



**EFFICACY, SAFETY AND TOLERABILITY OF TOFACITINIB FOR  
TREATMENT OF POLYARTICULAR COURSE JUVENILE IDIOPATHIC  
ARTHRITIS (JIA) IN CHILDREN AND ADOLESCENT SUBJECTS**

<b>Compound:</b>	—	CP-690,550
<b>Compound Name:</b>		Tofacitinib
<b>United States (US) Investigational New Drug (IND) Number:</b>		CCI [REDACTED]
<b>European Clinical Trials Database (EudraCT) Number:</b>		2015-001438-46
<b>Protocol Number:</b>		A3921104
<b>Phase:</b>		3



### Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 6	11 July 2018	<ul style="list-style-type: none"> <li>• Changed the minimum number of subjects with systemic JIA with active arthritis to be enrolled from 20 to no minimum (see Protocol Summary and Section 3 [Study Design]).</li> <li>• Updated Section 9.3 (Population Pharmacokinetics and Exposure Response Analyses) to account for the potential of not enrolling 12 subjects.</li> <li>• Applied clarification and administrative changes outlined in PACL dated 21 June 2016 (see Schedule of Activities [SOA], Sections 6.5 [Study Procedures Week 8, 12/Day 56, 84 Visit], 9.7 [Safety Endpoint Adjudication Committee], and Document History).</li> <li>• Applied clarification and administrative changes outlined in PACL dated 26 Aug 2016. (see Protocol Summary, Section 3 [Study Design], Appendix 1 [Allowed and Disallowed Treatments for JIA], and Appendix 5 [Rescue Therapy]).</li> <li>• Apply clarification and administrative changes outlined in PACL dated 08 Dec 2016 (see Section 6.1 [Study Procedures Screening Visit]).</li> </ul>
Amendment 5	08 March 2018	<p>For Investigative Sites in Germany Only –</p> <ul style="list-style-type: none"> <li>• Exclusion Criterion 30 revised to ‘Applicable to Investigative Sites in Germany Only: History of allergies, intolerance or hypersensitivity to lactose or CP-690,550 (tofacitinib).’ Rationale for change: Clarification of the exclusion criterion to focus on known allergies, intolerance or hypersensitivities to the study treatment (active substance or excipients). (Refer to</li> </ul>

		Section 4.2).
Amendment 4	21 November 2017	<ul style="list-style-type: none"> <li>• For Investigative Sites in Germany Only – Appendix 10 added to be in compliance with article 40 (4) No. 4 of the German Medicines Act. Reference to Appendix 10 added to the Schedule of Activities and Section 6 (Study Procedures). A new reference was also added to References (Section 16).</li> <li>• Revisions to the protocol made in Amendment 3 in response to European Union Regulatory Authority request apply to Germany. Therefore Germany has been added to the statement Investigative Sites in the United Kingdom, Spain, Poland, and Belgium Only so that it now reads Investigative Sites in the United Kingdom, Spain, Poland, Germany and Belgium Only” (Refer to Sections 4.1, 4.2, 4.4.1, 5.2, Schedule of Activity, Section 6.0, and Section 7.2.2, 7.2.6, 7.2.10, and Appendix 6. Further details provided below in this Document History for Amendment 3.</li> </ul>
Amendment 3	30 October 2017	<p>Revisions to protocol in response to European Union Regulatory Authority request. These changes are applicable to sites within the United Kingdom, Spain, Poland, and Belgium.</p> <ul style="list-style-type: none"> <li>• Added new exclusion criterion: History of allergies, intolerance or hypersensitivity to tofacitinib or any components of the formulation. 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 (Refer to Section 4.2).</li> <li>• Added modified contraception language (Refer to Section 4.4.1).</li> <li>• Added guidance for breaking the blind for</li> </ul>

		<p>study treatment (Refer to Section 5.2).</p> <ul style="list-style-type: none"> <li>• Added a full skin cancer examination to the complete physical examination (Refer to the Schedule of Activity, Section 6.0, and Section 7.2.2).</li> <li>• 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 7.2.6).</li> <li>• Added guidance regarding limiting the number of attempts for blood collection (Refer to Section 7.2.10).</li> <li>• Update the allowable total volume of blood taken during any period of 30 consecutive days during the study from 2.7 mL/kg to 2.4 mL/kg (Refer to Section 7.2.10).</li> <li>• Provide guidance for monitoring confirmed absolute neutrophils count levels of 500-1000 neutrophils/mm<sup>3</sup> (Refer to Appendix 6).</li> </ul>
Amendment 2	16 March 2016	<ul style="list-style-type: none"> <li>• Removed the text stating that recruitment was limited to those ≥6 years of age and weighing ≥15 kg in Summary and Section 3 Study Design, Section 4.1 Inclusion Criteria, and Section 5.5 Administration as this group is now eligible to participate.</li> <li>• Removed Canada-specific language limiting recruitment to subjects not &lt;6 years as noted in Amendment 1 per Canada Regulatory Authority agreement.</li> <li>• Added blood volume to Protocol Summary section upon request from country authorities.</li> <li>• CCI [REDACTED]</li> </ul>

		<p>CCI [REDACTED]</p> <ul style="list-style-type: none"><li>• Added varicella zoster IgG Antibody testing at Screening to confirm varicella zoster virus (VZV) exposure in subjects who have not received at least one dose of vaccine (KOL feedback).</li><li>• For subjects with psoriatic arthritis (PsA) only: added body surface area (BSA) and Physician's Global Assessment (PGA) to the Schedule of Activities, and in Sections 6, 7, and Appendices 8 and 9; updated PsA-related allowable/prohibited concomitant medications where relevant (KOL feedback).</li><li>• Modified pharmacokinetic (PK) sampling times and reduced number of samples throughout to reduce blood volume and time required in clinic which may facilitate recruitment (site feedback).</li><li>• Modified visit window for uveitis assessment from <math>\pm 5</math> days to <math>\pm 7</math> days at visits after screening in the Schedule of Activities and throughout Section 6 where applicable to enable flexibility in scheduling (site feedback). Clarified that at visits when an exam is not planned, subjects should be assessed for any changes in uveitis status.</li><li>• Added Duration of Morning Stiffness assessment to Schedule of Activities and related sections (administrative).</li><li>• Updated Section 1.2.2 Dose Rationale following completion of study A3921103 and available PK for ages 2 through &lt;18 years of age. Also updated based on FDA recommendation to cap dosing at 5 mg BID; weight-based dosing scaled accordingly.</li><li>• Section 3 Study Design updated to reflect adjusted number of planned investigator sites from 120 to 90 (administrative).</li></ul>
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		<ul style="list-style-type: none"><li>• Section 4.1 Inclusion Criterion #2 and Appendix 1 clarified allowable dose of methotrexate to align with related A392 protocols (KOLs/administrative).</li><li>• Section 4.2 Exclusion Criteria were updated with clarifications based on feedback from investigators.</li><li>• Section 4.1, 4.2 and 4.4.1 updated language around childbearing potential and allowable contraception (administrative).</li><li>• Updated language in Section 4.4.2 to clarify guidelines around vaccines and vaccine-related exposure (investigator feedback).</li><li>• Section 4.8 Dietary Supplements clarified use of herbal supplements is not allowed to be consistent with the exclusion criterion (investigator feedback).</li><li>• Section 5.2 Breaking the Blind section updated to indicate the process is electronic using the IRT system (administrative).</li><li>• Throughout the protocol clarified that discontinuation due to a single episode of flare was defined as meeting the specified PRCSG/PRINTO Disease Flare criteria (investigator feedback).</li><li>• Section 5.3 Subject Compliance was updated to clarify definition of non-compliance, meaning compliance calculated as &lt;80% or &gt;110% for pediatric population (administrative).</li><li>• Table 2 in Section 5.5 Administration updated to reflect revised weight-based dosing regimen (FDA request).</li><li>• Updated parent to parent/legal guardian throughout for consistency.</li><li>• Updated Schober's to Modified Schober's</li></ul>
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		<p>throughout for consistency.</p> <ul style="list-style-type: none"><li>• Added emphasis in Section 6.6 Day 126 (Week 18) Visit around eligibility to randomize into the double-blind phase which requires confirmation of ACR 30 from the Central Coordinating Center.</li><li>• Section 7.1.2 and 7.1.3, scale images were replaced with better quality images.</li><li>• Section 7.1.4 corrected Childhood to Child Health Questionnaire.</li><li>• Section 7.1, updated language to allow flexibility in completion of PROs for subjects aged 14 and older (site and KOL feedback).</li><li>• Section 7.1.4 corrected Childhood to Child Health Questionnaire.</li><li>• Section 7.1.11.3 replaced both overall back pain and nocturnal back pain 100 mm visual analog scale (VAS) with a 21-circle VAS to improve data quality exchange with Central Coordinating Center.</li><li>• Section 7.2.3 Uveitis Assessment clarified examination per local guidelines and visit window (site feedback).</li><li>• Section 7.2.9 Pregnancy Testing added clarification that females of choildbearing potential are those who have passed menarche (administrative).</li><li>• Updated Section 9.6 to reflect use of Data Safety Monitoring Board (DSMB) (administrative).</li><li>• Removed Appendix 2 Approximate Equivalent Morphine Doses of Opioid Analgesics as not applicable in this population (KOL feedback).</li><li>• Appendix 2 Permitted Adjustments in JIA Therapies was updated to clarify when changes</li></ul>
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		<p>are allowable and specify the maximum dosing limits in alignment with related tofacitinib studies.</p> <ul style="list-style-type: none"> <li>• Updated the glomerular filtration rate formula in Appendix 3 to the Bedside Schwartz method for all subjects (administrative).</li> <li>• Appendix 7 Dosing Rationale (Abbreviated Analysis Report) was updated with PK data from A3921103 that provides dose rationale for this study.</li> <li>• Added Appendix 8 and 9 for BSA and PGA of Psoriasis, respectively (KOL).</li> <li>• Other typographical or administrative edits to improve readability and consistency.</li> </ul>
Amendment 1	17 August 2015	Revisions to protocol in response to Canadian Regulatory Authority request (see Protocol Summary and Sections 3, 4.1, and 5.5). These changes are applicable to Canadian sites only.
Final Protocol	03 April 2015	Not Applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.



## **PROTOCOL SUMMARY**

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 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).

### **Study Objectives**

#### **Primary:**

- To compare the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA at Week 44/End of Study (Week 26 of the double-blind phase) as measured by the percentage of subjects with disease flare (according to Pediatric Rheumatology Collaborative Study Group/Pediatric Rheumatology International Trials Organization [PRCSG/PRINTO] Disease Flare criteria) after Week 18 of the open-label run-in phase.

#### **Secondary:**

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by the percentage of subjects with disease flare (according to PRCSG/PRINTO Disease Flare criteria) at various time points in the open-label run-in and double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by time to disease flare in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by achievement of JIA American College of Rheumatology (ACR) 30, 50, 70, 90, 100 response at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in Juvenile Arthritis Disease Activity Score (JADAS) 27 C-Reactive Protein (CRP) and JADAS-27 Erythrocyte Sedimentation Rate (ESR), and percentage of subjects achieving JADAS minimal disease activity and inactive disease at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for treatment of signs and symptoms of JIA as measured by the JIA ACR inactive disease and clinical remission rate at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in each JIA ACR core set variable at various time points in the double-blind phase;

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in Child Health Questionnaire (CHQ) responses at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in Childhood Health Assessment Questionnaire (CHAQ) responses at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by the occurrence of active uveitis (according to Standardized Uveitis Nomenclature [SUN] criteria) in the double-blind phase;
- In subjects with enthesitis-related arthritis (ERA): To evaluate the efficacy of tofacitinib for the treatment of ERA as measured by changes from baseline in the Tender Enthesal Assessment, Modified Schober's Test, and Overall Back Pain and Nocturnal Back Pain responses at various time points in the double-blind phase;
- In subjects with psoriatic arthritis (PsA): To evaluate the efficacy of tofacitinib for the treatment of PsA as measured by changes from baseline in body surface area (BSA) affected with psoriasis and Physician's Global Assessment (PGA) at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib in the open-label run-in phase;
- To evaluate the taste acceptability of tofacitinib oral solution, if applicable, on Day 14 of the open-label run-in phase;
- To evaluate safety and tolerability of tofacitinib in subjects with JIA during the study;
- To evaluate the pharmacokinetics (PK) of tofacitinib in subjects with JIA during the open-label run-in phase.

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## **Study Endpoints**

### **Primary:**

- Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) at Week 44/End of Study (Week 26 of the double-blind phase).

**Secondary:**

- Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) at various time points in the open-label run-in and double-blind phase;
- Time to disease flare in the open-label run-in and double-blind phase;
- JIA ACR 30, 50, 70, 90, 100 response at various time points in the open-label run-in and double-blind phase;
- Change from baseline in JADAS 27-CRP and JADAS-27 ESR, and occurrence of JADAS minimum disease activity and inactive disease at various time points in the open-label run-in and double-blind phase;
- Presence of JIA ACR inactive disease at various time points in the open-label run-in and double-blind phase and clinical remission on medication at various time points in the double-blind phase;
- Change from baseline in each JIA ACR core set variable at various time points in the open-label run-in and double-blind phase;
- Change from baseline in CHQ responses at various time points in the open-label run-in and double-blind phase;
- Change from baseline in CHAQ responses at various time points in the open-label run-in and double-blind phase;
- Occurrence of active uveitis (according to SUN criteria) at various time points in the open-label run-in and double-blind phase;
- In subjects with ERA: Change from baseline in the Tender Enthesal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain responses at various time points in the open-label run-in and double-blind phase;
- In subjects with PsA: Change from baseline in BSA affected with psoriasis and PGA of psoriasis assessments at various time points in the open-label run-in and double-blind phase;
- Taste acceptability of tofacitinib oral solution, if applicable, on Day 14 of the open-label run-in phase;
- Safety during the study, with focus on serious infections, cytopenias, malignancies, cardiovascular diseases, and validated assessments of growth and pubertal development;
- Plasma tofacitinib concentrations during the open-label run-in phase.

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### **Statistical Analysis**

For the primary endpoint, superiority of tofacitinib to placebo for the percentage of subjects with disease flare at Week 44/End of Study (Week 26 of the double-blind phase) in subjects with polyarticular course (ie, extended oligoarthritis, polyarthritis rheumatoid factor positive [RF+], polyarthritis rheumatoid factor negative [RF-], systemic JIA with active arthritis but without active systemic features) JIA will be tested using the normal approximation approach for the binomial populations. Subjects who discontinue from the study treatment for any reason will be considered as having a disease flare, except subjects who discontinue after maintaining JIA ACR inactive disease for at least 24 weeks in the double-blind phase. These discontinuations will be considered as non-disease flare.

All secondary efficacy endpoints that are collected in the double-blind withdrawal phase will be analyzed by treatment group. For the binary secondary endpoints, including occurrence of disease flare prior to Week 44 (Week 26 of the double-blind phase), JIA ACR responses, presence of JIA ACR inactive disease and clinical remission, JADAS minimum disease activity and inactive disease status, the normal approximation approach for the binary populations, as used for the primary analysis, will be performed. For the continuous secondary endpoints, including change from baseline in JADAS 27-CRP, JADAS 27-ESR, CHQ, CHAQ, and JIA ACR core set variables, a mixed-effect model with repeated measures, will be applied. The Kaplan-Meier plot will be generated for the secondary endpoint of time to flare. Descriptive/summary statistics for all endpoints, with 95% confidence interval (CI) for treatment difference, will be provided. Baseline demographic characteristics, primary and key secondary endpoints will also be summarized by JIA category, baseline CRP, concomitant methotrexate treatment, prior biologic failures, history of uveitis and age.

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 will be described in the Statistical Analysis Plan (SAP).

### **Study Design**

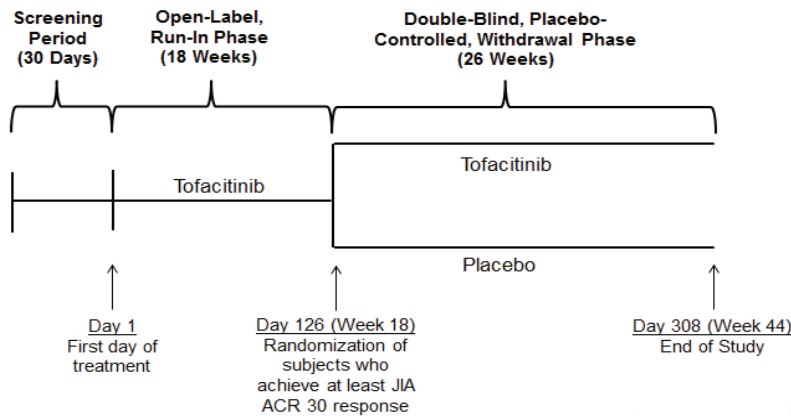
This is a randomized withdrawal, double-blind, placebo-controlled study of pediatric subjects (2 to <18 years of age) with JIA (see [Section 4.1](#), Inclusion Criteria).

All eligible subjects enrolled in the study will initially receive open-label tofacitinib for 18 weeks (run-in phase). At the end of the 18 week run-in phase, only subjects who achieve at least a JIA ACR 30 response will be randomized to the 26 week double-blind, placebo-controlled phase. Subjects who do not achieve a JIA ACR 30 response at this time point will be discontinued from the study. In addition, subjects who experience a single episode of disease flare (see [Section 7.1.7](#), PRCSG/PRINTO Disease Flare Criteria) at any time during the study (including the open-label run-in and double-blind phase) will also be discontinued from the study.



Subjects who are eligible for the 26 week double-blind phase will be randomized (1:1 ratio) to either active tofacitinib or placebo. For subjects with polyarticular course JIA (ie, extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, systemic JIA with active arthritis but without active systemic features), randomization will be stratified by JIA category and baseline CRP (normal, above normal). Subjects with psoriatic arthritis and enthesitis-related arthritis randomization will be stratified by JIA category.

A schematic of the study design is shown below:



Approximately 210 subjects will be enrolled in the open-label run-in phase. Among subjects with polyarticular course JIA, stratification will target enrollment of at least 50% with a baseline CRP above the upper limit of normal.

The cohort with polyarticular course JIA will have at least 170 subjects enrolled in the open-label run-in phase with the minimum number of JIA categories as follows: 24 with extended oligoarthritis, 20 with polyarthritis RF+, and 62 with polyarthritis RF-. There is no minimum number for the subjects with systemic JIA with active arthritis but without active systemic features. Additional cohorts (ie, psoriatic arthritis and enthesitis-related arthritis) will include a minimum of 20 subjects with psoriatic arthritis, and 20 subjects with enthesitis-related arthritis. The overall target minimum number of subjects to be enrolled in

the study by age is as follows: 20 subjects 2 to <6 years, 20 subjects 6 to <12 years, and 20 subjects 12 to <18 years. The Sponsor will monitor enrollment and periodically notify investigator sites regarding the status of enrollment in the various JIA categories and age groups.

Initial screening and enrollment of subjects (at least the first 12 subjects) into Study A3921104 must be limited to 12 years of age or greater for all eligible JIA subtypes (rheumatoid factor negative [RF-] and positive [RF+] polyarthritis, extended oligoarticular, psoriatic arthritis, enthesitis related arthritis and systemic arthritis without systemic features JIA subtypes).

The duration of subject participation among those who complete the study (without discontinuation) is expected to be approximately 44 weeks. The estimated blood volume for planned assessments over the course of the study (44 weeks) is approximately 99 mL. Pediatric blood tubes will be used (reduced volume) for testing to determine eligibility, monitor safety, and measure PK.

The study will be conducted over a period of approximately 3 years. CCI



## SCHEDULE OF ACTIVITIES

The schedule of activities (SOA) table provides an overview of the protocol visits and procedures. Please refer to [Section 6](#) (Study Procedures) and [Section 7](#) (Assessments) of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

For Investigative Sites in Germany Only: The degree of burden and the risk threshold should be assessed at each scheduled visit as outlined in [Appendix 10](#).

Protocol Activity	Screening	Day 1 <sup>1</sup>	Week 2	Week 4	Week 8, 12	Week 18	Week 20, 24, 28, 32, 36, 40	Week 44 (EOS) or Early Termination <sup>2</sup>
			Day 14 (±3 days)	Day 28 (±3 days)	Day 56, 84 (±3 days)	Day 126 (±3 days)	Day 140, 168, 196, 224, 252, 280 (±3 days)	Day 308 (±3 days)
Informed Consent/Assent	X							
Medical History, Family History	X							
Uveitis Assessment <sup>3</sup>	X						X (Day 168, Week 24 only)	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X
Complete Physical Examination <sup>21</sup>	X					X		X
Targeted Physical Examination <sup>4</sup>		X	X	X	X		X	
Vital Signs, Height, Weight <sup>5</sup>	X	X	X	X	X	X	X	X
Tanner Stage Assessment		X						X
<b>Assessments to be Faxed/Emailed to the Centralized Coordinating Center (CCC):</b>								
JIA Disease Status Worksheet Including:	X	X	X	X	X	X	X	X
Uveitis Status Assessment	X	X	X	X	X	X	X	X
Duration of Morning Stiffness Assessment	X	X	X	X	X	X	X	X
Signs and Symptoms of Systemic Disease (sJIA Only)	X	X	X	X	X	X	X	X
JIA Joint Assessment (Swelling, Pain on Motion and/or Tenderness, Limitations of Motion)	X	X	X	X	X	X	X	X
Physician's Global Evaluation of Overall Disease Activity	X	X	X	X	X	X	X	X
Childhood Health Assessment Questionnaire (CHAQ)	X	X	X	X	X	X	X	X
Child Health Questionnaire (CHQ) <i>(Not required by the CCC)</i>		X		X		X		X
Disease Flare Assessment (According to the PRINTO/PRCSG Criteria and confirmed by the CCC)	X	X	X	X	X	X	X	X

Protocol Activity	Screening	Day 1 <sup>1</sup>	Week 2	Week 4	Week 8, 12	Week 18	Week 20, 24, 28, 32, 36, 40	Week 44 (EOS) or Early Termination <sup>2</sup>
			Day 14 (±3 days)	Day 28 (±3 days)	Day 56, 84 (±3 days)	Day 126 (±3 days)	Day 140, 168, 196, 224, 252, 280 (±3 days)	Day 308 (±3 days)
<b>Subjects with Enthesitis-Related Arthritis (ERA) Only:</b>								
Tender Entheseal	X	X	X	X	X	X	X	X
Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment	X	X	X	X	X	X	X	X
<b>Subjects with Psoriatic Arthritis (PsA) Only (Not required by the CCC):</b>								
Body Surface Area (BSA)	X	X	X	X	X	X	X	X
Physician's Global Assessment (PGA) for Psoriasis	X	X	X	X	X	X	X	X
<b>Peripheral Blood Sample Collection for:</b>								
QuantiFERON-TB Gold In-Tube Test (or Purified Protein Derivative) <sup>6</sup>	X							
Erythrocyte Sedimentation Rate <sup>7</sup> (Fax/email result to the CCC)	X	X	X	X	X	X	X	X
C-Reactive Protein	X	X	X	X	X	X	X	X
Hematology <sup>8</sup> , Chemistry <sup>9</sup> , Urinalysis <sup>10</sup>	X	X	X	X	X	X	X	X
Lipid Panel <sup>11</sup>		X		X		X		X
Blood (serum) or Urine Pregnancy Test, Contraceptive Check <sup>12</sup>	X	X	X	X	X	X	X	X
Varicella Zoster Virus Serology (VZV IgG Ab) (if applicable) <sup>13</sup>	X							
Rheumatoid Factor (RF)	X							
Human Immunodeficiency Virus (HIV-1, HIV-2), Hepatitis B Surface Antigen (HBsAg), Hepatitis B Surface Antibody (HbsAb), Hepatitis B Core Antibody (HBcAb), Hepatitis C Antibody (HCV Ab), Hepatitis C Viral RNA (HCV RNA) <sup>14</sup>	X							
Anti-Cyclic Citrullinated Protein (anti-CCP) Antibodies, Antinuclear Antibodies (ANA), Human Leukocyte Antigen B27 (HLA-B27)		X						
Retained Biospecimens		X <sup>15</sup>			X <sup>16</sup>	X <sup>15</sup>		X <sup>15</sup>
<b>Pharmacokinetic Sampling:</b>								
Tofacitinib PK Sampling (first 40 subjects enrolled, excluding subjects with Systemic JIA)		X			X (Day 84) <sup>17</sup>			
Tofacitinib PK Sampling (after first 40 subjects enrolled, excluding subjects with Systemic JIA)			X <sup>18</sup>		X (Day 84) <sup>17</sup>			
Tofacitinib PK Sampling (subjects with Systemic JIA only)			X <sup>18</sup>		X (Day 84) <sup>17</sup>			
Randomization to Double-Blind Withdrawal Phase (only subjects who achieve JIA ACR 30 response, as confirmed by the Centralized Coordinating Center) <sup>19</sup>						X <sup>19</sup>		



Protocol Activity	Screening	Day 1 <sup>1</sup>	Week 2	Week 4	Week 8, 12	Week 18	Week 20, 24, 28, 32, 36, 40	Week 44 (EOS) or Early Termination <sup>2</sup>
			Day 14 (±3 days)	Day 28 (±3 days)	Day 56, 84 (±3 days)	Day 126 (±3 days)	Day 140, 168, 196, 224, 252, 280 (±3 days)	Day 308 (±3 days)
Investigational Product Dispensing		X	X	X	X	X	X	
Investigational Product Dosing			< -----Active Tofacitinib ----- >				<-Active Tofacitinib/Placebo ->	
Investigation Product Dosing Compliance			X	X	X	X	X	X
Tofacitinib Oral Solution Taste Acceptability Assessment			X					
Adverse Event Assessment	X <sup>20</sup>	X	X	X	X	X	X	X
Review Entry Criteria for A3921145								X

- Day 1 visit (ie, the first day of treatment with investigational product) must occur within 30 days of the first screening visit activity. If more than 30 days has elapsed, all screening procedures and assessments must be repeated. Sponsor approval must be obtained prior to re-screening a subject.
- Early termination (ET) procedures should be completed if a subject does not complete all 44 weeks 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, if possible; please use an unplanned Tanner Stage assessment CRF if this occurs.
- Uveitis exam at Screening is not required if there is documentation of uveitis assessment by an ophthalmologist (or qualified equivalent per local practice) within 3 months of the screening visit. If there is no documentation, a uveitis exam by an ophthalmologist (or qualified equivalent per local practice) must be performed prior to study treatment. There is a window of ±7 days for the Week 24 and Week 44/ET visits to allow for scheduling this assessment. At all other visits the investigator should assess and document if there are any potential changes in uveitis status; referral for formal evaluation should be done if deemed clinically necessary. If uveitis is confirmed, please capture as an AE and complete an unplanned uveitis CRF.
- Targeted physical exam consists of examination of heart, lungs, extremities for peripheral edema, abdomen and lymph nodes.
- Vital signs include blood pressure, pulse rate, and temperature assessment.
- A negative PPD test can be substituted for the QuantiFERON<sup>®</sup>-TB Gold In-Tube test only if the central laboratory is unable to perform the QuantiFERON<sup>®</sup>-TB Gold 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 7.2.6](#) for additional details.
- 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 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/mailed to the Centralized Coordinating Center.
- Hematology includes: Hemoglobin, hematocrit, red blood cells, white blood cells, neutrophils (% absolute), lymphocytes (% absolute), monocytes (% absolute), eosinophils (% absolute), basophils (% absolute), and platelets.
- 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).

10. 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).
11. Lipid profile 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.
12. Blood (serum) or urine pregnancy testing is required only for females who are of childbearing potential (see [Section 7.2.9](#)). Pregnancy testing will be performed locally or by the local or central lab at any time. 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.
13. VZV IgG antibody testing is required to confirm eligibility in subjects who have not received at least one dose of a varicella zoster vaccine (see [Section 7.2.8](#)).
14. To conserve blood volume at screening, HCV RNA sample collection may be deferred and collected only if required to confirm eligibility based on the HCV Ab results. See [Section 7.2.7](#) for details regarding viral testing and interpretation of results.
15. Prep B2.5 (2 mL) and Prep R1 (2.5 mL) should be collected pre-dose on Day 1, and at the Week 18 and Week 44/EoS/ET visits.
16. Prep D1.5 (2 mL EDTA) should be collected at Week 8.
17. PK sampling may be obtained at a later visit up to the Week 18/Day 126 visit; the subject and parent/legal guardian will be instructed that the subject should not take the morning dose until after the pre-dose PK sample is collected. See [Section 7.3](#) for details regarding PK sampling.
18. PK sampling may be obtained at a later visit up to at the Week 4/Day 28 visit; the subject and parent/legal guardian will be instructed that the subject should not take the morning dose until after the pre-dose PK sample is collected. See [Section 7.3](#) for details regarding PK sampling.
19. Only subjects who achieve at least a JIA ACR 30 response, as confirmed by the Centralized Coordinating Center, will be randomized to the double-blind, placebo-controlled phase. See [Section 6.6](#) and [Section 7.1.6](#) for details.
20. Serious adverse events (SAEs) are captured from the time of informed consent at Screening (see [Section 8.7](#)); adverse events (AEs) are captured following first dose of investigational product (see [Section 8.1](#)).
21. **Applicable to Investigative Sites in the United Kingdom (UK), Spain, Poland, Germany and Belgium Only:** a full skin cancer examination must be performed as part of the complete physical examination.

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## List of Abbreviations

<b>Abbreviation</b>	<b>Term</b>
Ab	Antibody
ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil counts
AST	Aspartate aminotransferase
BID	Twice daily
BQL	Below quantification limit
BSA	Body surface area
CCC	Centralized Coordinating Center
CDS	Core data sheet
CHAQ	Childhood Health Assessment Questionnaire
CHQ	Child Health Questionnaire
CI	Confidence interval
CL	Clearance
CRF	Case report form
CRP	C-reactive protein
CSA	Clinical study agreement
CTA	Clinical trial application
DMARD	Disease Modifying Antirheumatoid Drug
DMC	Data monitoring committee
DU	Dispensable unit
EC	Ethics committee
ECG	Electrocardiogram
EDMC	External data monitoring committee
EDP	Exposure during pregnancy
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
ERA	Enthesitis-related arthritis
ESR	Erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
HCG	Human Chorionic Gonadotropin
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICH	International Conference on Harmonisation
ID	Identification
IgG	Immunoglobulin G
ILAR	International League Against Rheumatism

<b>Abbreviation</b>	<b>Term</b>
IND	Investigational new drug application
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine system
JADAS	Juvenile Arthritis Disease Activity
JIA	Juvenile Idiopathic Arthritis
LFT	Liver function test
LSLV	Last subject last visit
MACE	Major adverse cardiovascular events
MAS	Macrophage-activation syndrome
MTX	Methotrexate
N/A	Not applicable
NMSC	Non-melanoma Skin Cancer
PCD	Primary completion date
PGA	Physician's Global Assessment
PK	Pharmacokinetics
POPPK	Population PK
PRCSG/PRINTO	Pediatric Rheumatology Clinical Study Group/Pediatric Rheumatology International Trials Organization
PsA	Psoriatic arthritis
PT	prothrombin time
RA	Rheumatoid arthritis
RF+	Rheumatoid Factor positive
RF-	Rheumatoid Factor negative
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
sJIA	Systemic JIA
SOA	Schedule of Activities
SOP	Standard operating procedure
SRSD	Single reference safety document
SUN	Standard Uveitis Nomenclature
TB	Tuberculosis
ULN	Upper limit of normal
UK	United Kingdom
US	United States
VAS	Visual analog scale
VZV	Varicella zoster virus
WCC	World Care Clinical

## 1. INTRODUCTION

### 1.1. Indication

Tofacitinib (also known as CP-690,550) is currently approved in the United States and more than 45 countries for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used in combination with methotrexate or other non-biologic disease modifying antirheumatic drugs (DMARDs).

### 1.2. Background

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 (Johnston 1996, Conklyn 2004, Changelian 2008).<sup>1,2,3</sup> 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) $\gamma$ . 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. The Sponsor is conducting a pediatric development program to determine the safety and efficacy of tofacitinib in subjects 2 to <18 years of age for the treatment of JIA.

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#### 1.2.1. Study Rationale

This Phase 3 study is intended to provide evidence of efficacy and safety of tofacitinib in subjects with JIA.

Due to the availability of effective treatments for subjects with JIA, a randomized withdrawal study design was selected to limit exposure to placebo treatment.

#### 1.2.2. Dose Rationale

Selection of doses for this first efficacy study of tofacitinib in JIA subjects is 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 RA patients. Based on the tofacitinib PK in the adult RA population, clearance (CL) of tofacitinib is not dependent on body weight (range

studied in the adult RA program was 40 kg to 140 kg). Thus, the dose of tofacitinib in adolescents with body weight  $\geq 40$  kg was set to 5 mg twice daily (BID), the only approved dose of tofacitinib in adult RA patients in most countries. The tofacitinib doses for the younger JIA subjects were selected to match the predicted steady state concentrations ( $C_{avg,ss}$ ) in JIA subjects with body weight  $\geq 40$  kg after administration of a 5 mg BID dose.

Generally, for approved DMARDs in the treatment of JIA, partial extrapolation of efficacy from the adults to pediatrics is well accepted (Dunne et al, Pediatrics 2011).<sup>12</sup> Thus, the dose range selected for JIA subjects across the weight-groups is predicted to achieve  $C_{avg,ss}$  values equivalent to those from efficacious doses in adult RA population (between 3 to 5 mg BID dose).

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

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

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

The PK study of tofacitinib in subjects with JIA has completed. A total of 26 subjects between 2 and 17 years of age and weighing between 13.9 and 70.9 kg were dosed with 2 to 5 mg BID doses of tofacitinib for 5 days in Study A3921103. Pharmacokinetic evaluations were performed on Day 5 at pre-dose, 0.5, 1, 2, 4 and 8 hours. Non-compartmental analysis (NCA) was performed on the PK profiles, and a summary of PK parameters are presented in [Table 1](#). The number of subjects dosed across three cohorts (C1, C2, C3) in this study was 26, with 8, 9, and 9 in each of the following age groups/cohorts: 12 to <18 years (C1), 6 to <12 years (C2), and 2 to <6 years (C3), respectively.

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

Cohort	No. Subjects	Weight (Kg)	AUC <sub>tau</sub> (ng·hr/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	CL/F (L/hr)
12 to <18 yrs (C1)	8	38.3-70.9	156.6 (25)	46.97 (40)	0.75 [0.5-6.9]	2.616 ± 0.454	28.09 (22)
6 to <12 yrs (C2)	9	20.3-48.9	118.8 (27)	41.67 (29)	1.0 [0.50-2.05]	1.949 ± 0.294	25.48 (40)
2 to <6 yrs (C3)	9	13.9-19.8	142.5 (32)	66.15 (28)	0.50 (0.50-1.92)	1.771 ± 0.406	20.53 (33)

\*Geometric Mean (CV%) for Area under the effect curve (AUC<sub>tau</sub>), C<sub>max</sub>, apparent clearance (CL/F) and arithmetic mean (±SD) for terminal half-life (T<sub>1/2</sub>); Median [range] for Time to C<sub>max</sub> (T<sub>max</sub>); Source: Table 14.4.3.1.1, date of table generation: 28 January 2016 (09:28).

The exposures from the first 16 subjects in Cohorts 1 and 2 (between 8 and 17 years of age) in Study A3921103 (as shown above) indicated higher CL/F values than predicted from Eq. 1 using an allometric component of 0.75 and thus resulting AUC<sub>tau,ss</sub> and C<sub>max,ss</sub> values 38-53% and 19-28% lower, respectively, as compared to adult RA subjects (252 ng·hr/mL and 58 ng/mL respectively; data on file). However, due to higher doses administered in Cohort 3 (protocol was amended based on interim analysis of PK data from Cohorts 1 and 2 to target systemic exposure equivalent to 5 mg BID in adult rheumatoid arthritis [RA] patients), AUC<sub>tau</sub> in Cohort 3 was comparable to Cohort 1 and higher than Cohort 2, and C<sub>max</sub> value was higher than both preceding cohorts.

A population PK model was developed, and concentrations from the 26 JIA subjects enrolled in study A3921103 were fitted adequately using a one compartment model with first-order absorption (K<sub>a</sub>) and linear elimination. In this model, body weight was used as an allometric covariate to describe changes in CL/F and V/F and the exponents were estimated. The estimated power exponents were 0.0.292 (%RSE: 40.1%) for CL/F and 0.843 (%RSE: 12.3%) for V/F. Similar to adult RA subjects, age, gender, and race were not found to be significant covariates to describe inter-subject variability in tofacitinib CL/F or V/F. Formulation (solution or tablets) was tested as a covariate for first order absorption constant K<sub>a</sub> and was found to not be statistically significant. Thus it was not included in the model.

Following model fitting, Monte Carlo simulations using the estimated population PK parameters and their inter individual variability were conducted to evaluate doses expected to provide C<sub>avg,ss</sub> and C<sub>max,ss</sub> concentrations comparable to efficacious concentrations in adult RA patients with maximum nominal dose capped at 5 mg BID for subjects with body weight >40 kg. With the current proposed dosing regimen (Section 5.5), the predicted C<sub>avg</sub> is similar to that of 3-5 mg BID in adult RA subjects across the expected weight range, with C<sub>max,ss</sub> not exceeding that of 10 mg BID in most subjects. Based on the results of the modeling using allometric scaling and the PK data from Study A3921103 it is expected that 2 to 5 mg BID (depending on body weight of the subjects), administered approximately 12 hours apart, will provide safe and efficacious exposures of tofacitinib in this study (see Section 5.5 for the planned doses and regimens).

PK collection time points (see [Section 7.3.1](#)) in this study were decided based on optimal PK sampling design utilizing the population PK (POPPK) model built on data from A3921103. Details of the POPPK model and simulation results leading to the proposed current dosing regimen for this study are presented in [Appendix 7](#).

### **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**

#### **Primary:**

- To compare the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA at Week 44/End of Study (Week 26 of the double-blind phase) as measured by the percentage of subjects with disease flare (according to PRCSG/PRINTO Disease Flare criteria) after Week 18 of the open-label run-in phase.

#### **Secondary:**

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by the percentage of subjects with disease flare (according to PRCSG/PRINTO Disease Flare criteria) at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by time to disease flare in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by achievement of JIA ACR 30, 50, 70, 90, 100 response at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in JADAS 27-CRP and JADAS-27 ESR, and percentage of subjects achieving JADAS minimum disease activity and inactive disease at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for treatment of signs and symptoms of JIA as measured by the JIA ACR inactive disease and clinical remission rate at various time points in the double-blind phase;

- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in each JIA ACR core set variable at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in CHQ responses at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in CHAQ responses at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by the occurrence of active uveitis (according to SUN criteria) in the double-blind phase;
- In subjects with ERA: To evaluate the efficacy of tofacitinib for the treatment of ERA as measured by changes from baseline in the Tender Enthesal Assessment, Modified Schober's Test, and Overall Back Pain and Nocturnal Back Pain responses at various time points in the double-blind phase;
- In subjects with PsA: To evaluate the efficacy of tofacitinib for the treatment of PsA as measured by changes from baseline in the BSA affected with psoriasis and PGA of psoriasis assessments at various time points in the double-blind phase;
- To evaluate the efficacy of tofacitinib in the open-label run-in phase;
- To evaluate the taste acceptability of tofacitinib oral solution, if applicable, on Day 14 of the open-label run-in phase;
- To evaluate safety and tolerability of tofacitinib in subjects with JIA during the study;
- To evaluate the PK of tofacitinib in subjects with JIA during the open-label run-in phase.

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## 2.2. Endpoints

### Primary:

- Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) at Week 44/End of Study (Week 26 of the double-blind phase).

**Secondary:**

- Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) at various time points in the open-label run-in and double-blind phase;
- Time to disease flare in the open-label run-in and double-blind phase;
- JIA ACR 30, 50, 70, 90, 100 response at various time points in the open-label run-in and double blind-phase;
- Change from baseline in JADAS 27-CRP and JADAS-27 ESR, and occurrence of JADAS minimum disease activity and inactive disease at various time points in the open-label run-in and double-blind phase;
- Presence of JIA ACR inactive disease and clinical remission at various time points in the double-blind phase;
- Change from baseline in each JIA ACR core set variable at various time points in the open-label run-in and double-blind phase;
- Change from baseline in CHQ responses at various time points in the open-label run-in and double-blind phase;
- Change from baseline in CHAQ responses at various time points in the open-label run-in and double-blind phase;
- Occurrence of active uveitis (according to SUN criteria) at various time points in the open-label run-in and double-blind phase;
- In subjects with ERA: Change from baseline in the Tender Entheses Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain responses at various time points in the open-label run-in and double-blind phase;
- In subjects with PsA: Change from baseline in the BSA affected with psoriasis and PGA of psoriasis assessments at various time points in the open-label run-in and double-blind phase;
- Taste acceptability of tofacitinib oral solution, if applicable, on Day 14 of the open-label run-in phase;
- Safety during the study, with focus on serious infections, cytopenias, malignancies, cardiovascular diseases, and validated assessments of growth and pubertal development;
- Plasma tofacitinib concentrations during the open-label run-in phase.



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### 3. STUDY DESIGN

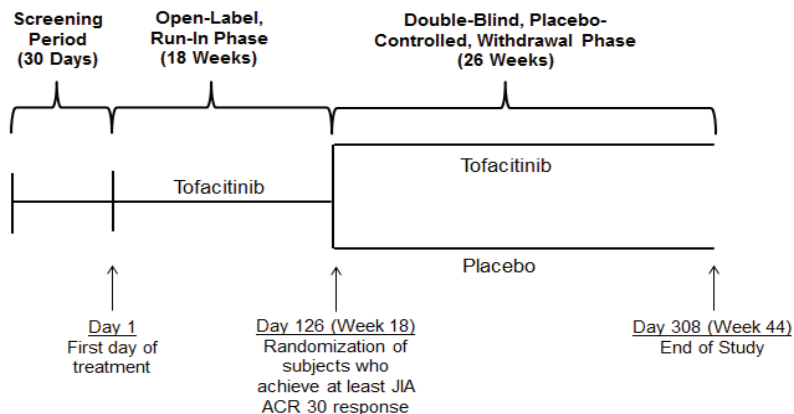
This is a randomized withdrawal, double-blind, placebo-controlled study of subjects from 2 to <18 years of age with JIA (see [Section 4.1](#), Inclusion Criteria).

All eligible subjects enrolled in the study will initially receive open-label tofacitinib for 18 weeks (run-in phase). At the end of the 18 week run-in phase, only subjects who achieve at least a JIA ACR 30 response will be randomized to the 26 week double-blind, placebo-controlled phase. Subjects who do not achieve a JIA ACR 30 response at this time point will be discontinued from the study. Subjects who experience a single episode of disease flare (see [Section 7.1.7](#), PRCSG/PRINTO Disease Flare Criteria) at any time during the study (including the open-label run-in and double-blind phase) will also be discontinued from the study.

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Subjects who are eligible for the 26 week double-blind phase will be randomized (1:1 ratio) to either active tofacitinib or placebo. For subjects with polyarticular course JIA (ie, extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, systemic JIA with active arthritis but without active systemic features), randomization will be stratified by JIA category and baseline CRP (normal, above normal). For subjects with psoriatic and enthesitis-related arthritis, randomization will be stratified by JIA category.

A schematic of the study design is shown below:




Approximately 210 subjects will be enrolled in the open-label run-in phase. Among subjects with polyarticular course JIA, stratification will target enrollment of at least 50% with a baseline CRP above the upper limit of normal.

The cohort of subjects with polyarticular course JIA will have at least 170 subjects enrolled in the run-in phase with the minimum number of JIA categories as follows: 24 with extended oligoarthritis, 20 with polyarthritis RF+, and 62 with polyarthritis RF-. There is no minimum number of subjects with systemic JIA with active arthritis but without active systemic features. Additional cohorts (ie, psoriatic and enthesitis-related arthritis) will include a minimum of 20 subjects with psoriatic arthritis, and 20 subjects with enthesitis-related arthritis. The overall target minimum number of subjects to be enrolled in the study by age is as follows: 20 subjects 2 to <6 years, 20 subjects 6 to <12 years, and 20 subjects 12 to <18 years. The Sponsor will monitor enrollment and periodically notify investigator sites regarding the status of enrollment in the various JIA categories and age groups.

Initial screening and enrollment of subjects (at least the first 12 subjects) into Study A3921104 must be limited to 12 years of age or greater for all eligible JIA subtypes (rheumatoid factor negative [RF-] and positive [RF+] polyarthritis, extended oligoarticular, psoriatic arthritis, enthesitis related arthritis and systemic arthritis without systemic features JIA subtypes).

The duration of subject participation among those who complete the study (without discontinuation) is expected to be approximately 44 weeks. Pediatric blood tubes will be used (reduced volume) for testing to determine eligibility, monitor safety, and measure PK.

The study will be conducted over a period of approximately 3 years. CCI



#### **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. Must meet International League Against Rheumatism (ILAR) JIA classification for one of the following categories and, in the opinion of the investigator, have active disease for at least 6 weeks prior to screening:
  - Extended oligoarthritis;
  - Polyarthritis (RF+);
  - Polyarthritis (RF-);
  - Systemic JIA with active arthritis but without active systemic features in the prior 6 months and at the time of enrollment;
  - Psoriatic arthritis;
  - Enthesitis-related arthritis.

Subjects with polyarticular course JIA (ie, extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, systemic JIA with active arthritis but without active systemic features) must have a minimum of 5 active joints (an active joint is defined as a joint with swelling or, in the absence of swelling, limited range of motion accompanied by either pain on motion or tenderness) at screening and baseline to be eligible for study entry.

Subjects with psoriatic or enthesitis-related arthritis must have a minimum of 3 active joints (an active joint is defined as a joint with swelling or, in the absence of swelling, limited range of motion accompanied by either pain on motion or tenderness) at screening and baseline to be eligible for study entry.

Treatment with stable doses of a Non-Steroidal Anti-inflammatory Drug (NSAID) and/or a stable dose of an oral glucocorticoid, and/or a stable dose of methotrexate is permitted.

For subjects receiving an oral glucocorticoid: Glucocorticoids may be administered at a maximum dose of 0.2 mg of prednisone equivalent per kilogram per day or 10 mg per day for  $\geq 2$  weeks before baseline, whichever is lower.

For subjects receiving methotrexate (MTX) treatment: MTX may be administered either orally or parenterally at doses not to exceed 25 mg/wk or 20 mg/m<sup>2</sup>/week (whichever is lower); participants must have taken MTX for  $\geq 3$  months and be at a stable dose for at least 6 weeks before baseline. Subjects taking MTX must be taking folic acid or folinic acid in accordance with local standards.

For subjects with psoriatic arthritis, the following topical treatments for psoriasis are allowed: non-medicated emollients for use over the whole body; topical steroids including hydrocortisone and hydrocortisone acetate  $\leq 1\%$  for the palms, soles, face, and intertriginous areas only; tar, salicylic acid preparations, and shampoos free of corticosteroids are permitted only for the scalp.

3. Inadequate response or intolerance to at least one Disease Modifying Anti-Rheumatic Drug (DMARD), which may include MTX or biologic agents (see [Appendix 1](#)); in the case of ERA and psoriatic arthritis, inadequate response to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).
4. No evidence or history of untreated or inadequately treated active or latent tuberculosis (TB) infection as evidenced by the following:
  - a. A negative QuantiFERON<sup>®</sup>-TB Gold In-Tube test performed within the 3 months prior to screening. A negative purified protein derivative (PPD) test can be substituted for the QuantiFERON<sup>®</sup>-TB Gold 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.
  - b. Chest radiograph without changes suggestive of active tuberculosis (TB) infection within 3 months prior to screening is recommended and should be performed according to local standards of care or country-specific guidelines.
  - c. No history of either untreated or inadequately treated latent or active TB infection.

If a subject has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are  $<5\%$  or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a PPD test nor a QuantiFERON-Gold<sup>®</sup>™ test need be obtained. A chest radiograph should be obtained if not done within the 3 months prior to screening (see [Section 7.2.6](#)). 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.

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. Note: Refer to [Section 4.4.1](#) for additional contraception requirements for investigative sites in UK, Spain, Poland, Germany and Belgium only.

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(s)/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. Systemic JIA (sJIA) with any active systemic features other than active joints and elevated acute phase reactants within 6 months of enrollment.
3. Persistent oligoarthritis.
4. Undifferentiated JIA.
5. Infections:
  - a. Chronic infections;
  - b. Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to be opportunistic by the investigator within the 6 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 7.2.7](#));
  - 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. Active uveitis (according to SUN criteria) within 3 months of enrollment.
8. Blood dyscrasias, including (see [Appendix 6](#)):
  - a. Hemoglobin <10 g/dL or Hematocrit <33%;
  - b. White Blood Cell count <3.0 x 10<sup>9</sup>/L;
  - c. Neutrophil count <1.2 x 10<sup>9</sup>/L;

- d. Platelet count  $<100 \times 10^9/L$ ;
  - e. Lymphocyte count  $<0.75 \times 10^9/L$ .
9. Estimated glomerular filtration rate [GFR]  $<40 \text{ mL/min/1.73 m}^2$  at Screening. GFR will be calculated by the central lab using the bedside Schwartz formula (see [Appendix 3](#)).
  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)  $\geq 1.5$  times the upper limit of normal or any other clinically significant laboratory abnormality (see [Appendix 6](#)).
  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 or attenuated vaccine within the 6 weeks prior to the first dose of study drug, or is expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of study drug.
  15. Subjects without documented evidence of having received at least one dose of the varicella vaccine in countries where the vaccine is approved and standard of care or those who do not have evidence of prior exposure to varicella zoster virus (VZV) based on serological testing (ie, VZV IgG Ab).
  16. Current malignancy or history of any malignancy with the exception of adequately treated or excised basal cell or squamous cell or cervical cancer *in situ*.
  17. Subjects who have previously failed more than 3 biologic therapies (with different mechanisms of action) for JIA.
  18. Subjects with a first degree relative with a hereditary immunodeficiency; IgA deficiency not exclusionary.
  19. Recent (within 28 days prior to first dose of study drug) significant trauma or major surgery.
  20. Subjects receiving potent and moderate CYP3A4 inhibitors or inducers ([Appendix 4](#)).

21. Prior treatment with non B cell-specific lymphocyte depleting agents/therapies (eg, almetuzumab [CAMPATH<sup>®</sup>], 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.
22. Use of prohibited prescription or non-prescription drugs and dietary supplements listed in [Appendix 1](#) and [Appendix 4](#) within the specified time frame prior to the first dose of study medication.
23. Herbal supplements must be discontinued at least 28 days prior to the first dose of study medication.
24. Use of certain biologic and non-biologic DMARDs are disallowed at any time during this study ([Appendix 1](#)).
25. For subjects with PsA, oral and topical medications and alternative treatments that could affect psoriasis are prohibited (see Inclusion Criterion 2 for exceptions). This includes topical corticosteroids, tars, keratolytics, anthralin, vitamin D analogs, and retinoids which must be discontinued at least 2 weeks prior to first dose of study drug. Also prohibited is ultraviolet B (UVB) (narrowband or broadband) phototherapy that must be discontinued at least 2 weeks prior to first dose of study drug. Psoralens + ultraviolet A (UVA) phototherapy (PUVA) must be discontinued at least 4 weeks prior to first dose of study drug.
26. 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.
27. 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.
28. 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.
29. Pregnant or nursing females are excluded.

30. **Applicable to Investigative Sites in Germany Only:** 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.

#### **4.3. Randomization Criteria**

All eligible subjects enrolled in the study will initially receive open-label tofacitinib for 18 weeks (run-in phase). At the end of the 18 week run-in phase, only subjects who achieve at least a JIA ACR 30 response will be randomized to the 26 week double-blind, placebo-controlled phase. Subjects who do not achieve a JIA ACR 30 response at this time point will be discontinued from the study. In addition, subjects who experience a single episode of disease flare (per JIA flare criteria as confirmed by the Centralized Coordinating Center) at any time during the study (including the open-label run-in and double-blind phase) will also be discontinued from the study.

Subjects who enter the 26 week double-blind phase will be randomized (1:1 ratio) to either active tofacitinib or placebo. For subjects with polyarticular course JIA (ie, extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, systemic JIA with active arthritis but without active systemic features), randomization will be stratified by JIA category and baseline CRP (normal, above normal). For subjects with psoriatic arthritis and ERA randomization will be stratified by JIA category.

#### **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) is allowed 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.

**Applicable to Investigative Sites in the UK, Spain, Poland, Germany and Belgium Only:**

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).

#### **4.4.2. Vaccine and Exposure to Infections Guidelines**

##### **4.4.2.1. 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. Vaccination of subjects with live components is prohibited within the 6 weeks prior to first dose of study drug. Subjects without documented evidence of having received at least one dose of the varicella vaccine or those who are without evidence of previous varicella zoster exposure as confirmed by VZV IgG Ab serological testing are excluded (Exclusion Criterion 15).

##### **4.4.2.2. Guidance Regarding Household Contact Vaccine-Related Exposure**

Current routine household contact with children and others who have been vaccinated with live vaccine components may pose a risk during treatment and for 6 weeks following completion of the study. Some of these vaccines include varicella (“chickenpox”) vaccine, oral polio vaccine, and the inhaled flu vaccine. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted. General guidelines for immunosuppressed subjects suggest that exposure (through routine contact) should be avoided following vaccination (of others) with these vaccines for the stated time period:

- a. Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination.
- b. Oral polio vaccination for 6 weeks following vaccination.
- c. Attenuated rotavirus vaccine for 10 days following vaccination.
- d. FluMist<sup>®</sup> (inhaled flu vaccine) for 1 week following vaccination.

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

##### **4.4.3. 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 related to JIA. For subjects with psoriatic arthritis, refer to Inclusion Criterion 2 and Exclusion Criterion 25.

##### **4.4.4. Elective Surgery**

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

Subjects who do require surgery should temporarily discontinue study medication for at least one week prior to the surgical procedure and remain off study medication after the surgical procedure until sutures/staples are removed. If 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.

#### **4.4.5. Dietary Supplements**

For the purposes of this protocol, dietary supplements are defined as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties (see [Section 5.8](#), Concomitant Treatments, for additional details).

Vitamins, minerals and purified food substances are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis).

Herbals supplements are prohibited.

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

All eligible subjects enrolled in the study will initially receive open-label tofacitinib for 18 weeks (run-in phase). At the end of the 18 week run-in phase, only subjects who achieve at least a JIA ACR 30 response will be randomized to the 26 week double-blind, placebo-controlled phase. Subjects who do not achieve a JIA ACR 30 response at this time point will be discontinued from the study. Subjects who experience a single episode of disease flare at any time during the study (including the open-label run-in and double-blind phase) will also be discontinued from the study.

Subjects who enter the 26 week double-blind phase will be randomized (1:1 ratio) to either active tofacitinib tablets/oral solution or matching placebo. For subjects with polyarticular course JIA (ie, extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, systemic JIA with active arthritis but without active systemic features), randomization will be stratified by JIA category and baseline CRP (normal, above normal). For subjects with psoriatic arthritis and ERA randomization will be stratified by JIA category.

Sites must receive confirmation of subject eligibility from the Centralized Coordinating Center indicating JIA ACR 30 response was achieved. Once confirmed, randomization of subjects into the 26 week double-blind placebo-controlled 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 and the date of birth of the subject. 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.

## **5.2. 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 electronic process for breaking the blind using the IRT system.

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 in the source documents for that subject.

### **Applicable to Investigative Sites in the UK, Spain, Poland, Germany and Belgium Only:**

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 in the source and the appropriate 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 study visits, the subject should be withdrawn from the study. Dosing interruptions of 14 days or more should be discussed with the sponsor.

### **5.4. Investigational Product Supplies**

#### **5.4.1. Dosage Form(s) and Packaging**

Tofacitinib will be provided as oral tablets (tofacitinib citrate 5 mg) and as an oral solution (CP-690,550-10 [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-690,550-10 (compound name for tofacitinib) oral solution will be provided for the run-in phase of the study.

Blinded-label bottles of tofacitinib tablets, CP-690,550-10 (compound name for tofacitinib) oral solution, and matching placebo, for oral administration, will be provided for the double-blind phase of the study.

#### **5.4.2. Preparation and Dispensing**

Investigational product will be supplied to subjects in bottles. Investigational product, 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 run-in phase (18 weeks), all subjects will receive active tofacitinib oral tablets or oral solution twice daily (BID) orally, approximately 12 hours ( $\pm$  2 hours) apart, in the morning and evening, at a dosage based on the subject's body weight as specified in [Table 2](#).

During the double-blind, placebo-controlled phase (26 weeks), subjects will receive either active tofacitinib oral tablets/oral solution or matching placebo oral tablets/oral solution, twice daily (BID), approximately 12 hours ( $\pm 2$  hours) apart, in the morning and evening, at a dosage based on the subject's body weight as specified in Table 2.

**Table 2. Study Treatment Dosing and Administration**

Body Weight (kg)	Dosage Regimen (Run-In Phase: Tofacitinib, Double-Blind Phase: Tofacitinib/Placebo)
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
$\geq 40$	5 mg (one 5 mg tablet or 5 mL oral solution) BID

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

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

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

### 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 parent/legal guardian/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. 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)**

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.

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 4](#), Prohibited Concomitant Medications. Topical administration (eg, cutaneous, ophthalmic, or intravaginal) of these concomitant medications, which are prohibited if administered

systemically, is allowed in the study. Disallowed 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.

Subjects will continue on their stable background arthritis therapy (see Inclusion Criterion 2), which can include nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, methotrexate (not to exceed 25 mg/wk or 20 mg/m<sup>2</sup>/week [whichever is lower]) (see [Appendix 1](#)), and corticosteroids (at a maximum dose of 0.2 mg of prednisone equivalent per kilogram per day or 10 mg per day, whichever is lower). Subjects taking methotrexate must be taking folic acid or folinic acid in accordance with local standards.

For subjects with psoriatic arthritis refer to Inclusion Criterion 2 and Exclusion Criterion 25 for concomitant treatments that are allowed or prohibited (see [Appendix 1](#)). See [Appendix 2](#) for instructions on permitted adjustments in concomitant JIA therapies during the study.

Herbal supplements are not allowed and must be discontinued for at least 4 weeks prior to first dose of study drug.

Any experimental or prohibited therapy must be discontinued for at least 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug (see [Appendix 1](#)). No investigational compounds, other than tofacitinib may be taken during participation in this study.

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

### **5.9. Rescue Therapy**

Refer to [Appendix 2](#) for permitted JIA rescue therapies.

## **6. STUDY PROCEDURES**

This section outlines study procedures and tests required to be performed at specified study visits. Please refer to [Section 7](#) for details regarding each procedure/test.

**Applicable to Investigative Sites in Germany Only:** The degree of burden and the risk threshold should be assessed at each scheduled visit as outlined in [Appendix 10](#).

### **6.1. Screening Visit**

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 8.2](#)).

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



Subjects who are on prohibited medications and are deriving a beneficial response from them should not be entered into this study. However, there may be subjects taking a prohibited medication who have experienced an ineffectual/suboptimal response or side effects and would consider entering the study. These subjects may require a washout period that extends beyond the screening duration (See [Section 5.8 Concomitant Medication\[s\]](#)). For these subjects written informed consent and a Study Subject Identification (SSID) number must be obtained prior to initiation of the washout period or, if washout has already begun for other reasons, upon decision that the study is an appropriate medical option. In no instance should the informed consent be signed more than 3 months prior to the conduct of the screening procedures.

*Please note that subjects must be enrolled within 30 days of the screening visit. If more than 30 days has elapsed, all screening procedures and assessment listed below must be repeated. Sponsor approval must be obtained prior to re-screening a subject.*

- Medical history and family history.
- Prior medications.
- Complete physical examination. (**Applicable to Investigative Sites in the UK, Spain, Poland, Germany and Belgium Only:** a full skin cancer examination must be performed as part of the complete physical examination).
- Vital signs, height and weight.
- Obtain blood sample for QuantiFERON<sup>®</sup>-TB Gold In-Tube test and send to central laboratory. Note: If the reference laboratory informs the investigator site that QuantiFERON<sup>®</sup>-TB Gold In-Tube testing cannot be performed on the submitted sample or if the result is indeterminate, then administer Purified Protein Derivative (PPD) skin test (Mantoux method) with Sponsor approval.
- Perform the following assessments and fax/email the result to the Centralized Coordinating Center:
  - Joint assessment (joints with active arthritis [swelling, pain on motion/tenderness, and limitation of motion]).
  - JIA Disease Status Worksheet:
    - Uveitis exam by an ophthalmologist (or qualified equivalent per local practice); not required if there is documentation of uveitis assessment by an ophthalmologist within the previous 3 months of screening;
    - Duration of morning stiffness;
    - Signs and symptoms of systemic disease (sJIA only);

- Physician's Global Assessment of Overall Disease Activity;
- Childhood Health Assessment Questionnaire (CHAQ);
- **ERA subjects only:** Tender Enteseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment.
- Erythrocyte sedimentation rate (ESR) determination (utilizing ESR test kit provided by the Sponsor); record result on appropriate CRF.
- **PsA subjects only:** Body surface area (BSA) and Physician's Global Assessment (PGA) for psoriasis (*not needed by the CCC*).
- Obtain blood or urine sample(s) for the following tests and send to central laboratory:
  - Hematology;
  - Chemistry;
  - C-reactive protein (CRP);
  - Rheumatoid Factor (RF);
  - Viral testing: Human Immunodeficiency Virus (HIV), Hepatitis B (Hep B), Hepatitis C (Hep C);
  - Varicella zoster virus (VZV) IgG Ab, if needed;
  - Urinalysis.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.

## 6.2. Day 1 Visit

The procedures and assessments listed below will be performed at the Day 1 visit.

*Please note that the Day 1 visit must occur within 30 days of the screening visit. If more than 30 days has elapsed, all screening procedures and assessment must be repeated. Sponsor approval must be obtained prior to re-screening a subject.*

*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.*

- Prior and concomitant medications;
- Targeted physical exam;

- Vital signs, height and weight;
- Tanner stage assessment.
- Perform the following assessments and fax/email the result to the Centralized Coordinating Center:
  - Joint assessment (joints with active arthritis [swelling, pain on motion/tenderness, and limitation of motion]);
  - JIA Disease Status Worksheet:
    - Uveitis status assessment;
    - Duration of morning stiffness;
    - Signs and symptoms of systemic disease (sJIA only).
- Physician's Global Assessment of Overall Disease Activity;
- CHAQ;
- Child Health Questionnaire (CHQ);
- **ERA subjects only:** Tender Enthesal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment;
- ESR determination (utilizing ESR test kit provided by Sponsor); record result on appropriate CRF;
- **PsA subjects only:** BSA and PGA of psoriasis (*not needed by the CCC*).
- Prior to dosing on Day 1, obtain blood or 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;

- Inflammatory markers: Anti-Cyclic Citrullinated Protein (anti-CCP) Antibodies, Antinuclear Antibodies (ANA), Human Leukocyte Antigen B27 (HLA-B27).
- Retained biospecimens:
  - Prep B2.5 serum collection;
  - Prep R1 whole blood collection.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- Assess for adverse events.
- Dispense investigational product; first dose to be administered at the study site for all subjects.
- **Only for first 40 subjects enrolled (excluding subjects with Systemic JIA):**
  - Obtain blood samples for PK analysis (see [Section 7.3.1.1](#) for details).

Day 1 PK Collection Time Points:

- 15 [10 – 20] minutes post dose;
- 45 [35 – 55] minutes post dose;
- 3 [2.75 – 4.0] hours post dose.

### 6.3. Week 2/Day 14 Visit

The procedures and assessments listed below will be performed at the Week 2/Day 14 visit. The window for this visit is  $\pm 3$  days.

- Prior and concomitant medications.
- Targeted physical exam.
- Vital signs, height and weight.
- Perform the following assessments and fax/email the result to the Centralized Coordinating Center:
  - Joint assessment (joints with active arthritis [swelling, pain on motion/tenderness, and limitation of motion]);
  - JIA Disease Status Worksheet:

- Uveitis status assessment;
- Duration of morning stiffness;
- Signs and symptoms of systemic disease (sJIA only);
- Physician's Global Assessment of Overall Disease Activity;
- CHAQ;
- **ERA subjects only:** Tender Entheses Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment.
- ESR determination (utilizing ESR test kit provided by Sponsor); record the result on the appropriate CRF.
- **PsA subjects only:** BSA and PGA of psoriasis (*not needed by the CCC*).
- Prior to dosing, obtain blood or urine sample(s) for the following tests and send to central laboratory:
  - Hematology;
  - Chemistry;
  - CRP;
  - Urinalysis.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- **PK sampling after first 40 subjects enrolled and in all subjects with systemic JIA:**
  - Obtain blood samples for PK analysis (PK sampling may be deferred to the Week 4/Day 28 visit) (see [Section 7.3.1.2](#) for details).

**\*\* Important Note \*\*** *The subject and parent/legal guardian should be instructed to hold the subject's morning dose to allow for pre-dose PK sampling.*

Week 2/Day 14 (or Week 4/Day 28) PK Collection Time Points:

- **Pre-dose** (12 hrs post the previous evening dose).
- Assess for adverse events.

- Administer tofacitinib oral solution taste acceptability assessment (not applicable for subjects taking tablets).
- Assess investigational product dosing compliance.
- Dispense investigational product.
- Administer AM dose at the clinic.
- Collect **post-dose PK** samples:
  - 45 [35 – 55] minutes post dose;
  - 3 [2.75 – 4.0] hours post dose.

#### **6.4. Week 4/Day 28 Visit**

The procedures and assessments listed below will be performed at the Week 4/Day 28 visit. The window for this visit is  $\pm 3$  days.

*For the Week 4/Day 28 Visit, subjects should be instructed to fast (for 9 to 12 hours prior to the scheduled visit), if possible, for lipid panel testing.*

- Prior and concomitant medications.
- Targeted physical exam.
- Vital signs, height and weight.
- Perform the following assessments and fax the result to the Centralized Coordinating Center:
  - Joint assessment (joints with active arthritis [swelling, pain on motion/tenderness, and limitation of motion]).
  - JIA Disease Status Worksheet:
    - Uveitis status assessment;
    - Duration of morning stiffness;
    - Signs and symptoms of systemic disease (sJIA only);
  - Physician's Global Assessment of Overall Disease Activity;
  - CHAQ;
  - CHQ;

- **ERA subjects only:** Tender Enthesal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment.
- ESR determination (utilizing ESR test kit provided by Sponsor); record the result on the appropriate CRF.
- **PsA subjects only:** BSA and PGA of psoriasis (*not needed by the CCC*).
- Prior to dosing, obtain blood or 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.
- Obtain **pre-dose and post-dose** blood sample(s) for PK analysis *if deferred from Day 14* (see [Section 7.3.1](#) for details).
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- Assess for adverse events.
- Assess investigational product dosing compliance.
- Dispense investigational product.

#### 6.5. Week 8, 12/Day 56, 84 Visit

The procedures and assessments listed below will be performed at the Week 8, 12/Day 56, 84 visit. The window for these visits is  $\pm 3$  days.

- Prior and concomitant medications.
- Targeted physical exam.
- Vital signs, height and weight.

- Perform the following assessments and fax/email the result to the Centralized Coordinating Center:
  - Joint assessment (joints with active arthritis [swelling, pain on motion/tenderness, and limitation of motion]).
  - JIA Disease Status Worksheet:
    - Uveitis status assessment;
    - Duration of morning stiffness;
    - Signs and symptoms of systemic disease (sJIA only).
  - Physician's Global Assessment of Overall Disease Activity.
  - CHAQ.
  - **ERA subjects only:** Tender Enthesal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment.
- ESR determination (utilizing ESR test kit provided by Sponsor); record the result on the appropriate CRF.
- **PsA subjects only:** BSA and PGA of psoriasis (*not needed by the CCC*).
- Prior to dosing, obtain blood sample(s) for the following tests and send to central laboratory:
  - Hematology;
  - Chemistry;
  - CRP.
  - **Week 8 only:** Retained biospecimen:
    - Prep D1.5 (K<sub>2</sub> edetic acid [ethylenediaminetetraacetic acid] [EDTA]) whole blood;
  - Urinalysis.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.



- **Week 12/Day 84 Visit: PK sampling in all subjects:**

- Obtain blood samples for PK analysis; PK sampling may be deferred to a later visit up to Week 18/Day 126; (see [Section 7.3.1](#) for details).

*\*\* Important Note \*\* The subject and parent/legal guardian should be instructed to hold the subject's morning dose to allow for pre-dose PK sampling.*

Week 12/Day 84 (or later visit up to Week 18/Day 126 visit) PK Collection Time Points:

- Pre-dose (12 hrs post the previous evening dose).
- Assess for adverse events.
- Assess investigation product dosing compliance.
- Dispense investigational product.
- Administer AM dose at the clinic.
- Collect **post-dose PK** sample:
  - 45 [35 – 55] minutes post dose.

### 6.6. Week 18/Day 126 Visit

The procedures and assessments listed below will be performed at the Week 18/Day 126 visit. The window for this visit is  $\pm 3$  days.

*For the Week 18/Day 126 Visit, subjects should be instructed to fast, if possible, for lipid panel testing.*

- Prior and concomitant medications.
- Complete physical exam. (**Applicable to Investigative Sites in the UK, Spain, Poland, Germany and Belgium Only:** a full skin cancer examination must be performed as part of the complete physical examination).
- Vital signs, height and weight.
- Perform the following assessments and fax/email the result to the Centralized Coordinating Center:
  - Joint assessment (joints with active arthritis [swelling, pain on motion/tenderness, and limitation of motion]).

- JIA Disease Status Worksheet:
  - Uveitis status assessment;
  - Duration of morning stiffness;
  - Signs and symptoms of systemic disease (sJIA only).
- Physician's Global Assessment of Overall Disease Activity.
- CHAQ.
- CHQ.
- **ERA subjects only:** Tender Enthesal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment.
- ESR determination (utilizing ESR test kit provided by Sponsor); record the result on the appropriate CRF page.
- **PsA subjects only:** BSA and PGA of psoriasis (*not needed by the CCC*).
- Prior to dosing, obtain blood or 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.
  - Retained biospecimens:
    - Prep B2.5 serum collection;
    - Prep R1 whole blood collection;
  - Urinalysis.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- Obtain **pre-dose and post-dose** blood samples for PK analysis *if deferred from Week 12/Day 84* (see [Section 7.3.1](#) for details).

- Assess for adverse events.
- Assess investigational product dosing compliance.
- **Randomize to the double-blind phase.**

**\*\*Important Note\*\* Only subjects who achieve a JIA ACR 30 response in the open-label phase based on receipt of confirmation from the Centralized Coordinating Center (see [Section 7.1.6](#) for details) are eligible for randomization.**

- Dispense investigational product.

#### **6.7. Week 20, 24, 28, 32, 36, 40/Day 140, 168, 196, 224, 252, 280 Visit**

The procedures and assessments listed below will be performed at the Week 20, 24, 28, 32, 36, 40/Day 140, 168, 196, 224, 252, 280 visit. The window for these visits is  $\pm 3$  days.

#### **Week 24/Day 168 Only:**

Uveitis assessment by ophthalmologist (or qualified equivalent per local practice) (the window for this particular assessment is  $\pm 7$  days).

#### **Week 20, 24, 28, 32, 36, 40/Day 140, 168, 196, 224, 252, 280 Visits:**

- Prior and concomitant medications;
- Targeted physical exam;
- Vital signs, height and weight.
- Perform the following assessments and fax/email the result to the Centralized Coordinating Center:
  - Joint assessment (joints with active arthritis [swelling, pain on motion/tenderness, and limitation of motion]).
  - JIA Disease Status Worksheet:
    - Uveitis status assessment; a uveitis exam by an ophthalmologist (or qualified equivalent per local practice) is required at the Week 24/Day 168 visit as noted above;
    - Duration of morning stiffness;
    - Signs and symptoms of systemic disease (sJIA only).
  - Physician's Global Assessment of Overall Disease Activity.

- CHAQ.
- **ERA subjects only:** Tender Enthesal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment.
- ESR determination (utilizing ESR test kit provided by Sponsor); record the result on the appropriate CRF.
- **PsA subjects only:** BSA and PGA of psoriasis (*not needed by the CCC*).
- Prior to dosing, obtain blood sample(s) for the following tests and send to central laboratory:
  - Hematology;
  - Chemistry;
  - CRP;
  - Urinalysis.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- Assess for adverse events.
- Assess investigational product dosing compliance.
- Dispense investigation product.

#### **6.8. Week 44, End of Study (EoS)/Day 308 or Early Termination (ET) Visit**

The procedures and assessments listed below will be performed at the Week 44/Day 308 visit. The window for this visit is  $\pm 3$  days.

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, an unplanned Tanner stage assessment CRF should be completed if possible as part of the early termination. If a subject discontinues outside of a regularly scheduled visit, all of the ET visit assessments should be completed, if possible.

*For the Week 44/Day 308 or Early Termination (ET) Visit, subjects should be instructed to fast, if possible, for lipid panel testing.*

- Prior and concomitant medications.

- Complete physical exam. (**Applicable to Investigative Sites in the UK, Spain, Poland, Germany and Belgium Only:** a full skin cancer examination must be performed as part of the complete physical examination).
- Vital signs, height and weight.
- Tanner stage assessment.
- Perform the following assessments and fax/email the result to the Centralized Coordinating Center:
  - Joint assessment (joints with active arthritis [swelling, pain on motion/tenderness, and limitation of motion]).
  - JIA Disease Status Worksheet:
    - Uveitis exam by an ophthalmologist (or qualified equivalent per local practice);
    - Duration of morning stiffness;
    - Signs and symptoms of systemic disease (sJIA only).
  - Physician's Global Assessment of Overall Disease Activity.
  - CHAQ.
  - CHQ.
  - **ERA subjects only:** Tender Enteseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment.
- ESR determination (utilizing ESR test kit provided by Sponsor); record the result on the appropriate CRF.
- **PsA subjects only:** BSA and PGA of psoriasis (*not needed by the CCC*).
- Obtain blood 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.

- Retained biospecimens:
  - Prep B2.5 serum collection;
  - Prep R1 whole blood collection;
- Urinalysis.
- **For females of childbearing potential:** Obtain blood (serum) or urine sample for local laboratory pregnancy testing.
- Assess for adverse events.
- Assess investigational product dosing compliance.
- **CCI**

## 6.9. Subject Withdrawal

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

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and parent/legal guardian and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved Adverse Events (AEs).

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

### 6.9.1. Subject Withdrawal Due to Failure to Achieve JIA ACR 30 Response or Disease Flare

All subjects enrolled in the study will initially receive open-label tofacitinib for 18 weeks (run-in phase). At the end of the 18 week run-in phase, only subjects who achieve at least a JIA ACR 30 response will be randomized to the 26 week double-blind, placebo-controlled phase. Subjects who do not achieve a JIA ACR 30 response at this time point will be discontinued from the study. Achievement of a JIA ACR 30 response at the end of the 18 week run-in phase will be based on the investigator and parent/legal guardian assessment of JIA core set variables and confirmed by the PRCSG/PRINTO Centralized Coordinating Center (see [Section 7.1.6](#)).

Subjects who experience a single episode of disease flare based on the PRCSSG/PRINTO disease flare criteria at any time during the study (including the open-label run-in and double-blind phase) will be discontinued from study treatment.

CCI

## 7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test 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).

### 7.1. Efficacy Assessments

#### 7.1.1. Number of Joints with Active Arthritis

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/mailed to the Centralized Coordinating Center (see [Section 7.1.13](#)).

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 and/or tenderness.

Swelling will be assessed in the following joints:

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

Pain/Tenderness will be assessed in the following joints:

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

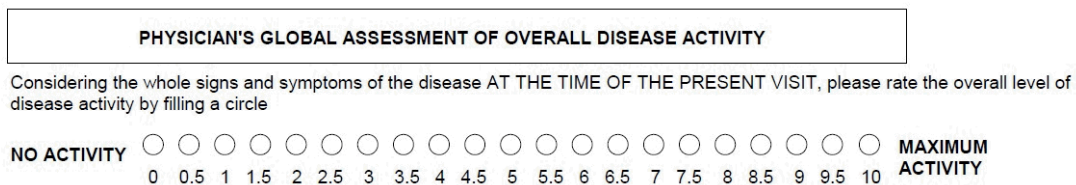
**Duration of morning stiffness:**

- 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.

**7.1.2. 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. The result will be faxed/mailed to the Centralized Coordinating Center (see [Section 7.1.13](#)).

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



**7.1.3. Childhood Health Assessment Questionnaire (CHAQ)**

At each study visit, the Childhood Health Assessment Questionnaire (CHAQ) assessment will be administered to the subject’s parent/legal guardian. Subjects aged 14 and older may complete this assessment if able to do so correctly and consistently for the duration of the



study. The results of the questionnaire will be faxed/mailed to the Centralized Coordinating Center (see [Section 7.1.13](#)). Every effort should be made to have the same individual complete the CHAQ throughout the course of the study.

The CHAQ (Singh 1994)<sup>5</sup> is a validated instrument and comprises two indices, Disability and Discomfort, and 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 (Ruperto 2001).<sup>6</sup>

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

### ***Disability Index***

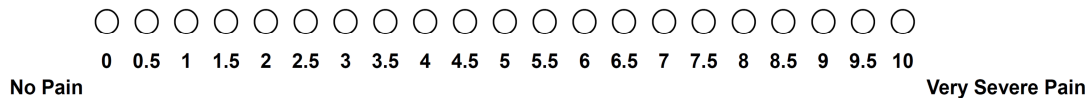
The parent/legal guardian/subject will be asked to provide responses to questions designed to assesses function in 8 areas, including dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities-distributed, among a total of 30 items. Each question is rated on a four-point scale 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/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/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.

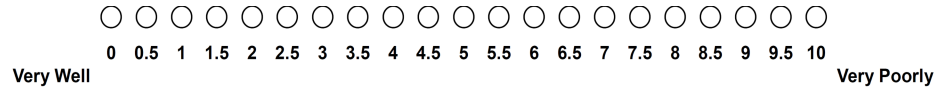


### ***Parent/Legal Guardian/Subject Global Assessment of Overall Well-Being***

For the assessment of overall well-being, the parent/legal guardian/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/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.



#### 7.1.4. Child Health Questionnaire (CHQ)

The Child Health Questionnaire (CHQ) assessment will be administered at each study visit to the parent/legal guardian. Subjects aged 14 and older may complete this assessment if able to do so correctly and consistently for the duration of study. The results of the questionnaire will be faxed/mailed to the Centralized Coordinating Center.

The CHQ (Landgraf 1996)<sup>20</sup> 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 impact-time, parent 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 questionnaire responses, as confirmed by the PRCSG/PRINTO Centralized Coordinating Center.

#### 7.1.5. Inflammatory Markers

In this study, testing for both Erythrocyte Sedimentation Rate and C-Reactive Protein will be performed in all subjects at each study visit.

##### 7.1.5.1. 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.

Following confirmation from the Centralized Coordinating Center of achievement of at least a JIA ACR 30 response at the end of the 18 week open-label, run-in phase, the baseline CRP result (obtained at Screening) will be entered into the IRT system by the investigator site for the purpose of appropriately stratifying and randomizing the subject to the double-blind, placebo controlled phase (see [Section 5.1](#)).

### 7.1.5.2. Erythrocyte Sedimentation Rate (ESR)

At each study visit, ESR 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/mailed to the Centralized Coordinating Center which, along with other JIA core set variables, will be used to perform efficacy assessments at each visit.

### 7.1.6. JIA Core Set Variables and Response Definition

The JIA ACR response determination is a derived measurement utilizing each component of the JIA core set variables (Giannini 1997),<sup>7</sup> 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/subject evaluation of overall well-being (from the CHAQ);
- Functional ability (Disability Index from the CHAQ);
- ESR will be used for the real-time assessment of ACR 30 response at Week 18 as well as flare and JIA ACR inactive disease status at all visits by the Centralized Coordinating Center; CRP may be used for analysis of other related endpoints (details will be provided in the Statistical Analysis Plan [SAP]).

The JIA ACR 30, 50, 70, 90, 100 response criteria are as follows: 3 out of 6 JIA core set variables improved  $\geq 30\%$ , 50%, 70%, 90%, 100%, respectively, with no more than 1 out of 6 JIA core set variables worsened by  $\geq 30\%$ . In subjects with systemic JIA, the absence of spiking fever related to systemic JIA is also required.

The JIA ACR 30, 50, 70, 90, 100 response will be determined based on the investigator's and parent/legal guardian/subject's assessment of components of the JIA core set variables.

#### **\* Important Note \***

*At the end of the 18 week open-label run-in phase (Week 18/Day 126 visit), only subjects who achieve at least a JIA ACR 30 response, based on the investigator's and parent/legal guardian/subject's assessment of components of the JIA core set variables (using ESR), will be randomized to the 26 week double-blind, placebo-controlled phase. Subjects who do not achieve at least a JIA ACR 30 response at this time point will be discontinued from the study.*

Achievement of a JIA ACR 30 response at Week 18 will be confirmed by the Centralized Coordinating Center following receipt of assessments of JIA core set variables from the investigator site. Investigators must receive confirmation from the Centralized Coordinating Center prior to randomizing the subject to the double-blind phase.

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

#### **7.1.7. PRCSG/PRINTO Disease Flare Criteria**

The PRCSG/PRINTO Disease Flare (Brunner 2002)<sup>8</sup> determination is a derived measurement utilizing each component of the JIA core set variables (see [Section 7.1.6](#)).

Flare is defined as a worsening of 30% or more in 3 or more of the 6 variables of the JIA core set (see [Section 7.1.6](#)), with no more than one variable improving by 30% or more. In addition, the following minimum worsening contingencies apply: if either the number of active joints or the number of joints with limited range of motion are included in the calculation of "flare" then there must be a worsening of at least two joints. If the Physician's or parent/legal guardian/subject global rating scores are used in the definition of "flare" then there must be a worsening of at least 2 units on the 10 unit scales. If the ESR is used in the definition of "flare" then the second value for the ESR used in the calculation must be above the upper limit of normal for the ESR. For subjects with sJIA, presence of spiking fever due to sJIA will be considered sufficient to determine disease flare.

At each visit, the investigator will evaluate the subject for evidence of disease flare, according to PRCSG/PRINTO Disease Flare criteria, and confirmed by the Centralized Coordinating Center. Subjects who experience a single episode of disease flare (based on the investigator's and parent/legal guardian/subject's assessment of components of the JIA core set variables, and as confirmed by the Centralized Coordinating Center) will be discontinued from the study.

PRCSG/PRINTO disease flare will be based on the investigator and parent/legal guardian/subject assessment of components of the JIA core set variables, as confirmed by the Centralized Coordinating Center.

#### **7.1.8. JIA ACR Clinical Inactive Disease and Clinical Remission Criteria**

The American College of Rheumatology (ACR) Clinical Inactive Disease and Clinical Remission (Wallace 2011)<sup>9</sup> criteria is 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 JIA;
- Physician global assessment of disease activity score of ‘best possible’ on the scale used;
- Duration of morning stiffness of  $\leq 15$  minutes.

**Clinical Remission on Medication:**

- Clinical inactive disease for 6 months continuously while on medications for JIA.

Inactive disease and clinical remission status will be based on the investigator’s assessment of the above components.

**7.1.9. 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).<sup>16</sup> Recently, the scoring system was adapted to use the 27-joint count (Bazso 2009),<sup>18</sup> and C-reactive protein (CRP) in place of Erythrocyte Sedimentation Rate (ESR) for the inflammatory marker component (Nordal 2012).<sup>19</sup>

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

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

**7.1.10. 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)<sup>17</sup> are defined as follows:

**Polyarthritis:**

- Inactive Disease:  $\leq 1$ ;
- Minimal Disease Activity:  $\leq 3.8$ .

**Oligoarthritis (<4 active joints):**

- Inactive Disease:  $\leq 1$ ;
- Minimal Disease Activity:  $\leq 2$ .

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

#### **7.1.11. Additional Assessments in Subjects with Enthesitis-Related Arthritis**

In addition to all other efficacy assessments specified in [Section 7](#), subjects with enthesitis-related arthritis (ERA) will undergo additional efficacy assessments, including Tender Enteseal Assessment, Modified Schober's Test, and Overall Back Pain and Nocturnal Back Pain Assessment as specified in the following subsections.

The result of this assessment will be faxed/mailed to the Centralized Coordinating Center.

##### **7.1.11.1. Tender Enteseal Assessment**

The Tender Enteseal Assessment will be performed at each study visit only in subjects with enthesitis-related arthritis.

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

*Y = Any tenderness upon firm palpation over the indicated enthesis*

*N = No tenderness upon firm palpation over the indicated enthesis*

##### **7.1.11.2. Modified Schober's Test**

The Modified Schober's Test (Macrae 1969, Moll 1971)<sup>13,14</sup> will be performed at each study visit only in subjects with enthesitis-related arthritis.

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



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

In addition to all other efficacy assessments specified in [Section 7](#), subjects with psoriatic arthritis (PsA) will undergo additional efficacy assessments, including affected body surface area (BSA) and Physician's Global Assessment (PGA) of psoriasis (Horneff 2014).<sup>15</sup> The PsA assessments are not required to be provided to the Centralized Coordinating Center.

#### **7.1.12.1. Body Surface Area (BSA)**

BSA will be measured as the percentage of BSA affected by psoriasis using the palm method; the subject's palm will be used for the calculation (see [Appendix 8](#)).

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

PGA of Psoriasis will assess the amount of induration, erythema, and scaling averaged over all psoriatic lesions on a scale of 0 to 5 (see [Appendix 9](#)).

### **7.1.13. Centralized Coordinating Center**

This study will utilize the Centralized Coordinating Center of PRCSG/PRINTO whose primary purpose is to review and confirm, in real time, a number of efficacy assessments. These primarily include verification of the JIA core set variables, JIA ACR 30 response (at Week 18), disease flare and inactive disease status at each visit.

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

- Joint assessment (including number of joints with swelling, pain on motion/tenderness, and limited range of motion).
- JIA Disease Status Worksheet:
  - Uveitis status assessment (exam required at certain visits per [SOA](#) and [Section 7.2.3](#));
  - Duration of morning stiffness;
  - Signs and symptoms of systemic disease (sJIA only);
- Physician's Global Assessment of Overall Disease Activity;
- Parent/legal guardian/subject's global assessment of overall well-being (CHAQ);
- Functional ability (Disability Index from the CHAQ);
- ESR.



- **In subjects with enthesitis-related arthritis (ERA) only:**
  - Tender enthesal assessment;
  - Modified Schober's Test assessment;
  - Overall Back Pain and Nocturnal Back Pain assessment.

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

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

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

## **7.2. 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 6](#) for guidelines for safety monitoring and discontinuations due to laboratory abnormalities, serious infections, opportunistic infections, and malignancies.

Please refer to [Section 9.7](#) for the evaluation of potentially malignant tumors, suspicious lymphadenopathy, or possible extra-nodal lymphoproliferative disorder.

### **7.2.1. 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.

### **7.2.2. 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. (**Applicable to Investigative Sites in the UK, Spain, Poland, Germany and Belgium Only:** 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 heart, lungs, lower extremities for peripheral edema, abdomen and lymph nodes. Any clinically significant changes from the baseline examination should be recorded as AEs.

#### **7.2.3. Uveitis Assessment**

Uveitis assessment must be performed by an ophthalmologist or qualified equivalent per local practice, and will be done at Screening (if no documented history of uveitis assessment within past 3 months is available), Week 24/Day 168 and Week 44/Day 308 (EoS) visits ( $\pm 7$  days), or Early Termination (ET) visit.

Uveitis assessment should be performed according to local standard of care and the results (ie, a report) recorded in the source document. At each visit subjects should be assessed for development of new uveitis or worsening of existing uveitis (according to SUN criteria); these changes should be reported as an adverse event. The Centralized Coordinating Center worksheet for each visit asks if the subject has active uveitis (yes/no).

The activity of the anterior chamber (AC) inflammation should be evaluated according to the SUN criteria, where the activity of AC inflammation is graded from 0 to 4 (grade/cells in field: 0/<1, 0.5+/1–5, 1+/6–15, 2+/16–25, 3+/26–50, 4+/>50) (Jabs 2005).<sup>21</sup>

#### **7.2.4. 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 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 using tympanic, oral or temporal methods and that the same method should be used consistently throughout the study.

### ***Height and Weight***

Height and weight should be reported at each visit with height preferentially measured utilizing a Harpenden stadiometer.

#### **7.2.5. Pubertal Development Assessment (Tanner Stages)**

Determination of physical and sexual maturation will be performed at the Day 1 and Week 44 or Early Termination visit using the Tanner stages (Dorn 1990, Taylor 2001)<sup>10,11</sup> 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.

#### **7.2.6. Tuberculosis Testing**

At the time of screening, all subjects will undergo tuberculosis (TB) testing. QuantiFERON<sup>®</sup>-TB Gold In-Tube Test is the preferred testing method. If the QuantiFERON<sup>®</sup>-TB Gold 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 the Purified Protein Derivative (PPD) Tuberculin Skin Test (Mantoux method) 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 of care and/or in countries with a high incidence rate of TB.

**Applicable to Investigative Sites in the UK, Spain, Poland, Germany and Belgium Only:**

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.

**7.2.6.1. QuantiFERON®-TB Gold In-Tube Test**

QuantiFERON®-TB Gold In-Tube test (Guidelines 2005)<sup>4</sup> is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10 and TB7.7 proteins to stimulate cells in heparinized whole blood. Detection of interferon- by Enzyme-Linked Immunosorbent Assay is used to identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection. QuantiFERON®-TB Gold 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 (approximately 3 mL) 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 test can be substituted for the QuantiFERON®-TB Gold 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.

**7.2.6.2. Purified Protein Derivative (PPD) Test**

If the QuantiFERON®-TB Gold In-Tube test cannot be performed, or if the results cannot be determined to be positive or negative, then subjects may be screened using the Purified Protein Derivative (PPD) Tuberculin Test (Mantoux method), 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 with induration of <5 mm required for inclusion.

**7.2.7. 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.

- **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 kinase (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), Anti-Cyclic Citrullinated Protein (anti-CCP) Antibodies, Antinuclear Antibodies (ANA), Human Leukocyte Antigen B27 (HLA-B27).

**\*\* Please note, ESR will be determined locally utilizing an ESR Testing Kit provided to the investigator site by the Sponsor (see [Section 7.1.5.2](#)).**

- **Pregnancy testing (all female subjects who have passed menarche):** Blood (serum) or urine pregnancy testing (for Human Chorionic Gonadotropin [hCG]) will be performed locally or by the local or central laboratory. A positive urine pregnancy must be confirmed by a blood (serum) pregnancy test performed either by the local or central laboratory.
- **Varicella zoster virus IgG Antibody testing (if applicable):** Please refer to [Section 7.2.8](#).
- **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 for confirmation of positive HCV Ab result). To conserve blood volume at screening, HCV RNA sample collection may be deferred and collected only if required to confirm eligibility based on the HCV Ab results.

***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 7.2.6](#).
- 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.

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

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

Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

**7.2.8. Varicella Zoster Virus (VZV) IgG Antibody (Ab) Testing**

Subjects without documented evidence of having received at least a single dose of the varicella vaccine in countries where the varicella vaccine is approved and standard of care will be tested for varicella zoster virus IgG Ab (ELISA method). Subjects that lack evidence of prior exposure to varicella zoster virus based on serological VZV IgG Ab testing are excluded.

### 7.2.9. 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 Week 44 (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 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 8.11](#) for additional information regarding Exposure During Pregnancy.

### 7.2.10. Blood Volume

Every effort will be made to minimize the number of blood sampling and volumes collected. Low volume pediatric tubes will be used where possible.

**Applicable to Investigative Sites in the UK, Spain, Poland, Germany and Belgium Only:** 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.

Total blood sampling volume for the individual subjects is approximately 99 mL over the 44 week period.

[Table 3](#) 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, provided the total volume taken during the study does not exceed 2.7 mL/kg during any period of 30 consecutive days.

**Applicable to Investigative Sites in the UK, Spain, Poland, Germany and Belgium Only:** In some instances additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 2.4 mL/kg during any period of 30 consecutive days.

**Table 3. Blood Volume**

Laboratory Test	Sample Collection Time (Blood Volume, mL)								
		Day 1	Week 2	Week 4	Week 8	Week 12	Week 18	Week 20, 24, 28, 32, 36, 40	Week 44/End of Study (EoS)
	Screening	Day 1	Day 14	Day 28	Day 56	Day 84	Day 126	Days 140, 168, 196, 224, 252, 280	Day 308/Early Termination (ET)
Chemistry	x (1.1)		x (1.1)		x (1.1)	x (1.1)		x (1.1)	
Chemistry, Lipids		x (1.1)		x (1.1)			x (1.1)		x (1.1)
Apo-A1, Apo-B1, CRP		x (2.5)		x (2.5)			x (2.5)		x (2.5)
Hematology	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)
QuantiFERON TB Gold	x (1.0)								
VZV IgG Ab	x (1.1)								
Serum pregnancy test <sup>1</sup>	x (1.1)								
CRP			x (1.1)		x (1.1)	x (1.1)		x (1.1)	
CRP, RF	x (2.5)								
Anti-CCP		x (1.1)							
ANA		x (1.1)							
HLA-B27		x (2.0)							
HIV-1, HIV-2	x (4.0)								
HBsAg, HBcAb, HCV Ab	x (2.5)								
HCV RNA	x (6.0)2								
PK		x (3.6)3	x (3.6)4			x (2.2)5			
Banked Biospecimens		x (4.5)6			x (2)7		x (4.5)6		x (4.5)6
<b>Total mL per visit</b>	<b>20.5 (14.52)</b>	<b>17.13 (13.5)</b>	<b>3.4 (7.0) 4</b>	<b>4.8</b>	<b>5.4</b>	<b>5.6</b>	<b>9.3</b>	<b>(3.4 per visit) 20.4</b>	<b>9.3</b>
<b>Total Blood Volume<sup>8</sup> = 99.4 mL (86.8 mL minimum)</b>									

- Alternatively, the investigator site may perform a urine pregnancy test.
- To conserve blood volume at screening, HCV RNA sample collection may be deferred and collected only if required to confirm eligibility based on the HCV Ab results.
- PK testing in the first 40 non-sJIA subjects; 3 samples total (each 1.2 mL).
- PK testing in all subjects enrolled after the first 40 non-sJIA subjects, and in all sJIA subjects; 4 samples total (each 1.2 mL).
- PK testing in all subjects; 3 samples total (each 1.2 mL).
- Prep B2.5 (2 mL) and Prep R1 (2.5 mL) collected pre-dose on Day 1, and at Week 18 and Week 44/EoS/ET.
- Prep D1.5 (2 mL EDTA) collected at Week 8.
- Total volume does not include unplanned laboratory tests, confirmatory serum pregnancy test (if a positive urine pregnancy test is obtained), or discarded blood from pre-draws used to remove fluid from flushed catheters.

### 7.3. Pharmacokinetic Assessment

Plasma samples for population pharmacokinetic (PK) analysis of tofacitinib will be collected from all subjects enrolled in the study at various time points.

Among the first 40 subjects enrolled (excluding subjects with systemic JIA), the Sponsor will attempt to enroll a minimum of 10 subjects from each age group (2 to <6 yrs, 6 to <12 yrs, 12 to <18 yrs), and approximately 20 subjects each with normal and above normal baseline CRP result. The Sponsor will track enrollment and notify investigators when the target



number of blood samples for PK analysis in first 40 subjects (excluding subjects with sJIA) has been reached.

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.

### **7.3.1. PK Blood Sample Collection Time**

#### **7.3.1.1. First 40 Subjects Enrolled (Excluding Subjects with Systemic JIA)**

In the first 40 subjects (excluding subjects with systemic JIA) enrolled in the study, blood samples for PK will be collected on Day 1 and Week 12/Day 84 (or later visit up to Week 18/Day 126 visit) at the time points indicated below.

##### Day 1 PK Collection Time Points:

- 15 [10 – 20] minutes post dose;
- 45 [35 – 55] minutes post dose;
- 3 [2.75 – 4.0] hours post dose.

##### Week 12/Day 84 (or later visit up to Week 18/Day 126 visit) 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 hrs post the previous evening dose);
- 45 [35 - 55] minutes post dose.

The Sponsor will track and notify investigators when the target number of blood samples for PK analysis in first 40 subjects enrolled (excluding subjects with sJIA) has been reached.

#### **7.3.1.2. After First 40 Subjects Enrolled (excluding Subjects with Systemic JIA)**

After the first 40 subjects (excluding subjects with systemic JIA) are enrolled in the study, in all subsequent subjects enrolled (excluding subjects with systemic JIA), blood samples for PK will be collected on Week 2/Day 14 (or Week 4/Day 28), and Week 12/Day 84 (or later visit up to Week 18/Day 126 visit) at the time points indicated below.

*Note, the subject and the parent/legal guardian will be instructed that the subject should not take the morning dose until after the pre-dose PK sample is collected.*

Week 2/Day 14 (or Week 4/Day 28) PK Collection Time Points:

- Pre-dose (approximately 12 hrs post the previous evening dose);
- 45 [35 – 55] minutes post dose;
- 3 [2.75 – 4.0] hours post dose.

Day 84 (or later visit up to Day 126 visit) PK Collection Time Points:

- Pre-dose (approximately 12 hrs post the previous evening dose);
- 45 [35 - 55] minutes post dose.

**7.3.1.3. Subjects with Systemic JIA**

In all subjects with systemic JIA, plasma samples for PK will be collected on Week 2/Day 14 (or Week 4/Day 28) and Week 12/Day 84 (or later visit up to Week 18/Day 126 visit) at the time points indicated below.

*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.*

Week 2/Day 14 (or Week 4/Day 28) PK Collection Time Points:

- Pre-dose (approximately 12 hrs post the previous evening dose);
- 45 [35 – 55] minutes post dose;
- 3 [2.75 – 4.0] hours post dose.

Week 12/Day 84 (or later visit up to the Week 18/Day 126 visit) PK Collection Time Points:

- Pre-dose (approximately 12 hrs post the previous evening dose);
- 45 [35 - 55] minutes post dose.

**7.3.2. Blood Sample Processing**

Blood samples (1 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.

### 7.3.3. 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.

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### 7.4. Tofacitinib Oral Solution Taste Acceptability Assessment

Oral solution will be used in subjects weighing <40 kg and in subjects who are unable to swallow tablets.

In subjects receiving tofacitinib oral solution, taste acceptability will be assessed at the Week 2/Day 14 visit.

Taste acceptability will be assessed by asking the subject to select one of several choices which most adequately reflects the subject's response to taste. Age appropriate tools (using wording and/or graphic facial expressions) will be used to assess taste acceptability.

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### 7.5.1. 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 patients in which to target a given treatment

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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 postmarketing 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<sub>2</sub> 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.

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## **8. ADVERSE EVENT REPORTING**

### **8.1. Adverse Events**

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

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

As part of ongoing safety reviews conducted by the sponsor, any 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.

## **8.2. Reporting Period**

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product.

Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

All adverse events (serious and nonserious) should be recorded on the Case Report Form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

## **8.3. Definition of an Adverse Event**

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

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

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;

- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

#### **8.4. Medication Errors**

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

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

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

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

##### **8.4.1. 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 4](#)) is assumed to result in a doubling of tofacitinib exposure. For further details, please refer to the SRSD (eg, the Investigator Brochure).

#### **8.5. Infections**

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

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

#### **8.5.1. Serious Infections**

A serious infection is any infection that requires hospitalization for treatment or requires parenteral antimicrobial therapy or meets other criteria that require it to be classified as a serious adverse event. A subject who experiences a serious infection must be discontinued from the study. This infection must be reported as a serious adverse event and should be listed as the reason for discontinuation in the 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 8.1](#) on [ADVERSE EVENT REPORTING](#).

#### **8.5.2. Treated Infections**

A treated infection is any infection that requires antimicrobial therapy by any route of administration or any surgical intervention (eg, incision and drainage). A subject who experiences a serious infection must be discontinued from the study. This information must be noted in the eCRF.

#### **8.6. 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.

#### **8.7. Serious Adverse Events**

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

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



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

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

#### **8.7.1. Protocol-Specified Serious Adverse Events**

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

#### **8.7.2. Potential Cases of Drug-Induced Liver Injury**

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

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

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values  $\geq 3$  times the upper limit of normal (X ULN) concurrent with a total bilirubin value  $\geq 2$  X ULN with no evidence of hemolysis and an alkaline phosphatase value  $\leq 2$  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  $\geq 2$  times the baseline values and  $\geq 3$  X ULN, or  $\geq 8$  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  $\geq 3$  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.

### **8.8. 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.

### **8.9. 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.

### **8.10. 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.

### **8.11. Exposure During Pregnancy**

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

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

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

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as 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.

### **8.12. Occupational Exposure**

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

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

### **8.13. Withdrawal Due to Adverse Events (See Also the Section on [Subject Withdrawal](#))**

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

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

#### **8.14. Eliciting Adverse Event Information**

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

#### **8.15. Reporting Requirements**

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

##### **8.15.1. Serious Adverse Event Reporting Requirements**

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This 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.

##### **8.15.2. 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.

### **8.15.3. 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.

## **9. 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.

### **9.1. Sample Size Determination**

A sample size of approximately 170 subjects (in the polyarticular cohort) will be enrolled in the open-label active treatment run-in phase to provide a power of approximately 90% or above to detect a difference in the rate of disease flares between study drug versus placebo in the double-blind phase, assuming a 54% to 65% response rate of ACR Pedi 30 from the run-in active treatment phase, a 2-sided 5% Type I error, and a true difference of at least 31% in flare rates between tofacitinib and placebo, with a placebo flare rate of 57%. Sample sizes for the polyarticular JIA categories were determined from a combination of prevalence data and precedents in the literature.

### **9.2. Efficacy Analysis**

#### **9.2.1. Analysis of Primary Endpoint**

Superiority of tofacitinib to placebo for the primary endpoint of percentage of subjects with disease flare at end of study Week 44 (Week 26 of the double-blind phase) for subjects with polyarticular course (polyarthritis RF+/RF-, extended oligoarthritis, and systemic JIA with active arthritis but without active systemic features) JIA will be tested using the normal approximation approach for the binomial populations. Subjects who discontinue from the study treatment for any reason will be considered as having a disease flare, except subjects who discontinue after maintaining JIA ACR inactive disease for at least 24 weeks in the double-blind phase. These discontinuations will be considered as non-disease flare.

Additional details of the analysis of the primary endpoint will be described in the Statistical Analysis Plan (SAP).

#### **9.2.2. Analysis of Secondary Endpoints**

All secondary efficacy endpoints that are collected in the double-blind withdrawal phase will be analyzed by treatment group. For the binary secondary endpoints, including occurrence of disease flare prior to Week 44/EoS (Week 26 of the double-blind phase), JIA ACR responses, presence of JIA ACR inactive disease and clinical remission, JADAS minimum disease activity and inactive disease status, the normal approximation approach for the binary populations, as used for the primary analysis, will be performed. For the continuous secondary endpoints, including change from baseline in JADAS 27-CRP, JADAS 27-ESR, CHQ, CHAQ, and JIA ACR core set variables, a mixed-effect model will be applied. The

estimated treatment difference and the associated 95% confidence interval will be presented. The Kaplan-Meier plot will be generated for the secondary endpoint of time to flare. Descriptive/summary statistics for all endpoints will also be provided. Baseline demographic characteristics, primary and key secondary endpoints will be summarized by JIA category, baseline CRP, methotrexate background therapy, prior biologic failures, history of uveitis, and age.

Forest plots will be provided for the primary and key secondary endpoints, and will also be presented for the subgroup analysis on these endpoints.

For subjects with ERA and subjects with PsA, efficacy endpoints will be assessed separately using summary and descriptive statistics by treatment group at each time point in the double-blind phase.

For the efficacy endpoints that are collected in the open-label run-in phase, the summary statistics or descriptive statistics will be presented at each visit for the binary or continuous efficacy endpoints, respectively.

Taste acceptability assessment questionnaire will be included in the CRF. Summary statistics will be provided for each category of the taste acceptability by treatment and by time point. Data will be listed as well.

Further details of the analysis of secondary endpoints will be described in the Statistical Analysis Plan (SAP).

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### **9.3. 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 JIA subject population. Effects of demographic and disease covariates (age, weight, CRP etc.) on tofacitinib PK may be explored if appropriate. PK data (on Day 1 in the run-in period) from approximately the first 20-40 subjects with polyarticular JIA (depending on the enrollment rate) will be analyzed to confirm the current dosing scheme for the double-blind phase and doses may be adjusted 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.



#### **9.4. 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.

#### **9.5. Interim Analysis**

No formal interim analysis is planned.

#### **9.6. 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.

#### **9.7. 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) and Gastrointestinal Perforation Review Committee (GIPRC). 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 World Care Clinical (WCC) for review by a WCC pathologist. In some instances, additional expert pathology review of submitted samples may be performed. Description of the scope of review and the processes used to obtain and assess biopsies is described in the Histopathology Review for Potential Malignancy charter.

## **10. QUALITY CONTROL AND QUALITY ASSURANCE**

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.

## **11. DATA HANDLING AND RECORD KEEPING**

### **11.1. Case Report Forms/Electronic Data Record**

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

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

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs 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.

### **11.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/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. ETHICS**

### **12.1. Institutional Review Board/Ethics Committee**

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

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

### **12.2. Ethical Conduct of the Study**

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

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

### **12.3. Subject Information and Consent**

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 he/she 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.

#### **12.4. 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.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information 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.

### **13. DEFINITION OF END OF TRIAL**

#### **13.1. End of Trial in the United States**

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.

#### **13.2. 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.

#### **13.3. End of Trial in All Other Participating Countries**

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

### **14. SPONSOR DISCONTINUATION CRITERIA**

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

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

### **15. PUBLICATION OF STUDY RESULTS**

#### **15.1. Communication of Results by Pfizer**

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov), or the European Clinical Trials Database (EudraCT), and/or [www.pfizer.com](http://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](http://www.clinicaltrials.gov)

Pfizer posts clinical trial US Basic Results on [www.clinicaltrials.gov](http://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 pre-specified protocol or was terminated.

EudraCT

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

[www.pfizer.com](http://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](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

## **15.2. 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 it is 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 Treatments for JIA**

### **Allowed DMARDs:**

The following DMARDs are allowed in doses consistent with local standards of care:

- Methotrexate may be taken orally or parenterally at doses not to exceed 25 mg/wk or 20 mg/m<sup>2</sup>/week [whichever is lower]). Participants must have taken MTX for ≥3 months and be at a stable dose for at least 6 weeks before baseline and should be on a stable dose for the duration of the study [open-label run-in and double-blind phases]). Subjects taking methotrexate must be taking folic acid or folinic acid in accordance with local standards.

### **Allowed Treatments for Psoriatic Arthritis:**

For subjects with PsA, the following topical treatments for psoriasis are allowed:

- Non-medicated emollients for use over the whole body;
- Topical steroids including hydrocortisone and hydrocortisone acetate ≤1% for the palms, soles, face, and intertriginous areas only;
- Tar, salicylic acid preparations, and shampoos free of corticosteroids are permitted only for the scalp.

### **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<sup>®</sup>) must have been discontinued 8 weeks prior to the first dose of study drug if no elimination procedure is followed;
- Anakinra (Kineret<sup>®</sup>), Enbrel (Etanercept<sup>®</sup>): Discontinued for 4 weeks prior to the first dose of study drug;
- Canakinumab (Ilaris<sup>®</sup>): Discontinued for 18 weeks prior to the first dose of study drug;
- Adalimumab (Humira<sup>®</sup>): Discontinued for 6 weeks prior to first dose of study drug;
- Infliximab (Remicade<sup>®</sup>): Discontinued for 8 weeks prior to the first dose of study drug;
- Golimumab (Simponi TM): Discontinued for 10 weeks prior to the first dose of study drug;

- Abatacept (Orencia<sup>®</sup>), Tocilizumab (Actemra<sup>®</sup>), Certolizumab pegol (Cimzia<sup>®</sup>): Discontinued for 12 weeks prior to first dose of study drug;
- Rituximab (Rituxan<sup>®</sup>) 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.

**Other Disallowed Agents:**

- Bucillamine, mizoribine, sulfasalazine, d-penicillamine, azathioprine, chloroquine, hydroxychloroquine, cyclosporine, tacrolimus, and staphylococcal protein A immuno-absorbant pheresis columns (eg, PROSORBA<sup>®</sup> 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 Treatments for PsA:**

For subjects with PsA, oral and topical medications and alternative treatments that could affect psoriasis are prohibited. This includes:

- Topical corticosteroids (except those described in the “[Allowed Treatments for Psoriatic Arthritis](#)” section of [Appendix 1](#)), tars, keratolytics, anthralin, vitamin D analogs, and retinoids which must be discontinued at least 2 weeks prior to first dose of study drug;
- Ultraviolet B (UVB) (narrowband or broadband) phototherapy that must be discontinued at least 2 weeks prior to first dose of study drug;
- Psoralens + ultraviolet A (UVA) phototherapy (PUVA) must be discontinued at least 4 weeks prior to first dose of study drug.

**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 6 months or 5 half-lives (whichever is longer) prior to the first dose of study drug.

## Appendix 2. Permitted Adjustments In JIA Therapies

The following adjustments of background medications are allowed for reasons of inadequate efficacy of current treatment. 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 dose should be stable for the duration of the study (open-label run-in and double-blind phases) and not exceed 0.2 mg/kg/day prednisone or equivalent or 10 mg per day, whichever is lower.
3. Methotrexate (MTX) may be administered either orally or parenterally at doses not to exceed 25 mg/wk or 20 mg/m<sup>2</sup>/week (whichever is lower) and should remain stable for the duration of the study (open-label run-in 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 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 remainder of the study and for efficacy assessments.**

### **Appendix 3. Estimated Glomerular Filtration Rate Calculation**

Bedside Schwartz (Schwartz, 2009)<sup>22</sup> GFR equation will be used to estimate glomerular filtration rate (GFR) from serum creatinine (creatinine method with calibration traceable to IDMS).

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 0.413 \times (\text{Ht} / \text{Scr})$$

Height (Ht) in cm;

Serum creatinine (Scr) in mg/dL;

#### Appendix 4. Prohibited Concomitant Medications

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

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

\*\* **Biologic and Non-Biologic DMARDs** which have specific washout periods are listed in [Appendix 1](#).

NOTE: <u>Topical</u> administration (eg, cutaneous, ophthalmic, or intravaginal) of listed concomitant medications, which are prohibited if administered systemically, <u>is</u> allowed in the study.	
<b><u>Moderate or Potent CYP3A Inhibitors</u></b>	<b><u>Moderate or Potent CYP3A Inducers</u></b>
<i>HIV antivirals:</i>	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)
<b>amiodarone (Cordarone, Pacerone)*</b>	rifabutin (Mycobutin)
cimetidine (Tagamet)	rifampin (Rifadin, Rifamate, Rifater)
clarithromycin (Biaxin, Prevpac)	rifapentine (Priftin)
telithromycin (Ketek)	St. John's Wort
clotrimazole	troglitazone (Rezulin)
chloramphenicol	<b><u>All Investigational Drugs</u></b>
diethyl-dithiocarbamate	<b><u>DMARDs</u></b>
diltiazem (Cardizem, Tiazac)	<b>All Biologics**</b> , such as:
erythromycin	anakinra (Kineret), etanercept (Enbrel),
fluconazole (Diflucan)	adalimumab (Humira), infliximab
fluvoxamine (Luvox)	(Remicade), abatacept (Orencia),
Grapefruit juice and marmalade	canakinumab (Ilaris), tocilizumab
itraconazole (Sporanox)	(Actemra), golimumab (Simponi),
ketoconazole (Nizoral)	rituximab (Rituxan),
mifepristone (Mifeprex, RU486)	<b>Other DMARDs**:</b>
nefazodone (Serzone)	leflunomide, sulfasalazine, d-penicillamine,
norfloxacin (Shibroxin, Noroxin)	bucillamine, mizoribin, azathioprine,
mibefradil	cyclosporine, tacrolimus, auranofin,
verapamil (Calan SR, Covera HS, Isoptin SR, Tarka, Verelan)	aurothioglucose, aurothiomalate,
voriconazole	staphylococcal protein A immuno-absorbant pheresis columns

## Appendix 5. Rescue Therapy

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

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

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

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

***For subjects who ARE on stable, background opioid therapy:***

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

Intravenous or intramuscular corticosteroids, biologic response modifiers and DMARDs other than those specified as allowed DMARDs ([Appendix 1](#)) are not allowed during this study. Intra-articular corticosteroids may 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. Injections should be avoided for 6 weeks before any study visit. 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 avoid dosing with rescue intervention within 24 hours prior to a study visit unless indicated for subject safety and individual case management at the discretion of the investigator.**

## Appendix 6. Guidelines For Safety Monitoring And Discontinuations

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

- Lymphocyte counts  $<500$  lymphocytes/mm<sup>3</sup>;
- Neutrophil counts  $<1000$  neutrophils/mm<sup>3</sup>.

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

- Platelet counts  $<100,000$  platelets/mm<sup>3</sup>.
- Any single AST and/or ALT elevation  $>3$  times the upper limit of normal (repeat laboratory testing must include CK, Total Bilirubin, Direct and Indirect Bilirubin, GGT, INR and alkaline phosphatase), regardless of the total Bilirubin.
- Any single hemoglobin value  $<8.0$  g/dL.
- Any single hemoglobin value that is  $\geq 2$  gm/dL below the baseline.

Treatment with CP-690,550 will be discontinued and the subject withdrawn from this study for:

- Serious infections (those requiring parenteral antimicrobial therapy or hospitalization), and opportunistic infections;
- Malignancies;
- Two sequential lymphocyte counts  $<500$  lymphocytes/mm<sup>3</sup>;
- Two sequential neutrophil counts  $<500$  neutrophils/mm<sup>3</sup>;
- Two sequential platelet counts  $<75,000$  platelets/mm<sup>3</sup>;
- 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;
- Single positive HBc Ab and a negative HBs Ab;
- Two sequential hemoglobins <8.0 g/dL or a decrease of more than 30% from baseline value;
- Two sequential increases in serum creatinine >100% over the average of screening and baseline values. For any increase in serum creatinine >50% over the average of screening and baseline, protocol-permitted adjustments in concomitant medications and/or dose of study drug are permitted within a 90 day period from the initial >50% serum creatinine increase. If the >50% increase in serum creatinine persists for ≥90 days, in spite of adjustments in concomitant medications and/or dose of study drug, treatment with CP-690,550 must be discontinued and the subject withdrawn from the study;
- Other serious or severe AEs, after consultation with the Pfizer Medical Monitor.

## Appendix 7. Dosing Rationale (Abbreviated Analysis Report)

Population Pharmacokinetics of Tofacitinib in Subjects with Juvenile Idiopathic Arthritis (JIA) and Dose Selection for A3921104.

### Objectives

The objectives of this analysis were:

- To characterize the population pharmacokinetics (POPPK) of tofacitinib in subjects with juvenile idiopathic arthritis (JIA) using available data from the Phase 1 study in JIA subjects;
- To select doses for future efficacy/safety study (A3921104) in polyarticular JIA subjects based on simulated steady state exposures generated using the POPPK analysis parameter values.

### Study Design and Assessments

Pharmacokinetic data from 26 subjects in study A3921103 (An Open-Label Multiple Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of CP-690,550 in Pediatric Subjects from 2 to <18 years of age with Juvenile Idiopathic Arthritis (JIA) were available for analysis.

Tofacitinib concentrations were determined using a validated analytical method in compliance with Pfizer standard operating procedures by the contract analytical laboratories. The minimum quantifiable concentration of the assay is 0.1 ng/ml, and the per-protocol (nominal) PK sampling schedules are listed in [Table S1](#).

**Table S1. PK Sampling Schedule in A3921103**

Study	PK sampling schedule/Period	Number of subjects planned	Treatment
A3921103	Pre-dose on Day 5 (approximately 11-13 h post-dose after second dose on Day 4) and 0.5, 1, 2, 4 and 8 hours post first dose on Day 5	26 (At least 24 with n=8 in each cohort) <sup>a</sup>	2-5 mg BID depending on body weight of the subjects as given below in <a href="#">Table S2</a>

**Table S2. Dosing Scheme in A3921103**

Body Weight (Kg)	Dose (mg)	Volume (mL)
5-11	1	1
12-18	1.5	1.5
19-24	2	2
25-31	2.5	2.5
32-39	3	3
≥40	5	5

Dosing Scheme for Age 2 to <6 years		
5-6	1	1
7-9	1.5	1.5
10-12	2	2
13-15	2.5	2.5
16-19	3	3
20-22	3.5	3.5
23-26	4	4
27-29	4.5	4.5
≥30	5	5

### Data for Analysis

The Information Strategy and Analytics function within Clinical Innovation and Informatics (CII) generated the PK data files used in this POPPK analysis. Data files were constructed and quality control evaluations completed according to all CII standard operating procedures and processes as documented in the programming plan.

PK samples were collected from all specified time points with no missing or below quantification limit (BQL) tofacitinib concentrations. All concentrations were included in the analysis. Actual time points instead of nominal time points of blood sample collection were used for the analysis.

### Methods

The POPPK analysis was conducted using a nonlinear mixed-effects modeling approach. NONMEM version 7.2 (ICON Development Solutions, Hanover, MD) was used for the execution of NONMEM. R version 3.0 (R Development Core Team) and R-Studio 0.98.484 were used for data handling, CCI

The estimation method was the first-order conditional estimation (FOCE).

The analyses were conducted in the following steps: 1) base structural model development; 2) final model development; 3) assessment of model adequacy; 4) model predictive performance (VPC) and 5) simulations to of steady state exposures at various doses of Tofacitinib to recommend dosing regimen for the upcoming Phase 3 study.

Tofacitinib PK was described by a one-compartment disposition model with first-order absorption parameterized in terms of apparent oral clearance (CL/F), apparent volume of distribution (V/F), and first-order absorption duration (D) using NONMEM subroutines, ADVAN2 and TRANS2. Inter-individual variability (IIV) on CL/F, V/F and Ka were modeled using exponential variance models. Residual variability was modeled with a proportional and additive error models.

Due to limited number of subjects available for the analysis, a full covariate modeling approach was not deemed appropriate. Instead, based on allometric theory, body weight (BWT) was used as a predictor of CL/F and V/F. Additionally, results from a prior relative bioavailability study of Tofacitinib (A3921105) in adult healthy volunteers indicated a decrease (~24% decrease at 50 mg dose, N=12) in C<sub>max</sub> (maximum observed concentrations post-dose) for tablets compared to OPC (oral powder for constitution) formulation. Therefore, formulation (solution or tablet) was explored as a categorical covariate to describe the between-subject variability of Ka. No additional covariate analysis besides these two was investigated.

Goodness of fit of different models to the data was evaluated using the following criteria: change in OFV, visual inspection of various diagnostic plots, and precision of the parameter estimates. Visual Predictive Checks (VPCs) were performed for the selected PK models to qualify the models with respect to the prediction of the concentration data prior to any simulation work.

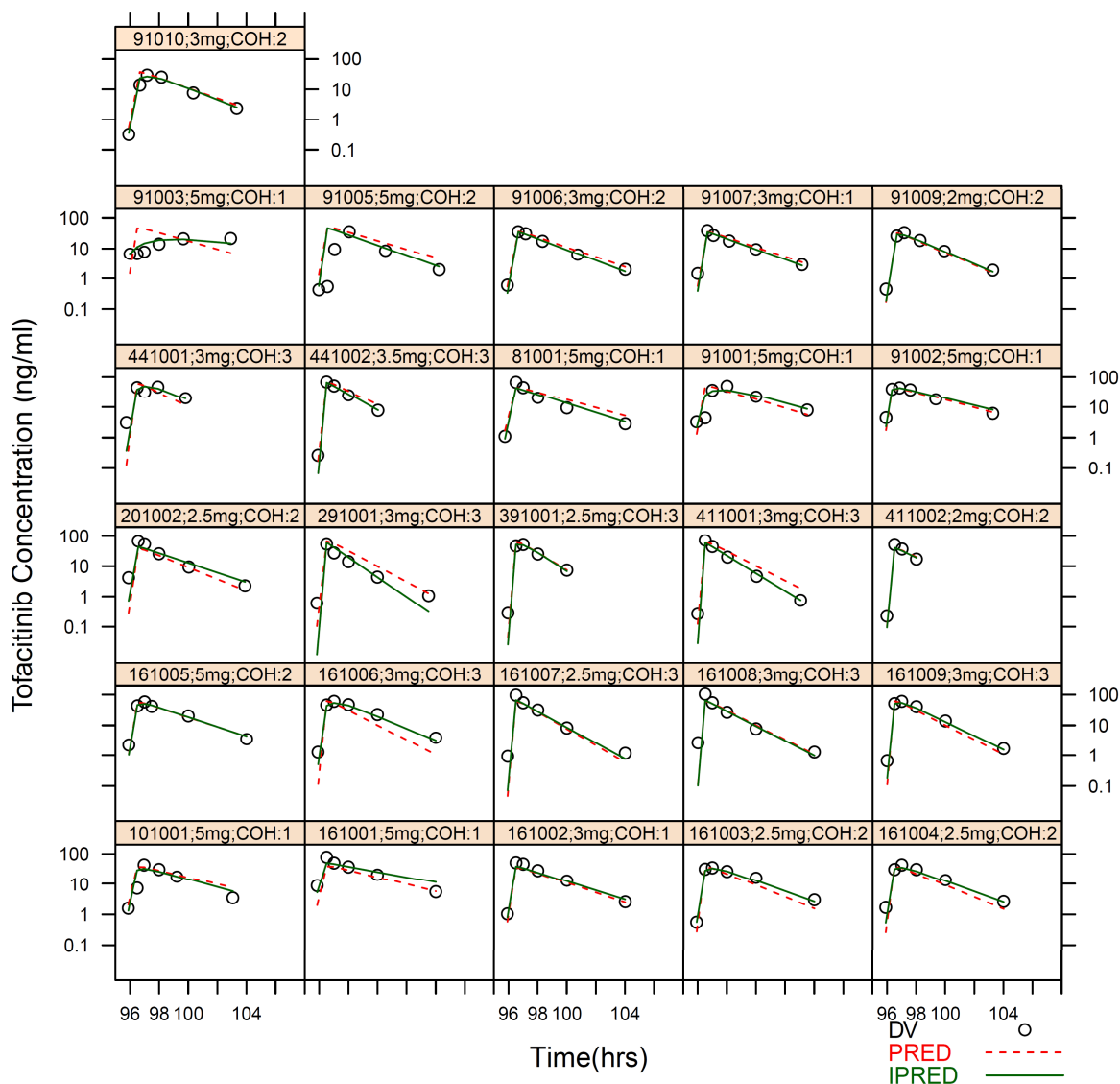
## Results

The Tofacitinib POPPK dataset from A3921103 consisted of 26 subjects (9 males and 17 females) and 151 plasma concentrations with mean ages of 14.1 years, 9.4 years, and 4 years for Cohort 1 (12 - <18 years), Cohort 2 (6 - <12 years), and Cohort 3 (2 <6 years), respectively. Median baseline body weights were 54.0 kg, 32.4 kg, and 17.3 kg for Cohort 1, Cohort 2, and Cohort 3, respectively, and mean CRP values were 3.8 mg/L, 5.7 mg/L, and 20.2 mg/L for Cohort 1, Cohort 2, and Cohort 3, respectively. The total number of subjects who received 2, 2.5, 3, and 5 mg BID doses was 1, 5, 10, and 8, respectively.

The final PK model was a one compartment model with first order absorption. Inter subject variabilites (IIV) on CL/F and Ka were modeled as exponential error models. The IIV for CL/F and V/F were assumed to be correlated. Covariance was assumed between CL/F and Ka. Residual random effects were described with a combination of proportional and additive error models.

In the final model, BWT was incorporated as power functions, normalized to standard adult weight of 70 Kg on CL/F and V/F. Although effect of formulation was explored as a potential predictor of the difference in absorption rate between tablet and solution formulation; the limited data did not support estimating separate Ka for each formulation. Individual predicted concentrations from the final model overlaid with population predictions and observed concentrations are shown in [Figure S1](#).

**Figure S1. Observed Individual Concentrations overlaid with IPRED and PRED from final model vs. Time after Dose**



ePharm Artifact ID: 10911469

The POPPK final model parameter estimates (%RSE) for the reference individual (Body weight 70 Kg), and the bootstrap generated 95% CI for each are provided in [Table S3](#). The diagnostic plots including visual predictive check (VPC) plots indicate that the final model described the tofacitinib concentrations well, adequately describing the concentration-time profiles for tofacitinib in subjects with JIA. The goodness of fit (GOF) plots and the VPC plots (comparing predicted AUC and  $C_{max}$  values from 500 simulations to range of observed values) are provided in [Figure S2](#) through [Figure S5](#).

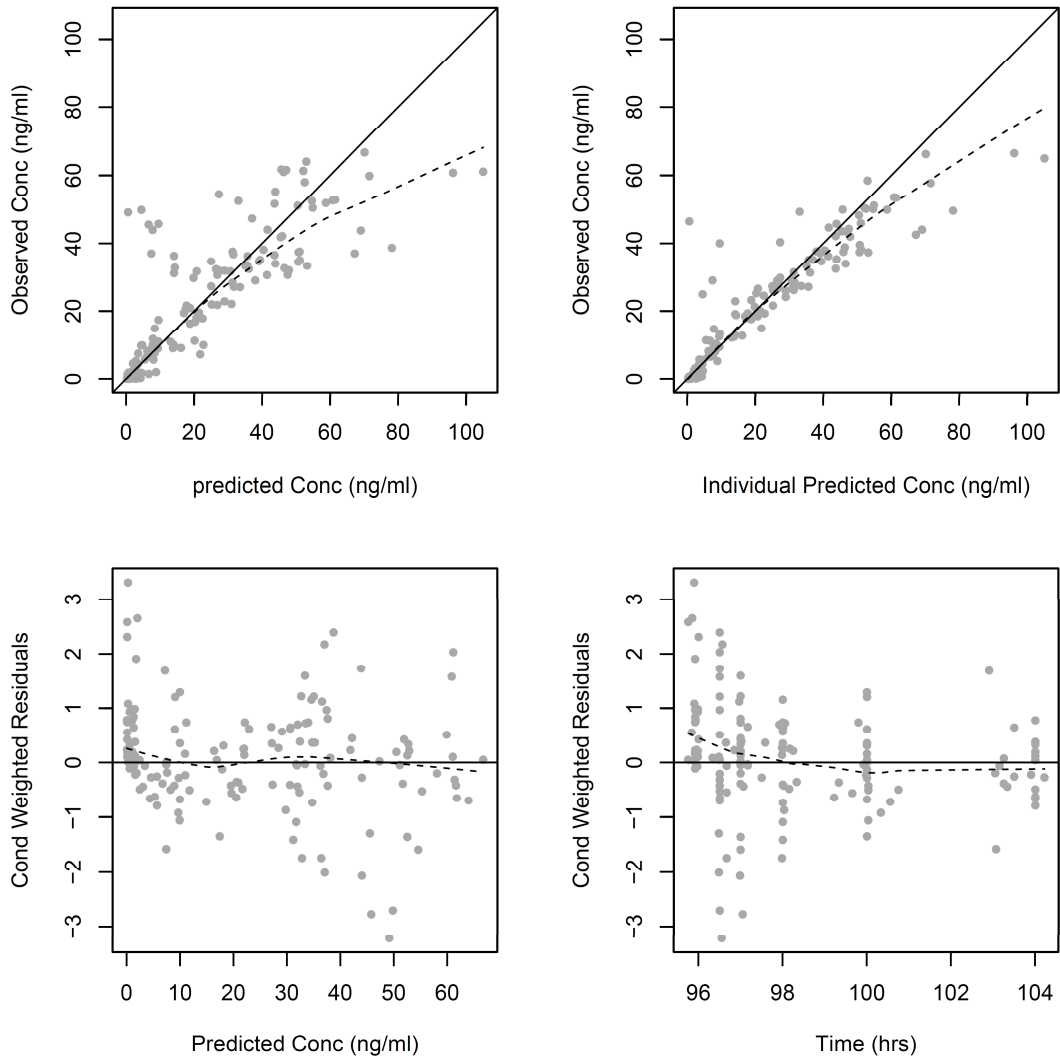
**Table S3. Parameter Estimates of the Final Model**

<b>Parameters</b>	<b>Point Estimate</b>	<b>%RSE<sup>a</sup></b>	<b>95% CI (Bootstrap)<sup>b</sup></b>
CL/F (L/h)	30.4	11.8	25.0-36.5
IIV on CL/F	20.3 (CV%)		
V/F (L)	114	8.9	99.1-131.1
Ka (hr <sup>-1</sup> )	4.53	18.1	3.02-60490
IIV on Ka	122.9 (%CV)		
Inter Individual Variance			
$\Omega^2_{CL/F}$	0.041	41.1	0.005-0.083
Scalar for IIV on V/F	0.232	103.4	0.001-0.795
$\Omega^2_{Ka}$	1.51	70.2	0.044-50.4
Residual Variance			
Prop. Error CV	30.0	32.6	22.7-38.7
Add Error	1.17	62.6	0.0242-2.57
BWT on CL/F	0.292	40.1	0.125-0.525
BWT on V/F	0.843	12.3	0.621-0.993
Objective Function Value	679.731		

a: ePharm Step ID: 604030; b: ePharm Artifact ID: 10911883

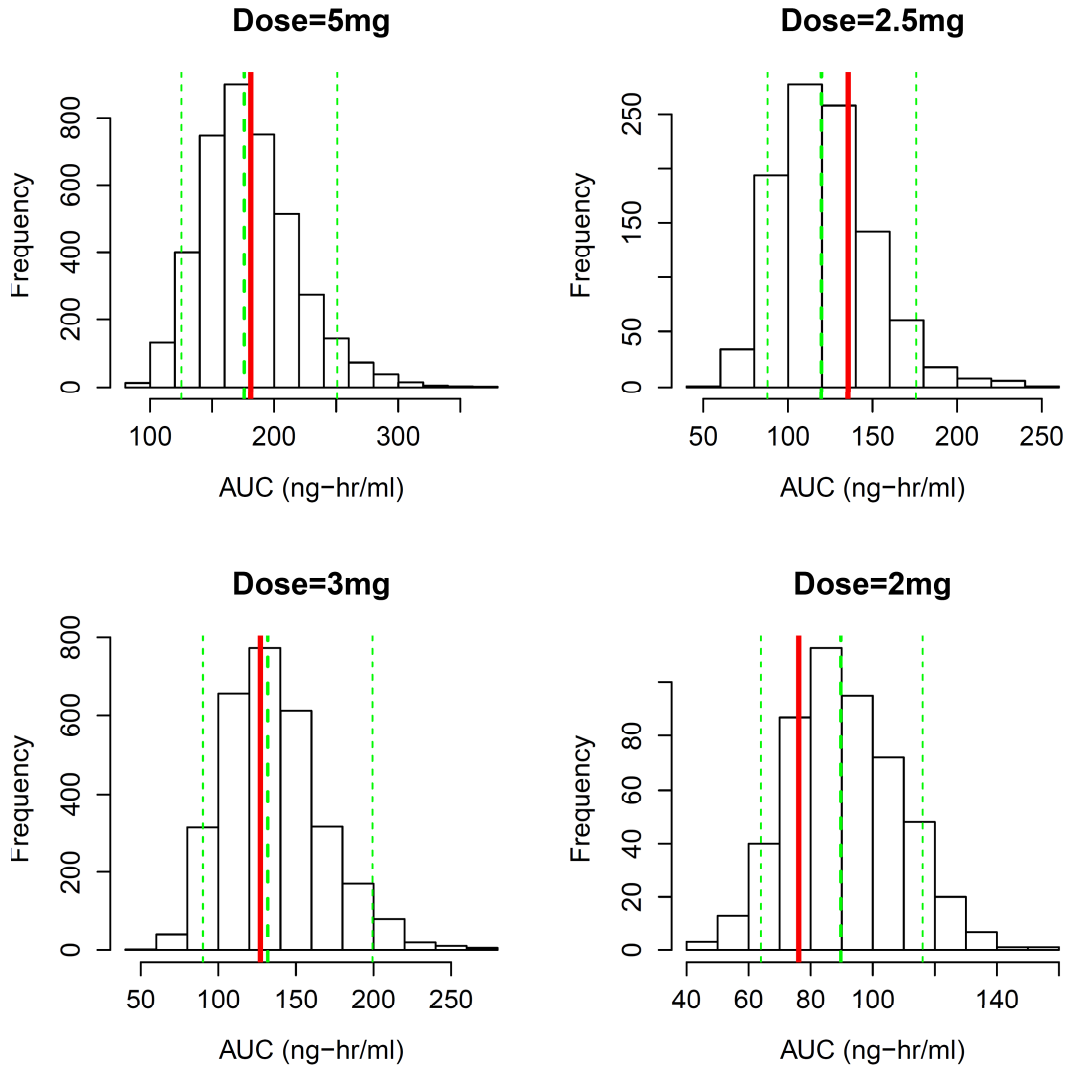


**Figure S2. Goodness of Fit Plots**



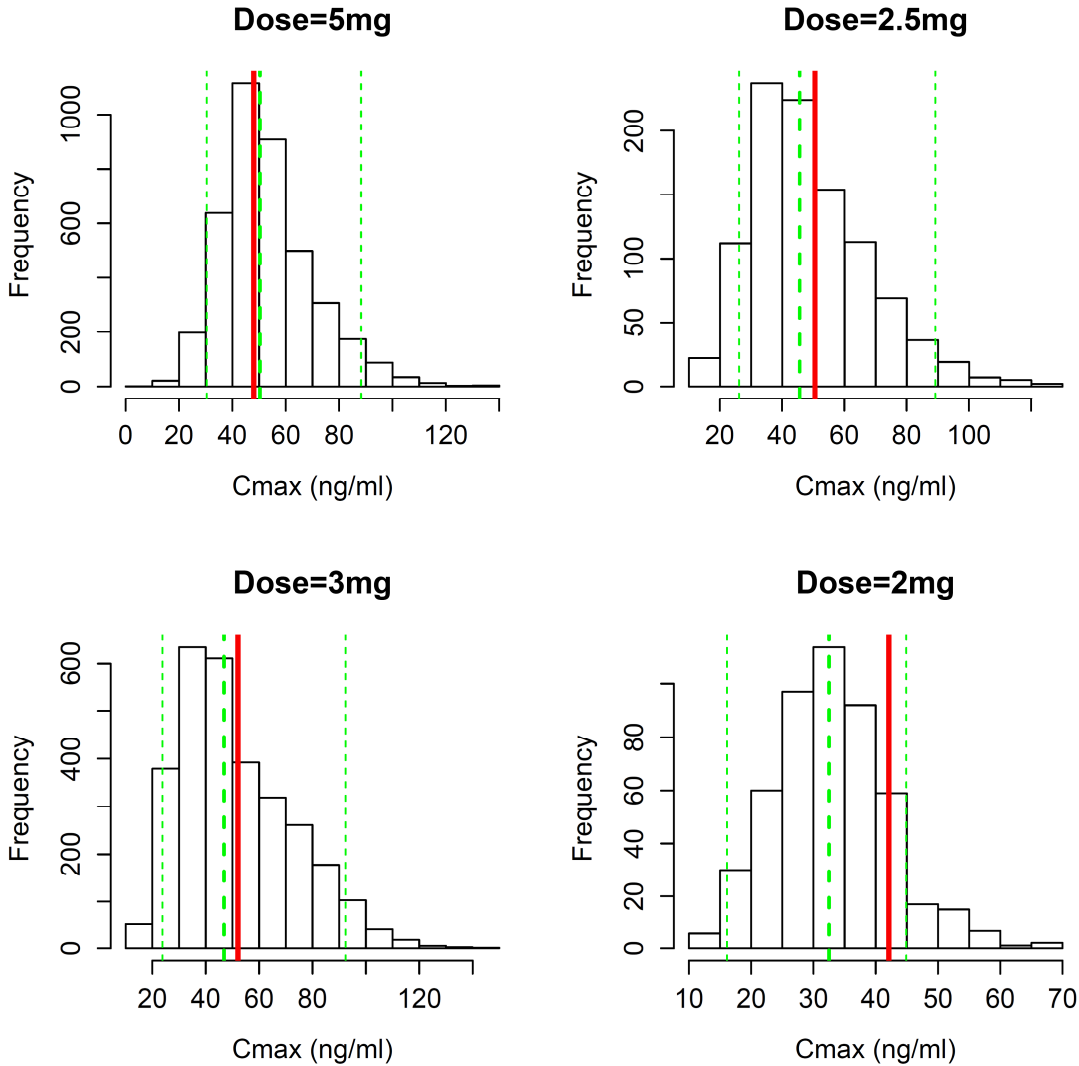
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**Figure S3. Visual Predictive Check Plots Comparing distribution of  $AUC_{ss}$  values (green: 90% PI) at various dose groups from simulations (N=500) to the observed (red) exposure metrics**



ePharm Artifact ID: 10919998

**Figure S4. Visual Predictive Check Plots Comparing distribution of  $C_{\max,ss}$  values (green: 90% PI) at various dose groups from simulations (N=500) to the observed (red) exposure metrics**



Epharm Artifact ID: 10919998

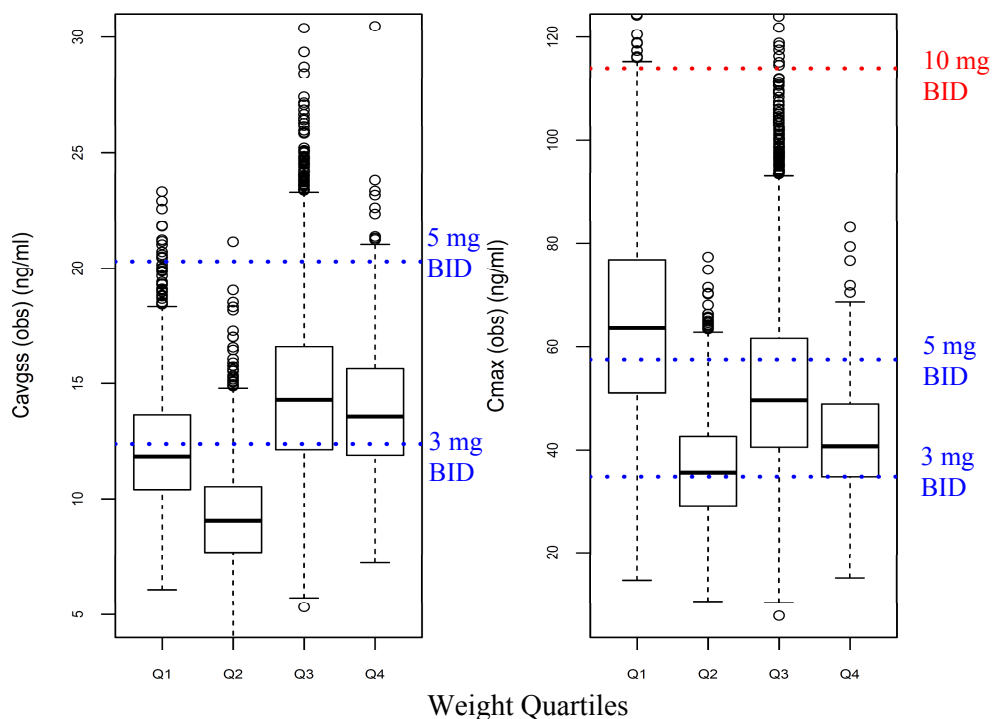
Some inferences could be made using the parameters from the final model:

- Subjects with 12 kg (median weight for 2 yr old girls), 20 kg (median weight for 6 yr old girls) and 40.5 kg (median weight for 12 yr old boys) body weights are estimated to have ~40%, ~31% and ~15% lower CL/F, respectively, compared to the CL/F of a subject with 70 kg body weight;
- Subjects with 12 kg (median weight for 2 yr old girls), 20 kg (median weight for 6 yr old girls) and 40.5 kg (median weight for 12 yr old boys) body weights are estimated to have ~77%, ~65% and ~37% lower V/F, respectively, compared to the V/F of a subject with 70 kg body weight;

- Clearance (CL/F) of a typical 70 kg JIA subject (30.4 L/h) is approximately 65% higher than in RA subjects (18.4 L/h).
- The reason for this difference in CL/F values could possibly be due to higher degree of systemic inflammation in adult RA subjects inhibiting metabolizing enzymes for tofacitinib.

Simulations (N=500) were performed using the parameters from the final model and their between-subject variability to predict secondary exposure metrics at steady state (area under the concentration-time curve at steady state (AUC) and maximum concentration post-dose [ $C_{max}$ ]) at the doses used in the A3921103 study. From the predicted AUC and  $C_{max}$  values, demonstrated in Figure S5, it is evident that over the range of weights examined, higher doses were needed to reach an efficacy target  $C_{avg,ss}$  of 21 ng/ml, the 5 mg BID equivalent in adult RA patients). However, concentrations were well within the range of 3 mg BID dose in adult RA patients (Figure S5, left panel). Also, there appears to be discordance between  $C_{avg,ss}$  and  $C_{max,ss}$ , rendering  $C_{max,ss}$  values that closely approximate median  $C_{max,ss}$  values in adult RA subjects after 5 mg BID dose unlike  $C_{avg,ss}$ .

**Figure S5. Impact of Weight on the Pharmacokinetics of Tofacitinib (The dotted lines indicate the median values of relevant exposure metrics at given doses)**



Q1: 13.9-24.5 kg, Q2: 24.5-38.4 kg, Q3: 38.4-53.3 kg, Q4: 53.3-70.9 kg.

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### Dose Selection for Phase 3 Study of Tofacitinib in Polyarticular JIA subjects

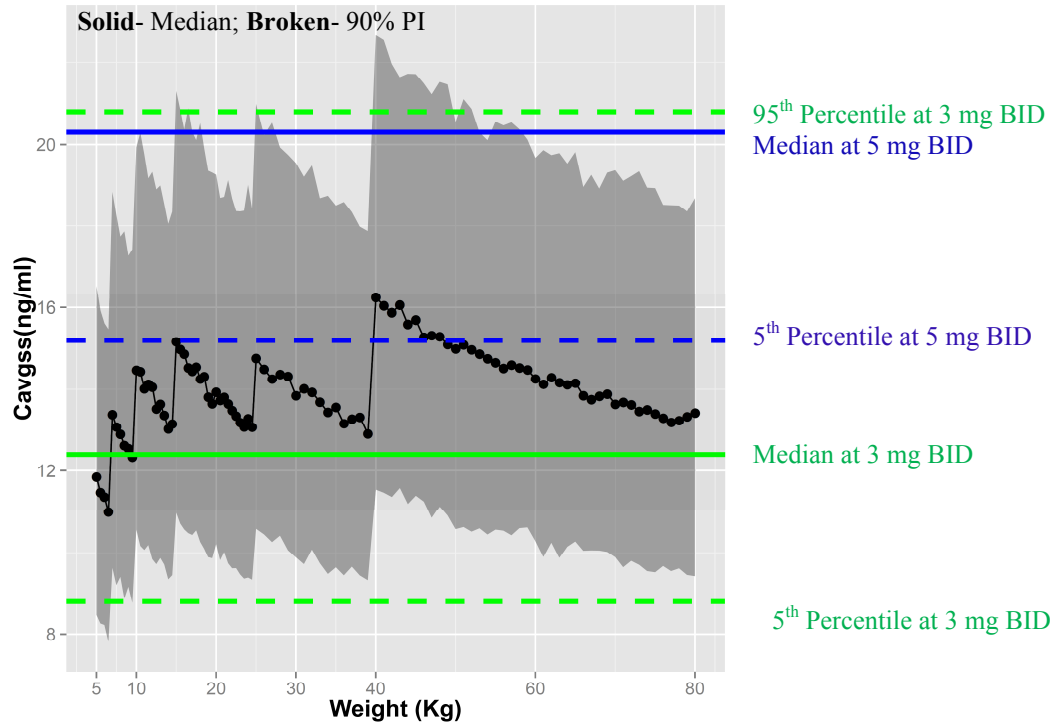
Based on the premise of matching exposures (primarily  $C_{avg,ss}$ ) observed in adult RA subjects, doses not exceeding the most widely approved dose of 5 mg BID (primarily in subjects >40 kg), and conditional on the available A3921103 data and analysis, various dosing schemes were simulated using the POPPK final model parameters and inter-subject parameter variabilities. Doses were identified that are expected to provide steady state exposure metrics similar to those from adult RA subjects following a 3 mg BID dose. The final dosing scheme proposed for Study A3921104 is given in [Table S5](#). In order to provide a practical dosing scheme based on age range and body weight, the body weight categories were specified such that the differences between the doses administered, and the doses required based on body weight, were not substantial.

**Table S5. Dosing Scheme in A3921104**

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

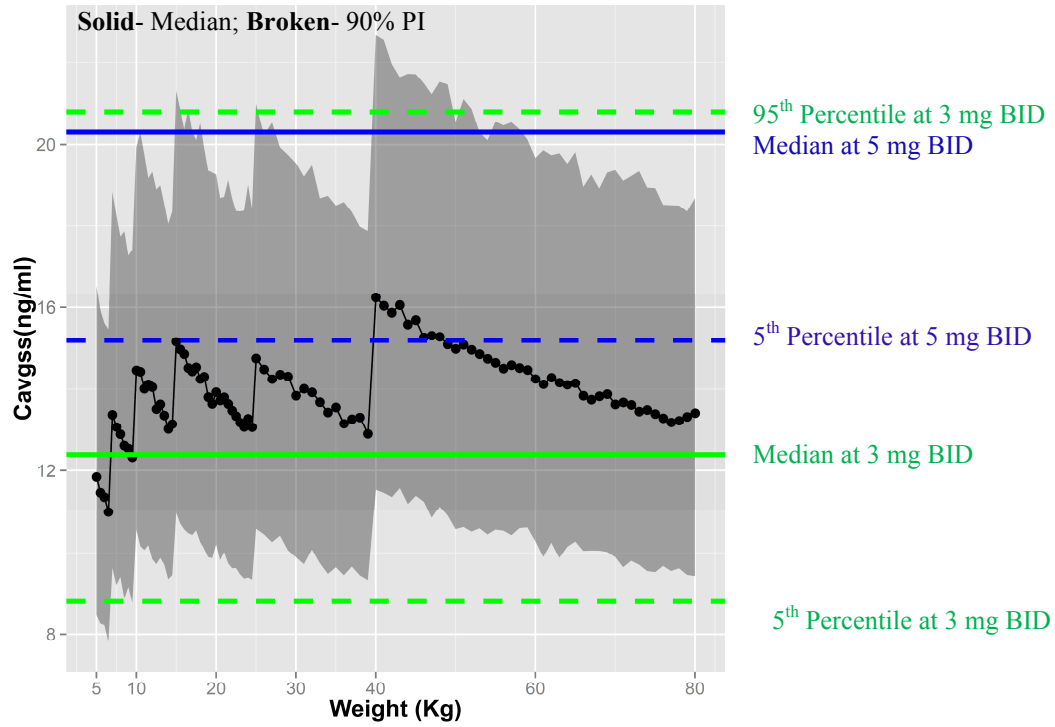
Based on the dosing scheme illustrated in [Table S5](#), steady state  $C_{avg,ss}$  and  $C_{max,ss}$  values were simulated. The predicted steady state  $C_{avg}$  and  $C_{max}$  (median and 90% PI) values are depicted in [Figure S6](#) and [Figure S7](#), overlaid with median and 90% CI of corresponding exposure metrics in RA subjects following 3, 5 and 10 mg BID doses as relevant.

**Figure S6. Predicted Average Steady-State Concentrations of Tofacitinib in Pediatric Subjects (JIA) with Weights Ranging from 5-80 Kg (Red and green solid and broken lines indicate Tofacitinib  $C_{avg,ss}$  in adult RA subjects)**

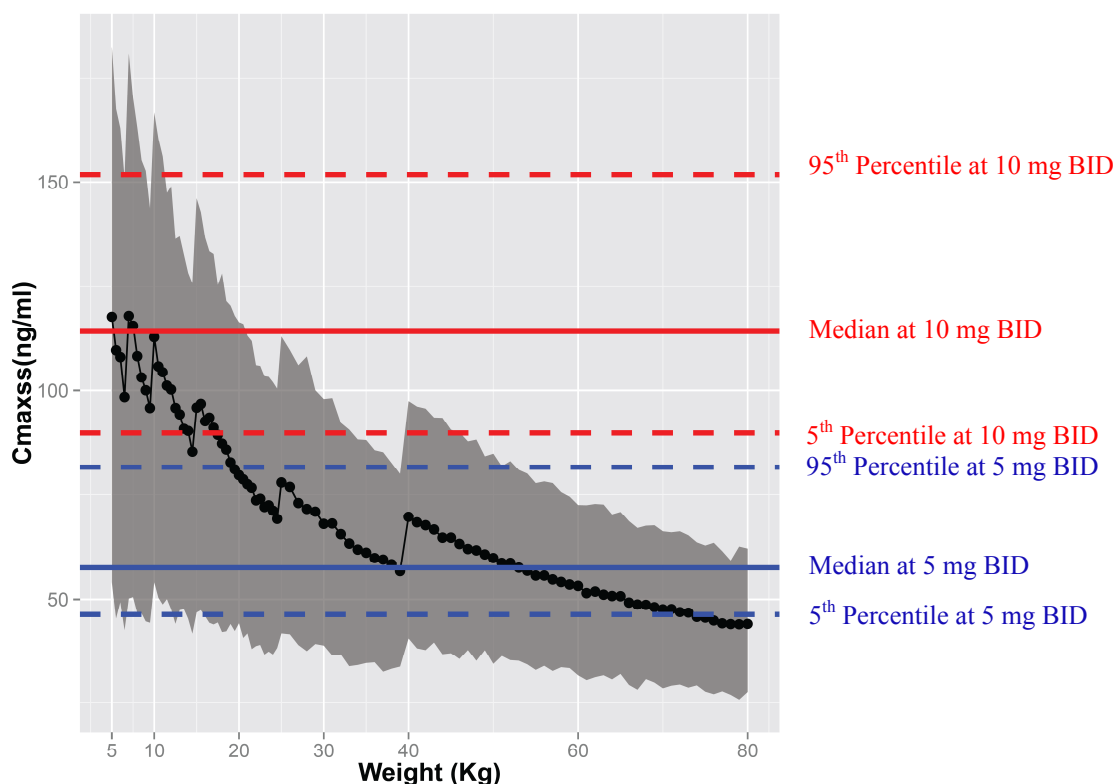


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**Figure S7. Predicted Maximum Steady-State Concentrations of Tofacitinib in Pediatric Subjects (JIA) with Weights ranging from 5-80 Kg (Red and green solid and broken lines indicate Tofacitinib  $C_{max,ss}$  in adult RA subjects)**



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ePharm Artifact ID: 10919369

## Conclusions

The population PK of tofacitinib in subjects with JIA was adequately described by a one-compartment model with first order absorption.

The power coefficients relating body weight to CL/F and V/F were lower than 0.75 and 1, respectively; nevertheless, CL/F and V/F decreased with decreasing body weight warranting dose adjustment at lower body weight.

Clearance (CL/F) of a typical 70 kg JIA subject (30.5 L/h) was approximately 65% higher than that for a typical adult RA subject (18.4 L/h). Variability in subjects with JIA was higher than the corresponding estimates in RA subjects - possibly due to limited number of subjects.

Considering the PK characteristics of tofacitinib in JIA subjects and benefit/risk profile of tofacitinib in adult RA patients, the doses for adolescent patients (body weight  $\geq 40$  kg) were capped at the maximum dose of 5 mg BID and doses for patients with  $< 40$  kg body weight were derived to achieve  $C_{avg,ss}$  equivalent to exposures in adolescent subjects. The predicted concentrations at the proposed doses for Study A3921104 will be equivalent to adult RA subjects receiving doses of 3-5 mg BID.



## Appendix 8. Body Surface Area (BSA)

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

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

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

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

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

## Appendix 9. Physician's Global Assessment of Psoriasis

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

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

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

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

- (0) Clear, except for residual discoloration
- (1) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 1**
- (2) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 2**
- (3) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 3**
- (4) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 4**
- (5) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 5**

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

- If total average  $\leq 1.49$ , score = 1;
- If total average  $\geq 1.50$ , score = 2.

## **Appendix 10. By Visit Assessment of the Degree of Burden and Risk Threshold During the Trial (Investigative Sites in Germany Only)**

As written in the protocol under the [Schedule of Activities](#) and [Section 6](#) and here summarised, at each visit (initially every two weeks and thereafter at 4 to 6 weekly intervals), the investigator will complete the following (including, but not limited to):

1. A medical history which includes at least one conversation regarding the child's wellbeing, generally at the beginning of the study and at each visit,
2. A physical examination including vital signs, growth, and maturation,
3. Laboratory testing, eg, haematology and liver enzymes, etc.,
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, the Tender Entheses Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Assessment for enthesitis related arthritis, psoriatic body surface area assessment; the Physician's Global Assessment (PGA) for psoriatic arthritis,
5. The investigator also will assess for flare and ACR responses 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 9.7](#), 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<sup>23</sup> 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 6](#) "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.