EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF TOFACITINIB FOR TREATMENT OF SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (sJIA) WITH ACTIVE SYSTEMIC FEATURES IN CHILDREN AND ADOLESCENT SUBJECTS

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Compound Name:	Tofacitinib
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Amendment 8	01 September 2023
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This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), and any protocol administration change letters(s).

Protocol Amendment Summary of Changes Table

Amendment 8 (01 September 2023)

Overall rationale for the amendment: This global amendment incorporates measures to further facilitate the interpretation of trial results. This includes a modification to the statistical analysis. Additionally, editorial and typographic changes have been made to clarify the wording without changing the intent.

Section # and Name	Description of Change	Brief Rationale
SUBSTANTIAL CHANGES		
Protocol Summary Statistical analysis	Deleted text relating to number of flares required for analysis.	Deleted as there will be potentially 2 planned analyses at least 20 flares and approximately 40 flares.
Protocol Summary Statistical analysis 10. Data Analysis/ Statistical Methods Power Analysis	The statistical design of the study is modified to allow for 2 planned analyses. The first analysis will be performed after at least 20 subjects have reported flare in the double-blind phase (approximately 50% of the total flares expected). The purpose of this analysis is to allow early stopping of the study for efficacy or futility, and to assess safety of tofacitinib. The final analysis will be performed after	Describe the current planned analyses.

Section # and Name	Description of Change	Brief Rationale
	flares have been reported in approximately 40 subjects.	
NON-SUBSTANTIAL CHANGES		
Protocol Summary Study Design 3. Study Design 3.1. Overview Figure 2. Study Design 3. Study Design 3.3. Randomized Withdrawal Phase 6.7. Double Blind Withdrawal Phase	Removed the specific number of flares in the protocol body and referenced the Data Analysis/Statistical Methods section.	The statistical analysis section describes the analysis plan how the number of flares relate to the end of the study.
Protocol Summary Study Design	Clarified that subjects who achieve ACR clinical remission will be considered completers in the study.	Clarification
Schedule of Activities Footnote 7 4. Subject Selection 4.1. Inclusion criteria 4. Bullet #1	Allow for local QuantiFERON-TB testing to be performed.	Local laboratories now have the capability to perform this test.
3. Study Design 3.1. Overview	Clarified that the Centralized Coordinating Centers will be blinded to study drug assignment in the double-blind withdrawal phase of the study.	Clarification
10. Data Analysis/ Statistical Methods 10.1. Sample Size Determination	Subjects who discontinue in the double-blind withdrawal phase due to clinical remission are considered as completers.	Clarify the difference for analysis purposes of subjects who discontinue versus those that complete the study.

Section # and Name	Description of Change	Brief Rationale
4. Subject Selection 4.1. Inclusion criteria 4. Bullet #1	Added: A negative QuantiFERON®-TB test performed locally or	Allow local lab to conduct a QuantiFERON®-TB test .
6.7. Double Blind Withdrawal Phase	Deleted referenced to 31 flares and added: until the requisite number of flares have been reported (refer to Section 10) and the study is considered completed.	To align with the revised statistical plan.
10. Data Analysis/ Statistical Methods 10.1. Sample Size Determination	Revised last paragraph: Subjects who discontinue Investigational Product in the double-blind phase of the study due to any reason will be counted as having an sJIA flare in the primary analysis for the primary endpoint of the study and will contribute to the requisite number of subjects with flare for the study to be considered complete. Subjects who achieve clinical remission during the double blind withdrawal phase are completers of the study and will not be counted as having an sJIA flare in the primary analysis.	Clarifying text to identify subjects who discontinue in the double-blind withdrawal phase due to clinical remission as completers.

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PROTOCOL SUMMARY

Background and Rationale

The safety and effectiveness of tofacitinib for the treatment of rheumatoid arthritis (RA) has been demonstrated in adult subjects. The Sponsor is conducting a pediatric investigational 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).

As part of this pediatric investigational program, study A3921165 will evaluate efficacy, safety, tolerability and pharmacokinetics of tofacitinib as treatment for systemic (s)JIA. In this study, after 12 to 40 weeks of treatment with open-label tofacitinib, sJIA patients who are able to taper corticosteroids (CS) while maintaining an Adapted JIA ACR 30 response will be identified as “responders”. These responders will proceed to a double-blind withdrawal phase in which they will be randomized to either continue with tofacitinib treatment or start placebo treatment. Sustained efficacy of tofacitinib to prevent disease flare will be evaluated in the randomized withdrawal phase.

Study Objectives

Primary:

- To assess the sustained efficacy of tofacitinib versus placebo in sJIA patients, as measured by time to sJIA flare in the double-blind randomized withdrawal phase.

Secondary:

- To assess efficacy of tofacitinib versus placebo in sJIA patients at various time points in the double-blind randomized withdrawal phase, as measured by:

a. Percentage of subjects with sJIA disease flares;

b. Percentage of subjects with Adapted JIA ACR 30/50/70/90/100 responses;

c. Changes from baseline in Juvenile Arthritis Disease Activity Score (JADAS-27);

d. Percentage of subjects achieving inactive disease and clinical remission (JIA ACR);

e. Percentage of subjects with inactive disease and minimal disease activity (JADAS-27);

f. Other evaluations specified under "Efficacy endpoints" for the double-blind phase.

- To assess the efficacy of tofacitinib in sJIA patients in the open-label treatment phase, as measured by:

  a. Percentage of subjects with successful corticosteroids tapering per protocol at the end of the open-label phase in subjects with sJIA receiving corticosteroids at start of open-label phase;

  b. Percentage of subjects with Adapted JIA ACR 30/50/70/90/100 responses at every visit from Day 7 onward;

  c. Other evaluations specified under "Efficacy endpoints" for the open-label phase.

- To assess the safety and tolerability of tofacitinib in sJIA patients.

- To assess the pharmacokinetics of tofacitinib in sJIA patients in the open-label phase.

Exploratory Objective

- To evaluate exploratory biomarker and genomic samples to characterize the effect of tofacitinib.

Study Endpoints

Primary Efficacy Endpoint:

- Time to sJIA disease flare in the double-blind randomized withdrawal phase.

Secondary Efficacy Endpoints:

- Occurrence of disease flares in the double-blind phase at each visit.

- Achievement of corticosteroid tapering per protocol at the end of the open-label active treatment period in applicable subjects receiving corticosteroids on study Day 1 of the open-label phase.

- Achievement of a corticosteroid dose of ≤0.2 mg/kg/day or 10 mg/day (whichever is lower) at the end of the open-label treatment period in subjects receiving corticosteroids on Day 1 of the open-label phase.

- Adapted JIA ACR 30/50/70/90/100 response at every visit from Day 7 onward in the open-label and the double-blind phase.

- Fever (Temp >38 Degrees Celsius/100.4° F) attributed to sJIA at Day 3, Day 7 and Day 14 of the open-label phase.

- CRP ≤10 mg/L at every visit of the open-label phase.

- "Absence of fever", defined as absence of fever due to sJIA in the week preceding the assessment at every visit from Day 7 onward in the open-label and double-blind phase.

- Time to first Adapted JIA ACR 30 response in Part 1 of the open-label phase.

- Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS 27) at every visit from Day 7 onward in the open-label and double-blind phase.

- Change from baseline in each JIA ACR core variable at every visit from Day 7 onward in the open-label and double-blind phase.

- Change from baseline in Child Health Questionnaire (CHQ) responses at the end of Part 1 and Part 2 of the open-label phase, at randomization and every 6 months thereafter.

- Change from baseline in Child Health Assessment Questionnaire (CHAQ) at every visit from Day 7 onward in the open-label and double-blind phase.

- Occurrence of inactive disease status and minimal disease activity at every visit from Day 7 onward (JADAS-27) in the open-label and double-blind phase.

- Occurrence of inactive disease status at every visit from Day 7 onward (JIA ACR) in the open-label phase.

- Occurrence of inactive disease status at every visit and clinical remission at every visit starting at Week 24 in the double-blind phase.

Exploratory Endpoints:

- Change from baseline in various genomic and serum biomarkers following treatment with tofacitinib.

Safety Endpoints:

- All adverse events (AEs), including Serious Adverse Events (SAEs).

- Macrophage activation syndrome (MAS) events.
- Serious infections, including tuberculosis, varicella and herpes zoster and opportunistic infections.
- Clinically significant abnormal laboratory parameters, including abnormal hematology parameters, lipid parameter changes, liver enzymes, serum creatinine elevation.
- Malignancies, including lymphoma and non-melanoma skin cancer.
- Gastrointestinal perforations.
- Cardiovascular diseases.
- Assessments of growth and pubertal development.

Pharmacokinetic Endpoints:

- Tofacitinib concentrations during the open-label phase.

Study Design

This is a 2-phase randomized withdrawal study to evaluate efficacy, safety and tolerability, and pharmacokinetics of tofacitinib as a treatment for sJIA. The study will enroll approximately 100 subjects from 2 to <18 years of age with sJIA with active systemic features.

Subjects will be enrolled into an open-label phase during which they will receive tofacitinib 5 mg twice daily (BID) oral tablets, or an equivalent weight-based lower dose of tofacitinib oral solution (1 mg/mL) BID for subjects <40 kg. The 5 mg BID dose level of tofacitinib will be evaluated in a staggered fashion (cohorts of 7 subjects followed by safety review), as described under "Dose Selection" in Section 3.4.

The open-label phase will be divided into two parts. In Part 1, all subjects must achieve and maintain a minimum level of clinical response for at least 4 weeks. In Part 2 of the open-label phase, subjects treated with background CSs >0.2 mg/kg/day oral prednisone (or equivalent) must taper their CS dose to a target range. Subjects who successfully taper their CS dose while maintaining the defined clinical response, will be eligible for the double-blind withdrawal phase of the study. The minimum total duration of treatment with a stable dose of tofacitinib for subjects completing Parts 1 and 2 must be 12 weeks to qualify to enter the randomized withdrawal phase of the study.

In the double-blind withdrawal phase, "responders" from the open-label phase will be randomized in a 1:1 ratio to either continue tofacitinib or start placebo. The primary endpoint of the study is time to sJIA flare in the double-blind phase.

Subjects who flare or achieve ACR clinical remission (ie, maintain JIA ACR inactive disease during 24 consecutive weeks) will be given the opportunity to participate in A3921145 and be treated with open-label tofacitinib.

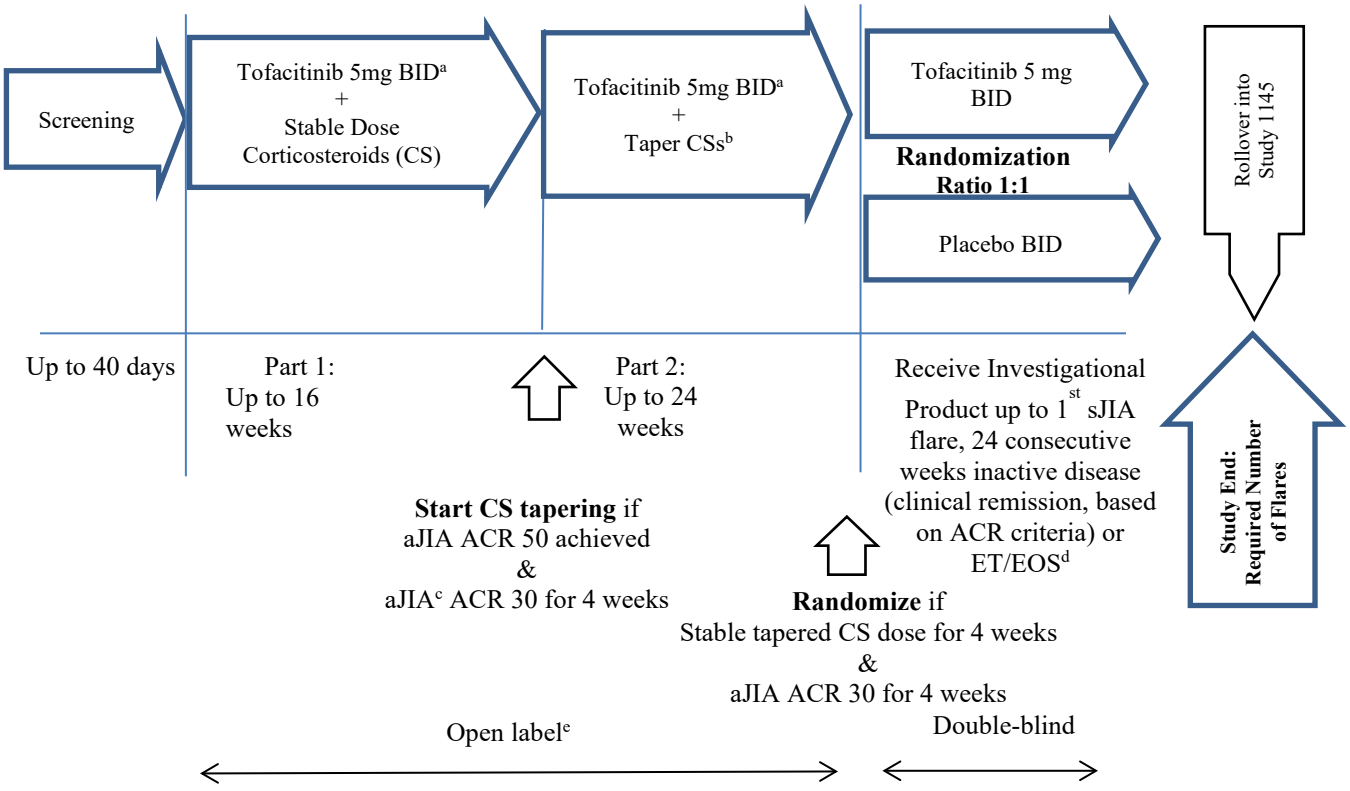
Subjects who discontinue Investigational Product in the double-blind phase and who do not enter A3921145 will continue in A3921165 for follow up of efficacy and safety endpoints. Subjects will be required to perform all scheduled visits until Week 52 after randomization or until the study concludes, whichever comes first. Subjects should receive standard-of-care treatment in accordance with local treatment guidelines.

All subjects participating in this study, including those discontinued, will have the option, if eligible, of enrolling in the tofacitinib long-term extension study (A3921145). The Sponsor's intent is to make tofacitinib available to pediatric subjects through Study A3921145.

Subjects who discontinue the study in the Open-Label Phase and do not enter A3921145, will be required to perform a follow-up visit 28 days after the last dose of study treatment.

A schematic of the study design is shown in Figure 1.

Figure 1. Study Design



a Subjects <40 kg will receive an equivalent weight-based lower dose of tofacitinib 5 mg BID.

b CS Tapering is only required for subjects treated with CS >0.2 mg/kg/day oral prednisone (or equivalent). During the active CS tapering period in Part 2 subjects must maintain an Adapted JIA ACR 50 response.

c aJIA: Adapted JIA.

d Subjects who discontinue Investigational Product in the randomized withdrawal phase continue in study until week 52 after randomization or until the study concludes, whichever comes first.

e Subjects who discontinue the study in the open-label phase and do not enter A3921145 within 4 weeks, will be required to perform a follow-up visit 28 days after the last dose of Investigational Product.

Statistical Analysis

Approximately 100 subjects will be enrolled in the open-label run-in phase of the study. Of these subjects, at least 12 subjects are targeted to be enrolled in each of the following age groups: from 12 to <18 years, from 6 <12 years and from 2 to <6 years. It is estimated that approximately 55 percent of subjects will enter the randomized withdrawal period of the study.

At the start of the double-blind phase, qualifying subjects receiving tofacitinib 5 mg BID in the active treatment phase will be randomized into a 5 mg BID tofacitinib sequence (continuation of the same tofacitinib treatment) or the placebo sequence (withdrawal of the tofacitinib treatment) with a 1:1 allocation ratio, stratified by age group.

There will be potentially 2 planned analyses. The First Analysis will be performed after at least 20 subjects have reported flare in the double-blind phase (approximately 50% of the total flares expected). The purpose of the First Analysis is to allow early stopping of the study for efficacy or futility, and to assess safety of tofacitinib. Depending on the number of flares in the first analysis, up to 40 subjects with flares may be required for the Final Analysis to yield an overall power of 80% using a log-rank test to detect the treatment difference. The investigators, subjects and sponsor study team will remain blinded to treatment assignment in the double-blind phase through the entire duration of the trial until final database release.

For the primary endpoint of time to flare in the double-blind phase, superiority of tofacitinib to placebo will be assessed using Kaplan-Meier methods. The median time to flare and corresponding 2-sided 95% confidence interval (CI) will be provided. Difference in time to flare between the two treatment groups (tofacitinib 5 mg BID vs. placebo) will be assessed using an unstratified log-rank test.

To protect the integrity of the study and to preserve the type I error rate at 0.025 (1-sided test) and overall study power at 80% (type II error rate β=0.2), a fraction of α for efficacy and a fraction of β for futility will be spent at the First Analysis and accounted for in the overall type I error rate and type II error rate, respectively. A formal efficacy boundary for rejecting the null hypothesis is constructed by using the spending function methodology of the gamma family design with γ= 4. Similarly, a formal futility boundary for not rejecting the null hypothesis is constructed by using the spending function methodology of the gamma family design with γ= -4.

- If the value of the test-statistic at the First Analysis crosses the efficacy boundary ($z \leq -2.014$, 1-sided $p \leq 0.022$), the trial may be stopped for efficacy.

- If the value of the test-statistic at the First Analysis crosses the futility boundary ($z \geq -0.286$, 1-sided $p \geq 0.387$), the trial may be stopped for futility.

- Otherwise, the trial will continue as planned. The Final Analysis will be performed after flares have been reported in approximately 40 subjects.

Secondary binary endpoints such as: occurrence of disease flare or inactive disease, achieving a response of Adapted JIA 30/50/70/90/100, absence of fever, etc., will be analyzed using statistical methods for binary variables; eg, normal approximation to binomial proportions. For the continuous endpoints, a linear mixed-model will be applied. Treatment differences along with the associated 2-sided 95% CIs, will also be calculated. In the double-blind analyses, descriptive/summary statistics by treatment group for the effect on the primary and secondary endpoints will be provided at each time point.

Secondary endpoints in the open-label run-in phase will be summarized descriptively by visit.

At the beginning of the double-blind randomized withdrawal phase, subjects from the open-label run-in phase will be randomized into 2 sequences: 5 mg BID tofacitinib (or placebo (withdrawal of tofacitinib). In the primary and most secondary analyses, the two treatment groups (tofacitinib or placebo) will be compared in order to better assess the treatment effect. Some descriptive analyses will be performed.

Safety analysis will be performed on all subjects who received at least one dose of study drug. Safety data will be subject to clinical review and summarized by appropriate descriptive statistics.

Details of the statistical analysis are found in Section 10 and will be further described in a Statistical Analysis Plan (SAP).

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Country-specific amendment for Germany: The degree of burden and the risk threshold should be assessed at each scheduled visit as outlined in Appendix 9.

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 any visits impacted by public emergencies, including the COVID-19 pandemic, refer to Appendix 10 for additional guidance and instructions.

		Open-Label Treatment Phase						**Randomized Withdrawal Phase**		**EOS Or ET**	**Follow-Up**
		Part 1 (Up to 16 Weeks)					**Part 2 (Up to 24 Weeks)**	**Treat to EOS[2] or Flare Once required number of flares are reported the study will conclude**			**Follow-Up if not entered in A3921145** ***For subjects discontinued in Open-Label Treatment Phase and for Subjects completing Randomized Withdrawal Phase***
Protocol Activity	**Screening**	**Day 1[1]**	**Day 3**	**Day 7**	**Day 14**	**Week 4, 8, 12, 16**	**Week 4, 8, 12 16, 20, 24**	**Randomization Visit**	**Every 4 Weeks[25]**		**Follow-Up 4 wks posttreatment discontinuation[3]**
Visit		1	2.1	2.2	2.3	2.4 to 2.7	3.1 to 3.6	4.1	4.2 to 4.X	5	6.1
Time Windows	Day – 40 to Day -1	Day 1	±1 day	±1 day	±1 day	±3 days	±3 days	±5 days	±5 days	±5 days	±7 days
Informed Consent/Assent	X									X[26]	
Medical History, Family History	X										
Uveitis Status[4]	X			X	X	X	X	X	X	X	X
Tanner Stages	X									X	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination[23]	X									X	

		Open-Label Treatment Phase						Randomized Withdrawal Phase		EOS Or ET	Follow-Up
		Part 1 (Up to 16 Weeks)					Part 2 (Up to 24 Weeks)	Treat to EOS[2] or Flare Once required number of flares are reported the study will conclude			Follow-Up if not entered in A3921145 *For subjects discontinued in Open-Label Treatment Phase and for Subjects completing Randomized Withdrawal Phase*
Protocol Activity	**Screening**	**Day 1[1]**	**Day 3**	**Day 7**	**Day 14**	**Week 4, 8, 12, 16**	**Week 4, 8, 12 16, 20, 24**	**Randomization Visit**	**Every 4 Weeks[25]**		**Follow-Up 4 wks posttreatment discontinuation[3]**
Targeted Physical Examination[5]		X	X	X	X	X	X	X	X		X
Vital Signs, Height, Weight[6]	X	X	X	X	X	X	X	X	X	X	X
QuantiFERON®-TB Gold or Gold Plus In-Tube Test[7]	X										
Chest X-ray to confirm TB status (per local SOC)	X										
Oral temperature and fever assessment	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion review		X									
"Absence of fever" Assessment				X	X	X	X	X	X	X	X
Number of Joints With Active Arthritis	X	X	X	X	X	X	X	X	X	X	X
Number of Joints With Limitation of Motion	X	X	X	X	X	X	X	X	X	X	X
Duration of Morning Stiffness	X	X	X	X	X	X	X	X	X	X	X
Assess extra-articular sJIA manifestations	X	X	X	X	X	X	X	X	X	X	X
Physician's Global Evaluation of Overall Disease Activity	X	X	X	X	X	X	X	X	X	X	X
Childhood Health Assessment Questionnaire (CHAQ)	X	X	X	X	X	X	X	X	X	X	X
Child Health Questionnaire (CHQ)[8]	X	X				X	X	X	X	X	X
CS tapering[9]							X				
Adapted JIA ACR Baseline		X									
Adapted JIA ACR 30 response				X	X	X	X	X	X	X	X
sJIA flare assessment								X	X	X	X
C-Reactive Protein	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte Sedimentation Rate (ESR) Westergren Method [10]	X	X	X	X	X	X	X	X	X	X	X
Rheumatoid Factor	X										
Ferritin[11]	X	X	X	X	X	X	X	X	X	X	X

		Open-Label Treatment Phase						Randomized Withdrawal Phase		EOS Or ET	Follow-Up
		Part 1 (Up to 16 Weeks)					Part 2 (Up to 24 Weeks)	Treat to EOS[2] or Flare Once required number of flares are reported the study will conclude			Follow-Up if not entered in A3921145 *For subjects discontinued in Open-Label Treatment Phase and for Subjects completing Randomized Withdrawal Phase*
Protocol Activity	**Screening**	**Day 1[1]**	**Day 3**	**Day 7**	**Day 14**	**Week 4, 8, 12, 16**	**Week 4, 8, 12 16, 20, 24**	**Randomization Visit**	**Every 4 Weeks[25]**		**Follow-Up 4 wks posttreatment discontinuation[3]**
Fibrinogen[11]	X	X	X	X	X	X	X	X	X	X	X
Hematology[12], Chemistry [13], Urinalysis[14]	X	X				X	X	X	X	X	X
Lipid Panel[15]		X				X	X	X	X	X	X
Blood (serum) or Urine Pregnancy Test[16]	X	X	X	X	X	X	X	X	X	X	X
Contraceptive Check[16]	X	X	X	X	X	X	X	X	X	X	X
Screening HIV-1, HIV-2, HBsAg, HbsAb, HBcAb, HCV Ab, HCV RNA	X										
VZV-ELISA[17]	X										
Only if MAS is suspected: laboratory testing (ferritin, fibrinogen, platelets, triglycerides)[18]	X	X	X	X	X	X	X	X	X	X	X
Tofacitinib PK Sampling[19]		X				X	X[19]				
Banked biospecimen collection[20]		X				X (Week 8)		X		X	
Confirmation eligibility for Double-Blind Phase								X			
Randomization to Double-Blind Phase								X			
Investigational Product Dispensing[21]		X			X	X	X	X	X		
Investigation Product Compliance			X	X	X	X	X	X	X	X	
Adverse Event Assessment[22]	X	X	X	X	X	X	X	X	X	X	X
Risk factor check for venous thromboembolism[24]	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Dosing		< ----------Active Tofacitinib ---------- >						<- Tofacitinib/Placebo ->			
Review Entry Criteria for A3921145										X	

1. Day 1 visit (ie, the first day of treatment with investigational product) must occur within 40 days of the first screening visit activity. If more than 40 days has elapsed, the subject should be screen-failed and may be re-screened, if eligible. Sponsor approval must be obtained prior to re-screening a subject.

2. Early termination (ET) procedures should be completed if a subject does not complete to the end of study. If a subject discontinues at a regularly scheduled visit, this may be considered the ET visit and all required procedures and visit-specific CRFs should be completed; please use an unplanned Tanner Stage assessment CRF if this occurs.
3. This visit will only be conducted if the subject did not rollover into study A3921145 within 4 weeks.
4. At the screening visit, a formal uveitis assessment will not be required, but documentation of previous uveitis assessment by an ophthalmologist (or qualified equivalent per local practice) should be reviewed to document absence/presence of uveitis. At every visit from Day 7 onward a confirmation of the subject's uveitis status will be required as part of the JIA ACR inactive disease evaluation.
5. Targeted physical exam consists of examination of heart, lungs, skin, extremities for peripheral edema, abdomen and lymph nodes.
6. Vital signs include blood pressure, pulse rate, and temperature (fever) assessment. Weight is evaluated at every visit; height is evaluation on a monthly basis. Subjects will be provided with a thermometer to measure their oral temperature. Each subject will receive a diary at Day 1 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. Refer to Section 8.1.2 for further details.
7. A negative QuantiFERON-TB test performed locally or a PPD or T-Spot 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 QuantiFERON®-TB Gold or Gold Plus In-Tube test or cannot determine the results to be positive or negative and the Sponsor approves it on a case-by-case basis. In addition to protocol required TB testing, sites should follow their local standards for TB status determination, which may include chest X-ray. See Section 8.2.8 for additional details. **In countries where TB incidence has been reported at a rate of >50 cases per 100,000 persons**, eg, China, India, Russian Federation; South Africa and Ukraine (World Health Organization): TB testing (QFT-TB Gold or Gold Plus) is required at screening visit and then on a yearly basis.
8. At baseline (Day 1), the end of Part 1 and Part 2 of the open-label phase, randomization and every 6 months thereafter the parent/legal guardian or an adult caregiver interacting daily with the subject will be asked to complete a Child Health Questionnaire (CHQ).
9. In Part 2 of the study CS tapering will be required in all subjects who receive CS doses >0.2 mg/kg/day of oral prednisone or equivalent in Part 1. Refer to Section 3.2 for further details.
10. The Erythrocyte Sedimentation Rate (ESR) will be determined locally utilizing an ESR Testing Kit provided to the investigator site by the Sponsor. Please refer to the ESR Testing Kit Manual for detailed instruction on how to perform this test appropriately. The ESR result will be recorded on the appropriate CRF. The ESR result also will be faxed to the Centralized Coordinating Center. A local lab ESR testing kit (Westergren method) can be substituted for a Sponsor kit only if supply issues have resulted in a Sponsor kit not being available at the time of the visit.
11. At every visit, if MAS is suspected in a febrile patient, an extra blood sample will be drawn to evaluate ferritin and fibrinogen.
12. Hematology includes: Hemoglobin, hematocrit, red blood cells, white blood cells, neutrophils (%, absolute), lymphocytes (%, absolute), monocytes (%, absolute), eosinophils (%, absolute), basophils (%, absolute), and platelets. Refer to Section 8.2.12 for details on sample collection.

13. Chemistry includes: Sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, glucose, calcium, total protein, total bilirubin (TB), direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), albumin, creatine phosphokinase kinase (CPK). Refer to Section 8.2.12 for details on sample collection.
14. Urinalysis includes specific gravity, pH, protein, glucose, ketones, blood and leukocyte esterase, urine microscopy (only if dipstick positive for blood or protein, or if clinically indicated).
15. Lipid profile testing will be required every 3 months after Day 1: includes total cholesterol, low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides, apolipoprotein A1, apolipoprotein B. Subjects should be instructed to fast for approximately 9 to 12 hours, if possible, prior to lipid panel testing.
16. Blood (serum) or urine pregnancy testing is required only for females who are of childbearing potential (see Section 4.4.1). Pregnancy testing will be performed locally. Pregnancy testing may be repeated more frequently if required by local practices, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected. A positive urine pregnancy test will be confirmed by a blood (serum) pregnancy test performed either locally or by the central laboratory. A contraceptive check also will be performed to confirm that contraception, if assigned, is being used consistently and correctly. Childbearing status also will be checked and contraception implemented in subjects who mature physically and behaviorally during the conduct of the study. See Section 8.2.9 for details regarding viral testing and interpretation of results.
17. Serologic testing for antibodies to varicella zoster virus (VZV) via ELISA is required for all subjects who do not have documented evidence from a health professional of having received 2 doses of varicella vaccine. If a subject does not have evidence of receipt of 2 doses of varicella vaccine, then a VZV ELISA test at screening is required
18. MAS laboratory testing: if MAS is suspected in a febrile subject, extra blood samples of for evaluation of ferritin and fibrinogen will need to be drawn. In case no hematology or lipid evaluation is done at the visit, platelets and triglycerides will also need to be assessed to confirm a MAS diagnosis. See Section 8.2.3 for details.
19. Blood samples for PK evaluation will be obtained 15 minutes (5-30 min) and 45 minutes (35-55 min) and 4 hours (3-6h) after tofacitinib administration on Day 1. An additional PK blood sample will be obtained 1.5 hours (1.25-2h) post tofacitinib administration if the subject is part of the first 14 subjects enrolled in Cohorts 1 and 2. After 8 weeks of open-label treatment with tofacitinib, PK blood samples will be obtained pre-dose and 1 hour (0.5-1.5h) and 3 hours (2-4h) after tofacitinib administration. Whenever feasible, a later time point within the last PK sample collection range is preferred. This PK sample may be obtained at Week 8 of Open-Label Part 1, or at Week 4 of Open-Label Part 2 in the case a subject started Open-Label Part 2 after 4 weeks of tofacitinib treatment in Part 1. See Section 8.4 for details regarding PK sampling. Subjects in India will not participate in PK evaluation.
20. A banked biospecimen for future exploratory assessments will be collected at baseline, Open Label Part 1 Week 8 (or at Week 4 of Open-Label Part 2 in the case a subject started Open Label Part 2 after 4 weeks of tofacitinib treatment in Part 1), at randomization, when the subject flares (at early termination or the end of study visit) and if/when the subject reaches inactive disease status. See Section 8.5 for details.
21. The first dose of study drug is to be dispensed at the study site during the Day 1 visit.
22. Serious adverse events (SAEs) are captured from the time of informed consent at Screening; adverse events (AEs) are captured following first dose of investigational product.

23. A skin examination for the presence of varicella (chickenpox) and herpes zoster should be performed and per a **country-specific amendment for EU sites (including UK sites):** a full skin cancer examination must be performed as part of the complete physical examination.
24. Per Amendment 3, all subjects will be asked at every study visit if they have any newly developed risk factors for venous thromboembolism as described in Section 8.2.13.
25. Subjects who discontinue Investigational Product in the double-blind phase and who do not enter A3921145 will continue in A3921165 for follow up of efficacy and safety endpoints. **Subjects will be required to perform all scheduled visits every 4 weeks until Week 52 after randomization or until the study concludes, whichever comes first. All visit activities should be performed with the exception of Investigational Product dispensing, dosing and compliance. Subjects should receive standard-of-care treatment in accordance with local treatment guidelines.**
26. For subjects considering entering A3921145 LTE study, an Informed Consent Document/Assent Document for A3921145 should be provided to the subject prior to the EOS visit, if possible, to allow an appropriate length of time to consider participation, .

1. INTRODUCTION

1.1. Indication

Tofacitinib was approved on 06 November 2012 in the United States at a dose of 5 mg twice daily (BID) for the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to MTX (Methotrexate). As of 03 December 2021, tofacitinib 5 mg BID is also approved for the treatment of adults with psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers. It may be used in combination with methotrexate or other non-biologic disease modifying antirheumatic drugs (DMARDs).

1.2. Background

1.2.1. Tofacitinib

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 and, to a lesser, extent Tyrosine Kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. 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.[1-3] 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 interferon (IFN)γ. At higher exposures inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling.

The safety and effectiveness of tofacitinib for the treatment of RA has been demonstrated in adult subjects. Both 5 mg BID and 10 mg BID dose regimens have been studied in adults and demonstrated efficacy. A greater number of adverse events were reported at the 10 mg BID dose level. The Sponsor is conducting a pediatric development program in subjects 2 to <18 years of age for the treatment of JIA. As part of this pediatric program, a Phase 1 PK study of tofacitinib in JIA subjects (A3921103) has been completed, and an open-label, non-comparative, long-term extension study (A3921145) is currently ongoing. In addition, a Phase 3 study of tofacitinib in polyarticular JIA subjects (A3921104) has been completed. The data from studies A3921103 and A3921104 demonstrated that tofacitinib dosed at 5 mg BID for subjects ≥40 kg, or weight based equivalent doses BID for subjects <40 kg, was efficacious and safe in subjects with polyarticular JIA, including supporting data from sJIA patients already evaluated in the A3921104/A3921145 studies.

1.2.2. Systemic JIA and the Role of Inflammatory Cytokines

Study A3921165 will be conducted in subjects from 2 to <18 years of age with active systemic Juvenile Idiopathic Arthritis (sJIA). Patients with active sJIA are a subgroup of JIA patients at higher risk for severe complications of the disease, including death, compared to other JIA subtypes.[4]

Active sJIA is characterized by quotidian, high spiking fever often associated with an evanescent, non-fixed, erythematous rash. Myalgias and abdominal pain may be intense during fever peaks. Other systemic features include hepato-splenomegaly, generalized lymphadenopathy and serositis. Laboratory examinations show a prominent inflammatory response characterized by leukocytosis (with neutrophilia), high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration, and thrombocytosis. A microcytic anemia is common. Arthritis is often symmetrical and polyarticular; it may be absent at onset and develop during disease.[5]

Recent evidence supports the concept that sJIA arises due to dysregulation of the innate immune system. Dysregulation of the innate immune system in sJIA results in increased production of inflammatory cytokines, leading to the distinctive clinical features of the disease. Cytokine profile studies have demonstrated a predominant role of the macrophage-derived cytokines IL-6, IL-1, and IL-18 in sJIA.[6]

Macrophage activation syndrome (MAS) is a potentially life-threatening complication of sJIA. MAS is characterized by continual activation and expansion of T lymphocytes and macrophages, which results in massive hyper-secretion 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, liver enzymes, lactate dehydrogenase, triglycerides, D-dimers, and soluble interleukin-2 (IL-2) receptor (also known as soluble CD25 [sCD25]), and decreased fibrinogen levels.[7]

The recognition of the importance of interleukin (IL)-1 and IL-6 in the pathogenesis of sJIA has recently led to the approvals of two treatments for this indication that target these mechanisms, canakinumab and tocilizumab, respectively. These treatments have proven to be efficacious in sJIA (Ruperto 2012, De Benedetti 2012)[14,25] and provide effective therapeutic options for these patients. A randomized withdrawal design has been selected to evaluate efficacy and safety of tofacitinib in subjects with sJIA in order to limit exposure to placebo treatment. The randomized withdrawal design is commonly used in pediatric research and it was used recently for a pivotal registrational study with canakinumab for sJIA.[14] This design will provide a higher level of scientific evidence as compared to the single arm design and minimizes the time that subjects will be exposed to placebo. The comparison of the experimental drug with placebo in an enriched population of responders (ie, randomize only the adapted JIA ACR 30 responders) increases the power (or equivalently, reduces the sample size) of the comparison.[28]

1.2.3. Study Rationale

Study A3921165 will evaluate tofacitinib treatment in subjects from 2 to <18 years of age with active sJIA in a randomized withdrawal model, thereby limiting the risk to sJIA patients associated with placebo treatment.

This Phase 3 study is intended to provide evidence of efficacy and safety of tofacitinib in subjects with sJIA when dosed to target exposures similar to 5 mg orally BID in adult subjects

with RA or weight-adjusted doses not to exceed 5 mg BID orally in pediatric subjects with polyarticular course JIA.

This study will evaluate efficacy, safety and tolerability, and pharmacokinetics of tofacitinib as treatment for sJIA. After 12 to 40 weeks of open-label treatment with tofacitinib, subjects with sJIA who are able to taper CSs to the predetermined target dose range or lower, while maintaining an Adapted JIA ACR 30 response, will be identified as "responders". These responders will proceed to a withdrawal phase in which they will be randomized to continue tofacitinib or start placebo treatment. The primary objective of the study will be to assess sustained efficacy of tofacitinib to prevent disease flare in subjects with active sJIA in the randomized withdrawal phase of the study.

1.2.4. Dose Rationale

The 5 mg BID dose of tofacitinib evaluated in A3921165 was selected based on the pharmacokinetic (PK) characteristics of tofacitinib in polyarticular JIA (pJIA) subjects from PK Study A3921103 and the exposure-response relationship of tofacitinib as previously demonstrated in the adult RA program. Based on tofacitinib PK in the RA population (body weight ranging from 40 kg-140 kg), clearance (CL) of tofacitinib is not dependent on body weight in adult subjects. Thus, the dose of tofacitinib in adolescents with body weight (BW) ≥40 kg was set to 5 mg twice daily (BID), an approved dose of tofacitinib in adult RA patients in most countries. The body weight based tofacitinib dosing scheme for subjects with sJIA weighing ≤40 kg is selected to match the predicted steady state concentrations ($C_{avg,ss}$) in pJIA patients with body weight ≥40 kg after a 5 mg BID dose. It was assumed that the PK of tofacitinib will be similar between pJIA and sJIA patients.

Systemic JIA is known to be a more severe form of childhood arthritis in which doses in excess of those used in pJIA patients are often needed to achieve efficacy in sJIA patients (eg, CSs, tocilizumab).[8]

There is evidence that sJIA is associated with dysregulation of the innate immune system leading to over-production of cytokine IL6.[6] IL6 induces body temperature increases and it plays a major role in development of systemic features in sJIA. Tofacitinib treatment, in various nonclinical and clinical studies, has shown to result in decreased level of IL-6 in the circulation.[9] Lack of fever control with tofacitinib may therefore be indicative of insufficient degree of attenuation of IL6 and this clinical feature will be utilized as an indicator to evaluate the efficacy of the 5 mg BID dose in the early cohorts of the study.

1.3. 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 Tofacitinib Investigator Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary

- To assess the sustained efficacy of tofacitinib versus placebo in sJIA patients, as measured by time to sJIA flare in the double-blind randomized withdrawal phase.

2.1.2. Secondary

- To assess efficacy of tofacitinib versus placebo in sJIA patients at various time points in the double-blind randomized withdrawal phase, as measured by:

  a. Percentage of subjects with sJIA disease flares;

  b. Percentage of subjects with Adapted JIA ACR 30/50/70/90/100 responses;

  c. Changes from baseline in Juvenile Arthritis Disease Activity Score (JADAS-27);

  d. Percentage of subjects achieving inactive disease and clinical remission (JIA ACR);

  e. Percentage of subjects with inactive disease and minimal disease activity (JADAS-27);

  f. Other evaluations specified under "Efficacy endpoints" for the double-blind phase.

- To assess the efficacy of tofacitinib in sJIA patients in the open-label treatment phase, as measured by:

  a. Percentage of subjects with successful corticosteroid tapering per protocol at the end of the open-label phase in subjects with sJIA receiving corticosteroids at start of open-label phase;

  b. Percentage of subjects with Adapted JIA ACR 30/50/70/90/100 responses at every visit from Day 7 onward;

  c. Other evaluations specified under "Efficacy endpoints" for the open-label phase.

- To assess the safety and tolerability of tofacitinib in sJIA patients.

- To assess the pharmacokinetics of tofacitinib in sJIA patients in the open-label phase.

2.1.3. Exploratory Objective

- To evaluate exploratory biomarker and genomic samples to characterize the effect of tofacitinib.

2.2. Endpoints

2.2.1. Primary

- Time to sJIA disease flare in the double-blind randomized withdrawal phase.

2.2.2. Secondary Efficacy Endpoints

Secondary:

Efficacy endpoints:

- Occurrence of disease flares in the double-blind phase at each visit.
- Achievement of corticosteroid tapering per protocol at the end of the open-label active treatment period in applicable subjects receiving corticosteroids on study Day 1 of the open-label phase.
- Achievement of a corticosteroid dose of ≤0.2 mg/kg/day or 10 mg/day (whichever is lower) at the end of the open-label treatment period in subjects receiving corticosteroids on Day 1 of the open-label phase.
- Adapted JIA ACR 30/50/70/90/100 response at every visit from Day 7 onward in the open-label and double-blind phase.
- Fever (Temp >38 Degrees Celsius/100.4° F) attributed to sJIA at Day 3, Day 7 and Day 14 of the open-label phase.
- CRP ≤10 mg/L at every visit of the open-label phase.
- "Absence of fever", defined as absence of fever due to sJIA in the week preceding the assessment at every visit from Day 7 onward in the open-label and double-blind phase.
- Time to first Adapted JIA ACR 30 response in Part 1 of the open-label phase.
- Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS 27) at every visit from Day 7 onward in the open-label and double-blind phase.
- Change from baseline in each JIA ACR core variable at every visit from Day 7 onward in the open-label and double-blind phase.
- Change from baseline in Child Health Questionnaire (CHQ) responses at the end of Part 1 and Part 2 of the open-label phase, at randomization and every 6 months thereafter.
- Change from baseline in Child Health Assessment Questionnaire (CHAQ) at every visit from Day 7 onward in the open-label and double-blind phase.

- Occurrence of inactive disease status and minimal disease activity at every visit from Day 7 onward (JADAS-27) in the open-label and double-blind phase.

- Occurrence of inactive disease status and clinical remission at every visit from Day 7 onward (JIA ACR) in the open-label and double-blind phase.

2.2.3. Exploratory

- Change from baseline in various genomic and serum biomarkers following treatment with tofacitinib.

2.2.4. Safety Endpoints

- All adverse events (AEs), including Serious Adverse Events (SAEs).

- Macrophage activation syndrome (MAS) events.

- Serious infections, including tuberculosis, varicella and herpes zoster and opportunistic infections.

- Clinically significant abnormal laboratory parameters, including abnormal hematology parameters, lipid parameter changes, liver enzymes, serum creatinine elevation.

- Malignancies, including lymphoma and non-melanoma skin cancer.

- Gastrointestinal perforations.

- Cardiovascular diseases.

- Assessments of growth and pubertal development.

2.2.5. Pharmacokinetic Endpoints

- Tofacitinib concentrations during the open-label phase.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

In prior studies of juvenile idiopathic arthritis with tofacitinib, there were no new safety signals or issues detected that were either unique to the JIA population treated with tofacitinib or new to the tofacitinib safety profile. Therefore, potential 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 7.8.3 (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

Tofacitinib was approved on 06 November 2012 in the United States at a dose of 5 mg twice daily (BID) for the treatment of adults with moderately to severely active RA who have had

an inadequate response or intolerance to MTX (methotrexate). As of 03 December 2021, tofacitinib 5 mg BID is also approved for the treatment of psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

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, and an open-label, non-comparative, long-term extension study (A3921145) is ongoing. Subjects from Study A3921104 were eligible to enter Study A3921145 to continue treatment with tofacitinib 5 mg BID IR tablets or weight equivalent dose of oral solution.

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. These results were supported by sensitivity analyses. 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 was conducted for Study A3921145, the long-term extension study for the pediatric studies, at the request of a health authority. At the time of 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 currently 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 A3921165 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

3.1. Overview

This is a 2-phase randomized withdrawal study to evaluate efficacy, safety and tolerability, and pharmacokinetics of tofacitinib as a treatment for sJIA. The study will enroll approximately 100 subjects from 2 to <18 years of age with sJIA with active systemic features, defined by either:

- Documented intermittently spiking temperature >38° C/100.4° F due to sJIA for at least 1 day in the screening period and within 1 week before the first dose, and

presence of at least 2 joints with active arthritis at screening and baseline, and ESR >30 mm/hr [1.5 X ULN] at screening;

OR

- Presence of at least 5 joints with active arthritis at screening and baseline, and ESR >30 mm/hr [1.5 X ULN] at screening.

The study will target enrollment of at least 12 subjects in the following age groups: from 12 to <18 years, from 6 <12 years, and from 2 to <6 years.

The study will conclude when the requisite number of flares are achieved during the double-blind phase of the study as described in Section 11, Data Analysis/Statistical Methods.

Subjects will be enrolled into an open-label phase during which they will receive tofacitinib 5 mg BID oral tablets, or an equivalent weight-based lower dose of tofacitinib oral solution (1 mg/mL) BID for subjects <40 kg. The 5 mg BID dose level of tofacitinib will be evaluated in a staggered fashion (cohorts of subjects followed by safety review), as described under "Dose Selection" in Section 3.4.

The open-label phase will be divided into two parts. In Part 1, all subjects must achieve and maintain a protocol defined minimum level of clinical response for at least 4 weeks. In Part 2 of the open-label phase, subjects treated with background CSs >0.2 mg/kg/day oral prednisone (or equivalent) will attempt to have their CS dose tapered to a predetermined target range, or lower; subjects who successfully taper their CS dose while maintaining the defined clinical response, will be eligible for the double-blind withdrawal phase of the study. The minimum total duration of treatment with a stable dose of tofacitinib for subjects completing Parts 1 and 2 must be 12 weeks to qualify to enter the randomized withdrawal phase of the study.

In the double-blind withdrawal phase of the study, "responders" from Part 1 and Part 2 of the open-label phase will be randomized in a 1:1 ratio to either continue tofacitinib or start placebo. The primary endpoint of the study is time to sJIA flare in the double-blind phase. The double-blind withdrawal phase will continue until a sufficient number of flares are reported as described in Section 11.

The Sponsor will use external Centralized Coordinating Centers to review and confirm applicable real-time assessments of efficacy, including the Adapted JIA ACR 30/50 response, sJIA flare, and inactive disease status (JIA-ACR). The Coordinating Centers will also monitor and offer recommendations on corticosteroid tapering of study participants. Refer to Section 8.1.12 for details on the coordinating centers. The Centralized Coordinating Centers will be blinded to study drug assignment in the double-blind withdrawal phase of the study.

All subjects participating in this study, including those who discontinued in the open-label or double-blind phase, will have the option, if eligible (based on inclusion and exclusion criteria), of enrolling in the tofacitinib JIA long-term extension study (A3921145) after completion of this study.

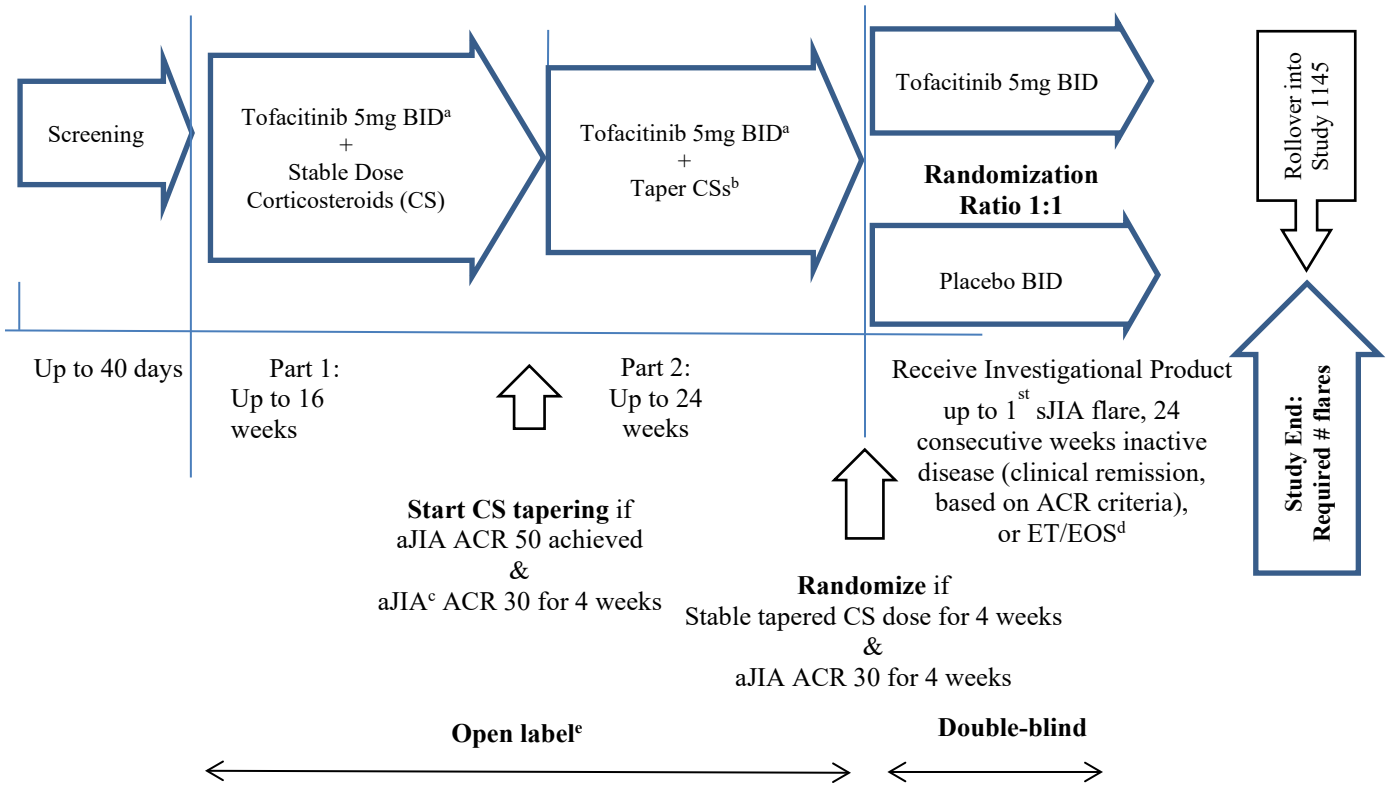
Subjects who flare in the double-blind withdrawal phase will be given the opportunity to participate in A3921145 and be treated with open-label tofacitinib. Subjects who achieve ACR clinical remission (ie, maintain JIA ACR inactive disease during 24 consecutive weeks) will complete their participation in A3921165 and be given the opportunity to enter A3921145.

Subjects who discontinue Investigational Product in the double-blind phase and who do not enter A3921145 will continue in A3921165 for follow up of efficacy and safety endpoints. Subjects will be required to perform all scheduled visits until Week 52 after randomization or until the study concludes, whichever comes first. Subjects should receive standard-of-care treatment in accordance with local treatment guidelines.

Subjects who discontinue the study in the Open-Label Phase and do not enter A3921145, will be required to perform a follow-up visit 28 days after the last dose of study treatment.

A schematic of the study design is shown below:

Figure 2. Study Design



a Subjects <40 kg will receive an equivalent weight-based lower dose of tofacitinib 5 mg BID.

b CS Tapering is only required for subjects treated with CS >0.2 mg/kg/day oral prednisone (or equivalent). During the active CS tapering period in Part 2 subjects must maintain an Adapted JIA ACR 50 response.

c aJIA: Adapted JIA.

d Subjects who discontinue Investigational Product in the randomized withdrawal phase continue in study until week 52 after randomization, or until the study concludes, which ever comes first.

e Subjects who discontinue the study in the open-label phase and do not enter A3921145 within 4 weeks, will be required to perform a follow-up visit 28 days after the last dose of Investigational Product.

3.2. Open-label Phase: Variable Duration of 12 to 40 Weeks

The open-label active treatment period will consist of two parts:

3.2.1. Open-label Phase, Part 1: Treatment with Tofacitinib while on Stable Background Therapy

Part 1 of the open-label active treatment phase is designed to identify tofacitinib-treated subjects who are able to achieve and maintain an Adapted JIA ACR 30 response for at least 4 weeks while continuing on the stable CS dose identified during the screening period prior to treatment with tofacitinib.

All subjects ≥40 kg will receive tofacitinib 5 mg BID oral tablets; however, subjects who cannot swallow oral tablets and all subjects <40 kg will receive a weight-based dose of tofacitinib oral solution (1 mg/mL) BID with a maximum dose of tofacitinib 5 mg BID. The 5 mg BID dose of tofacitinib will be evaluated in a staggered fashion (cohorts of 7 subjects followed by safety review, as described under "Dose Selection" in Section 3.4.

Clinical assessments, including laboratory testing, will be performed at Baseline (Day 1) prior to the start of tofacitinib treatment, on Day 3, Day 7, Day 14, Week 4, and thereafter on a monthly basis.

If subjects are using CS treatment at study start, doses must be stable and ≤1.0 mg/kg/day up to 30 mg/day oral prednisone (or equivalent), in the last week before the first study drug dose (Day 1) and remain stable for the full duration of the Open-label Phase Part 1. Subjects who are not taking CS or are not required to taper CS dosing (subjects taking doses of corticosteroids ≤0.2 mg/kg/day) must be able to maintain an Adapted JIA ACR 30 response for at least 4 weeks in the Open-label Phase Part 1 will be allowed to proceed to Part 2 of the Open-label Phase. CS doses >0.2 mg/kg/day must be tapered in Part 2 of the study. Before CS tapering can start in the Open-label Phase Part 2, subjects will be required to achieve an Adapted ACR 50 response in the Open-label Phase Part 1 in addition to maintaining an Adapted ACR 30 response for 4 weeks. The duration of the Open-Label Phase Part 1 for each subject is variable but will be no longer than 16 weeks.

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

- Number of joints with active arthritis;
- Number of joints with limited range of motion;

- Physician global evaluation of disease activity (21 circle VAS);
- Parent/legal guardian/Child evaluation of overall well-being (21 circle VAS);
- Functional ability (Childhood Health Assessment Questionnaire [C-HAQ]) without aids and devices;
- Erythrocyte Sedimentation Rate (ESR).*

  *Note: *For "real-time" assessment of the Adapted JIA ACR 30 Response during a study visit the subject's ESR will be used to determine the percent change in inflammation biomarker.*

Subjects who have recurrence of fever due to sJIA lasting more than 2 consecutive days, require an increase in their CS dose, fail to achieve an Adapted JIA ACR 30 response by Week 12, or maintain an Adapted JIA ACR 30 response for 4 weeks by the end of Part 1 will be discontinued from the study.

3.2.2. Open-label Phase, Part 2: Treatment with Tofacitinib while Tapering Corticosteroids

Part 2 of the open-label active treatment phase serves to taper CSs in subjects receiving CS doses >0.2 mg/kg/day to a target range as outlined in Table 1. Subjects will have study visits on a monthly basis in Part 2.

Subjects who are treated with stable oral prednisone (or equivalent) doses ≤0.2 mg/kg/day who are able to maintain an Adapted JIA ACR 30 response for 4 weeks in Part 1 are allowed to skip Part 2 and be randomized in the Double-Blind Withdrawal Phase of the study (12-week minimum tofacitinib treatment duration in the Open-Label Phase is required).

The time period of Part 2 is variable, but no longer than 24 weeks, and CS tapering will only be allowed in the first 20 weeks. A subject must be on the final tapered CS dose on or before the day after the week 20 visit in Open-label Part 2. CS tapering in the Open-label Phase Part 2 can continue as long as an Adapted JIA ACR 50 response is maintained. After CS tapering to the target range (Table 1), or lower (Table 2), a subject must remain on a stable tapered CS dose and maintain an Adapted JIA ACR 30 response (minimum) for at least 4 weeks before randomization to the double-blind withdrawal phase. Subjects taking CS doses >0.2 mg/kg/day who fail to achieve an Adapted ACR 50 response during Part 2 of the Open-label phase of the study will be discontinued from the study and will not be randomized into the double-blind phase of the study.

The minimum total duration of treatment with a stable dose of tofacitinib for subjects completing Open-label Phase Parts 1 and 2 must be 12 weeks to qualify to enter the randomized withdrawal phase of the study.

3.2.2.1. Mandatory CS Tapering before Randomization

The CS tapering criteria in Table 1 are the minimum target criteria that a subject has to meet by the end of Part 2 to be eligible for randomization; however, investigators are encouraged to

taper down to lower CS doses (Table 2), as long as an Adapted JIA ACR 50 response is maintained.

The Centralized Coordinating Centers will provide a suggested customized 4-week CS tapering schedule for each subject entering Part 2 based on protocol guidelines as per Table 1. In general, CS doses should be tapered by 0.1 mg/kg/week of oral prednisone or equivalent providing that subjects are able to maintain an Adapted JIA ACR 50 response.

Table 1. Mandatory Corticosteroid Tapering Required Before Randomization

Tapering criteria - Start dose at End Part 1		End dose after tapering by End Part 2
CS >0.8 mg/kg/day oral prednisone (or equivalent)	➡	≤0.5 mg/kg/day up to a maximum dose of 15 mg/day oral prednisone (or equivalent)
CS ≤0.8 mg/kg/day- ≥0.5 mg/kg/day oral prednisone (or equivalent)	➡	Reduction to ≤0.3 mg/kg/day up to a maximum of 12 mg/day oral prednisone (or equivalent)
CS <0.5 mg/kg/day – CS >0.2 mg/kg/day oral prednisone (or equivalent)	➡	≤0.2 mg/kg/day up to a maximum dose of 10 mg/day oral prednisone (or equivalent)

3.2.2.2. Two Corticosteroid Tapering Failures are Allowed

CS tapering can continue as long as:

Between study visits the subject does not report any sJIA associated fever or flares according to the investigator's judgment.

The subject maintains an Adapted JIA ACR 50 response at time of site visits.

CS tapering failure is defined as loss of Adapted JIA ACR 50 response. Subjects will be allowed to fail the CS tapering criteria twice in Part 2. If after 2 tapering failures the subject fails to taper CS a third time, they will be discontinued from the study and offered the possibility to enter the A3921145 study if eligible.

If a subject has a first CS tapering failure, continuation in the study will be allowed, but the steroid dose will be increased to the level of the previous visit, or higher, at the judgment of the investigator. The increased CS dose cannot exceed 1.0 mg/kg/day up to 30 mg/day of oral prednisone (or equivalent). This increased CS dose will be maintained for at least 2 weeks. Subsequent attempts of steroid tapering may occur only if the subject has re-achieved an Adapted JIA ACR 50 response. If after 2 weeks, the subject does not re-achieve an Adapted JIA ACR 50 response this will be considered a second tapering failure. If the subject fails a third CS tapering attempt they will be discontinued from the study.

3.2.2.3. Optional Further CS Tapering before Randomization

If and when the oral prednisone (or equivalent) dose is at 0.2 mg/kg/day (or 10 mg/day whichever is lower), the investigator is encouraged to consider further reduction of the CS dose according the criteria in Table 2, as long as the subject maintains an Adapted JIA ACR 50 response.

Optional CS tapering is at the Investigator's discretion:

Table 2. Optional Corticosteroid Tapering if Dose ≤0.2 mg/kg/day

CS Start dose ≤0.2 mg/kg/day		**CS End dose after tapering by End Part 2**
>0.1 mg/kg/day oral prednisone (or equivalent)	➡	Taper at 0.1 mg/kg per week until at dose of 0.1 mg/kg/day
= 0.1 mg/kg/day of oral prednisone (or equivalent)	➡	Taper to dose of 0.05 mg/kg/day for 1 week
<0.05 mg/kg/day of oral prednisone (or equivalent)	➡	Alternate dosing days (ie, take dose every 48 hours) for 2 weeks and then discontinue

3.3. Randomized Withdrawal Phase

Subjects who are able to maintain an Adapted JIA ACR 30 response for at least 4 weeks in the open-label phase are eligible for the double-blind withdrawal phase.

Eligible subjects will be randomized in a 1:1 ratio to either continue on the same dose of tofacitinib that they received in the open-label phase or start placebo. They will have monthly visits in the withdrawal phase. The sustained efficacy of tofacitinib will be assessed during this period by measurement of time to sJIA flare and other efficacy endpoints. The study will continue until a sufficient number of subjects have reported flare. Refer to Section 10.1 for details on the estimated number of flares required and estimated duration of the double-blind phase.

Subjects will continue in the double-blind phase of the study until one of the following events occur:

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

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

- Recurrence of fever [(>38° C/100.4° F) on 2 or more consecutive days] considered to be due to sJIA activity.

- Worsening of 30% or more in three or more of the six variables of the JIA core set with no more than one variable of the JIA core set improving by 30% compared to the day of randomization into the withdrawal phase.

  Note: For "real-time" assessment of sJIA flares during a study visit the subject's ESR will be used to determine the JIA core component related to percent change in inflammation biomarker.

After randomization, subjects will be required to maintain a stable dose of CSs during the withdrawal phase. Subjects who flare at any time during the randomized withdrawal phase, or who experience 24 consecutive weeks of inactive disease as assessed using JIA ACR (clinical remission) (Wallace 2011)[16], will complete their participation in the study. An end-of-study visit should be performed. Subjects who discontinue Investigational Product in the double-blind phase of the study due to any reason will be counted as having an sJIA flare in the primary analysis for the primary endpoint of the study and will contribute to the requisite number of subjects with flare for the study to be considered complete. Subjects who achieve clinical remission are completers of the study and will not be counted as having an sJIA flare in the primary analysis. Upon notification by the Sponsor, an end-of-study visit should be scheduled for all remaining subjects in the study in accordance with Section 6.8.

All subjects participating in this study, including those discontinued from the study, will have the option, if eligible, of enrolling in the tofacitinib long-term extension study (A3921145). The Sponsor's intent is to make tofacitinib available to pediatric subjects through Study A3921145.

Subjects who discontinue Investigational Product in the double-blind phase for reasons other than sJIA flare, and who do not enter A3921145 are required to continue in the study and perform all scheduled visits until Week 52 after randomization or until the study concludes, whichever comes first. Such subjects should transition to standard-of-care treatment in accordance with local treatment guidelines.

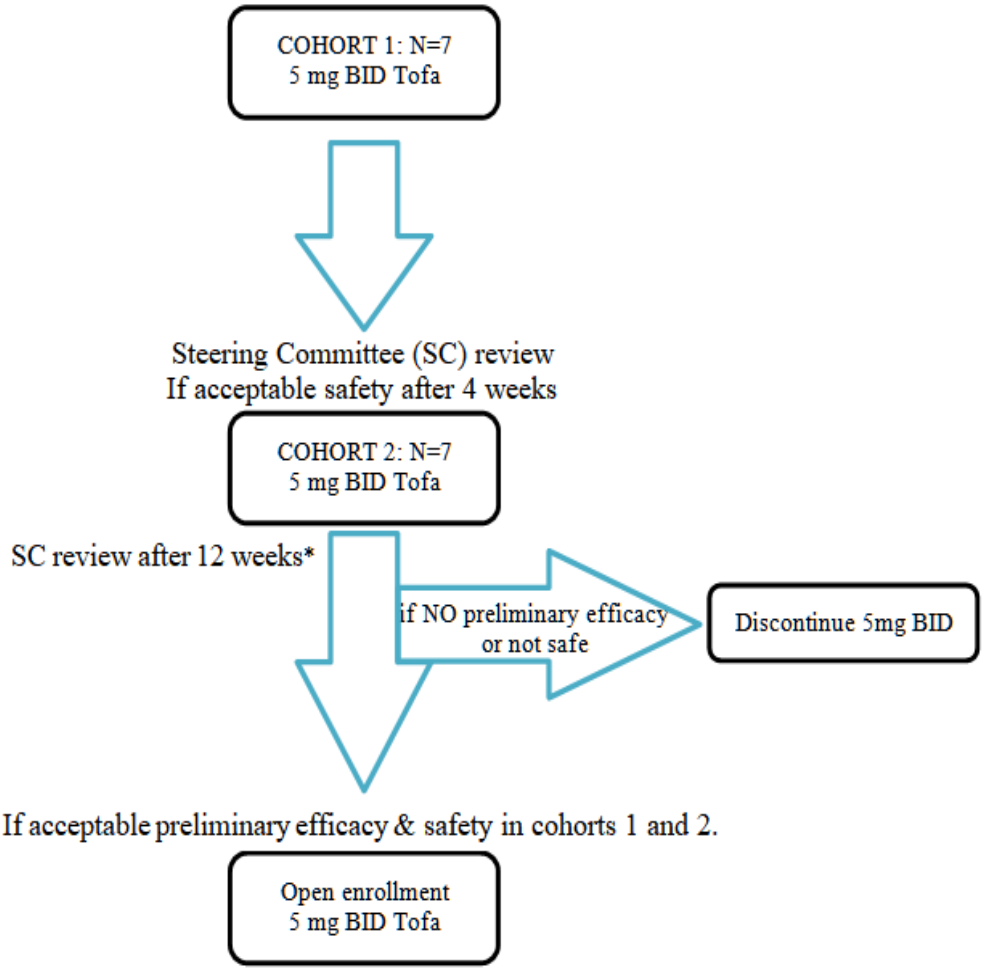
3.4. Sequential Evaluation of Tofacitinib 5 mg BID Dose in Cohorts in Part 1

Dosing will not exceed 5 mg BID, which is the approved dose for adult RA patients.

Tofacitinib 5 mg BID: Initially, only subjects aged ≥12 years, with active sJIA defined by the presence of fever (sJIA fever) and weighing ≥40 kg will be enrolled in a staggered fashion into 2 (or more) sequential cohorts of 7 subjects to receive tofacitinib 5 mg BID. The Sponsor, with the guidance of a Steering Committee, will assess safety, efficacy and pharmacokinetics of the tofacitinib 5 mg BID dose in these initial cohorts. Decisions to open enrollment at the 5 mg BID dose level to those weighing <40 kg, and those aged <12 years after completion of the initial cohorts will be based on observed safety, systemic exposure to tofacitinib and efficacy (based on the Adapted JIA ACR 30 response rate; Refer to Section 10.3 for details) in the initial cohorts. If the Sponsor and Steering Committee consider open enrollment at the tofacitinib 5 mg BID dose level warranted, additional subjects will be enrolled without restrictions, including those without sJIA fever and those weighing <40 kg or less than 12 years of age.

The recommended progression is outlined in Figure 3.

Figure 3. Tofacitinib Evaluation Schema



*The Steering committee may review the data of initial cohorts receiving 5 mg BID before all subjects have received 12 weeks of study treatment dependent on observed efficacy and safety.

3.4.1. Evaluation of 5 mg BID or Equivalent Weight-based Lower Dose

As of Amendment 6, Cohort 1 and Cohort 2 are completed; open enrollment is ongoing.

3.4.1.1. Cohort 1

Enrollment started in a first cohort of 7 subjects aged ≥12 years, weighing ≥40 kg and with sJIA fever who received tofacitinib 5 mg BID.

The Sponsor monitored this first cohort closely to evaluate safety and preliminary efficacy.

3.4.1.2. Cohort 2

As no significant safety issues were observed after 4 weeks of treatment in Cohort 1, a second confirmatory cohort of 7 subjects aged ≥12 years, weighing ≥40 kg and with sJIA fever were enrolled at the 5 mg BID dose level.

After 12 weeks of study treatment, the Sponsor submitted the available safety and efficacy data of each cohort for review by the Steering Committee. The Steering Committee provided guidance to the Sponsor regarding continuation of testing of tofacitinib at the 5 mg BID dose level. The Steering committee reviewed the data of initial cohorts receiving 5 mg BID before all subjects have received 12 weeks of study treatment.

3.4.1.3. Open Enrollment at the 5 mg BID Dose Level

Acceptable efficacy and safety of the 5 mg BID dose level was confirmed in the 2 cohorts at which time, enrollment was opened to additional subjects, including subjects less than 12 years old, without sJIA fever, and weighing less than 40 kg. Decisions to open enrollment at the 5 mg BID dose level were based on observed safety, systemic exposure to tofacitinib and efficacy based on the Adapted JIA ACR 30 response rate (Refer to Section 10.3 for details) in the initial cohorts. The details of composition and scope of the Steering Committee is described in the Steering Committee charter.

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 participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

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

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Male or female aged 2 to <18 years.

2. Diagnosed with sJIA according to International League Against Rheumatism (ILAR) criteria, and, in the opinion of the investigator, have active disease prior to screening. Subjects with first-degree relatives with history of psoriasis, ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis may be allowed for enrollment after consultation with the sponsor.[31] Subjects must have active disease at the time of enrollment, defined as:

    a. Documented intermittently spiking temperature >38° C/100.4° F for at least 1 day due to sJIA in the screening period and within 1 week before the first dose, and the

presence of at least 2 joints with active arthritis at screening and baseline, and an ESR >30 mm/hr. [1.5 X ULN] at screening.

OR

b. **Only after cohort review is completed and enrollment is opened without restrictions:** The presence of at least 5 joints with active arthritis at screening and baseline, and an ESR >30 mm/hr. [1.5 X ULN] at screening. Refer to Section 3.4 for details.

3. Treatment with stable doses of methotrexate (MTX) and/or oral CSs is permitted:

   - For subjects taking MTX: Treatment for ≥3 months with MTX and with a stable dose of MTX (dose must be ≤25 mg/wk or ≤20 mg/m^2/week, whichever is lower) for at least 4 weeks before the first study drug dose (Day 1). Subjects taking MTX must be taking folic acid or folinic acid in accordance with local standards;

   - For subjects taking CS: Treatment with a stable dose of oral prednisone (≤1 mg/kg/day up to a maximum of 30 mg/day), or equivalent, for at least 1 week before the first study drug dose (Day 1).

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

   - A negative QuantiFERON®-TB Gold or Gold Plus In-Tube test performed within the 3 months prior to screening. A negative QuantiFERON®-TB test performed locally or a negative purified protein derivative (PPD) or T-spot 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 and the Pfizer medical monitor is informed and agrees on a case-by-case basis;

   - 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;

   Note: 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®-TB Gold or Gold Plus test need be obtained. A chest radiograph may be obtained to aid in TB status determination, according to local standards and/or in countries with a high incidence rate of TB (see Section 8.2.8). 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, documentation of an adequate treatment regimen, and prior approval of the Sponsor.

The sponsor considers ongoing treatment with isoniazid or equivalent for at least 4 weeks before the first dose of tofacitinib (Day 1) adequate, provided that local rates of primary multi-drug resistant TB infection are <5%.

5. Fertile males and females who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must be willing and able to use a highly effective method of contraception as outlined in this protocol during the study and for at least 28 days after the last dose of study medication (see Section 4.4.1).

   Country-specific amendment for EU sites (including UK): Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of contraception (at least one of which is considered to be highly effective with low user dependency as defined below) throughout the study and for at least 28 days (90 days for male subjects) after the last dose of study drug where there is known or suspected teratogenicity (see Section 4.4.1).

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

7. Evidence of a personally signed and dated Informed Consent document and Assent document (as appropriate) indicating that the subject and a legally acceptable representative/parent/legal guardian has been informed of all pertinent aspects of the study.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Previous JIA treatment with tofacitinib.

2. Current symptoms or findings of myocarditis, endocarditis or more than minimal pericardial effusion associated with sJIA.

3. Current symptoms or findings of more than minimal pleuritis with sJIA.

4. Subjects who are still within the washout periods for disallowed nonbiological and biological DMARDs as indicated in Section 5.8.1.2.

5. Infections:

   a. Chronic infections;

   b. Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to be opportunistic by the investigator within the 3 months prior to the first dose of study drug;

   c. Any treated infections within 2 weeks of baseline;

d. A subject known to be infected with Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C (see Section 8.2.9);

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

6. History of recurrent (more than one episode) herpes zoster or disseminated (at least one episode) herpes zoster, or disseminated (at least one episode) herpes simplex.

7. Diagnosis of active Macrophage Activation Syndrome (MAS) within 3 months prior to the first dose of study drug.

8. Blood dyscrasias, including (see Appendix 7):

   a. Hemoglobin <9 g/dL;

   b. White Blood Cell count $<3.0 \times 10^9$/L;

   c. Absolute Neutrophil count $<1.2 \times 10^9$/L;

   d. Platelet count $<100 \times 10^9$/L;

   e. Absolute Lymphocyte count $<0.75 \times 10^9$/L.

9. Estimated glomerular filtration rate [eGFR] <40 mL/min/1.73 m^2 at Screening. eGFR will be calculated by the central lab using the bedside Schwartz formula (see Appendix 4).

10. Current or recent history of uncontrolled clinically significant renal, hepatic, hematologic, gastrointestinal, metabolic, endocrine, pulmonary, cardiac or neurologic disease.

11. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥1.5 times the upper limit of normal or any other clinically significant laboratory abnormality (see Appendix 7).

12. History of any other rheumatologic disease, other than Sjogren's syndrome.

13. History or current symptoms suggestive of lymphoproliferative disorders (eg, Epstein Barr Virus [EBV] related lymphoproliferative disorder, lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease).

14. Vaccinated or exposed to a live vaccine within the 6 weeks prior to the first dose of study drug, or is expected to be vaccinated or there are household members that require oral polio vaccination (see Section 4.5.2 Vaccination in Household Members) during treatment or during the 6 weeks following discontinuation of study drug.

15. Current malignancy or history of any malignancy with the exception of adequately treated or excised basal cell or squamous cell carcinoma of the skin or cervical carcinoma *in situ*.

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

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

18. Subjects receiving potent and moderate CYP3A4 inhibitors or inducers (Appendix 5).

19. 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.

20. Use of prohibited prescription or non-prescription drugs and dietary supplements listed in Appendix 1 and Appendix 5 within the specified time frame prior to the first dose of study medication.

21. Herbal supplements, unless discontinued at least 28 days prior to the first dose of study medication.

22. 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.

23. Participation in other studies involving investigational drug(s) within 4 weeks or 5 half-lives (whichever is longer) prior to study entry and/or during study participation. Exposure to investigational biologics should be discussed with the Sponsor.

24. 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.

25. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product or longer based upon the compound's half-life characteristics.

26. Any factors or clinical characteristics potentially related to the risk of venous thromboembolism (see Section 8.2.13, 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.

28. History of allergies, intolerance or hypersensitivity to lactose or CP-690,550 (tofacitinib), or any other excipients of the investigational medicinal products, including placebos. 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 investigators request.

4.3. Randomization Criteria

Before randomization, all subjects enrolled in the study will receive open-label tofacitinib 5 mg BID oral tablets or solution (1 mg/mL), or an equivalent weight-based lower dose of solution (1 mg/mL). Refer to Table 3 for details.

The time period of the open-label phase will be between 12 and 40 weeks. Only subjects who are able to maintain a minimal clinical response for 4 weeks in the open-label phase at an allowed CS dose will proceed to randomization. Eligibility of the subject must be confirmed before randomization.

Eligible subjects will be randomized in a 1:1 ratio into the double-blind withdrawal phase to either continue tofacitinib treatment or withdraw the tofacitinib dose and start placebo. Randomization will be stratified by age group.

4.4. Lifestyle Guidelines

4.4.1. 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 or 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 the 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 or 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 the subject's 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 or 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, this option is not appropriate.

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.

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.

Country specific amendment for EU sites (including UK): Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of contraception (at least one of which is considered to be highly effective with low user dependency as defined below) throughout the study and for at least 28 days (90 days for male subjects) after the last dose of study drug where there is known or suspected teratogenicity.

Highly effective methods of contraception with low user dependency (applies to female subjects at risk for pregnancy with their male partners):

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (inserted, injected, and implanted).

2. Correctly placed intrauterine device (IUD) or intrauterine system (IUS).

3. Male sterilization with absence of sperm in the post vasectomy ejaculate.

4. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion had been confirmed in accordance with the device's label).

4.5. Vaccine and Exposure to Infections Guidelines

4.5.1. Subject Specific Recommendations

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

Varicella vaccination is encouraged when appropriate, but if the participant is vaccinated, first dose of study drug (Day 1) may not be administered until at least 4 weeks after vaccination. Other live vaccines should not be administered to study subjects within the 6 weeks prior to the first dose of study drug and throughout the study for example: live attenuated influenza vaccine, MMR (measles, mumps, and rubella) vaccine, or MMR-V (measles, mumps, rubella and varicella) vaccine.

For subjects who have not been vaccinated for varicella and do not have a positive VZV IgG Ab serology test at screening, 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 Section 9.2.6 regarding the diagnosis and treatment of varicella and herpes zoster in study subjects. 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.

4.5.2. 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.

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.

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.

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.

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

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

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 infected persons and contact the Investigator promptly should they develop signs or symptoms of infection.

4.6. 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.

4.7. 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 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.

4.8. 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).

Subjects who are treated with methotrexate should be taking supplemental folic or folinic acid.

Herbals supplements are prohibited (see Section 5.8, Concomitant Treatments, for additional details).

4.9. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study 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 a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers,

contact information for the investigational site, and contact details for a contact center 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 subject's participation in the study. The contact center 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 the study team for advice on medical questions or problems that may arise during the study. The contact center number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

The study will enroll approximately 100 subjects from 2 to <18 years and target enrollment of at least 12 subjects in each of the following age groups: from 12 to <18 years, from 6 to <12 years, and from 2 to <6 years.

All eligible subjects enrolled in the study will initially be assigned to receive a stable dose of tofacitinib for up to 40 weeks in an open-label phase (Part 1 and 2). Only subjects who qualify as "responders" will afterwards be randomized in a 1:1 ratio, stratified by age group, into the double-blind phase to continue tofacitinib or start placebo.

Assignment of a subject number, allocation of tofacitinib in the open-label phase and randomization to tofacitinib or placebo in the double-blind phase will proceed through the use of an Interactive Response Technology (IRT) system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the subject number, the subject's weight and the date of birth of the subject (where permitted by local laws and regulations). The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when drug is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24 hour a day, 365 days a year IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

The IRT system is the source of the subject number. The IRT system will provide the subject number at the end of the first IRT subject transaction.

5.1.1. Open-Label Phase

In the open-label phase of the study subjects ≥40 kg will receive tofacitinib 5 mg BID oral tablets or solution (1 mg/mL) and subjects <40 kg a weight-proportional lower dose of tofacitinib oral solution (1 mg/mL) BID as specified in Table 3 (see Section 5.5).

Assignment to the 5 mg BID dose of tofacitinib in the open-label will proceed through the use of an Interactive Response Technology (IRT) system.

5.1.1.1. Enrollment in 5 mg BID Cohort

Initially, the 5 mg BID dose level was evaluated in cohorts of 7 subjects each. At the start of the open-label phase, subjects were assigned to tofacitinib 5 mg BID via the IRT system in 2 or more consecutive cohorts to allow for a preliminary assessment of PK, safety and clinical response. These first participants enrolled at the 5 mg BID dose level had to qualify for enrollment based on the presence of fever, weigh at least 40 kg and be 12 years of age or older. No additional subjects were allowed to enroll until the evaluation of the 5 mg BID dose level in the initial cohorts by the Sponsor and Steering Committee was complete. If the 5 mg BID dose level had not demonstrated acceptable efficacy and safety in the initial cohorts, all subjects treated with this dose level would have been discontinued.

5.1.1.2. Open Enrollment at the 5 mg BID Dose Level

After review of the 5 mg BID cohort data, the Sponsor and Steering Committee considered this dosing regimen to be effective and agreed that additional subjects could be enrolled without sJIA fever, and could include subjects weighing <40 kg or less than 12 years of age.

5.1.1.3. Double-Blind Phase

Subjects who enter the double-blind phase will be randomized via the IRT system in a 1:1 ratio to either continue treatment with the 5 mg BID dose of tofacitinib tablets/oral solution or matching placebo. Randomization will be stratified by age group.

5.2. Breaking the Blind

During the double-blind phase of the study, the Sponsor, subject and investigator site staff will be blinded to the subject's treatment assignment. At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or an electronic process. Blinding codes should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

Country specific amendment for EU sites (including UK): Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to

discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.3. Subject Compliance

Subject compliance will be assessed at each visit during the study and will be verified by interviewing subjects and through accounting of returned containers and trial medication at each visit.

Non-compliance (ie, missed or incorrect dosing where compliance is calculated to be <80% or >110%) will be documented on the Compliance Case Report Form (CRF). In subjects who demonstrate non-compliance between visit intervals, both the subject and parent/legal guardian will be counseled by study staff to address reasons for non-compliance. If after counseling the subject continues to exhibit non-compliance over two consecutive or nonconsecutive study visits, the subject may be withdrawn from the study after discussion with the Sponsor.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Tofacitinib will be provided as oral tablets (tofacitinib 5 mg) and as an oral solution (CP-690,550 [the compound name for tofacitinib] 1 mg/mL) by the Sponsor. Tofacitinib tablets, oral solution and matching placebo, for oral administration, will be supplied in child-resistant bottles to the investigator site.

Open-label bottles of tofacitinib tablets and CP-690,550 (compound name for tofacitinib) oral solution will be provided for the open-label phase of the study.

Blinded-label bottles of tofacitinib tablets, CP-690,550 (compound name for tofacitinib) oral solution, and matching placebo, for oral administration, will be provided for the double-blind withdrawal phase of the study.

5.4.2. Preparation and Dispensing

Investigational product will be supplied to subjects in bottles, which, along with written dosing instructions (dosing cards), will be dispensed by an appropriately qualified member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

Oral solution will be administered via oral dosing syringes which will be dispensed along with oral solution bottles.

5.5. Administration

During the open-label phase (12 to 40 weeks), all subjects will receive active tofacitinib oral tablets or oral solution twice daily (BID) orally, approximately 12 hours (±2 hours) apart, in the morning and evening, at a dosage based on the subject's body weight as specified in Table 3. In the open-label phase, subjects ≥40 kg will receive tofacitinib 5 mg BID as oral

tablets or solution (1 mg/mL). Subjects who are unable to swallow tablets will have the option of taking oral solution. All subjects <40 kg will receive an equivalent weight-based lower dose of tofacitinib oral solution (1 mg/mL) BID as specified in Table 3. At each visit the appropriate dose will be assigned via the IRT system based on the subject's weight.

Subjects should swallow investigational product tablets whole and not manipulate or chew them prior to swallowing. Dosing cards with clear written instructions on how to properly take study medication will be provided to the subject with study medication.

Table 3. Study Treatment Dosing and Administration

Body Weight (kg)	Dosage Regimen (Run-In Phase: Tofacitinib, Double-Blind Phase: Tofacitinib/Placebo)
	5 mg BID dose level
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

After the 12-40 weeks open-label phase, eligible subjects will proceed to the double-blind, placebo-controlled phase. They will be randomized in a 1:1 ratio to receive either active tofacitinib oral tablets/oral solution or matching placebo oral tablets/oral solution, twice daily (BID), approximately 12 hours (±2 hours) apart, in the morning and evening, at a dosage based on the subject's body weight as specified in Table 3.

5.6. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparator and/or marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label.

Storage conditions stated in the SRSD will be superseded by the storage conditions stated in the labeling.

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 that 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 the storage conditions as

described in the labeling, 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 investigational 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 on the proper storage requirements for take home investigational product.

All bottles must be returned to the investigator by the subject.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. 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 investigational product returned by the subjects.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of any unused investigational product (eg, at the site). 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.

5.8. Concomitant Treatment(s)

All concomitant medication taken during the study must be recorded with generic name of the medication, indication, daily dose, and start and stop dates of administration.

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 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.

5.8.1. Allowed sJIA Background Therapy

After enrollment, subjects are allowed to continue on their stable background arthritis therapy, which can include nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors (see Appendix 3), allowed DMARDs (methotrexate - Section 5.8.1.2), and Corticosteroids (CSs) (See Section 5.8.1.1).

See Appendix 3 for instructions on permitted adjustments in concomitant RA therapies during the study.

Herbal supplements must be discontinued for at least 4 weeks prior to first dose of study drug, unless there is sufficient data available regarding the duration of an herbal medication's pharmacokinetic and pharmacodynamic effects to allow a shorter washout to be specified (eg, 5 half-lives).

5.8.1.1. Corticosteroids (CSs)

Subjects who are treated with CSs before study start, will be allowed to continue CS treatment provided that doses are ≤1.0 mg/kg/day prednisone or equivalent (up to a maximum dose of 30 mg/day) and stable for at least 1 week before the first dose of tofacitinib (Day 1) throughout the full duration of Part 1 of the open-label phase.

For subjects who are receiving IV pulse CS during the Screening period, the last IV pulse should be 2 weeks prior to Baseline (Day 1) for methylprednisolone and 3 weeks prior to Baseline (Day 1) for dexamethasone. Maintenance oral CS may be started on the day following the last IV pulse. Dosing should be ≤1.0 mg/kg/day prednisone or equivalent (up to a maximum dose of 30 mg/day) and stable for at least 1 week prior to Baseline (Day 1).

CS use is encouraged to be tapered down to the lowest possible dose up to discontinuation during Part 2 of the open-label phase prior to entry into the double-blind randomized withdrawal phase of the study. The active CS tapering period will be up to 20 weeks in Part 2. Refer to Section 3.2.2 for further details about CS tapering in Part 2. During the double-blind phase the subject must remain on a stable tapered CS dose.

For use of CS intra articular injections, please refer to Appendix 3.

5.8.1.2. Disease Modifying Anti-Rheumatic Drugs (DMARDs)

The only nonbiological DMARD that subjects are allowed to receive during the study period is methotrexate (MTX). MTX may be administered either orally or parenterally at doses not to exceed 25 mg/wk or 20 mg/m^2/week, whichever is lower. Subjects who are treated with methotrexate should be taking supplemental folic or folinic acid.

If receiving MTX, participants must be on a stable dose of MTX for at least 4 weeks before the first dose of tofacitinib (Day 1 visit). The MTX dose will be maintained throughout the study unless dose modification is clinically indicated for safety reasons. All standard-of-care practices for administration of methotrexate, including laboratory testing and folate supplementation, should be performed according to local methotrexate labels.

All other biological and nonbiological DMARDs are disallowed during the study. The wash-out periods in Table 4 must be observed before the first dose of study drug (Day 1).

Table 4. DMARDs – Required Washout Period Prior to Day 1 of Study Drug

52 weeks	Rituximab or other selective B lymphocyte depleting agents. Only if CD19/20+ counts are normal by FACS analysis.
8 weeks	Immunoglobulin G (IgG), Leflunomide (Arava®), Auranofin (oral gold), aurothioglucose (injectable gold), aurothiomalate (injectable gold).
7 weeks	Canakinumab (Ilaris®).
4 weeks	Tocilizumab (Actemra®), Abatacept (Orencia®), Certolizumab pegol (Cimzia®), Golimumab (Simponi®), Baricitinib (Olumiant®), Upadacitinib (Rinvoq®), Thalidomide (Thalidomid®), , d-penicillamine, chloroquine, hydroxychloroquine, bucillamine, mizoribine and staphylococcal protein A immuno-absorbant pheresis columns.
3 weeks	Infliximab (Remicade®)
2 weeks	Adalimumab (Humira®), Etanercept (Enbrel®).
7 Days	Cyclosporine, tacrolimus, sulfasalazine, azathioprine.
3 Days	Anakinra (Kineret®)

Disallowed and allowed non-biologic and biologic DMARDS are listed in Appendix 1. If a subject requires (in the opinion of the investigator) treatment with one of the disallowed agents, the subject should be discontinued from the study.

5.8.1.3. Treatment for Latent Tuberculosis

Subjects who are diagnosed as having latent tuberculosis (ie, positive tuberculosis test, chest x-ray negative for active tuberculosis, and no evidence of active disease) at screening or during the course of the study must have either been previously treated with an adequate course of treatment or be currently taking isoniazid. Subjects that the Investigator considers to be at high-risk to develop tuberculosis (eg, residing in high-risk areas or travel to high-risk areas) may be started on isoniazid treatment at the discretion of the Investigator. The sponsor considers ongoing treatment with isoniazid or equivalent for at least 4 weeks before the first dose of tofacitinib (Day 1) adequate, provided that local rates of primary multi-drug resistant TB infection are <5%.

When indicated, isoniazid treatment is required to be administered in accordance with local standards at a maximum dose of 300 mg/day for a total of 9 months of treatment and the treatment must be recorded in the subject's case report form. If an alternate treatment regimen is implemented, the reason for this must be documented and a copy of the local standard of care guideline identifying such treatment must be provided to the study team. 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, rifampicin, rifabutin and rifapentine are prohibited concomitant medications in this study.

5.8.2. Prohibited Concomitant Medication

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 5,

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.

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.

5.9. Rescue Therapy

Refer to Appendix 3 for permitted adjustments in background sJIA therapies. Permitted rescue therapy can be found in Appendix 6.

6. STUDY PROCEDURES

This section outlines study procedures and tests required to be performed at specified study visits. The order in which procedures and tests are performed is left to the discretion of the investigator. Please refer to Section 8 for details regarding each procedure/test.

Country specific amendment for Germany: In accordance with article 40 (4) No. 4 of the German Medicines Act; the degree of burden and the risk threshold should be assessed at each scheduled visit as outlined in Appendix 9.

6.1. Screening Visit

Please note that subjects must be enrolled within 40 days of the screening visit.

If more than 40 days has elapsed, the subject should be screen-failed and if eligible, re-screened. All screening procedures and assessments listed below should be repeated. Sponsor approval must be obtained prior to re-screening a subject. Rescreening of subjects will be allowed in a limited number of circumstances as determined by the Pfizer Study Clinician (eg, subject requires washout of prohibited medications, requires antimicrobial therapy within 2 weeks prior to the first dose of study medication, requires emergency surgery) and should be confirmed with the Pfizer Study Clinician when rescreening can occur.

Following obtainment of Informed Consent from the parent/legal guardian (and Assent from the subject, as appropriate), the procedures and assessments listed below will be performed at the screening visit. Serious adverse events (SAEs) are captured starting with the Screening visit from the time of informed consent (Section 9.2).

- Medical history and family history.
- Uveitis assessment: if applicable, documentation of previous uveitis assessment(s) by an ophthalmologist (or qualified equivalent per local practice) should be reviewed to document presence/absence of active uveitis.
- Prior and concomitant medications. Refer to Section 5.8.

- Complete physical examination, including vital signs, height and weight. **Country specific amendment for EU sites (including UK)**: A full skin cancer examination must be performed as part of the complete physical examination.
- Perform a risk factor check for venous thromboembolism. Refer to Section 8.2.13 for details.
- Evaluate the pubertal development using the Tanner Stages.
- Obtain subject's oral temperature and assess "Fever", defined as temperature >38° C/100.4° F:
  - 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 8.2.11 for details regarding these blood sample collections.
- Assess the sJIA Disease Activity status:
  - Fever (see above);
  - Number of joints with limitation in range of motion;
  - Number of joints with active arthritis (swelling and/or pain/tenderness);
  - Assess duration of morning stiffness;
  - Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA;
  - Physician's Global Assessment of Overall Disease Activity;
  - Administer the Childhood Health Assessment Questionnaire (CHAQ); evaluate Patient wellbeing as part of the CHAQ on a 21 circle VAS;
  - ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF.
- Child Health Questionnaire;
- Obtain blood sample for QuantiFERON®-TB Gold or Gold Plus In-Tube test and send to central laboratory. Note: If the reference laboratory informs the investigator site that QuantiFERON®-TB Gold or Gold Plus In-Tube testing cannot be performed on the submitted sample or if the result is indeterminate, then administer a locally performed QuantiFERON®-TB test or Purified Protein Derivative (PPD) skin test (Mantoux method) or T-spot TB test with Sponsor approval.[10]
- **Only if according to local standards and/or in countries with a high TB incidence rate:** Perform a chest X-ray to aid in TB status determination.

- Obtain blood or urine sample(s) for the following tests and send to central laboratory. Refer to Section 8.2.12 for sample collection details.

Note: At screening 14.1 mL or 15.1 mL (according to Quantiferon®-TB test used) to maximally 25.8 mL of blood (only if serum pregnancy test, MAS laboratory evaluations, VZV IgG Antibody and HCV RNA test are required) will be collected. If preferred by the investigator, the laboratory evaluations at screening may be done at 2 separate visits within 40 days before enrolment on Day 1 to limit the blood volume collected in one day. One re-testing of a hematology or serum chemistry laboratory parameter is allowed if the abnormal lab(s) was an uncharacteristic result(s). Re-testing must be completed within the screening period.

  - Hematology;
  - Chemistry;
  - Inflammatory and rheumatic disease markers: CRP, Rheumatoid Factor (RF);
  - Viral testing: Human Immunodeficiency Virus (HIV), Hepatitis B (Hep B), Hepatitis C (Hep C); Varicella Zoster Virus (VZV) (if applicable);
  - Urinalysis.

- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- **For subjects using contraception:** perform a contraceptive check, to ensure contraception is consistently and correctly used.

6.2. Open-label Phase/Part 1: Day 1 Visit

The study will start with an open-label phase during which all subjects will receive a stable dose of tofacitinib oral tablets or oral solution BID. Part 1 of the open-label is meant to identify tofacitinib-treated subjects who are able to maintain an Adapted JIA ACR 30 response for 4 weeks.

Day 1 is the day of first study drug administration. The procedures and assessments listed below will be performed at the Day 1 visit.

For the Day 1 Visit, subjects should be instructed to fast (for 9 to 12 hours prior the scheduled visit), if possible, for lipid panel testing.

- Review prior and concomitant medications. Refer to Section 5.8;
- Targeted physical exam;
- Perform a risk factor check for venous thromboembolism. Refer to Section 8.2.13 for details.

- Vital signs, height and weight.
- Obtain subject's oral temperature and assess "Fever", defined as temperature >38° C/100.4° F:
  - 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 8.2.11 for details regarding these blood sample collections.
- Confirm that the subject meets all inclusion criteria and none of the exclusion criteria.
- Assess the sJIA Disease Activity status:
  - Fever (see above);
  - Number of joints with limitation in range of motion;
  - Number of joints with active arthritis (swelling and/or pain/tenderness);
  - Assess duration of morning stiffness;
  - Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA;
  - Physician's Global Assessment of Overall Disease Activity;
  - Administer the Childhood Health Assessment Questionnaire (CHAQ); evaluate Patient wellbeing as part of the CHAQ on a 21 circle VAS;
  - Administer the Child Health Questionnaire (CHQ);
  - ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF.
- Assess the Adapted JIA ACR baseline:
  - Record result for all core components of Adapted JIA ACR baseline in the eCRF for calculation of the baseline Adapted JIA ACR criteria based on ESR.*

    **For "real-time" assessment of the Adapted JIA ACR baseline during a study visit the subject's ESR will be used to determine the percent change in inflammation biomarker.*
  - Fax or email the sJIA Disease Assessment worksheets and JIA ACR core component CRF to the Coordinating Center for confirmation of the Adapted JIA ACR baseline response based on ESR.

- Record Adapted JIA ACR baseline value on relevant eCRF after receipt of result from the Coordinating Center.

- Obtain blood or urine sample(s) for the following tests and send to central laboratory. Refer to Section 8.2.9 for sample collection details:
  - Hematology;
  - Chemistry;
  - Lipid panel (under fasting conditions for approximately 9 to 12 hours, if possible);
  - CRP;
  - Ferritin;
  - Urinalysis.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- **For subjects using contraception:** perform a contraceptive check, to ensure contraception is consistently and correctly used.
- Assess for adverse events.
- Dispense investigational product; first dose to be administered at the study site.
- Obtain blood samples for PK analysis at 15 minutes (5-30 min), 45 minutes (35-55 min) and 4 hours (3-6h) post tofacitinib administration. If feasible for the subject, this blood sample should be drawn between 4 to 6 hours post dose, however any time between 3 to 6 hours post dose is allowed. Obtain an additional PK blood sample 1.5 hours (1.25-2h) post tofacitinib administration if the subject is part of the first 14 subjects enrolled in Cohorts 1 to 2. Refer to Section 8.4 for details.
- Obtain blood samples for banking of biospecimens before first dose of study drug. This blood sample collection is optional, at the parent/legal guardian's discretion. Refer to Section 8.5 for details.
- Provide diary to record 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.

6.3. Open-Label Phase/Part 1: Day 3, Day 7 and Day 14 Visit

Part 1 of the open-label active treatment phase is meant to identify tofacitinib-treated subjects who are able to maintain an Adapted JIA ACR 30 response for 4 weeks.

The procedures and assessments listed below will be performed at the Day 3, Day 7 and Day 14 visit. The window for these visits is ±1 days.

- Review concomitant medications. Refer to Section 5.8.
- Targeted physical exam, including skin examination for chickenpox or shingles.
- Perform a risk factor check for venous thromboembolism. Refer to Section 8.2.13 for details.
- Vital signs and weight.
- Review temperature diary and assess "Fever" and "Absence of fever":
  - Obtain subject's oral temperature and assess "Fever", defined as temperature >38° C/100.4° F;
  - **MAS diagnosis: Only if subject has fever and MAS is suspected:** obtain blood samples to evaluate Ferritin, Platelets, Triglycerides and Fibrinogen levels. Refer to Section 8.2.11 for details regarding these blood sample collections;
- **Only at the Day 7 and Day 14 visit:** Evaluate "Absence of fever", defined as documented absence of fever due to systemic JIA in the week preceding this visit. Record the outcome in the eCRF for calculation of the Adapted JIA ACR response. Assess the sJIA Disease Activity status:
  - Fever (see above);
  - Number of joints with limitation in range of motion;
  - Number of joints with active arthritis (swelling and/or pain/tenderness);
  - Assess duration of morning stiffness;
  - Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA.
- **Only at the Day 7 and Day 14 visit:** Uveitis status: document presence/absence of active uveitis.
- Physician's Global Assessment of Overall Disease Activity:
  - Administer the Childhood Health Assessment Questionnaire (CHAQ); evaluate Patient wellbeing as part of the CHAQ on a 21 circle VAS;
  - ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF.

**For "real-time" assessment of the Adapted JIA ACR 30 Response during a study visit the subject's ESR will be used to determine the percent change in inflammation biomarker.*

- **Only at the Day 7 and Day 14 visit:** Assess the Adapted JIA ACR response based on ESR:
  - Record result for the core components of JIA ACR pediatric criteria (besides the CRP level) on the appropriate eCRF for calculation of the Adapted JIA ACR 30 response based on ESR;*
  - Fax/email the sJIA Disease Assessment worksheets and JIA ACR core component CRF to the Coordinating Center for confirmation of the Adapted JIA ACR 30 response based on ESR;
  - Record Adapted JIA ACR 30 response value on relevant eCRF after receipt of result from the Coordinating Center.
- Obtain blood sample for CRP evaluation and send to central laboratory;
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- **For subjects using contraception:** perform a contraceptive check, to ensure contraception is consistently and correctly used.
- Assess for adverse events.
- Assess investigational product dosing compliance.
- **Only at Day 14:** Dispense investigational drug**.**

6.4. Open-label Phase/Part 1: Visits Every 4 Weeks from Week 8 up to Week 16

Part 1 of the open-label active treatment phase is meant to identify tofacitinib-treated subjects who are able to maintain an Adapted JIA ACR 30 response for 4 weeks. After the Week 4 visit, study visits will be performed on a monthly basis. The duration of Part 1 is variable for each subject but no longer than 16 weeks.

The procedures and assessments listed below will be performed at each visit. The window for these visits is ±3 days.

For each Visit, subjects should be instructed to fast (for 9 to 12 hours prior to the scheduled visit), if possible, for lipid panel testing.

- Review concomitant medications. Refer to Section 5.8.
- Targeted physical exam, including skin examination for chickenpox or shingles.

- Perform a risk factor check for venous thromboembolism. Refer to Section 8.2.13 for details.
- Vital signs, height and weight.
- Review temperature diary and assess "Fever" and "Absence of fever":
  - Obtain subject's oral temperature and assess "Fever", defined as temperature >38° C/100.4° F;
  - **MAS diagnosis: Only if subject has fever and MAS is suspected:** obtain blood samples to evaluate Ferritin, Platelets, Triglycerides and Fibrinogen levels. Refer to Section 8.2.11 for details regarding these blood sample collections;
  - Evaluate "Absence of fever", defined as documented absence of fever due to systemic JIA in the week preceding this visit. Record the outcome in the eCRF for calculation of the Adapted JIA ACR response.
- Assess the sJIA Disease Activity status:
  - Fever (see above);
  - Number of joints with limitation in range of motion;
  - Number of joints with active arthritis (swelling and/or pain/tenderness);
  - Assess duration of morning stiffness;
  - Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA;
  - Uveitis status: document presence/absence of active uveitis;
  - Physician's Global Assessment of Overall Disease Activity;
  - Administer the Childhood Health Assessment Questionnaire (CHAQ); evaluate Patient wellbeing as part of the CHAQ on a 21 circle VAS;
  - **Only if an Adapted JIA ACR 30 response for 4 weeks is confirmed and this visit concludes Part 1 of the open-label phase:** Administer Child Health Questionnaire;
  - ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF.*

    **For "real-time" assessment of the Adapted JIA ACR 30 Response during a study visit the subject's ESR will be used to determine the percent change in inflammation biomarker.*

- Assess the Adapted JIA ACR response based on ESR and record result on appropriate CRF:
  - Enter data for the core components of JIA ACR pediatric criteria in the eCRF to for calculation of the Adapted JIA ACR 30 response based on ESR;*
  - Fax or email the sJIA Disease Assessment worksheets and JIA ACR core component CRF to the Coordinating Center for confirmation of the Adapted JIA ACR 30 response based on ESR;
  - Record evaluation of the Adapted JIA ACR 30 Response on the relevant eCRF after receipt of faxed result from the Coordinating Center. Once a subject is able to maintain the Adapted JIA ACR 30 response for 4 weeks they can start Phase 2.
- Obtain blood or urine sample(s) for the following tests and send to central laboratory. Refer to Section 8.2.12 for sample collection details:
  - Hematology;
  - Chemistry;
  - Only every 3 months after Day 1: Lipid panel (under fasting conditions for approximately 9 to 12 hours, if possible);
  - CRP;
  - Urinalysis.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- **For subjects using contraception:** perform a contraceptive check, to ensure contraception is consistently and correctly used.
- Assess for adverse events.
- Assess investigational product dosing compliance.
- **Only at Week 8**:
  - Obtain the first blood sample for PK analysis before investigational product administration. Refer to Section 8.4 for details;
  - Dispense investigational product; administer the first dose at the study site;
  - Obtain blood samples for PK analysis at 1 hour (0.5-1.5h) and 3 hours (2-4h) post tofacitinib administration. If feasible for the subject, this blood sample should be

drawn between 3 to 4 hours post dose, however any time between 2 to 4 hours post dose is allowed. Refer to Section 8.4 for details.

6.5. Open-label Phase/Part 2: CS Tapering: Visits Every 4 Weeks after Start of Part 2

Part 2 of the open-label active treatment phase is to permit CS tapering in subjects treated with CSs. Subjects will have study visits on a monthly basis in Part 2.

The procedures and assessments listed below will be performed at every study visit. The window for these visits is ±3 days.

For each Visit, subjects should be instructed to fast (for 9 to 12 hours prior to the scheduled visit), if possible, for lipid panel testing.

- Review concomitant medications. Refer to Section 5.8.
- Targeted physical exam, including skin examination for chickenpox or shingles.
- Perform a risk factor check for venous thromboembolism. Refer to Section 8.2.13 for details.
- Vital signs, height and weight.
- Review temperature diary and assess "Fever" and "Absence of fever":
  - Obtain subject's oral temperature and assess "Fever", defined as temperature >38° C/100.4° F;
  - **MAS diagnosis: Only if subject has fever and MAS is suspected:** obtain blood samples to evaluate Ferritin, Platelets, Triglycerides and Fibrinogen levels. Refer to Section 8.2.11 for details regarding these blood sample collections;
  - Evaluate "Absence of fever", defined as documented absence of fever due to systemic JIA in the week preceding this visit. Record the outcome in the eCRF for calculation of the Adapted JIA ACR response.
- Assess the sJIA Disease Activity status:
  - Fever (see above);
  - Number of joints with limitation in range of motion;
  - Number of joints with active arthritis (swelling and/or pain/tenderness);
  - Assess duration of morning stiffness;
  - Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA;

- Uveitis status: document presence/ absence of active uveitis;
- Physician's Global Assessment of Overall Disease Activity;
- Administer the Childhood Health Assessment Questionnaire (CHAQ); evaluate Patient wellbeing as part of the CHAQ on a 21 circle VAS;
- **Only if an Adapted JIA ACR 30 response for 4 weeks is confirmed and this visit concludes Part 2 of the open-label phase:** Administer Child Health Questionnaire;
- ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF.

  **For "real-time" assessment of the Adapted JIA ACR 30 Response during a study visit the subject's ESR instead of CRP will be used to determine the percent change in inflammation biomarker.*

- Assess the Adapted JIA ACR response based on ESR:
  - Record results for the core components of JIA ACR pediatric criteria (besides the CRP level) in the eCRF for calculation of the Adapted JIA ACR 30 response based on ESR;*
  - Fax/email the sJIA Disease Assessment worksheets and JIA ACR core component CRF to the Coordinating Center for confirmation of the Adapted JIA ACR 30 response based on ESR;
  - Record the evaluation of the Adapted JIA ACR 30 response on the relevant eCRF after receipt of faxed result from the Coordinating Center.
- Obtain blood or urine sample(s) for the following tests and send to central laboratory. Refer to Section 8.2.12 for sample collection details:
  - Hematology;
  - Chemistry;
  - Only every 3 months after Day 1: Lipid panel (under fasting conditions for approximately 9 to 12 hours, if possible);
  - CRP;
  - Urinalysis.
  - **Only at Week 4 and only if a subject started Open-Label Part 2 after 4 weeks of study treatment:** Obtain the first blood sample for PK analysis before investigational product administration. Refer to Section 8.4 for details;

- Dispense investigational product; administer the first dose at the study site;
- Obtain blood samples for PK analysis at 1 hour (0.5-1.5h) and 3 hours (2-4h) post tofacitinib administration. If feasible for the subject, this second blood sample should be drawn between 3 to 4 hours post dose, however any time between 2 to 4 hours post dose is allowed. Refer to Section 8.4 for details.

- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- **For subjects using contraception:** perform a contraceptive check, to ensure contraception is consistently and correctly used.
- Assess for adverse events.
- Assess investigational product dosing compliance.
- Dispense investigational product.

6.6. Randomization Visit: Start Double-blind Withdrawal Phase

Subjects who are able to maintain an Adapted JIA ACR 30 response for 4 weeks on a stable tapered CS dose in the open-label phase are eligible for randomization into the double-blind withdrawal phase. At the randomization visit subjects will be assigned to continue treatment with a stable dose of tofacitinib or start placebo in a 1:1 ratio.

The randomization visit can be combined with the last visit of the Open-label phase. In such cases, the Randomization CRF will need to be completed, but evaluations done as part of the Open-label visit, do not need to be repeated.

The procedures and assessments listed below will be performed at the Randomization visit. The window for this visit is ±5 days.

- After confirmation that the subject is eligible, obtain a randomization number through the IRT system.
- Review concomitant medications. Refer to Section 5.8.
- Targeted physical exam, including skin examination for chickenpox or shingles.
- Perform a risk factor check for venous thromboembolism. Refer to Section 8.2.13 for details.
- Vital signs, height and weight.
- Review temperature diary and assess “Fever” and “Absence of fever”:

- Obtain subject's oral temperature and assess "Fever", defined as temperature >38° C/100.4° F;
- **MAS diagnosis: Only if subject has fever and MAS is suspected:** obtain blood samples to evaluate Ferritin, Platelets, Triglycerides and Fibrinogen levels. Refer to Section 8.2.11 for details regarding these blood sample collections;
- Evaluate "Absence of fever", defined as documented absence of fever due to systemic JIA in the week preceding this visit. Record the outcome in the eCRF for calculation of the Adapted JIA ACR response.

- Assess the sJIA Disease Activity status:
  - Fever (see above);
  - Number of joints with limitation in range of motion;
  - Number of joints with active arthritis (swelling and/or pain/tenderness);
  - Assess duration of morning stiffness;
  - Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA;
  - Uveitis status: document presence/ absence of active uveitis;
  - Physician's Global Assessment of Overall Disease Activity;
  - Administer the Childhood Health Assessment Questionnaire (CHAQ); evaluate Patient wellbeing as part of the CHAQ on a 21 circle VAS;
  - Administer Child Health Questionnaire;
  - ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF.

    **For "real-time" assessment of the Adapted JIA ACR 30 Response during a study visit the subject's ESR instead of CRP will be used to determine the percent change in inflammation biomarker.*

- Assess the Adapted JIA ACR response based on ESR and record result on appropriate CRF:
  - Enter data for the core components of JIA ACR pediatric criteria in the eCRF for calculation of the Adapted JIA ACR 30 response based on ESR;*

  - Fax the sJIA Disease Assessment worksheets and JIA ACR core component CRF to the Coordinating Center for confirmation of the Adapted JIA ACR 30 response based on ESR;

  - Record the evaluation of the Adapted JIA ACR 30 response on the relevant eCRF after receipt of faxed result from the Coordinating Center. Once a subject is able to maintain the Adapted JIA ACR 30 response for 4 weeks on a stable tapered CS dose in the open-label phase they can start the Double-blind Phase.

- Obtain blood or urine sample(s) for the following tests and send to central laboratory. Refer to Section 8.2.12 for sample collection details:

  - Hematology;

  - Chemistry;

  - Only every 3 months after Day 1: Lipid panel (under fasting conditions for approximately 9 to 12 hours, if possible);

  - CRP;

  - Urinalysis.

- Obtain blood samples for banking of biospecimens. This blood sample collection is optional, at the parent/legal guardian's discretion. Refer to Section 8.5 for details.

- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.

- **For subjects using contraception:** perform a contraceptive check, to ensure contraception is consistently and correctly used.

- Assess for adverse events.

- Assess investigational product dosing compliance.

- Dispense investigational product.

6.7. Double-blind Withdrawal Phase: Visits Every 4 Weeks after Randomization Visit

After randomization in the double-blind withdrawal phase, each subject will have visits on a monthly basis until they experience a sJIA flare, or experience 24 consecutive weeks of inactive disease as assessed using JIA ACR (clinical remission), or until the requisite number of flares have been reported (refer to Section 11) and the study is considered completed.

The procedures and assessments listed below will be performed at every visit of the double-blind withdrawal phase. The window for these visits is ±5 days.

- Evaluate concomitant medications. Refer to Section 5.8.
- Targeted physical exam, including skin examination for chickenpox or shingles.
- Perform a risk factor check for venous thromboembolism. Refer to Section 8.2.13 for details.
- Vital signs, height and weight.
- Review temperature diary and assess "Fever" and "Absence of fever":
  - Obtain subject's oral temperature and assess "Fever", defined as temperature >38° C/100.4° F;
  - **MAS diagnosis: Only if subject has fever and MAS is suspected:** obtain blood samples to evaluate Ferritin, Platelets, Triglycerides and Fibrinogen levels. Refer to Section 8.2.11 for details regarding these blood sample collections;
  - Evaluate "Absence of fever", defined as documented absence of fever due to systemic JIA in the week preceding this visit. Record the outcome in the eCRF for calculation of the Adapted JIA ACR response.
- Assess the sJIA Disease Activity status:
  - Fever (see above);
  - Number of joints with limitation in range of motion;
  - Number of joints with active arthritis (swelling and/or pain/tenderness);
  - Assess duration of morning stiffness;
  - Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA;
  - Uveitis status: document presence/absence of active uveitis;
  - Physician's Global Assessment of Overall Disease Activity;
  - Administer the Childhood Health Assessment Questionnaire (CHAQ); evaluate Patient wellbeing as part of the CHAQ on a 21 circle VAS;
  - Only every 6 months after the randomization visit: Administer Child Health Questionnaire;
  - ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF.

**For "real-time" assessment of the sJIA Flare during a study visit the subject's ESR will be used to determine the percent change in inflammation biomarker.*

- Assess sJIA flare and Adapted JIA ACR response based on ESR and record result on appropriate CRF:
  - Enter data for the core components of JIA ACR pediatric criteria (besides the CRP level) in the eCRF to determine if a subject has met the criteria for sJIA flare (with Adapted JIA ACR 30 response based on ESR*);
  - Fax/email the sJIA Disease Assessment worksheets and JIA ACR core component CRF to the Coordinating Center for confirmation of the Adapted JIA ACR 30 response based on ESR. A subject who is confirmed to have a sJIA flare should be discontinued;
  - Record the sJIA flare assessment on relevant eCRF after receipt of faxed result from the Coordinating Center.
- Obtain blood or urine sample(s) for the following tests and send to central laboratory. Refer to Section 8.2.12 for sample collection details:
  - Hematology;
  - Chemistry;
  - Only every 3 months after Day 1: Lipid panel (under fasting conditions for approximately 9 to 12 hours, if possible);
  - CRP;
  - Urinalysis.
  - **For subjects in countries where TB incidence has been reported at a rate of >50 cases per 100,000 persons**, eg, China, India, Russian Federation; South Africa and Ukraine (World Health Organization): every 12 months after screening: obtain blood sample for yearly TB testing (QFT-Gold or Gold Plus).
- **For subjects who meet the sJIA flare criteria or who reach inactive disease status:** Obtain blood samples for banking of biospecimens. This blood sample collection is optional, at the parent/legal guardian's discretion. Refer to Section 8.5 for details.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- **For subjects using contraception:** perform a contraceptive check, to ensure contraception is consistently and correctly used.

- Assess for adverse events.
- Assess investigational product dosing compliance.
- Dispense investigation product.

6.7.1. Discontinuation from Investigational Product during Randomized Withdrawal Phase

Subjects who discontinue Investigational Product in the double-blind phase, for reasons other than sJIA flare, and who do not rollover to A3921145 LTE study, should continue with the regular scheduled visits every 4 weeks up to and including Week 52. All required procedures and assessments listed above should be performed with the exception of IP dispensing and compliance. Subjects should receive standard-of-care treatment as per local guidelines. There are no protocol restrictions on the use of DMARDs and other disallowed agents, detailed in Appendix 1, for subjects receiving standard of care treatment.

6.8. End of Study or Early Termination Visit

Each subject's participation in the study will end once the subject experiences a first sJIA flare in the double-blind phase or 24 consecutive weeks of inactive disease (clinical remission). An end-of-study visit should be performed.

Subjects who are not able to maintain an Adapted JIA ACR 30 response for 4 weeks in the open-label phase, or who have fever due to sJIA lasting more than 2 consecutive days in Part 1, or who fail CS tapering more than twice in Part 2 of the open-label phase will need to be discontinued from the study.

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

- Subjects who discontinue investigational product in the double-blind phase and who do not enter A3921145 will be required to continue in the study and perform all scheduled visits until Week 52 after randomization or until the study concludes, whichever comes first. Such subjects should transition to standard-of care treatment in accordance with local guidelines.
- Subjects who discontinue in the Open-Label Phase and do not enter A3921145 will be required to return for a follow up visit 28 days after the last dose of study treatment.

The study will be completed once the requisite number of subjects have reported flare in the double-blind withdrawal phase (refer to Section 11). At that time and upon notification by the Sponsor, the investigator will be required to schedule an end-of-study visit for all remaining active subjects.

If a subject discontinues from the study at a regularly scheduled study visit, all assessments and procedures for that visit should be completed. In addition, a Tanner stage assessment should be done as part of the study termination. If a subject discontinues outside of a regularly scheduled visit, an Early Termination visit should be scheduled as soon as possible. The procedures and assessments listed below will be performed at the End of Study or Early Termination visit.

Subjects should be instructed to fast, if possible, for lipid panel testing.

- Review concomitant medications. Refer to Section 5.8.
- Complete physical exam, including skin examination for chickenpox or shingles. **Country specific amendment for EU sites (including UK):** a full skin cancer examination must be performed as part of the complete physical examination.
- Perform a risk factor check for venous thromboembolism. Refer to Section 8.2.13 for details.
- Vital signs, height and weight.
- Review temperature diary and assess "Fever" and "Absence of fever":
- Obtain subject's oral temperature and assess "Fever", defined as temperature >38° C/100.4° F.
    - **MAS diagnosis: Only if subject has fever and MAS is suspected:** obtain blood samples to evaluate Ferritin, Platelets, Triglycerides and Fibrinogen levels. Refer to Section 8.2.11 for details regarding these blood sample collections.
    - Evaluate "Absence of fever", defined as documented absence of fever due to systemic JIA in the week preceding this visit. Record the outcome in the eCRF for calculation of the Adapted JIA ACR response.
    - Evaluate the pubertal development using the Tanner Stages.
- Assess the sJIA Disease Activity status:
    - Fever (see above);
    - Number of joints with limitation in range of motion;
    - Number of joints with active arthritis (swelling and/or pain/tenderness);
    - Assess duration of morning stiffness;
    - Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA;

- Uveitis status: document presence/ absence of active uveitis;
- Physician's Global Assessment of Overall Disease Activity;
- Administer the Childhood Health Assessment Questionnaire (CHAQ); evaluate Patient wellbeing as part of the CHAQ on a 21 circle VAS;
- Administer Child Health Questionnaire;
- ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF.

- Assess Adapted JIA ACR 30 Response and sJIA flare and record result in appropriate CRF:
  - Record results for 6 core components of JIA ACR pediatric criteria in the eCRF for the calculation of the Adapted JIA ACR 30 response, JADAS-27 and sJIA flare.

    **For "real-time" assessment of the Adapted JIA ACR 30 Response and/or sJIA Flare during a study visit the subject's ESR will be used to determine the percent change in inflammation biomarker.*
  - Fax the sJIA Disease Assessment worksheets and JIA ACR core component CRF to the Coordinating Center for confirmation of the Adapted JIA ACR 30 response based on ESR.
  - Record the evaluation of the Adapted JIA ACR 30 Response on the relevant eCRF after receipt of faxed result from the Coordinating Center.
- Obtain blood sample(s) for the following tests and send to central laboratory. Refer to Section 8.2.12 for sample collection details:
  - Hematology;
  - Chemistry;
  - Lipid panel (under fasting conditions for approximately 9 to 12 hours, if possible);
  - CRP;
  - Urinalysis.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- **For subjects using contraception:** perform a contraceptive check, to ensure contraception is consistently and correctly used.

- **For subjects who meet the sJIA flare criteria or who reach inactive disease status:** Obtain blood samples for banking of biospecimens. Refer to Section 8.5 for details.
- Assess for adverse events.
- Assess investigational product dosing compliance.
- Review entrance criteria for long-term extension study (A3921145).

6.9. Follow-Up Visit (Only For Subjects Not Entering Study A3921145)

At least 28 days after the last dose of study medication, subjects who did not rollover into study A3921145 will return for a follow-up visit. This visit will not be required for subjects who discontinue investigational product in the double-blind phase and remain in the study. There is a +7 day window for this visit. The procedures and assessments listed below will be performed at this visit:

- Review concomitant medications. Refer to Section 5.8.
- Targeted physical exam, including skin examination for chickenpox or shingles.
- Perform a risk factor check for venous thromboembolism. Refer to Section 8.2.13 for details.
- Vital signs, height and weight.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- **For subjects using contraception:** perform a contraceptive check, to ensure contraception is consistently and correctly used.
- Assess for adverse events.
- **Only if subject discontinued in the double-blind phase for other reasons than "flare" per protocol before Week 24 (of the double-blind phase):**
  - Review temperature diary and assess "Fever" and "Absence of fever";
  - Obtain subject's oral temperature and assess "Fever", defined as temperature >38° C/100.4° F.
    - **MAS diagnosis: Only if subject has fever and MAS is suspected:** obtain blood samples to evaluate Ferritin, Platelets, Triglycerides and Fibrinogen levels. Refer to Section 8.2.11 for details regarding these blood sample collections;

- Evaluate "Absence of fever", defined as documented absence of fever due to systemic JIA in the week preceding this visit. Record the outcome in the eCRF for calculation of the Adapted JIA ACR response.

- Assess the sJIA Disease Activity status:
  - Fever (see above);
  - Number of joints with limitation in range of motion;
  - Number of joints with active arthritis (swelling and/or pain/tenderness);
  - Assess duration of morning stiffness;
  - Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA;
  - Uveitis status: document presence/absence of active uveitis;
  - Physician's Global Assessment of Overall Disease Activity;
  - Administer the Childhood Health Assessment Questionnaire (CHAQ); evaluate Patient wellbeing as part of the CHAQ on a 21 circle VAS;
  - ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF.
- Administer Child Health Questionnaire.
- Assess sJIA flare and record result in appropriate CRF:
  - Record results for 6 core components of JIA ACR pediatric criteria in the eCRF for the calculation of the sJIA flare;

    **For "real-time" assessment of the sJIA Flare during a study visit the subject's ESR will be used to determine the percent change in inflammation biomarker.*
  - Fax the sJIA Disease Assessment worksheets to the Coordinating Center for confirmation of the sJIA Flare status based on ESR;
  - Record the evaluation of the sJIA Flare status on the relevant eCRF after receipt of faxed result from the Coordinating Center.
- Obtain blood and urine sample(s) for the following tests and send to central laboratory:
  - Hematology;
  - Chemistry;

- Lipid panel (under fasting conditions for approximately 9 to 12 hours, if possible);
- CRP;
- Urinalysis.

- **For subjects who meet the sJIA flare criteria or who reach inactive disease status:** Obtain blood samples for banking of biospecimens. Refer to Section 8.5 for details.

6.10. Unscheduled Study Visit or Telephone Contact

The parent/legal guardian will be requested to contact the study staff by telephone if the subject has sJIA fever for more than 1 consecutive day, other symptoms of a sJIA exacerbation/MAS, or other adverse events of concern. The investigator will determine whether an additional study visit is required for further assessment of the subject's adverse event. If the subject is suspected to experience a sJIA flare, or MAS, an unscheduled visit is mandatory.

The unscheduled visit assessments may include the following:

- Complete physical exam, including skin examination for chickenpox or shingles, vital signs, height and weight. **Country specific amendment for EU sites (including UK):** a full skin cancer examination must be performed as part of the complete physical examination.
- Review concomitant medications. Refer to Section 5.8.
- Review temperature diary and assess "Fever" and "Absence of fever":
  - Obtain subject's oral temperature and assess "Fever", defined as temperature >38° C/100.4º F;
  - **MAS diagnosis: Only if subject has fever and MAS is suspected:** obtain blood samples to evaluate Ferritin, Platelets, Triglycerides and Fibrinogen levels. Refer to Section 8.2.11 for details regarding these blood sample collections;
  - Evaluate "Absence of fever", defined as documented absence of fever due to systemic JIA in the week preceding this visit. Record the outcome in the eCRF for calculation of the Adapted JIA ACR response.
- Assess the sJIA Disease Activity status:
  - Fever (see above);
  - Number of joints with limitation in range of motion;
  - Number of joints with active arthritis (swelling and/or pain/tenderness);
  - Assess duration of morning stiffness;

- Assess extra-articular sJIA manifestations: rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA;
- Uveitis status: document presence/absence of active uveitis;
- Physician's Global Assessment of Overall Disease Activity;
- Administer the Childhood Health Assessment Questionnaire (CHAQ); evaluate Patient wellbeing as part of the CHAQ on a 21 circle VAS;
- Administer Child Health Questionnaire;
- ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF;
- Assess Adapted JIA ACR 30 response, and/or sJIA flare and record result on appropriate CRF.
    - Enter data for 6 core components of JIA ACR pediatric criteria in the eCRF for the calculation of the Adapted JIA ACR 30 response, JADAS-27 and sJIA flare;

      **For "real-time" assessment of the Adapted JIA ACR 30 Response and/or sJIA Flare during a study visit the subject's ESR level will be used to determine the percent change in inflammation biomarker.*
    - Fax/email the sJIA Disease Assessment worksheets and JIA ACR core component CRF to the Coordinating Center for confirmation of the Adapted JIA ACR 30 response based on ESR;
    - Record the evaluation of the Adapted JIA ACR 30 response value on relevant eCRF after receipt of faxed result from the Coordinating Center.

- Assess for adverse events.
- Perform a risk factor check for venous thromboembolism. Refer to Section 8.2.13 for details.
- Obtain blood sample(s) for the following tests and send to central laboratory. Refer to Section 8.2.12 for sample collection details:
    - Hematology;
    - Chemistry;
    - Lipid panel (under fasting conditions for approximately 9 to 12 hours, if possible);
    - CRP;

- Urinalysis.

- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.

- **For subjects using contraception:** perform a contraceptive check, to ensure contraception is consistently and correctly used.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following;

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

The criteria for discontinuation of investigational product in the open-label phase, (part 1 and part 2), are detailed in Section 3.2.

If study intervention is permanently discontinued during the double-blind phase, and the participant does not enter A3921145, the participant should remain in the study for follow-up to be evaluated for safety and efficacy endpoints. See the SCHEDULE OF ACTIVITIES and Section 6 for data to be collected at the time of discontinuation of study intervention and follow-up visit requirements.

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

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up and/or future collection of additional information.

7.2. Subject Withdrawal from Study

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

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

7.2.1. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for/attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

7.2.2. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention, and who do not enter A3921145, will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent/assent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

8. 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 cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or 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.

Efficacy evaluators must receive and document protocol specific and efficacy assessment scales training prior to performing evaluations. To assure consistency and reduce variability, the same evaluator should assess the clinical evaluations for any individual subject throughout the study; a back-up experienced and qualified, protocol-trained evaluator is allowed in case of emergency or special situation when the designated evaluator is unable to perform the evaluation; this must be documented. The identity (eg, initials) of the evaluator should be captured on the source documentation (eg, worksheet).

8.1. Efficacy Assessments

Throughout the study the sJIA disease activity of each subject will be evaluated in a multidimensional manner and multiple signs and symptoms related to inflammation will be assessed. These include biochemical markers of inflammation (eg, ESR, CRP, See Section 8.1.6.3 for complete details), quantifying the amount of inflammatory tissue (eg, evaluation of joints), and assessing the clinical consequences of inflammation (eg, health questionnaires, Fever, Adapted JIA ACR response).

8.1.1. Number of Joints with Active Arthritis/Limitation of Motion

At each study visit, joints with swelling, pain on motion, tenderness and limitation of motion will be assessed and recorded on the appropriate CRF. The results will be faxed/emailed to the Centralized Coordinating Center (See Section 8.1.12).

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

Swelling will be assessed in the following joints:

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

Pain/Tenderness will be assessed in the following joints:

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

Metatarsophalangeal (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, Metacarpophalangeal (MCP I-V), Proximal Interphalangeal (PIP I-V), Distal Interphalangeal (II-V), Hip, Knee, Ankle, Subtalar joints, Intertarsal joints, Metatarsophalangeal (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.

8.1.2. Fever and Absence of Fever Assessment

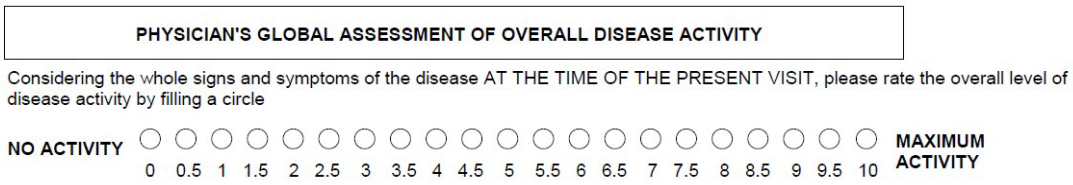
At each study visit, the subject's oral temperature will be taken. From Day 7 onward, the subject will also be asked if they had fever, defined as temperature >38° C (100.4° F), due to sJIA, in the last 7 days before the visit. "Absence of fever", defined as the documented absence of fever due to sJIA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

Subjects will be provided with a thermometer to measure their oral temperature on days that have fever symptoms. Each subject will receive a diary at Screening 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.

8.1.3. Physician's Global Assessment of Overall Disease Activity

At each study visit, following an assessment of the number of joints with swelling, pain/tenderness and limitation of motion, the investigator will provide an assessment of the subject's overall level of disease activity. This evaluation is based on the subject's disease signs, functional capacity and physical examination. This evaluation is based on the subject's disease signs, functional capacity and physical examination. The result will be faxed/emailed to the Centralized Coordinating Center (see Section 8.1.12).

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 a 21-numbered circle visual analog scale (VAS), as shown below.



8.1.4. Childhood Health Assessment Questionnaire (CHAQ)

At each study visit, the Childhood Health Assessment Questionnaire (CHAQ) assessment will be administered to the parent/legal guardian or an adult caregiver interacting daily with the subject. Parents/legal guardians or an adult caregiver interacting daily with the subject will complete this assessment for the duration of study. The results of the questionnaire will be faxed/emailed to the PRCSG/PRINTO Centralized Coordinating Center (see Section 8.1.12). Every effort should be made to have the same individual complete the CHAQ throughout the course of the study. The CHAQ (Singh 1994)[11] is a validated instrument and comprises two indices, Disability and Discomfort, and a global assessment of arthritis (overall well-being). The CHAQ has been cross-culturally adapted and validated in more than 30 languages by the PRINTO group.[12]

The CHAQ assessment will be based on the responses, as confirmed by the Centralized Coordinating Center.

Disability Index

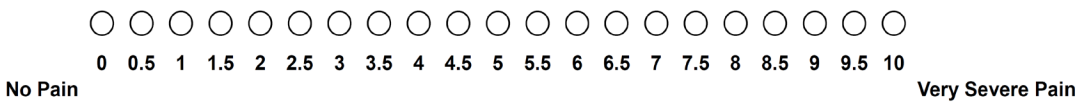
The parent/legal guardian or adult caregiver interacting daily with the subject will be asked to provide responses to questions designed to assesses function in 8 areas, including dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities-distributed, among a total of 30 items. 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.

Discomfort Index

For the assessment of discomfort, the parent/legal guardian or 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:"

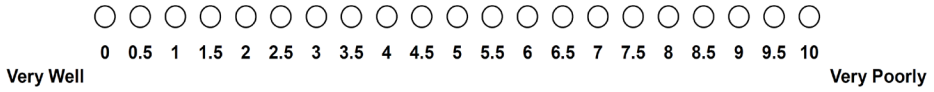
The parent/legal guardian or adult caregiver interacting daily with the subject will rate the overall pain by entering a number from 0 to 10 (in 0.5 increments), with '0' as 'No Pain' and '10' as 'Very Severe Pain' on a 21-circle visual analog scale (VAS), as shown below.



Parent/Legal Guardian/Adult Caregiver Global Assessment of Overall Well-Being

For the assessment of overall well-being, the parent/legal guardian or 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/or legal guardian or adult caregiver interacting daily with the subject will rate the 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-circle visual analog scale (VAS), as shown below.



8.1.5. Child Health Questionnaire (CHQ)

At baseline (Day 1), the end of Part 1 and Part 2 of the open-label phase, randomization and every 6 months thereafter the parent/legal guardian or adult caregiver interacting daily with the subject will be asked to complete a Child Health Questionnaire (CHQ). Parents/legal guardians or adult caregiver interacting daily with the subject will complete this assessment for the duration of study.

The CHQ (Landgraf 1996)[13] is a validated general pediatric quality of life instrument. The CHQ assesses for 14 physical and psychosocial domains: general health perceptions, physical functioning, role/social physical functioning, bodily pain, role/social emotional functioning, role/social behavioral functioning, parent/legal guardian/adult caregiver impact-time, parent/legal guardian/adult caregiver impact-emotional, self-esteem, mental health, behavior, family activities, family cohesion, and change in health.

The response options for the CHQ are ordinal scales that vary by the item. Each item consists of 4–6 response options. Additionally, each scale consists of varying numbers of items.

The CHQ score will be determined based on the parent/legal guardian/adult caregiver's questionnaire responses.

8.1.6. Inflammatory, Rheumatic Disease and MAS Markers

Laboratory markers of active disease in sJIA include the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In this study, testing for both ESR and CRP will be performed in all subjects at each study visit.

8.1.6.1. C-Reactive Protein (CRP)

At each study visit, a blood sample for CRP testing will be collected and sent to the central laboratory for determination.

8.1.6.2. Erythrocyte Sedimentation Rate (ESR)

At each study visit, ESR (Westergren Method) will be determined locally utilizing an ESR Testing Kit which will be provided to the investigator site by the Sponsor. Please refer to the ESR Testing Kit for detailed instructions on how to perform this test appropriately.

The ESR result will be recorded on the appropriate CRF. The ESR result will also be faxed/emailed to the Centralized Coordinating Center which, along with other JIA core set variables, will be used to perform efficacy assessments at each visit. A local lab ESR testing kit (Westergren method) can be substituted for a Sponsor kit only if supply issues have resulted in a Sponsor kit not being available at the time of the visit.

8.1.6.3. Other Inflammatory and Rheumatic Disease Markers

At screening, additional inflammatory and rheumatic disease markers, such as Rheumatoid Factor (RF) and albumin (as part of serum chemistry) will also be assessed. On Day 1 ferritin levels, will be evaluated as another marker of rheumatic disease status.

8.1.6.4. Macrophage Activation Syndrome (MAS) Markers

If MAS is suspected in a febrile subject during a study visit, an extra blood sample will be collected to assess Ferritin (1.1 mL blood), Platelets (part of hematology assessment), Triglycerides (part of lipid assessment) and Fibrinogen serum levels (1.4 mL blood) in order to confirm a diagnosis of MAS. Refer to Section 8.2.3 for further details.

8.1.7. Adapted ACR 30 Pediatric Criteria: JIA Core Set Variables and Response

The disease activity of sJIA will be measured using an adaptation of the JIA American College of Rheumatology (ACR) 30 response. The Adapted JIA ACR 30 Response criteria include the components of the pediatric ACR core set along with the absence of fever due to sJIA in the preceding 7 days.[14] Fever is defined as temperature >38° C (100.4° F). The Adapted JIA ACR 30, 50, 70, 90, 100 response is defined as the absence of fever due to sJIA in the preceding 7 days along with at least 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%, which include:

- Number of joints with active arthritis;
- Number of joints with limited range of motion;
- Physician global evaluation of disease activity;
- Parent/ legal guardian/Child evaluation of overall well-being;
- Functional ability (CHAQ Disability Index);

- ESR.*

The Adapted JIA ACR 30, 50, 70, 90, 100 response rate will be determined at every visit from Day 7 onward based on the investigator's and parent/legal guardian's assessment of components of the JIA core set variables.

*For "real-time" assessment of the Adapted JIA ACR 30 Response during a study visit the subject's ESR will be used to determine the percent change in inflammation biomarker. CRP may be used for analysis of other related endpoints (details will be provided in the Statistical Analysis Plan [SAP]).

At the end of the open-label phase, only subjects who were able to maintain an Adapted JIA ACR 30 response for at least 4 weeks in accordance with the protocol requirements of Section 3.2, will be randomized into the double-blind, placebo-controlled phase.

Achievement and maintenance of an Adapted JIA ACR 30 response in the open-label phase will need be confirmed by the Centralized Coordinating Center. Investigators must enter this confirmation in the eCRF at every study visit from the Day 7 visit onward.

Following confirmation, the investigator site will randomize the subject utilizing the Sponsor's Interactive Response Technology (IRT) system (see Section 5.1).

8.1.8. Disease Flare Criteria

The Disease Flare (Brunner 2002)[15] determination is a derived measurement utilizing each component of the JIA core set variables (see Section 8.1.7).

Flare is defined as a worsening of 30% or more in 3 or more of the 6 variables of the JIA core set, with no more than one variable improving by 30% or more. In addition, for sJIA a Disease Flare may also constitute a recurrence of fever.

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

- Recurrence of fever (>38° C/100.4° F) on 2 or more consecutive days) considered to be due to SJIA activity.

- Worsening of 30% or more in three or more of the six variables of the JIA core set with no more than one variable of the JIA core set improving by 30% compared to the day of randomization into the withdrawal phase.*

  **Note: For "real-time" assessment of sJIA flares during a study visit the subject's ESR will be used to determine the JIA core component related to percent change in inflammation biomarker. However, CRP may be used for analysis of other related endpoints (details will be provided in the Statistical Analysis Plan [SAP]).*

For evaluation of sJIA flare the following applies: If the Physician or parent/legal guardian global scores are used in the definition of flare, then there must be an increase of at least 2 units on a 0-10 VAS scale. If the number of active joints or number of joints with loss of

motion is used in the definition of flare, then there must be an increase of at least 2 joints. If the ESR is used in the definition of flare, then the value at the visit in which flare is being assessed must be out of the normal range (ESR >20 mm/hr). Investigators will be required to complete relevant CRF pages regarding sJIA Disease Status while the subject is at the clinic, and email or fax the sJIA Disease Assessment worksheets to the Coordinating Center for confirmation of the sJIA flare based on ESR. The confirmation whether a subject has a sJIA Flare per protocol will need to be entered in the eCRF upon receipt of the assessment from the Coordinating Center. At each visit ***in the double-blind phase***, the investigator will evaluate the subject for evidence of disease flare. Subjects who experience a single episode of disease flare in the double-blind phase (based on the investigator's and parent/legal guardian's assessment of components of the JIA core set variables), will be discontinued from the study.

8.1.9. JIA ACR Clinical Inactive Disease and Clinical Remission Criteria

The American College of Rheumatology (ACR) Clinical Inactive Disease and Clinical Remission (Wallace 2011)[16] criteria are defined as follows:

Clinical Inactive Disease:

- No joints with active arthritis;
- No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to sJIA;
- No active uveitis (as defined by the SUN Working Group);
- Normal ESR* (within normal limits of the method used where tested) or, if elevated, not attributable to s JIA;
- Physician global assessment of disease activity score of 'best possible' on the scale used;
- Duration of morning stiffness of ≤15 minutes.

**The subject's ESR result will be used for "real-time" assessment.*

Clinical Remission:

- Clinical Inactive disease for 6 months continuously while on medications.

Inactive disease and clinical remission based on the ACR criteria will be evaluated at every visit from Day 7 onward based on the investigator's and parent/legal guardian's assessment of components of the sJIA disease status.

8.1.10. Juvenile Arthritis Disease Activity (JADAS-27 CRP; JADAS-27 ESR) Score

The Juvenile Arthritis Disease Activity score is a validated composite disease activity measure for JIA (Consolaro 2009).[18] Recently, the scoring system was adapted to use the

27-joint count (Bazso 2009),[20] and C-reactive protein (CRP) in place of Erythrocyte Sedimentation Rate [ESR]) for the inflammatory marker component (Nordal 2012).[21]

JADAS-27 CRP (JADAS-27 ESR) score will be determined based on four components:

- Physician global assessment of disease activity;
- Parent/legal guardian global assessment of well-being (from the CHAQ);
- Number of joints with active disease (27 joint assessment);
- CRP or ESR as applicable.

8.1.11. 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)[18] 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 score will be determined based on the investigator and parent/legal assessment of the above components.

8.1.12. Centralized Coordinating Center

This study will utilize a Centralized Coordinating Center to review and confirm, in real time, efficacy assessments, including sJIA fever assessment, JIA core set variables, extra-articular sJIA features, Adapted JIA ACR 30, 50 response, sJIA disease flare and inactive disease, according to validated criteria, at various time points throughout the study.

In addition, the Centralized Coordinating Centers will review CS regimens of study participants. The Centralized Coordinating Centers will suggest a customized 4-week CS tapering schedule for each subject entering the Open-label Phase Part 2. Subjects are required to contact the investigator if they experience any symptoms of a sJIA flare; if required, an extra unscheduled visit will be conducted to assess the adverse event. The tapering schedule will be re-evaluated in consultation with the Coordinating Centers.

The Centralized Coordinating Center will also provide recommendations in case participants are not able to maintain a stable CS dose in the double-blind phase. Furthermore, the

Centralized Coordinating Center will provide guidance regarding discontinuation of any subject based on CS regimen.

To facilitate this evaluation, at each visit study visit the investigator site will fax/email the results of each of the following JIA core set variable assessments to the Centralized Coordinating Center:

- Complete joint examination form;
- Physician's Global Assessment of Overall Disease Activity;
- Parent's global assessment of overall well-being (CHAQ);
- Assessment of extra-articular sJIA manifestations;
- Functional ability (CHAQ);
- ESR for same-day assessment;
- CS regimen changes since last visit (only in Part 2 of the Open-label phase).

Evaluation of faxed results will be performed in real time (within 90 minutes of receipt) by independent evaluators at the Centralized Coordinating Center. The Centralized Coordinating Center will provide the investigator site with confirmation of receipt of faxed information.

The Centralized Coordinating Center may contact the investigator site directly to confirm the accuracy of information submitted following review and assessment.

Faxed results of efficacy evaluations by the Centralized Coordinating Center will need to be entered promptly in the eCRF during a subject's study visit.

Please refer to the Centralized Coordinating Center manual for details regarding instructions relating to submission of required information and other logistical information.

8.2. Safety Assessments

Safety will be assessed by the spontaneous reporting of adverse events (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.

Please refer to Appendix 7 for guidelines for safe monitoring and discontinuations due to laboratory abnormalities, serious infections, opportunistic infections, and malignancies.

Please refer to Section 10.9 for the evaluation of potentially malignant tumors, suspicious lymphadenopathy, possible extra-nodal lymphoproliferative disorder.

8.2.1. Medical and Family History

At the time of screening, a medical and family history will be obtained. Medical history should include information on the subject's primary arthritis-related diagnosis (including duration), any other baseline medical conditions, allergies, and tobacco and alcohol use. Family history should include inquiry about family members with immunodeficiency and premature coronary heart disease.

8.2.2. 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.

If a rash is present, the type of rash should be noted (eg, typical sJIA rash, varicella rash, herpes zoster lesions, or other types of rash). Please refer to Section 9.2.6.

Country specific amendment for EU sites (including UK): 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 (presence of rash), heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes. Any clinically significant changes from the baseline examination should be recorded as AEs.

If a rash is present, the type of rash should be noted (eg, typical sJIA rash, varicella rash, herpes zoster lesions, or other types of rash). Please refer to Section 9.2.6.

8.2.3. Macrophage Activation Syndrome Assessment (MAS)

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.[7]

Subjects 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/EULAR/PRINTO Criteria,[17] 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 10^9/L;
- AST >48 U/L;
- Triglycerides >156 mg/Dl;
- Fibrinogen ≤360 mg/dL.

8.2.4. Uveitis Assessment

At screening a formal uveitis assessment will not be required, but, if applicable, documentation of previous uveitis assessment(s) by an ophthalmologist (or qualified equivalent per local practice) should be reviewed to document presence/absence of active uveitis. At every visit from Day 7 onward a confirmation of the subject's uveitis status will be required as part of the JIA ACR inactive disease evaluation referenced in Section 8.1.9.

8.2.5. Vitals Signs Assessment

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 to be collected in the sitting position, supine position is allowed. Position should be documented in the CRF and should be consistent throughout the study.

Pulse Rate

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

Temperature

It is preferred that body temperature be collected orally using a digital thermometer and that the same method should be used consistently throughout the study.

Height and Weight

Weight should be reported at each visit with height preferentially measured utilizing a Harpenden stadiometer. Height will be evaluated on a monthly basis.

8.2.6. Varicella (chickenpox) and Herpes Zoster (shingles) Assessment and Guidance

All 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 screening. 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 (eg, 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 also 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.

8.2.7. Pubertal Development Assessment (Tanner Stages)

Determination of physical and sexual maturation will be performed at the Screening and at the End of Study or Early Termination visit using the Tanner stages (Dorn 1990, Taylor 2001)[19,26] by a trained physician/clinician in the presence of a parent/legal guardian or clinic staff member.

In the event the parent/legal guardian or subject 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.

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 United States begins as early as age 8 and completes as late as age 17.

8.2.8. Tuberculosis Testing

At the time of screening, all subjects will under tuberculosis (TB) testing. QuantiFERON®-TB Gold or Gold Plus (according to the country regulations and approvals) In-Tube Test is the preferred testing method. If the QuantiFERON®-TB Gold or Gold Plus In-Tube test cannot be performed, or if the results cannot be determined by the reference laboratory to be either positive or negative, then subjects may be screened using a negative Quantiferon®-TB test performed locally or the Purified Protein Derivative (PPD) Tuberculin Skin Test (Mantoux method) or T-Spot TB test with Sponsor approval.

In addition to TB testing as specified in this clinical protocol, a chest X-ray may be performed to aid in TB status determination, according to local standards and/or in countries with a high incidence rate of TB.

Annual TB testing: In addition to the TB testing performed at screening, 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; India, South Africa and Ukraine. (World Health Organization).

Country-specific amendment for EU sites (including UK): 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.

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

QuantiFERON®-TB (QTF-TB) Gold or Gold Plus test will be available according to the country regulations and approvals.

QuantiFERON®-TB Gold and Gold Plus In-Tube test (Guidelines 2005)[10] are in vitro diagnostic tests using a peptide cocktail simulating ESAT-6, CFP-10 proteins (QTF-TB Gold Plus) or ESAT-6, CFP-10 and TB7.7 proteins (QTF-TB Gold) 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 In-Tube 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.

A blood sample of approximately 3 mL (QTF-TB Gold) or 4 mL (QTF-TB Gold Plus) will be collected at screening for QuantiFERON®-TB Gold In-Tube testing.

Following sample processing, the sample will be shipped to the Sponsor's designated reference laboratory for testing. The procedure for processing and preparing the sample for shipment is described fully in the laboratory manual, which will be provided to investigators.

A negative PPD or T-Spot TB 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 and the Pfizer Medical Monitor approves it, on a case-by-case basis.

8.2.8.2. Purified Protein Derivative (PPD) Test or T-Spot TB Test

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, then subjects can be screened using the Purified Protein Derivative (PPD) Tuberculin Test (Mantoux method) or T-Spot TB test, with the approval of the Pfizer Medical Monitor.

Subjects must have the PPD 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 and interpreted in consultation with the Sponsor.

8.2.9. Laboratory Testing

Blood and/or urine samples for tests specified below will be collected at the time points specified in the SOA and sent to the Sponsor's designated central laboratory for testing. The shipment address of the central laboratory contact information will be provided to investigator sites prior to initiation of the study. One re-testing of a screening hematology or serum chemistry laboratory parameter is allowed if the abnormal lab(s) was an uncharacteristic result(s). Re-testing must be completed within the screening period.

- **Hematology:** Hemoglobin, hematocrit, red blood cells, white blood cells, neutrophils (%, absolute), lymphocytes (%, absolute), monocytes (%, absolute), eosinophils (%, absolute), basophils (%, absolute), platelets.

- **Chemistry:** Sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, glucose, calcium, total protein, total bilirubin (TB), direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), albumin, creatine phosphokinase (CPK).

- **Lipids (under fasting conditions for approximately 9 to 12 hours):** Total cholesterol, direct HDL, direct LDL, triglycerides, apolipoprotein A-1 and B.

- **Urinalysis:** Specific gravity, pH, protein, glucose, ketones, blood and leukocyte esterase, urine microscopy (only if dipstick positive for blood or protein, or if clinically indicated).

- **Inflammatory markers and other RA related tests:** C-reactive protein (CRP), Rheumatoid Factor (RF), albumin, ferritin.

  ***** Please note, ESR will determined locally utilizing an ESR Testing Kit provided to the investigator site by the Sponsor (see*** Section 9.1.6.2***).*** *Please refer to the ESR Testing Kit Manual for detailed instruction on how to perform this test appropriately. The ESR result will be recorded on the appropriate CRF. The ESR result also will be faxed to the Centralized Coordinating Center.*

- **Pregnancy testing (women of childbearing potential only):** Blood (serum) or urine pregnancy testing (for Human Chorionic Gonadotropin [HCG]) will be performed locally. A positive urine pregnancy will be confirmed by a blood (serum) pregnancy test performed either locally or by the central laboratory.

- **Hepatitis B testing:** HB surface antigen (HBsAg), HB core antibody (HBcAb), HB surface antibody (HBsAb).

  Interpretation of Hepatitis B Testing Results:

  - HBsAg negative and HBcAb negative: Subject is eligible for the study;

  - HBsAg positive and HBcAb negative: Subject is excluded from study participation;

  - HBsAg negative and HBcAb positive and HBsAb positive: Subject is eligible for study;

  - HBsAg negative and HBcAb positive and HBsAb negative: Subject is excluded from study participation.

- **Hepatitis C testing:** Hepatitis C Antibody (HCV Ab), Hepatitis C Viral RNA (HCV RNA).

  Interpretation of Hepatitis C Testing Results:

  - HCV Ab positive and HCV RNA positive: Subject is excluded from study participation.

- **Tuberculosis testing**: Please refer to Section 9.2.8.

- **VZV-specific ELISA testing:** This test will be done at the screening visit in all subjects who do not have a health professional documented history of having received 2 vaccinations for VZV.

- **MAS diagnostic laboratory testing**: 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.

- **Human Immunodeficiency Virus testing:** HIV-1/HIV-2 antibody.

  Interpretation of HIV Testing Results:

  - HIV-1 or HIV-2 antibody positive: Subject is excluded from study participation.

8.2.10. Pregnancy Testing

For female subjects of childbearing potential (those who have passed menarche), a blood (serum) or urine pregnancy test, with sensitivity of at least 25 mIU/mL for hCG, will be performed locally at screening, before investigational product administration at the baseline visit, at each study visit, and at the End of Study or Early Termination visit. If preferred, urine and/or serum pregnancy testing may be performed at any time using the local or central laboratory.

Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of Institutional Review Boards (IRBs)/Ethics Committees (ECs) or if required by local regulations.

A negative pregnancy test (based on the local result) is required before the subject may receive the investigational product.

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 test, the subject will be withdrawn from administration of investigational product and from the study. Please refer to Section 10.11 for additional information regarding Exposure During Pregnancy.

8.2.11. Contraceptive Check

A contraceptive check also will be performed to confirm that contraception, if assigned, is being used consistently and correctly. Childbearing status also will be checked, and contraception implemented in subjects who mature physically and behaviorally during the conduct of the study.

8.2.12. 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.

Country specific amendment for EU sites (including UK): If blood collection is difficult for individual subjects, venipuncture will be limited to 3 attempts, with additional attempts within 3–5 business days unless there is a medical emergency. Every effort should be made to ensure that blood volume collections do not exceed 1% of the total blood volume at any single time and 3% of the total blood volume during any period of 4 weeks.

At screening 14.1 mL or 15.1 mL (according to QTF-TB test used) to maximally 25.8 mL blood (only if serum pregnancy test, MAS laboratory evaluations, VZV IgG Antibody and HCV RNA test are required) will be collected. If preferred by the investigator, the laboratory evaluations at screening may be done at 2 separate visits within 40 days before enrolment on Day 1 to limit the blood volume collected in one day. Every effort should be made to ensure that blood volume collections do not exceed 1% of the total blood volume at any single time and 3% of the total blood volume during any period of 4 weeks. One re-testing of a hematology or serum chemistry laboratory parameter is allowed if the abnormal lab(s) was an uncharacteristic result(s). Re-testing must be completed within the screening period.

In the first month of the open-label phase 20.8 mL blood will be collected (including blood collection at Week 4), unless optional blood collection of banked biospecimens is also obtained, or subjects require additional serum pregnancy testing, or extra laboratory evaluations for diagnosis of MAS. At Week 4 and all monthly visits thereafter, 4.6 mL to 12.7 mL blood will be collected.

In case of insufficient blood sample or poor sample quality (eg, due to hemolysis or clotting) the subject must return within 1 week for a new sample collection.

Table 5 reflects approximate sample volumes needed for each measured endpoint. The actual times of blood sampling may change. In some instances, additional blood samples may be taken for safety assessments at times specified by Pfizer.

Table 5. Maximum Blood Volume Collection at Each Study Visit

	Screening[1]	Day 1	Day 3	Day 7	Day 14	Week 4, 8, 12 up to 16 Part 1 Open-label	Week 4, 8, 12, 16 up to 24. Part 2 Open-label	Randomization	Every 4 weeks until ET/EOS	End of Study/Early Termination
Chemistry, Lipids[1]	x (1.1)	x (1.1)	x (1.1)[3]	x (1.1)[3]	x (1.1)[3]	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)

Hematology	x (1.2)	x (1.2)	x (1.2)[3]	x (1.2)[3]	x (1.2)[3]	x (1.2)	x (1.2)	x (1.2)	x (1.2)	x (1.2)
Quantiferon® TB Gold or Gold Plus[8,9]	x (3.0 or 4.0)									
Urine/Serum Pregnancy test[2]	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)
CRP		x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)	x (1.1)
CRP, RF	x (1.1)									
ESR (local kit)	X (1.2)	X (1.2)	X (1.2)	X (1.2)	X (1.2)	X (1.2)	X (1.2)	X (1.2)	X (1.2)	X (1.2)
Ferritin[3]	X (1.1)[3]	X (1.1)	X (1.1)[3]	X (1.1)[3]	X (1.1)[3]	X (1.1)[3]	X (1.1)[3]	X (1.1)[3]	X (1.1)[3]	X (1.1)[3]
Fibrinogen[3]	X (1.4)[3]	X (1.4)[3]	X (1.4)[3]	X (1.4)[3]	X (1.4)[3]	X (1.4)[3]	X (1.4)[3]	X (1.4)[3]	X (1.4)[3]	X (1.4)[3]
VZV IgG Ab[4]	X (1.1)									
HIV-1, HIV-2	x (4.0)									
HBsAg, HbcAb, HCAb	x (2.5)									
HCV RNA[5]	x (6.0)									
PK[6]		x (3.6 to 4.8)				x (3.6)	x (3.6)[6]			
Banked biospecimens[7]		X (4.5)				X at Wk8 (2.0)		X (4.5)		X (4.5)
Total	**14.1 or 15.1 mL to 25.8mL**	**9.4 mL to 17.5mL**	**2.3 mL to 8.2mL**	**2.3 mL to 8.2mL**	**2.3 mL to 8.2mL**	**4.6 mL to 13.8mL**	**4.6 mL to 11.8mL**	**4.6 mL to 12.7mL**	**4.6 mL to 8.2mL**	**4.6 mL to 12.7mL**

1. Lipid panel will be evaluated every 3 months after Day 1.
2. For female subjects of childbearing potential, a blood (serum) or urine pregnancy test, will be performed locally at screening, before investigational product administration at the baseline visit, at each study visit, and at the End of Study or Early Termination visit.
3. If MAS is suspected in a febrile subject, 2.5 mL additional blood will be collected for evaluation of Ferritin and Fibrinogen levels. If no hematology and lipid evaluation is part of the visit (on Day 3, Day 7, Day 14, or at unscheduled visits), hematology and chemistry blood samples for assessment of platelets and triglycerides will also be required to confirm a MAS diagnosis.
4. Serologic testing for antibodies to varicella zoster virus (VZV) via ELISA is required for all subjects who do not have documented evidence from a health professional of receiving 2 doses of varicella vaccine.
5. RNA sample collection may be deferred and collected only if required to confirm eligibility based on the HCV Ab results.
6. Blood samples for PK evaluation will be collected at Day 1 and after 8 weeks of study treatment. PK testing will be done at 15 minutes (5-30 min), 45 minutes (35-55 min) and 4 hours (3-6h) after tofacitinib administration on Day 1. In the first 14 subjects enrolled in Cohorts 1-2 (N=7 in each cohort), PK testing will also be done at 1.5 hours (1.25-2h) after tofacitinib administration. After 8 weeks of study treatment, PK samples will be collected pre-dose and 1 hour (0.5-1.5h) and 3 hours (2-4h) after tofacitinib administration. These PK samples may be obtained at Week 8 of Open-Label Part 1, or at Week 4 of Open-Label Part 2 in the case a subject started Open-Label Part 2 after 4 weeks of tofacitinib treatment in Part 1. Whenever feasible, later time point within the last PK sample collection range is preferred. In total 3 samples (each 1.2 mL) will be collected for PK evaluation from all subjects enrolled after the 2nd cohort. From the first 14 subjects of Cohorts 1-2, a 4th blood sample of 1.2 mL for PK will also be collected at the Day 1 visit. Subjects in India will not participate in PK evaluation.

7. 4.5 mL blood will be collected for banked biospecimens at baseline, randomization, when the subject flares (Early Termination visit in Open-Label phase, or End of Study visit in Double-blind phase), and if applicable when inactive disease status is reached. This blood sample collection is optional.
8. QuantiFERON®-TB Gold (3mL) or QuantiFERON®-TB Gold Plus (4 mL) test will be available according to the country regulations and approvals.
9. **In countries where TB incidence has been reported at a rate of >50 cases per 100,000 persons**, eg, China, India, Russian Federation; South Africa and Ukraine (World Health Organization): TB testing (QFT-TB Gold or Gold Plus) is required at screening visit and then on a yearly basis. Therefore, in addition of the volume listed, 4 mL of blood will be collected for TB testing on a yearly basis as long as the subject will remain this study.

8.2.13. 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.[27] 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 they:

- have heart failure or prior myocardial infarction within past 3 months;
- have inherited coagulation disorders;
- have had venous thromboembolism, either deep venous thrombosis or pulmonary embolism;
- are taking combined hormonal contraceptives or hormone replacement therapy;
- have malignancy (association is strongest with cancers other than nonmelanoma skin cancers);
- are 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 one or more of the risk factors for venous thromboembolism listed above under Amendment 3 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 3, they will remain on their assigned tofacitinib dose.

8.2.14. Temporary Withholding of Study Drug

Withholding of study drug is not necessary when administering non-live vaccines, including inactivated influenza vaccine and non-live COVID-19 vaccines.

Study drug may be temporarily discontinued for up to 28 consecutive days, for more severe cytopenia, 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. Subjects who withhold study drug for any of these reasons will not be considered non-compliant with study medication and a PD will not be recorded.

Per Amendment 3, for subjects with suspected venous thromboembolism, treatment with study drug should be temporarily withheld while the subject is evaluated. If venous thromboembolism is confirmed, discontinue treatment with study drug.

8.3. Monitoring Hematology and Serum Laboratory Parameters and specific adverse events

8.3.1. Monitoring Criteria

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

- Absolute neutrophil count (ANC) <1.0 x 10^9/L (<1000/mm^3);
- Absolute lymphocyte counts <0.5 x 10^9/L (<500/mm^3);
- Platelet count <100 x 10^9/L (<100,000/mm^3);
- Any single hemoglobin value <8.0 g/dL or one that drops ≥2 gm/dL below baseline;
- Any single AST and/or ALT elevation ≥3 x upper limit of normal (ULN), regardless to total bilirubin. Repeat testing must include the following tests: albumin, creatine kinase (CK), total bilirubin, direct and indirect bilirubin, GGT, PT/INR, and alkaline phosphatase;
- Any single serum creatinine increase >50% over the average of screening (most recent value prior to baseline) and baseline values OR an absolute increase in serum creatinine ≥0.5 mg/dL (≥44.2 umol/L) over the average of screening (most recent value prior to baseline) and baseline values AND any single CrCl decrease of >30% over the average of screening (most recent value prior to baseline) and baseline values;
- Increased lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) should be monitored and treated according to local guidance (eg, diet and behavior modification, statin therapy).

If the abnormality is confirmed after re-test, follow-up should be discussed with the sponsor and frequency of monitoring increased.

Country specific amendment for EU sites (including UK sites): 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.

Confirmation should be done based upon central laboratory results, but local laboratory results will be acceptable, particularly if these may be done more promptly.

For additional laboratory abnormalities that require prompt retesting, preferably within 48 hours from awareness of the abnormal results, see Section 9.7.1: Potential Cases of Drug-Induced Liver Injury.

8.3.2. Discontinuation of Study Drug Criteria

Study drug will be discontinued in the event of any of the following:

- Serious infections defined as any infection (viral, bacterial, or fungal) requiring parenteral antimicrobial therapy or hospitalization for treatment, or meeting other criteria that require the infection to be classified as a serious adverse event (see Section 9.5.1);
- Opportunistic infection judged significant by investigator;
- Two sequential absolute neutrophil counts <0.5 x 10^9/L (<500/mm^3);
- Two sequential hemoglobin values <8.0 g/dL (80 g/L) or decreases of >30% from baseline value;
- Two sequential absolute lymphocyte counts <0.5 x 10^9/L (<500/mm^3) by repeat testing;
- Two sequential platelet counts <75 x 10^9/L (<75,000/mm^3);
- Two sequential AST or ALT elevations >3 times ULN with a total bilirubin value ≥2 times the upper limit of normal;[a]
- Two sequential AST or ALT elevations >3 times ULN with an elevated INR;[a]
- Two sequential AST or ALT elevations >3 times ULN accompanied by signs or symptoms consistent with hepatic injury;[a]
- Two sequential AST or ALT elevations >5 times ULN, regardless of total bilirubin or accompanying symptoms;
    - The subject must return to the study site for prompt retesting and include the following: albumin, creatine kinase (CK), total bilirubin, direct and indirect bilirubin, GGT, PT/INR, and alkaline phosphatase. Additional investigations include a detailed history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, work exposure, history of ethanol, recreational drug and dietary supplement consumption. Testing for acute hepatitis A, B or C infection and biliary tract imaging may be considered.

- Two sequential increases in serum creatinine >50% over the average of screening and baseline values OR an absolute increase in serum creatinine ≥0.5 mg/dL (≥44.2 umol/L) over the average of screening and baseline values AND a confirmed (two sequential) CrCl decrease of >30% over the average of screening and baseline CrCl values. If the serum creatinine increase and the CrCl decrease have an identifiable and reversable reason (eg, concomitant medication), then an additional retest may be considered after discussion with the Sponsor study clinician or medical monitor. After retest, a decision for the subject to continue in the study will be made after discussion with the Sponsor study clinician or medical monitor.

- Other serious or severe adverse events, in the opinion of the investigator or sponsor. Whenever possible, the investigator should consult with a member of the Pfizer study team before discontinuation of the subject;

- Malignancies, excluding adequately treated or excised basal cell or squamous cell carcinoma of the skin and cervical carcinoma in situ.

- If venous thromboembolism is confirmed, discontinue treatment with tofacitinib.

8.4. Pharmacokinetic Assessment

Plasma samples for population pharmacokinetic (PK) analysis of tofacitinib will be collected over a 3-hour to 4-hour time period from all subjects enrolled in the study, at baseline (Day 1 of tofacitinib administration) and after 8 weeks of study treatment.

In general, every effort should be made to collect blood samples for PK analysis within the specified time windows. At all times, it is essential to accurately record the date and time study treatment is administered and PK samples are collected. This includes the date and time of the dose taken on the evening prior to the specified PK visit.

On days 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 until after the pre-dose PK sample is collected.

Blood samples for PK analysis at additional time points and/or in additional subjects may be collected, as determined by the Sponsor.

8.4.1. PK Blood Sample Collection Time

In all subjects in Cohorts 1-2: in Part 1 of the study (N=7 in each cohort), 4 blood samples of 1.2 mL for PK will be collected at the Day 1 visit (first day of tofacitinib administration) and 3 blood samples of 1.2 mL will be collected after 8 weeks of tofacitinib treatment at the time points indicated below:

Day 1 - PK Collection Time Points:

- 0.25 hours [5 – 30 minutes] = 15 minutes post dose;

- 0.75 hours [35 – 55 minutes] = 45 minutes post dose;

- 1.5 hours [1.25 – 2h] post dose;

- 4 hours [3 – 6h] post dose. If feasible for the subject, this blood sample should be drawn between 4 to 6 hours post dose, however any time between 3 to 6 hours post dose is allowed.

Week 8 PK Collection Time Points:

Note, 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.

- Pre-dose (approximately 12 hours post the previous evening dose);

- 1 hour [0.5 – 1.5h] post dose;

- 3 hours [2 – 4h] post dose. If feasible for the subject, this blood sample should be drawn between 3 to 4 hours post dose, however any time between 2 to 4 hours post dose is allowed.

In all subjects after initial cohorts of the study who consented to provide PK samples, only 3 blood samples of 1.2 mL for PK will be collected at the Day 1 visit (first day of tofacitinib administration) and 3 blood samples of 1.2 mL will be collected after 8 weeks of tofacitinib treatment at the time points indicated below:

Day 1 - PK Collection Time Points:

- 0.25 hours [5 - 30 minutes] = 15 minutes post dose;

- 0.75 hours [35 – 55 minutes] = 45 minutes post dose;

- 4 hours [3 – 6h] post dose. If feasible for the subject, this blood sample should be drawn between 4 to 6 hours post dose, however any time between 3 to 6 hours post dose is allowed.

Week 8 PK Collection Time Points:

Note, 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.

- Pre-dose (approximately 12 hours post the previous evening dose);

- 1 hours [0.5-1.5h] post dose;

- 3 hours [2– 4h] post dose. If feasible for the subject, this blood sample should be drawn between 3 to 4 hours post dose, however any time between 2 to 4 hours post dose is allowed.

8.4.2. Blood Sample Processing

Blood samples (1.2 mL) to provide a minimum of 0.4 mL of plasma for PK analysis will be collected into appropriately labeled tubes containing lithium heparin.

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.

8.4.3. PK Sample Shipment

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

At the assay laboratory, samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical report. Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

8.5. Banked Biospecimens

Banked biospecimens will be collected to provide an opportunity for exploratory retrospective analyses associated with study- and program-related endpoints (eg, safety, efficacy), the subjects' disease (sJIA), the drug's mechanism of action, and/or to potentially support future personalized medicine approaches. Collection of banked biospecimens is optional for all subjects.

8.5.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is an optional

study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post marketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A single 2 mL blood biospecimen **Prep D1.5 (K_2 edetic acid [ethylenediaminetetraacetic acid] [EDTA] whole blood collection optimized for DNA analysis)** will be collected at the Week 8 visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

Additional biospecimens to be retained for exploratory analyses in this study include the following:

Prep B2.5 (serum collection optimized for biomarker/proteomics/metabonomic analysis): A 2 mL blood biospecimen will be collected at Day 1 (pre-dose), at randomization, when the subject flares (at the Early Termination or End of Study visit), and if applicable when a subject reaches inactive disease status.

Prep R1 (PAXGene whole blood collection optimized for RNA analysis): A 2.5 mL blood biospecimen will be collected at Day 1 (pre-dose), at randomization, when the subject flares (at the Early Termination or End of Study visit), and if applicable when a subject reaches inactive disease status for the first time.

The banked biospecimens will be collected from all subjects **unless prohibited by local regulations or ethics committee decision**. Detailed collection, processing, storage, and shipment instructions are provided in the Central Laboratory Manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/subject information sheet that they will not be compensated in this event.

8.5.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions;
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation among people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimen specified in the Section 9.5.1 will be used. Subjects may still participate in the clinical study if they elect not to allow their bank banked biospecimens to be used for the additional purposes described in this section.

9. ADVERSE EVENT REPORTING

9.1. 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 nonserious AE 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.

9.2. 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 they consider 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.

9.3. 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.

9.4. 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.

9.4.1. Tofacitinib Overdose

There is no experience with overdose of tofacitinib (CP-690,550). Pharmacokinetic data up to and including a single dose of 100 mg in healthy adult volunteers indicates 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 medical treatment.

Concomitant treatment with prohibited potent CYP3A inhibitors (Appendix 5) is assumed to result in a doubling of tofacitinib exposure. For further details, please refer to the SRSD (eg, the Investigator Brochure).

9.5. 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 and/or treated infections, as defined below.

9.5.1. 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 Investigational Product. This infection must be reported as a serious adverse event and should be listed as the reason for discontinuation of study drug in the CRF. 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 9.1 on Adverse Event Reporting.

9.5.2. 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). A subject who experiences a serious infection must be discontinued from the study. This information must be noted in the eCRF.

9.6. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE 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 study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

9.7. 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.

9.7.1. 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 Section 0 SAE Reporting Requirements).

9.7.2. 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 ULN, the following threshold values should be used in the definition mentioned above:
    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

Concurrent with:

- For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN **or** if the value reaches ≥3 X ULN (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 SAEs.

9.8. Hospitalization

Hospitalization is defined as any initial admission (even 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, or 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 AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup 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 AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned 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 noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

9.9. Severity Assessment

If required on the AE 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 the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

9.10. Causality Assessment

The investigator’s assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE 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 section on 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.

9.11. 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 preprocedural 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 SAEs 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 Pregnant Partner Release of Information Form to provide to his partner.

9.12. 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.

9.13. Withdrawal Due to Adverse Events

Withdrawal from Investigational Product 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 from Investigational Product because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

9.14. Eliciting Adverse Event Information

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

9.15. 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.

9.15.1. 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 time frame 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 or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames 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.

9.15.2. Nonserious 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.

9.15.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

10. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol: however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Note: All references in Section 10 to the nominal 5 mg BID dose include the respective equivalent weight-based lower doses.

10.1. Sample Size Determination

Approximately 100 subjects will be enrolled in the open-label run-in phase of the study. The study will target to enroll at least 12 subjects in each of the following age groups: from 2 to <6 years, from 6 <12 years, and from 12 to <18 years. Based on results from a similarly designed sJIA clinical trial,[14] it is estimated that approximately 55% of the subjects enrolled in the open-label run-in phase will enter the randomized withdrawal double-blind phase of the study.[14] It is reasonable to assume that tofacitinib can achieve this target rate by the end of the open-label phase.

At the start of the double-blind phase, qualifying subjects receiving tofacitinib 5 mg BID in the open-label active treatment phase will be randomized into a tofacitinib sequence (continuation of tofacitinib treatment) or a placebo sequence (withdrawal of the tofacitinib treatment) with a 1:1 allocation ratio, stratified by age group.

Subjects who discontinue Investigational Product in the double-blind phase of the study due to any reason will be counted as having an sJIA flare in the primary analysis for the primary endpoint of the study and will contribute to the requisite number of subjects with flare for the study to be considered complete. Subjects who achieve clinical remission during the double blind withdrawal phase are completers of the study and will not be counted as having an sJIA flare in the primary analysis.

10.1.1. Power Analysis

At the start of the double-blind randomized withdrawal phase, qualified subjects who are Adapted JIA ACR 30 responders (and maintained response for at least 4 weeks), will be randomized to receive tofacitinib 5 mg BID or a placebo (withdrawal of the tofacitinib dose) with a 1:1 allocation ratio.

The primary objective in the double-blinded phase of the study is to test the superiority of tofacitinib (5 mg BID) over placebo as measured by the time to flare. There will be potentially 2 planned analyses. The First Analysis will be performed after at least 20 subjects have reported flare in the double-blind phase (approximately 50% of the total flares expected). The purpose of the First Analysis is to allow early stopping of the study for efficacy or futility, and to assess safety of tofacitinib. Depending on the number of flares in the First Analysis, up to 40 subjects with flares may be required for the Final Analysis to yield an overall power of 80% using a log-rank test to detect the treatment difference, assuming a 1-sided type-I error rate of 2.5% (or equivalently two-sided type-I error rate of 5%), and a

64% improvement in median time to flare (ie, a hazard ratio of 0.36 and a median time to flare of 236 days for placebo; assumptions based on a similar sJIA randomized withdrawal trial).[14] The investigators, subjects and sponsor study team will remain blinded to treatment assignment in the double-blind phase through the entire duration of the trial until final database release. A limited duration unblinded study team will be constructed to perform the First Analysis.

To protect the integrity of the study and to preserve the type I error rate at 0.025 (1-sided test) and overall study power at 80% (type II error rate β=0.2), a fraction of α for efficacy and a fraction of β for futility will be spent at the First Analysis and accounted for in the overall type I error rate and type II error rate, respectively. A formal efficacy boundary for rejecting the null hypothesis is constructed by using the spending function methodology of the gamma family design with γ= 4. Similarly, a formal futility boundary for not rejecting the null hypothesis is constructed by using the spending function methodology of the gamma family design with γ= -4.

- If the value of the test-statistic at the First Analysis crosses the efficacy boundary ($z \leq$ -2.014, 1-sided $p \leq$ 0.022), the trial may be stopped for efficacy.
- If the value of the test-statistic at the First Analysis crosses the futility boundary ($z \geq$ -0.286, 1-sided $p \geq$ 0.387), the trial may be stopped for futility.
- Otherwise, the trial will continue as planned. The Final Analysis will be performed after flares have been reported in approximately 40 subjects.

The efficacy and futility boundaries will depend on the number of flares. For logistical and administrative reasons, the actual number of flares at the First Analysis and the Final Analysis might differ slightly from those that have been pre-specified here. In that case appropriate adjustments will be made to the efficacy and futility boundaries based on the gamma family spending functions. The actual boundary used for the First or the Final Analysis will be re-calculated from the specified spending function based on the actual number of flares achieved at the time of First or Final analysis. These boundaries will be calculated and finalized prior to the evaluation of comparative data. More details regarding the calculation of futility and efficacy boundaries will be provided in the SAP.

Applying a 1:1 allocation ratio to treatment groups and an Adapted JIA ACR response rate of approximately 55% at the end of the open-label phase, it is estimated that approximately 100 subjects would need to be enrolled in the open-label phase to randomize 54 subjects in the double-blind phase. As of November 2022, 23 subjects have been randomized during the accrual period of 225 weeks. Assuming a future accrual rate of 0.315 subjects per week, it is anticipated that it will take a total of 262 and 358 weeks to achieve the requisite number of flares for the First and Final Analyses, respectively.

10.2. Efficacy Analysis

10.2.1. Analysis of Primary Endpoint

The primary objective of the study is to determine if tofacitinib 5 mg BID is superior to placebo as measured by time to flare in the double-blind phase.

Time to flare will be assessed using Kaplan-Meier methods and displayed graphically. The median time to flare and corresponding 2-sided 95% confidence interval (CI) will be provided. Difference in time to flare between the two treatment groups (tofacitinib vs. placebo) will be assessed using an unstratified log-rank test.

In the primary analysis, subjects who complete study treatment due to inactive disease for at least 24 weeks in the double-blind phase without flare will be censored at the last available flare assessment while on investigational product. Treatment discontinuations for any other reasons will be considered as flares in the primary analysis.

A supportive analysis will be performed in support of the primary analysis whereby subjects discontinued investigational product from double-blind treatment for any reason other than flare, including inactive disease for at least 24 weeks in the double-blind phase, will be censored at the last available flare assessment while on investigational product.

Moreover, per Sections 6.9 Pfizer will make every effort to collect flare data for subjects discontinuing from investigational product early, before reaching 52 weeks of double-blind treatment, for reasons other than flare. Such subjects rolling over into study A3921145 will continue to be followed for sJIA exacerbation (flares) in the long-term extension (LTE). Subjects who discontinue from investigational product in the double-blind phase and who do not enter A3921145 will continue in A3921165 for follow up of efficacy and safety endpoints. Subjects will be required to perform all scheduled visits until Week 52 after randomization or until the study concludes, whichever comes first.

In an additional supportive analysis, all the flare data collected both on- and off-study treatment in the double-blind phase of this study, A3921165, will be used. For subjects who discontinue study early, before reaching 52 weeks of double-blind treatment in this study and enrolled in the LTE study (Study A3921145), the flare data collected through Week 52 post randomization from both studies A3921165 and A3921145 will be included. Investigational product discontinuation will not be considered as disease flares in this analysis.

Additional details regarding the analysis of the primary endpoint will be provided in the SAP.

10.2.2. Analysis of Secondary Endpoints

As this is a time-to-event trial, patients will have varying follow-up times during the double-blind phase. For efficacy endpoints analyzed by visit, only the data through 52 weeks in the double-blind phase will be analyzed statistically. The data after week 52 will not be analyzed statistically but summarized descriptively. The reason for choosing 52 weeks is that majority of the patients are expected to complete 52 weeks of the study in the double-blind phase and 52 weeks are deemed adequate to evaluate secondary efficacy by visit.

For the double-blind phase, the majority of the analyses will be performed by treatment group. Secondary binary endpoints such as: occurrence of disease flare or inactive disease status, achieving a response of adapted JIA 30/50/70/90/100, absence of fever, etc., will be analyzed using statistical methods for binary variables; eg, normal approximation to binomial proportions. For the continuous endpoints, a linear mixed-model will be applied. Treatment differences along with the associated 2-sided 95% CIs and p-values, will also be calculated. In the double-blind phase analyses, descriptive/summary statistics by treatment group for the effect on the primary and secondary endpoints will be provided at each time point.

Secondary endpoints in the open-label run-in phase will be summarized descriptively by visit.

In the open-label phase, the study will target enrollment of at least 12 subjects in each of the following age groups: from 2 to <6 years, from 6 <12 years, and from 12 to <18 years. Consistency across all age groups with the overall results will be evaluated by informally comparing confidence intervals graphically with the use of forest plots. In addition, descriptive statistics of baseline demographic characteristics and all endpoints, broken down by age group will be provided.

Baseline definitions: This study will have a separate type of baseline for each of its two phases. The open-label baseline will be defined as the last value collected prior to tofacitinib administration in this phase. For the analyses in the double-blind phase, baseline will refer to the values collected at the randomization visit – before the start of the double-blind phase- for all endpoints, with the exception of Adapted ACR responses. For Adapted JIA ACR responses the open-label baseline will be utilized as the reference point. Selected analyses in the double-blind phase, such as changes in laboratory parameters and changes in the JIA core set variables , may also refer back to the open-label baseline as a separate analysis, in addition to using the double-blind baseline.

10.3. Guidance to Open Enrollment following Cohort Review

In Part 1 of the open-label phase, dosing decisions will be made based on the evaluation of cohorts of 7 subjects treated with tofacitinib. Enrollment will be conducted in a staggered fashion. The Sponsor, under the guidance of a Steering Committee, will assess safety, efficacy, and pharmacokinetics of the 5 mg BID dose and advise on further enrollment and dosing with 5 mg BID in the study.

For efficacy, the upper limit of a 95% confidence interval (shown below) for an Adapted JIA ACR 30 response will serve as guidance to evaluate the initial cohorts of 7 subjects dosed with tofacitinib 5 mg BID.

Table 6. 95% Confidence Intervals for Adapted JIA ACR 30 Response in Open Label Cohorts

			95% CI for p	
N (Total)	**n (Responder)**	**p (Response Rate)**	**Lower Limit**	**Upper Limit**
7	0	0	0	0.410
7	1	0.143	0.004	0.579
7	2	0.285	0.037	0.710
7	3	0.429	0.099	0.816
7	4	0.571	0.184	0.901

A 95% confidence interval can be interpreted as: There is a 95% probability that the calculated confidence interval from sampling encompasses the true response rate for the population. Thus, if 1 out of 7 responders were observed in a cohort, a response rate of approximately 58% or higher could be ruled out with 95% confidence. Using the confidence interval, a given cohort will be deemed to have sufficient efficacy for further study if at least 2 responders out of 7 subjects are observed. The following will serve as guidance for making decisions about the cohorts:

- If ≤1 out of 7 responders is observed in 2 consecutive cohorts, the dose level will be discontinued.

- If ≥2 out of 7 responders are observed in each of 2 consecutive cohorts at the 5 mg BID dose level, efficacy at this dose level will be considered sufficient to allow further evaluated in additional subjects.

- In the event that intermediate response rates are observed (for example, 1 out of 7 in the first cohort and 2 out of 7 in the second), the decision on whether or not to evaluate the dose level in additional subjects would be based on review of the totality of the data by the Sponsor and Steering Committee and further cohort(s) may be needed to evaluate this dose.

In general, the safety and efficacy data in each cohort will be reviewed by the Steering Committee and Sponsor in order to make decisions concerning a given dose level. Further details about guidelines for evaluation and management of initial dose cohorts will be provided in a Steering Committee Charter.

Other details of the statistical analyses for all endpoints in both phases will be described in the SAP.

10.4. Population Pharmacokinetics and Exposure-Response Analyses

Plasma concentration-time data for tofacitinib will be analyzed using a nonlinear mixed effects modeling approach to characterize PK in sJIA subject population. Effects of demographic and disease covariates (age, weight, CRP etc.) on PK may be explored if appropriate. PK data (on Day 1 in the run-in open-label phase) from the two cohorts (5 mg BID dose) will be analyzed and utilized along with efficacy and safety data to advance to open enrollment at the 5 mg BID dose. Concentrations from the two cohorts

(approximately 14 subjects) will be analyzed to confirm the current dosing scheme for the remaining subjects based on the results of this analysis.

Relationships between various measures of systemic exposure of tofacitinib and efficacy and safety outcomes may be explored, using similar methodology, if considered necessary or useful upon review of the available data. The details of the analysis plan will be provided in a separate document (population PK modeling plan or PMAP) and the results may be reported separately (population PK modeling report or PMAR) from the clinical study report.

10.5. Safety Analysis

Safety analysis will be performed on all subjects who received at least one dose of study drug. The Sponsor has standard algorithms for reporting adverse events and clinical laboratory test results, and these will be employed in the analysis of the data from this trial. Safety data will be subject to clinical review and summarized by appropriate descriptive statistics. Details will be presented in the SAP.

10.6. Interim Analysis

The planned analysis is as outlined in Section 10.1. The analysis will be performed after approximately 20 subjects have reported flare in the double-blind phase (approximately 50% of the total flares expected).

10.7. Data Safety Monitoring Board (DSMB)

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.

10.8. Steering Committee

The Sponsor will use a Steering Committee to provide guidance regarding evaluation of the 5 mg BID dose level of tofacitinib in the initial cohorts of this study. In the open-label phase the Steering Committee will assess preliminary efficacy and safety of the 5 mg BID dose level based on a review of 2 cohorts, each receiving tofacitinib 5 mg BID. The Steering Committee will provide recommendations regarding further enrollment at the 5 mg BID dose level and open-enrollment in the study.

Refer to Section 10.3 for details regarding the evaluation of cohorts. Additional details will be provided in a separate Steering Committee Charter.

10.9. Safety Endpoint Adjudication Committee

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 (HPR) for Potential Malignancy charter.

11. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct 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 are 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. This verification may also occur after study completion.

During study conduct and/or after study completion, 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.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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.

12. DATA HANDLING AND RECORD KEEPING

12.1. 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 are true. Any corrections to entries made in the CRFs or 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 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.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems

12.2. 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/assent 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, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, 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 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.

12.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

13. ETHICS

13.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP Guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

13.2. 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 regulatory authority in any area of the world, or if the investigator is aware of any new

information that might influence the evaluation of the benefits and risks of the study intervention, 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 participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

Netherlands country-specific amendment requires that in the Netherlands, patients will be evaluated for enrollment in this study if previous treatments recommended by the JVN Medicamenteuze behandeling van kinderen met jeugdreuma (Dutch Guidelines: JVN Drug Treatment of Children with Juvenile Rheumatism) have failed to control their systemic JIA disease.

13.3. Subject Information and Consent

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 law.

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

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

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

The investigator must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, 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 they cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, 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 or 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 re-consent 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, they must provide documentation of legal status to give consent without the permission of a 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 and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

13.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of IRB/EC committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

13.5 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 that 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.

14. DEFINITION OF END OF TRIAL

14.1. 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 a sufficient number of 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.

14.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as Last Subject Last Visit (LSLV).

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

15. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, investigational product 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 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

16. PUBLICATION OF STUDY RESULTS

16.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies 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.clinicaltrials.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 prespecified 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.

16.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed. The investigator will provide any publication 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 before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. 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 (CSA) between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Allowed and Disallowed DMARDs

Allowed DMARDs:

The following DMARDs are allowed in doses:

- Methotrexate: stable dose ≤25 mg/week or 20 mg/m^2/week for at least 4 weeks before the first dose of tofacitinib (Day 1 Visit).
- If treated with MTX, treatment must be for ≥3 months before the first study drug dose.

Disallowed Biologic and Non-Biologic DMARDs:

The following biologic agents and DMARDs are disallowed at any time during this study. If a subject requires (in the opinion of the investigator) treatment with one of these agents, the subject should be discontinued from the study:

- Leflunomide (Arava®) must have been discontinued 8 weeks prior to the first dose of study drug if no elimination procedure is followed;
- Cyclosporine, tacrolimus, sulfasalazine and azathioprine: Discontinued for 7 days prior to the first dose of study drug;
- Anakinra (Kineret®): Discontinued for 3 days prior to the first dose of study drug;
- Baricitinib (Olumiant®) and Upadacitinib (Rinvoq®): Discontinued for 4 weeks prior to the first dose of study drug;
- Etanercept (Enbrel®): Discontinued for 2 weeks prior to the first dose of study drug;
- Canakinumab (Ilaris®): Discontinued for 7 weeks prior to the first dose of study drug;
- Adalimumab (Humira®): Discontinued for 2 weeks prior to first dose of study drug;
- Infliximab (Remicade®): Discontinued for 3 weeks prior to the first dose of study drug;
- Golimumab (Simponi TM): Discontinued for 4 weeks prior to the first dose of study drug;
- Abatacept (Orencia®), Tocilizumab (Actemra®), Certolizumab pegol (Cimzia®): Discontinued for 4 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 FACS analysis.

- Immunoglobulin G (IgG): Discontinued for 8 weeks prior to the first dose of study drug.

Other Disallowed Agents:

- Thalidomide (Thalidomid®), bucillamine, mizoribine, d-penicillamine, chloroquine, hydroxychloroquine, 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.

Disallowed Investigational Drugs:

- **Investigational 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.

Note: The above prohibited agents are permitted during the study only for subjects permanently withdrawn from Investigational Product and continuing in the study on standard-of-care in accordance with local treatment policies.

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 sJIA Therapies

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.

1. NSAIDs/COX-2 inhibitors: dose adjustments may be made, or background NSAID/COX-2 inhibitors may be switched, but should be no more frequently than every 3 months, and should be more than 14 days prior to a study visit.

2. Oral Corticosteroid (CS) dose should be stable for the duration of Part 1 of the open-label phase and not exceed 1.0 mg/kg/day up to 30 mg/day oral prednisone or equivalent daily. In Part 2 at each study visit if the subject continues to meet an adapted ACR 50 level of response, then the daily prednisone dose can be tapered in accordance with the tapering criteria of Section 3.2. During the double-blind phase of the study the oral CS dose must remain stable unless the subject meets the flare criteria. At that time the subject will be discontinued from the study and the oral CS dose can be adjusted as necessary in the physician's judgment.

3. Methotrexate (MTX) may be administered either orally or parenterally MTX at doses not to exceed 25 mg/wk or 20 mg/m^2/week (whichever is lower). The dose should be stable for at least 4 weeks before the first dose of investigational drug and remain stable for the duration of the study (open-label and double-blind phases).

4. Intra-articular steroids should be administered in a total dosage of no more than 2 mg/kg (up to 80 mg) of methylprednisolone or equivalent every 6 months. No more than two joints should be injected 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 active joints for the following 3 months.**

Appendix 4. Estimated Glomerular Filtration Rate Calculation and Creatinine Clearance Calculation

The Bedside Schwartz[23] GFR equation will be used to estimate glomerular filtration rate (eGFR) from serum creatinine (creatinine method with calibration traceable to IDMS). eGFR will be evaluated at screening to determine if a subject is eligible.

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

Height (Ht) in cm;

Serum creatinine (Scr) in mg/dL.

In addition, at every study visit a subject's creatinine clearance (CrCl) will be evaluated.

The Modified Schwartz equation will be used to estimate creatinine clearance in participants <12 yrs old.[30]

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

Female Child <12 years: K = 0.55
Male Child<12 years: K = 0.70

The Cockcroft-Gault equation will be used to estimate the creatinine clearance for the participants ≥12 years of age.[30]

CrCl (ml/min) = [(140 - age) x weight in kg] / [Scr x 72] (x 0.85 if female)

Appendix 5. Prohibited Concomitant Medications

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

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

All herbal supplements are prohibited during the study and require a 28-day washout.

** ***Biologic and Non-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 (Actemra), golimumab (Simponi), rituximab (Rituxan), Immunoglobulin G (IgG)
erythromycin	
fluconazole (Diflucan)	
fluvoxamine (Luvox)	
Grapefruit juice and marmalade	
itraconazole (Sporanox)	
ketoconazole (Nizoral)	***Other DMARDs*****: leflunomide, sulfasalazine, d-penicillamine, bucillamine, mizoribin, azathioprine, cyclosporine, tacrolimus, auranofin, aurothioglucose, aurothiomalate, staphylococcal protein A immuno-absorbant pheresis columns
mifepristone (Mifeprex, RU486)	
nefazodone (Serzone)	
norfloxacin (Shibroxin, Noroxin)	
mibefradil	
verapamil (Calan SR,Covera HS, Isoptin SR, Tarka, Verelan)	
voriconazole	

Appendix 6. 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:

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.

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 CSs, biologic response modifiers and DMARDs other than those specified as allowed DMARDs (Appendix 1) are not allowed during this study. Intra-articular CSs be given in no more than two joints, in a cumulative dose of no more than 80 mg methylprednisolone or its equivalent in any 6-month study period. Injected joints will also be considered as having their pre-injection status (tender/painful and swollen) 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.

Appendix 7. Guidelines For Safety Monitoring And Discontinuations

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

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

Temporary Withholding and discontinuation of Investigational Product related to Venous Thromboembolism:

- Per Amendment 3, for subjects with suspected venous thromboembolism, investigational product treatment should be temporarily withheld while the subject is evaluated. If venous thromboembolism is confirmed, discontinue investigational product. Refer to Section 8.2.14.

Investigational Product will be discontinued for:

- Serious infections (those requiring parenteral antimicrobial therapy or hospitalization), and opportunistic infections;
- Malignancies, excluding adequately treated or excised basal cell or squamous cell carcinoma of the skin and cervical carcinoma in situ;
- Confirmed venous thromboembolism;
- 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 hemoglobins <8.0 g/dL or a decrease of more than 30% from baseline value;
- 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;
- Two sequential AST or ALT elevations >3 times the upper limit of normal with an abnormal INR;
- Two sequential AST or ALT elevations >3 times the upper limit of normal accompanied by symptoms consistent with hepatic injury;
- Two sequential AST or ALT elevations >5 times the upper limit of normal, regardless of Total Bilirubin or accompanying symptoms;
- Two sequential increases in serum creatinine >50% over the average of screening and baseline values OR an absolute increase in serum creatinine ≥0.5 mg/dL (≥44.2 umol/L) over the average of screening and baseline values AND a confirmed (two sequential) CrCl decrease of >30% over the average of screening and baseline CrCl values. If the serum creatinine increase and the CrCl decrease have an identifiable and reversable reason (eg, concomitant medication), then an additional retest may be considered after discussion with the Sponsor study clinician or medical monitor. After retest, a decision for the subject to continue in the study will be made after discussion with the Sponsor study clinician or medical monitor;
- Single positive HBc Ab and a negative HBs Ab;
- Other serious or severe AEs, after consultation with the Pfizer Medical Monitor.

Appendix 8. List of Abbreviations

Abbreviation	Term
Ab	Antibody
ACR	American College of Rheumatology
AE	adverse event
ANC	Absolute neutrophil counts
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	Twice daily
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDS	core data sheet
CHAQ	Childhood Health Assessment Questionnaire
CHQ	Child Health Questionnaire
COVID-19	coronavirus disease 2019
CrCl	Creatinine clearance
CRF	case report form
CRP	C-reactive protein
CS	Corticosteroids
CSA	clinical study agreement
CSF	cerebrospinal fluid
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DAI	dosage and administration instructions
DB	Double-blind
DMARD	Disease Modifying Antirheumatoid Drugs
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECG	Electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Term
HBV	Hepatitis B Virus
HCG	Human Chorionic Gonadotropin
HIV	human immunodeficiency virus
HCV	Hepatitis C Virus
HRQL	health-related quality of life
IB	investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IgG	Immunoglobulin G
ILAR	International League Against Rheumatism
IND	investigational new drug application
INR	international normalized ratio
IOBU-SDMC	Internal Oncology Business Unit-Safety Data Monitoring Committee
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine system
IVR	interactive voice response
IWR	interactive web response
JADAS	Juvenile Arthritis Disease Activity
JAK	Janus Kinase
JIA	Juvenile Idiopathic Arthritis
LTE	Long Term Extension *(Study A3921145)*
LFT	liver function test
LPD	local product document
LSLV	last subject last visit
MACE	lymphomas, major adverse cardiovascular events
MAS	Macrophage Activation Syndrome
N/A	not applicable
NMSC	non-melanoma skin cancer
OBU	Oncology Business Unit
PCD	primary completion date
PFS	pre-filled syringe
pJIA	Polyarticular Juvenile Idiopathic Arthritis
PK	Pharmacokinetics
PRCSG/PRINTO	Pediatric Rheumatology Clinical Study Group/Pediatric Rheumatology International Trials Organization
PsA	psoriatic arthritis
PT	prothrombin time
QTF-Gold	QuantiFERON®-TB Gold test
QTF-TB	QuantiFERON®-TB In-Tube test
RA	rheumatoid arthritis

Abbreviation	Term
RF+	Rheumatoid Factor positive
RF-	Rheumatoid Factor negative
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SCL	Supply Chain Lead
Scr	Serum creatinine
SIB	suicidal ideation and behavior
sJIA	Systemic JIA
SOA	Schedule of Activities
SOC	Standard of Care
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
SUN	Standard Uveitis Nomenclature
TB	Tuberculosis
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States package insert
VTE	Venous thromboembolism
VZV	Varicella Zoster Virus

Appendix 9. The Degree of Burden and the Risk Threshold Assessment required at each visit. [article 40 (4) No. 4 of the German Medicines Act]

As written in the protocol under the Schedule of Activities, in Study Procedures and Assessments sections, and here summarized, at each visit, the physician 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.

4. Various functional and global assessments depending on the child's specific rheumatologic diagnosis such as the JIA joint assessment, CHAQ, CHQ, and the PRCSG/PRINTO Disease Flare Assessment; the Physician's Global Evaluation of Overall Disease Activity.

5. The investigator also will assess for flare and ACR responses as determined by PRINTO/PRCSG.

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 10.7, serious infections, opportunistic infections, tuberculosis, herpes zoster, malignancies (excluding NMSC), non-melanoma skin cancer (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[24] at any time during the study, (including the open-label run-in and double-blind phase) will be discontinued from study, and offered the possibility to continue receiving drug in the long term extension study, based on fulfilling certain safety criteria and judgement of the treating physician. Additionally, the investigator refers to Appendix 7 "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 10. Temporary Measures for Study Visits Occurring During Public Emergencies

In response to public emergencies, including the ongoing global pandemic COVID-19, and increasing restrictions and concerns on public health, the following changes are incorporated into this A3921165 protocol to clarify alternative solutions to accommodate study procedures. These alternate solutions should only be implemented after discussion with the Sponsor. If public emergencies other than the COVID-19 global pandemic occur, there may be additional or different alternate solutions provided to the sites at that time.

For subjects unable to return to the investigational site for study visits due to local restrictions put in place the following temporary options may be implemented and must be documented in the medical record:

- Section 6: STUDY PROCEDURES**: Study visits, except the baseline (Day 1) and randomization visit: In-home visits or Telephone Calls (may include video) for safety assessment by the study staff:** may replace a site visit only in case a subject has controlled sJIA disease, and is quarantined, or self-isolating. Follow the protocol schedule of activities when possible.

  In-home visits: Assessment of Adapted JIA ACR response and review of the results from the Coordinating Center may occur after the in-home visit after faxing/emailing the sJIA Disease Assessment worksheets and JIA ACR core component CRF to the Coordinating Center. Instructions to the study participants regarding background treatment, ie, corticosteroid tapering in Part 2 may be provided after the visit via a telephone call. Likewise, blood samples can be sent to the central laboratory after the in-home visit.

  Telephone Calls: It is expected that all subjects should at least have a safety assessment via phone call at the time of their scheduled visit.

  During telephone calls at a minimum the following must be assessed and documented:

  - Absence of fever via remote review of the fever diary;
  - Adverse events;
  - Compliance of dosing of investigational product;
  - Use of concomitant medication;
  - Partial assessment of disease status by asking how the subject is feeling.

  If a subject is due for a site visit but has uncontrolled sJIA the subject should be evaluated on site. Please notify the clinical team if this happens.

Refer to protocol mandated discontinuation criteria (Section 3.2.1, 4.2.2.2, 4.3, 6.3, Section 8.3.2, Appendix 7). Any subject for whom in the opinion of the investigator the benefit/risk of continuing investigational product is no longer favorable should be discontinued.

- Section 6: STUDY PROCEDURES and Section 8.2.9 Laboratory Testing:
  Protocol-specified safety laboratory tests: must be performed per protocol, but may be performed at a local laboratory, where allowable by law or local guidance, if the study participant is unable to visit the study site. In this case, local laboratory reference ranges and accreditation need to be documented. Local laboratory results should include all assays as required by the protocol. If laboratory testing is not performed, this must be documented as a Protocol Deviation related to the public emergency, including COVID-19.

- Section 6: STUDY PROCEDURES and Section 5.4.2 Preparation and Dispensing:
  Investigational Product Dispensing: In situations where participants are quarantined or self-isolating, temporary arrangements to send medicinal product via courier may be implemented where allowable by law or by local guidance and with the participant's verbal consent. Sites may ship Investigational Product only if there is no safety concern and only to participants known to have controlled sJIA disease with recent laboratory testing indicating no relevant laboratory abnormalities for haematology, serum chemistry and lipids that would require retesting, or discontinuation per protocol Section 8.3 and confirmed negative pregnancy test (if required per protocol Section 4.4.1 Contraception).

- Section 3.3 Randomized Withdrawal Phase and Section 6.6 Randomization Visit: Start Double-blind Withdrawal Phase: **Open-label Part 2 and randomization**: Subjects with controlled sJIA who meet the criteria to proceed to randomization, but are at risk of restricted access to care by the study staff will be allowed to remain in open-label Part 2, provided that the overall duration does not exceed 24 weeks.

- **Compliance with protocol and data entry:** Investigators should continue to follow the protocol and data entry timeliness. Any deviations to the protocol related to the public emergency, including COVID-19 pandemic, should be documented and recorded as deviation as requested by Health Authorities.

- If the sponsor determines that the impact of the public emergency, including COVID-19, on protocol visits and procedures and associated timeframe needs to be reported on a case report form (CRF), this will be requested. For participant discontinuation reporting in the CRF: select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, check the "OTHER" box and enter "COVID-19" in the "Specify" field.

- **Adapted JIA ACR response**: If a telephone call replaces a site visit this response cannot be assessed and a Protocol Deviation related to the public emergency, including COVID-19 will be recorded. The overall duration of the Open-label (OL) phase may not be extended to more than 16 weeks for Part 1 and 24 weeks for Part 2, even if site visits are missed.

  The following rules will apply to assess maintenance of a stable Adapted JIA ACR 30 response for 4 weeks in the **Open-Label phase**:

  - If site visits are missed between Day 3 and Week 4: any Adapted JIA ACR 30 response that a subject achieved within the first month will not count towards the 4 weeks of stable Adapted JIA ACR 30 response. The subject will be required to achieve and maintain the Adapted JIA ACR 30 after Week 4 to proceed to OL Part 2 or randomization.

  - If only 1 monthly site visit is missed after Week 4: The Adapted JIA ACR 30 response at the visit immediately before the missed visit will count towards the 4 weeks of stable response if the subject continues to demonstrate an Adapted JIA ACR 30 response at the next site visit, even if more than 4 weeks have passed between the site visits.

  - If 2 consecutive monthly site visits are missed after Week 4: any Adapted JIA ACR 30 response that a subject achieved before the missed visits will not count towards the 4 weeks of stable Adapted JIA ACR 30 response.

  - If 3 consecutive monthly site visits are missed after Week 4: the subject will have to be discontinued.

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

For German sites only: The alternative measures outlined above will only apply to the COVID-19 pandemic and not other public emergencies.

Appendix 11. Summary of Changes from Original Protocol through Amendment 7

Document	Version Date	Summary of Changes and Rationale
Amendment 7	22 Aug 2022	**3. Study Design** *The following update to the study design is made throughout the protocol:* Subjects who discontinue Investigational Product (IP) in the double-blind phase and who do not enter A3921145 will continue in A3921165 for follow up of efficacy and safety endpoints. Subjects will be required to perform all scheduled visits until Week 52 after randomization or until the study concludes, whichever comes first. Subjects should receive standard-of-care treatment in accordance with local treatment guidelines. The telephone contact visit at 24 weeks post randomization (for subjects not entered in A3921145 LTE study) is no longer applicable and removed. *No study design change is made to the follow-up of subjects discontinuing in the Open Label phase; however, the following wording is added for clarification throughout the protocol:* Subjects who discontinue the study in the Open-Label Phase and do not enter A3921145, will be required to perform a follow-up visit 28 days after the last dose of study treatment. **3. Study Design Figure 1 / Figure 2** Clarification that subjects in randomized withdrawal phase will receive Investigational Product up to 1st sJIA flare, 24 consecutive weeks inactive disease or ET/EOS visit. Added footnote that subjects who discontinue IP in randomized phase will continue in the study. **Schedule of Activities** Footnote #25 added: Subjects who discontinue Investigational Product in the double-blind phase and who do not enter A3921145 will continue in A3921165

Document	Version Date	Summary of Changes and Rationale
		for follow up of efficacy and safety endpoints. Subjects will be required to perform all scheduled visits until Week 52 after randomization, or until the study concludes, whichever comes first. Subjects should receive standard-of-care treatment in accordance with local treatment guidelines. All visit activities should be performed with the exception of Investigational Product dispensing, dosing and compliance. **5.8.1.2. Disease Modifying Anti Rheumatic Drugs (DMARDs)** **Appendix 1. Allowed and Disallowed DMARDs** Shortened washout periods of tacrolimus, sulfasalazine and azathioprine from 4 weeks to 7 days. **6.7.1 Discontinuation from Investigational Product during Randomized Withdrawal Phase** New sub-section added: Subjects who discontinue Investigational Product in the double-blind phase, for reasons other than sJIA flare or clinical remission, and who do not rollover to A3921145 Long Term Extension (LTE) study, should continue with the regular scheduled visits every 4 weeks. All required procedures and assessments should be performed with the exception of IP dispensing and compliance. Subjects should receive standard-of-care treatment as per local guidelines. There are no protocol restrictions on the use of DMARDs and other disallowed agents, detailed in Appendix 1, for subjects receiving standard-of care treatment. **6.10. Follow Up Telephone Contact** This section is removed. **6.12 Subject Withdrawal** **7. Discontinuation of Study Intervention and Subject Withdrawal**

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		Subject Withdrawal Section is removed and replaced with **Section 7. Discontinuation of Study Intervention and Subject Withdrawal** The following sub-sections are added: • Discontinuation of Study Intervention • Subject Withdrawal from Study • Lost to Follow-Up • Withdrawal of Consent **8.2.14 Temporary Withholding of Study Drug** **8.3.2 Discontinuation of Study Drug Criteria** **9.13 Withdrawal due to Adverse Events** **Appendix 7: Guidelines for Safety Monitoring and Discontinuation** Updated language to clarify that subjects are not withdrawn from the study if study drug is discontinued. **8.2.12 Blood Volume Table 5** Clarified that samples are collected every 4 weeks until ET/EOS not just until a subject flares. **Statistical Analysis** **10.2 Efficacy analysis** The log-rank test is updated from stratified to unstratified. **Appendix 1 : Allowed and Disallowed DMARDS** Added clarification that protocol prohibited agents can be used for subjects discontinued from Investigational Product and continuing in study on standard-of-care. **Protocol Summary: Study design** Duration of study updated from approximately 5 years to approximately 7 years. **Schedule of Activities** Footnote #26 added:

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		At the ET/EOS visit, for subjects considering entering A3921145 LTE study, an Informed Consent/Assent Document for A3921145 should be provided to the subject prior to the visit, if possible. **Schedule of Activities Footnote #3** The wording of "flare evaluations will only be done if the subject discontinued due to other reasons than flare before Week 24 of the double-blind phase" is removed. **Schedule of Activities Footnote #10** **8.1.6.2 Erythrocyte Sedimentation Rate** A local lab ESR testing kit (Westergren method) can be substituted for a Sponsor kit only if supply issues have resulted in a Sponsor kit not being available at the time of the visit. **3.3 Randomized Withdrawal Phase** Clarification that participation in the study ends for subjects who experience 24 consecutive weeks of inactive disease, as well as subjects who flare. An EOS visit should be performed for these subjects who complete the study. **6.7 Double-blind withdrawal phase** **6.8 End of Study or Early Termination Visit** Clarification that participation in the study ends for subjects who experience 24 consecutive weeks of inactive disease, as well as subjects who flare. **Schedule of Activities** A banked biospecimen is collected at the Open Label Part 1 Phase Week 8 visit. This was previously omitted in the table. **8.1.2 Fever and Absence of Fever Assessment** Each subject to receive a temperature diary at the screening visit instead of day 1. **8.1.9. JIA ACR Clinical Inactive Disease and Clinical Remission Criteria**

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		Clinical Inactive disease will be defined only using ESR and not CRP. **8.1.11. JADAS 27 Minimal Disease Activity and Inactive Disease** Clarified polyarthritis is more than 4 active joints, and oligoarthritis is 4 or less. **12.1 Case Report Forms/Electronic Data Record** Added language: When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems. **12.3 Data Protection** New section added to describe the requirements for storage of personal data. **13 Ethics** New language added on regulatory and ethical considerations. **Appendix 5: Prohibited Concomitant Medications** Clarified that required washout is 4 weeks or ≥5 half-lives, whichever is longer. **Appendix 10:** **Temporary Measures for Study Visits Occurring During Public Emergencies** For German sites only: The alternative measures will only apply to the COVID-19 pandemic and not other public emergencies.
Amendment 6	09 Feb 2022	**Protocol Summary** Secondary Efficacy Endpoints: • Occurrence of inactive disease status at every visit from Day 7 onward (JIA ACR) in the open label phase and the double-blind phase and assessment of clinical remission in the double-blind phase as clinical remission is not evaluated in the open-label phase.

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		Statistical Analysis: • Difference in time to flare between the two treatment groups (tofacitinib 5 mg BID vs. placebo) will be assessed using a stratified log rank test if enough events are observed in each stratum. Otherwise, the unstratified log-rank test will be used. **Schedule of Activities** Footnote 1: • Clarified that if more than 40 days in screening elapsed, subjects should be screen failed and rescreened if eligible. Footnote 6: • Added skin examinations Footnote 8: • Added India to countries where annual TB testing is required as the incidence of TB is >50 cases per 100,000 people. Footnote 18: • Removed the requirement that only subjects with positive VZV serology tests can be enrolled in the study. Footnote 20: • Clarified that subjects in India would not participate in PK testing. Footnote 24: • Added skin examinations for rash related to varicella (chickenpox) and herpes zoster are required. **Section 1.1 Indication** • Updated the text regarding the approved indications for tofacitinib as of 03 December 2021, tofacitinib 5 mg BID is also approved for the treatment of psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers. **Section 2.3 Benefit/Risk Assessment**

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		• Discussion of the risks and benefits of using tofacitinib in the pediatric population added to the body of the protocol at the request of an ethics committee. **Section 3.2.1 Open label Phase, Part 1: Treatment with Tofacitinib while on Stable Background Therapy** • Clarified the text relating to Part 1 of the Open-label Phase **Section 3.2.2 Open label Phase, Part 2: Treatment with Tofacitinib while on Stable Background Therapy** Clarified the text relating to Part 2 of the Open-label Phase **Section 3.3 Randomized Withdrawal Phase** • Clarified the definition of 'flare' and how it will contribute to the primary endpoint. **Section 3.4.1 Evaluation of 5 mg BID or Equivalent Weight based Lower Dose** • Informed that Cohorts 1 and 2 had completed and the study is now in open enrollment. **Section 4.1 Inclusion Criteria** • Criteria #4 removed 3rd bullet as it was redundant with the first sentence of the criteria. **Section 4.2 Exclusion Criteria** • Criteria #14 revised exclusion regarding household contacts to align with IDSA Clinical Practice Guidelines for Vaccination of the Immunocompromised Host. • Criteria #15 removed the requirement for evidence of 2 doses of varicella (chickenpox) vaccination or positive

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		VZV serology testing to qualify for enrollment in the study. **Section 4.5 Vaccine and Exposure to Infections Guidelines** • **Section 4.5.1 Subject Specific Recommendations** was revised to clarify what vaccines can and cannot be administered to study participants and stated requirement for skin examinations for varicella vaccinated (inspect for herpes zoster rash) and varicella unvaccinated (inspect for chickenpox rash). • **Section 4.5.2 Guidance Regarding Household Contact Vaccine Related Exposure** was revised to align with IDSA Clinical Practice Guidelines for Vaccination of the Immunocompromised Host. **Section 4.7 Elective Surgery** • This section was modified to allow investigator discretion for withholding study treatment if surgery is required. **Section 5.1 Allocation to Treatment** • Section 5.1.1.1 Enrollment in 5 mg BID Cohort was revised to clarify the cohort was complete and the study could continue to the next phase. • Section 5.1.1.2 Open Enrollment at the 5 mg BID Dose Level was revised to clarify that the previous cohort requirements were satisfied and the study was now in open enrollment. **Section 5.8 Concomitant Treatment(s)** • Section 5.8.1.1 Corticosteroids (CS) was revised to clarify the transition and timing of pre-study IV corticosteroid use (IV pulse). **Section 6 Study Procedures**

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		• Section 6.1 Screening Visit text was clarified to inform that the screening visit window is no more than 40 days and that if it extends beyond that time, the subject must be screen failed and rescreened with all assessments repeated. • Section 6.3 through Section 6.9 added at all regularly scheduled visits that all examinations should include skin examination for chickenpox or shingles. • Section 6.10 Follow Up Telephone Contact added an assessment for adverse events, including skin rash that could potentially indicate the presence of chickenpox or shingles, sJIA flare, and other manifestations of sJIA exacerbations. • Section 6.11 Unscheduled Study Visit or Telephone Contact added an assessment for skin rash that could indicate the presence of chickenpox or shingles. **Section 7.2.6 Varicella (chickenpox) and Herpes zoster (shingles) Assessment and Guidance** • This section was added to describe the rash and other symptoms that may accompany these events and how they differ from the typical sJIA rash. This section also added 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. **Section 7.2.9 Laboratory Testing** • VZV-specific ELISA testing was modified to remove the requirement of VZV seropositivity for subject to enroll if they do not have a history of having received 2 doses of varicella vaccine.

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		Table 5. Maximum Blood Volume Collection at Each Study Visit • Footnote 6 noted that India will not participate in PK sampling. • Footnote 9 updated to include India in annual TB testing. **Section 7.2.14 Temporary Withholding of Study Drug** • Section Title was changed from citing tofacitinib rather than study drug as during the double-blind phase of the study, subjects could be receiving placebo. • Text of section was revised to identify study drug instead of tofacitinib, identifies when study drug does not require withholding, and informs that when drug is withheld for protocol-related reasons (e.g., adverse events, laboratory abnormalities) missed doses would not contribute to non-compliance. **Section 9.1 Sample Size Determination** • Further clarified that subjects discontinuing study drug in the double-blind phase of the study for reasons other than clinical remission will be counted as having an sJIA flare in the primary analysis for the primary endpoint of the study. **Section 9.2.1 Analysis of Primary Endpoint** • Clarified the text regarding the planned supportive analyses. **Section 9.2.2 Analysis of Secondary Endpoints** • Clarified that secondary endpoints would not be statistically analyzed beyond 52 weeks but will be summarized descriptively. **Section 12.2**

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		• Add country-specific requirement for the Netherlands that in the Netherlands, patients will be evaluated for enrollment in this study if previous treatments recommended by the JVN Medicamenteuze behandeling van kinderen met jeugdreuma (Dutch Guidelines: JVN Drug Treatment of Children with Juvenile Rheumatism) have failed to control their systemic JIA disease. **Appendix 10 Temporary Measures for Study Visits Occurring During Public Emergencies** • Clarified that these temporary measures should not be implemented by the study sites without conversation with the Sponsor and that if other public emergencies other than the COVID pandemic occur additional or different alternate solutions may be provided. • Removed the restriction that CRP cannot be performed locally, as CRP is not blinded in this study. **Appendix 11 Summary of Changes from Original Protocol through Amendment 5** • Updated the title to include Amendment 5 and added the summary of changes and rationale from Amendment 5 to the table.
Amendment 5	21 July 2021	This global amendment incorporates updates to facilitate enrollment of sJIA patients who were previously treated with biological DMARDs or JAK-inhibitors: • Section 5.8.1.2 (Table 4), Appendix 1: The washout period for biological DMARDs has been shortened from 5 half-lives to 2 half-lives. This change is made to minimize the length of time that sJIA patients with active disease must go without adequate treatment. This update is supported by previous analyses with tofacitinib in rheumatoid

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		arthritis (RA) and psoriatic arthritis (PsA) patients who were switched from adalimumab to tofacitinib without a washout period; no increase in adverse events after the switch was noted in these analyses. • Section 4.2 (Excl Criterion #4) and Section 5.8.1.2: Removed the restriction that only 40% of subjects are allowed to have previously failed two biologic DMARDs. All subjects are allowed to have previously failed two or more biologic DMARDs, provided washout periods are respected. • Section 4.2, Section 5.8.1.2 and Appendix 1: Updated Exclusion Criterion #1: Previous treatment with baricitinib or JAK-inhibitors, other than tofacitinib, is allowed provided washout periods are respected. Baricitinib (Olumiant®) and Upadacitinib (Rinvoq®) are added to list of DMARDs requiring a washout. These changes are made to address the changed landscape with more sJIA patients being treated with JAK-inhibitors. In addition, this amendment reflects: • Section 4.1: Inclusion Criterion #2: Clarified that subjects diagnosed with sJIA who have first-degree relatives with history of psoriasis, ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis may be allowed for enrollment after consultation with the sponsor. These excluding conditions for siblings no longer apply to the definition of sJIA according to the revised ILAR

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		criteria agreed during the Printo 1st consensus meeting in 2019. • Section 3.2.2: Clarified the Corticosteroid tapering in Open-label Part 2. A subject must be on the final tapered CS dose on or before the day after the open-label Part 2 Week 20 visit. • Schedule of Activities, Figure 1, Figure 2, Section 6.1, Section 6.2, Section 7.2.11: Updated the screening period with 10 additional days for additional flexibility. • Section 6.1: Clarified the circumstances in which re-screening is allowed. • Section 6.1, Section 7.2.8, & Section 7.2.11: Clarification that a one-time repeat testing of screening hematology and serum chemistry laboratory abnormalities is allowed if the abnormal laboratory result was uncharacteristic for the participant. This change is made to avoid screen failures as a result of laboratory errors. • Section 6.6: Correction of error: once a subject is able to maintain the Adapted JIA ACR 30 response for 4 weeks on a stable tapered CS dose in the open-label phase he/she can start the double-blind phase (not open-label Part 2). • Section 9.9: Clarified that from study start, the Sponsor is using an independent Macrophage Activation Syndrome (MAS) Review Committee to adjudicate events of MAS reported during the study. • Section 5.3: Updated to state that subjects who exhibit non-compliance

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		may be discontinued from the study after discussion with the Sponsor. • Schedule of Activities, Section 7.1.4, Section 7.1.5: Updated to include that an adult caregiver interacting daily with the subject can complete the CHAQ and CHQ assessments during the course of the study. This change is made to accommodate study participants who are accompanied by caregivers during study visits. • Section 1.1: Updated to include the current number of countries in which tofacitinib is approved for RA. • Schedule of Activities, Appendix 10: Updated to expand the Temporary Measures for Study Visits for any public emergency, including COVID-19. This change is made to cover all public emergencies that may require alternatives to clinic visits. Minor updates made for general clarity and consistency throughout the document.
Amendment 4	17 March 2021	This global amendment incorporates updates to address enrollment challenges: • Section 4.1 (Inclusion Criterion #2): Subjects must have active disease at the time of screening and enrollment. Six (6) weeks of active disease before screening are no longer required (previous minimum). This change is made to minimize the length of time that sJIA patients with active disease must go without adequate treatment. • Section 4.1 (Inclusion Criterion #3); Appendix 1; Appendix 3; Section 5.8.1.2 Allowed DMARDs: A stable dose of methotrexate in the last

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		4 (instead of 6) weeks before Dose 1 is required in subjects who receive background methotrexate. This change is justified by the half-life of methotrexate. • Section 4.2 (Exclusion Criterion #1): Subjects who received previous JIA treatment with tofacitinib, baricitinib or any other JAK-inhibitor will be excluded. This exclusion criterion was broadened to include any JAK-inhibitor. • Section 4.2 (Exclusion Criterion #5b): Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to be opportunistic by the investigator within the 3 months (instead of 6 months) prior to the first dose of study drug will exclude a subject. This change reflects the current safety profile of tofacitinib. In addition, this amendment reflects: • Background, Section 1.2.1: Added a sentence that Study A3921104 in pJIA patients is completed and results demonstrated that tofacitinib was safe and efficacious. Section 1.2.2: Added further justification for the randomized withdrawal study design. • Section 4.2 (Exclusion Criterion #15), Section 4.5.1, Section 6.1, Section 7.2.8, Section 7.2.11, Schedule of Activities: Subjects who have documented evidence from a health professional of receiving 2 vaccinations for varicella zoster virus (VZV) are eligible for inclusion and do not require a positive VZV IgG serology test at screening. This change is consistent with CDC guidelines that do not recommend

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		testing for VZV immunity after receiving 2 doses of varicella vaccine.[29] • Monitoring and Discontinuation Criteria, Section 7.3.1 and 7.3.2; Appendix 4, Appendix 7: the creatinine monitoring and discontinuation criteria were updated: in addition to a single increase or 2 sequential increases in serum creatinine >50% over the average of screening and baseline values OR an absolute increase in serum creatinine ≥0.5 mg/dL (≥44.2 umol/L), a single or 2 sequential Creatinine Clearance (CrCl) decreases of >30% over the average of screening and baseline CrCl values are required to monitor (retest creatinine) or discontinue a subject from the study, respectively. Appendix 4: Clarified that estimated glomerular filtration rate will be calculated at screening to determine subject eligibility and Creatinine Clearance will be calculated at all visits (via Modified Schwartz equation for subjects <12 years old and Cockcroft-Gault equation for subjects ≥12 years old). These updates were made to account for potential increases in creatinine due to physical activity, age and growth and to align with FDA/CDER 2014 guidelines regarding monitoring of kidney function in pediatric studies.[30] • Section 4.2: Exclusion Criterion #28: This country-specific exclusion criterion is made global to ensure consistent eligibility criteria for the study population, and is broadened to exclude subjects with a history of allergies, intolerance or hypersensitivity to any other excipients of the investigational product, including placebos, at the request of the German regulatory agency: subjects will be excluded if they

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		have a history of allergies, intolerance or hypersensitivity to lactose or CP-690,550 (tofacitinib), or any other excipients of the investigational medicinal products, including placebos. 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 investigators request. • Section 4.5.1: Clarification that 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. • Schedule of Activities, Section 6.4, Section 6.5, Section 7.2.11: Clarification of PK sample collection in accordance with Section 7.4.1: the PK sample after 8 weeks of tofacitinib treatment may be obtained at Week 8 Part 1, or at Week 4 Part 2 in case a subject moves from Part 1 to Part 2 after 4 weeks of tofacitinib treatment. • Appendix 1: Correction of the washout period for investigational drugs to be 4 weeks in accordance with exclusion criterion #24. • Appendix 3: Correction of administrative error. The maximum dose of corticosteroids is 30 mg/**day** of oral prednisone, not 30 mg/kg. • Section 4.2: Exclusion Criterion #16, Appendix 7, and Section 7.3.2: Consistent nomenclature in accordance with other tofacitinib protocols to state "basal cell or squamous cell carcinoma

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		of the skin" instead of "NMSC (non melanoma skin cancer)" and "cervical carcinoma" instead of "cervical cancer."
Amendment 3	4 May 2020	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. In addition, it includes temporary measures for visits occurring during the COVID-19 pandemic, updates in accordance with recent PACLs and some clarifications of text. The following sections have been updated to reflect these changes: • Schedule of Activities, Section 4.2 (Exclusion Criteria), Section 6 (Study Procedures), Section 7.2.12 (Risk Factor Check for Venous Thromboembolism), Section 7.2.13 (Tofacitinib Temporary Withholding), Section 7.3.2 (Discontinuation Criteria) and Appendix 7. • Temporary measures for visits occurring during COVID-19 are added in Appendix 10. • Update in accordance with JIA protocol A3921145: Clarified under what conditions temporary withholding of tofacitinib up to 28 days is allowed in Section 7.2.13 (Tofacitinib Temporary Withholding). • Update in accordance with PACL#9: In countries with an incidence rate of Tuberculosis (TB) of >50 cases per 100,000 persons, eg, China, Russian Federation; South Africa and Ukraine (World Health Organization): yearly TB testing is required after screening. The Schedule of Activities, Section 6.7 (Visits every 4 weeks in Double-blind Withdrawal phase), Section 7.2.7 (Tuberculosis Testing), and

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		Section 7.2.11 (Blood Volume) have been updated accordingly. • Table 4: Correction in accordance with PACL#9: the incorrect statement that the washout of Anakinra is 4 weeks before Day 1 is removed. • Childhood Health Questionnaire (CHQ) and Childhood Health Assessment Questionnaire (CHAQ): Parents/legal guardians are required to complete the CHQ and CHAQ throughout the study. Subjects >18 yrs will not complete the CHQ and CHAQ. Sections 7.1.4 and 7.1.5 (Efficacy assessments) have been updated accordingly. • Correction in accordance with PACL#9: the CHQ is required every 6 months (not every 3 months) after randomization. The protocol summary and Section 2.2 (Secondary Endpoints) have been updated accordingly. • Update in accordance with Amendment 2: an additional PK blood sample must be obtained 1.5 hours (1.25-2h) post tofacitinib administration in the first 14 subjects enrolled in Cohorts 1 and 2. Footnote 20 of the SOA, Section 6.2 (Day 1 Visit) and Section 7.2.11 (Blood Volume) have been updated accordingly. • Section 8.2 (Time Period and Frequency for collecting AE and SAE Information) was updated according to the new standard text. • Update for consistency with LTE protocol A3921145: in Section 7.2.11 (Blood Volume) is added that in case of insufficient blood sample or poor sample quality a subject must return within 1 week for a new sample collection. A reference to Section 7.2.11 is added to

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		the SOA and Section 6 (Study Procedures). • Section 3.4: Clarified the sentence regarding open enrollment, which will occur after completion of initial cohorts of subjects ≥40 kg and aged ≥12 years.
Amendment 2	16 May 2019	• Tofacitinib 10 mg BID dose will no longer be evaluated. References to the 10mg BID group and 10 mg BID dose increase at Day 14 are removed throughout the protocol. At the time of this amendment (Amendment 2) only Cohort 1 (5 mg BID dose evaluation) has been completed and Cohort 2 (5 mg BID dose evaluation) is ongoing. There were 2 subjects that required a dose escalation to 10 mg BID after 14 days of dosing due to uncontrolled fever. One subject discontinued 4 days after the dose increase due to sJIA exacerbation and one subject has decreased their dose to 5 mg BID. • Reference to the Section 7.1.2 added in the schedule of activities. • Minor editorial corrections throughout the document.
Amendment 1	14 December 2018	• EudraCT number corrected (front page); PACL issued 09-May-2017. • Schedule of activities updated to clarify that the End of Study (EOS)/Early Termination (ET) visit is required for all subjects who discontinue from the study outside of a regular scheduled visit regardless of the phases; PACL issued 29-Jun-2017. • Background section updated to reflect the start of the A3921104 study (Refer to Section 1.2.1 Tofacitinib). • Inclusion criterion #4 and protocol section 7.2.7 Tuberculosis Testing updated to clarify which treatment is considered "adequate" prior to enrollment of a subject with latent tuberculosis; the Sponsor considers ongoing

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		treatment with isoniazid or equivalent for at least 4 weeks before the first dose of tofacitinib (Day 1) adequate, provided that local rates of primary multi-drug resistant TB infection are <5%; PACL issued 02-Jan-2018. • Exclusion criterion #4 updated to clarify that only discontinuation of a biologic DMARD due to safety concerns, or lack of efficacy would be considered a treatment failure. A switch from the IL-1 inhibitor Anakinra (Kineret®) to the IL-1 inhibitor Canakinumab (Ilaris®) for convenience would not count as a biologic DMARD failure; PACL issued 23-Oct-2017. • Exclusion Criterion #15 changed to exclude any subjects without documented evidence of prior exposure to varicella zoster virus based on positive serological testing at screening. Schedule of activities, protocol Section 4.2 Exclusion criteria, 4.5.1 Subject Specific Recommendations, 6.1 Screening Visit, 7.2.8 Laboratory Testing and 7.2.11 Blood Volume have been updated accordingly. • Washout period for Anakinra and Cyclosporine corrected to 7 days in Section 5.8.1.2 Disease Modifying AntiRheumatic Drugs and Appendix 1; PACL issued 23-Oct-2017/PACL issued 15-Oct-2018. • Immunoglobulin IV added to list of prohibited medication, a washout period of 20 weeks or 5 half-lives (whichever is longer) is required prior to the first dose of study drug (Section 5.8.1.2 Disease Modifying AntiRheumatic Drugs and Appendix 1); PACL issued 31-May-2018. • Child Health Questionnaire added in Section 6.1 Screening Visit; PACL issued 29-Jun-2017. • Duplicated procedures " sJIA disease activity status" removed in Section 6.1

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		Screening Visit; PACL issued 29-Jun-2017. • Protocol section 6.3 Open-Label Phase /Part 1: Day 3, Day 7 and Day 14 visit updated to clarify that the assessment of the Adapted JIA ACR response based on ESR is Only required at the Day 7 and Day 14 visit; PACL 15-Oct-2018. • Telephone contact at 11 Weeks for subject who had a dose increase at Day 14 added to the list of visits in the Section 6.5.1 Telephone Contact 1,3,5,7,9 and 11 weeks after Dose Increase, PACL issued 29-Jun-2017. • List of analysis required at the biweekly visit after dose increase corrected to include Hematology, Chemistry, Lipid panel, CRP and urinalysis in Section 6.5.2 Extra Visits at 4, 8, and 12 weeks after Tofacitinib Dose Increase from 5mg to 10 mg BID; PACL issued 15-Oct-2018. • Child Health Questionnaire added in Section 6.10 Follow-up Visit (only for subject not entering study A3921145); PACL issued 29-Jun-2017. • List of analysis required at the Follow-up visit corrected to include Hematology, Chemistry, Lipid panel, CRP and urinalysis Section 6.10 Follow-up Visit (only for subject not entering study A3921145); PACL issued 14-Aug-2018. • Tanner stage assessment required at screening visit instead of Day 1 in Section 7.2.6 Pubertal Development Assessment (Tanner Stage); PACL 29-Jun-2017. • Guidelines about blood volume collection in pediatric study added to Section 7.2.11 Blood Volume. (PACL issued 15-Oct-2018). • Reference to"QuantiFERON®-TB Gold Plus" In-tube Test added, QuantiFERON®-TB Gold or

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		QuantiFERON®-TB Gold Plus will be available according to the country."QuantiFERON®-TB Gold or Gold Plus" added throughout the protocol and the required volume of blood updated to 3 mL or 4 mL (Section 7.2.7 Tuberculosis Testing, Section 7.2.11 Blood Volume and Schedule of Activities), PACL issued 11-Sep-2018.
		• Correction in Table 5 Maximun Blood Volume Collection at Each Study Visit:
		  • Minimum volume of blood required at Day1 visit corrected to 9.4 mL instead of 9.3 mL.
		  • Volume of blood required for banked biospecimen at Week 8 corrected to 2mL in line with protocol Section 7.5 Banked Biospecimens.
		  • Volume of blood required at screening updated to include QuantiFERON®-TB Gold Plus and the varicella zoster virus testing (Refer to Section 6.1 Screening Visit and Section 7.2.11 Blood Volume.
		• Pharmacokinetic (PK) samples to be collected at baseline (day of tofacitinib administration) and after 8 weeks of study treatment, instead of at baseline (day of tofacitinib administration) and after 8 or 12 weeks of study treatment. Schedule of activities, protocol Section 6.4 Open-Label Phase/Part 1: Visits Every 4 Weeks from Week 8 up to Week 16, Table 5 Maximum Blood Volume Collection at Each Study Visit, and 7.4 Pharmacokinetic Assessment have been updated accordingly.
		• PK samples timing updated in order to more accurately characterize the tofacitinib exposure profile, the last PK sampling time point was revised. (Refer to Section 7.4 Pharmacokinetic Assessment).
		Country Specific Amendment for European Union (EU), (including United Kingdom [UK]):

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		Protocol amended in line with the European Union Regulatory Authority requirements for the protocol A3921104 which is part of the same program. These changes are applicable to sites within the EU (including UK). • Added clarification on the contraception requirements specific to subjects included by EU sites, including UK sites. (Refer to Section 4.1 Inclusion Criteria and 4.4.1 Contraception). • Added guidance for breaking the blind for study treatment. (Refer to Section 5.2 Breaking the Blind). • Added a full skin cancer examination to the complete physical examination. (Refer to the Schedule of Activity, Section 6, and Section 7.2.2 Physical Examination). • Added guidance regarding participants who have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or have underlying conditions that may predispose them to infection. (Refer to Section 7.2.7 Tuberculosis Testing). • Added guidance regarding limiting the number of attempts for blood collection. (Refer to Section 7.2.11 Blood Volume). • Added guidance regarding the blood volume limit recommended in pediatric studies. (Refer to Section 7.2.11 Blood Volume). • Provided guidance for monitoring confirmed absolute neutrophils count levels of 500 – 1000 neutrophils/mm^3. (Refer to Section 7.3.1 Monitoring Criteria). • Dose increase restriction: dose increase at Day 14 from tofacitinib 5 mg BID to 10 mg BID in the case that sJIA fever is not controlled within the first 2 weeks of treatment, will be allowed following confirmation of the safety and efficacy of the 10 mg BID dose for at least 12 weeks from subjects in cohorts 3 and 4. (Refer to the Section 5.1.1.3 Dose Increase from 5 to

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		10 mg BID Dose Level for Individual Subjects, and the Schedule of Activities). **Country specific amendment for Germany:** • The Degree of Burden and the Risk Threshold Assessment required at each visit to be in compliance with the article 40 (4) No. 4 of the German Medicines Act] (Refer to the Schedule of Activities, Section 6 Study Procedures and Appendix 9). • Added new exclusion criterion: History of allergies, intolerance or hypersensitivity to lactose or CP-690,550 (tofacitinib). 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. **Country specific amendment for South Africa:** • Due to the high incidence rate of Tuberculosis (TB) in South Africa; additional TB testing is required every year. (Refer to Schedule of Activities and protocol Section 7.2.7 Tuberculosis Testing). Protocol Section 7.2.11. Blood Volume has been updated accordingly.
Original protocol	15 March 2017	Not Applicable (N/A)