A LONG-TERM, OPEN-LABEL FOLLOW-UP STUDY OF TOFACITINIB FOR TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS (JIA)

Compound:	CP-690,550
Compound Name:	Tofacitinib
United States IND Number:	117400
European Clinical Trial Database (EudraCT) Number:	2011-004915-22
Protocol Number:	A3921145
Phase:	2/3

Document History

Document	Version Date
Amendment 12	06 May 2022
Amendment 11	26 May 2021
Amendment 10	04 May 2020
Amendment 9	23 May 2019
Amendment 8	07 February 2018
Amendment 7	10 August 2017
Amendment 6	07 April 2016
Amendment 5	17 August 2015
Amendment 4	03 April 2015
Amendment 3	27 August 2014
Amendment 2	22 August 2013
Amendment 1	18 September 2012
Original protocol	16 November 2011

This amendment incorporates all revisions to date including amendments made at the request of country health authorities, Institutional Review Board (IRB)/Ethics Review Board (ERB), and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 12 (06 May 2022)

Overall rationale for the amendment: This global amendment incorporates updates made to Qualifying Study A3921165 GPA#5 and GPA#6 and makes additional modifications to text for clarification purposes.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Schedule of Activities Footnote #17 6.0 Study Procedures	Added requirement for skin examination for chicken pox or shingles at all visits, applicable for subjects enrolled from A3921165 only.	Requirement added to A3921165 GPA#6	Substantial
2.3 Benefit/Risk Assessment	New section added on risk/benefits of tofacitinib.	Included to align with information added in A3921165 GPA#6.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
4.2 Exclusion Criteria #25	Removed to allow previous treatment with baricitinib or JAK-inhibitors.	Updated to align with A3921165 GPA#6.	Substantial
4.3.3 Vaccine and Exposure to Infections	Clarification on allowed vaccines, including guidance on COVID-19 vaccines. Section added on varicella vaccination for participants enrolled from A3921165. Guidance Regarding Household Contact Vaccine-Related Exposure is revised.	Guidelines updated to align with A3921165 GPA#6	Substantial
7.2.7 Physical Examination Appendix 16	The requirement that parent/guardian/subject perform at least weekly skin checks between visits and any concern for potential chickenpox or shingles be reported to the investigator immediately is added	Requirement for skin examinations added to A3921165 GPA#6	Substantial
Appendix 1: Allowed and Disallowed Treatments for JIA	The washout periods for biological DMARDs are shortened from 5 half-lives to 2 half-lives.	Updated to align with the updates to washout periods made in A3921165 GPA#5	Substantial
Appendix 16: Varicella (chickenpox) and Herpes zoster (shingles) Assessment and Guidance	New appendix applicable to subjects enrolled from A3921165 added to describe the rash and other symptoms that may accompany chickenpox and shingles events and how they differ from the typical sJIA rash.	Requirement added to A3921165 GPA#6	Substantial
1.1 Indication	Updated number of countries in which tofacitinib is approved and included additional indication approvals	To provide updated information	Non-substantial
4.1 Inclusion Criteria #6 5.5.2 Permitted Medications	Removed need for Medical Monitor agreement for use of higher prednisone-equivalent doses for subjects enrolled from A3921165	Medical Monitor agreement is not considered necessary as allowed doses are	Non-Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
And/Or Treatments Appendix 3		well-defined in the protocol	
4.3.4 Elective Surgery	Modification to allow investigator discretion for withholding study treatment if surgery is required.	Added for clarification	Non-substantial
5.2.1 Tofacitinib Temporary Withholding	Clarification that withholding study drug is not necessary when administering non-live vaccines.	Added for clarification	Non-substantial
5.3.4 Compliance	Clarification that protocol allowed temporary discontinuation of study drug for SAEs/AEs, surgical procedures and other allowed reasons is not considered as noncompliance and a PD will not be recorded	Added for clarification	Non-substantial
7.1.4 CHAQ	Clarification that an adult caregiver interacting daily with the subject can complete the CHAQ.	Added for clarification	Non-substantial
7.1.9 JADAS 27 Minimal Disease Activity and Inactive Disease	Polyarthritis corrected to more than 4 joints, and oligoarthritis to 4 or less	Correction to > and ≤ symbols	Non-substantial
Section 7.2.2. QuantiFERON®-TB Gold Plus In-Tube Test Schedule of Activities Footnote#3	Added India to countries where annual TB testing is required as the incidence of TB is >50 cases per 100,000 people.	Added for clarification	Non-substantial
7.2.5 Uveitis exam	Clarified that uveitis exam by ophthalmologist at the EOS/ET Visit is not required if an exam	To reduce patient burden	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	has been performed within the past 6 months of the EOS/ET visit.		
Section 7.2.9 Laboratory Tests Schedule of Activities footnote #5	Clarified that lipid panel is required at the EOS/ET visit.	Added for clarification	Non-substantial
7.3 Pregnancy testing	Clarification that a positive urine pregnancy test will be confirmed by a serum pregnancy test performed either locally or by the central laboratory.	Added for clarification	Non-substantial
7.4.1 PK Sampling Timepoints for All Subjects Schedule of Activities footnote #6	Clarified that participants in India will not participate in PK testing.	Incorporates country-specific requirement (India PACL 14Jan22)	Non-substantial
8.5.2 Treated Infections	Removed need to obtain Medical Monitor approval for temporary discontinuation of study drug in subjects who experience infections	Medical Monitor agreement is not considered necessary as requirements for discontinuation of study drug are well-defined in the protocol	Non-substantial
9.5 Interim Analysis	Added that IA may be performed for purposes of planned publications.	Clarifies that IA is allowed for planned publications	Non-substantial
9.7 Safety Endpoint Adjudication Committees	Clarification that the Sponsor is using an independent Macrophage Activation Syndrome (MAS) Review Committee to adjudicate events of MAS.	Added for clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Appendix 4: Permitted Adjustments (Tapering) of JIA Medications	Removed requirement to notify Pfizer Clinical or Medical Monitor of medication adjustments	Notification is not considered necessary as the permitted adjustments are well-defined in the protocol	Non-substantial
Appendix 17: Summary of Changes	Summary of changes from original protocol through to Amendment 11 moved to end of protocol document.	To align with protocol template	Non-substantial

PROTOCOL SUMMARY

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

Tofacitinib pediatric development program is designed to demonstrate both efficacy, as demonstrated by a reduction in signs and symptoms of Juvenile Idiopathic Arthritis (JIA) in subjects 2 years of age and older, and safety supporting the use of tofacitinib for the treatment of pediatric subjects with JIA.

The rationale of this study is to enable subjects potentially benefitting from treatment in a previous qualifying/index study to continue to receive tofacitinib at the same dose as the qualifying/index study (unless further analysis of the qualifying/index study data indicate otherwise), and to characterize long-term safety and tolerability of tofacitinib for the treatment of JIA.

It is anticipated that benefit of continued treatment with tofacitinib for individual subjects in this study will have been established in the qualifying/index study as per the Investigator's assessment. Potential risks of continued treatment are expected to be consistent with those described in the Single Reference Safety Document (current version of the tofacitinib Investigator Brochure).

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the current version of the Investigator's Brochure.

STUDY OBJECTIVES AND ENDPOINTS:

Objectives

Primary

- The primary objective of this study is to determine the long term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA.

Secondary

- The secondary objective of this study is to evaluate the persistence of efficacy of tofacitinib for treatment of the signs and symptoms of JIA.

Exploratory

The exploratory objectives of this study are:

- To assess tofacitinib pharmacokinetics (PK) in pediatric subjects on a stable dose of tofacitinib in the setting of a long-term, open label study.

- To assess changes in PK parameters (within subject) with increase in weight in this pediatric population and to explore exposure-response relationships of tofacitinib for various efficacy and safety endpoints after long-term exposure of tofacitinib in this pediatric population.

Endpoints

Primary

- Standard laboratory safety data and adverse event (AE) reports. Body weight, height and Tanner Stages will be collected to assess growth and physical development.

Secondary

The following efficacy parameters will be assessed:

- Physician global evaluation of disease activity at each visit.

- Number of joints with active arthritis at each visit.

- Number of joints with limitation of motion at each visit.

- Index of inflammation (C-reactive protein [CRP] and Erythrocyte Sedimentation Rate [ESR]) at each visit.

- Childhood Health Assessment Questionnaire (CHAQ) at each visit.

    - Parent's Assessment of Physical Function (CHAQ Disability Index).

    - Parent's Assessment of Child's Arthritis Pain (CHAQ Discomfort Index, Visual Analog Scale [VAS]).

    - Parent's Global Assessment of Overall Wellbeing (CHAQ subsection, Visual Analog Scale [VAS]).

- JIA American College of Rheumatology (ACR) response at each visit and occurrence of JIA ACR disease flare after Month 3.

- JIA ACR Clinical Inactive Disease status and Clinical Remission on Medication at each visit.

- Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS) 27- CRP and JADAS 27-ESR, and occurrence of JADAS minimum disease activity and inactive disease at each visit.

- Eligibility of tapering defined per protocol for corticosteroids, MTX/leflunomide, and tofacitinib.

- In subjects with **sJIA**: "Absence of Fever", defined as absence of fever due to sJIA in the week preceding the assessment at each visit.

- In subjects with Enthesitis Related Arthritis (**ERA)**: Change from baseline in the Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain responses at various visits.

- In subjects with psoriatic arthritis (**PsA**): Change from baseline in body surface area (BSA) affected by psoriasis and Physician's Global Assessment (PGA) of psoriasis) at various visits.

Exploratory

- Plasma concentration time data for tofacitinib will be analyzed to characterize the PK in this subject population. Exposure-response relationships will be explored for various efficacy and safety endpoints after long-term exposure of tofacitinib.

Statistical Analysis

Statistical analyses will be focused on descriptions of long term safety and tolerability of tofacitinib for the treatment of signs and symptoms of JIA. Safety endpoints will be measured by scheduled physical examinations and safety laboratory tests, and described over time. In addition, spontaneous reporting of AEs and serious adverse events (SAE) throughout the trial will be evaluated in all subjects. Measurements of efficacy will be summarized using descriptive statistics, such as number and percent, mean, standard deviation and quartiles at each visit where measured. Displays of results will be performed combining and stratifying by qualifying studies. Details will be specified in a statistical analyses plan.

STUDY DESIGN:

This is a Phase 2/3, long term, open-label, follow-up study. Subjects will have previously participated in qualifying/index JIA studies of tofacitinib. Those who have already completed such participation and enroll outside the 14 day window following completion of the End of Study (EOS) Visit of the qualifying/index study will participate in a screening Visit to determine eligibility. A Baseline Visit will then occur within 28 days after the Screening Visit. For subjects who are completing participation in a qualifying study of tofacitinib and enrolling on the same day of the EOS Visit of the qualifying/index study, the EOS Visit of the qualifying/index study can be combined with the Screening and Baseline Visits for this study. The subjects who enroll within the 14 day window following completion of the EOS Visit of the qualifying/index study will participate in a combined

Screening and Baseline Visit for this study. After the Baseline Visit, visits will occur at 1 month (1 month=30 days) and 3 months, then every 3 months thereafter as long as the subject remains in the study.

Approximately 340 participants are projected to enroll into this open label extension study after completing a qualifying/index study (ie, A3921103, A3921104 or A3921165) in the JIA program.

For subjects who entered this study from the A3921103 and A3921104 qualifying/index studies, their participation in this study ends after the first marketing approval of tofacitinib for the treatment of polyarticular course Juvenile Idiopathic Arthritis (pJIA) 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 systemic JIA, whichever comes first.

The total duration of an individual subject's participation may vary depending upon when they enter the trial.

Applicable to Canadian Investigator Sites Only: The duration of subject participation will be restricted to a maximum of 3 years, unless, in the Investigator's opinion, it is in the subject's best interest to continue receiving tofacitinib (to be determined on a case-by-case basis and in consultation with the Sponsor).

Depending on local regulatory requirements, and as per the EU Voluntary Harmonisation Procedure (EU VHP), access to tofacitinib may be made available to patients after the conclusion of this study via, but not limited to, an expanded access/compassionate use program until either 1) commercially available for JIA; 2) no longer beneficial to a patient as determined by the treating investigator; 3) the benefit-risk for JIA is determined to be unfavorable; or 4) the sponsor's application for marketing authorization is denied/disapproved for any reason by both US Food And Drug Administration (FDA) and European Medicines Agency (EMA).

The Sponsor may continue to provide tofacitinib to patients benefitting from this treatment in situations where the patient cannot access treatment through typical post-approval channels. Availability of the oral solution formulation may be limited or discontinued when patients taking the oral solution have either discontinued treatment or have transitioned to use of the oral tablet formulation consistent with applicable weight based dosing guidance.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

The Investigator may schedule visits (unplanned visits) in addition to those listed on the Schedule of Activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

For Investigative Sites in Belgium Only: The degree of burden and the risk threshold should be assessed at each scheduled visit as outlined in Appendix 13.

For any visits impacted by public emergencies, including the COVID-19 pandemic, refer to Appendix 14 for additional guidance and instructions.

Protocol Activity	**Subjects >14 days after EOS[7] Visit**		**Combined with EOS[7] Visit**	**Separate Visit within 14 days after EOS[7] Visit**	**Year 1** **Months 1, 3, 6, 9, 12[8]**	**Years 2-5** **Every 3 Months[8]**	**Years 6-10** **Every 3 months (except at Months 72, 84, 96, 108, 120)[8]**	**Years 6-10** **Months 72, 84, 96, 108, 120[8]**	**End of Study /Early Termination**
	Screening	**Baseline**	**Screening /Baseline**	**Screening /Baseline**					
Informed Consent/Assent	X		X	X					
Medical History	X								
Adverse Events (AE) assessment	X[d]	X[d]	X[d]	X[d]	X	X	X	X	X
Risk Factor Check for Venous Thromboembolism[16]	X[d]	X[d]	X[d]	X[d]	X	X	X	X	X
Prior/Concomitant Medications	X	X		X	X	X	X	X	X
Childhood Health Assessment Questionnaire (CHAQ)		X			X	X	X	X	X
Vital signs: Blood pressure (BP), Pulse Rate (PR), Temperature[1]	X	X		X	X	X	X	X	X
Complete Physical Exam[15, 17]	X				X[a]	X[a]		X[a]	X[a]
Targeted Physical Exam[2, 17]		X		X	X	X	X		

Protocol Activity	Subjects >14 days after EOS[7] Visit		Combined with EOS[7] Visit	Separate Visit within 14 days after EOS[7] Visit	Year 1 Months 1, 3, 6, 9, 12[8]	Years 2-5 Every 3 Months[8]	Years 6-10 Every 3 months (except at Months 72, 84, 96, 108, 120)[8]	Years 6-10 Months 72, 84, 96, 108, 120[8]	End of Study /Early Termination
	Screening	Baseline	Screening /Baseline	Screening /Baseline					
Tanner Stage Assessment		X[b]			(annually)[b]	(annually)[b]		(annually)[b]	X[b]
Physician Global Evaluation of Disease Activity	X	X		X	X	X	X	X	X
Joint Assessment of Active Arthritis (Swelling, Pain/Tenderness) and Limitation of Motion	X	X		X	X	X	X	X	X
Duration of Morning Stiffness Assessment	X	X		X	X	X	X	X	X
Signs and symptoms of Systemic Disease (sJIA ONLY)	X	X		X	X	X	X	X	X
Assessment of JIA-associated Fever (sJIA ONLY)[14]	X	X		X	X	X	X	X	X
Tender Entheseal Assessment (ERA ONLY)[11]		X			X[11]	X[11]	X[11]	X	X
Modified Schober's Test (ERA ONLY)[11]		X			X[11]	X[11]	X[11]	X	X
Overall Back Pain and Nocturnal Back Pain Assessment (ERA ONLY)[11]		X			X[11]	X[11]	X[11]	X	X
PGA of Psoriasis (PsA ONLY)[12]		X			X[12]	X[12]	X[12]	X	X
BSA affected by psoriasis (PsA ONLY)[12]		X			X[12]	X[12]	X[12]	X	X
Investigator ACR30 Response Assessment (Applicable to Canadian Investigator Sites Only)[10]					X[10]	X[10]	X[10]	X[10]	
QuantiFERON or Mantoux PPD/Chest Radiograph, if Applicable[3]	X[3]				(annually)[3]	(annually)[3]		(annually)[3]	
Safety Laboratory Testing[4]	X	X		X	X	X	X	X	X
Contraception check[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Lipid Panel[5]		X			X[5]	X[5]		X	X

Protocol Activity	Subjects >14 days after EOS[7] Visit		Combined with EOS[7] Visit	Separate Visit within 14 days after EOS[7] Visit	Year 1 Months 1, 3, 6, 9, 12[8]	Years 2-5 Every 3 Months[8]	Years 6-10 Every 3 months (except at Months 72, 84, 96, 108, 120)[8]	Years 6-10 Months 72, 84, 96, 108, 120[8]	End of Study /Early Termination
	Screening	Baseline	Screening /Baseline	Screening /Baseline					
Human Immunodeficiency Virus (HIV) Serology, Hepatitis B, Hepatitis C[9]	X								
C-Reactive Protein (CRP)	X	X		X	X	X	X	X	X
Erythrocyte Sedimentation Rate (ESR)-Westergren method[13]	X	X		X	X	X	X	X	X
Pharmacokinetic Sampling[6]					X	X			X
Uveitis Exam	X[c]				(annually)[c]	(annually)[c]		(annually)[c]	X[c]
Investigation Product Dosing Compliance					X	X	X	X	X
Dispense/Collect Drug		X	X	X	X	X	X	X	X

1. Temperature for all subjects, excluding those with sJIA: oral, tympanic or temporal methods preferred. For subject with sJIA: temperature must be measured orally using a digital thermometer, with the exception of very young children or others who cannot tolerate an oral thermometer. In these cases temperature may be measured rectally using a digital thermometer. The definition of fever with a rectal thermometer is one degree Fahrenheit higher. (Example >101.4°F/38.6°C rectally compared to >100.4°F/38°C orally). See Section 7.1.10.1 for addition detail on the presence of absence of JIA-associated fever.
2. Targeted physical exam consists of weight, height, examination of heart, lungs, extremities for peripheral edema, abdomen and lymph nodes. For children under 40 kg body weight obtained at study visits will be used to adjust dosing as the child grows.
3. Annual TB testing (QFT-TB Gold or Gold Plus) is required in countries where TB incidence has been reported at a rate of >50 cases per 100,000 persons, eg, China, Russian Federation; South Africa, India and Ukraine. (World Health Organization). Subjects who enroll more than 14 days after their EOS Visit in their qualifying/index study must have a QuantiFERON®-TB Gold or Gold Plus In-Tube test administered at screening and reported as negative in order to be eligible for enrollment in the study, unless one was performed and documented within the last 3 months. Subjects having a Purified Protein Derivative (PPD) test must return within 48-72 hour for evaluation. Annual TB screening will be conducted using QuantiFERON®-TB Gold or Gold Plus In-Tube test. QuantiFERON® -TB Gold or Gold Plus In-Tube test is not performed in subjects who had positive result during prior testing (screening visit or prior annual visits) and/or who previously received adequate treatment for TB. Sites must perform chest radiograph for TB status determination when subjects have a positive annual QFT-TB test for the first time. For more information, including chest x-rays, refer to Section 7.2.2.
4. Laboratory testing includes hematology (Complete Blood Count [CBC] with differential); Chemistry Panel includes urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alanine transferase (ALT), aspartate transferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), albumin, and creatine kinase (CK); urinalysis (U/A), and urine pregnancy test (βhCG) for females of childbearing potential. Safety laboratory testing as appropriate for standard of care for subjects receiving background Disease-Modifying Antirheumatic Drugs (DMARDs. In case of insufficient sample or

Protocol Activity	Subjects >14 days after EOS[7] Visit		Combined with EOS[7] Visit	Separate Visit within 14 days after EOS[7] Visit	Year 1 Months 1, 3, 6, 9, 12[8]	Years 2-5 Every 3 Months[8]	Years 6-10 Every 3 months (except at Months 72, 84, 96, 108, 120)[8]	Years 6-10 Months 72, 84, 96, 108, 120[8]	End of Study /Early Termination
	Screening	Baseline	Screening /Baseline	Screening /Baseline					

issue on the sample quality (eg, hemolysis or clotting) the subject should return within 1 week for a new sample collection. Creatinine Clearance will be calculated at all study visits (see Appendix 5)

5. Lipid panel (total cholesterol, direct Low Density Lipoprotein [LDL], indirect High Density Lipoprotein [HDL], apolipoprotein A-1 and B, and triglycerides) will be collected at the baseline visit for subjects who roll over more than 14 days after their End of Study (EOS) Visit for their qualifying/index study, every 6 months through year 5 and then every 12 months after year 5 for all subjects, and at the End of Study/Early Termination Visit. Subjects should be instructed to fast for approximately 9 to 12 hours, if possible, prior to lipid panel testing.
6. Pharmacokinetic (PK) blood samples will be collected at Month 12 and at approximately yearly intervals thereafter up to Month 36 (ie, Month 12, Month 24, Month 36). Samples will be collected at pre-dose and 0.5 hr (time window: 0.25-0.75 hr) and 2 hr (time window: 1.75-2.5 hr) post-dose. PK samples will be collected at the End of study/Early Termination Visit up to Month 36; this collection may not be possible or feasible if drug has been discontinued prior to this visit; a comment should be included in the applicable PK CRF page. The subject and parent/legal guardian will be instructed that the subject should not take the morning dose until after the pre dose PK sample is collected. See Section 7.4 for details regarding PK sampling. PK blood samples will not be collected from participants in India.
7. End of Study (EOS) Visit for the qualifying/index study.
8. Visits will occur every 3 months after the Month 1 visit and throughout the study. Visit windows: Months 1 and 3 Visits (±5 days); Months 6 and subsequent visits (±10 days).
9. Collected in all subjects who enroll more than 14 days after their EOS Visit for their qualifying/index study. Hepatitis B: HBs Ag and HBc Ab are tested in all subjects who undergo a Screening visit. HBs Ab is analyzed in subjects who test negative for HBsAg but positive for HBcAb. If when tested, the HBsAb test is negative (surface antibody negative), the subject will be excluded from the study. Hepatitis B testing will not be performed in subjects determined to be HBs Ab positive in their qualifying study. Hepatitis C: HCV RNA tested in case a positive HCV Ab result is obtained. To conserve blood volume at screening, HCV RNA sample collection may be deferred and collected only if required to confirm eligibility based on the HCV Ab results. See Section 7.2.9.
10. **Applicable to Canadian Investigator Sites Only:** Excluding the Month 1 visit, calculate the subject's ACR30 response (see Section 7.1.6.1) at each visit. Subjects with less than an ACR30 response at 2 consecutive visits, beginning with the Month 3 visit and anytime thereafter, should be discontinued from study treatment, unless in the opinion of the Investigator, it is in the subject's best interest to continue receiving tofacitinib (to be determined on a case-by-case basis and in consultation with the Sponsor).
11. Tender Entheseal Assessment, Modified Schober's Test, and Overall Back Pain and Nocturnal Back Pain Assessment will be performed in subjects with Enthesitis Related Arthritis (ERA) ONLY at baseline visit for subjects who roll over more than 14 days after the EOS Visit for their qualifying/index study, at Month 3 Visit, Month 6 Visit, then every 6 months and at the End of study/Early Termination Visit for all subjects.
12. Physician's Global Assessment (PGA) of Psoriasis, Body Surface Area (BSA) affected by psoriasis will be performed in subjects with Psoriatic Arthritis (PsA) ONLY at baseline visit for subjects who roll over more than 14 days after the EOS Visit for their qualifying/index study, at Month 3 Visit, Month 6 Visit, then every 6 months and at the End of study/Early Termination Visit for all subjects.

Protocol Activity	Subjects >14 days after EOS[7] Visit		Combined with EOS[7] Visit	Separate Visit within 14 days after EOS[7] Visit	Year 1 Months 1, 3, 6, 9, 12[8]	Years 2-5 Every 3 Months[8]	Years 6-10 Every 3 months (except at Months 72, 84, 96, 108, 120)[8]	Years 6-10 Months 72, 84, 96, 108, 120[8]	End of Study /Early Termination
	Screening	Baseline	Screening /Baseline	Screening /Baseline					

13. The Erythrocyte Sedimentation Rate (ESR) will be determined locally utilizing the Westergren method ESR which will be provided by the Sponsor or their local laboratory ESR Testing Kit (Westergren method). The ESR Testing Kit provided by the sponsor should be the preferred choice for ESR testing. Every effort should be made to use the same ESR Testing Kit (whether provided by the sponsor or local) throughout the course of the study.
14. For the definition of JIA-associated fever refer to Section 7.1.10.1.
15. Applicable to Investigative Sites in the United Kingdom (UK) and Belgium: a full skin cancer examination must be performed as part of the complete physical examination.
16. Per Amendment 10, all subjects will be asked at every study visit if they have any newly-developed risk factors for venous thromboembolism as described in Section 7.2.10).
17. **Applicable only to participants enrolled from Study A3921165**. A skin examination for the presence of varicella (chicken pox) and herpes zoster should be performed (see Appendix 16).

Frequency of assessments:

a. Complete physical exam is performed at Month 12 and every 12 months after Month 12 (ie, on yearly basis) in place of Targeted Physical Exam and at the End of Study/Early Termination Visit.

b. Tanner stage is performed at Baseline Visit and annually thereafter. No need to be repeated after the subject has reached Tanner Stage 5.

c. Uveitis Exam by an ophthalmologist (or qualified equivalent per local practice) is performed at Screening (if no exam is done within past 6 months), then annually thereafter, and at End of study/Early Termination Visit. If the exam was performed within the past 6 months the next uveitis exam should occur 1 year after the previous exam and annually thereafter. The window for this particular examination is ±30 days relative to the visits where uveitis exam is performed (see Section 6.2 and Section 6.2.5 for additional details). At all other visits the investigator should assess if there are potential changes in uveitis status and refer for formal evaluation if deemed clinically necessary. For JIA subtypes that may require more frequent uveitis examination, investigators should manage this type of examination according to local standard of care. For subjects with sJIA, this exam is not required but if available, documentation of previous uveitis assessment(s) by an ophthalmologist (or qualified equivalent per local practice) should be reviewed, the date of the prior examination recorded, and the presence/absence of active uveitis documented.

d. Serious adverse events (SAEs) are captured from the time of informed consent at Screening. For more information see Section 7.2.5. Adverse events (AEs) are captured following the first dose of investigational product.

e. The contraception check is an opportunity to confirm that contraception is used consistently and correctly. Also, it is the opportunity to assess changing potential to father/bear children and allows for implementing contraception and pregnancy testing as children mature physically and behaviorally during conduct of the study.

TABLE OF CONTENTS

PROTOCOL SUMMARY 7
SCHEDULE OF ACTIVITIES 11
LIST OF TABLES 21
LIST OF FIGURES 21
APPENDICES 22
1. INTRODUCTION 23
1.1. Indication 23
1.2. Background 23
1.2.1. Study Rationale 23
1.2.2. Dose Rationale 24
1.2.3. Single Reference Safety Document 26
2. STUDY OBJECTIVES AND ENDPOINTS 26
2.1. Objectives 26
2.1.1. Primary 26
2.1.2. Secondary 26
2.1.3. Exploratory 26
2.2. Endpoints 27
2.2.1. Primary 27
2.2.2. Secondary 27
2.2.3. Exploratory 28
2.3. Benefit/Risk Assessment 28
2.3.1. Risk Assessment 28
2.3.2. Benefit Assessment 29
2.3.3. Overall Benefit/Risk Conclusion 30
3. STUDY DESIGN 31
4. SUBJECT SELECTION 32
4.1. Inclusion Criteria 32
4.2. Exclusion Criteria 34
4.3. Life Style Guidelines 37
4.3.1. Contraception 37
4.3.2. Non-Pharmacologic Interventions 38

4.3.3. Vaccine and Exposure to Infections Guidelines 38
4.3.4. Elective Surgery 39
4.3.5. Dietary Supplements 40
4.4. Sponsor Qualified Medical Personnel 40
5. STUDY TREATMENTS 40
5.1. Dosing Scheme 40
5.2. Allocation to Treatment 41
5.2.1. Tofacitinib Temporary Withholding 41
5.3. Drug Supplies 42
5.3.1. Formulation and Packaging 42
5.3.2. Preparation and Dispensing 42
5.3.3. Administration 42
5.3.4. Compliance 42
5.4. Drug Storage and Drug Accountability 42
5.5. Concomitant Medication(s) 43
5.5.1. Prohibited Medications And/Or Treatments 44
5.5.2. Permitted Medications And/Or Treatments 44
5.5.2.1. Permitted Dose Adjustments in Background JIA Therapies (Worsening Disease) 45
5.5.2.2. Permitted Dose Adjustments (Tapering) in Background JIA Therapies (Inactive Disease) 45
5.5.2.3. Rescue Therapy 45
6. STUDY PROCEDURES 45
6.1. Screening and Baseline Visits 45
6.1.1. Subjects Requiring Separate Screening and Baseline Visits 45
6.1.1.1. Screening Visit 46
6.1.1.2. Baseline Visit 47
6.1.2. Subjects with Combined End of Qualifying/Index Study Visit/LTE Screening/Baseline Visit 49
6.1.3. Subjects with Separate End of Qualifying/Index Study Visit and Combined LTE Screening/Baseline Visit 49
6.2. Study Period 51

6.2.1. Year 1: Months 1 and 3 Visits (Visit Window ±5 Days); Months 6, 9 and 12 Visits (Visit Window ±10 Days) 51
6.2.2. Years 2-5: Months 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60 Visits (Visit Window ±10 Days) 53
6.2.3. Years 6-10: Month 63, 66, 69, 75, 78, 81, 87, 90, 93, 99, 102, 105, 111, 114, 117 Visits (Visit Window ±10 Days) 55
6.2.4. Years 6-10: Month 72, 84, 96, 108, 120 Visits (Visit Window ±10 Days) 57
6.2.5. End of Study Visit/Early Termination Visit 60
6.2.6. Subject Withdrawal 61
7. ASSESSMENTS 62
7.1. Efficacy 62
7.1.1. Continued Disease Activity Assessment 63
7.1.2. Physician Global Evaluation of Disease Activity 63
7.1.3. Joint Assessment 63
7.1.4. Childhood Health Assessment Questionnaire (CHAQ) 64
7.1.4.1. Parent's Assessment of Physical Function (CHAQ Disability Index) 65
7.1.4.2. Parent's Assessment of Child's Arthritis Pain (CHAQ Discomfort Index) 65
7.1.4.3. Parent's Global Assessment of Overall Well-Being (CHAQ Subsection) 65
7.1.5. Inflammatory Markers 66
7.1.5.1. C-Reactive Protein (CRP) 66
7.1.5.2. Erythrocyte Sedimentation Rate (ESR) 66
7.1.6. JIA ACR Response and Flare Criteria 66
7.1.6.1. JIA ACR Response Criteria 66
7.1.6.2. JIA ACR Flare Criteria 67
7.1.7. JIA ACR Clinical Inactive Disease Status Determination and Clinical Remission Criteria 67
7.1.8. Juvenile Arthritis Disease Activity (JADAS 27- CRP and JADAS 27- ESR) Score 68
7.1.9. JADAS 27 Minimal Disease Activity and Inactive Disease 68
7.1.10. Additional Assessments in Subjects with Systemic JIA 69

7.1.10.1. Presence or Absence of JIA-associated Fever....69
7.1.11. Additional Assessments in Subjects with Enthesitis-Related Arthritis....69
7.1.11.1. Tender Entheseal Assessment....69
7.1.11.2. Modified Schober's Test....70
7.1.11.3. Overall Back Pain and Nocturnal Back Pain Assessment....71
7.1.12. Additional Assessments in Subjects with Psoriatic Arthritis (PsA)....71
7.1.12.1. Body Surface Area (BSA)....71
7.1.12.2. Physician's Global Assessment (PGA) of Psoriasis....72
7.2. Safety....72
7.2.1. Blood Pressure, Pulse Rate and Temperature....72
7.2.2. QuantiFERON®-TB Gold or Gold-Plus In-Tube Test....72
7.2.3. Tuberculin Test (PPD)....73
7.2.4. Radiograph of Chest....74
7.2.5. Uveitis Exam....74
7.2.6. Macrophage Activation Syndrome (MAS) Markers (sJIA Only)....75
7.2.7. Physical Examination....76
7.2.8. Assessment of Pubertal Development....76
7.2.9. Laboratory Tests....77
7.2.9.1. Blood Volume....79
7.2.10. Risk Factor Check for Venous Thromboembolism....79
7.3. Pregnancy Testing....80
7.4. Pharmacokinetic Sampling....81
7.4.1. PK Sampling Time Points for All Subjects....81
7.4.2. Plasma for Analysis of Tofacitinib....81
7.4.3. Shipment of Pharmacokinetic Samples....81
8. ADVERSE EVENT REPORTING....82
8.1. Adverse Events....82
8.2. Time Period and Frequency for collecting AE and SAE Information....82
8.3. Definition of an Adverse Event....83
8.4. Medication Errors....83
8.4.1. Tofacitinib Overdosage....84

8.5. Infections 84
8.5.1. Serious Infections 84
8.5.2. Treated Infections 85
8.6. Abnormal Test Findings 85
8.7. Serious Adverse Events 85
8.7.1. Protocol-Specified Serious Adverse Events 86
8.7.2. Potential Cases of Drug-Induced Liver Injury 86
8.8. Hospitalization 87
8.9. Severity Assessment 89
8.10. Causality Assessment 89
8.11. Exposure During Pregnancy 89
8.12. Occupational Exposure 91
8.13. Withdrawal Due to Adverse Events (See Also the Section 6.2.6 Subject Withdrawal) 91
8.14. Eliciting Adverse Event Information 91
8.15. Reporting Requirements 91
8.15.1. Serious Adverse Event Reporting Requirements 91
8.15.2. Non-Serious Adverse Event Reporting Requirements 92
8.15.3. Sponsor Reporting Requirements to Regulatory Authorities 92
9. DATA ANALYSIS/STATISTICAL METHODS 92
9.1. Sample Size Determination 92
9.2. Efficacy Analysis 93
9.2.1. Analysis of Primary Endpoint 93
9.2.2. Analysis of Secondary Endpoints 93
9.3. Safety Analysis 93
9.4. PK Analysis 94
9.5. Interim Analysis 94
9.6. Data Safety Monitoring Board 94
9.7. Safety Endpoint Adjudication Committees 94
10. QUALITY CONTROL AND QUALITY ASSURANCE 95
11. DATA HANDLING AND RECORD KEEPING 96
11.1. Case Report Forms/Electronic Data Record 96

11.2. Record Retention 96
12. ETHICS 97
12.1. Institutional Review Board (IRB)/ Ethics Committee (EC) 97
12.2. Ethical Conduct of the Study 97
12.3. Subject Information and Consent/Assent 97
12.4. Subject Recruitment 98
12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP 98
13. DEFINITION OF END OF TRIAL 98
13.1. End of Trial in a Member State 98
13.2. End of Trial in all Participating Countries 99
14. SPONSOR DISCONTINUATION CRITERIA 99
15. PUBLICATION OF STUDY RESULTS 99
15.1. Communication of Results by Pfizer 99
15.2. Publications by Investigators 100
16. REFERENCES 101

LIST OF TABLES

Table 1. Summary of Tofacitinib Pharmacokinetic Parameter Values (CV%) in JIA Subjects from Study A3921103 25
Table 2. Study Treatment Dosing and Administration 41
Table 3. Laboratory Testing 78

LIST OF FIGURES

Figure 1. Modified Schober's Test 70

APPENDICES

Appendix 1. Allowed And Disallowed Treatments for JIA 104
Appendix 2. Approximate Equivalent Morphine Doses of Opioid Analgesics.....107
Appendix 3. Permitted Adjustments In JIA Therapies for Worsening Disease 108
Appendix 4. Permitted Adjustments (Tapering) of JIA Medications for Subjects with Inactive Disease for at Least 24 Weeks.....109
Appendix 5. Estimated Glomerular Filtration Rate (GFR) and Creatinine Clearance (CrCl) Calculations.....111
Appendix 6. Prohibited Concomitant Medications.....112
Appendix 7. Rescue Therapy.....114
Appendix 8. Guidelines For Safety Monitoring And Discontinuations 116
Appendix 9. Evaluation Of Potentially Malignant Tumors, Suspicious Lymphadenopathy, Possible Extra-Nodal Lymphoproliferative Disorder (LPD) 119
Appendix 10. Body Surface Area 120
Appendix 11. Physician's Global Assessment Of Psoriasis 121
Appendix 12. Dosing Scheme For Subjects Rolling Over From Study A3921103 Under Protocol Amendment 5 123
Appendix 13. By Visit Assessment of the Degree of Burden and Risk Threshold During the Trial (Investigative Sites in Belgium Only) 124
Appendix 14. Alternative Measures During Public Emergencies 125
Appendix 15. End of Study.....128
Appendix 16. Varicella (chickenpox) and Herpes Zoster (shingles) Assessment and Guidance. *(Applicable for subjects enrolled from A3921165 only)* 129
Appendix 17. Summary of Changes from Original Protocol through Amendment 11 130

1. INTRODUCTION

1.1. Indication

Tofacitinib (also known as CP-690,550) is currently approved in the United States and more than 98 countries for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. In adults, it is also approved for the treatment of psoriatic arthritis (PsA), ulcerative colitis and ankylosing spondylitis. It may be used in combination with methotrexate or other non biologic disease modifying antirheumatic drugs (DMARDs). In the pediatric population, from 2 to less than 18 years of age, tofacitinib is approved for active polyarticular course JIA in the United States and polyarticular JIA and juvenile PsA in the EU.

1.2. Background

Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays tofacitinib, inhibits JAK1, JAK2, JAK3, to a lesser extent TyK2. In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including interleukins (IL) IL-2, -4,-7,-9, -15 and -21.[1,2,3] These cytokines are integral to lymphocyte activation, proliferation, and function and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and IFN γ. At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling.

1.2.1. Study Rationale

The tofacitinib pediatric development program is designed to demonstrate both efficacy, as demonstrated by a reduction in signs and symptoms of JIA in subjects 2 years of age and older, and safety supporting the use of tofacitinib for the treatment of pediatric subjects with JIA.

The rationale of this study is to enable subjects potentially benefitting from treatment in a previous qualifying/index study to continue to receive tofacitinib at the same dose as the qualifying/index study (unless further analysis of the qualifying/index study data indicate otherwise), and to characterize long-term safety and tolerability of tofacitinib for the treatment of JIA.

It is anticipated that benefit of continued treatment with tofacitinib for individual subjects in this study will have been established in the qualifying/index study as per the Investigator's assessment. Potential risks of continued treatment are expected to be consistent with those described in the Single Reference Safety Document (current version of the tofacitinib Investigator Brochure).

1.2.2. Dose Rationale

Selection of the 5 mg BID dose of tofacitinib for this long term extension (LTE) study of tofacitinib in JIA subjects is supported by pharmacokinetic (PK) data from the completed Phase 1 PK study of tofacitinib in JIA subjects (A3921103) and the benefit/risk profile of tofacitinib in adult RA subjects.

Tofacitinib clearance is not dependent on body weight for weights >40 kg based on tofacitinib PK in the adult RA population [body weight range of the population studied was 40 kg-140 kg]. Thus the dose of tofacitinib in adolescents with body weight ≥40 kg was set to 5 mg twice a day (BID), the only approved dose of tofacitinib in adult RA subjects in most countries. The doses for JIA subjects with lighter weight were selected to match the predicted steady state concentrations ($C_{avg,ss}$) in JIA subjects with body weight ≥40 kg after administration of a 5 mg BID dose.

Generally, for approved DMARDs in the treatment of JIA, partial extrapolation of efficacy from the adults to pediatrics is well accepted (Dunne et al, Pediatrics 2011).[11] Thus, the dose range selected for JIA subjects across the weight-group is predicted to achieve $C_{avg,ss}$ values equivalent to efficacious doses in adult RA population (between 3 to 5 mg BID dose).

Due to lack of prior PK data for tofacitinib in the pediatric population, initial doses for the PK study (A3921103) were selected using allometric (weight-based) scaling of the adult PK parameters with an exponent of 0.75 (θ in Eq. 1 and 2). For most small molecules, the relationship between clearance (CL) and body weight (BWT) is best described by a non-linear relationship; whereby clearance is commonly scaled to the 0.75 power of BWT and volume of distribution (V) is linearly correlated with BWT. Following these principles, with $C_{avg,ss}$ as the target, CL and dose were allometrically scaled and the exponent estimated (Eq. 1 and Eq. 2, respectively), assuming bioavailability (F) to be similar between adults and children. These relationships were used to obtain pediatric doses that were expected to provide similar $C_{avg,ss}$ to adult RA tofacitinib 5 mg BID dosing (assuming 70 kg BWT for an adults).

$$CL(ped)/F = CL(adult)/F \times \left(\frac{BWT}{70}\right)^{\theta} \quad \text{Eq. 1}$$

$$Dose(ped) = Dose(adult) \times \left(\frac{BWT}{70}\right)^{\theta} \quad \text{Eq. 2}$$

The PK study of tofacitinib in subjects with JIA has completed. A total of 26 subjects between 2 and 17 years of age and weighing between 13.9 and 70.9 kg were dosed with 2 to 5 mg BID doses of tofacitinib for 5 days in Study A3921103. Pharmacokinetic evaluations were performed on Day 5 at pre-dose, 0.5, 1, 2, 4 and 8 hours. Non-compartmental analysis (NCA) was performed on the PK profiles, and a summary of PK parameters is presented in Table 1.

Table 1. Summary of Tofacitinib Pharmacokinetic Parameter Values (CV%) in JIA Subjects from Study A3921103

Cohort	No. Subjects	Weight (Kg)	AUC_{tau} (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	CL/F (L/hr)
Cohort 1 12 to <18 yrs	8	38.3-70.9	156.6 (25)	46.97 (40)	0.75 [0.5-6.9]	2.616 ± 0.454	28.09 (22)
Cohort 2 6 to <12 yrs	9	20.3-48.9	118.8 (27)	41.67 (29)	1.0 [0.50-2.05]	1.949 ± 0.294	25.48 (40)
Cohort 3 2 to <6 yrs	9	13.9-19.8	142.5 (32)	66.15 (28)	0.50 (0.50-1.92)	1.771 ± 0.406	20.53 (33)

*Geometric Mean (CV%) for Area under the effect curve (AUC_{tau}), C_{max}, apparent clearance (CL/F) and arithmetic mean (±SD) for terminal half-life ($T_{1/2}$); Median [range] for Time to C_{max} (T_{max}); Source: Table 14.1.2.1.1, date of table generation: 18 January 2016 (08:42) and Table 14.4.3.1.1, date of table generation: 02 February 2016 (05:22).

The exposures from the first 16 subjects in Cohort 1 and Cohort 2 in Study A3921103 (as shown above) indicated higher CL/F values than predicted from Eq. 1 using an allometric component of 0.75 and thus resulting $AUC_{tau,ss}$ and $C_{max,ss}$ values 38-53% and 19-28% lower, respectively, as compared to adult RA subjects (252 ng·hr/mL and 58 ng/mL respectively; data on file). However, due to higher doses administered in Cohort 3 (protocol was amended based on interim analysis of PK data from Cohorts 1 and 2 to target systemic exposure equivalent to 5 mg BID in adult rheumatoid arthritis [RA] subjects), AUC_{tau} in Cohort 3 was comparable to Cohort 1 and higher than Cohort 2, and C_{max} value was higher than both preceding cohorts.

A population PK model was developed, and concentrations from the 26 JIA subjects enrolled in study A3921103 were fitted adequately using an one compartment model with first-order absorption (Ka) and linear elimination. In this model, body weight was used as an allometric covariate to describe changes in CL/F and V/F with changes in weight and the exponents being estimated. The estimated power exponents were 0.292 (%RSE: 40.1%) for CL/F and 0.843 (%RSE: 12.3%) for V/F. Similar to adult RA subjects, age, gender and race were not found to be significant covariates to describe inter-subject variability in tofacitinib CL/F or V/F. Formulation (solution or tablets) was tested as a covariate for first order absorption constant, Ka , and was found to be not statistically significant. Thus it was not included in the final model.

Following model fitting, Monte Carlo simulations using the estimated population PK parameters and their inter individual variability were conducted to evaluate doses expected to provide $C_{avg,ss}$ and $C_{max,ss}$ concentrations comparable to efficacious concentrations in adult RA subjects with maximum nominal dose capped at 5 mg BID. With the current proposed dosing regimen (Section 5.1), the predicted $C_{avg,ss}$ is similar to that of 3-5 mg BID in adult RA subjects across the expected weight range, with $C_{max,ss}$ not exceeding that of 10 mg BID in most subjects. Based on the results of the modeling using allometric scaling and the PK data from Study A3921103, it is expected that doses of 2 to 5 mg BID (depending on body weight of the subjects), administered approximately 12 hours apart will provide safe and efficacious exposures of tofacitinib in this study (see Section 5.1 for the planned doses and regimens).

PK collection time points (see Section 7.4.1) in this study were decided based on optimal PK sampling design utilizing the population PK (POPPK) model built on data from A3921103.

1.2.3. Single Reference Safety Document

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the current version of the Investigator's Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary

- The primary objective of this study is to determine the long term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA.

2.1.2. Secondary

- The secondary objective of this study is to evaluate the persistence of efficacy of tofacitinib for treatment of the signs and symptoms of JIA.

2.1.3. Exploratory

The exploratory objectives of this study are:

- To assess tofacitinib pharmacokinetics (PK) in pediatric subjects on a stable dose of tofacitinib in the setting of a long-term, open label study.

- To assess changes in PK parameters (within subject) with increase in weight in this pediatric population and to explore exposure-response relationships of tofacitinib for various efficacy and safety endpoints after long-term exposure of tofacitinib in this pediatric population.

2.2. Endpoints

2.2.1. Primary

- Standard laboratory safety data and adverse event (AE) reports. Body weight, height and Tanner stages will be collected to assess growth and physical development.

2.2.2. Secondary

The following efficacy parameters will be assessed:

- Physician global evaluation of disease activity at each visit.
- Number of joints with active arthritis at each visit.
- Number of joints with limitation of motion at each visit.
- Index of inflammation (C-reactive protein [CRP] and Erythrocyte Sedimentation Rate [ESR]) at each visit.
- Childhood Health Assessment Questionnaire (CHAQ) at each visit.
    - Parent's Assessment of Physical Function (CHAQ Disability Index).
    - Parent's Assessment of Child's Arthritis Pain (CHAQ Discomfort Index, Visual Analog Scale [VAS]).
    - Parent's Global Assessment of Overall Wellbeing (CHAQ subsection, Visual Analog Scale [VAS]).
- JIA American College of Rheumatology (ACR) response at each visit and occurrence of JIA ACR disease flare after Month 3.
- JIA ACR Clinical Inactive Disease status and Clinical Remission on Medication at each visit.
- Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS) 27- CRP and JADAS 27-ESR, and occurrence of JADAS minimum disease activity and inactive disease at each visit.
- Eligibility of tapering defined per protocol for corticosteroids, MTX/leflunomide, and tofacitinib.
- In subjects with **sJIA**: "Absence of Fever", defined as absence of fever due to sJIA in the week preceding the assessment at each visit.

- In subjects with Enthesitis Related Arthritis (**ERA)**: Change from baseline in the Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain responses at various visits.

- In subjects with psoriatic arthritis (**PsA**): Change from baseline in body surface area (BSA) affected by psoriasis and Physician's Global Assessment (PGA) of psoriasis) at various visits.

2.2.3. Exploratory

- Plasma concentration time data for tofacitinib will be analyzed to characterize the PK in this subject population. Exposure-response relationship will be explored for various efficacy and safety endpoints after long-term exposure of tofacitinib.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Safety concerns have been identified based on the totality of nonclinical and clinical data across the entire tofacitinib development programs (all indications) and/or are considered due to experience with other immunosuppressive agents. The nature and degree of the risk varies with the patient population; however, safety findings that may be associated with the use of tofacitinib include lipid elevations, decreases in hemoglobin, decreases in neutrophil and lymphocyte counts, increases in serum creatinine, increases in serum creatine kinase, infection risk, lymphoproliferative disorder/lymphoma risk, malignancy risk, non-melanoma skin cancer (NMSC), gastrointestinal perforations, viral reactivation, including herpes zoster, tuberculosis, cardiovascular (CV) disease, venous thromboembolism (VTE, manifested as pulmonary embolism and deep vein thrombosis), transaminase elevations, drug hypersensitivity and effects on pregnancy and the fetus. Interstitial lung disease (ILD) is also observed; ILD is a serious comorbidity for some populations in which tofacitinib has been studied and has been reported as a potential risk associated with other disease modifying anti-rheumatic drugs therapies.

Upon completion of a large randomized open-label post authorization safety surveillance (PASS) study in RA subjects who were 50 years or older with at least one additional cardiovascular (CV) risk factor, evaluating the safety profile of tofacitinib compared to TNF inhibitors, additional new potential risks for tofacitinib were identified. Those include Major Adverse Cardiovascular Events (MACE), myocardial infarction, lymphoma, lung cancer and fractures.

As per the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) conclusion to a recent safety signal assessment on the data from this study (EPITT 19382), myocardial infarction, lung cancer and lymphoma are categorized as important identified risks and malignancy excluding NMSC continues to be categorized as an important potential risk in the context of the EU risk management plan and EU Summary of Product Characteristics. Recommendations for use of the marketed product (Xeljanz [tofacitinib]) in the EU were also adopted by PRAC, advising healthcare professionals that tofacitinib should only be used in patients over 65 years of age, patients who are current or

past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors, if no suitable treatment alternatives are available.

Additionally, the risk of herpes zoster in tofacitinib-treated Asian patients may be higher than for non-Asian patients; further analyses showed that the increased rate among Asian patients is largely due to an increased incidence rate in Japanese and Korean patients. The reason for the increased risk of HZ in Japan and Korea is unclear.

Safety assessments, including physical examinations, skin examinations, clinical laboratory tests, adverse event monitoring vital signs and VTE risk assessment will be performed in this study at every study visit. Safety assessments, inclusion/exclusion criteria, monitoring and discontinuation criteria including criteria for the discontinuation of a subject with a VTE event were designed to manage and mitigate the safety risks associated with tofacitinib therapy.

A complete discussion of the possible risks associated with the administration of tofacitinib is summarized in Section 7.2.2.3 (Special Populations), Section 7.4 (Special Warnings and Precautions) and Section 7.8.1.2 (Characterization of Select Adverse Drug Reactions) of the current Tofacitinib Investigator's Brochure. Interpretation of these results and the possible risks associated with the administration of tofacitinib are summarized in Section 6.2.3 (Special Safety) and Section 7 (Summary of Data and Guidance for the Investigator) of the Investigators' Brochure.

2.3.2. Benefit Assessment

Adults with Rheumatoid Arthritis

In the Phase 3 RA development program, the primary endpoint, American College of Rheumatology (ACR) 20 response rate at Month 3 or 6, was consistently and statistically significantly different for the tofacitinib 5 mg BID group compared with the placebo group. Tofacitinib demonstrated statistically significant and clinically meaningful reductions in signs and symptoms of RA over placebo. Results of ACR50 and ACR70 response rates were consistent with the ACR20 results in these Phase 3 studies. ACR50 and ACR70 response rates were consistently greater in the tofacitinib treatment groups compared with the placebo groups in all the Phases 3 studies. Other efficacy parameters include measures of the proportion of patients achieving Disease Activity Score (DAS)28-4(Erythrocyte Sedimentation Rate [ESR]) <2.6 (primary) and ⩽3.2 [DAS28-4(ESR) is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity and erythrocyte sedimentation rate] and physical function status (as measured by Health Assessment Questionnaire Disability Index [HAQ-DI]). Tofacitinib may also help in cartilage preservation as demonstrated by reductions in modified Total Sharp Score (mTSS) and radiographic joint space narrowing in adults with RA.

Pediatric Patients with Juvenile Idiopathic Arthritis

Pfizer has undertaken a pediatric development program to determine the safety and efficacy of tofacitinib in subjects 2 to <18 years of age for the treatment of juvenile idiopathic arthritis

(JIA). JIA is an umbrella term for several distinct arthritides each lasting more than 6 weeks and involving both autoimmune and genetic factors, but with unknown etiology. Currently, to be classified as juvenile, the arthritis must have had onset prior to 16 years of age. As part of this pediatric program, a Phase 1 pharmacokinetic (PK) study of tofacitinib in JIA subjects (A3921103) was completed in 2015, a Phase 3 study of tofacitinib in polyarticular JIA subjects (A3921104) was completed in 2019, and a Phase 3 efficacy, safety, tolerability and PK study of tofacitinib in sJIA subjects (A3921165) is on-going.

Study A3921104 was designed to provide evidence of efficacy and safety of tofacitinib in subjects with JIA. To limit exposure to placebo in this pediatric population, a randomized withdrawal study design was used. Selection of doses for this first efficacy study of tofacitinib in subjects with JIA was supported by PK data from the completed Phase 1 PK study of tofacitinib in JIA subjects (A3921103) and the benefit/risk profile of tofacitinib in adult patients with RA.

The primary efficacy endpoint of Study A3921104 was met; subjects treated with tofacitinib 5 mg BID had a significantly lower occurrence of disease flare by Week 44 compared to placebo-treated subjects. The type I error controlled (key) secondary endpoints for the study were also met at Week 44. A significantly greater proportion of subjects treated with tofacitinib 5 mg BID achieved JIA ACR 50, 30, and 70 responses compared to subjects treated with placebo, and the LS mean change from the double-blind baseline in CHAQ disability index indicated a statistically significant treatment effect favoring tofacitinib over placebo. The proportions of subjects with TEAEs, SAEs, severe TEAEs, dose reductions or temporary discontinuations due to TEAEs were similar between the tofacitinib 5 mg BID and placebo groups during the double-blind phase. A larger proportion of subjects in the placebo group had TEAEs related to the underlying JIA disease than subjects in the tofacitinib 5 mg BID group. A smaller proportion of subjects treated with tofacitinib 5 mg BID discontinued the study because of an AE compared to subjects who received placebo. Disease progression and JIA were the most frequent AEs leading to study discontinuation.

In summary, Study A3921104 showed that tofacitinib 5 mg BID treatment in subjects 2 to <18 years of age with JIA resulted in significant improvements in the occurrence of disease flare at Week 44 compared to subjects treated with placebo. Secondary efficacy results supported the primary conclusion.

An interim analysis (data cutoff 04 Jun 2019, data snapshot 03 Jul 2019) was conducted for Study A3921145. At the time of the data cutoff, 227 subjects had enrolled in the study (signed informed consent), and 2 subjects from Study A3921104 were enrolled but not treated; 177 subjects were ongoing. Insufficient clinical response was the most common discontinuation reason to date. In general, available efficacy data of long-term treatment with tofacitinib showed stable improvement in JIA symptoms from baseline of the qualifying/index studies.

2.3.3. Overall Benefit/Risk Conclusion

Based on the totality of the data, the sponsor is of the opinion that the overall risk-benefit assessment for this study is favorable for children with sJIA. Study A3921145 provides an

opportunity for careful evaluation of tofacitinib in sJIA patients in a clinical study environment, guided by risk factors specifically described in this protocol. Thorough safety monitoring and staggering of cohorts based on age for index studies will be used to minimize risk in the pediatric population.

Further background information on tofacitinib can be obtained from the current version of the Tofacitinib IB.

3. STUDY DESIGN

This is a Phase 2/3, long term, open-label, follow-up study. Subjects will have previously participated in qualifying/index study in the tofacitinib JIA program. Those who have already completed such participation and enroll outside the 14 day window following completion of the End of Study (EOS) Visit of the qualifying/index study will participate in a Screening Visit to determine eligibility. A Baseline Visit will then occur within 28 days after the Screening Visit. For subjects who are completing participation in a qualifying study of tofacitinib and enrolling on the same day of the EOS Visit of the qualifying/index study, the EOS Visit of the qualifying/index study can be combined with the Screening and Baseline Visits for this study. The subjects who enroll within the 14 day window following completion of the EOS Visit of the qualifying/index study will participate in a combined Screening and Baseline Visit for this study. After the Baseline Visit, visits will occur at 1 month (1 month=30 days) and 3 months, then every 3 months thereafter as long as the subject remains in the study.

Approximately 340 participants are projected to enroll into this open label extension study after completing a qualifying/index study (ie, A3921103, A3921104 or A3921165) in the JIA program.

For subjects who entered this study from the A3921103 and A3921104 qualifying/index studies, their participation in this study ends after the first marketing approval of tofacitinib for the treatment of polyarticular course Juvenile Idiopathic Arthritis (pJIA) 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 systemic JIA, whichever comes first.

The total duration of an individual subject's participation may vary depending upon when they entered the trial.

Applicable to Canadian Investigator Sites Only: The duration of subject participation will be restricted to 3 years, unless, in the Investigator's opinion, it is in the subject's best interest to continue receiving tofacitinib (to be determined on a case-by-case basis and in consultation with the Sponsor).

Depending on local regulatory requirements, and as per the EU Voluntary Harmonisation Procedure (EU VHP), access to tofacitinib may be made available to patients after the conclusion of this study via, but not limited to, an expanded access/compassionate use

program until either 1) commercially available for JIA; 2) no longer beneficial to a patient as determined by the treating investigator; 3) the benefit-risk for JIA is determined to be unfavorable; or 4) the sponsor's application for marketing authorization is denied/disapproved for any reason by both US FDA and EMA. The Sponsor may continue to provide tofacitinib to patients benefitting from this treatment in situations where the patient cannot access treatment through typical post-approval channels. Availability of the oral solution formulation may be limited or discontinued when patients taking the oral solution have either discontinued treatment or have transitioned to use of the oral tablet formulation consistent with applicable weight based dosing guidance.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

All subjects must meet Inclusion Criteria 1-11 to be eligible for enrollment into the study:

1. Pediatric subjects with JIA aged from 2 to less than 18 years who met entry criteria for the qualifying/index study and in the opinion of the investigator have sufficient evidence of JIA disease activity to warrant use of tofacitinib as a DMARD. Subjects turning 18 years of age during participation in the qualifying/index study or subsequently will be eligible for participation in this study.

2. The subject has discontinued disallowed concomitant medications for the required time prior to the first dose of study drug, as defined in Appendix 1 (Allowed and Disallowed Treatments for JIA), and is taking only those concomitant medications in doses and frequencies allowed by the protocol.

3. Fertile male subjects and female subjects of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must be using a highly effective method of contraception as outlined in this protocol throughout the study and for at least 28 days after the last dose of study medication.

4. Subjects must have previously completed participation in a qualifying study of tofacitinib for the treatment of JIA. Subjects who have required earlier discontinuation of treatment in a qualifying study for reasons other than tofacitinib related serious adverse events may be eligible.

5. For subjects receiving methotrexate (MTX) treatment, MTX may be administered either orally or parenterally at doses not to exceed 25 mg/week or 20 mg/m^2/week,

whichever is lower. Subjects taking methotrexate must be taking folic acid or folinic acid in accordance with local standards.

6. For subjects receiving an oral glucocorticoid, glucocorticoids may be administered at a maximum dose of 0.20 mg/kg/day or 10 mg/day, prednisone or equivalent, whichever is lower (intramuscular and intravenous corticosteroids are not permitted in the 4 weeks preceding the first dose of study medication and throughout the study). For subjects coming from the systemic JIA study A3921165, a higher prednisone-equivalent dose may be continued or started (doses must be ≤1.0 mg/kg/day up to 30 mg/day oral prednisone [or equivalent]).

7. For subjects receiving leflunomide treatment, leflunomide may be administered according to the following dosing scheme:

   - 10 mg every other day for subjects weighing less than 20 kg;
   - 10 mg every day for subjects weighing between 20 and 40 kg;
   - 20 mg every day for subjects weighing over 40 kg;
   - Or as according to local standards.

8. For subjects receiving sulfasalazine, chloroquine, or hydroxychloroquine treatment, these medications may be administered according to local standards.

9. Evidence of a personally signed and dated informed consent document with assent as appropriate indicating that the subject (or a legally acceptable representative/parent(s)/legal guardian) has been informed of all pertinent aspects of the study.

10. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

11. Subjects for whom, in the Investigator's opinion, treatment with tofacitinib is considered clinically appropriate while also taking into consideration currently available therapies and prior response to these therapies.

Subjects who enroll outside the 14 day window of the EOS Visit of their qualifying/index study must also meet Inclusion Criterion 12 to be eligible for enrollment into the study:

12. No evidence of active tuberculosis (TB) or inadequately treated tuberculosis (TB) infection (active or latent) as evidenced by all of the following:

    a. A negative QuantiFERON®-TB Gold or Gold Plus In-Tube test[4] performed within the 3 months prior to screening. A negative purified protein derivative (PPD) test with a result of <5 mm induration can be substituted for the QuantiFERON®-TB

Gold or Gold Plus In-Tube test only if the central laboratory is unable to perform the test or cannot determine the results to be positive or negative.

b. Chest radiograph without changes suggestive of active tuberculosis(TB) infection within 3 months prior to screening is recommended and should be performed according to local standards of care or country-specific guidelines (see Section 7.2.4).

c. No history of either untreated or inadequately treated latent or active TB infection.

If a subject has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a PPD test nor a QuantiFERON®- Gold or Gold Plus test need be obtained. A chest radiograph should be obtained if not done within the 3 months prior to screening (see Section 7.2.4). To be considered eligible for the study, the chest radiograph must be negative for active tuberculosis infection.

A subject who is currently being treated for latent TB infection can only be enrolled with confirmation of current incidence rates of multi-drug resistant TB infection (<5%) and documentation of an adequate treatment regimen.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

For subjects who enroll outside the 14 day window of the EOS Visit of their qualifying/index study (Exclusion 13-15):

1. Blood dyscrasias, including:

   a. Hgb <10 g/dL or Hct <33%;

   b. WBC <3.0 x 109/L;

   c. Neutrophil count <1.2 x 109/L;

   d. Platelet count <100 x 109/L;

   e. Lymphocyte count of <0.75 x 109/L.

2. Estimated glomerular filtration rate [GFR] <40 mL/min/1.73 m^2 calculated using Bedside Schwartz formula (Appendix 5) at the Screening Visit.

3. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥1.5 times the upper limit of normal or any other clinically significant laboratory abnormality.

For all subjects:

4. Persistent oligoarthritis and undifferentiated JIA.

5. Current or recent history of uncontrolled clinically significant renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, or neurological disease.

6. History of any other rheumatic autoimmune disease, other than Sjogren's syndrome.

7. History or current symptoms suggestive of any lymphoproliferative disorder, such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.

8. 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 drug.

    c. Any treated infections within 2 weeks of baseline visit. (excluding those treated with topicals only).

    d. A subject known to be infected with human immunodeficiency virus (HIV), hepatitis B or hepatitis C virus.

    e. History of infected joint prosthesis with prosthesis still in situ.

9. History of recurrent (more than one episode) herpes zoster or a single episode of disseminated herpes zoster or a single episode of disseminated (both oral and genital lesions simultaneously, or widespread lesions not contained to oral or genital regions alone) herpes simplex.

10. Subjects taking potent and moderate cytochrome P450 3A4 (CYP3A4) inhibitors (Appendix 6).

11. Subjects taking potent and moderate CYP3A4 inducers (Appendix 6).

12. Participation in studies of investigational compounds (excluding qualifying/index study with tofacitinib) within 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug. Subjects cannot participate in studies of other investigational compounds at any time during their participation in this study. Exposure to investigational biologics should be discussed with the Pfizer Medical Monitor.

13. Any prior treatment with non B cell-specific lymphocyte depleting agents/therapies [eg, alemtuzumab (CAMPATH®), alkylating agents (eg, cyclophosphamide or chlorambucil), total lymphoid irradiation, etc]. Subjects who have received rituximab or other selective B lymphocyte depleting agents (including experimental agents) are eligible if they have not received such therapy for at least 1 year prior to study baseline and have normal CD 19/20+ counts by FACS analysis.

14. Pregnant or nursing females are excluded.

15. Intramuscular or intravenous corticosteroids in the 4 weeks preceding first dose of study medication (oral corticosteroids permitted as per inclusion criterion).

16. Subjects who have been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study medication. All study participants should be up-to-date with respect to standard of care vaccinations (as defined by their country health ministry). (See Life Style Guidelines for further information regarding avoidance of household contacts who may be vaccinated).

17. Use of prohibited prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication.

18. Herbal supplements must be discontinued at least 4 weeks prior to the first dose of study medication.

19. Subjects with a first degree relative with a hereditary immunodeficiency; IgA deficiency not exclusionary.

20. Subjects with a malignancy or with a history of malignancy with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

21. Recent (within 28 days prior to first dose of study drug) significant trauma or major surgery.

22. Unwilling or unable to comply with the Life Style Guidelines described in this protocol.

23. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

24. Subjects who are children of or related to investigational site staff members, site staff members otherwise supervised by the investigator, or Pfizer employees directly involved in the conduct of the study.

25. Any factors or clinical characteristics potentially related to the risk of venous thromboembolism (see Section 7.2.10, Risk Factor Check for VTE) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

26. History of allergies, intolerance or hypersensitivity to lactose or CP-690,550 (tofacitinib), or any other excipients of the Investigational Medicinal Product. This includes subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. The investigators of potential subjects with acquired lactose intolerance should consider whether this is sufficiently concerning so as to preclude participation. As the oral solution does not include lactose, subjects with hereditary or acquired lactose intolerance may be treated with the tofacitinib oral solution, instead of the tablet, at the investigator's request.

4.3. Life Style Guidelines

4.3.1. Contraception

All fertile male subjects and female subjects of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s), must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his/her designee, in consultation with the subject and his/her legally acceptable representative/parent(s)/legal guardian, will confirm that the subject has selected an appropriate method of contraception from the list of permitted contraception methods (see below). At time points indicated in the schedule of activities (SOA), the investigator or designee will instruct the subject of the need to use highly effective contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception (eg, EU), this option is

not appropriate. (Note: In the UK and Belgium, a condom plus spermicide is not accepted as highly effective contraception).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

Also, all subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s), and are on background medications (including DMARDs) that require contraceptive measures according to the local drug label must meet those requirements during the study and after therapy for 3 months or for the duration specified in the local drug label.

4.3.2. Non-Pharmacologic Interventions

The subject may continue, add, or remove all non-pharmacological therapies, such as physical therapy, as indicated and deemed appropriate for his/her physical condition. For subjects with psoriatic arthritis, refer to Section 5.5.2.

4.3.3. Vaccine and Exposure to Infections Guidelines

It is recommended that all study participants should be up-to-date with respect to standard of care vaccinations (as defined by their country health ministry) or JIA guidelines.

Vaccination with live components (e.g. live attenuated influenza vaccine, MMR (measles, mumps, and rubella) vaccine, or MMR-V (measles, mumps, rubella and varicella) vaccine) is prohibited within the 6 weeks prior to first dose of study drug. At the discretion of the investigator, subjects may be vaccinated with a live or live-attenuated vaccine at any time during the study only if tofacitinib is discontinued for a minimum of 6 weeks prior to vaccination and a minimum of 6 weeks after vaccination.

Inactivated vaccines, including inactivated influenza vaccine, pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccines, may be administered to study subjects during the conduct of the study.

Administration of non-live COVID-19 vaccines that are fully approved or approved for emergency use is permitted during the study, provided that the vaccination is not part of another clinical study. Examples include, but are not limited to, mRNA vaccines, adenovirus vector vaccines and inactivated COVID-19 vaccine. If a participant receives a non-live COVID-19 vaccine during the study, it should be recorded as a concomitant medication and standard AE collection and reporting processes would be followed.

4.3.3.1 Varicella vaccination for participants enrolled from A3921165

Varicella vaccination is encouraged when appropriate, and if the participant is vaccinated, the first dose of study drug may not be administered until at least 4 weeks after vaccination.

For subjects who have not been vaccinated for varicella and did not have a positive VZV IgG Ab serology test at the A3921165 screening visit, evaluate the subject for varicella at every study visit. For those subjects who have been vaccinated or have a positive VZV IgG Ab serology test at screening, evaluate the subject for herpes zoster at every visit. Please refer to Appendix 16 regarding the diagnosis and treatment of varicella and herpes zoster in study subjects.

4.3.3.2 Guidance regarding Household Contact Vaccine-Related Exposure

In accordance with the Infectious Disease Society of America's guidance for vaccination in immunocompromised individuals, the following is a guide for study subjects and their household contacts.

i. Immunocompetent individuals who live in a household with the study subject can safely receive inactivated vaccines based on the standard of care vaccination schedules for children and adults or for travel (as defined by their country health ministry) or JIA guidelines.

ii. Individuals who live in a household with a study subject should receive influenza vaccine annually. They can receive either: (a) inactivated influenza vaccine or (b) live attenuated influenza vaccine (LAIV) provided they are healthy and otherwise eligible.

iii. Healthy immunocompetent individuals who live in a household with a study subject should receive the following live vaccines based on the CDC annual schedule: combined measles, mumps, and rubella (MMR) vaccines; rotavirus vaccine in infants aged 2–7 months; varicella vaccine; and zoster vaccine. Also, these individuals can safely receive the following vaccines for travel: yellow fever vaccine and oral typhoid vaccine.

iv. Oral polio vaccine (OPV) **should not be administered** to individuals who live in a household with a study subject.

v. Study subjects should avoid handling diapers of infants who have been vaccinated with rotavirus vaccine for 4 week after vaccination.

vi. Immunocompromised patients should avoid contact with persons who develop skin lesions after receipt of varicella or zoster vaccination until the lesions clear

Subjects should avoid exposure to vaccinated or infected persons and contact the Investigator promptly should they develop signs and symptoms of infections.

4.3.4. Elective Surgery

During the course of this trial, no elective surgery should be scheduled without first consulting with the Pfizer Medical Monitor.

Subjects who do require surgery should temporarily discontinue study medication for at least one week prior to the surgical procedure and remain off study medication after the surgical

procedure until sutures/staples are removed, if the investigator determines this is clinically appropriate for the subject. If absorbing sutures or chemical closure methods are utilized, study medication can be resumed when the operative site is sufficiently healed and risk of infection is minimal.

4.3.5. Dietary Supplements

For the purposes of this protocol, dietary supplements are defined as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties.

Vitamins, minerals and purified food substances are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis). Herbals must be discontinued for at least 4 weeks prior to first dose of study drug.

4.4. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the study manual.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with an emergency contact card. The card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Dosing Scheme

Oral solution (1 mg/mL concentration) will be used for subjects weighing <40 kg. Oral tablets (5 mg) will be used for subjects weighing ≥40 kg; subjects who are unable to swallow tablets will have the option of taking oral solution.

Subjects will swallow study tablets whole and will not manipulate or chew tablets prior to swallowing.

Dosing cards with clear written instructions on how to properly take study medication will be provided to the parent/legal guardian/subject at the time study medication is dispensed.

Tofacitinib will be administered orally BID (twice daily) approximately 12 hours (±2 hours) apart, once in the morning and once in the evening, based on body weight as provided in the Table 2 below. Body weight will be assessed at each visit and entered into Interactive Response Technology (IRT) system; study drug dose will be dispensed based on the subject body weight.

Table 2. Study Treatment Dosing and Administration

Body Weight (kg)	Dosage Regimen
5 - <7	2 mg (2 mL oral solution) BID
7 - <10	2.5 mg (2.5 mL oral solution) BID
10 - <15	3 mg (3 mL oral solution) BID
15 - <25	3.5 mg (3.5 mL oral solution) BID
25 - <40	4 mg (4 mL oral solution) BID
≥40	5 mg (one 5 mg tablet or 5 mL oral solution) BID

Important Note: *For subjects rolling over from study A3921103 and actively participating in this study at the time of Protocol Amendment 6 and receiving a dosage of tofacitinib in accordance with the dosing scheme specified in Protocol Amendment 5 (see Appendix 12), investigators will have the option of maintaining the subject's current dosage regimen from index study A3921103(if the desired clinical response has been attained with no safety concern) or adjusting the dosage regimen in accordance with the dosing scheme specified in this section.*

5.2. Allocation to Treatment

Subjects will have previously participated in tofacitinib studies within the JIA program and will participate in a Screening Visit to determine eligibility.

Eligible subjects will continue their dose regimen from the qualifying/index study until PK or efficacy/safety assessments are made based on the data from the qualifying/index study that may warrant dose modification.

5.2.1. Tofacitinib Temporary Withholding

Dosage of tofacitinib may be temporarily discontinued for up to 28 consecutive days, for more severe cytopenias, for infections which do not meet criteria for serious infections (those requiring parenteral antimicrobial therapy or hospitalization), for surgical procedures or other moderately severe AEs. Additionally, tofacitinib must be temporarily discontinued for a minimum of 6 weeks prior to giving live or live-attenuated vaccines. Tofacitinib would then be restarted a minimum of 6 weeks after receiving the vaccine. Withholding of study drug is not necessary when administering non-live vaccines, including inactivated influenza vaccine and non-live COVID-19 vaccines.

Per Amendment 10, for subjects with suspected venous thromboembolism, treatment with tofacitinib should be temporarily withheld while the subject is evaluated. If venous thromboembolism is confirmed, discontinue treatment with tofacitinib and withdraw the subject from the study (see Section 6.2.6: Subject Withdrawal).

5.3. Drug Supplies

5.3.1. Formulation and Packaging

CP-690,550-10, compound name for Tofacitinib Citrate, will be provided as tablets and as an oral solution by the Sponsor. Tablets and solution will be supplied in bottles to the sites.

5.3.2. Preparation and Dispensing

The study medication will be supplied in bottles. The study medication will be packaged and labeled in such a manner that the subject and study staff will be able to determine the assigned treatment. Study medication along with written dosing instructions will be dispensed by a qualified study site staff member.

5.3.3. Administration

Tofacitinib should be administered orally, twice daily, approximately 12 hours apart, once in the morning and once in the evening. Tofacitinib may be administered with or without food. If a tofacitinib dose is missed and the interval to the next scheduled dose is less than 6 hours, the missed dose of tofacitinib should not be administered; if a tofacitinib dose is missed and the interval to the next scheduled dose is more than 6 hours, the missed dose of tofacitinib should be administered as soon as possible. Subjects should be instructed to document any missed doses.

5.3.4. Compliance

Subject compliance with dosing administration will be verified by accounting of returned containers and trial medication and will be captured in the source document at each visit. The subject dosing compliance should be within the range of 80% and 110% between two regularly scheduled study visits. Subjects with noncompliance will be retrained to follow dosing instruction. PLEASE NOTE: the protocol-allowed temporary discontinuation of study drug for SAEs/AEs, surgical procedures and other allowed reasons (see Section 5.2.1) is not considered as noncompliance and a PD will not be recorded.

Subjects who demonstrate significant noncompliance, ie, ≥30% noncompliance between two regularly scheduled visits, both the subject and parent/legal guardian should be counseled by study staff to address reasons for noncompliance. If after counseling the subject continues to exhibit significant noncompliance (ie, ≥30% noncompliance over two consecutive visits or over two nonconsecutive visits in 12-month time frame), then the subject should be withdrawn from the study.

5.4. Drug Storage and Drug Accountability

The investigator, or an approved representative (eg, Pharmacist), will ensure that study drug is stored in a secured (locked) area with restricted access under recommended storage conditions and in accordance with applicable regulatory requirements.

Storage conditions stated in the single reference safety document (SRSD) (ie, Investigator Brochure [IB], United States Package Insert [USPI], Summary of Product Characteristics

[SPC], or Local Product Document [LPD] will be superseded by the storage conditions stated on the investigational product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigation product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct subjects and parent/legal guardian on the storage requirements for take home medications including how to report temperature excursions.

The investigator's site must maintain adequate records documenting receipt, use, loss, or disposition of study drug supply. To ensure adequate records, all drug supplies will be accounted for in the drug accountability inventory forms as instructed by Pfizer and will be monitored by the accounting of unused study medication returned by the subjects. At the end of the study, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

All bottles must be returned to the investigator by the parent/legal guardian /subject, and the investigator will return the bottles to Pfizer.

5.5. Concomitant Medication(s)

A subject who is receiving an allowed concomitant medication for any reason must be on a locally-approved medication and dose that is considered standard-of-care for the treated indication. Medications that are taken after informed consent is obtained but before the first dose of study medication will be documented as prior medications. Medications taken after the first dose of study drug has been administered will be documented as concomitant medications. All concomitant medication taken during the study must be recorded with indication, daily dose, and start and stop dates of administration.

5.5.1. Prohibited Medications And/Or Treatments

Examples of medications that are prohibited from use during subject participation, due to potential for drug interactions or confounding of data interpretation, are listed in Appendix 6, Prohibited Concomitant Medications. Topical administration (eg, cutaneous, ophthalmic, or intravaginal) of these concomitant medications, which are prohibited if administered systemically, is allowed in the study. Disallowed DMARDS and biologics are listed in Appendix 1.

Herbal supplements must be discontinued for at least 4 weeks prior to first dose of study drug.

Any experimental or prohibited therapy must be discontinued for 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug. No investigational compounds, other than tofacitinib may be taken during participation in this study.

Additional prohibited medications and/or treatment for subjects with PsA:

- Ultraviolet B (UVB) (narrowband or broadband) phototherapy must be discontinued at least 2 weeks prior to first dose of study drug. Psoralens + ultraviolet A (UVA) phototherapy (PUVA) must be discontinued at least 4 weeks prior to first dose of study drug.
- Oral and topical retinoids must be discontinued at least 2 weeks prior to first dose of study drug.

5.5.2. Permitted Medications And/Or Treatments

Subjects will continue on their stable background arthritis therapy, which can include nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, allowed DMARDs (MTX, leflunomide, sulfasalazine, chloroquine, and hydroxychloroquine) (see Appendix 1), opioids (Appendix 2) and oral corticosteroids (≤0.20 mg/kg/day or 10 mg/day, prednisone or equivalent, whichever is lower). For subjects entering from the sJIA study, a higher prednisone-equivalent dose may be continued or started (doses must be ≤1.0 mg/kg/day up to 30 mg/day oral prednisone [or equivalent]). Subjects taking MTX during this trial must be taking folic acid or folinic acid according to local standards.

Additional permitted medications for subjects with PsA:

The dose and type of the following may be adjusted at the discretion of the investigator:

- Topical steroids and tar based shampoos on all regions;
- Topical vitamin A or D analog preparations;
- Anthralin.

5.5.2.1. Permitted Dose Adjustments in Background JIA Therapies (Worsening Disease)

For subjects who experience worsening JIA symptoms refer to Appendix 3 for permitted adjustments in background JIA therapies.

5.5.2.2. Permitted Dose Adjustments (Tapering) in Background JIA Therapies (Inactive Disease)

For subjects who experience improvement in JIA symptoms refer to Appendix 4 for permitted tapering of background JIA therapies. See Section 7.1.7 for definition of inactive disease.

5.5.2.3. Rescue Therapy

Permitted rescue therapy can be found in Appendix 7.

6. STUDY PROCEDURES

For Investigative Sites in Belgium Only: The degree of burden and the risk threshold should be assessed at each scheduled visit as outlined in Appendix 13.

6.1. Screening and Baseline Visits

Subjects from qualifying/index tofacitinib studies who elect to participate should complete a combined Screening/Baseline Visit on the same day they end participation in the previous randomized tofacitinib study (EOS) or within 14 days to be eligible for rollover into A3921145. Subjects enrolling outside the 14 day window will be required to participate in the full Screening Visit and Baseline Visit.

6.1.1. Subjects Requiring Separate Screening and Baseline Visits

Subjects who do not roll over into this study from their qualifying/index study within the 14-day window after their EOS in the qualifying/index study must participate in separate Screening and Baseline Visits to determine eligibility for enrollment in this study.

The study investigator or a sub-investigator will discuss, with each subject, the nature of the study, its requirements, and its restrictions. Written informed consent must be obtained prior to performance of any protocol specific procedures.

Subjects who are on prohibited medications and are deriving a beneficial response from them should not be entered into this study. However, there may be subjects taking a prohibited medication who have experienced an ineffectual/suboptimal response or side effects and would consider entering the study. These subjects may require a washout period that extends beyond the screening duration (See Section 5.5 Concomitant Medication(s)). For these subjects written informed consent and a Study Subject Identification (SSID) number must be obtained prior to initiation of the washout period or, if washout has already begun for other reasons, upon decision that the study is an appropriate medical option. In no instance should the informed consent be signed more than 3 months prior to the conduct of the screening procedures.

6.1.1.1. Screening Visit

The following procedures and assessments will be performed for all subjects:

- Informed consent/Assent obtained.
- Medical history: The medical history should include previous vaccination history (eg, varicella, influenza, and etc.), smoking status; average weekly alcohol consumption (if applicable) and family history of premature coronary heart disease (CHD). Premature coronary heart disease is defined as CHD in a male first-degree relative first observed at <55 years or CHD in female first-degree relative first observed at <65 years.
- Risk factor check for venous thromboembolism (see Section 7.2.10).
- Document Prior medication ongoing or started since last visit in the qualifying/index study not exceeding the last 12 months.
- Vital signs: temperature (oral, tympanic or temporal preferred), blood pressure (BP) and pulse rate (PR). For subjects with sJIA: temperature must be measured orally using a digital thermometer, with the exception of very young children or others who cannot tolerate an oral thermometer. In these cases temperature may be measured rectally using a digital thermometer. The definition of fever with a rectal thermometer is one degree Fahrenheit higher. (Example >101.4°F/38.6°C rectally compared to >100.4°F/38°C orally).
- Complete physical examination, including height and weight measurements. (**Applicable to Investigative Sites in the UK and Belgium:** a full skin cancer examination must be performed as part of the complete physical examination. **Applicable to subjects enrolled from Study A3921165**: a skin examination for chicken pox or shingles must be performed).
- Physician global evaluation of disease activity.
- Joint assessment of active arthritis (swelling, pain/tenderness), and limitation of motion.
- Duration of morning stiffness.
- QuantiFERON®- TB Gold or Gold Plus In-Tube test or Mantoux Purified Protein Derivative (PPD) skin test where applicable and/or chest radiograph where applicable (unless done in the prior 3 months). If the Mantoux PPD tuberculin skin test is done, the subject must return 48-72 hours post test for evaluation.
- Safety laboratory testing: this includes hematology, urinalysis, chemistry panel, estimated GFR (Appendix 5), urine pregnancy test (β-hCG, female of childbearing

potential only), HIV Serology, Hepatitis B (HBsAg, HBc Ab and if needed, HBs Ab), Hepatitis C (HCVAb and if needed, HCV RNA).

- C-reactive protein (CRP).
- Erythrocyte sedimentation rate (ESR) determination (Westergren method).
- Confirm highly effective contraception is being used.
- Referred for uveitis exam by an ophthalmologist (or qualified equivalent per local practice) if not done within previous 6 months. For subjects with sJIA, this exam is not required, but if available documentation of previous uveitis assessment(s) by an ophthalmologist (or qualified equivalent per local practice) should be reviewed, the date of the prior exam recorded, and the presence/absence of active uveitis documented.
- Serious Adverse Event reporting.
- To prepare for study participation, subjects and their legally acceptable representative/parent(s)/legal guardians will be instructed on the use of the Life Style Guidelines and Concomitant Medication(s) sections of the protocol.

sJIA subjects ONLY:

- Assessment of JIA-associated fever: Fever is defined as temperature >38°C/100.4°F). Refer to Section 7.1.10.1 for details.
    - MAS diagnosis: Only if subject has fever and Macrophage Activation Syndrome (MAS) is suspected: obtain blood samples to evaluate ferritin, platelets, triglycerides and fibrinogen levels. Refer to Section 7.2.9 for details regarding these blood sample collections.
- Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA.

6.1.1.2. Baseline Visit

Baseline visit will take place 2-28 days after Screening. The following procedures and assessments will be performed for all subjects unless otherwise indicated:

- AE assessment.
- Risk factor check for venous thromboembolism (see Section 7.2.10).
- Document concomitant medications taken since Screening Visit.
- Childhood Health Assessment Questionnaire (CHAQ).

- Vital signs: temperature (oral, tympanic or temporal preferred), BP and PR. For subjects with sJIA: temperature must be measured orally using a digital thermometer, with the exception of very young children or others who cannot tolerate an oral thermometer. In these cases temperature may be measured rectally using a digital thermometer. The definition of fever with a rectal thermometer is one degree Fahrenheit higher. (Example >101.4°F/38.6°C rectally compared to >100.4°F/38°C orally).

- Targeted physical examination, including height and weight measurements. (**Applicable to subjects enrolled from Study A3921165**: a skin examination for chicken pox or shingles must be performed)

- Tanner stage assessment.

- Physician global evaluation of disease activity.

- Joint assessment of active arthritis (swelling, pain/tenderness), and limitation of motion.

- Duration of morning stiffness.

- Safety laboratory testing (chemistry, hematology, urinalysis), including urine pregnancy testing (β-hCG) for females of child-bearing potential.

- Confirm highly effective contraception is being used.

- Lipid panel (total cholesterol, indirect LDL (low-density lipoprotein), direct HDL (high-density lipoprotein), apolipoprotein A-1 and B, triglycerides).

  ***** Important Note ** Subjects should be instructed to fast (for 9 to 12 hours prior the scheduled visit), if possible, for lipid panel testing.***

- CRP.

- ESR determination (Westergren method).

- Dispense study medication and provide dosing instructions/schedule next visit.

sJIA subjects ONLY:

- Assessment of JIA-associated fever: Fever is defined as temperature >38°C/100.4°F). Refer to Section 7.1.10.1 for details.

  - MAS diagnosis: Only if subject has fever and Macrophage Activation Syndrome (MAS) is suspected: obtain blood samples to evaluate ferritin, platelets,

triglycerides and fibrinogen levels. Refer to Section 7.2.9 for details regarding these blood sample collections.

- Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA.

ERA subjects ONLY:

- Tender Entheseal Assessment.
- Modified Schober's Test.
- Overall Back Pain.
- Nocturnal Back Pain Assessment.

PsA subjects ONLY:

- Body surface area (BSA) with psoriasis rash.
- Physician's Global Assessment (PGA) for psoriasis.

6.1.2. Subjects with Combined End of Qualifying/Index Study Visit/LTE Screening/Baseline Visit

Subjects who complete their combined Screening/Baseline Visit on the same day as EOS in the qualifying/index tofacitinib study must also complete the following procedures:

- Informed consent/Assent obtained.
- AE assessment.
- Risk factor check for venous thromboembolism (see Section 7.2.10).
- Confirm highly effective contraception is being used.
- Dispense study medication and provide dosing instructions/schedule next visit.

6.1.3. Subjects with Separate End of Qualifying/Index Study Visit and Combined LTE Screening/Baseline Visit

Subjects who complete their combined Screening/Baseline Visit within 14 days of EOS in the qualifying/index tofacitinib study but not on the same day as EOS must complete the following procedures at the combined Screening/Baseline Visit:

- Informed consent/Assent obtained.
- AE assessment.

- Risk factor check for venous thromboembolism (see Section 7.2.10).
- Concomitant medications (ongoing or started since last visit in qualifying/index study).
- Vital signs: temperature (oral, tympanic or temporal preferred), BP and PR. For subjects with sJIA: temperature must be measured orally using a digital thermometer, with the exception of very young children or others who cannot tolerate an oral thermometer. In these cases temperature may be measured rectally using a digital thermometer. The definition of fever with a rectal thermometer is one degree Fahrenheit higher. (Example >101.4°F/38.6°C rectally compared to >100.4°F/38°C orally).
- Targeted physical exam, including weight and height.
(**Applicable to subjects enrolled from Study A3921165**: a skin examination for chicken pox or shingles must be performed).
- Physician global evaluation of disease activity.
- Joint assessment of active arthritis (swelling, pain/tenderness), and limitation of motion.
- Duration of morning stiffness.
- Safety laboratory testing (chemistry, hematology, urinalysis), including urine pregnancy testing (β-hCG) for females of child-bearing potential.
- Confirm highly effective contraception is being used.
- CRP.
- ESR determination (Westergren Method).
- Dispense study medication and provide dosing instructions/schedule next visit.

sJIA subjects ONLY:

- Assessment of JIA-associated fever: Fever is defined as temperature >38°C/100.4°F). Refer to Section 7.1.10.1 for details.
    - MAS diagnosis: Only if subject has fever and Macrophage Activation Syndrome (MAS) is suspected: obtain blood samples to evaluate ferritin, platelets, triglycerides and fibrinogen levels. Refer to Section 7.2.9 for details regarding these blood sample collections.

- Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA.Assess Flare: Refer to Flare Criteria in Section 7.1.6.2.

6.2. Study Period

6.2.1. Year 1: Months 1 and 3 Visits (Visit Window ±5 Days); Months 6, 9 and 12 Visits (Visit Window ±10 Days)

The following procedures and assessments will be performed for all subjects unless otherwise indicated:

- AE assessment.
- Risk factor check for venous thromboembolism (see Section 7.2.10).
- Document concomitant medications (ongoing or started since previous visit).
- Childhood Health Assessment Questionnaire (CHAQ).
- Vital signs: temperature (oral, tympanic or temporal preferred), BP and PR. For subjects with sJIA: temperature must be measured orally using a digital thermometer, with the exception of very young children or others who cannot tolerate an oral thermometer. In these cases temperature may be measured rectally using a digital thermometer. The definition of fever with a rectal thermometer is one degree Fahrenheit higher. (Example >101.4°F/38.6°C rectally compared to >100.4°F/38°C orally).
- Physical examination: Targeted physical examination is done at Months 1-9. Complete physical examination is done at Month 12. (**Applicable to Investigative Sites in the UK and Belgium:** a full skin cancer examination must be performed as part of the complete physical examination. **Applicable to subjects enrolled from Study A3921165**: a skin examination for chicken pox or shingles must be performed as part of the complete or targeted physical examination).
- Tanner stage assessment (Month 12 only).
- Physician global evaluation of disease activity.
- Joint assessment of active arthritis (swelling, pain/tenderness), and limitation of motion.
- Duration of morning stiffness.
- QuantiFERON® Gold or Gold Plus In-Tube Test (QFT) is performed annually ONLY for subject enrolled in countries where TB incidence has been reported at a rate of >50 cases per 100,000 persons, eg, China, Russian Federation; South Africa, India

and Ukraine. (World Health Organization). Sites must perform chest radiograph for TB status determination when subjects have a positive annual QFT-TB test for the first time. Refer to Section 7.2.2 for further guidance.

- Safety laboratory testing (chemistry, hematology, urinalysis), including urine pregnancy testing (β-hCG) for females of child-bearing potential.
- Confirm highly effective contraception is being used.
- Lipid panel (total cholesterol, indirect LDL, direct HDL, apolipoprotein A-1 and B, triglycerides) done at Months 6 and 12.

  ***** Important Note ** Subjects should be instructed to fast (for 9 to 12 hours prior the scheduled visit), if possible, for lipid panel testing at Month 6 and Month 12 visits.***

- CRP.
- ESR determination (Westergren method).
- PK blood samples (pre-dose, and post dose at 0.5 hr [time window: 0.25-0.75 hr] and 2 hr [time window: 1.75-2. 5 hr]) obtained at Month 12.

  **** Important Note ** Subject and parent/legal guardian should be instructed that the subject should NOT take the morning dose at home. The subject's morning dose will be taken at the study site after pre-dose PK sampling.**

- Uveitis exam performed by an ophthalmologist (or qualified equivalent per local practice) annually beginning 1 year after the previous exam (the window for this particular examination is ±30 days). Refer to Section 7.2.5 for further guidance.
- Assess investigational product dosing compliance.
- Dispense/collect study medication/schedule next visit.

sJIA subjects ONLY:

- Assessment of JIA-associated fever: Fever is defined as temperature >38°C/100.4°F). Refer to Section 7.1.10.1 for details.
  - MAS diagnosis: Only if subject has fever and Macrophage Activation Syndrome (MAS) is suspected: obtain blood samples to evaluate ferritin, platelets, triglycerides and fibrinogen levels. Refer to Section 7.2.9 for details regarding these blood sample collections.
- Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA.

ERA subjects ONLY (Months 3, 6, and 12):

- Tender Entheseal Assessment.
- Modified Schober's Test.
- Overall Back Pain.
- Nocturnal Back Pain Assessment.

PsA subjects ONLY (Months 3, 6, and 12):

- Body surface area (BSA) with psoriasis rash.
- Physician's Global Assessment (PGA) for psoriasis.

Applicable to Canadian Investigator Sites Only: Excluding the Month 1 visit, calculate the subject's ACR30 response (see Section 7.1.6.1) at each visit. Subjects with less than an ACR30 response at 2 consecutive visits, beginning with the Month 3 visit and anytime thereafter, should be discontinued from study treatment, unless, in the opinion of the Investigator, it is in the subject's best interest to continue receiving tofacitinib (to be determined on a case-by-case basis and in consultation with the Sponsor).

6.2.2. Years 2-5: Months 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60 Visits (Visit Window ±10 Days)

The following procedures and assessments will be performed:

- AE assessment.
- Risk factor check for venous thromboembolism (see Section 7.2.10).
- Document concomitant medications (ongoing or started since previous visit).
- Childhood Health Assessment Questionnaire (CHAQ).
- Vital signs: temperature (oral, tympanic or temporal preferred), BP and PR. For subjects with sJIA: temperature must be measured orally using a digital thermometer, with the exception of very young children or others who cannot tolerate an oral thermometer. In these cases temperature may be measured rectally using a digital thermometer. The definition of fever with a rectal thermometer is one degree Fahrenheit higher. (Example >101.4°F/38.6°C rectally compared to >100.4°F/38°C orally).
- Physical examination: Complete physical examination is done annually (ie, Months 24, 36, 48, and 60). Targeted physical examination is done at all other visits (ie, Months 15, 18, 21, 27, 30, and etc.). **(Applicable to Investigative Sites in the**

UK and Belgium: a full skin cancer examination must be performed as part of the complete physical examination. **Applicable to subjects enrolled from Study A3921165**: a skin examination for chicken pox or shingles must be performed as part of the complete or physical examination).

- Tanner stage assessment (Months 24, 36, 48 and 60).
- Physician global evaluation of disease activity.
- Joint assessment of active arthritis (swelling, pain/tenderness), and limitation of motion.
- Duration of morning stiffness.
- QuantiFERON® Gold or Gold Plus In-Tube test (QFT) performed annually: ONLY for subjects enrolled in countries where TB incidence has been reported at a rate of >50 cases per 100,000 persons, eg, China, Russian Federation; South Africa, India and Ukraine. (World Health Organization). Sites must perform chest radiograph for TB status determination when subjects have a positive annual QFT-TB test for the first time. Refer to Section 7.2.2 for further guidance.
- Safety laboratory testing (chemistry, hematology, urinalysis), including urine pregnancy testing (β-hCG) for females of child-bearing potential.
- Confirm highly effective contraception is being used.
- Lipid panel (total cholesterol, indirect LDL, direct HDL, apolipoprotein A-1 and B, triglycerides) done at Months 18, 24, 30, 36, 42, 48, 54, and 60.

  ***** Important Note ** Subjects should be instructed to fast (for 9 to 12 hours prior the scheduled visit), if possible, for lipid panel testing.***
- CRP.
- ESR determination (Westergren method).
- PK blood samples (pre-dose, and post dose at 0.5 hr [time window: 0.25-0.75 hr] and 2 hr [time window: 1.75-2. 5 hr]) obtained at Months 24 and 36.

  ***** Important Note ** Subject and parent/legal guardian should be instructed that the subject should NOT take the morning dose at home. The subject's morning dose will be taken at the study site after pre-dose PK sampling.***
- Uveitis exam performed by an ophthalmologist (or qualified equivalent per local practice) annually (the window for this particular examination is ±30 days). Refer to Section 7.2.5 for further guidance.

- Assess investigational product dosing compliance.
- Dispense/collect study medication/schedule next visit.

sJIA subjects ONLY:

- Assessment of JIA-associated fever: Fever is defined as temperature >38°C/100.4°F). Refer to Section 7.1.10.1 for details:
  - MAS diagnosis: Only if subject has fever and Macrophage Activation Syndrome (MAS) is suspected: obtain blood samples to evaluate ferritin, platelets, triglycerides and fibrinogen levels. Refer to Section 7.2.9.1 for details regarding these blood sample collections.
- Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA.

ERA subjects ONLY (Months 18, 24, 30, 36, 42, 48, 54, and 60):

- Tender Entheseal Assessment.
- Modified Schober's Test.
- Overall Back Pain.
- Nocturnal Back Pain Assessment.

PsA subjects ONLY (Months 18, 24, 30, 36, 42, 48, 54, and 60):

- Body surface area (BSA) with psoriasis rash.
- Physician's Global Assessment (PGA) for psoriasis.

Applicable to Canadian Investigator Sites Only: Calculate the subject's ACR30 response (see Section 7.1.6.1) at each visit. Subjects with less than an ACR30 response for 2 consecutive visits, beginning with the Month 3 visit and anytime thereafter, should be discontinued from study treatment, unless, in the opinion of the Investigator, it is in the subject's best interest to continue receiving tofacitinib (to be determined on a case-by-case basis and in consultation with the Sponsor).

6.2.3. Years 6-10: Month 63, 66, 69, 75, 78, 81, 87, 90, 93, 99, 102, 105, 111, 114, 117 Visits (Visit Window ±10 Days)

The following procedures and assessments will be performed:

- AE assessment.
- Risk factor check for venous thromboembolism (see Section 7.2.10).

- Document concomitant medications (ongoing or started since previous visit).
- Childhood Health Assessment Questionnaire (CHAQ).
- Vital signs: temperature (oral, tympanic or temporal preferred), BP and PR. For subjects with sJIA: temperature must be measured orally using a digital thermometer, with the exception of very young children or others who cannot tolerate an oral thermometer. In these cases temperature may be measured rectally using a digital thermometer. The definition of fever with a rectal thermometer is one degree Fahrenheit higher. (Example >101.4°F/38.6°C rectally compared to >100.4°F/38°C orally).
- Targeted physical examination.
  (**Applicable to subjects enrolled from Study A3921165**: a skin examination for chicken pox or shingles must be performed).
- Physician global evaluation of disease activity.
- Joint assessment of active arthritis (swelling, pain/tenderness), and limitation of motion.
- Duration of morning stiffness.
- QuantiFERON® Gold or Gold Plus In-Tube test (QFT) performed annually: ONLY for subjects enrolled in countries where TB incidence has been reported at a rate of >50 cases per 100,000 persons, eg, China, Russian Federation; South Africa, India and Ukraine. (World Health Organization). For subjects who have a positive annual QFT-TB for the first time, sites must perform chest radiograph for TB status determination. Refer to Section 7.2.2 for further guidance.
- Safety laboratory testing (chemistry, hematology, urinalysis), including urine pregnancy testing (β-hCG) for females of child-bearing potential.
- Confirm highly effective contraception is being used.
- CRP.
- ESR determination (Westergren method).
- Assess investigational product dosing compliance.
- Dispense/collect study medication.

sJIA subjects ONLY:

- Assessment of JIA-associated fever: Fever is defined as temperature >38°C/100.4°F Refer to Section 7.1.10.1 for details.
    - MAS diagnosis: Only if subject has fever and Macrophage Activation Syndrome (MAS) is suspected: obtain blood samples to evaluate ferritin, platelets, triglycerides and fibrinogen levels. Refer to Section 7.2.9 for details regarding these blood sample collections.
- Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA.

ERA subjects ONLY (Months 66, 78, 90, 102, and 114):

- Tender Entheseal Assessment.
- Modified Schober's Test.
- Overall Back Pain.
- Nocturnal Back Pain Assessment.

PsA subjects ONLY (Months 66, 78, 90, 102, and 114):

- Body surface area (BSA) with psoriasis rash.
- Physician's Global Assessment (PGA) for psoriasis.

Applicable to Canadian Investigator Sites Only: Calculate the subject's ACR30 response (see Section 7.1.6.1) at each visit. Subjects with less than an ACR30 response for 2 consecutive visits, beginning with the Month 3 visit and anytime thereafter, should be discontinued from study treatment, unless, in the opinion of the Investigator, it is in the subject's best interest to continue receiving tofacitinib (to be determined on a case-by-case basis and in consultation with the Sponsor).

6.2.4. Years 6-10: Month 72, 84, 96, 108, 120 Visits (Visit Window ±10 Days)

The following procedures and assessments will be performed:

- AE assessment.
- Risk factor check for venous thromboembolism (see Section 7.2.10).
- Document concomitant medications (ongoing or started since previous visit).
- Childhood Health Assessment Questionnaire (CHAQ).

- Vital signs: temperature (oral, tympanic or temporal preferred), BP and PR. For subjects with sJIA: temperature must be measured orally using a digital thermometer, with the exception of very young children or others who cannot tolerate an oral thermometer. In these cases temperature may be measured rectally using a digital thermometer. The definition of fever with a rectal thermometer is one degree Fahrenheit higher. (Example >101.4°F/38.6°C rectally compared to >100.4°F/38°C orally).

- Complete physical examination. (**Applicable to Investigative Sites in the UK and Belgium:** a full skin cancer examination must be performed as part of the complete physical examination. **Applicable to subjects enrolled from Study A3921165**: a skin examination for chicken pox or shingles must be performed).

- Tanner stage assessment.

- Physician global evaluation of disease activity.

- Joint assessment of active arthritis (swelling, pain/tenderness), and limitation of motion.

- Duration of morning stiffness.

- QuantiFERON® Gold or Gold Plus In-Tube test (QFT) performed annually: ONLY for subjects enrolled in countries where TB incidence has been reported at a rate of >50 cases per 100,000 persons, eg, China, Russian Federation; South Africa, India and Ukraine. (World Health Organization). Sites must perform chest radiograph for TB status determination when subjects have a positive annual QFT-TB test for the first time. Refer to Section 7.2.2 for further guidance.

- Safety laboratory testing (chemistry, hematology, urinalysis), including urine pregnancy testing (β-hCG) for females of child-bearing potential.

- Confirm highly effective contraception is being used.

- Lipid panel (cholesterol, indirect LDL, direct HDL, apolipoprotein A-1 and B, triglycerides).

  ***** Important Note ** Subjects should be instructed to fast (for 9 to 12 hours prior the scheduled visit), if possible, for lipid panel testing.***

- CRP.

- ESR determination (Westergren method).

- Uveitis exam performed by an ophthalmologist (or qualified equivalent per local practice) annually (the window for this particular examination is ±30 days). Refer to Section 7.2.5 for further guidance.

- Assess investigational product dosing compliance.

- Dispense/collect study medication/schedule next visit.

sJIA subjects ONLY:

- Assessment of JIA-associated fever: Fever is defined as temperature >38°C/100.4°F). Refer to Section 7.1.10.1 for details.

    - MAS diagnosis: Only if subject has fever and Macrophage Activation Syndrome (MAS) is suspected: obtain blood samples to evaluate ferritin, platelets, triglycerides and fibrinogen levels. Refer to Section 7.2.9 for details regarding these blood sample collections.

- Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA.

ERA subjects ONLY:

- Tender Entheseal Assessment.

- Modified Schober's Test.

- Overall Back Pain.

- Nocturnal Back Pain Assessment.

PsA subjects ONLY:

- Body surface area (BSA) with psoriasis rash.

- Physician's Global Assessment (PGA) for psoriasis.

Applicable to Canadian Investigator Sites Only: Calculate the subject's ACR30 response (see Section 7.1.6.1) at each visit. Subjects with less than an ACR30 response for 2 consecutive visits, beginning with the Month 3 visit and anytime thereafter, should be discontinued from study treatment, unless, in the opinion of the Investigator, it is in the subject's best interest to continue receiving tofacitinib (to be determined on a case-by-case basis and in consultation with the Sponsor).

6.2.5. End of Study Visit/Early Termination Visit

The following procedures and assessments will be performed:

- AE assessment.
- Risk factor check for venous thromboembolism (see Section 7.2.10).
- Document concomitant medications (ongoing or started since previous visit).
- Childhood Health Assessment Questionnaire (CHAQ).
- Vital signs: temperature (oral, tympanic or temporal preferred), BP and PR. For subjects with sJIA: temperature must be measured orally using a digital thermometer, with the exception of very young children or others who cannot tolerate an oral thermometer. In these cases temperature may be measured rectally using a digital thermometer. The definition of fever with a rectal thermometer is one degree Fahrenheit higher. (Example >101.4°F/38.6°C rectally compared to >100.4°F/38°C orally).

  Complete physical examination. (**Applicable to Investigative Sites in the UK and Belgium:** a full skin cancer examination must be performed as part of the complete physical examination. **Applicable to subjects enrolled from Study A3921165**: a skin examination for chicken pox or shingles must be performed).
- Tanner stage assessment.
- Physician global evaluation of disease activity.
- Joint assessment of active arthritis (swelling, pain/tenderness), and limitation of motion.
- Duration of morning stiffness.
- Safety laboratory testing (chemistry, hematology, urinalysis), including urine pregnancy testing (β-hCG) for females of child-bearing potential.
- Confirm highly effective contraception is being used.
- Please note: Subjects must use contraception consistently and correctly for at least 28 days after the last dose of investigational product.
- Lipid panel (cholesterol, indirect LDL, direct HDL, apolipoprotein A-1 and B, triglycerides).

  ***** Important Note ** Subjects should be instructed to fast (for 9 to 12 hours prior the scheduled visit), if possible, for lipid panel testing.***

- CRP.
- Erythrocyte sedimentation rate (ESR) determination (Westergren method).
- PK blood samples (pre-dose, and post-dose at 0.5 hr [time window: 0.25-0.75 hr] and 2 hr [time window: 1.75-2. 5 hr] if early termination occurs within 36 months.

  ***** Important Note ** Subject and parent/legal guardian should be instructed that the subject should NOT take the morning dose at home. The subject's morning dose will be taken at the study site after pre-dose PK sampling.***

- Uveitis exam performed by an ophthalmologist (or qualified equivalent per local practice) (the window for this particular examination is ±30 days).
- Collect study medication.

Assess investigational product dosing compliance **sJIA subjects ONLY:**

- Assessment of JIA-associated fever: Fever is defined as temperature >38°C/100.4°F). Refer to Section 7.1.10.1 for details.
- MAS diagnosis: Only if subject has fever and Macrophage Activation Syndrome (MAS) is suspected: obtain blood samples to evaluate ferritin, platelets, triglycerides and fibrinogen levels. Refer to Section 7.2.9 for details regarding these blood sample collections.
- Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA.

ERA subjects ONLY: Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment.

PsA subjects ONLY: Body surface area (BSA) with psoriasis rash and Physician's Global Assessment (PGA) for psoriasis.

6.2.6. Subject Withdrawal

Guidelines for monitoring and discontinuing subjects from this study are listed in Appendix 8. If a subject is discontinued for safety reasons an Early Termination Visit should be conducted whenever possible.

If venous thromboembolism is confirmed, discontinue treatment with tofacitinib and withdraw the subject from the study (Appendix 8, Guidelines for Monitoring and Discontinuation).

All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline level or are deemed clinically stable. In addition, any subject with a confirmed increase in serum creatinine >33% above the

average of screening and baseline values, will be followed up with retesting every one to two weeks until the creatinine elevation has fully reversed to within 10% of the average of screening and baseline values or has stabilized.

Subjects may withdraw from the trial at any time at their own request/or request of their parent or legal guardian, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject and parent/legal guardian. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Applicable to Canadian Investigator Sites Only: Subjects with less than an ACR30 response (see Section 7.1.6.1) for 2 consecutive visits, beginning with the Month 3 visit and anytime thereafter, should be discontinued from study treatment, unless, in the opinion of the Investigator, it is in the subject's best interest to continue receiving tofacitinib. If continuation of treatment is warranted, the Investigator must contact the Sponsor to discuss the case and obtain prior approval.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test can not be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Efficacy

Measures of arthritis efficacy that will be collected throughout the study are described in this section.

7.1.1. Continued Disease Activity Assessment

Subjects who enroll >14 days after their EOS Visit in their qualifying/index study must, in the opinion of the investigator, have sufficient evidence of JIA disease activity to warrant use of tofacitinib as a DMARD.

7.1.2. Physician Global Evaluation of Disease Activity

The investigator will assess how the overall arthritis appears at the time of the visit. This is an evaluation based on the subject's disease signs, functional capacity and physical examination.

The investigator will rate the overall level of disease activity by entering a number from 0 to 10 (in 0.5 increments), with '0' as 'No Activity' and '10' as 'Maximum Activity' on the 21- numbered circle visual analog scale (VAS), as shown below.

PHYSICIAN GLOBAL ASSESSMENT OF OVERALL DISEASE ACTIVITY

Considering the whole signs and symptoms of the disease AT THE TIME OF THE PRESENT VISIT, please rate the overall level of disease activity by filling a circle below:

NO ACTIVITY	○ 0	○ 0.5	○ 1	○ 1.5	○ 2	○ 2.5	○ 3	○ 3.5	○ 4	○ 4.5	○ 5	○ 5.5	○ 6	○ 6.5	○ 7	○ 7.5	○ 8	○ 8.5	○ 9	○ 9.5	○ 10	MAXIMUM ACTIVITY

7.1.3. Joint Assessment

At each study visit, joints with swelling, pain on motion and tenderness, and limitation of motion will be assessed and recorded on the appropriate CRF. The duration of morning stiffness will also be assessed.

The ACR defines a joint with active arthritis as a joint with swelling due to inflammation or, in the absence of swelling, limitation of motion accompanied by pain on motion, and/or tenderness.

Swelling will be assessed in the following joints:

- Temporomandibular, Sternoclavicular, Acromioclavicular, Shoulder, Elbow, Wrist, Metocarpophalangeal (MCP I-V), Proximal Interphalangeal (PIP I-V), Distal Interphalangeal (II-V), Knee, Ankle, Subtalar joints, Intertarsal joints, Metotarsophalangeal (MTP I-V), Toe Interphalangeal (I-V).

Pain/Tenderness will be assessed in the following joints:

- Temporomandibular, Sternoclavicular, Acromioclavicular, Shoulder, Elbow, Wrist, Metocarpophalangeal (MCP I-V), Proximal Interphalangeal (PIP I-V), Distal Interphalangeal (II-V), Hip, Knee, Ankle, Subtalar joints, Intertarsal joints,

Metotarsophalangeal (MTP I-V), Toe interphalangeal (I-V), Cervical spine, Thoracic spine, Lumbar spine, Sacroiliac joints.

Limitation of motion will be assessed in the following joints:

- Temporomandibular, Shoulder, Elbow, Wrist, Metocarpophalangeal (MCP I-V), Proximal Interphalangeal (PIP I-V), Distal Interphalangeal (II-V), Hip, Knee, Ankle, Subtalar joints, Intertarsal joints, Metotarsophalangeal (MTP I-V), Toe Interphalangeal (I-V), Cervical spine, Thoracic spine, Lumbar spine.

- Duration of morning stiffness.

- Subjects should be queried about the approximate duration of morning stiffness by asking "Since the last visit, or in the past 7 days, has the duration of morning stiffness lasted for more than 15 minutes?" The duration (in minutes) should be recorded in the source/worksheet and CRF.

7.1.4. Childhood Health Assessment Questionnaire (CHAQ)

The CHAQ,[5] derived from the adult Health Assessment Questionnaire, comprises two indices, Disability and Discomfort, and parent global assessment of Overall Well Being. The CHAQ has been cross-culturally adapted and validated in more than 30 languages by the PRINTO group (Ruperto 2001).[20]

- The Disability Index assesses function in 8 areas - dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities-distributed among a total of 30 items. In each functional area, at least one question is relevant to children of all ages. Each question is rated on a four-point scale of difficulty in performance, scored from 0-3. The question with the highest score determines the score for the functional area. If aids or devices are used or assistance is required, the minimum score for that functional area is 2. The Disability Index is calculated as the mean of the 8 functional areas.

- Discomfort Index is determined by the presence of pain measured by a 21-numbered circle VAS.

- Parent Assessment of Global Well-Being is measured on a 21- numbered circle VAS scale.

The CHAQ will be obtained at Baseline Visit for subjects entering the study more than 14 days after the EOS Visit for their qualifying/index study, then at all study visits and at the End of Study/Early Termination visit for all subjects.

Note: The parent/legal guardian (or an adult caregiver interacting daily with the subject) will complete the CHAQ. Every effort should be made to have the same individual complete the CHAQ throughout the course of the study.

7.1.4.1. Parent's Assessment of Physical Function (CHAQ Disability Index)

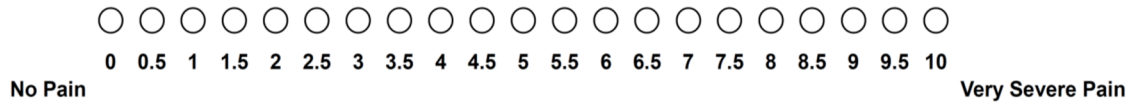
The parent/legal guardian (or an adult caregiver interacting daily with the subject) will answer the CHAQ subsection questions concerning eight areas of daily function. The parent/legal guardian will indicate their child's ability to perform these activities as: without any difficulty, with some difficulty, with much difficulty, or unable to do (Grades 0-3, respectively); and whether or not help from another person or use of an assistive device is required to perform these activities. The parent/legal guardian is required to answer all questions. The Parent's Assessment of Physical Function is to be completed before performing any other arthritis assessments at the visit.

7.1.4.2. Parent's Assessment of Child's Arthritis Pain (CHAQ Discomfort Index)

For the assessment of arthritis pain, the parent/legal guardian (or an adult caregiver interacting daily with the subject) will be asked to provide a response to the following question:

"How much pain do you think your child had because of his or her illness IN THE PAST WEEK? Please fill a circle below to indicate how severe your child's pain has been".

The parent/legal guardian (or an adult caregiver interacting daily with the subject) will rate the subject's arthritis pain by entering a number from 0 to 10 (in 0.5 increments), with '0' as 'No Pain' and '10' as 'Very Severe Pain' on a 21-numbered circle visual analog scale (VAS), as shown below.

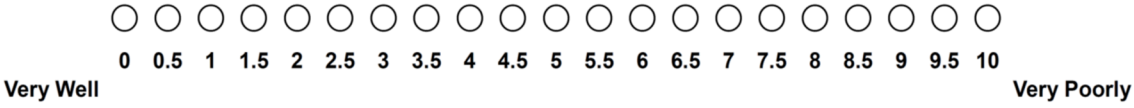


7.1.4.3. Parent's Global Assessment of Overall Well-Being (CHAQ Subsection)

For the assessment of overall well-being, the parent/legal guardian (or an adult caregiver interacting daily with the subject) will be asked to provide a response to the following question:

"Considering all the ways in which the illness affects your child AT THIS TIME, please indicate below how your child is doing by filling a circle."

The parent/legal guardian (or an adult caregiver interacting daily with the subject) will rate the subject's overall well-being by entering a number from 0 to 10 (in 0.5 increments), with '0' as 'Very Well' and '10' as 'Very Poorly' on a 21-numbered circle visual analog scale (VAS), as shown below.



7.1.5. Inflammatory Markers

In this study, testing for both Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) will be performed in all subjects at each study visit except Screening/Baseline Visit for subjects who roll over on the same day of EOS from their Index Studies (see Schedule Of Activities).

7.1.5.1. C-Reactive Protein (CRP)

At the study visits as specified in Schedule Of Activities, a blood sample for CRP testing will be collected and sent to the central laboratory for determination.

7.1.5.2. Erythrocyte Sedimentation Rate (ESR)

At the study visit as specified in Schedule Of Activities, ESR (Westergren method) will be collected and determined locally, utilizing an ESR Testing Kit which will be provided by the sponsor or their local laboratory ESR Testing Kit (Westergren method). The ESR Testing Kit provided by the sponsor should be the preferred choice for ESR testing. Every effort should be made to use the same ESR Testing Kit (whether provided by the sponsor or local) throughout the course of the study. Please refer to the ESR Testing Kit manual for detailed instructions on how to perform this test appropriately.

7.1.6. JIA ACR Response and Flare Criteria

The JIA ACR Response and Flare Criteria assessment[6,7] is a derived measurement of the 6 components of the JIA core set variables, which includes:

- Physician global evaluation of disease activity.
- Number of joints with active arthritis.
- Number of joints with limited range of motion.
- Parent/legal guardian/subject evaluation of overall well-being (from the CHAQ).
- Functional ability (Disability Index from the CHAQ).
- ESR or CRP.

Additional details regarding JIA ACR response criteria in Section 7.1.6.1 and additional details regarding disease flare in all subtypes are provided in Section 7.1.6.2.

7.1.6.1. JIA ACR Response Criteria

The assessments using JIA ACR 30, 50, 70, 90 and 100 will be performed. Other responder criteria may be assessed if appropriate. The JIA ACR 30, 50, 70, 90, 100 response criteria are as follows: 3 out of 6 JIA core set variables improved ≥30%, 50%, 70%, 90%, 100%, respectively, with no more than 1 out of 6 JIA core set variables worsened by ≥30%.

In subjects with systemic JIA, absence of fever due to sJIA in the preceding 7 days is also required (Ruperto et al. 2012).[22] (see Section 7.1.10.1).

Applicable to Canadian Investigator Sites Only: The Investigator will calculate and record the subject's ACR30 response using ESR as the acute phase reactant at the Month 3 Visit and each subsequent visit thereafter. Subjects with less than an ACR30 response at 2 consecutive visits, beginning with the Month 3 visit and anytime thereafter, should be discontinued from study treatment, unless, in the opinion of the Investigator, it is in the subject's best interest to continue receiving tofacitinib (to be determined on a case-by-case basis and in consultation with the Sponsor). If continuation of treatment is warranted, the Investigator must contact the Sponsor to discuss the case and obtain prior approval.

7.1.6.2. JIA ACR Flare Criteria

JIA ACR flare is defined as a worsening of 30% or more in 3 or more of the 6 variables of the JIA core set listed above, with no more than one variable improving by 30% or more. In addition, the following minimum worsening contingencies apply: if either the number of active joints or the number of joints with limited range of motion are included in the calculation of "flare" then there must be a worsening of at least two joints. If the Physician's or parent/legal guardian global rating scores are used in the definition of "flare" then there must be a worsening of at least 2 units on the 10 unit scales. If the ESR is used in the definition of "flare" then the second value for the ESR used in the calculation must be above the upper limit of normal for the ESR.

In addition, for subjects with sJIA, a disease flare may also constitute a recurrence of fever due to sJIA of >38°C/100.4°F (oral) or >101.4°F/38.6°C (rectal) on 2 or more consecutive days.

7.1.7. JIA ACR Clinical Inactive Disease Status Determination and Clinical Remission Criteria

The American College of Rheumatology (ACR) JIA Clinical Inactive Disease and Clinical Remission (Wallace 2011)[8] criteria is defined as follows:

The Clinical Inactive Disease:

The Clinical Inactive Disease Status Determination assessment[8] is a derived measurement and defined as follows: which includes:

- No joints with active arthritis.
- No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA.
- No active uveitis (as defined by the SUN Working Group).
- ESR or CRP levels within normal limits in the laboratory where tested or, if elevated, not attributable to JIA.

- Physician global evaluation of disease activity score of 'best possible' on the scale used.

- Duration of morning stiffness of ≤15 minutes.

Clinical Remission on Medications:

- Inactive disease for 6 months continuously while on medications.

Clinical inactive disease and clinical remission status will be based on the investigator's assessment of the above components.

7.1.8. Juvenile Arthritis Disease Activity (JADAS 27- CRP and JADAS 27- ESR) Score

The Juvenile Arthritis Disease Activity score is a validated composite disease activity measure for JIA (Consolaro 2009).[13] Recently, the scoring system was adapted to use the 27 joint count (Bazso 2009),[15] and C- reactive protein in place of Erythrocyte Sedimentation Rate (ESR) for the inflammatory marker component (Nordal 2012).[16]

JADAS 27- CRP and JADAS 27-ESR score consists of four components:

- Physician global assessment of disease activity;

- Parent/legal guardian/subject global assessment of Child well being (from the CHAQ);

- Number of joints with active disease (27 joint assessment);

- CRP or ESR.

The JADAS 27- CRP and JADAS 27- ESR score will be determined based on the investigator and parent/legal guardian assessment of the above components.

7.1.9. JADAS 27 Minimal Disease Activity and Inactive Disease

The cutoff values in the JADAS 27 that correspond to inactive disease and minimal disease activity (Consolaro 2012)[14] are defined as follows:

Polyarthritis (>4 active joints):

- Inactive Disease: ≤1.

- Minimal Disease Activity: ≤3.8.

Oligoarthritis (≤4 active joints):

- Inactive Disease: ≤1.

- Minimal Disease Activity: ≤2.

The JADAS 27- CRP and JADAS 27- ESR score will be determined based on the investigator and parent/legal guardian/subject assessment of the above components.

7.1.10. Additional Assessments in Subjects with Systemic JIA

7.1.10.1. Presence or Absence of JIA-associated Fever

At each study visit, the subject's oral temperature will be taken. The subject will also be asked if he/she had fever, defined as temperature >38°C (100.4°F) if taken orally or >101.4°F/38.6°C if taken rectally, due to sJIA, in the last 7 days before the visit. "Absence of fever", defined as the documented absence of fever due to sJIA in the week preceding the assessment, will be evaluated at every visit, as a key component of the Adapted JIA ACR response.

Subjects will be provided with a digital thermometer to measure their oral temperature on days that they have fever symptoms. Each subject will receive a diary to record their temperature. The parent/legal guardian should complete the diary or supervise the completion of the diary by the subject. If subjects have a fever, the temperature should be recorded twice daily (in the morning and evening); the highest temperature since previous diary recording should be reported in the diary. Subjects will return the diary to the clinic at each study visit.

7.1.11. Additional Assessments in Subjects with Enthesitis-Related Arthritis

In addition to all other efficacy assessments specified in Section 7.1, subjects with enthesitis-related arthritis (ERA) will undergo additional efficacy assessments, including Tender Entheseal Assessment, Modified Schober's Test, and Overall Back Pain and Nocturnal Back Pain Assessment as specified in the following subsections. These assessments will be performed at baseline visit for subjects who roll over more than 14 days after the EOS Visit from index study, at Month 3 Visit, Month 6 Visit, then every 6 months and at the End of Study/Early Termination Visit for all subjects (see Schedule Of Activities).

7.1.11.1. Tender Entheseal Assessment

The Tender Entheseal Assessment will be performed at the study visits as specified in Schedule Of Activities only in subjects with enthesitis-related arthritis.

Following anterior/posterior and left/right joint assessment, the investigator will enter one of the following codes for each enthesis on the appropriate CRF. Palpation should be performed per standard practice (eg, using fingertips) for this assessment.

Y = Any tenderness upon firm palpation over the indicated enthesis

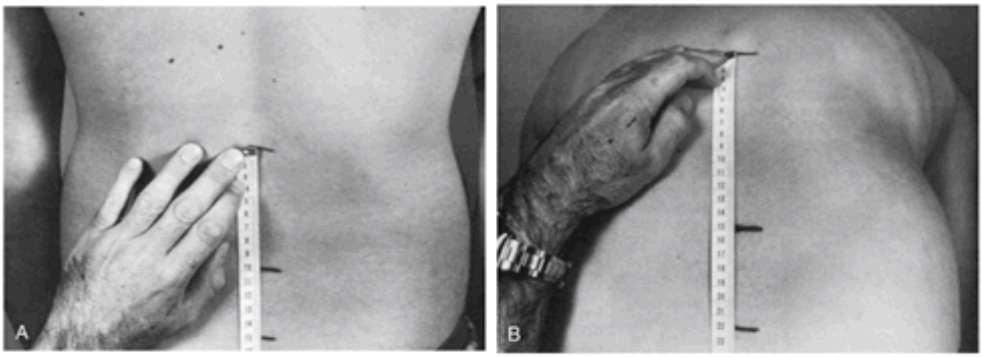
N = No tenderness upon firm palpation over the indicated enthesis

7.1.11.2. Modified Schober's Test

The Modified Schober's Test (Macrae 1969, Moll 1971)[17,18] will be performed at the study visits as specified in Schedule Of Activities only in subjects with enthesitis-related arthritis.

With the subject standing erect and with feet together, a line joining the posterior superior iliac spines (the dimples of Venus) is used as a landmark for the lumbosacral junction. A mark is made 5 cm below and 10 cm above the lumbosacral junction. With the subject in maximum forward flexion with the knees straight, the investigator will measure the distance between the two marks in centimeters. The full measurement between the two lines will be recorded to the nearest tenth of a centimeter (eg, 15.2 cm) on the appropriate CRF.

Figure 1. Modified Schober's Test



A. Measurement 10 cm above and 5 cm below the lumbosacral junction (the dimples of Venus) in the upright position.
B. Measurement of the distance between the upper and the lower marks when the child is bending forward.

7.1.11.3. Overall Back Pain and Nocturnal Back Pain Assessment

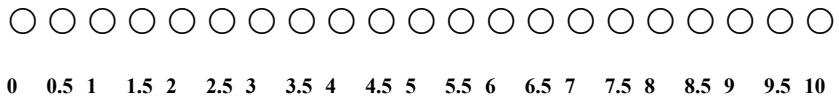
The Overall Back Pain and Nocturnal Back Pain assessment will be performed at the study visits as specified in Schedule Of Activities only in subjects with enthesitis-related arthritis.

Overall back pain (at any time) and nocturnal back pain will be measured on a 21-numbered circle visual analog scale (VAS).

The parent/legal guardian (subject may complete if at least 14 years of age and able to complete correctly and consistently for duration of study) will be asked to fill a circle on the scale shown below in response to the following questions:

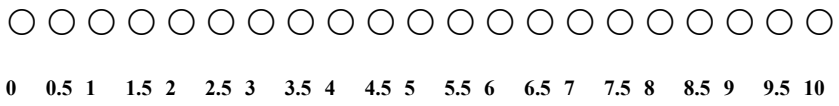
Overall Back Pain (Please fill a circle)

What is the amount of back pain at any time that your child experienced in the past week?



Nocturnal Back Pain (Please fill a circle)

What is the amount of back pain at night that your child experienced in the past week?



7.1.12. Additional Assessments in Subjects with Psoriatic Arthritis (PsA)

In addition to all other efficacy assessments specified in Section 7.1, subjects with psoriatic arthritis (PsA) will undergo additional efficacy assessments, including assessment of body surface area (BSA) affected by Psoriasis and Physician's Global Assessment (PGA) of psoriasis (Horneff 2014).[19] These assessments will be performed at baseline visit for subjects who roll over more than 14 days after EOS Visit from index study, at Month 3 Visit, Month 6 Visit, then every 6 months and at the End of Study/Early Termination Visit for all subjects with PsA.

7.1.12.1. Body Surface Area (BSA)

BSA will be measured as the percentage of BSA affected by psoriasis using the palm method; the subject's palm will be used for the calculation with 1 of the subject's palms to PIP and thumb equal to 1% of BSA (see Appendix 10).

7.1.12.2. Physician's Global Assessment (PGA) of Psoriasis

PGA of Psoriasis will assess the amount of induration, erythema, and scaling averaged over all psoriatic lesions on a scale of 0 to 5 (see Appendix 11).

7.2. Safety

Safety will be assessed by the spontaneous reporting of AEs, physical examinations, and clinical laboratory results in all subjects who received at least 1 dose of study medication. Investigators and Pfizer clinicians will review individual subject data throughout the conduct of the trial to ensure subjects' well-being.

7.2.1. Blood Pressure, Pulse Rate and Temperature

Blood Pressure

Blood pressure will be measured in the subject's arm and recorded to the nearest mmHg. The same arm should be used throughout the study using an appropriate cuff size. All blood pressure readings should be measured after resting for at least 5 minutes. The same position and blood pressure cuff appropriately sized, positioned and properly calibrated should be used to measure blood pressure each time. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained first. It is preferred that blood pressure be collected in the sitting position, supine position is allowed. Position should be documented in the CRF and should be consistent for the subject throughout the study.

Pulse Rate

Pulse rate should be obtained after resting for at least 5 minutes.

Temperature

For subjects with all JIA subtypes, other than sJIA, it is preferred that body temperature be collected using tympanic, oral or temporal methods and that the same method should be used consistently throughout the study.

For subjects with sJIA, body temperature must be collected **orally** using a digital thermometer, with the exception of very young children or others who cannot tolerate an oral thermometer. In these cases temperature may be measured **rectally** using a digital thermometer. The same method should be used consistently throughout the study.

Refer to Section 7.1.10.1 for guidance on the presence and absence of JIA-associated fever.

7.2.2. QuantiFERON®-TB Gold or Gold-Plus In-Tube Test

Quantiferon®-TB (QTF-TB) Gold or Gold Plus test will be available according to local regulations and approvals.

Annual TB testing (QFT-TB Gold or Gold Plus) is required in countries where TB incidence has been reported at a rate of >50 cases per 100,000 persons, eg, China, Russian Federation; South Africa, India and Ukraine. (World Health Organization).

Subjects who enroll within 14 days after their EOS visit in their qualifying/index study must have a QuantiFERON®-TB Gold or Gold Plus In-Tube test administered 1 year ±30 days from the date of the last examination in the qualifying study.

Subjects who enroll more than 14 days after their EOS Visit in their qualifying/index study must have a QuantiFERON®-TB Gold or Gold Plus In-Tube test administered at screening and reported as negative in order to be eligible for enrollment in the study, unless one was performed and documented within the last 3 months.

A negative PPD test can be substituted for the QuantiFERON®-TB Gold or Gold Plus In-Tube test only if the central laboratory is unable to perform the test or cannot determine the results to be positive or negative. Annual TB testing will be performed using Quantiferon®-TB Gold or Gold Plus In-Tube test (PPD test may be substituted only as outlined above). For subjects with positive results, sites must perform chest radiograph for TB status determination; the radiograph must be negative for active TB infection for the subject to continue study participation. **Note:** Quantiferon®-TB Gold or Gold Plus In-Tube test is not be performed in subjects who had a positive result during prior testing (screening visit or prior annual visits) and/or who previously received adequate treatment for TB. However, sites are recommended to perform a chest radiograph for TB status determination or as per local standards of care or country-specific guidelines.

Applicable to Investigative Sites in the UK and Belgium: Participants who have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or have underlying conditions that may predispose them to infection must be monitored closely per applicable local guidelines. Consultation with a health care professional with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

QuantiFERON®-TB Gold or Gold Plus In-Tube test is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10 and TB7.7 proteins to stimulate cells in heparinized whole blood. Detection of interferon- by Enzyme-Linked Immunosorbent Assay is used to identify in vitro responses to these peptide antigens that are associated with Mycobacterium tuberculosis infection. QuantiFERON®-TB Gold or Gold Plus In-Tube test is an indirect test for M. tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

The procedure for using this test and interpreting the results is described fully in the laboratory manual, which will be provided to investigators.

7.2.3. Tuberculin Test (PPD)

If the QuantiFERON®-TB Gold or Gold Plus In-Tube test cannot be performed, or if the results cannot be determined to be positive or negative, subjects can be screened using the

PPD Tuberculin Test. Subjects must have a Mantoux tuberculin test administered and evaluated by a health care professional 48 to 72 hours later in order to be eligible for the study, unless performed and documented within the last 3 months. The test should be performed according to local standards. A negative PPD Tuberculin Test is one that is <5 mm induration.

7.2.4. Radiograph of Chest

For subjects who enroll more than 14 days after their EOS Visit from their qualifying study, a chest radiograph without changes suggestive of active tuberculosis (TB) infection within 3 months prior to screening is recommended and should be considered in accordance with local standards of care or country-specific guidelines. To be considered eligible for the study, the radiograph, if performed, must be negative for active tuberculosis infection.

During the course of this study, annual screening for latent and/or active TB will be conducted using the QuantiFERON®-TB Gold or Gold Plus In-Tube test. All subjects with a positive result must have a chest radiograph performed and the radiograph must be negative for active tuberculosis infection for the subject to continue study participation. Subjects identified as having latent TB (ie, positive tuberculosis test, chest radiograph negative for active tuberculosis, and no evidence of active disease) should be treated appropriately (Section 8.5.2).

7.2.5. Uveitis Exam

Uveitis exam must be performed by an ophthalmologist (or qualified equivalent per local practice) and will be done at Screening if no documented history of uveitis exam within past 6 months is available) then annually thereafter, and at the End of Study/Early Termination Visit if required

If there is documented history of uveitis exam within the past 6 months, the next exam will be done one year from the date of the previous exam, then annually thereafter, and at the End of Study/Early Termination Visit if required.

A uveitis exam at the End of Study/Early Termination Visit is not required if an exam has been performed within the past 6 months of the EOS/ET visit.

The window for this particular examination is ±30 days relative to the visits where uveitis exam is to be performed. At all other visits the investigator should assess if there are potential changes in uveitis status and refer for formal evaluation if deemed clinically necessary. For JIA subtypes that may require more frequent uveitis examination, investigators should manage this type of examination according to local standard of care.

For subjects with sJIA, this exam is not required but if available, documentation of previous uveitis assessment(s) by an ophthalmologist (or qualified equivalent per local practice) should be reviewed, the date of the prior examination recorded, and the presence/absence of active uveitis documented. For subject with sJIA, the investigator should assess at all visits if there are potential changes in uveitis status and refer for formal evaluation if deemed clinically necessary.

Uveitis exam should be performed according to standard of care and the results (ie, a report) recorded in the source document. Development of new uveitis or worsening of existing uveitis according to Standardization of Uveitis Nomenclature (SUN) criteria should be reported as adverse events in the CRF.

The activity of the anterior chamber (AC) inflammation will be evaluated according to the SUN criteria, where the activity of AC inflammation is graded from 0 to 4 (grade/cells in field: 0/<1, 0.5+/1–5, 1+/6–15, 2+/16–25, 3+/26–50, 4+/>50) (Jabs 2005).[12]

7.2.6. Macrophage Activation Syndrome (MAS) Markers (sJIA Only)

Macrophage activation syndrome (MAS) is a potentially life-threatening complication of sJIA. MAS is characterized by an overwhelming inflammatory reaction due to an uncontrolled and dysfunctional immune response involving the continual activation and expansion of T lymphocytes and macrophages, which results in massive hypersecretion of pro-inflammatory cytokines. Characteristic clinical features of MAS are high, non-remitting fever, hepatosplenomegaly, generalized lymphadenopathy, central nervous system dysfunction, and hemorrhagic manifestations. Typical laboratory abnormalities include pancytopenia, increased levels of ferritin, triglycerides, and decreased fibrinogen levels. A key histopathological feature of MAS is evidence of macrophage hemophagocytosis in the bone marrow (Ravelli et al. 2016).[23]

Subjects with sJIA are encouraged to contact the investigator by telephone if they have fever for more than 1 consecutive day. If a subject is suspected to experience MAS, an unscheduled visit will need to be performed as soon as possible for further evaluation. During the unscheduled visit an extra blood sample will be collected to assess Ferritin, Platelets, Triglycerides and Fibrinogen serum levels in order to confirm a diagnosis of MAS.

In accordance with the 2016 ACR/European Union League Against Rheumatology (EULAR)/Paediatric Rheumatology International Trials Organisation (PRINTO) Criteria, (Ravelli A. et al. 2016)[24] a subject is classified as having MAS if the subject has:

- Fever plus Ferritin >684 ng/ml; AND
- At least 2 of the following 4 laboratory variables:
  - Platelets ≤181 x 109 /L;
  - AST >48 U/L;
  - Triglycerides >156 mg/dL;
  - Fibrinogen ≤360 mg/dL.

7.2.7. Physical Examination

Complete Physical Examination

The following parameters and body systems will be examined and any abnormalities described: General appearance, weight and height, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), lower extremities (peripheral edema), abdominal (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes. For children under 40 kg, body weight obtained at study visits will be used to adjust dosing as the child grows.

Applicable to Investigative Sites in the UK and Belgium: a full skin cancer examination must be performed as part of the complete physical examination.

Targeted Examination

An abbreviated physical examination will be performed assessing the following: examination of skin, heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes, weight and height. Any clinically significant changes from the baseline examination should be recorded as AEs.

Applicable for subjects enrolled from A3921165:

If rash is present, the type of rash should be noted (e.g., typical sJIA rash, varicella rash, herpes zoster lesions, or other types of rash). The parent/guardian/subject should perform at least weekly skin checks between visits and any concern for potential chickenpox or shingles be reported to the investigator immediately. Please refer to Appendix 16.

7.2.8. Assessment of Pubertal Development

Determination of physical and sexual maturation will be performed annually at study visits using the Tanner stages by a trained physician/clinician in the presence of a parent/legal guardian or clinic staff member, until the subject has reached Tanner Stage 5.

In the event the parent/legal guardian or child 9 years or older refuses the examination for sexual maturity, or if not possible per site practice or local regulations, subject self-assessment of Tanner staging that uses photographs or line drawings corresponding to the Tanner stages will be offered to obtain information on pubertal status while avoiding intrusiveness.

Based on a multi-informant investigation, Dorn et al. (1990)[9] and Taylor et al. (2001)[10] found that when boys and girls were shown schematic drawings (5 ordinally-scaled drawings/photographs corresponding to the Tanner stages), their self-ratings correlated quite well with health-care-provider examination Tanner staging.

The Tanner stage rating will be assigned by the clinician/physician based on the exam or based on the subject self-report. If the clinician believes the subject's self-report may reflect an earlier or later pubertal stage than the clinician believes is correct, the clinician will review

the self-report form with the subject and/or parent/legal guardian to clarify the subject's responses. This review will be done in the presence of another person, either the parent/legal guardian or a clinic staff member. At the end of the review, the clinician will then assign a best estimate Tanner stage rating.

Note that pubertal development in the U.S. begins as early as age 8 and completes as late as age 17. Once a subject has reached the highest stage of development (Stage 5) then that score may be carried forward for the remainder of the study.

7.2.9. Laboratory Tests

Blood and urine samples will be collected at the time points identified in Schedule of Activities and Section 6 the protocol. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Protocol required testing includes hematology (CBC with differential), urinalysis, chemistry panel (sodium, potassium, chloride, bicarbonate, calcium, glucose, urea nitrogen, creatinine, creatine kinase, total protein, total bilirubin, direct and indirect bilirubin, alkaline phosphatase, gamma-glutamyl transferase, albumin, aspartate aminotransferase, alanine aminotransferase, and urine pregnancy testing (females of childbearing potential only).

Lipid Panel (cholesterol, indirect LDL, direct HDL, apolipoproteins A-1 and B, triglycerides) will be collected under fasting conditions, if possible, at the baseline visit for subjects who roll over more than 14 days after their EOS Visit from their qualifying/index study, every 6 months through year 5 and then every 12 months after year 5, and at the End of Study/Early Termination Visit for all subjects who enroll in this study.

Hepatitis B, Hepatitis C virus antibody (HCV Ab), and HIV-1/HIV-2 antibody screen will be obtained at the screening visit for subjects who enroll more than 14 days after their EOS Visit from their qualifying/index study.

In case of insufficient sample or issue on the sample quality (eg, hemolysis or clotting) the subject should return within 1 week to collect a new sample.

Creatinine clearance will be evaluated at every study visit using the Modified Schwartz equation or Cockcroft-Gault equation. (Appendix 5)

Hepatitis B testing:

The blood sample will first be analyzed for HBsAg and HBcAb. If HBsAg is positive, the subject is excluded from the study. If the sample is HBsAg negative but HBcAb positive, the subject will be tested for HBsAb. If when tested, the HBsAb test is negative, the subject will be excluded from the study. Hepatitis B testing will not be performed in subjects determined to be HBs Ab positive in their qualifying study.

Hepatitis C testing:

HCV RNA is tested in case a positive HCV Ab result is obtained. Only subjects with negative HCV Ab or HCV RNA will be allowed to enroll in the study. To conserve blood volume at screening, HCV RNA sample collection may be deferred and collected only if required to confirm eligibility based on the HCV Ab results.

Subjects who are receiving concomitant MTX, leflunomide, sulfasalazine, chloroquine, or hydroxychloroquine should have Hematology (CBC with differential) and chemistry laboratory tests (eg, electrolytes, BUN, creatinine, liver function tests, etc.) obtained as appropriate for standard of care.

Tuberculosis testing

QuantiFERON®-TB Gold or Gold Plus In-Tube will be obtained at the screening visit for subjects who enroll more than 14 days after their EOS Visit from their qualifying/index study. Annual TB testing will be performed using the QuantiFERON®-TB Gold or Gold Plus In-Tube test. Subjects should withhold study medication on the day of the visit to limit the number of potential false positive results.

The following Table 3 lists the components of all laboratory testing (mandatory and optional) that will be conducted during the course of this study.

Table 3. Laboratory Testing

Laboratory Testing Profile	Tests Included
Infections	QuantiFERON®-TB Gold or Gold Plus In-Tube test, hepatitis C virus antibody (and hepatitis C virus RNA if needed), hepatitis B surface antigen and hepatitis B core antibody (and hepatitis B surface antibody if needed), HIV-1/HIV-2 antibody screen.
Hematology	Hemoglobin, hematocrit, RBC, WBC, neutrophils (%, abs), lymphocytes (%, abs), Monocytes (%, abs), eosinophils (%, abs), basophils (%, abs), platelets.
Chemistry Panel	Urea nitrogen, creatinine, glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), albumin, creatine kinase (CK).
Lipid Panel (fasting, if possible)	Total cholesterol, direct HDL, indirect LDL, apolipoprotein A-1 and B, triglycerides.
Urine	Specific gravity, pH, protein, glucose, ketones, blood and leukocyte esterase, urine microscopy.[a] Urine HCG pregnancy testing for women of childbearing potential.
Acute Phase Reactants	C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).
Macrophage activation syndrome (MAS)[b]	Ferritin, fibrinogen, platelets, triglycerides.

Table 3. Laboratory Testing

Laboratory Testing Profile	Tests Included

a. Only if dipstick positive for blood or protein or clinically indicated.
b. **MAS diagnostic laboratory testing (sJIA subjects only)**: if MAS is suspected in a febrile subject, a blood sample will be collected to assess Ferritin and Fibrinogen serum levels in order to confirm the diagnosis of MAS. Platelet and triglyceride levels from the standard hematology and lipid evaluations will also be reviewed for confirmation of a MAS diagnosis.

Clinically significant abnormal findings should be recorded as AEs if they meet any of the following criteria:

- Test result is associated with accompanying symptom; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an adverse event by the Investigator or sponsor.

Abnormal test results determined to be caused from laboratory error should not be reported as AEs. Clinically significant laboratory findings at the final assessment should be followed to resolution or until determined by the Investigator to be stabilized. Repeat tests may be indicated to establish this. Refer to Appendix 8 for laboratory discontinuation criteria.

7.2.9.1. Blood Volume

Every effort will made to minimize the number of blood sampling and volumes collected. Low volume pediatric tubes will be used where possible. Maximum blood volume during the first year of the study will be approximately 90 mL. After the first year of participation, annual blood volume will be approximately 30 mL. The total volume taken during the study does not exceed 2.4 mL/kg during any period of 30 consecutive days.

7.2.10. Risk Factor Check for Venous Thromboembolism

All subjects will undergo a risk factor check at each study visit to check for newly developed risk factors for venous thromboembolism.[26] This information is to be captured in the subject's source file and on the relevant case report form.

A subject may be at high risk for venous thromboembolism if he/she:

- has heart failure or prior myocardial infarction within the past 3 months;
- has inherited coagulation disorders;

- has had venous thromboembolism, either deep venous thrombosis or pulmonary embolism;
- is taking combined hormonal contraceptives or hormone replacement therapy;
- has malignancy (association is strongest with cancers other than non melanoma skin cancers);
- is undergoing major surgery or is immobilized.

Additional risk factors for venous thromboembolism, such as age, diabetes, obesity (BMI>30), smoking status, hypertension, and first degree family history of VTE should also be taken into consideration by the investigator and the Sponsor medical monitor when evaluating the benefit:risk for each individual subject whether to modify their dose of tofacitinib.

If a subject has 1 or more of the risk factors for venous thromboembolism listed above, investigator judgement based on Exclusion Criterion 25 will apply to determine whether the subject is appropriate for entry into this study.

If a subject has 1 or more of the risk factors for venous thromboembolism listed above under Amendment 10 and is receiving tofacitinib 5 mg BID, they may remain on tofacitinib 5 mg BID after careful investigator assessment of benefit:risk.

For subjects who do not have any of the risk factors for venous thromboembolism listed above under Amendment 10, he/she will remain on their assigned tofacitinib dose.

7.3. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with a sensitivity of at least 25 mIU/mL for hCG, will be performed locally at Screening and Baseline Visits for subjects who roll over within 14 days or more than 14 days after their EOS Visit from their qualifying/index study, at all study visits and at the End of Study/Early Termination for all subjects. If preferred, urine and/or serum pregnancy test may be performed at any time using the local laboratory.

A negative pregnancy result is required before the subject may receive the tofacitinib.

Pregnancy tests will also be done whenever one menstrual cycle is missed during the treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

A positive urine pregnancy test will be confirmed by a blood (serum) pregnancy test performed either locally or by the central laboratory.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from study medication and from the study.

7.4. Pharmacokinetic Sampling

7.4.1. PK Sampling Time Points for All Subjects

Blood samples for PK analyses of tofacitinib will be collected from all subjects at Month 12, Month 24, Month 36 visits, and/or at the End of Study/Early Termination (if feasible) up to Month 36. While PK sampling is desired at the End of Study/Early Termination visit (up to Month 36), it is recognized that this collection may not be possible or feasible if drug has been discontinued prior to this visit; a comment should be included in the applicable PK CRF page.

PK samples should be obtained pre-dose and post-dose at 0.5 hr (time window: 0.25-0.75 hr), and 2hr (time window: 1.75-2.5 hr) after the dose is given at the study site.

Before the visits where a pre-dose PK sample is collected, the subject and parent/legal guardian will be instructed that the subject should not take the morning dose of study medication on the visit day until after the pre-dose PK sample is collected.

Note: PK samples will not be collected from subjects participating at India sites.

7.4.2. Plasma for Analysis of Tofacitinib

Blood samples (1.2 mL) to provide a minimum of 0.6 mL of plasma for PK will be collected into appropriately labeled tubes containing lithium heparin.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within the specified time window will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C within 1 hour of collection.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

7.4.3. Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Time Period and Frequency for collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention or until study completion or withdrawal, whichever is longer.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event

to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication

error case report form (CRF) which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

In addition, all overdoses are medication errors. For the purpose of this study, medication errors will be reported as protocol deviations if the subject reported taking 2-fold or more of their prescribed dose for one or more days or were identified as consuming more than 110% of their prescribed dose over the visit interval.

8.4.1. Tofacitinib Overdosage

There is no experience with overdose of tofacitinib. Pharmacokinetic data up to and including a single dose of 100 mg in healthy adult volunteers indicate that more than 95% of the administered dose is expected to be eliminated within 24 hours. There is no specific antidote for overdose with tofacitinib. In case of an overdose, it is recommended that the subject be monitored for signs and symptoms of adverse reactions. Subjects who develop adverse reactions should receive appropriate treatment.

Please note, that concomitant treatment with a prohibited potent CYP3A4 inhibitor (Appendix 6) is assumed to result in a doubling of exposure. For further details, please refer to the tofacitinib Investigator Brochure.

8.5. Infections

All treated infections occurring during the study, including, but not limited to, respiratory infections, cutaneous infections, urinary tract infections and episodes of suspicious or febrile diarrhea, should be cultured and any identified organisms noted in the case report form.

Infections should be classified as either serious infections or treated infections, as defined below.

8.5.1. Serious Infections

A serious infection is any infection that requires hospitalization for treatment or requires parenteral antimicrobial therapy or meets other criteria that require it to be classified as a serious adverse event. A subject who experiences a serious infection must be discontinued from the study. This infection must be reported as a serious adverse event and should be listed as the reason for discontinuation in the eCRF. Appropriate laboratory investigations,

including but not limited to cultures should be performed to establish the etiology of any serious infection. All adverse events, including serious adverse events, must be reported as described in Section 8.1 on ADVERSE EVENT REPORTING.

8.5.2. Treated Infections

A treated infection is any infection that requires antimicrobial therapy by any route of administration or any surgical intervention (eg, incision and drainage). Subjects who experience infections that require treatment can have their study drug temporarily discontinued during antimicrobial therapy. A subject who experiences a serious infection should be discontinued from the study. This information should be noted in the eCRF.

A subject who experiences a latent TB infection (ie, positive tuberculosis test, chest radiograph negative for active tuberculosis, and no evidence of active disease) may remain in the study, provided that current local incidence rate of multi-drug resistant TB infection is <5% and the subject is willing to have an adequate treatment regimen (9 months of isoniazid or an acceptable alternative regimen) which is documented. Within approximately one month of initiating treatment with isoniazid, the subject should have transaminase levels checked.

PLEASE NOTE: although commonly used in the treatment of tuberculosis, rifampin, rifabutin and rifapentine are prohibited concomitant medications in this study.

8.6. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.7. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.7.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the Section 8.15.1 Serious Adverse Event Reporting Requirements).

8.7.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available.

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

- Concurrent with:
    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least one time the upper limit of normal or if the value reaches ≥3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as serious adverse events.

8.8. Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.9. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.10. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE, generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the Section 8.15 Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.11. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Subject Partner Release of Information Form to provide to his partner.

8.12. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however, a copy of the completed SAE Report form is maintained in the investigator site file.

8.13. Withdrawal Due to Adverse Events (See Also the Section 6.2.6 Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.14. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/ parent/legal guardian. In addition, each study subject/parent/legal guardian will be questioned about AEs.

8.15. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.15.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an

expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.15.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.15.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Methodology for summary and statistical analyses of the data collected in this trial are given here and further detailed in a statistical analysis plan, which will be dated and maintained by Pfizer. This analysis plan may modify what is outlined in the protocol; however, any major modifications of the endpoint definitions or their analyses will also be reflected in a protocol amendment.

For purpose of analysis, for all safety and efficacy endpoints except for JIA ACR disease flare, the baseline values will come from the baseline of the qualifying/index study for subjects who enroll in this study within 14 days of the last visit of the qualifying/index study; for the subjects whose enrollment are out of 14-day window, their baseline values will come from the baseline visit of this study. For JIA ACR disease flare, baseline values will come from Month 3 visit of this study. Details will be specified in the Statistical Analysis Plan.

9.1. Sample Size Determination

Sample size will be determined by the number of subjects who enroll from the qualifying/index studies. Feedback from literature and Investigators indicates about 90% of subjects from qualifying/index studies would enter into this study. Therefore, approximately 340 subjects are expected to join from currently planned studies (ie, A3921103, A3921104 and A3921165). Enrollment will depend on the timing of the initiation of on-going and planned studies. Analyses performed, including interim analyses, if any, will primarily be for safety though some measures of efficacy may be analyzed, and no adjustment of sample size due to interim analyses is needed (No hypothesis testing is planned in this study).

9.2. Efficacy Analysis

9.2.1. Analysis of Primary Endpoint

The primary focus of this study is the long term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA. Safety endpoints will include standard laboratory safety data (as listed in Section 7.2.9) and AE reports (including SAE). Body weight, height and Tanner stages will be collected to assess growth and physical development.

Analyses for safety will be based on Pfizer reporting standards unless otherwise specified or noted (as described in Section 9.3 below).

9.2.2. Analysis of Secondary Endpoints

The measures of efficacy (as listed in Section 7.1) will be summarized using descriptive statistics, such as number and percent for binary endpoints, mean, standard deviation and quartiles for continuous endpoints at each visit where measured. Displays combining and stratifying by qualifying studies will also be included. Exploratory analyses may also be performed.

Complete details will be specified in the statistical analysis plan.

9.3. Safety Analysis

All the safety data, including the following, will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations:

- Adverse events will be summarized according to Pfizer standards.
- Safety laboratory tests will be summarized according to Pfizer standards.
- Special attention will be given to the following safety criteria: neutrophil counts, lymphocyte counts, serum creatinine levels, liver tests, hyperlipidemia, diabetes, anemia and hypertension.
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials or meets other criteria that require it to be classified as a serious adverse event, will be summarized.
- Special attention will be given to the following safety endpoints: MAS, uveitis, cytopenias, malignancies, cardiovascular diseases, gastrointestinal perforations and validated assessments of growth and pubertal development.

9.4. PK Analysis

Plasma concentration-time data for tofacitinib will be analyzed using a nonlinear mixed effects modeling approach to characterize PK in this subject population if data is collected from ≥40% of the subjects. Subjects' current weight will be used as one of the primary covariates for CL/F and V/F in the model to characterize body weight mediated changes in CL/F within a subject. Relationship between various measures of systemic exposure of tofacitinib (eg, observed or model predicted trough or 2 hour post-dose concentrations) and efficacy/long-term safety outcomes may be explored using appropriate methodology. Details will be captured in a separate Population Modeling Analysis Plan (PMAP).

9.5. Interim Analysis

There are no planned formal interim analyses. Interim analyses may be performed for study monitoring for internal decision making, regulatory purposes or for planned publications. As this is an open-label long term follow-up study with no control group and no hypothesis testing. There are no issues of protecting the Type I error rate.

9.6. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB), a group of experts external to Pfizer, will review accumulating safety data from this study on an ongoing basis within the context of the Phase 3 pediatric program as well as adult program. Based on these reviews, the DSMB will have the capacity to make recommendations to Pfizer that might impact the future conduct of the trial. The recommendations made by the DSMB to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate. The DSMB will have access to unblinded treatment information from concurrently ongoing double-blind studies during the clinical trial. The management and process of this committee will be in accordance with Pfizer's Standard Operating Procedures and will be documented in the DSMB Charter. The DSMB members will all be individuals who are independent of Pfizer. A DSMB Liaison will be appointed; this is an individual who represents Pfizer to coordinate communications and facilitates access to Pfizer's resources, but is not involved in the study design, study management, site management, data accrual, or study analysis. Records of DSMB meetings, interactions with Pfizer contacts, assessments and recommendations and materials reviewed will be maintained and kept proprietary and confidential by the DSMB. Further information about the DSMB can be found in the DSMB Charter, which outlines the operating procedures of the committee, including specific description of the scope of their responsibilities, including a plan where communication timelines are defined.

9.7. Safety Endpoint Adjudication Committees

To help assess specific safety events in this and other studies in the tofacitinib program, adjudication committees have been established to harmonize and standardize selected safety event assessment. Members of these safety event adjudication committees will be blinded to treatment assignment in order to allow for unbiased assessments. These committees include 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. Further information about these committees can be found in the respective charters, including specific descriptions of the scope of their responsibilities and the processes and definitions used to review and assess specific safety events.

In addition to these external committees, an internal committee of medically qualified Pfizer personnel with expertise in the assessment and diagnosis of respiratory disease will review and categorize potential events of interstitial lung disease (Interstitial Lung Disease Committee, ILDRC).

Additional safety event adjudication or review committees may be established to harmonize and standardize selected safety event assessments. As described above, individual committee charters will provide specific descriptions of the scope of responsibilities and the processes and definitions used to review and assess specific safety events.

In addition to the event adjudication or review committees described above, all biopsies of potentially malignant tumors, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder should be submitted to the central laboratory for review by central laboratory pathologists. In some instances, additional expert pathology review of submitted samples may be performed. Description of the scope of review and the processes used to obtain and assess biopsies is described in the Histopathology Review for Potential Malignancy charter.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/ Ethics Committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/ Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator File. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent/Assent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any, reports, publications, or other disclosures, except where required by laws.

When study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the study subject. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

The informed consent and assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent and assent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his/her legally acceptable representative or parent or legal guardian, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonable be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his/her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent/legal guardian, spouse) and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must be re-consented as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, the must provide documentation of legal status to give consent without the permission of the parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative/parent(s) or legal guardian before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tofacitinib at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within one week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.ClincialTrials.gov for Pfizer-sponsored interventional studies conducted in subjects that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual subjects has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by an investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

If the study is part of a multi-centre study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. Johnston JA, Bacon CM, Riedy MC, et al. Signaling by IL-2 and related cytokines: JAKs, STATs, and relationship to immunodeficiency. J Leukocyte Biol 1996; 60(4):441-52.

2. Conklyn M, Andresen C, Changelian P et al. The JAK3 inhibitor CP-690550 selectively reduces NK and CD8+ cell numbers in cynomolgus monkey blood following chronic oral dosing. J Leukoc Biol. 2004; 76(6):1248-55.

3. Changelian PS, Moshinsky D, Kuhn CF et al. The specificity of JAK3 kinase inhibitors. Blood. 2008 Feb 15; 111(4):2155-7.

4. Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States. Online. Available: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm. 16 December 2005.

5. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994; 37:1761–1769.

6. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997; 40: 1202-1209.

7. Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. J Rheumatol 2002; 29(5):1058-64.

8. Wallace CA, Giannini EH, Huang B, Itert L, Ruperto N for the Childhood Arthritis and Rheumatology Research Alliance (CARRA), the Pediatric Rheumatology Collaborative Study Group (PRCSG), and the Pediatric Rheumatology InterNational Trials Organisation (PRINTO). American College of Rheumatology provisional criteria for defining clinically inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res 2011;63;929-936.

9. Dorn, LD, et al. Perceptions of puberty: Adolescent, parent, and health care personnel. Developmental Psychology 1990; 26(2): 322-329.

10. Taylor, SJ. et al. Performance of a new pubertal self-assessment questionnaire: a preliminary study. Paediatr Perinat Epidemiol 2001; 15(1):88-94.

11. Dunne J, et al. Extrapolation of Adult Data and Other Data in Pediatric Drug-Development. Pediatrics 2011;128; e1242.

12. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509–16.

13. Consolaro A, Ruperto N, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Care and Research, 2009; 61(5):658-666.

14. Consolaro A, Bracciolini G, et al. Remission, minimal disease activity and acceptable symptom state in juvenile idiopathic arthritis, 2012;64:2366 -74.

15. Bazso A, Consolaro A, et al. Development and testing of reduced joint counts in juvenile idiopathic arthritis. J Rheumatol, 2009; 36:183 -90.

16. Nordal EB, Zak M, et al. Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population based setting. Ann Rheum Dis, 2012;71:1122 -7.

17. Macrae IF, Wright V. Measurement of back movement. Ann Rheum Dis, 1969;28:584-589.

18. Moll JM, Wright V. Normal range of spinal mobility: an objective clinical study. Ann Rheum Dis, 1971;30:381-386.

19. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari I, Vojinovic J, Chasnyk VG, Dehoorne J, Panaviene V, Susic G, Stanevica V, Kobusinska K, Zuber Z, Mouy R, Rumba-Rozenfelde I, Breda L, Dolezalova D, Job-Deslandre C, Wulffraat N, Alvarez D, Zang C, Wajdula J, Woodworth D, Vlahos B, Martini A, Ruperto N, for the Paediatric Rheumatology International Trials Organisation (PRINTO). Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study. Ann Rheum Dis, 2014;73:1114–1122.

20. Ruperto N, Ravelli A, Pistorio A, Malattia C, Cavuto S, Gado-West L, Tortorelli A, Landgraf JM, Singh G, Martini A, for the Paediatric Rheumatology International Trials Organisation (PRINTO). Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. Clin Exp Rheumatol. 2001; 19 (Suppl. 23): S1-9.

21. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, and Furth SL. New Equations to Estimate GFR in Children with CKD. J Am Soc Nephrol 2009; 20: 629–637.

22. Ruperto N, Brunner H, Lovell D, Martini At et al. Two randomized trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. New England Journal of Medicine, Dec 2012, 367, 25.

23. Ravelli et al. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis. Arthritis and Rheumatology, Vol 68, Nr. 3, March 2016. Pg 566 – 576.

24. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, Aricò M, Avcin T, Behrens EM, De Benedetti F, Filipovich L, Grom AA, Henter J, Ilowite NT, Jordan MB, Khubchandani R, Kitoh T, Lehmberg K, Lovell DJ, Miettunen P, Nichols KE, Ozen S, Pachlopnick-Schmid J, Ramanan AV, Russo R, Schneider R, Sterba G, Uziel Y, Wallace C, Wouters C, Wulffraat N, Demirkaya E, Brunner HI, Martini A, Ruperto N, Cron RQ on behalf of the Pediatric Rheumatology International Trials Organization (PRINTO); the Childhood Arthritis & Rheumatology Research Alliance (CARRA); the Pediatric Rheumatology Collaborative Study Group (PRCSG); the Histiocyte Society. 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–489.

25. Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. The Journal of Rheumatology. 2002 May 1;29(5):1058-64.

26. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the ERS. European Heart Journal (2020) 41;543-603.

27. US Food and Drug Administration, Center for Drug evaluation and Research. Draft Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-and-biological-products. Published: Dec 2014. Accessed: 06 Apr 2021

Appendix 1. Allowed And Disallowed Treatments for JIA

Allowed DMARDs

Subjects <18 years of age may take no more than 1 of the 5 following permitted non-biologic DMARDs at the same time. Subjects ≥18 years of age may take no more than 2 of the 5 following permitted non-biologic DMARDs at the same time (hydroxychloroquine and chloroquine must not be taken at the same time). Subjects may either start a permitted non-biologic DMARD, continue at same dose, reduce the dose, stop taking the permitted non-biologic DMARD, or switch to a different permitted non-biologic DMARD; subjects ≥18 years may also add 1 of the permitted DMARDs to the existing DMARD.

- Methotrexate (≤20 mg/m^2/week or 25 mg/week, whichever is lower);
- Leflunomide (Arava®) (10 mg every other day for body weight of <20 kg; 10 mg every day for body weight of 20 to 40 kg; 20 mg every day for body weight >40 kg; or as according to local standards);
    - Hydroxychloroquine (≤ maximum recommended dose per local product information). Subjects may not start treatment with hydroxychloroquine while participating in A3921145. Continued treatment with hydroxychloroquine is permitted for those taking this concomitant medication prior to enrollment.
    - Chloroquine (≤ maximum recommended dose per local product information). Subjects may not start treatment with chloroquine while participating in A3921145. Continued treatment with chloroquine is permitted for those taking this concomitant medication prior to enrollment.
    - Sulphasalazine (≤ maximum recommended dose per local product information). Subjects may not start treatment with sulphasalazine while participating in A3921145. Continued treatment with sulphasalazine is permitted for those taking this concomitant medication prior to enrollment.

Allowed Treatments for Psoriatic Arthritis:

The dose and type of the following may be adjusted at the discretion of the investigator:

- Topical steroids and tar based shampoos on all regions;
- Topical vitamin A or D analog preparations;
- Anthralin.

Disallowed DMARDs and Biologic Agents:

The following DMARDS and biologic agents are disallowed at any time during this study. If a subject needs to be treated with one of these agents, the subject should be discontinued from the study.

- Anakinra (Kineret®) must be discontinued for 3 days prior to the first dose of study drug.
- Cyclosporine must be discontinued for 7 days prior to the first dose of study drug.
- Etanercept (Enbrel®) must be discontinued for 2 weeks prior to the first dose of study drug.
- Adalimumab (Humira®): Discontinued for 2 weeks prior to first dose of study drug.
- Canakinumab (Ilaris®): Discontinued for 7 weeks prior to the first dose of study drug.
- Golimumab (Simponi TM): Discontinued for 4 weeks prior to the first dose of study drug.
- Infliximab (Remicade®) must be discontinued for 3 weeks prior to the first dose of study drug.
- Abatacept (Orencia®), Certolizumab pegol (Cimzia®), secukinumab (Cosentyx®), and tocilizumab (Actemra®) must be discontinued for 4 weeks prior to the first dose of study drug.
- Bucillamine, mizoribine, d-penicillamine, azathioprine, tacrolimus, and staphylococcal protein A immuno-absorbant pheresis columns (eg, PROSORBA® device/column) must be discontinued for 4 weeks prior to first dose of study drug.
- Auranofin (oral gold), aurothioglucose (injectable gold), aurothiomalate (injectable gold) must be discontinued for 8 weeks prior to first dose of study drug.
- Rituximab (Rituxan®) or other selective B lymphocyte depleting agents (either marketed or investigational): Discontinued for 1 year prior to the first dose of study drug and if CD19/20+ counts are normal by fluorescence-activated cell sorting (FACS) analysis.
- Baricitinib (Olumiant®), Upadacitinib (Rinvoq®) or other JAK inhibitors must be discontinued 4 weeks prior to the first dose of study drug.
- Immunoglobulin intravenous (IV) must be discontinued 8 weeks or 2 half-lives (whichever is longer) prior to the first dose of study drug.

Disallowed Treatments for PsA:

- Ultraviolet B (UVB) (narrowband or broadband) phototherapy must be discontinued at least 2 weeks prior to first dose of study drug. Psoralens + ultraviolet A (UVA) phototherapy (PUVA) must be discontinued at least 4 weeks prior to first dose of study drug.

- Oral and topical retinoids must be discontinued at least 2 weeks prior to first dose of study drug.

Disallowed Investigational Drugs

- NSAIDs: Any experimental non-steroidal anti-inflammatory drug (NSAID), including selective COX-2 inhibitors, must be discontinued for 4 weeks prior to the first dose of study drug.

- Other Investigational Drugs: Any other experimental therapy must be discontinued for 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug.

Appendix 2. Approximate Equivalent Morphine Doses of Opioid Analgesics

Common opioid analgesics

Drug	Maximum Allowed Total Daily Dose	Relative potency to oral morphine	Half-Life
Morphine	0.2-0.5 mg/kg/dose, up to 15 mg/dose. No more than 5 doses/day.	1	1.5-4 hrs
Hydromorphone (Dilaudid)	0.03-0.08 mg/kg/dose, up to 2 mg/dose. No more than 5 doses/day.	4	2.5 hrs
Codeine (Paveral, Tylenol #2 and #3)	0.5-1.0 mg/kg/dose, up to 60 mg/dose. No more than 5 doses a day.	0.15	2.5-3.5 hrs
Oxycodone [Roxicodone; Percocet, Tylox]	0.05-0.15 mg/kg/dose, up to 5 mg/dose. No more than 5 doses a day.	~2	3.2 hrs

Sites should contact project team for acceptable alternative preparations and related data.

Lexi Comp Pediatric Dosage Handbook 15th Edition
Sick Kids Drug Handbook & Formulary 2008-2009
Rx Files Pediatric Pain: Treatment Considerations, Q & A's. Oct. 08

Appendix 3. Permitted Adjustments In JIA Therapies for Worsening Disease

The following adjustments of background medications are allowed for reasons of inadequate efficacy of current treatment, or may be tapered or discontinued due to disease improvement. Adjustments for safety reasons may be done at any time, but if this leads to changes in excess of those allowed below, the investigator must receive approval from the Pfizer project team to allow the subject to continue in the trial. Adjustment in background meds due to disease improvement can begin upon enrollment in this study.

1. NSAIDs/COX-2 inhibitors: dose adjustments may be made, or background NSAID/COX-2 inhibitors may be switched but should be more than 14 days prior to a study visit.
2. Oral corticosteroid dose should not exceed 0.20 mg/kg/day or 10 mg/day, prednisone or equivalent daily, whichever is lower. For subjects coming from the systemic JIA study A3921165, a higher prednisone-equivalent dose may be continued or started (doses must be ⩽1.0 mg/kg/day up to 30 mg/day oral prednisone [or equivalent]).
3. Methotrexate (≤20 mg/m^2/week or 25 mg/week, whichever is lower), leflunomide (10 mg every other day for body weight of <20 kg; 10 mg every day for body weight of 20 to 40 kg; 20 mg every day for body weight of >40 kg; or as according to local standards) may be added and/or adjusted. Increases should be no more frequently than every month. Adjustments should be made more than 4 weeks prior to a study visit.
4. Sulfasalazine (≤ maximum recommended dose per local product information) may be adjusted. Increases should be no more frequently than every month. Adjustments should be made more than 4 weeks prior to a study visit. (Note: this only applies to subjects who enter the study on concomitant sulphasalazine since subjects may not start treatment with sulphasalazine while participating in A3921145).
5. Chloroquine (≤ maximum recommended dose per local product information) and hydroxychloroquine (≤ maximum recommended dose per local product information) should be adjusted no more frequently than every month. Adjustments should be made more than 8 weeks prior to a study visit. (Note: this only applies to subjects who enter the study on concomitant cholorquine or hydroxychloroquine since subjects may not start treatment with cholorquine or hydroxychloroquine while participating in A3921145).
6. Intra-articular steroid (eg, triamcinolone (KENALOG®, Aristospan®)) should be administered to no more than four joints in any given 6 month period and individual joints should not be injected any more frequently than once in a 6-month period. Injected joints will be considered as not assessed during the remainder of the study. Intra-articular injections should be avoided during the 6 weeks prior to a study visit.

A UNIFORM TAPERING OF A MEDICATION OR TITRATING UP ON A DOSAGE OF MEDICATION TOWARD A SPECIFIC PRE-DETERMINED GOAL DOSAGE (INCLUDING DISCONTINUATION) WILL BE CONSIDERED A SINGLE CHANGE IF ACCOMPLISHED WITHIN 1 MONTH.

Appendix 4. Permitted Adjustments (Tapering) of JIA Medications for Subjects with Inactive Disease for at Least 24 Weeks

Subjects who have inactive disease for at least 24 consecutive weeks may begin to taper off of concomitant JIA therapies and tofacitinib. Tapering of therapies is to be completed in the following order: oral corticosteroids, MTX/leflunomide, tofacitinib.

- For subjects who are not taking concomitant oral corticosteroids, tapering will start with MTX/leflunomide, followed by tofacitinib.
- For subjects who are not taking concomitant MTX/leflunomide, tapering will start with oral corticosteroids, followed by tofacitinib.
- For subjects not taking concomitant oral corticosteroids or MTX/leflunomide, tapering will start with tofacitinib.

The rate at which each drug is tapered is described below.

Oral Corticosteriods: The dose of oral corticosteroids may be reduced or discontinued for subjects who have inactive disease for at least 24 consecutive weeks (time in parent study and A3921145 inclusive). The dose can be reduced by 0.1mg/kg each week. Once the dose of corticosteroids is at 5 mg/day then an absolute decrease by 1 mg/day each week can be implemented.

Methotrexate/leflunomide: The dose of MTX/leflunomide may be decreased or discontinued for subjects who continue to have inactive disease for at least 24 consecutive weeks after receiving the last dose of oral corticosteroids. MTX/leflunomide may be discontinued with or without tapering based on local practice; it is acceptable to stop the drug abruptly or by tapering the dose.

Tofacitinib: The dose of tofacitinib may be decreased or discontinued for subjects who continue to have inactive disease for at least 24 consecutive weeks after receiving the last dose of MTX/leflunomide. The dose is to be reduced by 5 mg every 12 weeks as long as the subject's disease remains inactive. The evening dose should always be reduced before the morning dose. For example, a subject receiving a total daily dose (TDD) of 10 mg (5 mg BID) prior to tapering will step down to a TDD of 5 mg by taking 5 mg in the morning and 0 mg in the evening. If they continue to have inactive disease for a least 12 consecutive weeks while receiving a TDD of 5 mg, the 5 mg morning dose may also be discontinued.

Subjects will be followed for 6 months (24 weeks) after tofacitinib is discontinued by returning to the site for schedule visits and completing all visit assessments.

If at any time during the tapering process or after discontinuation of tofacitinib, the subject is not able to maintain the inactive disease status (as defined in the protocol Section 7.1.7), concomitant JIA therapies (eg, oral corticosteroid, methotrexate/leflunomide) and tofacitinib can resume if appropriate according to investigator judgment.

Tofacitinib will restart at 5 mg BID. Concomitant JIA therapies and doses should be adjusted at the discretion of the investigator.

Appendix 5. Estimated Glomerular Filtration Rate (GFR) and Creatinine Clearance (CrCl) Calculations

1. eGFR will be evaluated at screening to determine if a subject is eligible.

   The Bedside Schwartz GFR equation[21] will be used to estimate glomerular filtration rate (eGFR) from serum creatinine (creatinine methods with calibration traceable to IDMS).

   eGFR (mL/min/1.73 m^2) = 0.413 × (Ht / Scr)

   Height (Ht) in cm;

   Serum creatinine (Scr) in mg/dL

2. Creatinine clearance (CrCl) will be evaluated at every study visit.

   (i) Participants <12 years of age

   The Modified Schwartz equation[27] will be used to estimate creatinine clearance in participants < 12 years of age

   CrCl (mL/min/1.73 m^2) = (K x Ht)/ Scr

   K (proportionality constant):
   Female Child < 12 years of age: K = 0.55
   Male Child< 12 years of age: K = 0.70

   (ii) Participants ≥ 12 years of age

   The Cockcroft-Gault equation[27] will be used to estimate the creatinine clearance for participants ≥ 12 years of age.

$$\textbf{CrCl (ml/min)} = \frac{\textbf{(140 - age) x Body Weight (kg)}}{\textbf{Serum Creatinine (mg/dL) x 72}} \quad \textbf{(x 0.85 if female)}$$

Appendix 6. Prohibited Concomitant Medications

All prohibited drugs require a 4 week (≥5 half-lives) washout, except:

* ***Amiodarone*** half-life averages about 58 days and requires a 290 day washout (5 half-lives);

** ***Biologic DMARDs*** which have specific washout periods listed in Appendix 1.

NOTE: Topical administration (eg, cutaneous, ophthalmic, or intravaginal) of listed concomitant medications, which are prohibited if administered systemically, is allowed in the study. **Moderate or Potent CYP3A Inhibitors**	Moderate or Potent CYP3A Inducers
HIV antivirals:	efavirenz (Sustiva)
-delavirdine (Rescriptor)	nevirapine (Viramune)
-indinavir (Crixivan)	Barbiturates
-nelfinavir (Viracept)	carbamazepine (Carbatrol, Tegretol)
-ritonavir (Kaletra, Norvir)	modafinil (Provigil)
-saquinavir (Fortovase)	Phenobarbital
-atazanavir	phenytoin (Dilantin, Phenytek)
amiodarone (Cordarone, Pacerone)*	rifabutin (Mycobutin)
cimetidine (Tagamet)	rifampin (Rifadin, Rifamate, Rifater)
clarithromycin (Biaxin, Prevpac)	rifapentine (Priftin)
telithromycin (Ketek)	St. John's Wort
Clotrimazole	troglitazone (Rezulin)
Chloramphenicol	**All Investigational Drugs**
diethyl-dithiocarbamate	**DMARDs**
diltiazem (Cardizem, Tiazac)	***All Biologics*****, such as: anakinra (Kineret), etanercept (Enbrel), adalimumab (Humira), infliximab (Remicade), abatacept (Orencia), canakinumab (Ilaris), tocilizumab
erythromycin	
fluconazole (Diflucan)	

fluvoxamine (Luvox)	(Actemra), golimumab (Simponi), rituximab (Rituxan), baricitinib (Olumiant), certolizumab (Cimzia), secukinumab (Cosentyx).
Grapefruit juice and marmalade	
itraconazole (Sporanox)	
ketoconazole (Nizoral)	Other DMARDs**: d-penicillamine, bucillamine, mizoribin, azathioprine, cyclosporine, tacrolimus, auranofin, aurothioglucose, aurothiomalate, staphylococcal protein A immuno-absorbant pheresis columns and Immunoglobulin IV.
mifepristone (Mifeprex, RU486)	
nefazodone (Serzone)	
norfloxacin (Shibroxin, Noroxin)	
mibefradil	
verapamil (Calan SR,Covera HS, Isoptin SR, Tarka, Verelan)	
Voriconazole	

Appendix 7. Rescue Therapy

Acetaminophen/paracetamol is allowable as rescue medication if dosed no more than 10-15 mg/kg/dose orally or 15-20 mg/kg/dose rectally (not exceeding 5 doses in 24 hours) for no more than 10 consecutive days. If a subject is already taking stable background doses of acetaminophen/ paracetamol, (s)he may increase the dose up to the maximum dose stated above for up to 10 consecutive days for rescue purposes.

The following paradigm should be used to determine appropriate opioid rescue therapy:

For patients who are NOT on stable, background opioid therapy: any of the following single opioid agents may be given as rescue medication (with or without acetaminophen/ paracetamol) for no more than 10 consecutive days in the following total daily doses:

Morphine	0.2-0.5 mg/kg/dose, up to 15 mg/dose. No more than 5 doses/day.
Hydromorphone (Dilaudid)	0.03-0.08 mg/kg/dose, up to 2 mg/dose. No more than 5 doses/day.
Codeine (Paveral, Tylenol #2 and #3)	0.5-1.0 mg/kg/dose, up to 60 mg/dose. No more than 5 doses a day.
Oxycodone (Roxicodone; Percocet, Tylox)	0.05-0.15 mg/kg/dose, up to 5 mg/dose. No more than 5 doses a day.

For patients who ARE on stable, background opioid therapy:

- They may NOT add a second opioid agent for rescue.
- If their background medication is 1 of the 4 listed above, they may, within the above maximum total dosage limits, increase the dosage for up to 10 consecutive days for rescue purposes.
- If their background medication is a short-acting (half-life <5 hrs, Appendix 2) opioid that is not one of those listed above, they may increase the dosage for up to 10 consecutive days (up to a total daily dose which must not exceed the potency equivalent of 30 mg of orally-administered morphine Appendix 2) for rescue purposes.
- Sustained release opioid formulations (eg, OxyContin®, MS Contin®) and opioids with half lives greater than 5 hours (eg, methadone, propoxyphene) may NOT be USED for rescue medication or increased for rescue purposes.

Intravenous or intramuscular corticosteroids, biologic response modifiers and DMARDs other than those specified as allowed DMARDs (Appendix 1) are not allowed during this study. Intra-articular corticosteroids (eg, triamcinolone (KENALOG®, Aristospan®)) may be given in no more than four joints in a six month period. Injections should be avoided for 6 weeks before any study visit. Injected joints will also be considered as not assessed for the remainder of the trial

Acetaminophen/paracetamol is not permitted as a part of combination products such as over-the-counter "cold remedies" or in combination with opioids if the acetaminophen/paracetamol dose will exceed 2.6 gm/day. Subjects who require rescue for more than 10 consecutive days should be considered for allowed JIA medication adjustments or discontinued from the trial. In addition, subjects should not be dosed with rescue acetaminophen/paracetamol or opioids during the 24 hours prior to a study visit. Baseline stable acetaminophen/paracetamol or opioids should NOT be discontinued in advance of study visits.

Subjects should not be dosed with any rescue intervention within 24 hours prior to a study visit unless indicated for subject safety and individual case management at the discretion of the investigator.

Appendix 8. Guidelines For Safety Monitoring And Discontinuations

For the purpose of safety monitoring for serum creatinine, creatinine clearance (CrCl) and hemoglobin levels in Study A3921145, baseline values are defined as:

- For subjects who enroll in study A3921145 on the same day and within 14 days following previous participation in there tofacitinib qualifying/index study.
    - For serum creatinine, the average of qualifying/index study screening and baseline visit values will be used.
    - For creatinine clearance, the average of qualifying/index study screening and baseline visit values will be used.
    - For hemoglobin, the qualifying/index study baseline visit value will be used.
- For subjects who enroll in study A3921145 greater than 14 days after participating in the tofacitinib qualifying/index study.
    - For serum creatinine, the average of A3921145 screening and baseline visit values will be used.
    - For creatinine clearance, the average of A3921145 screening and baseline visit values will be used.
    - For hemoglobin, the A3921145 baseline visit values will be used.

The following laboratory abnormality requires monitoring:

- Increased lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) should be monitored and treated according to local guidance (eg, diet and behavior modification, statin therapy).

The following laboratory abnormalities require prompt retesting, ideally within 3-5 days:

- Lymphocyte counts <500 lymphocytes/mm^3.
- Neutrophil counts <1000 neutrophils/mm^3.
- **Applicable to Investigative Sites in the UK and Belgium:** Study drug will be discontinued temporarily for confirmed absolute neutrophil counts (ANC) levels of 500 – 1000 neutrophils/mm^3. The subject will be monitored closely through unscheduled visits and laboratory retesting until ANC is >1000 neutrophils/mm^3. Dosing may be resumed when ANC returns to >1000 neutrophils/mm^3.

- Platelet counts <100,000 platelets/mm^3.

- Any single AST and/or ALT elevation >3 times the upper limit of normal (repeat laboratory testing must include CK, Total Bilirubin, Direct and Indirect Bilirubin, GGT, INR and alkaline phosphatase), regardless of the total Bilirubin.

- Any single hemoglobin value <8.0 g/dL.

- Any single hemoglobin value that is ≥2 gm/dL below the baseline (defined above) within the first 12 months of participation in A3921145. For the decreased hemoglobin (≥2 gm/dL below baseline) still within the reference range, retesting hemoglobin can be performed once prior to the next scheduled study visit.

- After the first 12 months of participation in A3921145, any hemoglobin value that is ≥2 gm/dL below the highest hemoglobin level reported within the previous 12 month period.

- Any single increase in serum creatinine >50% over the average of screening and baseline values (as defined above) OR an absolute increase in serum creatinine ≥ 0.5mg/dL (≥44.2 µmol/L) over the average of screening and baseline values (as defined above)
  AND
  Any single CrCl decrease of >30% over the average of screening and baseline values (as defined above)

  (N.B. Screening and baseline values to be used for this monitoring criteria are defined at the beginning of Appendix 8)

Tofacitinib Temporary Withholding or Discontinuation for Venous Thromboembolism:

- Per Amendment 10, for subjects with suspected venous thromboembolism, treatment with tofacitinib should be temporarily withheld while the subject is evaluated. If venous thromboembolism is confirmed, discontinue treatment with tofacitinib and withdraw the subject from the study.

Treatment with tofacitinib will be discontinued and the subject withdrawn from this study for:

- Serious infections (those requiring parenteral antimicrobial therapy or hospitalization).

- Two sequential lymphocyte counts <500 lymphocytes/mm^3;

- Two sequential neutrophil counts <500 neutrophils/mm^3.

- Two sequential platelet counts <75,000 platelets/mm^3.

- Two 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.[1]

- Two sequential AST or ALT elevations >3 times the upper limit of normal with an abnormal INR.[1]

- Two sequential AST or ALT elevations >3 times the upper limit of normal accompanied by symptoms consistent with hepatic injury.[1]

- Two sequential AST or ALT elevations >5 times the upper limit of normal, regardless of Total Bilirubin or accompanying symptoms.[1]

- Single positive HBc Ab and a negative HBs Ab (refer to Section 7.2.9 for additional testing required).

- Two sequential hemoglobins <8.0 g/dL or a decrease of more than 30% from baseline value (defined above).

- Two sequential increases in serum creatinine >50% over the average of screening and baseline values (as defined above) OR an absolute increase in serum creatinine ≥ 0.5mg/dL (≥44.2 µmol/L) over the average of screening and baseline values (as defined above)
  AND
  A confirmed (two sequential) CrCl decrease of >30% over the average of screening and baseline values (as defined above).

  (N.B. Screening and baseline values to be used for this discontinuation criteria are defined at the beginning of Appendix 8)

  If the serum creatinine increase and the CrCl decrease have an identifiable and reversable cause (e.g. concomitant medication), then an additional retest may be considered after discussion with Sponsor study clinician or medical monitor. After retest, a decision for the subject to continue in the study will be made with the Sponsor study clinician or medical monitor.

- Other serious or severe AEs, after consultation with the Pfizer Medical Monitor. For example, subjects with a malignancy (exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ) must be discontinued from the study. All malignancy events should be reported as serious AEs.

[1] In each case, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the Pfizer Medical Monitor.

Appendix 9. Evaluation Of Potentially Malignant Tumors, Suspicious Lymphadenopathy, Possible Extra-Nodal Lymphoproliferative Disorder (LPD)

The following steps should be taken in the event of potentially malignant tumors, suspicious lymphadenopathy or possible extra-nodal lymphoproliferative disorder (LPD) which might arise in the course of this study.

When there is a decision to biopsy a potentially malignant tumor, lymph node, or other tissue, the investigator and/or consultants should contact the Pfizer study team to discuss the issue and any decisions as soon as possible. It is recommended that specialists with experience in the evaluation of immunosuppressed subjects be consulted.

If a biopsy for lymphadenopathy or lymphoma is to be performed, the investigator or consultant should refer to the instructional slide deck in the Lymph Node Biopsy kit and review the following points with the surgeon and pathologist:

- Fine needle aspiration and core needle biopsy are strongly discouraged; excisional biopsy is required for accurate diagnosis.
- Tissue must be sent fresh to the pathology laboratory; the pathologist must be consulted before the procedure.
- Archive multiple frozen tissue samples, if possible.
- Include flow cytometry and cytogenetics as part of the pathologic evaluation.
- Culture for mycobacterium and fungi, if indicated.
- Collect and snap freeze peripheral blood lymphocytes for germ line evaluation (DNA).
- Archive multiple aliquots of serum samples.

For all biopsies, please request the pathologist to send the original slides used to make the definitive diagnosis, ancillary study reports, and the pathologist's report to the central laboratory for blinded review by central pathologists, to be paid for by Pfizer. Should the central pathologists make a diagnosis that is not essentially similar to the local pathologist's diagnosis, the local pathologist will be notified and provided with an opportunity to consult with the central pathologists (paid for by Pfizer). Translation during this consultation, if needed, will be provided by the staff of the Pfizer Country Office (PCO).

Both the local pathologist's diagnosis and the central pathologist's diagnosis will be reported in the study database.

Appendix 10. Body Surface Area

The percentage of body surface area affected by psoriasis will be estimated using the palm method:

One (1) of the *subject's palm* to PIP and thumb equals 1% of BSA.

- Head and Neck = 10% (10 palms)
- Upper extremities = 20% (20 palms)
- Trunk (axillae and groin) = 30% (30 palms)
- Lower extremities (buttocks) = 40% (40 palms)
- Total BSA = 100% (100 palms)

Based on the above, the Physician's Assessment of Total BSA affected by psoriasis will be estimated using the following formula:

Region of the Body	**Number of Palms Within the Region Affected by Psoriasis**
Head and Neck	
Upper extremities	
Trunk (including the axillae and groin)	
Lower extremities (including the buttocks)	
Physician's Assessment of Total BSA Affected by Psoriasis (addition of the individual regions):	**%**

Appendix 11. Physician's Global Assessment Of Psoriasis

Physician's static global assessment (PGA) of psoriasis (averaged over all lesions):

The PGA of psoriasis is used to determine the subject's psoriasis lesions overall at a given time point. Overall lesions are graded for induration, erythema, and scaling based on the scales below. The sum of the 3 scales is then divided by 3 to obtain the final PGA of psoriasis score.

Please circle one response each for induration, erythema, and scaling:	
Induration (I) (averaged over all lesions): 0 = no evidence of plaque elevation 1 = minimal plaque elevation - 0.5 mm 2 = mild plaque elevation - 1 mm 3 = moderate plaque elevation - 1.5 mm 4 = marked plaque elevation - 2 mm 5 = severe plaque elevation - 2.5 mm or more	**Erythema (E)** (averaged over all lesions): 0 = no evidence of erythema, hyper pigmentation may be present 1 = faint erythema 2 = light red coloration 3 = moderate red coloration 4 = bright red coloration 5 = dusky to deep red coloration
Scaling (S) (averaged over all lesions): 0 = no evidence of scaling 1 = minimal; occasional fine scale over less than 5% of the lesion 2 = mild; fine scale predominates 3 = moderate; course scale predominates 4 = marked; thick, non-tenacious scale predominates 5 = severe; very thick tenacious scale predominates	

Add I + E + S = _____ / 3 = _____ (Total Average)

- ☐ (0) Clear, except for residual discoloration
- ☐ (1) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 1**

☐ (2) Majority of lesions have individual scores for [(I + E + S)/3] that **averages 2**

☐ (3) Majority of lesions have individual scores for [(I + E + S)/3] that **averages 3**

☐ (4) Majority of lesions have individual scores for [(I + E + S)/3] that **averages 4**

☐ (5) Majority of lesions have individual scores for [(I + E + S)/3] that **averages 5**

Note: Scores should be rounded to the nearest whole number:

If total average ≤1.49, score = 1

If total average ≥1.50, score = 2

Appendix 12. Dosing Scheme For Subjects Rolling Over From Study A3921103 Under Protocol Amendment 5

Subjects Completing Index Study A3921103 (Age 2 to <6 years)

Body Weight (kg)	Dosage Regimen
5-6	1 mg (1 mL oral solution) BID
7-9	1.5 mg (1.5 mL oral solution) BID
10-12	2 mg (2 mL oral solution) BID
13-15	2.5 mg (2.5 mL oral solution) BID
16-19	3 mg (3 mL oral solution) BID
20-22	3.5 mg (3.5 mL oral solution) BID
23-26	4mg (4 mL oral solution) BID
27-29	4.5mg (4 mL oral solution) BID
≥30	5 mg (one 5 mg tablet or 5 mL oral solution) BID

Subjects Completing Index Study A3921103 (Age 6 to <18 years)

Body Weight (kg)	Dosage Regimen
5-11	1 mg (1 mL oral solution) BID
12-18	1.5 mg (1.5 mL oral solution) BID
19-24	2 mg (2 mL oral solution) BID
25-31	2.5 mg (2.5 mL oral solution) BID
32-39	3 mg (3 mL oral solution) BID
≥40	5 mg (one 5 mg tablet or 5 mL oral solution) BID

Note: Investigators will have the option of maintaining the A3921103 subject's current dosage regimen (if the desired clinical response has been attained with no safety concern) or adjusting the dosage regimen in accordance with dosing scheme specified in Section 5.1.

Appendix 13. By Visit Assessment of the Degree of Burden and Risk Threshold During the Trial (Investigative Sites in Belgium Only)

As written in the protocol under the Schedule of Activities and Section 6 and here summarised, at each visit (initially at 1 month, 3 months, and every 3 months thereafter), the investigator will complete the following (including, but not limited to):

1. A medical history which includes at least one conversation regarding the child's wellbeing, generally at the beginning of the study and at each visit;

2. A physical examination including vital signs, growth, and maturation;

3. Laboratory testing, eg, haematology and liver enzymes, etc., and uveitis examination;

4. Various functional and global assessments depending on the child's specific rheumatologic diagnosis such as the JIA joint assessment, flare assessment CHAQ, and the CHQ; the Physician's Global Evaluation of Overall Disease Activity, the Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment for enthesitis related arthritis, psoriatic body surface area assessment; the Physician's Global Assessment (PGA) for psoriatic arthritis;

5. The investigator also will assess for flare and ACR responses using the JIA ACR Response and Flare Criteria provided in Section 7.1.6 of this protocol;

6. Adverse events such as and including blood cell numbers, liver enzyme test, renal function tests, lipid panel, evaluating for the presence of, for example, as in protocol Section 9.7, serious infections, opportunistic infections, tuberculosis, herpes zoster, malignancies (excluding non-melanoma skin cancer [NMSC]), NMSC, lymphomas, major adverse cardiovascular events (MACEs), interstitial lung disease, macrophage-activation syndrome (MAS), and GI perforations.

Subjects who experience a single episode of disease flare based on the JIA disease flare criteria[25] at any time during the study will be evaluation for discontinuation from study. Additionally, the investigator refers to Appendix 8 "Guidelines for Safety Monitoring and Discontinuations". At each visit, the investigator considers all of this and any additional information, assesses the burden of disease and the risks of continued participation, and confirms whether continued participation by the minor subject is permissible.

Appendix 14. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

1. Eligibility

Subjects from the A3921165 study will be able to enter this study if eligible (See Section 4 SUBJECT SELECTION).

While SARSCoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per Section 4.2 Exclusion Criteria.

2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits.

Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including reminders, education, and safety monitoring.

Follow the protocol schedule of activities when possible, except for the patient reported outcomes which cannot be completed over the phone. The following assessments must be performed during a telehealth visit :

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. (See Section 8 ADVERSE EVENT REPORTING).
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. See Section 4.3.1 Contraception.

3. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider condiucting an in-person study visit at the participants location, rather than an in-person visit at the site. Refer to protocol Section 6 Study procedures, for the list of assessment which may be performed during a home health visit.

4. Laboratory Testing.

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Haematology, urinalysis, chemistry panel, lipid panel, pregnancy testing

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

5. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Investigational product may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the Investigational product. Pfizer does not permit the shipment of Investigational product by mail. The tracking record of shipments and the chain of custody of investigational product must be kept in the participant's source documents/medical records.

Investigational product may be shipped only if there is no safety concern and negative pregnancy test is confirmed (if required per protocol Section 7.3 Pregnancy Testing and Section 4.3.1 Contraception). Participants must consent verbally to providing contact details for shipping purposes, and consent is to be documented in the medical record.

6. Adverse Events and Serious Adverse Events.

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

Per protocol Section 8.5.1 Serious Infections a subject who experiences a serious infection must be discontinued from the study.

In such case, if the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the CRF "Specify" field.

Appendix 15. End of Study

Subjects participation in this study will end in 2 phases :

- For subjects who entered this study from the A3921103 and A3921104 qualifying/index studies, their participation in the study will end, after the first marketing approval of tofacitinib for the treatment of polyarticular course JIA 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 systemic JIA, whichever comes first.

In advance of each phase, sites will receive a communication letter to schedule an End of Study visit for the applicable subjects.

Please refer to the Schedule of Activities and Section 6.2.5 End of Study Visit/Early Termination Visit for the list of procedures and assessments to be completed at this visit.

Depending on local regulatory requirements, and as per the EU Voluntary Harmonisation Procedure (EU VHP), access to tofacitinib may be made available in situations where the subject cannot access treatment through typical post-approval channels after the subjects last visit in this study.

Availability of the oral solution formulation may be limited or discontinued when patients taking the oral solution have either discontinued treatment or have transitioned to use of the oral tablet formulation consistent with applicable weight based dosing guidance.

Appendix 16. Varicella (chickenpox) and Herpes Zoster (shingles) Assessment and Guidance. ***(Applicable for subjects enrolled from A3921165 only)***

Subjects should notify the investigator immediately if they exhibit any skin lesions that could be attributed to varicella or herpes zoster. This is especially important for subjects who do not have documented evidence of having received 2 doses of VZV or evidence of previous varicella zoster exposure as confirmed by VZV-specific IgG Ab serological testing at the A3921165 screening visit.

Subjects and/or their parents or guardians should be especially diligent in conducting self-exams between visits. Any suspicion of varicella or herpes zoster should be treated immediately per standard of care for immunocompromised subjects (e.g., IV acyclovir started within 24 hours of rash appearance) and study drug must also be discontinued immediately. Unless confirmed not to be varicella or herpes zoster, the subject should be discontinued from the study. This will be considered a serious infection event.

At each study visit, the subject will be assessed either by direct skin examination or parent/legal guardian/subject questioning to identify the presence of any rash that could potentially indicate the presence of chickenpox or shingles. The parent/guardian/subject should perform at least weekly skin examinations between visits. At any time there is concern that the presence of any signs or symptoms may indicate chickenpox or shingles, the investigator should be notified immediately.

Rash that indicates the presence of chickenpox or shingles differs from the typical sJIA rash. The typical sJIA rash is a spotty pale red or pinkish salmon-colored rash. It rarely occurs on the face and typically appears on chest, upper arms and upper thighs, although can be found on other parts of the body. sJIA rash usually does not recur in the same location. It is generally flat, but can emerge in raised, small patches. It is rarely accompanied by itching.

The classic symptom of varicella (chickenpox) is a rash that turns into itchy, fluid-filled blisters that eventually turn into scabs. The rash may first show up on the chest, back, and face, and then spread over the entire body, including inside the mouth, eyelids, or genital area. It usually takes about one week for all of the blisters to become scabs. Other typical symptoms that may begin to appear one to two days before rash include: fever, tiredness, loss of appetite, and headache.

Herpes zoster (shingles) is a painful rash that develops on one side of the face or body. The rash consists of blisters that typically scab over in 7 to 10 days. Before the rash appears, people often have pain, itching, or tingling in the area where it will develop. This may happen several days before the rash appears. Most commonly, the rash occurs in a single stripe around either the left or the right side of the body. In other cases, the rash occurs on one side of the face. Shingles on the face can affect the eye and cause vision loss. In rare cases (usually in people with weakened immune systems), the rash may be more widespread on the body and look similar to a chickenpox rash. Other symptoms of shingles can include: fever, headache, chills, and upset stomach.

Appendix 17. Summary of Changes from Original Protocol through Amendment 11

Document	Version Date	Summary of Change
Protocol Amendment 11	26 May2021	Global Amendment Protocol is amended as follows: • Protocol summary Section 3 study design: end of study text updated to clarify that subjects participation to the A3921145 study will end in 2 phases. • Schedule of Activities and Study Procedures Section 6.2.5 updated to clarify which procedures are required at the End of Study/Early Termination visit. • Addition of monitoring criteria related to Creatinine and Lipids increase for continuous assessment of subject's safety in the Appendix 8. • Creatinine discontinuation criteria wording updated in Appendix 8 to require two sequential increases in serum creatinine >50% over the average of screening/baseline and a confirmed creatinine clearance (CrCl) decrease of >30%. These updates are made to account for potential increases in creatinine due to physical activity, age and growth. CrCl added to the schedule of activities footnote and Section 7.2.9 laboratory tests. • Exclusion criterion #27 related to history of allergies, intolerance or hypersensitivity to lactose or CP-690,550 (tofacitinib): This country-specific exclusion criterion is made global to ensure consistent eligibility criteria for the study population. • Exclusion #8 is updated such that any infection requiring hospitalization, parenteral antimicrobial therapy or

Document	Version Date	Summary of Change
		judged to be opportunistic by the investigator within the 3 months (updated from 6 months) prior to the first dose of study drug will exclude a subject. • Appendix #5: Updated to include CrCl equations to be used for the new monitoring and discontinuation criteria related to CrCl. • Reference to "QuantiFERON®-TB Gold" added throughout the protocol. QuantiFERON®-TB Gold or QuantiFERON®-TB Gold Plus will be available according to local regulations and approvals. • Protocol wording updated to clarify that a chest x-ray is required when subjects have a positive annual QFT-TB test for the first time. • Clarification made to JIA ACR disease flare assessment timing for analysis in Protocol Summary and Section 2.2.2. Secondary endpoints. • Clarification made to baseline definition in Section 9 Data Analysis/Statistical Methods. • Requirement of Pfizer medical monitor approval removed from Section 4.1 inclusion criterion 12, Section 7.2.2 QFT test, Section 7.2.3 Tuberculin Test: Protocol includes all information required for the monitoring of subject's safety. • Protocol Section 7.1.5.2 Erythrocyte Sedimentation Rate (ESR) updated to clarify that sites can use the ESR testing kit provided by the Sponsor or use their local laboratory ESR Kit. Reference to Covance lab kit removed throughout the protocol.

Document	Version Date	Summary of Change
		• Appendix 1: Correction of the washout period for investigational drugs to be 4 weeks, in accordance with exclusion #12 • Appendix 14: Updated to include alternative measures during public emergencies in addition to COVID-19 pandemic • Editorial changes to correct typographical errors throughout the protocol.
Protocol Amendment 10	04 May 2020	Global Amendment This global amendment incorporates venous thromboembolism (VTE) risk factor checks. Pfizer has determined that VTE is identified as an important identified risk/dose dependent adverse drug reaction for tofacitinib. • Instructions for the assessment and monitoring of Venous Thromboembolism have been added to Schedule of activities, Section 5.2 Allocation to Treatment; 6 Study Procedures, 6.2.6 Subject Withdrawal, 7.2.10 Risk Factor Check for Venous Thromboembolism, Reference 26 and Appendix 8 Guidelines for Safety Monitoring and Discontinuations. • Protocol updated to clarify that annual TB testing is required for subjects included in countries where TB incidence rate is >50 cases per 100,000 persons. Schedule of Activities, Section 6. Study Procedures and 7.2.2 Quantiferon Gold Plus In-Tube Test updated accordingly. • Protocol updated to clarify that in case of insufficient sample or issue on

Document	Version Date	Summary of Change
		the sample quality (eg, hemolysis or clotting) the subject should return within 1 week for a new sample collection. Schedule of Activities and 7.2.9 laboratory Tests updated accordingly. • Removal of the text allowing subjects aged 14 and older to complete the CHAQ and text added to clarify that every effort should be made to have the same individual complete the CHAQ throughout the course of the study, in Section 7.1.4 CHAQ. • Time Period and Frequency for collecting AE and SAE Information updated according to the new standard text, in Section 8.2. • Washout period required for Anakinra (Kineret®) and cyclosporine corrected to 7 days prior the first dose of study drug in Appendix 1 Protocol (Administrative Change Letter [PACL] issued 11 July 2019). • Washout period required for Immunoglobulin IV which is 20 weeks or 5 half-lives (whichever is longer) prior the first dose of study drug added in Appendix 1 (PACL issued 11 July 2019). • Appendix 3 and Appendix 7. Updated to clarify that after intra-articular steroid injection, the injected joints will be considered "not assessed" during the remainder of the study (PACL issued 20 November 2019). • Appendix 4 updated to clarify that concomitant JIA therapies and tofacitinib treatment can resume at

Document	Version Date	Summary of Change
		any time during or after the tapering if the subject is not able to maintain the inactive disease status. • Appendix 6 updated to include Immunoglobulin IV to the list of prohibited concomitant medications. • Temporary measures for study visit occurring during the COVID-19 Pandemic added in Appendix 14 (PACL issued 27 March 2020 and 07 April 2020). • Editorial changes to corrected typographical errors throughout the protocol.
Protocol Amendment 9	23 May 2019	Global Amendment • Removed the tofacitinib 10 mg BID dose (Refer to Section 1.2.2.2, Section 5.1, and Appendix 4). Note: At the time of this amendment no subjects were receiving, or had received the 10 mg BID dose during participation in this study. • Removed baseline PK sample for subjects from A3921165 who do not enroll in the LTE on the same day they complete the qualifying study (Refer to Schedule of Activities [SOA], Section 6.1.1.2, Section 6.1.3, and Section 7.4.1.1). Per PACL dated 16-November 2017, update made to SOA to correct formatting issues. Per PACL dated 18-December-2017, updates made to clarify inconsistencies between Appendix 1, Appendix 3, and Appendix 4 that occurred with the addition of

Document	Version Date	Summary of Change
		tapering JIA medications in Amendment 7. • Per PACL dated 16-November 2018, updates made to allow vaccination with live or live-attenuated vaccines during the study. (Refer to Section 4.3.3 and Section 5.2). • Name of QuantiFERON®-TB Gold Plus In-Tube test updated (Refer to SOA, Section 4.1, Section 6.1, Section 6.2, Section 7.2.2, Section 7.2.3, Section 7.2.4, and Section 7.2.9). • Timing of QuantiFERON® -TB Gold Plus In-Tube test updated for consistency within the protocol and clarity. (Refer to Section 6.2, Section 7.2.2, and Section 7.2.9). • Timing of Uveitis Examination updated for consistency within the protocol and clarity. (Refer to SOC, Section 6.2, and Section 7.2.5).
Protocol Amendment 8	07 February 2018	• For Investigative Sites in Belgium and the United Kingdom (UK): • Add Exclusion Criterion 26: History of allergies, intolerance or hypersensitivity to lactose or CP-690,550 (tofacitinib). (Refer to Section 4.2). • Added text to clarify that a condom plus spermicide is not accepted as highly effective contraception. (Refer to Section 4.3.1). • Added guidance regarding participants who have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or

Document	Version Date	Summary of Change
		have underlying conditions that may predispose them to infection. (Refer to Section 7.2.2). • Added a full skin cancer examination to the complete physical examination. (Refer to the Schedule of Activity (SOA), Section 6.0, and Section 7.2.7). • Provide guidance for monitoring confirmed absolute neutrophils count levels of 500 – 1000 neutrophils/mm3. (Refer to Appendix 8).
		• For Investigative Sites in Belgium only: • Added Appendix 13: By Visit Assessment of the Degree of Burden and Risk Threshold During the Trial. Also added statement in SOA and Section 6.0 referencing Appendix 13.
Protocol Amendment 7	10 August 2017	Changes made to accommodate the inclusion of subjects rolling over from sJIA Study A3921165. Updated Dose Rationale to include 10 mg BID dose of tofacitinib (see Section 1.2.2.2). • Added endpoints for subjects with sJIA: "Absence of Fever", defined as absence of fever due to sJIA in the week preceding the assessment at each visit (see Protocol Summary and Section 2.2.2). Changed number of subjects to be enrolled in the study from approximately

Document	Version Date	Summary of Change
		290 to approximately 340 (see Protocol Summary, Sections 3 and 9.1). • Updated Inclusion Criterion 6 to allow subjects coming from sJIA study to continue or start higher prednisone-equivalent doses (doses must be ≤1.0 mg/kg/day up to 30 mg/day oral prednisone [or equivalent]) than permitted for subjects from other qualifying studies (with the agreement of the Pfizer medical monitor). See Section 4.1). Updated Exclusion # Criterion 4 to only exclude subjects with persistent oligoarthritis and undifferentiated JIA (see Section 4.2). Updated study treatments to include tofacitinib 10 mg BID. Changes included reorganizing section and adding headers for clarification (see Section 5.1). • Updated permitted medications and/or treatments to allow for the use of higher prednisone-equivalent doses in subjects from the sJIA study (with agreement from Pfizer medical monitor). (see Section 5.5.2). • Updated uveitis exam to provide guidance regarding sJIA subjects (see Schedule of Activities [SOA] and Section 6.1). • Updated vital sign assessment to specify that oral or rectal temperature must be taken with a digital thermometer in subjects with sJIA (see Section 6.1). • Added assessments specific to subjects with sJIA: Assessment of

Document	Version Date	Summary of Change
		JIA-associated Fever and assessment of extra-articular sJIA manifestations. In addition, assessments for Macrophage Activation Syndrome (MAS) were added for sJIA subjects with fever and where MAS is suspected. (see Sections 6.1). • Add/Update Assessment Section 7. • Update JIA ACR Flare Criteria to provide guidance for assessing subjects with sJIA, specifically fever assessment (see Section 7.1.6.2). • Add Presence or Absence of JIA-associated Fever to Assessment section (see Section 7.1.10.1). • Update Temperature to provide guidance for assessing oral or rectal temperature in subjects with sJIA (see Section 7.2.1). • Add Macrophage Activation Syndrome (MAS) Markers for subjects with sJIA (see Section 7.2.6). • Update Table 4 Laboratory Testing, to include tests for assessing MAS. • Add baseline and post-date change PK sampling time points for subjects from the sJIA study A3921165 as preparation for potential dose increase to tofacitinib 10 mg BID (see SOA and Section 7.4.1.1).

Document	Version Date	Summary of Change
		• Added Exclusion Criterion 25 - Previously failed treatment with another JAK inhibitor, such as baricitinib. Prior to Amendment 7 there were no approved JAK inhibitors other than tofacitinib. Change made so that subject who fail a drug with the same mechanism of action as tofacitinib are not enrolled in the study. (see Section 4.2). Changes made to allow the tapering of concomitant JIA medications (corticosteroids, methotrexate, and tofacitinib) in subjects with improved symptoms-All JIA subtypes. Added endpoint: Eligibility of tapering defined per protocol for corticosteroids, MTX/ leflunomide, and tofacitinib (see Protocol Summary and Section 2.2.2). Revised Section 5.5.2 *Permitted Medications and/or Treatments* to include permitted dose adjustments in background JIA therapies for inactive disease. Changes included reorganizing and adding headers for clarity. Appendix 3: Changed title from *Permitted Adjustments in JIA Therapies* to *Permitted Adjustments in JIA Therapies for Worsening Disease.* Added new Appendix 4: *Tapering of JIA Medications for Subjects with Inactive Disease.* Within this appendix is guidance for tapering doses of oral corticosteroids, methotrexate, and tofacitinib in subjects who have had inactive disease for at least 24 weeks. Appendix 1 *Allowed and Disallowed Treatments for JIA* was updated to

Document	Version Date	Summary of Change
		included baricitinib, (Olumiant®) and secukinumab (Cosentyx®), which were approved since the last protocol amendment. Appendix 6 *Prohibited Concomitant Medications* was updated to included baricitinib, (Olumiant), certolizumab (Cimzia), secukinumab (Cosentyx), which were approved since the last protocol amendment. Lab Assessments: Lipid Panel: LDL-direct method will be changed to an LDL-indirect method. The change was required because one of the analysis reagents for LDL direct will no longer be produced. Added "(fasting, if possible)" to provide guidance (see Sections 6.1, 7.2, and Table 4). Triglycerides are added as a lab assessment since values over 400 mg/dL could affect the results of the LDL (see Sections 6.1, 7.2 and Table 4). Per PACL dated 08-December-2016, wording to clarify washout and timing of consent was added to Section 6.1.1 *Subjects Requiring Separate Screening and Baseline Visits*. Administrative changes made to provide clarification. Updated wording for Inclusion Criterion 6 to clarify corticosteroid use before and during the study (see Section 4.1). • Updated wording for Exclusion Criterion 8c with following: "(excluding those treated with topical only)" to provide additional guidance

Document	Version Date	Summary of Change
		on what is meant by "treated infection" (see Section 4.2). Updated wording for Exclusion Criterion 9 to provide further guidance regarding herpes zoster and herpes simplex (see Section 4.2). Updated wording for Exclusion Criterion 15 to clarify corticosteroid use before and during the study (see Section 4.2). Order of assessments reorganized by all subjects and by subtype to simplify operational conduct of the study (see Section 6). • Added "with psoriasis rash" to the body surface area assessment for subjects with psoriatic arthritis (PsA) only, to provide further guidance on what is being assessed (see Section 6). Added "Westergren Method" to ESR assessment to provide clarity as to the method sites should be using for this study (see SOA and Sections 6. and 7.5). Per PACL dated 13 January 2017, change made to correct typographical error, "total volume take during the study does not exceed *2.7* mL/kg during any period of 30 consecutive days" was changed to "…does not exceed *2.4* mL/kg…" (see Section 7.2.9.1). • The option to send urine and serum samples to the central laboratory was removed from Section 7.3 Pregnancy Testing. Covance, the central laboratory for the study, provides urine pregnancy kits with the protocol-specified sensitivity to all

Document	Version Date	Summary of Change
		sites. Sites continue to have the option to have serum and/or urine pregnancy test analyzed by their local laboratory. Analysis of Secondary Endpoints were clarified as follows: efficacy will be summarized using descriptive statistics, such as number and percent for binary endpoints, mean, standard deviation and quartiles for continuous endpoints (see Section 9.2.2). Added to Section 9.3 Safety Analysis for clarity: Special attention will be given to the following safety endpoints: MAS, uveitis, cytopenias, malignancies, cardiovascular diseases, gastrointestinal perforations and validated assessments of growth and pubertal development.
Protocol Amendment 6	07 April 2016	Changed Study Drug Dosing following completion of PK study A3921103 and available PK for 2 through <18 years of age and also based on FDA recommendation to cap dosing at 5 mg BID for index study A3921104. Updated Dose Rationale with PK data from A3921103 that provides dose rationale for this study (see Section 1.2.2). Deleted former Appendix 10 Dose Rationale as the dosing rationales are already established and explained in Section 1.2.2. Changed Dosing Scheme to reflect revised dosing regimen and supplied the dosing instruction for the active subjects under Amendment 5 (see Section 5.1 and Appendix 11).

Document	Version Date	Summary of Change
		Added languages to allow Temporary Discontinuation of Study Drug for up to 28 consecutive days under conditions of AEs/SAEs and surgical procedures (see Section 5.2). Incorporated Assessment of Investigational Product Dosing Compliance into Study Procedure (see Schedule of Activities, Section 6.1.4.1, Section 6.1.4.2, Section 6.1.4.3, Section 6.1.4.4, and Section 6.1.5). Clarified Investigational Product Dosing Compliance and Noncompliance (see Section 5.3.4). Clarified tofacitinib medication errors as Protocol Deviations (PDs) and tofacitinib overdose for consistency with adult rheumatoid arthritis (RA) studies (see Section 8.4 and Section 8.4.1). Updated Introduction paragraph to reflect the current global approval status of tofacitinib (see Protocol Summary and Section 1.1). Added benefit/risk wording per Protocol Review Committee (PRC) feedback (see Protocol Summary and Section 1.2.1). Added language on post-trial access of study drug based on KOL's feedback (see Study Design and Section 3). Added erythrocyte sedimentation rate (ESR) determination for consistency with Index Study A3921104 (see Study Objectives and Endpoints, Schedule of Activities, Section 2.2.2, Section 6.1.1. Section 6.1.3, Section 6.1.4, Section 6.1.5, Section 7.1.5.2, Section 7.1.6,

Document	Version Date	Summary of Change
		Section 7.1.7, Section 7.1.8, and Section 7.1.9). Added a section on inflammatory markers (ESR and CRP) for clarity (see Section 7.1.5). Added JADAS 27- CRP and JADAS 27-ESR, JADAS minimum disease activity and inactive disease criteria to secondary endpoints for consistency with Index Study A3921104 (see Study Objectives and Endpoints, Section 2.2.2, Section 7.1.8, Section 7.1.9 and Section 16). For subjects with Enthesitis Related Arthritis (ERA) only: added Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment for consistency with Index Study A3921104 (see Study Objectives and Endpoints, Schedule of Activities, Section 6.1.1.2, Section 6.1.4, Section 6.1.5, and Section 7.1.10). For subjects with Psoriatic Arthritis (PsA) only: added body surface area (BSA) affected by psoriasis and Physician's Global Assessment (PGA) of psoriasis for consistency with Index Study A3921104 (see Study Objectives and Endpoints, Schedule of Activities, Section 6.1.1.2, Section 6.1.4, Section 6.1.5, Section 7.1.11, Appendix 9 and Appendix 10). Incorporated new contraception template languages (see Schedule of Activities, Section 4.1., Inclusion Criterion 3, Exclusion Criterion 14, Section 4.3.1 and Section 7.3). Added an Inclusion Criterion to further clarify the eligibility for the subjects

Document	Version Date	Summary of Change
		completed participation in a Qualifying JIA Study and especially for the subjects discontinued in a Qualifying JIA Study for reasons other than tofacitinib related Serious Adverse Events (see Inclusion Criterion 4). Updated wording for Exclusion Criterion 24 to adapt for pediatric population (see Exclusion Criterion 24). Added the other required evidences for negative Tuberculosis (TB) on Eligibility Criteria including the negative outcome of chest radiograph per local standards of care or country-specific guidelines and no history of either untreated or inadequately treated latent or active TB infection for clarity (see Inclusion Criterion 12). Added Annual Tuberculosis (TB) Screening and chest radiograph for Tuberculosis (TB) status determination for consistency with tofacitinib adult long-term studies (see Schedule of Activities, Section 6.1.4.1, Section 6.1.4.2, Section 6.1.4.4, Section 6.1.5, Section 7.2.2, Section 7.2.4, Section 7.2.8, and Section 8.5.2). Deleted Reflex Hepatitis B Testing at Screening Visit for Subjects who roll over on the Same Day or within 14 Days after the EOS Visit from Index Studies to avoid the duplicated tests with Index Studies (see Section 6.1.2, Section 6.1.3, and Section 7.2.8). Changed exclusion cut-off on lymphocyte count from <0. 5 x 10^9/L to <0.75 x 10^9/L for consistency with Index Study A3921104 (see Exclusion Criterion 1e).

Document	Version Date	Summary of Change
		Clarified the active systemic features for Systemic JIA in Exclusion Criterion 4 by adding "other than active joints and elevated acute phase reactants" (see Exclusion Criterion 4). Updated Exclusion Criterion 6 with clarifications "other than Sjogren's syndrome." for consistency with tofacitinib adult RA program. Deleted "latent or active TB or any history of previous TB" from Exclusion Criterion 8 to avoid the duplicates with Inclusion Criterion 12 (see Exclusion Criterion 8). Updated Exclusion Criterion 19 with clarifications "IgA deficiency not exclusionary" based on feedback from investigators. Changed the maximum dose of methotrexate (MTX) from "not to exceed 20 mg/week or 15 mg/m^2/week" to "not to exceed 25 mg/week or 20 mg/m^2/week, whichever is lower" based on Investigator's feedback (see Inclusion Criterion 5 and Appendix 1). Added the maximum dose of glucocorticoid as an inclusion criterion for consistency with Section 5.5 Concomitant Medication(s) and also Index Study A3921104 (see Inclusion Criterion 6). Added sulfasalazine, chloroquine, hydroxychloroquine as allowed DMARDS for consistency with adult tofacitinib long-term safety studies (see Inclusion 8, Section 5.5, Appendix 1, and Appendix 3).

Document	Version Date	Summary of Change
		Deleted intra-articular hyaluronate sodium injections from Permitted Adjustments in RA Therapies and Rescue Therapy as intra-articular hyaluronate sodium injections are not indicated for JIA based on Investigators' feedback (see Appendix 3 and Appendix 6). Updated Disallowed DMARDS and Prohibited Concomitant Medications Lists for consistency with Index Study A3921104 (see Appendix 1 and Appendix 5). Changed the maximum dose of corticosteroids from 0.15 mg/kg/day (prednisone or equivalent) to 0.20 mg/kg/day or 10 mg/day (prednisone or equivalent), whichever is lower, for consistency with Index Study A3921104 (see Section 5.5 and Appendix 3). Clarified Herbal Supplements in Dietary Supplements and Concomitant Medication for consistency with Exclusion Criterion 18 (see Section 4.3.5 and Section 5.5). Added additional prohibited and permitted medications and/or treatments for subjects with PsA (see Section 5.5 and Appendix 1). Incorporated the component of Duration of Morning Stiffness assessment for the JIA ACR inactive disease into study procedures (see Schedule of Activities, Sections 6.1.1. Section 6.1.3, Section 6.1.4, Section 6.1.5, and Section 7.1.3). Incorporated the component of Signs and Symptoms of Systemic Disease (sJIA

Document	Version Date	Summary of Change
		ONLY) for the JIA ACR inactive disease status determination into study procedures (see Schedule of Activities, Sections 6.1.1. Section 6.1.3, Section 6.1.4, and Section 6.1.5). Modified PK time point from 1 h to 2 h for better sampling separation from 0.5 h (see Schedule of Activities, Section 6.1.4.1, Section 6.1.4.2, Section 6.1.5, and Section 7.4.1). Added wording for PK sampling at Early Termination for clarity (see Schedule of Activities and Section 7.4.1). Modified Years 6-10 assessment frequency for Childhood Health Assessment Questionnaire CHAQ, Physician Global Evaluation of Disease Activity, Joint Assessment of Active Arthritis and Limitation of Motion, and CRP for consistency across all visits (see Schedule of Activities, Section 6.1.4.3 and Section 7.1.5). Changed Childhood Health Assessment Questionnaire (CHAQ) Overall Wellbeing and Arthritis Pain Visual Analog Scale (VAS) from 100 mm VAS line to 21- numbered circle VAS for consistency with Index Study A3921104 (see Section 7.1.4, Section 7.1.4.2, and Section 7.1.4.3). Added Childhood Health Assessment Questionnaire (CHAQ) completion instruction on completers for clarity (see Section 7.1.4). Deleted the image for Childhood Health Assessment Questionnaire in former Appendix 9 to avoid the duplicates with Section 7.1.4.

Document	Version Date	Summary of Change
		Included 21- numbered circle VAS in Physician Global Evaluation of Disease Activity Instruction for consistency with Index Study A3921104 (see Section 7.1.2). Added JIA ACR Flare definition for consistency with Index Study A3921104 (see Section 7.1.6.2). Added JIA ACR Clinical Remission on Medication definition for consistency with Index Study A3921104 (see Study Objectives and Endpoints, Section 2.2, and Section 7.1.7). Added Language on Fasting Requirement for Lipid Panel for consistency with Index Study A3921104 (see Section 6.1.1.2, Section 6.1.4.1, Section 6.1.4.2, Section 6.1.4.4, Section 6.1.5, and Section 7.2.8). Deleted Lipid Panel at Screening/ Baseline Visit for subjects who enroll on the same day or within 14 days of the EOS Visit from Index Studies to avoid the repeated measurement in the EOS Visit of Index Studies (see Section 6.1.2 and Section 6.1.3). Modified Years 2-5 Lipid Panel Time Points for consistency with year 1 lipid panel time points (see Schedule of Activities and Section 6.1.4.2). Removed Tanner Stage Assessment at Screening/Baseline Visit for subjects who enroll within 14 days of the EOS Visit from Index Studies to avoid the repeated measurement in the EOS Visit of Index Studies (see Schedule of Activities and Section 6.1.2 and Section 6.1.3).

Document	Version Date	Summary of Change
		Added Uveitis Exam window after screening as ± 30 days relative to the visits and qualified equivalent for Uveitis Exam per local practice, and changed Uveitis Exam frequency for the first year from every 6 months to annually (see Schedule of Activities, Section 6.1.1.1, Section 6.1.4.1, Section 6.1.4.2, Section 6.1.4.4, and Section 6.1.5), and added SUN Criteria for Uveitis Exam (see Section 7.2.5 and Section 16) for clarity. Clarified that at visits when a Uveitis Exam is not planned, subjects should be assessed for any changes in uveitis status and, for JIA subtypes that may require frequent uveitis examination, local standard of care should be followed (see Schedule of Activities and Section 7.2.5). Modified visit window for Month 1 and Month 3 visits from ±2 days to ±5 days and visit window for Month 6, Month 9, and Month 12 visits from ±7 days to ±10 days to enable flexibility in scheduling based on Investigator's feedback (see Schedule of Activities and Section 6.1.4). Added instruction on the morning dose for PK sample collection for clarity (see Schedule of Activities, Section 6.1.4.1, Section 6.1.4.2, Section 6.1.5 and Section 7.4.1). Changed the wording of the Baseline Visit Window from "within a month" to "within 28 days" in Study Design for consistency with the Study Procedures (see Study Design and Section 3). Defined a Month (1 Month = 30 Days) for the guidance of scheduling on study

Document	Version Date	Summary of Change
		visits after the baseline visit (see Study Design and Section 3). Clarified Childhood Health Assessment Questionnaire (CHAQ) Secondary Endpoint by putting the 3 CHAQ subsections as the sub-bullet points under CHAQ and added specifications for the 3 CHAQ subsections for accuracy and clarification (see Study Objectives and Endpoints and Section 2.2.2). Clarified JIA ACR 30, 50, 70, 90, 100 Response Criteria (see Section 7.1.6.1). Added "Hepatomegaly" Component for Active Systemic Features of Systemic JIA in Inactive Disease Status Determination for consistency with Index Study A3921104 (see Section 7.1.7). Removed German Investigator Sites which are no longer participating in study for Investigator ACR30 Response Assessment (see Schedule of Activities, Section 3, Section 6.1.4.1, Section 6.1.4.2, Section 6.1.4.3, Section 6.1.4.4, Section 6.2, and Section 7.1.6.1). Clarified the starting point for AE/SAE reporting in Schedule of Activities (see Schedule of Activities). Clarified malignancy safety reporting and malignancy discontinuation criteria for consistency with tofacitinib adult long-term studies (see Appendix 7). Changed estimated glomerular filtration rate (GFR) calculation from "modified Schwartz formula or Cockgroft-Gault equation depending on age" to "Bedside Schwartz formula" based on

Document	Version Date	Summary of Change
		investigator's feedback (see Exclusion Criterion 2 and Appendix 4). Clarified the negative purified protein derivative (PPD) test as the one with a result of <5 mm induration for consistency with RA adult studies (see Inclusion Criterion 12a and Section 7.2.3). Clarified access/compassionate use program after the conclusion of this study (see Study Design and Section 3). Updated parent to parent/legal guardian and patient to subject throughout for consistency. Replaced CP-690,550 with tofacitinib throughout for consistency with index studies. • Made other administrative edits to improve readability and consistency.
Protocol Amendment 5	17 August 2015	• Revisions to protocol in response to Canadian Regulatory Authority request (see Protocol Summary; Schedule of Activities; Sections 3, 6.1.4.1, 6.1.4.2, 6.1.4.3, 6.1.4.4, 6.2, 7.1.6). These changes are applicable to Canadian sites only.
Protocol Amendment 4	03 April 2015	Included dosing scheme for subjects completing index study A3921104 in order to permit continuation of dosing received in study A3921104 (Section 5.2). Updated Safety Endpoint Adjudication Committee related language to include currently established committees, and to update description of committee roles (Section 9.7).

Document	Version Date	Summary of Change
		Updated introductory section to clarify CP-690, 550 mechanism of action, and to include dosing rationale. Exclusion criteria #3: Changed estimated glomerular filtration rate calculation to use the modified Schwartz formula for subject ≤12 yrs of age and Cockcroft-Gault formula for subjects >12 yrs age. Other minor administration changes.
Protocol Amendment 3	27 August 2014	• Revision of dosing scheme (see Section 5). • Revisions to protocol in response to German Regulatory Authority request (see Protocol Summary; Schedule of Activities; Sections 3, 4.1, 6.1.4.1, 6.1.4.2, 6.1.4.3, 6.1.4.4, 6.2, 7.1.6). • Update to standard protocol template text in accordance with latest Standard Operating Procedures/current protocol template (see Sections 4.2, 4.3.1, 5.2.3, 5.3, 6.2, 7.3, 8.4, 8.7.2, 8.8, 8.11, 8.12, 8.13, 8.14, 8.15.1, 12.3, 15.1).
Protocol Amendment 2	22 August 2013	Lab testing updated: Screening/Baseline Hepatitis B testing updated and baseline lipid panel added (Schedule of Activities, and Section 6 and 7.2.7). Assessment of Pubertal Development description added; Tanner stage self-assessment offered as option in case of refusal (Section 7.2.6). JAMAR changed to CHAQ (Protocol Summary, Schedule of Activities, and Section 2.2.2, 6, 7.1.5 and Appendix 9). Wording on Endpoint Adjudication Committee updated (Section 9.7).

Document	Version Date	Summary of Change
		CT-02 required protocol language updates; Section 4.4, 8.2, 8.7.1, 15.1.
Protocol Amendment 1	18 September 2012	Duration of the study clarified. Protocol Summary and Study Design. PK sampling times corrected. Schedule of Activities and Section 7.4.1. Exclusion criteria for lymphocyte levels added. Section 4.2. New text on medication errors added. Section 5.2.3. Use of topical prohibited medications clarified. Section 5.4 and Appendix 5. Visit windows added. Section 6.1.4 and Schedule of Activities. Month 66 Visit added. Schedule of Activities and Section 6.1.4.4. Vital signs and targeted physical examination added to Months 66, 78, 90, 102, and 104 Visits. Schedule of Activities and Section 6.1.4.4. New text on AE reporting added. Sections 8.1, 8.2, 8.3, 8.5.2, 8.7, 8.7.1, 8.10. New text on assessment of drug induced liver injury added. Section 8.7.1. New text on safety endpoint adjudication added. Section 9.7. Typos and administrative inconsistencies corrected.
Original protocol	16 November 2011	N/A

Document Approval Record

Document Name:	JAK JIA A3921145 Amendment 12_clean_06May2022
Document Title:	JAK JIA A3921145 Amendment 12_clean_06May2022

Signed By:	Date(GMT)	Signing Capacity
PPD	18-May-2022 12:25:30	Final Approval
PPD	18-May-2022 13:36:46	Final Approval