results of study A3921165 and proposed labeling. PeRC agreed with the Division that the study data are insufficient to demonstrate efficacy and that tofacitinib is not recommended for pediatric use in sJIA.

9 Labeling Recommendations

9.1. Prescription Drug Labeling

As Study A3921165 did not meet its primary endpoint, the Applicant has submitted for a post-approval supplement to include safety information for patients with sJIA in Section 8.4 Pediatric Use of the USPI.

The Applicant initially proposed (b) (4) based on best labeling practices, the Division asked the Applicant to remove these references. Section 8.4, Pediatric Use will be updated based on information from Study A3921165 and will now read as follows:

8.4 Pediatric Use

Safety and efficacy of XELJANZ/XELJANZ Oral Solution in pediatric patients for indications other than pcJIA have not been established.

The safety and effectiveness of XELJANZ XR in pediatric patients have not been established.

Systemic Juvenile Idiopathic Arthritis (sJIA)
The safety and effectiveness of XELJANZ/XELJANZ Oral Solution in the treatment of pediatric patients with sJIA have not been established.

The results from a two-part study (an open-label, run-in phase, followed by a double-blind, placebo-controlled, randomized event-driven withdrawal phase) in 100 patients with sJIA with active systemic features (2 years to 17 years of age) did not demonstrate that XELJANZ/XELJANZ Oral Solution (dosed at 5 mg twice daily or body weight-based equivalent twice daily) is efficacious in the treatment of sJIA with active systemic features.

Of the 100 patients enrolled in the open-label run-in phase, 59 (59%) patients achieved a clinical response and were eligible for the double-blind withdrawal phase. There were 28 patients randomized to XELJANZ/XELJANZ Oral Solution and 31 patients to placebo. The study data are insufficient to demonstrate efficacy and, therefore, XELJANZ/XELJANZ Oral Solution is not recommended for pediatric use in sJIA.

Adverse reactions observed in pediatric patients with sJIA receiving XELJANZ/XELJANZ Oral Solution were consistent with those reported in pcJIA and RA patients *[see Adverse Reactions (6.1)]*.

10 Risk Evaluation and Mitigation Strategies (REMS)

No new safety issues have been identified in this post-approval labeling supplemental application. No new risk management plans are submitted as part of this supplement and no REMS is necessary based on the current submission.

11 Postmarketing Requirements and Commitment

There are no potential or new safety or efficacy issues determined from this review that warrant further assessment with a postmarketing requirement (PMR) or postmarketing commitment (PMC).

12 Division Director (Clinical) Comments

On March August 23, 2024, Pfizer submitted the current NDA supplement seeking a post-approval labeling update to include the results of study A3921165. The labeling updates will not result in a new indication or changes to the currently approved pediatric population. No new indication is being sought. This labeling supplement with clinical data was reviewed on a priority review clock.

The primary data in support of this supplemental Application was from Study A3921165, a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability and pharmacokinetics of tofacitinib in children 2 to <18 year of age with active sJIA. This study was also submitted to fulfill the requirements of a PWR. There was no statistically significant difference observed in the primary endpoint of time to sJIA disease flare between the tofacitinib 5 mg BID and placebo groups in the DB phase of the study, and the study was stopped for futility.

The current submission also includes the CSR from the second interim data cut for Study A3921145, a long-term open-label extension study which included patients with JIA ages 2 years and older who had previously completed other studies (A3921103, A3921104 or A3921165) in the JIA program. Study A3921145 provided additional supportive safety information for patients with JIA and was also part of the PWR.

The review team concluded, and I agree, that the observed safety for tofacitinib in sJIA was generally consistent with the established safety of tofacitinib in RA and pcJIA patients. No new safety signals were identified.

The regulatory action for this submission is Approval of labeling changes agreed upon with the Applicant.

13 Appendices

13.1. References

See Footnotes.

13.2. Financial Disclosure

The Applicant has adequately disclosed the potential financial interests/arrangements with clinical investigators as recommend in the FDA Guidance for Industry Financial Disclosure of Clinical Investigators[3]. The provided financial certification and disclosure forms attest that no clinical investigators reported disclosable financial interest or arrangements that would result in a conflict of interest.

Covered Clinical Study (Name and/or Number): Study A3921165

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 191		
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): 0		
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: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from Applicant)

[3] For further information, see Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEFANIE H FREEMAN
02/20/2025 02:45:21 PM

ERIC J GAPUD
02/20/2025 02:45:56 PM

LEI HE
02/20/2025 02:47:44 PM

JIANMENG CHEN
02/20/2025 02:49:08 PM

RABAB M ELNAIEM
02/20/2025 02:50:26 PM

DONG HYUN N AHN
02/20/2025 02:51:31 PM

OZLEM A BELEN
02/20/2025 02:53:26 PM