Official Title: **A PHASE IV STUDY TO EVALUATE DECREASED DOSE FREQUENCY IN PATIENTS WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA) WHO EXPERIENCE LABORATORY ABNORMALITIES DURING TREATMENT WITH TOCILIZUMAB**

NCT Number: NCT01734382

Document Date: Protocol Version 3: 07 January 2016

PROTOCOL

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PROTOCOL NUMBER:	WA28029
VERSION NUMBER:	3
EUDRACT NUMBER:	2012-000444-10
IND NUMBER:	11972
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 16 July 2012
DATES AMENDED:	Version 2: 18 March 2013 Version 3: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	07-Jan-2016 19:25:33

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol WA28029 has been amended to include the addition of a preliminary **screening** assessment (Screening Evaluation 1) and a run-in phase of ≤24 weeks (Part 1). The proposed modifications are intended to increase enrollment by helping to identify patients with resolved laboratory abnormalities in Part 1 on the tocilizumab (TCZ) Q2W regimen who will be eligible to participate in the decreased dose frequency phase (Part 2).

The preliminary screening evaluation (Screening Evaluation 1) followed by a run-in phase (Part 1) of ≤24 weeks will enable both TCZ naive and non-naive patients to enter the study. Patients who fulfil all eligibility criteria in the Screening Evaluation 1 may enter Part 1 and receive TCZ dosed by body weight (12 mg/kg for patients <30 kg; 8 mg/kg for patients ≥30 kg) by IV infusion Q2W until they experience an event of neutropenia, thrombocytopenia, or liver enzyme abnormality as per the criteria provided in Section 4.1, Table 5. Following the occurrence and resolution of this laboratory abnormality, patients who have a successful final screening evaluation (Screening Evaluation 2) may enter the main study (Part 2), which will evaluate a reduction on TCZ dosing frequency to Q3W and Q4W. Patients who have experienced a resolved laboratory abnormality on commercially available TCZ Q2W may enter Part 2 directly without participating in Part 1, as per the initial protocol, following a successful screening evaluation (Screening Evaluation 2) (Section 3.1.1, Synopsis, and Appendix 1).

Additional changes to the protocol are as follows:

- Change in the time between diagnosis of systemic juvenile idiopathic arthritis (sJIA) and treatment with biologics from 6 months to 1 month for entry into Part 1 and 2. This change is to align with the 2013 update of the American College of Rheumatology recommendations (Ringold et al. 2013) for the treatment of children with sJIA, which allows earlier therapy with biologic agents (including TCZ) (Section 4.1).
- Change in the requirement for withdrawal from Part 2 due to flare from an obligatory requirement to withdraw to withdrawal at the discretion of the investigator (Sections 3.1.1, 3.1.2.1, 3.1.2.2, 3.1.3, 3.4.1, 4.5.1.1, 6.4).
- Clarify that the patient must have 5 consecutive Q3W infusions (12 weeks on Q3W) before moving onto Q4W dosing (Section 3.1.1, 3.1.2.1, 3.1.2.2., 4.2.2.1).
- The requirement to collect growth velocity as data (for assessment of growth rate and Tanner stages) was removed as it is not required to be collected for this study (Section 4.4.1.2).
- Clarify that samples for anti-TCZ antibodies, TCZ PK, and sIL-6R will be collected for patients who prematurely withdraw (at Withdrawal Visit 1) (Appendix 1).

- Clarify the conditions under which a chest radiograph is required at study entry. A chest X-ray is only required at screening for patients who test positive for tuberculosis [TB] and have not previously received TB treatment (Section 4.4.1.11).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 3: SUMMARY OF CHANGES

GLOBAL CHANGES

"Non-serious" was removed when referring to serious adverse events of special interest throughout the protocol.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.1: BACKGROUND ON SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

…Anakinra, a receptor antagonist to interleukin (IL)-1, has met with some success for the treatment of the systemic complaints associated with sJIA but has not been utilized as frequently as expected due to the daily requirements for a subcutaneous injection (Haines 2007). *Canakinumab is an antagonist to the cytokine IL-1β and was approved in the EU in September 2013 for the treatment of sJIA in patients aged 2 years and older who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.…*

SECTION 1.2: BACKGROUND ON TOCILIZUMAB

TCZ ~~8 mg/kg~~ IV has been approved in more than 110 countries, including Japan, the European Union, and the United States, for use in adult patients with *moderately to severely active* RA who have an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs) *including* ~~and/or~~ tumor necrosis factor (TNF) antagonists (Summary of Product Characteristics for RoACTEMRA ~~2009~~; ACTEMRA®, English-Translated Version 7 ~~2008~~). ~~In the United States, TCZ IV has been approved in patients with RA who have had an inadequate response to TNF antagonist therapies~~ (USPI for ACTEMRA® [tocilizumab] ~~2011~~). Additionally, TCZ was approved for use in JIA, sJIA, and Castleman's disease in India and Japan (ACTEMRA®, English Translated Version 7 ~~2008~~). TCZ is approved for the treatment of active sJIA arthritis in patients 2 years of age and older in several countries, including Japan, India, Switzerland, Mexico, the European Union and the United States. In the United States and European Union, the approved dose regimen is 8 mg/kg every 2 weeks (Q2W) for sJIA patients weighing $\geq$30 kg and 12 mg/kg Q2W for sJIA patients weighing $<$30 kg (Summary of Product Characteristics for RoACTEMRA ~~2009~~; USPI for ACTEMRA® [tocilizumab] ~~2011~~).

SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The efficacy and safety of TCZ in children with sJIA was demonstrated in the ~~ongoing~~ pivotal study, WA18221.…

Patients who have experienced a laboratory abnormality on Q2W TCZ may benefit from reducing their TCZ dose by increasing the interval between doses to 3 or 4 weeks.

Increasing the TCZ dosing interval carries the risk of underexposure to drug leading to disease flare or MAS but the likelihood of this is reduced in this study by recruiting patients *into Part 2* with good disease control and reducing the dosing interval in a controlled stepwise manner (to every 3 weeks [Q3W] then every 4 weeks [Q4W] if required).

SECTION 2: OBJECTIVES *FOR PART 2*

SECTION 2.1: EFFICACY OBJECTIVE

The primary efficacy objective for *Part 2 of* this study is as follows:

- To explore the efficacy of TCZ in reduced dosing frequency regimens (Q3W and Q4W, as appropriate) using Juvenile Arthritis Disease Activity Score (JADAS)-71, JIA flare, and fever *(attributable to sJIA).*

SECTION 2.2: SAFETY OBJECTIVE

The safety objective for *Part 2 of* this study is as follows:

- To evaluate the safety of TCZ in reduced dosing frequency regimens

SECTION 2.3: PHARMACODYNAMIC OBJECTIVE

The primary pharmacodynamic (PD) objective for *Part 2 of* this study is as follows:

- To describe the pharmacodynamics, using sIL-6R and C-reactive protein (CRP), and immunogenicity of TCZ in reduced dosing frequency regimens

SECTION 2.4: PHARMACOKINETIC OBJECTVE

The pharmacokinetic (PK) objective for *Part 2 of* this study is as follows:

- To describe the pharmacokinetics of TCZ in reduced dosing frequency regimens

SECTION 2.5: PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for *Part 2 of* this study are as follows:

- To describe parent/patient global assessment of ~~disease activity~~ *overall well-being* with TCZ in reduced dosing frequency regimens.

SECTION 3.1.1: Overview

This is a *96*~~52~~-week*, 2 part*, Phase IV study to explore the efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity of TCZ in reduced dosing frequency regimens in patients with adequately controlled sJIA (JADAS Minimal Disease Activity cut-off of 3.8 at screening and baseline *for Part 2*~~[Consolaro et al. 2012]~~) who have experienced a laboratory abnormality which has resolved (per inclusion criteria in Section 4.1.1) ~~at any time~~ on TCZ twice weekly dosing. ~~Following a successful screening evaluation,~~

Run-In Phase (Part 1)

At the Screening Evaluation 1 (see Appendix 1-A), TCZ naive patients or TCZ non-naive patients who fulfil all eligibility criteria for Screening Evaluation 1 may enter the open-label run-in phase (Part 1) and receive TCZ dosed by body weight

(12 mg/kg for patients <30 kg; 8 mg/kg for patients ≥30 kg) by IV infusion Q2W for up to 24 weeks or until they experience a laboratory abnormality of neutropenia, thrombocytopenia, or liver enzyme abnormality as per the criteria provided in Table 5. The TCZ dose will be calculated using the baseline body weight (<30 kg or ≥30 kg) and will not be changed until a patient's weight falls into the other body weight category on three separate, consecutive occasions in Part 1. Patients will be assessed Q2W for safety. No reductions or changes of concomitant MTX dosing can occur during Part 1 of the study (i.e., due to improvement or worsening of symptoms) except for documented safety reasons.

Patients who do not experience a laboratory abnormality in Part 1, or experience a laboratory abnormality but do not meet the eligibility criteria for Part 2, will complete Part 1 through to Week 24, followed by the Part 1 withdrawal visits.

Main Study (Part 2)

Patients on TCZ Q2W who have experienced a laboratory abnormality (per Table 5; either during Part 1 or prior to the study) that has subsequently resolved, who have adequate disease control, *and* who fulfil all the inclusion criteria and none of the exclusion criteria *of Screening Evaluation Part 2, may enter the main study (Part 2). Once patients have entered Part 2 of the study, they* will receive TCZ dosed by body weight (12 mg/kg for patients <30 kg; 8 mg/kg for patients ≥30 kg) by IV infusion Q3W for a minimum of 4*5* consecutive infusions. The dose will be calculated using ~~the~~ *Part 2 baseline* body weight and will not be changed during the first 12 weeks of the *Part 2 of the* study. Patients *on Q3W* will be assessed ~~Q3W~~ for safety and efficacy responses. No reductions or changes of concomitant NSAIDs, corticosteroids, or MTX dosing can occur during the first 12 weeks of *Part 2 of* the study (and until *5* ~~4~~ consecutive Q3W infusions have been given) except for documented safety reasons, including laboratory abnormalities. In addition, the doses of NSAIDs, corticosteroids, and MTX should remain stable in any patient who moves to Q4W dosing, during the first 12 weeks of Q4W dosing.

In Part 2, e~~E~~ach patient will start and maintain Q3W dosing of TCZ in the study up to 52 weeks unless the patient experiences an event of neutropenia, thrombocytopenia, or liver enzyme abnormality as per the criteria provided in Section 3.1.2. Following the occurrence and resolution of this laboratory abnormality, patients who have maintained adequate disease control *(JADAS ≤ 3.8 and absence of fever attributable to sJIA)* will move to Q4W dosing of TCZ. Patients who have not completed a minimum of ~~4~~ *5* consecutive Q3W infusions will remain on Q3W dosing until *5*~~4;~~ consecutive Q3W doses have been completed before moving to Q4W dosing. If during this time, a patient should experience any additional laboratory abnormalities as per the criteria provided in Section 3.1.2, he or she may move directly to Q4W dosing after resolution, at the discretion of the investigator, and the Sponsor must be notified.

Patients who do not meet the criteria to switch from Q3W to Q4W will complete Part 2 through to Week 52, followed by the Part 2 withdrawal visits.

Patients who experience a JIA flare or fever attributable to sJIA (see definition in Section 4.5.1.1) at any time *during Part 2* ~~will~~*may* be withdrawn from the study *at the discretion of the investigator.*

Patients will undergo safety *and safety laboratory assessments during Part 1 of the study. Safety, safety* laboratory, PK, PD, and efficacy assessments *will be performed during Part 2* as described in the schedule of assessments (see Appendix 1). *During Part 1, and* ~~A~~*a*fter the first 12 weeks *of Part 2* of the study, the dose of TCZ can be adjusted according to changes in body weight: if a patient's body weight increases above 30 kg ~~for~~ *on* 3 ~~successive~~ *consecutive* visits (while it was below 30 kg at baseline *for Part 1 or Part 2, respectively*), on the third visit the dose of TCZ will be decreased to 8 mg/kg; if a patient's body weight decreases below 30 kg (while it was above 30 kg at baseline *for Part 1 or Part 2, respectively)* ~~for~~ *on* 3 ~~successive~~ *consecutive* visits, the dose of TCZ will be increased on the third visit to 12 mg/kg.

All patients who are discontinued from *Part 1 or Part 2 of* the study for any reason must return for the Withdrawal Visit 1 and ~~for~~ follow-up safety assessments*,* ~~(~~Withdrawal Visits 2, 3, *and* 4*,*~~)~~ up to and including 12 weeks after the last administration of study drug. They may be required to return for visits beyond 12 weeks after discontinuation from treatment with TCZ for safety reasons (to be documented in the electronic Case Report Form [eCRF] and interactive voice response system [IXRS]).

Figure 1 below provides an overview of ~~the proposed~~ Phase IV *of this* study design.

SECTION 3.1.2: Management of Laboratory Abnormalities and TCZ Dose Frequency

Management of neutropenia, thrombocytopenia, and elevated liver function tests to be implemented in this protocol for patients *in Part 1 and Part 2* ~~who have achieved a JADAS 71 minimal disease activity of 3.8 at screening and at baseline (and maintained adequate disease control at the time of any subsequent laboratory abnormalities experienced during the study)~~ are summarized below.

SECTION 3.1.2.1: Hematologic Abnormalities

For patients *in Part 1 and Part 2* ~~(achieving and maintaining a JADAS 71 minimal disease activity of 3.8)~~, the laboratory abnormality guidance in Table 2 *and* Table 3~~, and Table 4~~ should be followed. Patients experiencing a JIA flare or fever attributable to sJIA should be withdrawn from the study *(at the discretion of the investigator).*

SECTION 3.1.2.2: Elevated Liver Enzymes

For patients in Part 1 and Part 2, the laboratory abnormality guidance in Table 4 should be followed. Patients experiencing a JIA flare or fever attributable to sJIA should be withdrawn from the study (at the discretion of the investigator).

SECTION 3.1.3: Criteria for Withdrawal from the Study

Patients who experience a JIA flare or fever attributable to sJIA *relative to baseline of Part 2* (as per the definition provided in Section 4.4.1.1) at any *visit in Part 2 of* ~~time on~~ the study ~~or experience fever associated with sJIA at any visit will~~ *may* be withdrawn from the study *at the discretion of the investigator*.

Patients who experience any adverse event that in the opinion of the investigator or the Sponsor precludes further study participation *(in Part 1 or 2)* will be withdrawn from the study.

SECTION 3.3.1: Rationale for Test Product Dosage

In Part 2 of the study, i~~I~~nstead of being given Q2W, TCZ will be administered IV every 3 or 4 weeks for up to 1 year in patients who have previously experienced at least one laboratory abnormality on the previous Q2W dose regimen *(either in Part 1 or on commercial TCZ prior to entry into Part 2).* Efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity will be assessed upon reduction of dosing frequency in these patients.

SECTION 3.4.1: Efficacy Outcome Measures

The efficacy outcome measures for *Part 2 of* this study are as follows:

- JIA flare *relative to baseline of Part 2* will be used to determine those patients not maintaining efficacy who ~~are to~~ *can* be withdrawn from the study *at the discretion of the investigator* (as per Section 4.5.1.1).
- Fever *(attributable to sJIA)* will be measured at each study visit *of Part 2* in patients on Q3W and Q4W dosing (as appropriate) to describe efficacy and to determine patients not maintaining efficacy *who* ~~are to~~*can* be withdrawn from the study *at the discretion of the investigator* (as per Section 4.5.1.1 and Section 4.5.1.2).

SECTION 3.4.2: Safety Outcome Measures

The safety outcome measures *in Part 1 and 2 of* this study are as follows:

SECTION 3.4.3: Pharmacokinetic and Pharmacodynamic Outcome Measures

The PK/PD outcome measures for *Part 2 of the* study are as follows:

SECTION 3.4.4: Patient-Reported Outcome Measures

The PRO outcome measures for ~~this~~*Part 2 of the* study are as follows:

- The CHAQ (see Appendix 2)
- Parents/patients global assessment of ~~disease activity~~*overall well-being*

SECTION 4.1: PATIENTS

Children aged 2 years up to and including aged 17 years with sJIA ≥ *1*~~6~~ month~~s~~ and currently receiving TCZ who have experienced a predefined, resolved laboratory

abnormality (see Section 4.1.1, Inclusion Criteria *Part 2*4) ~~at any time~~ during TCZ Q2W treatment will be eligible to participate in ~~this~~*Part 2 of the* study.

SECTION 4.1.1: Inclusion Criteria

Part 1 and Part 2

All patients entering Part 1 or entering Part 2 without participating in Part 1~~Patients~~ must meet the following criteria for ~~study~~ entry *into Part 1 or Part 2*:

- *sJIA symptoms lasting for at least 1 month since diagnosis of sJIA*
- Fertility:

  ~~Female not of child bearing potential, or~~

  ~~Female of child bearing potential practicing effective contraceptive measures, having a negative urine pregnancy test within 3 weeks prior to randomization; or~~

  ~~Sterile male, or~~

  ~~Non-sterile male practicing effective contraceptive measures with female partner of child bearing potential. (Females of childbearing potential must be using a reliable means of contraception [abstinence being a possible option] throughout the study and up to 12 weeks after the last infusion of study drug.)~~

  For female patients of reproductive potential (unless surgically sterile with absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose of TCZ

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of < 1% per year include tubal ligation; male sterilization; hormonal implants; established, proper use of combined oral or injected hormonal contraceptives; and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods, such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

  For male patients of reproductive potential: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose of TCZ

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation,

symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Must meet one of the following:

  Not receiving MTX or discontinued MTX at least 4 weeks prior to *the Part 1 or Part 2* baseline visit, or

  Taking MTX for at least 12 weeks immediately prior to the *Part 1 or Part 2* baseline visit and on a stable dose of ≤ 20 mg/m^2 for at least 8 weeks prior to the *Part 1 or Part 2* baseline visit, together with either folic acid or folinic acid according to local standard of care

Patients entering Part 1 who are naïve to TCZ therapy must also meet the following inclusion criterion:

- *History of inadequate clinical response (in the opinion of the treating physician) to NSAIDs and corticosteroids*

Part 2

All patients entering Part 2 (either directly without participating in Part 1, or via Part 1) must meet the following additional criteria for entry into Part 2:

- JADAS-71 score of 3.8 or less and absence of fever (related to sJIA) at screening and baseline of Part 2 ~~(Consolaro et al. 2012)~~
- Neutropenia, thrombocytopenia, or elevated ALT/AST (as per criteria in Table 5) previously experienced (and resolved) on the labeled dose (Q2W) of TCZ ~~at any time.~~
- Not currently receiving oral corticosteroids, or taking oral corticosteroids at a stable dose for a minimum of 2 weeks prior to the *Part 2* baseline visit at no more than 10 mg/day or 0.2 mg/kg/day, whichever is less
- Not taking NSAIDs, or taking no more than one type of NSAID at a stable dose for a minimum of 2 weeks prior to the *Part 2* baseline visit, with the dose being less than or equal to the maximum recommended daily dose

SECTION 4.1.2: Exclusion Criteria

Patients *entering Part 1, or entering Part 2 without participating in Part 1,* who meet any of the following criteria will be excluded from study entry:

General

- Not fully recovered from recent surgery or less than 6 weeks since surgery, at the time of screening visit; or planned surgery during *Part 1 and* the initial 12 weeks of *Part 2 of* the study *(for patients entering Part 1) or the initial 12 weeks of Part 2 of the study (for patients entering Part 2 without participating in Part 1)*

General Safety

- Pregnant, lactating, or intending to become pregnant during study conduct and up to *6 months*~~12 weeks~~ after the last administration of study drug

- Significant cardiac [e.g., congenital heart disease, valvular heart disease, constrictive pericarditis (unrelated to sJIA), myocarditis] or pulmonary disease, (e.g., asthma for which the patient has required the use of oral or parenteral corticosteroids for ≥ 2 weeks within 6 months prior to the baseline visit *of Part 1 or Part 2, or* cystic fibrosis)

Laboratory Exclusions at Screening

The following additional laboratory exclusion criteria apply to patients entering Part 1 of the study who are TCZ-naive and are initiating therapy with TCZ:

- *AST or ALT > 1.5 ULN (upper limit of normal for age and sex)*
- *Total bilirubin > 1.3 mg/dL (> 23 µmol/L)*
- *Platelet count < 150 x 10^3/µL (< 150,000/mm^3)*
- *WBC count < 5,000/mm^3 (< 5.0 x 10^9/L)*
- *Neutrophil count < 2,500/ mm^3 (< 2.5 x 10^9/L)*

SECTION 4.2.1.1: Tocilizumab

All TCZ vials must be stored at a controlled temperature of 2°C–8°C, and handled according to Good Manufacturing Practice and Good Clinical Practice (GCP) procedures. A temperature log must be kept recording the storage temperature of the TCZ ~~and placebo~~ and infusion bags at least once a day.

SECTION 4.2.2.1: Tocilizumab

Part 1

TCZ dosed by body weight (12 mg/kg for patients < 30 kg; 8 mg/kg for patients ≥ 30 kg) will be administered IV Q2W for ≤24 weeks or until the patient experiences an event of neutropenia, thrombocytopenia, or liver enzyme abnormality as per the criteria provided in Table 5. Following the occurrence and resolution of this laboratory abnormality, patients who have a final successful screening evaluation (Screening Evaluation 2) may enter Part 2 of the study.

Patients who do not experience a laboratory abnormality in Part 1, or experience a laboratory abnormality but do not meet the eligibility criteria for Part 2, will complete Part 1 through to Week 24, followed by the Part 1 withdrawal visits.

Part 2

TCZ dosed by body weight (12 mg/kg for patients < 30 kg; 8 mg/kg for patients ≥ 30 kg) will be administered IV Q3W for a minimum of 12 consecutive weeks (~~4~~ *5* consecutive infusions), switching to Q4W ~~(if required),~~ in response to predefined laboratory abnormalities for patients eligible to continue treatment for the duration of the study (52 weeks in total).

Patients who do not meet the criteria to switch from Q3W to Q4W will complete Part 2 through to Week 52, followed by the Part 2 withdrawal visits.

TCZ will be supplied in vials containing 10 mL of a sterile solution of 20 mg TCZ/mL. ~~One vial will be used for any child ≤16.5 kg. A 2 vial combination will be used for a body weight of >16.5 but ≤50 kg. A 3 vial combination will be used for patients with a body weight of >50 kg but ≤75 kg. A 4 vial combination will be used for patients with a body weight of >75 but ≤100 kg. A 5 vial combination will be used for patients with a body weight of >100 kg but ≤125 kg. A 6 vial combination will be used for patients with a body weight of >125 kg but ≤150 kg. The last recorded body weight of a patient should be used for calculating TCZ volume for each infusion.~~ *The TCZ dose will be calculated using the Part 1 or Part 2 baseline body weight (<30 kg or ≥30 kg) and will not be changed until a patient's weight falls into the other body weight category on three separate, consecutive occasions. The number of vials to be used for each body weight category is described in Table 6.*

For a 50-mL infusion bag the initial infusion speed should also be 10 mL/hr for 15 minutes and then increased to 65 mL/hr. Total infusion time should be no less than 1 hour. In order to flush the remaining study drug through the IV set, 10 mL of normal saline will be administered immediately following the infusion of study drug. The volume of the saline flush should not be included in the total infusion volume recorded in the eCRF. The time the "saline flush" is completed should be noted as the time when the infusion is complete. ~~along with t~~*T*he timing of any related post-infusion blood draws (PK) that are required *should also be noted*.

SECTION 4.2.3: Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (TCZ) *during Part 1 and Part 2* will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, using the IXRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

SECTION 4.2.4: Post-Trial Access to TCZ

The Sponsor ~~does not intend~~*will offer post-trial access* to ~~provide~~*the study drug* TCZ ~~or other study interventions~~*free of charge to eligible* patients ~~after conclusion of the study or any earlier~~*in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.*

A patient ~~withdrawal as TCZ~~*will be eligible to receive study drug after the end of the study if all of the following conditions are met*:

- *The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being*
- *There are no appropriate alternative treatments available to the patient*
- *The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- *The study drug* is commercially ~~available~~ *marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)*
- *The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective* for sJIA ~~patients, within the countries selected to participate in this trial.~~
- *The Sponsor has reasonable safety concerns regarding the study drug as treatment for sJIA*
- *Provision of study drug is not permitted under the laws and regulations of the patient's country*

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site: http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf.

SECTION 4.3.1: Permitted Therapy

Methotrexate:

Part 1 and 2, MTX is permitted but not required during this study. If a patient has been on MTX in the past they should have discontinued MTX at least 4 weeks prior to the baseline visit *of Part 1 and 2 of the study.* Those patients receiving MTX should have been taking MTX for at least 12 weeks immediately prior to the baseline visit *of Part 1 and Part 2* and should be receiving a stable dose of $\leq$20 mg/m^2 for at least 8 weeks prior to the baseline visit *of Part 1 and 2 of the study*, together with at least the minimum recommended dose of either folic acid or folinic acid according to the local standard of care. During the study, if applicable, the MTX dose may be decreased at any time for documented reasons of safety but not for efficacy (improvement in symptoms) during *Part 1 and* the first 12 weeks of *Part 2 of* the study (and until 54 consecutive Q3W infusions have been given). If any patient should move to Q4W dosing, *the* MTX dose should also remain stable until 3 consecutive Q4W infusions of TCZ have been given.

Steroids:

There are no restrictions on the use of steroids in Part 1 of the study.

For Part 2 of the study, ~~P~~*p*atients who are not currently receiving *oral* corticosteroids or *are* taking oral corticosteroids at *a* stable dose for a minimum of 2 weeks prior to the *Part 2* baseline visit at no more than 10 mg/day or *0.*2 mg/kg/day*,* whichever is less*,* are allowed in the study. *If patients are receiving oral corticosteroids, the dose should remain stable during the first 12 weeks of Part 2 (until 5 consecutive 3 weekly infusions have been given), and for patients moving to 4 weekly dosing, until 3 consecutive 4 weekly infusions of TCZ have been given.*

Intra-articular (IA), intramuscular (IM), IV, and long-acting corticosteroids (such as dexamethasone) are not permitted within 4 weeks of baseline *of Part 2* or throughout *Part 2 of* the study.

Injection of IA corticosteroids during the first 12 weeks of *Part 2 of* the study (and until 4*5* consecutive 3 weekly infusions have been given) is strongly discouraged as these may affect the exploratory efficacy endpoints. The same applies for patients moving to 4 weekly dosing, until 3 consecutive 4 weekly infusions of TCZ have been given. Injections of IA corticosteroids are not permitted within 4 weeks of baseline *of Part 2 of the study; during Part 2*~~;~~ a maximum of 2 joint injections will be allowed in 1 year ~~during the study~~, and the related joint will be considered active for 3 months following the injection. If an IA injection is absolutely required, no more than 1 joint should be injected with the smallest possible dose appropriate to the size of the joint being injected.

Corticosteroids can be changed for reasons of safety (e.g., asthma attack, serositis) to maximum of 30 mg/day or 0.5 mg/kg/day prednisone or equivalent, whichever is less, for a maximum dosing period of $<$14 days, after which the corticosteroid dosage must be returned to *the Part 2* baseline *dosage*.

NSAIDs:

There are no restrictions on the use of NSAIDs in Part 1 of the study.

For Part 2 of the study, ~~P~~*p*atients who are not taking NSAIDs, or taking no more than one type of NSAID at a dose that has remained stable for $>$2 weeks prior to the baseline visit *of Part 2 of the study* and is less than or equal to the maximum recommended daily dose are included in *Part 2 of* the study. The dose of NSAID must remain stable throughout the first 12 weeks of *Part 2 of* the study (and until 4*5* consecutive Q3W infusions have been given). In addition, for patients moving to Q4W dosing, the dose of NSAIDs should remain stable for the first 12 weeks of Q4W dosing. The dose may be lowered for documented reasons of safety and only tapered for efficacy after 4*5* consecutive doses have been completed for Q3W dosing *(12 weeks), and 3 consecutive doses have been completed for Q4W dosing (12 weeks).*

Acetaminophen (Paracetamol) and Other Analgesics:

Normal-release acetaminophen (not extended release) may be used for pain as required. Analgesics should not be taken within 6 hours prior to a visit where clinical efficacy assessments are performed *in Part 2 of the study.* The administration of analgesics should always be recorded in the eCRF.

Iron and Folic Acid:

Iron supplementation can be prescribed based on investigator's assessment of risk–benefit for treatment of the anemia with iron. Folic acid should be administered to patients receiving MTX *in Part 1 and Part 2 of the study*.

~~Contraceptives:~~

~~Female patients of childbearing potential should use a reliable means of contraception during and for a minimum of 3 months after TCZ therapy. Patients who use oral contraceptives, hormone replacement therapy, or other maintenance therapy should continue their use.~~

SECTION 4.3.2: <u>Prohibited Therapy</u>

DMARDs:

Leflunomide is not allowed *at any time* during the study. Discontinuation of leflunomide should be followed by standardized cholestyramine washout. Leflunomide levels must be documented to be below the limit of detection prior to the baseline visit *of Part 1 or Part 2*.

Cyclophosphamide is not permitted *at any time* during the study and within 3 months prior to the baseline visit *of Part 1 or Part 2*.

Etoposide (VP16) is not permitted *at any time* during the study or within 3 months prior to the baseline visit *of Part 1 or Part 2.*

Treatment with DMARDs (other than MTX) or immunosuppressants, including but not limited to: hydroxychloroquine, chloroquine, gold, azathioprine, D-penicillamine, sulfasalazine, cyclosporine, thalidomide, ~~or biologics (e.g., anti TNFs, anti IL 1 agents)~~ must have been discontinued within 6 weeks prior to the baseline visit *(Part 1 or Part 2)* and leflunomide must have been discontinued within 12 weeks prior to the *Part 1 or Part 2* baseline visit.

If the patient has received previous treatment with any of the following biologic agents other than TCZ, these must have been discontinued according to the following timelines prior to the baseline visit of either Part 1 or 2, and are not permitted during the study:

- *Etanercept must have been discontinued within ≥2 weeks prior to baseline.*
- *Anakinra must have been discontinued within ≥4 days prior to baseline.*
- *Abatacept must have been discontinued within ≥12weeks prior to baseline.*
- *Infliximab or adalimumab must have been discontinued within ≥8 weeks prior to baseline.*
- *Canakinumab must have been discontinued within ≥20 weeks prior to baseline.*
- *Rilonacept must have been discontinued within ≥6 weeks prior to baseline.*
- *Golimumab must have been discontinued within ≥10 weeks prior to baseline.*

- *Certrolizumab pegol must have been discontinued within ≥10 weeks prior to baseline.*

IA, IM, IV, and long-acting corticosteroids (such as dexamethasone) are not permitted within 4 weeks of baseline *of Part 2* or throughout *Part 2 of* the study.

Immunoglobulin:

Administration of IV immunoglobulin is not permitted during the *entire* study or within 4 weeks prior to the baseline visit *of Part 2 of the study*. For active varicella infection (chickenpox) or significant exposure to varicella zoster infection in a patient without a history of chickenpox (varicella IgG titer available from screening), varicella zoster immunoglobulins can be given at the discretion of the investigator.

Hyaluronic Acid and Plasmapheresis:

IA injections of hyaluronic acid and plasmapheresis are not permitted *at any time* during the study.

Cell-Depleting Therapies:

Previous treatment with any cell depleting therapy, including any investigational agents, (e.g., anti-CD19 and anti-CD20) *or cell-depleting therapy during the study at any time* is not permitted ~~in the study~~.

Stem Cell Transplant:

~~Patients~~*Previous treatment* with ~~a history of~~ prior stem cell transplant*, or stem cell transplant during the study* at any time*,* ~~are~~ *is* not permitted ~~in the study~~.

Vaccines:

Live or attenuated vaccines are not permitted within 4 weeks of the baseline visit *of Part 1 or 2 of the study, or at any time* during *the* study ~~conduct~~, or within 12 weeks following the last administration of study drug. Patients are advised to be brought up to date with vaccines prior to start of the study, as appropriate.

SECTION 4.4.1.1: Efficacy-Clinical Assessments

For the efficacy assessments *in Part 2 of the study*, the baseline score will be taken as the assessment prior to dosing at Visit 1 Day 1 *of Part 2*. Clinical measures of efficacy will be evaluated for patients on Q3W and Q4W TCZ as applicable.

- Fever *(attributable to sJIA)*
- JIA definition of disease flare (worsening in patients with JIA) is defined in this trial:

  Recurrence of fever or JIA flare defined as any 3 of the 6 core outcome variables worsening by at least 30% *relative to baseline visit of Part 2,* with no more than 1 of the remaining variables improving by more than 30% since the *Part 2* baseline evaluation at *Part 2* Visit 1, Week 0.

SECTION 4.4.1.2: Medical History and Demographic Data

Medical history and demographic data will be taken at the times indicated in the Schedule of Assessments *for Part 1 or Part 2 of the study* (see Appendix 1). Demographic data will be recorded as well as medical history and concomitant illnesses. A history of all DMARDs used in the past will be recorded, and the use of biologic medications will be specifically asked for. Medical history will also include prior immunizations/vaccines ~~and growth velocity~~.

SECTION 4.4.1.3: Vital Signs

Vital signs (pulse rate, systolic, and diastolic blood pressure, and temperature) will be taken at the times indicated in the Schedule of Assessments *in Part 1 and 2 of the study* (see Appendix 1). Assessments will be taken with the patient having been in a semi-supine position for at least 5 minutes.

Vital signs will be taken pre-infusion, every 30 minutes during infusion, and 30 minutes after the infusion is completed. All readings will be recorded in the eCRF. Additional readings may be taken at the discretion of the investigator in the event of an infusion-related reaction ~~(hypotension and/or fever)~~.

Vital signs recordings will start with the screening period and continue throughout the study up to and including the ~~Week 52 visit or~~ last dosing visit, as outlined in the Schedule of Assessments (see Appendix 1).

SECTION 4.4.1.4: Height and Weight Measurements

Height and weight will be measured as outlined in the Schedule of Assessments *in Part 1 and 2 of the study* (see Appendix 1). Height will be measured in a standing position using a wall mounted stadiometer or equivalent as per local practice. Weight should be determined to the nearest 0.1 kg. For body weight measurements, the patient will wear typical daytime clothes but shoes, outerwear, and accessories should be removed.

SECTION 4.4.1.5: Physical Examinations

A general physical examination will be performed and recorded as “normal” or “abnormal” at the times indicated in the Schedule of Assessments *in Part 1 and 2 of the study* (see Appendix 1).…

SECTION 4.4.1.6: Physician’s Global Assessment of Disease Activity

The physician’s global assessment of disease activity is the physician’s assessment of the patient’s current disease activity on a 100 mm horizontal VAS. The extreme left end of the line should be described as “arthritis inactive” (symptom-free and no arthritis symptoms) and the extreme right end as “arthritis very active.” This should be completed by the treating physician at the times indicated in the Schedule of Assessments *for Part 2 of the study* (see Appendix 1).

SECTION 4.4.1.7: Joint Assessments

The joint assessor will evaluate if the joints are swollen, tender/painful, and limited as per standard Rheumatology International Trials Organisation/Pediatric Rheumatology Collaborative Study Group (PRINTO/PRCSG) rheumatologic examination form (or equivalent). The joint counts (swollen, tender/painful, limited, and active) will be evaluated at the times indicated in the Schedule of Assessments *for Part 2 of the study* (see Appendix 1)….

SECTION 4.4.1.8: Temperature

The patient's temperature will be taken at the times indicated in the Schedule of Assessments *for Part 1 and 2 of the study* (see Appendix 1). Additional supplemental temperatures may be measured as deemed necessary. Temperature recordings will start with the screening period *for Part 1 and 2 of the study* and continue throughout the study up to and including the ~~Week 52 visit~~/withdrawal (WD1) or the last dosing visit as outlined in the schedule of assessments.

SECTION 4.4.1.9: Laboratory Assessments

Samples of blood and urine will be obtained as indicated in the Schedule of Assessments (see Appendix 1) for the tests listed below *for Part 1 and 2 of the study*. On days when fasting labs are required (such as lipid profiles), blood samples will be taken after an 8-hour fast. These visits are identified in the schedule of assessments as fasting labs. Normal ranges for the local site study laboratory parameters must be supplied to Roche before the study starts.

Hematology ***(Parts 1 and 2):*** CBC: hemoglobin, hematocrit, RBC, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, WBC and differential, platelets, reticulocytes (centrally)

Blood chemistry ***(Parts 1 and 2):*** AST, ALT, alkaline phosphatase, total protein, albumin, total, direct and indirect bilirubin, urea, uric acid, creatinine, glucose, potassium, sodium, chloride, calcium, phosphorous, LDH

Urinalysis ***(Parts 1 and 2):*** Dipstick for blood, protein and glucose (performed locally or microscopic examination fresh specimen sent to central laboratory, if abnormal and applicable), pregnancy testing when applicable (Tanner stage 2 or above or onset of menarche during the study)

Screening tests ***(Parts 1 or 2):*** Hepatitis B surface antigen, hepatitis C antibody, HgbA1c, high-sensitivity C-reactive protein (hsCRP), fibrinogen, Epstein-Barr virus (EBV) titer, varicella IgG testing, ESR

Acute phase reactants ***(Part 2):*** hsCRP, serum ferritin, C4, C3, ESR to be performed locally. [redacted] has defined an ESR of $<$20mm/hr for both girls and boys as normal utilizing the [redacted]-supplied kits).

Fibrinogen, D-dimer *(Part 2)*:

Lipid profile *(Part 2):* Total cholesterol, HDL, LDL, triglycerides

Immunology profile *(Part 2):* IgG, immunoglobulin M, immunoglobulin A

PK/PD *(Part 2):* TCZ, IL-6, sIL-6R

Immunogenicity assessments/anti-TCZ antibodies *(Parts 1 and 2):* Anti-TCZ antibodies will be collected for all study patients to evaluate immunogenicity of TCZ as described in Section 5.1.1.6.

SECTION 4.4.1.10: Patient-Reported Outcomes

PRO data will be elicited from the patients in *Part 2 of the* study to more fully characterize the clinical profile of TCZ. The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the parent/guardian/patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

SECTION 4.4.1.10.1: Childhood Health Assessment Questionnaire

The CHAQ takes less than 10 minutes to administer and in this study the version that is completed by the parent or guardian will be used. This assessment will be done at visits as specified in the Schedule of Assessments *for Part 2 of this study* (see Appendix 2). The form should be completed by the parent/guardian as appropriate. To ensure consistency the form should be completed throughout the study by the same individual who completed the baseline global assessment *of overall well-being* (see Appendix 2).

Disability Index

The functional ability instrument used in *Part 2 of* this study for calculating the JIA flare is the Disability Index of the CHAQ (see Appendix 2). It is an adaptation of the Stanford Health Assessment Questionnaire (HAQ) for use in children. Three components are evaluated: 1) difficulty in performing daily functions, 2) use of special aids, and 3) assistance from other people. The CHAQ was adapted from the HAQ by adding several new questions, so that there is at least one question for each function that is relevant to children of all ages. This way, bias due to developmental difference can be minimized.

Parent's/Patient's Global *Overall Well-Being*~~Assessment of Disease Activity~~

The patient's overall assessment of their ~~current disease activity~~ *overall well-being* is recorded on a 100 mm horizontal visual analogue scale (VAS) *in Part 2 of this study.* The left-hand extreme of the line should be described as "very well" (symptom-free and no arthritis symptoms) and the right-hand extreme as "very poor" (maximum arthritis disease activity).

Parental/Patient Pain Index

In addition to the Disability Index, in the CHAQ (see above) there is a Pain Index, which is measured separately *in Part 2 of this study.* The level of pain is determined by the presence of pain, which is measured on a 100 mm horizontal VAS. This scale is anchored at the left-hand extreme of the line as "no pain" and the right-hand extreme as "very severe pain."

SECTION 4.4.1.11: PPD and Chest Radiograph ~~(CXR)~~

Patients will have a PPD test (5 TU) (or equivalent as per local practice, e.g., Quantiferon gold) performed at screening *(of Part 1 or 2 of the study)* unless a negative PPD has already been documented within the last year. ~~Those patients with a positive PPD at screening may not participate in the study unless they have initiated therapy for latent TB for at least 4 weeks prior to baseline with the remaining course of therapy continuing during study participation, and have negative a chest X-ray for active disease within 6 months of screening, as per local practice requirements.~~ The PPD test will be considered positive according to the local guidelines for immunosuppressed patients. The definition of a positive PPD test may be applied as determined by the clinical circumstances and investigator according to published guidelines and/or local standards endorsed by the medical society. If no published guidelines are available for a given country outside the United States, the U.S. guidelines must be followed.

Patients will have a TB screening test per local standard (e.g., PPD skin test or Quantiferon® test).

A chest X-ray (CXR) is required under the following conditions:

- *If a patient's TB testing is positive at screening (of Part 1 or Part 2) and the patient has not previously received TB treatment, then a CXR is required at screening.*
- *If a patient eventually is enrolled (Part 1 or Part 2), TCZ administration would be delayed until the patient has received at least 4 weeks of TB treatment therapy per exclusion criteria.*

A chest x-Ray may be required under the following conditions:

- *If a patient's TB testing is negative at screening (of Part 1 or 2), then a CXR should be done if consistent with local requirements but is not strictly required.*

A chest X-ray is not required under the following conditions:

- *If a patient's TB testing is positive and the patient has previously completed TB treatment or has been receiving TB treatment for at least 4 weeks prior to receiving TCZ and has had a negative CXR ≤6 months of screening (of Part 1 or 2), then he/she is eligible to enroll without repeat CXR at screening (if consistent with local practice requirements).*

- *A CXR obtained ≤90 days of baseline (of Part 1 or 2) can be utilized for screening purposes, if consistent with local practices.*

Patients asked to participate in this study will have received corticosteroid therapy and often other immunosuppressive drugs. It has been reported that the PPD response alone is not always sufficient for screening children with JIA for TB (Kasapcopur et al. 2006). In addition, patients with significant cardiac abnormalities are excluded from study participation (see Section 4.1.2, Exclusion Criteria *for General Safety*~~20~~). As a result, a negative chest radiograph is required at the time that TCZ therapy was *or is* initiated*,* or as per local practice requirements. The chest radiograph should be interpreted by a board-certified radiologist and the interpretation should include a statement of the following at a minimum:

SECTION 4.4.2.1: Screening and Pretreatment Assessments

Patients whose guardian has given written informed consent will undergo ~~a thorough~~ *two* screening examination*s: one* within 4 weeks before the start of ~~the~~ *Part 1 (Screening Evaluation 1, for patients entering Part 1) and one within 4 weeks of Part 2 of the* study *(Screening Evaluation 2, for patients entering into Part 2 directly, or entering Part 2 via Part 1).* TCZ infusions may continue to be received during ~~the s~~*S*creening ~~period~~*Evaluation 2,* but there must be at least 10 days clear between the last TCZ infusion during screening and the first study TCZ infusion received at baseline. During the Screening *Evaluation visits 1 and 2 (for patients entering the study via Part 1 or Part 2)*~~(visit(s)~~, inclusion/exclusion criteria ~~will be checked, a medical examination (including~~ *; and demographics,* medical history, concomitant *medication,* ~~medications, demographics,~~ and ~~complete,~~ physical examination), ~~body,~~ *height and* weight, vital signs ~~and temperature, and;~~ laboratory safety tests (screening labs [hepatitis B surface antigen, hepatitis C antibody, HgbA1c, hsCRP, fibrinogen, EBV titer, and varicella IgG, and ESR]; hematology; blood chemistry,~~ and~~; urine pregnancy [female patients who are able to become pregnant]) ~~will all be performed;~~ TB screening and chest X-ray (if applicable~~)~~ will ~~also~~ be performed. The CHAQ score, the number of joints with active arthritis and number of joints with limited range of motion (joint assessment), global assessment of the severity of the disease by the physician (physician global), and global assessment of overall well-being by the patient or parent (patient/parent global) will *also* be evaluated *at Screening Evaluation 2* as per the schedule of assessments (see Appendix 1).

Patients must fulfill all entry criteria to be accepted into the study. Patients who fail to meet the entry criteria may be rescreened once *for Part 1 or Part 2 of the study*, at the discretion of the investigator.

Patients, who have experienced a laboratory abnormality that has subsequently resolved during Part 1, may be screened to enter the Part 2. If a patient fails Screening Evaluation 2, the patient may continue participating in Part 1 (returns to Part 1 at the visit after their last visit) up to 24 weeks. If the patient is still not eligible for Part 2

after 24 weeks, the patient will be withdrawn from Part 1 and attend the Part 1 withdrawal visits. However if the patient experiences the relevant laboratory requirements (per Table 5) after discontinuing the study while on commercial TCZ, they may be rescreened once for Part 2 of the study at the discretion of the investigator. Patients can be screened for Part 2 a total of two times.

Under no circumstances will patients who enroll in *Part 1 or Part 2* ~~this study~~ and have completed treatment as specified, be permitted to re-enroll *into the same part of* ~~in~~ the study. *However, patients who have participated in Part 1 without meeting eligibility criteria for Part 2 may be rescreened for Part 2 (see above).*

See Appendix 1 for the schedule of screening and pretreatment assessments *for Part 1 and Part 2*.

SECTION 4.4.2.2: Assessments during Treatment

See Appendix 1 for the Schedule of Assessments performed during the treatment period *in Part 1 and Part 2*.

SECTION 4.4.2.3: Assessments at Study Completion/Early Termination Visit

Patients who complete ~~all infusion~~ visits in the study *in Part 1 and Part 2* as outlined in the Schedule of Assessments, or discontinue from the study early, will be asked to return to the clinic 2 weeks after the last dose of study drug for a follow-up visit (WD1) and then subsequently 2 weeks later for WD2, another 4 weeks later for WD3 and ~~a~~ further 4 weeks later for WD4. *If the investigator withdraws a patient due to sJIA flare or fever attributable to sJIA, t*~~T~~he visit at which JIA flare assessment shows flare of disease may be used as the study completion/early termination visit.

See Appendix 1 for the Schedule of Assessments performed at the study completion/early termination visit *for Part 1 and 2*.

SECTION 4.4.2.4: Follow-up Assessments

After the study completion/early termination visit, adverse events should be followed as outlined in Section 5.5 and Section 5.6 *for Part 1 and Part 2 of the study.*

SECTION 4.5.1: Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time *(Part 1 and 2)*. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following*:*

SECTION 4.5.1.1: Discontinuation from Study Drug

Patients must discontinue *the* study drug if they experience any of the following *at any time (Part 1 and 2):*

- *s*JIA flare *(Part 2 only and at the discretion of the investigator)*
- Fever attributable to sJIA *(Part 2 only and at discretion of investigator)*

~~In the case that the patient prematurely discontinues from the study the parents/guardians should be asked if they can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the eCRF. If lost to follow up, the investigator should contact the patient's parents/guardian or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.~~

SECTION 4.5.1.2: Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study *in both Part 1 and Part 2. Parents/guardians should be asked if they can still be contacted for further information.* The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

If lost to follow-up, the investigator should contact the patient's parents/guardian or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

SECTION 5.1: SAFETY PLAN

The safety of patients *in Part 1 and Part 2 of the study* will be assessed by physical examination, assessment of vital signs, screening for TB and treatment as applicable, laboratory assessments (see Section 4), and the collection of adverse events.

SECTION 5.1.1.: ~~Adverse Events of Special Interest and Risk Mitigation Strategies~~*Risks associated with TCZ Therapy and Risk Mitigation Strategies*

This section describes the known and potential risks of TCZ therapy, and risk mitigation strategies that should be followed during this study (Part 1 and Part 2).

Adherence to the planned dose regimen of TCZ is required unless an adjustment is necessary for safety reasons. The following risk mitigation and dose modification rules apply to patients receiving the study drug *in Part 1 and 2 of the study.* Recommendations for vigilance with signs and symptoms of particular safety events of interest are summarized in the following sections. For study visits *(Part 1 and Part 2)* at which the study drug dose is held due to toxicity, all other study assessments should be performed as per study schedule. For management of neutropenia, thrombocytopenia, and elevated liver enzymes in the study, see Section 3.1.2.

SECTION 5.1.1.6: Hypersensitivity or Anaphylaxis

…A blood sample for the presence of anti-TCZ antibodies should be obtained (refer to the schedule of assessments). The patient must be withdrawn from *Part 1 or 2 of* the study.

Samples for a~~A~~nti-TCZ antibodies, *TCZ PK, and sIL-6R* will be collected for all study patients to evaluate immunogenicity of TCZ at baseline *and Week 24 for patients on Q2W in Part 1; baseline*, Week 6*, 12, 24, 36, and 48* (for patients on Q3W dosing *in Part 2*) ~~or~~ *and at baseline, 8 weeks, and 12 weeks after switching to Q4W* ~~Week 8~~ (for patients on Q4W dosing *in Part 2*~~)~~ and at the last study visit, or at the time of early withdrawal from the study (visit WD1*) for Part 1 or Part 2.* Event-driven sampling (at the time of the event and also at least 6 weeks after the last dose) will occur for all patients experiencing serious infusion-related or allergic reactions or any hypersensitivity event (including non-serious events) leading to treatment withdrawal *in Part 1 or Part 2*.

SECTION 5.1.2: Laboratory Test Abnormalities

Laboratory test results *in Part 1 and Part 2 of the study* will be recorded on the laboratory results e-form of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.…

The following laboratory abnormalities are considered exempt from the above, and should not be recorded as adverse events in the eCRF: serum amyloid A, serum ferritin, hsCRP *and ESR*.

SECTION 5.2.3: ~~Non Serious~~ Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

~~Non serious~~ *All* adverse events of special interest are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

Adverse events of special interest for this study include the following:

- Suspected transmission of an infectious agent by the study drug *(Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from*

clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.).

- *Adverse events of special interest for Actemra in this study are provided in the current AESI guidance document.*
- ~~Infections, including all opportunistic infections, and non serious infections as defined by those treated with IV anti-infectives)~~
- ~~Myocardial infarction/acute coronary syndrome~~
- ~~GI perforations and related events~~
- ~~Malignancies~~
- ~~Anaphylaxis/hypersensitivity reactions~~
- ~~Demyelinating disorders~~
- ~~Stroke~~
- ~~Bleeding events~~
- ~~Hepatic events~~

SECTION 5.3.1: Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient*, parent or guardian,* or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies*; see Section 5.4.2 for instructions for reporting serious adverse events*).

SECTION 5.3.4: Assessment of Causality of Adverse Events

For patients receiving *TCZ in* combination *with other* therapies~~y~~, causality *to TCZ* will be assessed *for TCZ* individually ~~for each protocol-mandated therapy~~.

SECTION 5.3.5.3: Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this. *If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that*

the event became serious, and completing all data fields related to serious adverse events.

SECTION 5.3.5.10: Hospitalization or Prolonged Hospitalization

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- *Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.*

SECTION 5.3.5.11: *Adverse Events Associated with an* Overdose~~s~~ *or Error in Drug Administration*

SECTION 5.4: IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report the following events to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events *(see Section 5.4.2 for further details)*
- ~~Non serious a~~*A*dverse events of special interest *(see Section 5.4.2 for further details)*
- Pregnancies *(see Section 5.4.3 for further details)*

SECTION 5.4.2.1: *Events That Occur after Study Drug Initiation*

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 3 months after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

SECTION 5.4.3.1: Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or 90 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk

Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. *Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.*

In the event that the EDC system is unavailable*, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.* ~~a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information and List of Investigators").~~

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Safety data will be presented for the safety population and efficacy data will be presented for the all TCZ population. All patients *in Part 1 will commence treatment with the TCZ Q2W regimen; all patients in Part 2* will commence treatment with a Q3W dosing frequency regimen.

Basic safety reporting will occur for Part 1 of the study and full reporting (including PK, PD, and efficacy assessments) will occur for Part 2.

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

Part 2 of the study will enroll patients already receiving TCZ who have experienced a predefined laboratory abnormality on Q2W TCZ. A sample size of approximately 20 patients in Part 2 who complete 5 consecutive Q3W treatments up to Week 12 has been deemed adequate for the objectives of this study. In addition, 20 patients in Part 2 would ensure 95% probability of observing at least one adverse event when the underlying incidence of that event is ≥14%.

In addition to the 6 patients enrolled in Part 2 as of May 2015 (under Protocol Version 2), approximately an additional 65 patients will be enrolled into Part 1 of the study (under Protocol Version 3). On investigation of Study WA18221 data, it was found that 46% (52 of 112) of patients experienced a resolved laboratory abnormality on TCZ Q2W, per the Part 2 entry criteria at any point during the study: 25% (28 of 112) of TCZ naive patients during the study from 0-6 months, and 31% (32 of 102) of TCZ non-naive patients between Months 12 and 18 in the study. Based on these percentages, 65 patients enrolled in the run-in period of this study (Part 1)

will result in approximately 16-20 TCZ naive/non-naive patients eligible for Part 2, which when added to the 6 patients currently enrolled in Part 2, will result in approximately 20 patients in Part 2, even taking into account the JADAS (and absence of fever attributable to sJIA) entry requirement for Part 2, and the possibility of withdrawals.

~~The study will enroll a minimum of 20 patients already receiving TCZ who have experienced a predefined laboratory abnormality at any time on Q2W TCZ prior to enrolment in the study. A sample size of approximately 20 patients who complete 4 consecutive Q3W treatments up to Week 12 has been deemed adequate for the objectives of this study. In addition, a sample size of 20 would ensure 95% probability of observing at least one adverse event when the underlying incidence of that event is≥14%.~~

SECTION 6.3: SUMMARIES OF TREATMENT GROUP COMPARABILITY

No formal assessment of treatment group comparability will be performed. All patients will receive TCZ, dose determined based on weight (8 mg/kg≥30 kg or 12 mg/kg<30 kg) and given *TCZ Q2W (Part 1), and then TCZ* Q3W *(Part 2)* and Q4W (for those patients who experience a repeat laboratory abnormality *during Part 2*). All baseline data, including demographics, baseline characteristics, patient disposition, infusion data, and concurrent treatment, will be summarized. No testing of baseline characteristics will be performed.

Part 1 Baseline is defined as the first dose of TCZ received in *Part 1 of* the study. *Part 2 baseline is defined as the first dose of TCZ received in Part 2 of the study (see Appendix 1 for the schedule of assessments).*

SECTION 6.4: EFFICACY ANALYSES

No formal hypothesis testing is planned for this study. All efficacy data will be presented descriptively. Summaries by visit will be presented for the all TCZ population (all patients to commence treatment with a Q3W dosing frequency regimen at baseline *of Part 2* [Week 0]). In addition, separate subgroup summaries for patients moving on to a Q4W dosing frequency regimen during the study will be produced if sufficient data exists. Data will be summarized from the first Q4W dosing visit. All summaries will be based on observed case data. No imputation of missing data will be performed.

Assessment of efficacy will be based on JADAS-71 ~~scores~~ during *Part 2 of* the study and assessment of fever *(attributable to sJIA).*

JIA flare relative to *Part 2* baseline will be assessed at each visit *in Part 2* to determine if a patient should be withdrawn based on lack of efficacy *at the discretion of the investigator*. Component scores in the assessment of JIA flare (physician global assessment of disease activity [100 mm horizontal VAS], patient/parent global assessment of overall well-being [100 mm horizontal VAS], number of joints with active

arthritis [0–71], number of joints with limitation of movement, CHAQ, and ESR) will be summarized or listed as appropriate.

SECTION 6.5: SAFETY ANALYSES

Safety will be assessed based on reporting of adverse events, vital signs, clinical laboratory assessments, concomitant medications, and physical examination *(for Part 1 and Part 2 of the study separately).* All safety data will be reported based on the safety population and will be listed or summarized descriptively as appropriate. Full details of all safety reporting will be provided in the SAP.

SECTION 6.6: PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Nonlinear mixed effects modeling (using NOMMEM software) (Beal et al. 1992) will be used to analyze the serum TCZ concentration-time data collected in this study *in Part 2 of the study*. The current PK model developed for sJIA patients from previous studies (Studies MRA316JP, LRO320, and WA18221) will be used to analyze the serum TCZ concentration-time data.

The following systemic exposure parameters will be estimated for all patients who provide adequate PK samples:

- AUCτ during a dosing interval at week 12 *of Part 2*; $\tau = 3$ weeks for Q3W and $\tau = 4$ weeks for Q4W
- C_{max} post infusion at Week 12 *of Part 2*
- C_{min} at end of a dosing interval at Week 12 *of Part 2*

SECTION 6.7: PATIENT-REPORTED OUTCOMES

PROs in this study include the CHAQ questionnaire (see Section 4.4.1.10.1 and Appendix 2) and the patient/parent global assessment of overall well-being 100 mm horizontal VAS. The left-hand extreme of the line should be described as “very well” (symptom-free and no arthritis symptoms) and the right-hand extreme as “very poor” (maximum arthritis disease activity), which are *all* part of the 6 core *JIA* American College of Rheumatology components. Data will be summarized or listed as appropriate.

SECTION 9.4: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Authorship will be determined by mutual agreement *(with the Paediatric Rheumatology International Trials Organisation (PRINTO at www.printo.it) and the Pediatric Rheumatology Collaborative Study Group (PRCSG at www.prcsg.org)* and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

FIGURE 1: Overview of Study Design

Figure 1 has been updated to reflect changes to the protocol.

TABLE 2: Neutropenia Management

Table 2 has been updated to reflect changes to the protocol.

TABLE 3: Thrombocytopenia Management

Table 3 has been updated to reflect changes to the protocol.

TABLE 4: Management of Elevated Liver Enzymes

Table 4 has been updated to reflect changes to the protocol.

TABLE 5: Laboratory Abnormalities Serving as Inclusion Criteria *for Part 2* When Experienced (with Resolution) on *Q2W*~~2 Weekly~~ TCZ

APPENDIX 1: Schedule of Assessments

The Schedule of Assessments has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IV STUDY TO EVALUATE DECREASED DOSE FREQUENCY IN PATIENTS WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA) WHO EXPERIENCE LABORATORY ABNORMALITIES DURING TREATMENT WITH TOCILIZUMAB**
PROTOCOL NUMBER:	WA28029
VERSION NUMBER:	3
EUDRACT NUMBER:	2012-000444-10
IND NUMBER:	11972
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please ret*ain* the original form *in your study files*. Please ret*urn* a copy *to the study monitor*.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IV STUDY TO EVALUATE DECREASED DOSE FREQUENCY IN PATIENTS WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA) WHO EXPERIENCE LABORATORY ABNORMALITIES DURING TREATMENT WITH TOCILIZUMAB**
PROTOCOL NUMBER:	WA28029
VERSION NUMBER:	3
EUDRACT NUMBER:	2012-000444-10
IND NUMBER:	11972
TEST PRODUCT:	Tocilizumab (RO4877533)
PHASE:	IV
INDICATION:	systemic Juvenile Idiopathic Arthritis (sJIA)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objective

The primary efficacy objective for *Part 2 of* this study is as follows:

- To explore the efficacy of tocilizumab (TCZ) in reduced dosing frequency regimens (every 3 weeks [Q3W] and every 4 weeks [Q4W], as appropriate) using Juvenile Arthritis Disease Activity Score (JADAS)-71, JIA flare, and fever *(attributable to systemic Juvenile Idiopathic Arthritis [sJIA])*

Safety Objective

The safety objective for *Part 2 of* this study is as follows:

- To evaluate the safety of TCZ in reduced dosing frequency regimens

Pharmacodynamic Objective

The primary pharmacodynamic (PD) objective for *Part 2 of* this study is as follows:

- To describe the pharmacodynamics, using sIL-6R and C-reactive protein (CRP), and immunogenicity of TCZ in reduced dosing frequency regimens

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for *Part 2 of* this study is as follows:

- To describe the pharmacokinetics of TCZ in reduced dosing frequency regimens

Patient-Reported Outcome Objectives

The patient-reported outcome (PRO) objectives for *Part 2 of* this study are as follows:

- To describe the Child Health Assessment Questionnaire (CHAQ) outcomes with TCZ in reduced dosing frequency regimens
- To describe parent/patient global assessment of *overall well-being* with TCZ in reduced dosing frequency regimens

Study Design

Description of Study

This is a 96-week, two part, Phase IV study to explore the efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity of TCZ in reduced dosing frequency regimens in patients with adequately controlled sJIA (JADAS Minimal Disease Activity cut-off of 3.8 at screening and baseline for Part 2 who have experienced a laboratory abnormality which has resolved (per inclusion criteria in protocol) on TCZ twice weekly dosing.

Run-In Phase (Part 1)

At the Screening Evaluation 1 (see protocol), TCZ naive patients or TCZ non-naive patients who fulfil all eligibility criteria for Screening Evaluation 1 may enter the open-label run-in phase (Part 1) and receive TCZ dosed by body weight (12 mg/kg for patients < 30 kg; 8 mg/kg for patients ≥ 30 kg) by IV infusion every 2 weeks [Q2W] for up to 24 weeks or until they experience a laboratory abnormality of neutropenia, thrombocytopenia, or liver enzyme abnormality as per the criteria provided in the protocol. The TCZ dose will be calculated using the baseline body weight (< 30 kg or ≥ 30 kg) and will not be changed until a patient's weight falls into the other body weight category on three separate, consecutive occasions in Part 1. Patients will be assessed Q2W for safety. No reductions or changes of concomitant methotrexate [MTX] dosing can occur during Part 1 of the study (i.e., due to improvement or worsening of symptoms) except for documented safety reasons.

Patients who do not experience a laboratory abnormality in Part 1, or experience a laboratory abnormality but do not meet the eligibility criteria for Part 2, will complete Part 1 through to Week 24, followed by the Part 1 withdrawal visits.

Main Study (Part 2)

Patients on TCZ Q2W who have experienced a laboratory abnormality (per protocol; either during Part 1 or prior to the study) that has subsequently resolved, who have adequate disease control, *and* who fulfil all the inclusion criteria and none of the exclusion criteria *of Screening Evaluation Part 2, may enter the main study (Part 2). Once patients have entered Part 2 of the study, they* will receive TCZ dosed by body weight (12 mg/kg for patients < 30 kg; 8 mg/kg for patients ≥ 30 kg) by IV infusion Q3W for a minimum of 5 consecutive infusions. The dose will be calculated using *Part 2 baseline* body weight and will not be changed during the first 12 weeks of the *Part 2 of the* study. Patients *on Q3W* will be assessed for safety and efficacy responses. No reductions or changes of concomitant NSAIDs, corticosteroids, or MTX dosing can occur during the first 12 weeks of *Part 2 of* the study (and until 5 consecutive Q3W infusions have been given) except for documented safety reasons, including laboratory abnormalities. In addition, the doses of NSAIDs, corticosteroids, and MTX should remain stable in any patient who moves to Q4W dosing, during the first 12 weeks of Q4W dosing.

*In Part 2, e*ach patient will start and maintain Q3W dosing of TCZ in the study up to 52 weeks unless the patient experiences an event of neutropenia, thrombocytopenia, or liver enzyme abnormality as per the criteria provided in protocol. Following the occurrence and resolution of this laboratory abnormality, patients who have maintained adequate disease control *(JADAS ≤3.8 and absence of fever attributable to sJIA)* will move to Q4W dosing of TCZ. Patients who have not completed a minimum of 5 consecutive Q3W infusions will remain on Q3W dosing until 5 consecutive Q3W doses have been completed before moving to Q4W dosing. If during this time, a patient should experience any additional laboratory abnormalities as per the criteria provided in the protocol, he or she may move directly to Q4W dosing after resolution, at the discretion of the investigator, and the Sponsor must be notified.

Patients who move to Q4W dosing of TCZ because of an event of neutropenia, thrombocytopenia, or liver enzyme abnormality will remain on Q4W dosing for the remainder of the study.

Patients who do not meet the criteria to switch from Q3W to Q4W will complete Part 2 through to Week 52, followed by the Part 2 withdrawal visits.

Patients who experience a JIA flare or fever attributable to sJIA (see definition in the protocol) at any time *during Part 2 may* be withdrawn from the study *at the discretion of the investigator.*

Patients will undergo safety *and safety laboratory assessments during Part 1 of the study. Safety, safety* laboratory, PK, PD, and efficacy assessments *will be performed during Part 2* as described in the schedule of assessments. *During Part 1, and a*fter the first 12 weeks *of*

Part 2 of the study, the dose of TCZ can be adjusted according to changes in body weight: if a patient's body weight increases above 30 kg *on* 3 *consecutive* visits (while it was below 30 kg at baseline *for Part 1 or Part 2, respectively*), on the third visit the dose of TCZ will be decreased to 8 mg/kg; if a patient's body weight decreases below 30 kg (while it was above 30 kg at baseline *for Part 1 or Part 2, respectively) on* 3 *consecutive* visits, the dose of TCZ will be increased on the third visit to 12 mg/kg.

All patients who are discontinued from *Part 1 or Part 2 of* the study for any reason must return for the Withdrawal Visit 1 and follow-up safety assessments*,* Withdrawal Visits 2, 3, *and* 4 up to and including 12 weeks after the last administration of study drug. They may be required to return for visits beyond 12 weeks after discontinuation from treatment with TCZ for safety reasons (to be documented in the electronic Case Report Form [eCRF] and interactive voice response system [IXRS]).

Number of Patients

Approximately 65 patients will be enrolled in the *Part 1 with an aim to enroll 20 patients into Part 2 of the study.*

Target Population

Inclusion Criteria

Part 1 and Part 2

All patients entering Part 1 or entering Part 2 without participating in Part 1 must meet the following criteria for entry *into Part 1 or Part 2*:

- Aged 2 years up to and including 17 years at screening into trial
- sJIA according to International League of Associations for Rheumatology (ILAR) classification (2001)
- *sJIA symptoms lasting for at least 1 month since diagnosis of sJIA*
- Fertility:

  For female patients of reproductive potential (unless surgically sterile with absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of < *1% per year during the treatment period and for at least 6 months after the last dose of TCZ*

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of < *1% per year include tubal ligation; male sterilization; hormonal implants; established, proper use of combined oral or injected hormonal contraceptives; and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods, such as a condom and a cervical cap) may be combined to achieve a failure rate of* < *1% per year. Barrier methods must always be supplemented with the use of a spermicide.*

  For male patients of reproductive potential: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < *1% per year during the treatment period and for at least 6 months after the last dose of TCZ*

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Must meet one of the following:

  Not receiving MTX or discontinued MTX at least 4 weeks prior to *the Part 1 or Part 2* baseline visit, or

  Taking MTX for at least 12 weeks immediately prior to the *Part 1 or Part 2* baseline visit and on a stable dose of ≤ 20 mg/m^2 for at least 8 weeks prior to the

Part 1 or Part 2 baseline visit, together with either folic acid or folinic acid according to local standard of care

- Written informed consent for study participation obtained from parent or legal guardian, with assent as appropriate by the patient, depending on the level of the patient's understanding
- Parental or guardian written agreement to comply with the requirements of the study protocol

Patients entering Part 1 who are naïve to TCZ therapy must also meet the following inclusion criterion:

- *History of inadequate clinical response (in the opinion of the treating physician) to NSAIDs and corticosteroids*

Part 2

All patients entering Part 2 (either directly without participating in Part 1, or via Part 1) must meet the following additional criteria for entry into Part 2:

- JADAS-71 score of 3.8 or less and absence of fever (related to sJIA) at screening and baseline of Part 2
- Neutropenia, thrombocytopenia, or elevated ALT/AST (as per criteria in protocol) previously experienced (and resolved) on the labeled dose (Q2W) of TCZ
- *Not currently receiving oral corticosteroids, or taking oral corticosteroids at a stable dose for a minimum of 2 weeks prior to the Part 2 baseline visit at no more than 10 mg/day or 0.2 mg/kg/day, whichever is less*
- *Not taking NSAIDs, or taking no more than one type of NSAID at a stable dose for a minimum of 2 weeks prior to the Part 2 baseline visit, with the dose being less than or equal to the maximum recommended daily dose*

Exclusion Criteria

Patients *entering Part 1, or entering Part 2 without participating in Part 1,* who meet any of the following criteria will be excluded from study entry:

General

- Wheelchair bound or bedridden
- Any other auto-immune, rheumatic disease, or overlap syndrome other than sJIA
- Not fully recovered from recent surgery or less than 6 weeks since surgery, at the time of screening visit; or planned surgery during *Part 1 and* the initial 12 weeks of *Part 2 of* the study *(for patients entering Part 1) or the initial 12 weeks of Part 2 of the study (for patients entering Part 2 without participating in Part 1)*
- Lack of peripheral venous access

General Safety

- Pregnant, lactating, or intending to become pregnant during study conduct and up to *6 months* after the last administration of study drug
- Any significant concurrent medical or surgical condition which would jeopardize the patient's safety or ability to complete the trial
- History of significant allergic or infusion reactions to prior TCZ infusion, and/or presence of anti-TCZ antibodies by confirmatory and/or neutralizing assay at screening
- Inborn conditions characterized by a compromised immune system
- Known HIV infection or other acquired forms of immune compromise
- History of alcohol, drug, or chemical abuse within 6 months of screening
- Evidence of serious uncontrolled concomitant diseases, including but not limited to the nervous, renal, hepatic, or endocrine systems

- Any active acute, subacute, chronic, or recurrent bacterial, viral, or systemic fungal infection including but not limited to:
    - Acute or chronic renal / bladder infections
    - Acute or chronic pulmonary infections
- History of atypical tuberculosis (TB)
- Active TB requiring treatment within 2 years prior to the screening visit
- Positive purified protein derivative (PPD) at screen (or equivalent result based on local methodology, e.g., Quantiferon gold), unless treated with anti-TB therapy for at least 4 weeks prior to receiving study drug and chest radiograph is negative for active TB within 6 months of screening visit according to local practice
- Any major episode of infection requiring hospitalization or treatment during screening or treatment with IV antibiotics completing within 4 weeks of the screening visit or oral antibiotics completing within 2 weeks of the screening visit
- History of reactivation or new onset of a systemic infection, such as herpes zoster or Epstein Barr virus, within 2 months of the screening visit
- Hepatitis B surface Antigen or hepatitis C Ab positive
- Chronic hepatitis—viral or autoimmune
- Significant cardiac [e.g., congenital heart disease, valvular heart disease, constrictive pericarditis (unrelated to sJIA), myocarditis] or pulmonary disease, (e.g., asthma for which the patient has required the use of oral or parenteral corticosteroids for $\geq$ 2 weeks within 6 months prior to the baseline visit *of Part 1 or Part 2, or* cystic fibrosis)
- History or concurrent serious gastrointestinal (GI) disorders, such as ulcer or inflammatory bowel disease, Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions, including ulcer and perforation
- History of or current cancer or lymphoma
- Uncontrolled diabetes mellitus with elevated hemoglobin (Hgb) A1c as defined by age-specific standards
- History of macrophage activation syndrome (MAS) within 3 months prior to the screening visit

Excluded Previous or Concomitant Therapy

- Participation in another interventional clinical trial within the past 30 days or 5 serum half-lives of the investigative medication or the PD effect of the investigative medication, whichever is longer
- Prior stem cell transplant at any time
- Prohibited therapy as described in protocol

Laboratory Exclusions at Screening

- Serum creatinine $>$ 1.5 $\times$ upper limit of normal (ULN) (for age and sex)
- Hemoglobin $<$ 7.0 g/dL ($<$ 4.3 mmol/L)

The following additional laboratory exclusion criteria apply to patients entering Part 1 of the study who are TCZ-naive and are initiating therapy with TCZ:

- *AST or ALT > 1.5 ULN (upper limit of normal for age and sex)*
- *Total bilirubin >1.3 mg/dL (> 23 µmol/L)*
- *Platelet count < 150 x 103/µL (< 150,000/mm3)*
- *WBC count < 5,000/mm3 (< 5.0 x 109/L)*
- *Neutrophil count < 2,500/ mm3 (< 2.5 x 109/L)*

Length of Study

The total length of this study will be approximately *6* years *and 1 month* from screening of the first patient to completion of the last patient visit. For an individual patient the length of time in the study (from screening to completion) may be up to *96 weeks (i.e., Part 1 screening up to 4 weeks, Part 1 up to 24 weeks, Part 2 screening up to 4 weeks, Part 2 up to 52 weeks, followed by safety follow-up to 12 weeks).*

End of Study

The end of the study will occur when the last participating patient completes the last scheduled visit in the study, or if the Sponsor decides to discontinue the study.

Efficacy Outcome Measures

The efficacy outcome measures for *Part 2 of* this study are as follows:

- JADAS-71 will be utilized to describe efficacy in patients on Q3W and Q4W dosing as appropriate in this study
- JIA flare *relative to baseline of Part 2* will be used to determine those patients not maintaining efficacy who *can* be withdrawn from the study *at the discretion of the investigator*
- Fever *(attributable to sJIA)* will be measured at each study visit *of Part 2* in patients on Q3W and Q4W dosing (as appropriate) to describe efficacy and to determine patients not maintaining efficacy *who can* be withdrawn from the study *at the discretion of the investigator*

Safety Outcome Measures

The safety outcome measures *in Part 1 and 2* for this study are as follows:

- Adverse events (including adverse events of special interest)
- Serious adverse events
- Clinical laboratory results

Pharmacodynamic and Pharmacokinetic Outcome Measures

The PK/PD outcome measures for *Part 2 of the* study are as follows:

- Serum TCZ concentration and population PK model predicted PK exposures (area under the serum concentration-time profile [$AUC\tau$], maximum concentration observed [C_{max}], and minimum concentration under steady-state conditions within a dosing interval [C_{min}]) for Q3W and Q4W dosing regimens as appropriate
- Serum IL-6 and sIL-6R levels and inflammatory markers (CRP and erythrocyte sedimentation rate [ESR])
- Anti-TCZ antibodies

Patient-Reported Outcome Measures

The PRO outcome measures for this *Part 2 of the* study are as follows:

- The *CHAQ*
- Parents/patients global assessment of *overall well-being*

Investigational Medicinal Products

TCZ (200 mg/10 mL) vial (concentrate for solution for infusion) RO 487-7533/F01 will be supplied. Study drug packaging will be overseen by the Roche clinical trial supplies department and will include a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labeling of the study drug will be in accordance with Roche standard and local regulations. The study drug must be stored according to the details on the product label.

All TCZ vials must be stored at a controlled temperature of 2°C–8°C, and handled according to Good Manufacturing Practice and Good Clinical Practice procedures.

For further details, see the most recently published version of the Investigator's Brochure for TCZ.

Statistical Methods

Basic safety reporting will occur for Part 1 of the study and full reporting (including efficacy, PK, and PD assessments) will occur for Part 2.

Efficacy Analysis

No formal hypothesis testing is planned for this study. All efficacy data will be presented descriptively. Summaries by visit will be presented for the all TCZ population (all patients to commence treatment with a Q3W dosing frequency regimen at baseline *of Part 2* [Week 0]). In addition, separate subgroup summaries for patients moving on to a Q4W dosing frequency regimen during the study will be produced if sufficient data exists. Data will be summarized from the first Q4W dosing visit. All summaries will be based on observed case data. No imputation of missing data will be performed.

Full details of all planned efficacy analyses will be provided in the SAP.

Assessment of efficacy will be based on JADAS-71 during *Part 2 of* the study and assessment of fever *(attributable to sJIA).*

JIA flare relative to *Part 2* baseline will be assessed at each visit *in Part 2* to determine if a patient should be withdrawn based on lack of efficacy *at the discretion of the investigator.* Component scores in the assessment of JIA flare (physician global assessment of disease activity [100 mm horizontal VAS], patient/parent global assessment of overall well-being [100 mm horizontal VAS], number of joints with active arthritis [0–71], number of joints with limitation of movement, CHAQ, and ESR) will be summarized or listed as appropriate.

Determination of Sample Size

The purpose of this study is to explore the efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity of TCZ in a reduced dosing frequency regimen in patients with adequately controlled sJIA who have experienced a predefined resolved laboratory abnormality on TCZ Q2W dosing. This is a non-powered, descriptive study.

Part 2 of the study will enroll patients already receiving TCZ who have experienced a predefined laboratory abnormality on Q2W TCZ. A sample size of approximately 20 patients in Part 2 who complete 5 consecutive Q3W treatments up to Week 12 has been deemed adequate for the objectives of this study. In addition, 20 patients in Part 2 would ensure 95% probability of observing at least one adverse event when the underlying incidence of that event is ≥14%.

In addition to the 6 patients enrolled in Part 2 as of May 2015 (under Protocol Version 2), approximately an additional 65 patients will be enrolled into Part 1 of the study (under Protocol Version 3). On investigation of Study WA18221 data, it was found that 46% (52 of 112) of patients experienced a resolved laboratory abnormality on TCZ Q2W, per the Part 2 entry criteria at any point during the study: 25% (28 of 112) of TCZ naive patients during the study from 0-6 months, and 31% (32 of 102) of TCZ non-naive patients between Months 12 and 18 in the study. Based on these percentages, 65 patients enrolled in the run-in period of this study (Part 1) will result in approximately 16-20 TCZ naive/non-naive patients eligible for Part 2, which when added to the 6 patients currently enrolled in Part 2, will result in approximately 20 patients in Part 2, even taking into account the JADAS (and absence of fever attributable to sJIA) entry requirement for Part 2, and the possibility of withdrawals.

Interim Analyses

Interim analyses may be performed at the discretion of the sponsor, for regulatory reporting purposes.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AUC_{τ}	area under the serum concentration-time profile
CHAQ	Childhood Health Assessment Questionnaire
C_{max}	maximum concentration observed
C_{min}	minimum concentration under steady-state conditions within a dosing interval
CRP	C-reactive protein
CXR	chest X-ray
DMARDs	disease modifying anti-rheumatic drugs
EC	Ethics Committee
eCRF	electronic Case Report Form
EBV	Epstein-Barr virus
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HAQ	Health Assessment Questionnaire
Hgb	hemoglobin
hsCRP	high-sensitivity C-reactive protein
IA	intra-articular
ICH	International Conference on Harmonisation
IL	interleukin
ILAR	International League of Associations for Rheumatology
IM	intramuscular
IMP	investigational medicinal product
IND	Investigational New Drug application
IXRS	interactive voice response system
IRB	Institutional Review Board
IV	intravenous
JADAS	Juvenile Arthritis Disease Activity Score
JIA	juvenile idiopathic arthritis
MAS	macrophage activation syndrome
MTX	methotrexate
NCEP	National Cholesterol Education Program
NSAID	nonsteroidal anti-inflammatory drug

Abbreviation	Definition
PD	pharmacodynamic
PK	pharmacokinetic
PPD	purified protein derivative
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RA	rheumatoid arthritis
SAP	statistical analysis plan
sIL-6	soluble interleukin-6
sJIA	systemic Juvenile Idiopathic Arthritis
TB	tuberculosis
TCZ	tocilizumab
TNF	tumour necrosis factor
ULN	upper limit of normal
USPI	U.S. Prescribing Information
VAS	visual analogue scale
WD	withdrawal

1. BACKGROUND

1.1 BACKGROUND ON SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

Systemic Juvenile Idiopathic Arthritis (sJIA) is a subset of juvenile idiopathic arthritis (JIA), which comprises between 10% and 20% of all cases of JIA. sJIA is characterized by arthritis of at least 6 weeks duration accompanied by fever of at least 2 weeks duration and extra-articular features, with onset under the age of 16 years and no identifiable cause. The onset of fever can precede the development of arthritis by a few weeks to several years, although most patients have arthritis at disease onset. Patients with sJIA may follow a monocyclic course with complete remission within 2 years of disease onset, a polycyclic course characterized by exacerbations of systemic disease, or a course of persistent polyarthritis. The mean duration of active disease is 5 to 6 years, but some patients have persistent disease well into their adult years. sJIA has the highest mortality rate among all subsets of JIA (Cassidy 2001). The increased mortality is principally due to macrophage activation syndrome (MAS) and infections (Ravelli and Martini 2007).

Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids are used for symptomatic treatment of sJIA and pulses of intravenous (IV) methylprednisolone have been found to be effective against clinical and biological parameters of inflammation. It remains unclear whether these treatments prevent progressive joint destruction. Methotrexate (MTX) is the most commonly used second-line agent but its benefit remains unclear. Anakinra, a receptor antagonist to interleukin (IL)-1, has met with some success for the treatment of the systemic complaints associated with sJIA but has not been utilized as frequently as expected due to the daily requirements for a subcutaneous injection (Haines 2007). *Canakinumab is an antagonist to the cytokine IL-1β and was approved in the EU in September 2013 for the treatment of sJIA in patients aged 2 years and older who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.* Cyclosporin is used primarily for MAS. Tocilizumab (TCZ) is approved for the treatment of active sJIA in the European Union, United States, Japan, and other regions (Summary of Product Characteristics for RoACTEMRA; U.S. Prescribing Information [USPI] for ACTEMRA® [tocilizumab]).

1.2 BACKGROUND ON TOCILIZUMAB

The clinical and laboratory features of sJIA are suggestive of a cytokine-mediated process (Woo 2000). Patients with sJIA have been found to have significantly elevated soluble IL-6 (sIL-6) levels during active disease but not during remission (De Benedetti et al. 1991; Keul 1998). During active disease, patients with sJIA demonstrate fluctuations in serum IL-6 that parallel the classical daily fever (Prieur 1996). sIL-6 levels have been found to correlate with the extent and severity of joint involvement and with platelet counts (De Benedetti et al. 1991), and elevations in sIL-6 have been associated with growth stunting in sJIA (De Benedetti et al. 1997). The large

quantities of sIL-6 present in IL-6/sIL-6R complexes have been found to be of biological relevance in vivo (De Benedetti et al. 1994).

TCZ (RO4877533) is a recombinant, humanized, anti-human monoclonal antibody of the IgG1 sub-class directed against the sIL-6R and membrane-IL-6R (Tocilizumab [RO4877533] Investigator's Brochure). It inhibits the function of IL-6. IL-6 is a pleiotropic cytokine, present at elevated levels in patients with rheumatoid arthritis (RA) (Tocilizumab [RO4877533] Investigator's Brochure). IL-6 signaling involves both a specific IL-6R and a ubiquitous signal-transducing protein, gp130, that is also utilized by other members of the IL-6 family. The biological activities of IL-6 contribute to both systemic and local arthritis symptoms. The ability of IL-6 to induce B-cell differentiation may lead to the formation of rheumatoid factor and other autoantibodies. In joints, IL-6 promotes osteoclast activation and induces the release of matrix metalloproteinases, thus contributing to joint damage. In patients with RA or sJIA, IL-6 levels correlate with markers of disease activity and clinical symptoms, and animal studies support the concept that this cytokine plays a role in the development of inflammatory arthritis. Clinical trials with TCZ have shown that blocking IL-6 signaling reduces RA and sJIA symptoms and markers of disease activity. Current evidence thus strongly supports the association between IL-6 and RA and sJIA (Tocilizumab [RO4877533] Investigator's Brochure).

TCZ IV has been approved in more than 110 countries, including Japan, the European Union, and the United States, for use in adult patients with *moderately to severely active* RA who have an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs) *including* tumor necrosis factor (TNF) antagonists (Summary of Product Characteristics for RoACTEMRA; ACTEMRA®, English-Translated Version 7; USPI for ACTEMRA® [tocilizumab]). Additionally, TCZ was approved for use in JIA, sJIA, and Castleman's disease in India and Japan (ACTEMRA®, English Translated Version 7). TCZ is approved for the treatment of active sJIA arthritis in patients 2 years of age and older in several countries, including Japan, India, Switzerland, Mexico, the European Union and the United States. In the United States and European Union, the approved dose regimen is 8 mg/kg every 2 weeks (Q2W) for sJIA patients weighing $\geq$30 kg and 12 mg/kg Q2W for sJIA patients weighing $<$30 kg (Summary of Product Characteristics for RoACTEMRA; USPI for ACTEMRA® [tocilizumab]).

See the most recently published Tocilizumab Investigator's Brochure for details on nonclinical and clinical studies (Tocilizumab [RO4877533] Investigator's Brochure).

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The efficacy and safety of TCZ in children with sJIA was demonstrated in the pivotal study, WA18221. In addition, supportive data are available from three completed Japanese studies; MRA316JP, a Phase III study; MRA317JP, a long-term extension study; and MRA324JP, an expanded-use study. Results from study WA18221 and supportive data led to the approval of TCZ for treatment of children with active sJIA in

the European Union, United States, and other regions (Tocilizumab [RO4877533] Investigator's Brochure).

TCZ treatment is associated with certain laboratory abnormalities, including thrombocytopenia, neutropenia, and liver enzyme abnormalities. Current recommendations in sJIA are to stop TCZ dosing until the laboratory abnormality resolves as shown in Table 1 (Tocilizumab [RO4877533] Investigator's Brochure). The purpose of this study is to investigate the use of less frequent dosing upon reinitiating treatment in patients who have achieved a high level of efficacy with TCZ but have experienced these laboratory abnormalities.

Table 1 Guidelines Per Current E.U. SmPC and USPI Labels for Managing Laboratory Abnormalities

Neutropenia	ANC $> 1.0 \times 10^9$/L • Maintain dose ANC 0.5 to 1.0×10^9/L • Interrupt TCZ • When ANC increases to $> 1.0 \times 10^9$/L resume TCZ ANC $< 0.5 \times 10^9$/L • Discontinue TCZ
Thrombocytopenia	Platelets 50 to 100×10^9/L • Dose modify concomitant MTX if appropriate • Interrupt TCZ • When platelet count is $> 100 \times 10^9$/L resume TCZ Platelets $< 50 \times 10^9$/L • Discontinue TCZ
Elevated Liver Enzymes	ALT/AST > 1 to 3 × ULN • Dose modify MTX if appropriate • For persistent increases in this range, interrupt TCZ until ALT/AST have normalized. ALT/AST > 3 to 5 × ULN • Dose modify MTX if appropriate • Interrupt TCZ dosing until < 3 × ULN and follow recommendations above for > 1 to 3 × ULN ALT/AST > 5 × ULN • Discontinue TCZ

MTX = methotrexate; SmPC = Summary of Product Characteristics; TCZ = tocilizumab; ULN = upper limit of normal; USPI = United States product insert.

Patients who have experienced a laboratory abnormality on Q2W TCZ may benefit from reducing their TCZ dose by increasing the interval between doses to 3 or 4 weeks. Increasing the TCZ dosing interval carries the risk of underexposure to drug leading to disease flare or MAS but the likelihood of this is reduced in this study by recruiting patients *into Part 2* with good disease control and reducing the dosing interval in a

controlled stepwise manner (to every 3 weeks [Q3W] then every 4 weeks [Q4W] if required).

2. OBJECTIVES *FOR PART 2*

2.1 EFFICACY OBJECTIVE

The primary efficacy objective for *Part 2 of* this study is as follows:

- To explore the efficacy of TCZ in reduced dosing frequency regimens (Q3W and Q4W, as appropriate) using Juvenile Arthritis Disease Activity Score (JADAS)-71, JIA flare, and fever *(attributable to sJIA)*

2.2 SAFETY OBJECTIVE

The safety objective for *Part 2 of* this study is as follows:

- To evaluate the safety of TCZ in reduced dosing frequency regimens

2.3 PHARMACODYNAMIC OBJECTIVE

The primary pharmacodynamic (PD) objective for *Part 2 of* this study is as follows:

- To describe the pharmacodynamics, using sIL-6R and C-reactive protein (CRP), and immunogenicity of TCZ in reduced dosing frequency regimens

2.4 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for *Part 2 of* this study is as follows:

- To describe the pharmacokinetics of TCZ in reduced dosing frequency regimens

2.5 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for *Part 2 of* this study are as follows:

- To describe the Child Health Assessment Questionnaire (CHAQ) outcomes with TCZ in reduced dosing frequency regimens
- To describe parent/patient global assessment of *overall well-being* with TCZ in reduced dosing frequency regimens

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview

This is a *96*-week*, 2 part*, Phase IV study to explore the efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity of TCZ in reduced dosing frequency regimens in patients with adequately controlled sJIA (JADAS Minimal Disease Activity cut-off of 3.8 at screening and baseline *for Part 2* who have experienced a laboratory abnormality which has resolved (per inclusion criteria in Section 4.1.1) on TCZ twice weekly dosing.

Run-In Phase (Part 1)

At the Screening Evaluation 1 (see Appendix 1-A), TCZ naive patients or TCZ non-naive patients who fulfil all eligibility criteria for Screening Evaluation 1 may enter the open-label run-in phase (Part 1) and receive TCZ dosed by body weight (12 mg/kg for patients <30 kg; 8 mg/kg for patients ≥30 kg) by IV infusion Q2W for up to 24 weeks or until they experience a laboratory abnormality of neutropenia, thrombocytopenia, or liver enzyme abnormality as per the criteria provided in Table 5. The TCZ dose will be calculated using the baseline body weight (<30 kg or ≥30 kg) and will not be changed until a patient's weight falls into the other body weight category on three separate, consecutive occasions in Part 1. Patients will be assessed Q2W for safety. No reductions or changes of concomitant MTX dosing can occur during Part 1 of the study (i.e., due to improvement or worsening of symptoms) except for documented safety reasons.

Patients who do not experience a laboratory abnormality in Part 1, or experience a laboratory abnormality but do not meet the eligibility criteria for Part 2, will complete Part 1 through to Week 24, followed by the Part 1 withdrawal visits.

Main Study (Part 2)

Patients on TCZ Q2W who have experienced a laboratory abnormality (per Table 5; either during Part 1 or prior to the study) that has subsequently resolved, who have adequate disease control, *and* who fulfil all the inclusion criteria and none of the exclusion criteria *of Screening Evaluation Part 2, may enter the main study (Part 2). Once patients have entered Part 2 of the study, they* will receive TCZ dosed by body weight (12 mg/kg for patients <30 kg; 8 mg/kg for patients ≥30 kg) by IV infusion Q3W for a minimum of *5* consecutive infusions. The dose will be calculated using *Part 2 baseline* body weight and will not be changed during the first 12 weeks of the *Part 2 of the* study. Patients *on Q3W* will be assessed for safety and efficacy responses. No reductions or changes of concomitant NSAIDs, corticosteroids, or MTX dosing can occur during the first 12 weeks of *Part 2 of* the study (and until *5* consecutive Q3W infusions have been given) except for documented safety reasons, including laboratory abnormalities. In addition, the doses of NSAIDs, corticosteroids, and MTX should remain stable in any patient who moves to Q4W dosing, during the first 12 weeks of Q4W dosing.

*In Part 2, e*ach patient will start and maintain Q3W dosing of TCZ in the study up to 52 weeks unless the patient experiences an event of neutropenia, thrombocytopenia, or liver enzyme abnormality as per the criteria provided in Section 3.1.2. Following the occurrence and resolution of this laboratory abnormality, patients who have maintained adequate disease control *(JADAS ≤3.8 and absence of fever attributable to sJIA)* will move to Q4W dosing of TCZ. Patients who have not completed a minimum of *5* consecutive Q3W infusions will remain on Q3W dosing until *5* consecutive Q3W doses have been completed before moving to Q4W dosing. If during this time, a patient should experience any additional laboratory abnormalities as per the criteria provided in

Section 3.1.2, he or she may move directly to Q4W dosing after resolution, at the discretion of the investigator, and the Sponsor must be notified.

Patients who move to Q4W dosing of TCZ because of an event of neutropenia, thrombocytopenia, or liver enzyme abnormality will remain on Q4W dosing for the remainder of the study.

Patients who do not meet the criteria to switch from Q3W to Q4W will complete Part 2 through to Week 52, followed by the Part 2 withdrawal visits.

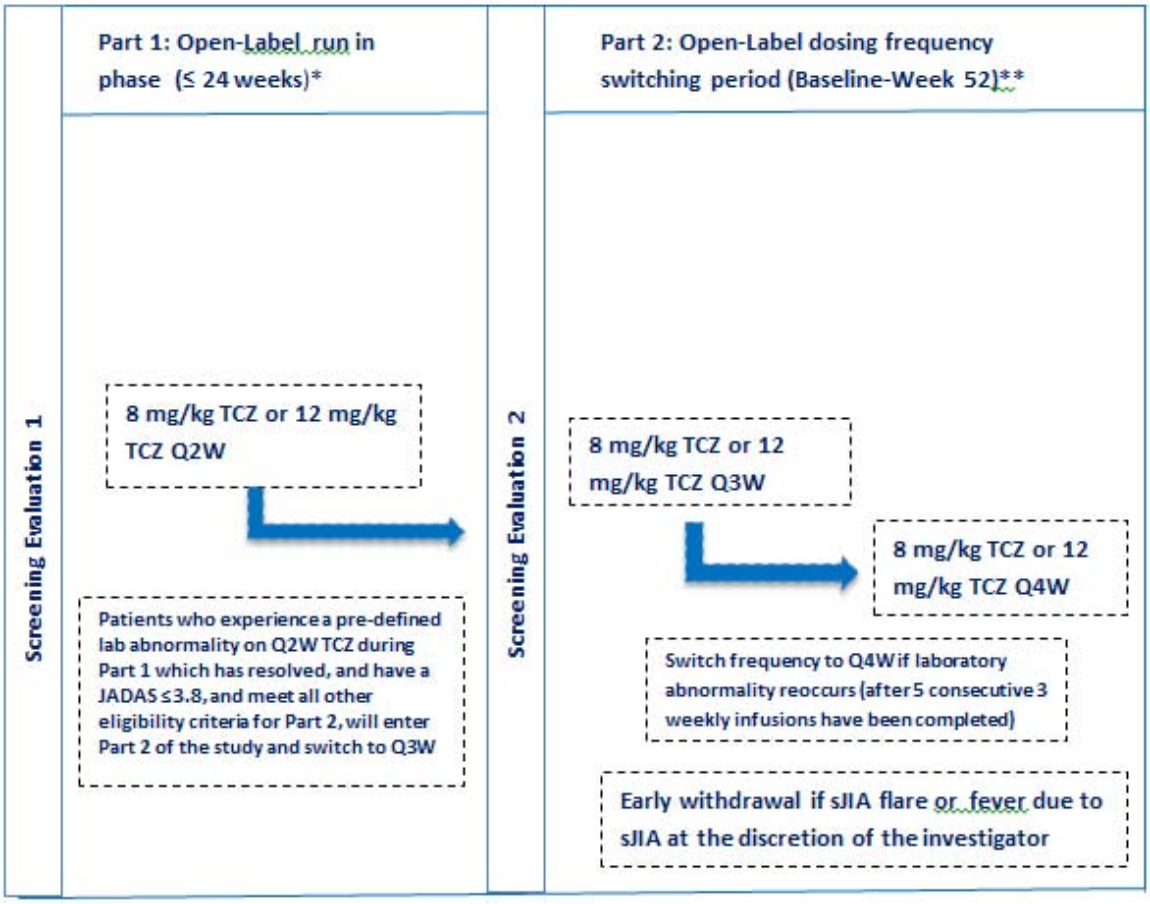
Patients who experience a JIA flare or fever attributable to sJIA (see definition in Section 4.5.1.1) at any time *during Part 2 may* be withdrawn from the study *at the discretion of the investigator.*

Patients will undergo safety *and safety laboratory assessments during Part 1 of the study. Safety, safety* laboratory, PK, PD, and efficacy assessments *will be performed during Part 2* as described in the schedule of assessments (see Appendix 1). *During Part 1, and a*fter the first 12 weeks *of Part 2* of the study, the dose of TCZ can be adjusted according to changes in body weight: if a patient's body weight increases above 30 kg *on* 3 *consecutive* visits (while it was below 30 kg at baseline *for Part 1 or Part 2, respectively*), on the third visit the dose of TCZ will be decreased to 8 mg/kg; if a patient's body weight decreases below 30 kg (while it was above 30 kg at baseline *for Part 1 or Part 2, respectively) on* 3 *consecutive* visits, the dose of TCZ will be increased on the third visit to 12 mg/kg.

All patients who are discontinued from *Part 1 or Part 2 of* the study for any reason must return for the Withdrawal Visit 1 and follow-up safety assessments*,* Withdrawal Visits 2, 3, *and* 4 up to and including 12 weeks after the last administration of study drug. They may be required to return for visits beyond 12 weeks after discontinuation from treatment with TCZ for safety reasons (to be documented in the electronic Case Report Form [eCRF] and interactive voice response system [IXRS]).

Figure 1 below provides an overview of Phase IV *of this* study design.

Figure 1 Overview of Study Design



JIA = juvenile idiopathic arthritis; TCZ = tocilizumab; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks.

* *Patients who do not experience a laboratory abnormality in Part 1, or experience a laboratory abnormality but do not meet the eligibility criteria for Part 2, will complete Part 1 through to Week 24 followed by the Part 1 withdrawal visits.*

** *Patients who have experienced a predefined laboratory abnormality on commercially available Q2W TCZ that has resolved, and have a JADAS ≤3.8 and who meet all other eligibility criteria, can directly enter Part 2.*

The schedule of assessments is provided in Appendix 1.

3.1.2 Management of Laboratory Abnormalities and TCZ Dose Frequency

Decreases in neutrophil and platelet counts and elevations in ALT and AST have been observed following treatment with TCZ (approximately 40% of patients experienced at least 1 of these laboratory abnormalities in the first year of the WA18221 study).

Management of neutropenia, thrombocytopenia, and elevated liver function tests to be implemented in this protocol for patients *in Part 1 and Part 2* are summarized below.

For patients taking other concomitant medications associated with hematologic or hepatic toxicity, the reduction or interruption of the suspected medication is recommended prior to modifying TCZ. If any of the laboratory criteria in Section 3.1.2.1 and Section 3.1.2.2 are met, MAS must be excluded (see Appendix 3).

3.1.2.1 Hematologic Abnormalities

For patients *in Part 1 and Part 2*, the laboratory abnormality guidance in Table 2 *and* Table 3 should be followed. Patients experiencing a JIA flare or fever attributable to sJIA should be withdrawn from the study *(at the discretion of the investigator).*

Table 2 Neutropenia Management

Patients on Q2W TCZ	Patients on Q3W TCZ	Patients on Q4W TCZ
ANC > 1.0 × 10⁹/L • *Maintain Q2W dosing frequency for TCZ*	ANC > 1.0×10^9/L • Maintain Q3W dosing frequency for TCZ	ANC > 1.0×10^9/L • Maintain Q4W dosing frequency for TCZ

ANC 0.5 to 1.0 × 10⁹/L
• *Interrupt TCZ*
• *When ANC increases to > 1.0 × 10⁹/L resume Q2W TCZ dosing frequency and assess eligibility for Part 2.*
	ANC *0.5 to* 1.0×10^9/L
	• Interrupt TCZ
	• When ANC increases to > 1.0×10^9/L *and*
	  • *If JADAS-71 ≤ 3.8 and patient has no fever (due to sJIA),* resume TCZ with modified Q4W dosing frequency
	  • If patient has not completed *5* consecutive Q3W infusions, resume Q3W dosing until *5* consecutive infusions are completed and then start Q4W dosing for TCZ
	  • *If JADAS-71 >3.8 or patient has fever (due to sJIA) resume TCZ at Q3W dosing frequency*
		ANC *0.5 to* 1.0×10^9/L
		• Interrupt TCZ
		• When ANC increases to > 1.0×10^9/L resume TCZ Q4W dosing frequency for TCZ

ANC <0.5 ×10⁹/L • *Discontinue TCZ*	ANC < 0.5×10^9/L • Discontinue TCZ	ANC < 0.5×10^9/L • Discontinue TCZ

JADAS=Juvenile Arthritis Disease Activity Score; TCZ=tocilizumab; *Q2W=every 2 weeks;* Q3W=every 3 weeks; Q4W=every 4 weeks; sJIA=systemic juvenile idiopathic arthritis.

Table 3 Thrombocytopenia Management

Patients on Q2W TCZ	Patients on Q3W TCZ	Patients on Q4W TCZ
Platelets > 100 × 10⁹/L • *Maintain Q2W dosing frequency for TCZ*	Platelets > 100 × 10^9/L • Maintain Q3W dosing frequency for TCZ	Platelets > 100 × 10^9/L • Maintain Q4W dosing frequency for TCZ

Platelets 50 to 100 × 10⁹/L
• *Interrupt TCZ*
• *If platelets improve to > 100 × 10⁹/L resume TCZ Q2W dosing frequency and assess eligibility for Part 2*
	Platelets 50 to 100 × 10^9/L
	• Interrupt TCZ
	• If platelets improve to > 100 × 10^9/L *and*
	  • *If JADAS-71 ≤ 3.8 and patient has no fever (due to sJIA),* resume TCZ with modified Q4W dosing frequency
	  • If patient has not completed *5* consecutive Q3W infusions, resume Q3W dosing until *5* consecutive infusions are completed then start Q4W dosing for TCZ
	  • *If JADAS-71 > 3.8 or patient has fever (due to sJIA), resume TCZ at Q3W dosing frequency*
		Platelets 50 to 100 × 10^9/L
		• Interrupt TCZ
		• If platelets improve to > 100 × 10^9/L resume Q4W dosing frequency for TCZ

Platelets < 50 × 109/L • *Discontinue TCZ*	Platelets < 50 × 10^9/L • Discontinue TCZ	Platelets < 50 × 109/L • Discontinue TCZ

JADAS=Juvenile Arthritis Disease Activity Score; TCZ=tocilizumab; *Q2W=every 2 weeks;* Q3W=every 3 weeks; Q4W=every 4 weeks; sJIA=systemic juvenile idiopathic arthritis.

3.1.2.2 Elevated Liver Enzymes

For patients in Part 1 and Part 2, the laboratory abnormality guidance in Table 4 should be followed. Patients experiencing a JIA flare or fever attributable to sJIA should be withdrawn from the study (at the discretion of the investigator).

Table 4 Management of Elevated Liver Enzymes

Patients on Q2W TCZ	Patients on Q3W TCZ	Patients on Q4W TCZ
ALT/AST ≤ ULN • *Maintain Q2W dosing frequency for TCZ*	ALT/AST ≤ ULN • Maintain Q3W dosing frequency for TCZ	ALT/AST ≤ ULN • Maintain Q4W dosing frequency for TCZ

ALT/AST > 1 to 3 × ULN
• *Dose modify MTX if appropriate*
• *If persistent increases in this range interrupt TCZ*
• *When ALT/AST returns to ≤ 1 × ULN resume Q2W TCZ dosing and assess eligibility for Part 2*
	ALT/AST > 1 to 3 × ULN
	• Dose modify MTX if appropriate
	• If persistent increases in this range interrupt TCZ
	• When ALT/AST returns to ≤ 1 × ULN
	  • *If JADAS-71 ≤ 3.8, and patient has no fever due to sJIA,* resume TCZ at modified Q4W dosing frequency
	  • If patient has not completed *5* consecutive Q3W *infusions*, resume Q3W dosing until *5* consecutive infusions are completed then start Q4W dosing for TCZ
	  • *If JADAS-71 > 3.8 or patient has fever (due to sJIA), resume TCZ at Q3W dosing frequency*
		ALT/AST > 1 to 3 × ULN
		• Dose modify MTX if appropriate
		• If persistent increases in this range interrupt TCZ
		• When ALT/AST returns to ≤ 1 × ULN resume Q4W dosing frequency for TCZ

ALT/AST > 3 to 5 × ULN • *Dose modify MTX if appropriate* • *Interrupt TCZ* • *When ALT/AST returns to < 3 × ULN follow recommendations above for > 1 to 3 × ULN*	ALT/AST > 3 to 5 × ULN • Dose modify MTX if appropriate • Interrupt TCZ • When ALT/AST returns to < 3 × ULN follow recommendations above for > 1 to 3 × ULN	ALT/AST > 3 to 5 × ULN • Dose modify MTX if appropriate • Interrupt TCZ • When ALT/AST returns to < 3 × ULN follow recommendations above for > 1 to 3 × ULN
ALT/AST > 5 × ULN • *Discontinue TCZ*	ALT/AST > 5 × ULN • Discontinue TCZ	ALT/AST > 5 × ULN • Discontinue TCZ

JADAS = Juvenile Arthritis Disease Activity Score; MTX = methotrexate; TCZ = tocilizumab; ULN = upper limit of normal; *Q2W = every 2 weeks;* Q3W = every 3 weeks; Q4W = every 4 weeks sJIA = systemic juvenile idiopathic arthritis.

If total bilirubin is > 3 mg/dL do not dose study drug (repeat bilirubin, liver function tests [including AST, ALT] in 1 week). If bilirubin returns to below the upper limit of normal (ULN) continue TCZ infusions. Discontinuation of treatment is recommended if 2 consecutive total bilirubin values taken at least 1 week apart are > 3 mg/dL.

If any of the above abnormal laboratory criteria are met, MAS must be excluded. Cases of MAS will be treated according to standard of care for treatment of MAS per the investigator's discretion, and the Sponsor must be notified.

If a liver biopsy is performed for any reason, the biopsy report should be forwarded to Roche. The prepared histologic slides will be requested by Roche and centrally reviewed by a third party. Patients who are withdrawn from the study due to elevated liver function tests must have repeat tests performed, as clinically appropriate, until levels return to baseline. If the patient's liver function tests have not returned to baseline within 6 months (or sooner, if deemed necessary by the investigator), an ultrasound and/or liver biopsy should be considered.

3.1.3 Criteria for Withdrawal from the Study

Patients who experience a JIA flare or fever attributable to sJIA *relative to baseline of Part 2* (as per the definition provided in Section 4.4.1.1) at any *visit in Part 2 of* the study *may* be withdrawn from the study *at the discretion of the investigator*.

Patients who experience any adverse event that in the opinion of the investigator or the Sponsor precludes further study participation *(in Part 1 or 2)* will be withdrawn from the study.

3.2 END OF STUDY

The end of the study will occur when the last participating patient completes the last scheduled visit in the study, or if the Sponsor decides to discontinue the study.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Test Product Dosage

In this study, doses of 8 mg/kg for patients ≥ 30 kg and 12 mg/kg for patients < 30 kg will be used, as per the approved global TCZ sJIA label.

*In Part 2 of the study, i*nstead of being given Q2W, TCZ will be administered IV every 3 or 4 weeks for up to 1 year in patients who have previously experienced at least one laboratory abnormality on the previous Q2W dose regimen *(either in Part 1 or on commercial TCZ prior to entry into Part 2).* Efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity will be assessed upon reduction of dosing frequency in these patients.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures for *Part 2 of* this study are as follows:

- JADAS-71 will be utilized to describe efficacy in patients on Q3W and Q4W dosing as appropriate in this study (as per Section 4.4.1.1)
- JIA flare *relative to baseline of Part 2* will be used to determine those patients not maintaining efficacy who *can* be withdrawn from the study *at the discretion of the investigator* (as per Section 4.5.1.1)
- Fever *(attributable to sJIA)* will be measured at each study visit *of Part 2* in patients on Q3W and Q4W dosing (as appropriate) to describe efficacy and to determine patients not maintaining efficacy *who can* be withdrawn from the study *at the discretion of the investigator* (as per Section 4.5.1.1 and Section 4.5.1.2).

3.4.2 Safety Outcome Measures

The safety outcome measures *in Part 1 and 2 of* this study are as follows:

- Adverse events (including adverse events of special interest)
- Serious adverse events
- Clinical laboratory results

3.4.3 Pharmacokinetic and Pharmacodynamic Outcome Measures

The PK/PD outcome measures for *Part 2 of the* study are as follows:

- Serum TCZ concentration and population PK model predicted PK exposures (area under the serum concentration-time profile [AUC_{τ}], maximum concentration observed [C_{max}], and minimum concentration under steady-state conditions within a dosing interval [C_{min}]) for Q3W and Q4W dosing regimens as appropriate
- Serum IL-6 and sIL-6R levels and inflammatory markers (CRP and erythrocyte sedimentation rate [ESR])
- Anti-TCZ antibodies

3.4.4 Patient-Reported Outcome Measures

The PRO outcome measures for *Part 2 of the* study are as follows:

- The CHAQ (see Appendix 2)
- Parents/patients global assessment of *overall well-being*

4. MATERIALS AND METHODS

4.1 PATIENTS

Children aged 2 years up to and including aged 17 years with sJIA ≥ 1 month and currently receiving TCZ who have experienced a predefined, resolved laboratory abnormality (see Section 4.1.1, Inclusion Criteria *Part 2*) during TCZ Q2W treatment will be eligible to participate in *Part 2 of the* study.

4.1.1 Inclusion Criteria

Part 1 and Part 2

All patients entering Part 1 or entering Part 2 without participating in Part 1 must meet the following criteria for entry *into Part 1 or Part 2*:

- Aged 2 years up to and including 17 years at screening into trial
- sJIA according to International League of Associations for Rheumatology (ILAR) classification (2001)
- *sJIA symptoms lasting for at least 1 month since diagnosis of sJIA*
- Fertility:

  For female patients of reproductive potential (unless surgically sterile with absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose of TCZ

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of < 1% per year include tubal ligation; male sterilization; hormonal implants; established, proper use of combined oral or injected hormonal contraceptives; and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods, such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

  For male patients of reproductive potential: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose of TCZ

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Must meet one of the following:

  Not receiving MTX or discontinued MTX at least 4 weeks prior to *the Part 1 or Part 2* baseline visit, or

  Taking MTX for at least 12 weeks immediately prior to the *Part 1 or Part 2* baseline visit and on a stable dose of ≤ 20 mg/m^2 for at least 8 weeks prior to the *Part 1 or Part 2* baseline visit, together with either folic acid or folinic acid according to local standard of care

- Written informed consent for study participation obtained from parent or legal guardian, with assent as appropriate by the patient, depending on the level of the patient's understanding
- Parental or guardian written agreement to comply with the requirements of the study protocol

Patients entering Part 1 who are naïve to TCZ therapy must also meet the following inclusion criterion:

- *History of inadequate clinical response (in the opinion of the treating physician) to NSAIDs and corticosteroids*

Part 2

All patients entering Part 2 (either directly without participating in Part 1, or via Part 1) must meet the following additional criteria for entry into Part 2:

- JADAS-71 score of 3.8 or less and absence of fever (related to sJIA) at screening and baseline of Part 2
- Neutropenia, thrombocytopenia, or elevated ALT/AST (as per criteria in Table 5) previously experienced (and resolved) on the labeled dose (Q2W) of TCZ

Table 5 Laboratory Abnormalities Serving as Inclusion Criteria *for Part 2* When Experienced (with Resolution) on *Q2W* TCZ

Abnormality	Results Range
Neutropenia	ANC 0.5 to 1.0×10^9/L
Thrombocytopenia	Platelets 50 to 100×10^9/L
Elevated liver enzymes	ALT/AST > 1 to 3 × ULN

TCZ = tocilizumab; ULN = upper limit of normal.

- Not currently receiving oral corticosteroids, or taking oral corticosteroids at a stable dose for a minimum of 2 weeks prior to the *Part 2* baseline visit at no more than 10 mg/day or 0.2 mg/kg/day, whichever is less
- Not taking NSAIDs, or taking no more than one type of NSAID at a stable dose for a minimum of 2 weeks prior to the *Part 2* baseline visit, with the dose being less than or equal to the maximum recommended daily dose

4.1.2 Exclusion Criteria

Patients *entering Part 1, or entering Part 2 without participating in Part 1,* who meet any of the following criteria will be excluded from study entry:

General

- Wheelchair bound or bedridden
- Any other auto-immune, rheumatic disease, or overlap syndrome other than sJIA

- Not fully recovered from recent surgery or less than 6 weeks since surgery, at the time of screening visit; or planned surgery during *Part 1 and* the initial 12 weeks of *Part 2 of* the study *(for patients entering Part 1) or the initial 12 weeks of Part 2 of the study (for patients entering Part 2 without participating in Part 1)*
- Lack of peripheral venous access

General Safety

- Pregnant, lactating, or intending to become pregnant during study conduct and up to *6 months* after the last administration of study drug
- Any significant concurrent medical or surgical condition which would jeopardize the patient's safety or ability to complete the trial
- History of significant allergic or infusion reactions to prior TCZ infusion, and/or presence of anti-TCZ antibodies by confirmatory and/or neutralizing assay at screening
- Inborn conditions characterized by a compromised immune system
- Known HIV infection or other acquired forms of immune compromise
- History of alcohol, drug, or chemical abuse within 6 months of screening
- Evidence of serious uncontrolled concomitant diseases, including but not limited to the nervous, renal, hepatic, or endocrine systems
- Any active acute, subacute, chronic, or recurrent bacterial, viral, or systemic fungal infection including but not limited to:

    Acute or chronic renal/bladder infections

    Acute or chronic pulmonary infections
- History of atypical tuberculosis (TB)
- Active TB requiring treatment within 2 years prior to the screening visit
- Positive purified protein derivative (PPD) at screen (or equivalent result based on local methodology, e.g., Quantiferon gold), unless treated with anti-TB therapy for at least 4 weeks prior to receiving study drug and chest radiograph is negative for active TB within 6 months of screening visit according to local practice
- Any major episode of infection requiring hospitalization or treatment during screening or treatment with IV antibiotics completing within 4 weeks of the screening visit or oral antibiotics completing within 2 weeks of the screening visit
- History of reactivation or new onset of a systemic infection, such as herpes zoster or Epstein Barr virus, within 2 months of the screening visit
- Hepatitis B surface Antigen or hepatitis C Ab positive
- Chronic hepatitis—viral or autoimmune
- Significant cardiac [e.g., congenital heart disease, valvular heart disease, constrictive pericarditis (unrelated to sJIA), myocarditis] or pulmonary disease, (e.g., asthma for which the patient has required the use of oral or parenteral

corticosteroids for ≥ 2 weeks within 6 months prior to the baseline visit *of Part 1 or Part 2, or* cystic fibrosis)

- History or concurrent serious gastrointestinal (GI) disorders, such as ulcer or inflammatory bowel disease, Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions, including ulcer and perforation
- History of or current cancer or lymphoma
- Uncontrolled diabetes mellitus with elevated hemoglobin (Hgb) A1c as defined by age-specific standards (Silverstein et al. 2005)
- History of MAS within 3 months prior to the screening visit

Excluded Previous or Concomitant Therapy

- Participation in another interventional clinical trial within the past 30 days or 5 serum half-lives of the investigative medication or the PD effect of the investigative medication, whichever is longer
- Prior stem cell transplant at any time
- Prohibited therapy as described in Section 4.3.2

Laboratory Exclusions at Screening

- Serum creatinine > 1.5 × ULN (for age and sex)
- Hemoglobin < 7.0 g/dL (< 4.3 mmol/L)

The following additional laboratory exclusion criteria apply to patients entering Part 1 of the study who are TCZ-naive and are initiating therapy with TCZ:

- *AST or ALT >1.5 ULN (upper limit of normal for age and sex)*
- *Total bilirubin >1.3 mg/dL (>23 µmol/L)*
- *Platelet count <150 x 10^3/µL (<150,000/mm^3)*
- *WBC count <5,000/mm^3 (<5.0 x 10^9/L)*
- *Neutrophil count <2,500/ mm^3 (<2.5 x 10^9/L)*

4.2 Study Treatment

Category	Treatment
Investigational medicinal products: test product	TCZ
Concomitant therapy	MTX, NSAIDs, prednisone, or corticosteroid equivalent

NSAID = nonsteroidal anti-inflammatory drug;
MTX = methotrexate; TCZ = tocilizumab.

4.2.1 Formulation, Packaging, and Handling

4.2.1.1 Tocilizumab

TCZ (200 mg/10 mL) vial (concentrate for solution for infusion) RO 487-7533/F01 will be supplied. Study drug packaging will be overseen by the Roche clinical trial supplies department and will include a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labeling of the study drug will be in accordance with Roche standard and local regulations. The study drug must be stored according to the details on the product label.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals, and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

All TCZ vials must be stored at a controlled temperature of 2°C–8°C, and handled according to Good Manufacturing Practice and Good Clinical Practice (GCP) procedures. A temperature log must be kept recording the storage temperature of the TCZ and infusion bags at least once a day.

The investigator or designated person (e.g., pharmacist) will be responsible for maintaining accurate records for all supplies used. Opened TCZ vials will be stored, still containing any residual volume of fluid, at room temperature for the purposes of monitoring of drug accountability.

After accounting of supplies, the Sponsor will give written authorization to the investigator to return or destroy any remaining study drug as instructed. Under no circumstances is the investigator to allow the study drugs to be used other than as directed by the protocol.

For further details, see the most recently published version of the Investigator's Brochure for TCZ.

4.2.2 Dosage, Administration, and Compliance

4.2.2.1 Tocilizumab

Part 1

TCZ dosed by body weight (12 mg/kg for patients < 30 kg; 8 mg/kg for patients ≥ 30 kg) will be administered IV Q2W for ≤24 weeks or until the patient experiences an event of neutropenia, thrombocytopenia, or liver enzyme abnormality as per the criteria provided in Table 5. Following the occurrence and resolution of this laboratory abnormality, patients who have a final successful screening evaluation (Screening Evaluation 2) may enter Part 2 of the study.

Patients who do not experience a laboratory abnormality in Part 1, or experience a laboratory abnormality but do not meet the eligibility criteria for Part 2, will complete Part 1 through to Week 24, followed by the Part 1 withdrawal visits.

Part 2

TCZ dosed by body weight (12 mg/kg for patients < 30 kg; 8 mg/kg for patients ≥ 30 kg) will be administered IV Q3W for a minimum of 12 consecutive weeks (*5* consecutive infusions), switching to Q4W in response to predefined laboratory abnormalities for patients eligible to continue treatment for the duration of the study (52 weeks in total).

Patients who do not meet the criteria to switch from Q3W to Q4W will complete Part 2 through to Week 52, followed by the Part 2 withdrawal visits.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

TCZ will be supplied in vials containing 10 mL of a sterile solution of 20 mg TCZ/mL. *The TCZ dose will be calculated using the Part 1 or Part 2 baseline body weight (<30 kg or ≥30 kg) and will not be changed until a patient's weight falls into the other body weight category on three separate, consecutive occasions. The number of vials to be used for each body weight category is described in Table 6.*

Table 6 Tocilizumab Dosage

Weight (kg)	Number of Vials	Dose
≤16.5	1	12 mg/kg
>16.5–≤30	2	12 mg/kg
>30–≤50	2	8 mg/kg
>50–≤75	3	8 mg/kg
>75–≤100	4	8 mg/kg
>100–≤125	5	8 mg/kg
>125–≤150	6	8 mg/kg

For the preparation of the infusion bag for a patient<30 kg, 0.6 mL per kg of the patient's body weight will be withdrawn from a 50 mL infusion bag. This volume will be replaced in the saline bag with an equal volume of TCZ. For a patient≥30 kg, 0.4 mL per kg of the patient's body weight will be withdrawn from a 100 mL infusion bag. This volume will be replaced in the saline bag with an equal volume of TCZ.

The TCZ vials will be stored at a temperature of 2°C–8°C. The infusion bag of study drug (after it has been prepared) may be stored at 2°C–8°C for 24 hours providing that the infusion is prepared aseptically and allowed to return to room temperature before

administration (1 to 2 hours depending on ambient room temperatures). A temperature log must be kept in order to monitor the ambient temperature in the pharmacy and the refrigerators storing the vials of study drug.

For a 50-mL infusion bag the initial infusion speed should also be 10 mL/hr for 15 minutes and then increased to 65 mL/hr. Total infusion time should be no less than 1 hour. In order to flush the remaining study drug through the IV set, 10 mL of normal saline will be administered immediately following the infusion of study drug. The volume of the saline flush should not be included in the total infusion volume recorded in the eCRF. The time the "saline flush" is completed should be noted as the time when the infusion is complete. *T*he timing of any related post-infusion blood draws (PK) that are required *should also be noted*.

All study drug volumes must be recorded in eCRF. Additional details of the infusion preparation and medication volumes will be provided by the Sponsor and in the infusion bag preparation instructions.

TCZ will be administered at room temperature by controlled infusion into a peripheral vein over a 1-hour period. The option to administer study drug via a pre-existing central line may be considered under certain circumstances and must be discussed with the clinical pharmacologist and/or medical monitor prior to the implementation.

4.2.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (TCZ) *during Part 1 and Part 2* will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, using the IXRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.2.4 Post-Trial Access to TCZ

The Sponsor *will offer post-trial access* to *the study drug* TCZ *free of charge to eligible* patients *in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.*

A patient *will be eligible to receive study drug after the end of the study if all of the following conditions are met*:

- *The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being*
- *There are no appropriate alternative treatments available to the patient*
- *The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- *The study drug* is commercially *marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)*
- *The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective* for sJIA
- *The Sponsor has reasonable safety concerns regarding the study drug as treatment for sJIA*
- *Provision of study drug is not permitted under the laws and regulations of the patient's country*

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site: http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf.

4.3 CONCOMITANT THERAPY

4.3.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study completion/early termination visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Methotrexate:

Part 1 and 2, MTX is permitted but not required during this study. If a patient has been on MTX in the past they should have discontinued MTX at least 4 weeks prior to the baseline visit *of Part 1 and 2 of the study.* Those patients receiving MTX should have been taking MTX for at least 12 weeks immediately prior to the baseline visit *of Part 1 and Part 2* and should be receiving a stable dose of $\leq$20 mg/m^2 for at least 8 weeks prior to the baseline visit *of Part 1 and 2 of the study*, together with at least the minimum recommended dose of either folic acid or folinic acid according to the local standard of care. During the study, if applicable, the MTX dose may be decreased at any time for documented reasons of safety but not for efficacy (improvement in symptoms) during

Part 1 and the first 12 weeks of *Part 2 of* the study (and until 5 consecutive Q3W infusions have been given). If any patient should move to Q4W dosing, *the* MTX dose should also remain stable until 3 consecutive Q4W infusions of TCZ have been given.

Steroids:

There are no restrictions on the use of steroids in Part 1 of the study.

*For Part 2 of the study, p*atients who are not currently receiving *oral* corticosteroids or *are* taking oral corticosteroids at *a* stable dose for a minimum of 2 weeks prior to the *Part 2* baseline visit at no more than 10 mg/day or *0.*2 mg/kg/day*,* whichever is less*,* are allowed in the study. *If patients are receiving oral corticosteroids, the dose should remain stable during the first 12 weeks of Part 2 (until 5 consecutive 3 weekly infusions have been given), and for patients moving to 4 weekly dosing, until 3 consecutive 4 weekly infusions of TCZ have been given.*

Intra-articular (IA), intramuscular (IM), IV, and long-acting corticosteroids (such as dexamethasone) are not permitted within 4 weeks of baseline *of Part 2* or throughout *Part 2 of* the study.

Injection of IA corticosteroids during the first 12 weeks of *Part 2 of* the study (and until *5* consecutive 3 weekly infusions have been given) is strongly discouraged as these may affect the exploratory efficacy endpoints. The same applies for patients moving to 4 weekly dosing, until 3 consecutive 4 weekly infusions of TCZ have been given. Injections of IA corticosteroids are not permitted within 4 weeks of baseline *of Part 2 of the study; during Part 2* a maximum of 2 joint injections will be allowed in 1 year, and the related joint will be considered active for 3 months following the injection. If an IA injection is absolutely required, no more than 1 joint should be injected with the smallest possible dose appropriate to the size of the joint being injected.

Corticosteroids can be changed for reasons of safety (e.g., asthma attack, serositis) to maximum of 30 mg/day or 0.5 mg/kg/day prednisone or equivalent, whichever is less, for a maximum dosing period of $<$14 days, after which the corticosteroid dosage must be returned to *the Part 2* baseline *dosage*.

NSAIDs:

There are no restrictions on the use of NSAIDs in Part 1 of the study.

*For Part 2 of the study, p*atients who are not taking NSAIDs, or taking no more than one type of NSAID at a dose that has remained stable for $>$2 weeks prior to the baseline visit *of Part 2 of the study* and is less than or equal to the maximum recommended daily dose are included in *Part 2 of* the study. The dose of NSAID must remain stable throughout the first 12 weeks of *Part 2 of* the study (and until *5* consecutive Q3W infusions have been given). In addition, for patients moving to Q4W dosing, the dose of NSAIDs should remain stable for the first 12 weeks of Q4W dosing. The dose may be

lowered for documented reasons of safety and only tapered for efficacy after *5* consecutive doses have been completed for Q3W dosing *(12 weeks), and 3 consecutive doses have been completed for Q4W dosing (12 weeks).*

Acetaminophen (Paracetamol) and Other Analgesics:

Normal-release acetaminophen (not extended release) may be used for pain as required. Analgesics should not be taken within 6 hours prior to a visit where clinical efficacy assessments are performed *in Part 2 of the study.* The administration of analgesics should always be recorded in the eCRF.

Iron and Folic Acid:

Iron supplementation can be prescribed based on investigator's assessment of risk–benefit for treatment of the anemia with iron. Folic acid should be administered to patients receiving MTX *in Part 1 and Part 2 of the study*.

4.3.2 Prohibited Therapy

DMARDs:

Leflunomide is not allowed *at any time* during the study. Discontinuation of leflunomide should be followed by standardized cholestyramine washout. Leflunomide levels must be documented to be below the limit of detection prior to the baseline visit *of Part 1 or Part 2*.

Cyclophosphamide is not permitted *at any time* during the study and within 3 months prior to the baseline visit *of Part 1 or Part 2*.

Etoposide (VP16) is not permitted *at any time* during the study or within 3 months prior to the baseline visit *of Part 1 or Part 2.*

Treatment with DMARDs (other than MTX) or immunosuppressants, including but not limited to: hydroxychloroquine, chloroquine, gold, azathioprine, D-penicillamine, sulfasalazine, cyclosporine, thalidomide, must have been discontinued within 6 weeks prior to the baseline visit *(Part 1 or Part 2)* and leflunomide must have been discontinued within 12 weeks prior to the *Part 1 or Part 2* baseline visit.

If the patient has received previous treatment with any of the following biologic agents other than TCZ, these must have been discontinued according to the following timelines prior to the baseline visit of either Part 1 or 2, and are not permitted during the study:

- *Etanercept must have been discontinued within ≥2 weeks prior to baseline.*
- *Anakinra must have been discontinued within ≥4 days prior to baseline.*
- *Abatacept must have been discontinued within ≥12weeks prior to baseline.*
- *Infliximab or adalimumab must have been discontinued within ≥8 weeks prior to baseline.*
- *Canakinumab must have been discontinued within ≥20 weeks prior to baseline.*

- *Rilonacept must have been discontinued within ≥6 weeks prior to baseline.*
- *Golimumab must have been discontinued within ≥10 weeks prior to baseline.*
- *Certrolizumab pegol must have been discontinued within ≥10 weeks prior to baseline.*

IA, IM, IV, and long-acting corticosteroids (such as dexamethasone) are not permitted within 4 weeks of baseline *of Part 2* or throughout *Part 2 of* the study.

Immunoglobulin:

Administration of IV immunoglobulin is not permitted during the *entire* study or within 4 weeks prior to the baseline visit *of Part 2 of the study*. For active varicella infection (chickenpox) or significant exposure to varicella zoster infection in a patient without a history of chickenpox (varicella IgG titer available from screening), varicella zoster immunoglobulins can be given at the discretion of the investigator.

Hyaluronic Acid and Plasmapheresis:

IA injections of hyaluronic acid and plasmapheresis are not permitted *at any time* during the study.

Cell-Depleting Therapies:

Previous treatment with any cell depleting therapy, including any investigational agents, (e.g., anti-CD19 and anti-CD20) *or cell-depleting therapy during the study at any time* is not permitted.

Stem Cell Transplant:

Previous treatment with prior stem cell transplant*, or stem cell transplant during the study* at any time*, is* not permitted.

Vaccines:

Live or attenuated vaccines are not permitted within 4 weeks of the baseline visit *of Part 1 or 2 of the study, or at any time* during *the* study, or within 12 weeks following the last administration of study drug. Patients are advised to be brought up to date with vaccines prior to start of the study, as appropriate.

4.4 STUDY ASSESSMENTS

4.4.1 Description of Study Assessments

4.4.1.1 Efficacy-Clinical Assessments

For the efficacy assessments *in Part 2 of the study*, the baseline score will be taken as the assessment prior to dosing at Visit 1 Day 1 *of Part 2*. Clinical measures of efficacy will be evaluated for patients on Q3W and Q4W TCZ as applicable.

- JADAS-71 composite disease activity score for JIA, composed of the following 4 measures:

  Physician global assessment of disease activity by visual analogue scale (100 mm horizontal visual analogue scale [VAS])

  Parent/patient global assessment of overall well-being (100 mm horizontal VAS)

  Number of joints with active arthritis (out of 71)

  ESR

- Fever *(attributable to sJIA)*

  Absence of fever at screening visit is defined as a temperature measurement $<38°C$.

  Presence of fever at each study visit (per the Schedule of Assessments in (see Appendix 1) is defined as a temperature measurement $\geq 38°C$ (Ruperto et al. 2010).

- JIA definition of disease flare (worsening in patients with JIA) is defined in this trial:

  Recurrence of fever or JIA flare defined as any 3 of the 6 core outcome variables worsening by at least 30% *relative to baseline visit of Part 2,* with no more than 1 of the remaining variables improving by more than 30% since the *Part 2* baseline evaluation at *Part 2* Visit 1, Week 0.

  If either the number of joints with active arthritis or the number of joints with limitation of motion is used in the calculation of flare for a study visit in a patient, then a minimum worsening of at least 2 active joints or 2 joints with limitation of motion must be present.

  If either the physician global assessment or the parent/patient global assessment are used in the calculation of flare for a study visit in a patient, then a minimum worsening of at least 2 units on a scale from 0 to 10 must be present (Lovell et al. 2000).

  For ESR, a worsening of at least 30% will not be considered if the value of ESR is still within normal ranges.

The JIA core outcome variables consist of:

- Physician Global Assessment of Disease Activity (100 mm horizontal VAS)
- Parent/patient global assessment of overall well-being (100 mm horizontal VAS)
- Number of joints with active arthritis (out of 71)
- Number of joints with limitation of movement (out of 67)
- Laboratory measure of acute phase reaction (ESR will be used in this study)
- Functional ability determined by CHAQ Disability Index

Assessments should be made as described in the Schedule of Assessments in Appendix 1.

4.4.1.2 Medical History and Demographic Data

Medical history and demographic data will be taken at the times indicated in the Schedule of Assessments *for Part 1 or Part 2 of the study* (see Appendix 1). Demographic data will be recorded as well as medical history and concomitant illnesses. A history of all DMARDs used in the past will be recorded, and the use of biologic medications will be specifically asked for. Medical history will also include prior immunizations/vaccines.

4.4.1.3 Vital Signs

Vital signs (pulse rate, systolic, and diastolic blood pressure, and temperature) will be taken at the times indicated in the Schedule of Assessments *in Part 1 and 2 of the study* (see Appendix 1). Assessments will be taken with the patient having been in a semi-supine position for at least 5 minutes.

Vital signs will be taken pre-infusion, every 30 minutes during infusion, and 30 minutes after the infusion is completed. All readings will be recorded in the eCRF. Additional readings may be taken at the discretion of the investigator in the event of an infusion-related reaction.

Vital signs recordings will start with the screening period and continue throughout the study up to and including the last dosing visit, as outlined in the Schedule of Assessments (see Appendix 1).

4.4.1.4 Height and Weight Measurements

Height and weight will be measured as outlined in the Schedule of Assessments *in Part 1 and 2 of the study* (see Appendix 1). Height will be measured in a standing position using a wall mounted stadiometer or equivalent as per local practice. Weight should be determined to the nearest 0.1 kg. For body weight measurements, the patient will wear typical daytime clothes but shoes, outerwear, and accessories should be removed.

4.4.1.5 Physical Examinations

A general physical examination will be performed and recorded as “normal” or “abnormal” at the times indicated in the Schedule of Assessments *in Part 1 and 2 of the study* (see Appendix 1). Abnormalities should be specified. Any persisting abnormalities should be stated each time the examination is performed. Diagnosis of new abnormalities should be recorded as adverse events if clinically appropriate. The presence of specific physical examination findings that are associated with active sJIA, such as splenomegaly, hepatomegaly, and lymphadenopathy, will be recorded. Entries in the musculoskeletal examination portion should only record findings such as deformities, dislocations, subluxations contractures fusions, or specific muscle atrophy or weakness and not the presence or absence of signs of joint inflammation such as swelling or tenderness.

4.4.1.6 Physician's Global Assessment of Disease Activity

The physician's global assessment of disease activity is the physician's assessment of the patient's current disease activity on a 100 mm horizontal VAS. The extreme left end of the line should be described as "arthritis inactive" (symptom-free and no arthritis symptoms) and the extreme right end as "arthritis very active." This should be completed by the treating physician at the times indicated in the Schedule of Assessments *for Part 2 of the study* (see Appendix 1).

4.4.1.7 Joint Assessments

The joint assessor will evaluate if the joints are swollen, tender/painful, and limited as per standard Rheumatology International Trials Organisation/Pediatric Rheumatology Collaborative Study Group (PRINTO/PRCSG) rheumatologic examination form (or equivalent). The joint counts (swollen, tender/painful, limited, and active) will be evaluated at the times indicated in the Schedule of Assessments *for Part 2 of the study* (see Appendix 1). The trained and certified joint assessor should be a pediatric rheumatologist or skilled arthritis assessor. Roche will ensure that primary joint assessors have received training to become qualified and will require documentation that such training was received. One back-up joint assessor can be trained at the site by the primary joint assessor for planned or unscheduled absences. To ensure consistent joint evaluation throughout the trial, it is requested that joint assessments be carried out by the primary joint assessor for all study visits, whenever possible.

4.4.1.8 Temperature

The patient's temperature will be taken at the times indicated in the Schedule of Assessments *for Part 1 and 2 of the study* (see Appendix 1). Additional supplemental temperatures may be measured as deemed necessary. Temperature recordings will start with the screening period *for Part 1 and 2 of the study* and continue throughout the study up to and including the withdrawal (WD1) or the last dosing visit as outlined in the schedule of assessments.

4.4.1.9 Laboratory Assessments

Samples of blood and urine will be obtained as indicated in the Schedule of Assessments (see Appendix 1) for the tests listed below *for Part 1 and 2 of the study*. On days when fasting labs are required (such as lipid profiles), blood samples will be taken after an 8-hour fast. These visits are identified in the schedule of assessments as fasting labs. Normal ranges for the local site study laboratory parameters must be supplied to Roche before the study starts.

For samples collected at non-dosing visits as indicated in the Schedule of Assessments (see Appendix 1), there is the option to have these samples collected at home if consent is obtained. If a patient decides to participate in the home nursing for collection of blood at non-dosing visits, the home nursing network will communicate with the patient's site to organize a nurse to visit the patient at home on scheduled non-dosing visit days to collect the relevant samples.

The total volume of blood loss for laboratory assessments (including all safety, efficacy, and PK/PD samples) does not exceed the per visit and per cumulative visits recommendations by the Seattle Children's Hospital (Seattle Children's Hospital Research Foundation 2001) and the National Institutes of Health for the expected average weights of the patient population from age 2 years (13 kg) up to and including age 17 years (65 kg).

Biological samples taken from all patients may be infectious and will be classified as "infectious specimens" for dispatch purposes.

The procedures for the collection, handling, and shipping of laboratory samples are specified in the Study Laboratory Reference Manual.

Hematology *(Parts 1 and 2):* CBC: hemoglobin, hematocrit, RBC, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, WBC and differential, platelets, reticulocytes (centrally)

Blood chemistry *(Parts 1 and 2):* AST, ALT, alkaline phosphatase, total protein, albumin, total, direct and indirect bilirubin, urea, uric acid, creatinine, glucose, potassium, sodium, chloride, calcium, phosphorous, LDH

Urinalysis *(Parts 1 and 2):* Dipstick for blood, protein and glucose (performed locally or microscopic examination fresh specimen sent to central laboratory, if abnormal and applicable), pregnancy testing when applicable (Tanner stage 2 or above or onset of menarche during the study)

Screening tests *(Parts 1 or 2):* Hepatitis B surface antigen, hepatitis C antibody, HgbA1c, high-sensitivity C-reactive protein (hsCRP), fibrinogen, Epstein-Barr virus (EBV) titer, varicella IgG testing, ESR

Acute phase reactants *(Part 2):* hsCRP, serum ferritin, C4, C3, ESR to be performed locally. [redacted] has defined an ESR of $<$20 mm/hr for both girls and boys as normal utilizing the [redacted]-supplied kits).

Fibrinogen, D-dimer *(Part 2)*:

Lipid profile *(Part 2):* Total cholesterol, HDL, LDL, triglycerides

Immunology profile *(Part 2):* IgG, immunoglobulin M, immunoglobulin A

PK/PD *(Part 2):* TCZ, IL-6, sIL-6R

Immunogenicity assessments/anti-TCZ antibodies *(Parts 1 and 2):* Anti-TCZ antibodies will be collected for all study patients to evaluate immunogenicity of TCZ as described in Section 5.1.1.6.

4.4.1.10 Patient-Reported Outcomes

PRO data will be elicited from the patients in *Part 2 of the* study to more fully characterize the clinical profile of TCZ. The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the parent/guardian/patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

4.4.1.10.1 Childhood Health Assessment Questionnaire

The CHAQ takes less than 10 minutes to administer and in this study the version that is completed by the parent or guardian will be used. This assessment will be done at visits as specified in the Schedule of Assessments *for Part 2 of this study* (see Appendix 2). The form should be completed by the parent/guardian as appropriate. To ensure consistency the form should be completed throughout the study by the same individual who completed the baseline global assessment *of overall well-being* (see Appendix 2).

Disability Index

The functional ability instrument used in *Part 2 of* this study for calculating the JIA flare is the Disability Index of the CHAQ (see Appendix 2). It is an adaptation of the Stanford Health Assessment Questionnaire (HAQ) for use in children. Three components are evaluated: 1) difficulty in performing daily functions, 2) use of special aids, and 3) assistance from other people. The CHAQ was adapted from the HAQ by adding several new questions, so that there is at least one question for each function that is relevant to children of all ages. This way, bias due to developmental difference can be minimized.

Parent's/Patient's Global *Overall Well-Being*

The patient's overall assessment of their *overall well-being* is recorded on a 100 mm horizontal visual analogue scale (VAS) *in Part 2 of this study.* The left-hand extreme of the line should be described as "very well" (symptom-free and no arthritis symptoms) and the right-hand extreme as "very poor" (maximum arthritis disease activity).

Parental/Patient Pain Index

In addition to the Disability Index, in the CHAQ (see above) there is a Pain Index, which is measured separately *in Part 2 of this study.* The level of pain is determined by the presence of pain, which is measured on a 100 mm horizontal VAS. This scale is anchored at the left-hand extreme of the line as "no pain" and the right-hand extreme as "very severe pain."

4.4.1.11 PPD and Chest Radiograph

Patients will have a PPD test (5 TU) (or equivalent as per local practice, e.g., Quantiferon gold) performed at screening *(of Part 1 or 2 of the study)* unless a negative PPD has already been documented within the last year. The PPD test will be considered positive according to the local guidelines for immunosuppressed patients.

The definition of a positive PPD test may be applied as determined by the clinical circumstances and investigator according to published guidelines and/or local standards endorsed by the medical society. If no published guidelines are available for a given country outside the United States, the U.S. guidelines must be followed.

Patients will have a TB screening test per local standard (e.g., PPD skin test or Quantiferon® test).

A chest X-ray (CXR) is required under the following conditions:

- *If a patient's TB testing is positive at screening (of Part 1 or Part 2) and the patient has not previously received TB treatment, then a CXR is required at screening.*
- *If a patient eventually is enrolled (Part 1 or Part 2), TCZ administration would be delayed until the patient has received at least 4 weeks of TB treatment therapy per exclusion criteria.*

A chest x-Ray may be required under the following conditions:

- *If a patient's TB testing is negative at screening (of Part 1 or 2), then a CXR should be done if consistent with local requirements but is not strictly required.*

A chest X-ray is not required under the following conditions:

- *If a patient's TB testing is positive and the patient has previously completed TB treatment or has been receiving TB treatment for at least 4 weeks prior to receiving TCZ and has had a negative CXR ≤6 months of screening (of Part 1 or 2), then he/she is eligible to enroll without repeat CXR at screening (if consistent with local practice requirements).*
- *A CXR obtained ≤90 days of baseline (of Part 1 or 2) can be utilized for screening purposes, if consistent with local practices.*

Patients asked to participate in this study will have received corticosteroid therapy and often other immunosuppressive drugs. It has been reported that the PPD response alone is not always sufficient for screening children with JIA for TB (Kasapcopur et al. 2006). In addition, patients with significant cardiac abnormalities are excluded from study participation (see Section 4.1.2, Exclusion Criteria *for General Safety*). As a result, a negative chest radiograph is required at the time that TCZ therapy was *or is* initiated, or as per local practice requirements. The chest radiograph should be interpreted by a board-certified radiologist and the interpretation should include a statement of the following at a minimum:

- No evidence of active TB
- No evidence of any active infection including TB
- No evidence of malignancy
- No evidence of significant heart disease

4.4.2 Timing of Study Assessments

4.4.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

The legal guardian for each patient must sign and date the most current Institutional Review Board (IRB)/Ethics Committee (EC) approved written informed consent before any study-specific assessments or procedures are performed. Assent may be obtained from the patient depending on his/her understanding. An original signed consent form will be retained by the investigator and the parent/guardian/patient will receive a copy to take home.

Patients whose guardian has given written informed consent will undergo *two* screening examination*s: one* within 4 weeks before the start of *Part 1 (Screening Evaluation 1, for patients entering Part 1) and one within 4 weeks of Part 2 of the* study *(Screening Evaluation 2, for patients entering into Part 2 directly, or entering Part 2 via Part 1).* TCZ infusions may continue to be received during *S*creening *Evaluation 2,* but there must be at least 10 days clear between the last TCZ infusion during screening and the first study TCZ infusion received at baseline. During the Screening *Evaluation visits 1 and 2 (for patients entering the study via Part 1 or Part 2),* inclusion/exclusion criteria, *demographics,* medical history, concomitant *medication,* physical examination, *height and* weight, vital signs, laboratory safety tests (screening labs [hepatitis B surface antigen, hepatitis C antibody, HgbA1c, hsCRP, fibrinogen, EBV titer, and varicella IgG, and ESR]; hematology; blood chemistry; urine pregnancy [female patients who are able to become pregnant]), TB screening, and chest X-ray (if applicable) will be performed. The CHAQ score, the number of joints with active arthritis and number of joints with limited range of motion (joint assessment), global assessment of the severity of the disease by the physician (physician global), and global assessment of overall well-being by the patient or parent (patient/parent global) will *also* be evaluated *at Screening Evaluation 2* as per the schedule of assessments (see Appendix 1).

Patients must fulfill all entry criteria to be accepted into the study. Patients who fail to meet the entry criteria may be rescreened once *for Part 1 or Part 2 of the study*, at the discretion of the investigator.

Patients, who have experienced a laboratory abnormality that has subsequently resolved during Part 1, may be screened to enter the Part 2. If a patient fails Screening Evaluation 2, the patient may continue participating in Part 1 (returns to Part 1 at the visit after their last visit) up to 24 weeks. If the patient is still not eligible for Part 2 after 24 weeks, the patient will be withdrawn from Part 1 and attend the Part 1 withdrawal visits. However if the patient experiences the relevant laboratory requirements (per Table 5) after discontinuing the study while on commercial TCZ,

they may be rescreened once for Part 2 of the study at the discretion of the investigator. Patients can be screened for Part 2 a total of two times.

An Eligibility Screening Form documenting the investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed and signed by the investigator (or designee). A screen failure log must be maintained by the investigator.

Patients cannot commence enrolment procedures until all entry criteria have been fulfilled. Where the clinical significance of abnormal laboratory test results is considered uncertain, screening laboratory tests may be repeated.

Once a patient has fulfilled the entry criteria, patients will be enrolled into the study. The patient numbers will be generated by Roche or its designee.

Under no circumstances will patients who enroll in *Part 1 or Part 2* and have completed treatment as specified*,* be permitted to re-enroll *into the same part of* the study. *However, patients who have participated in Part 1 without meeting eligibility criteria for Part 2 may be rescreened for Part 2 (see above).*

See Appendix 1 for the schedule of screening and pretreatment assessments *for Part 1 and Part 2*.

4.4.2.2 Assessments during Treatment

See Appendix 1 for the Schedule of Assessments performed during the treatment period *in Part 1 and Part 2*.

4.4.2.3 Assessments at Study Completion/Early Termination Visit

Patients who complete visits in the study *in Part 1 and Part 2* as outlined in the Schedule of Assessments*,* or discontinue from the study early*,* will be asked to return to the clinic 2 weeks after the last dose of study drug for a follow-up visit (WD1) and then subsequently 2 weeks later for WD2, another 4 weeks later for WD3 and further 4 weeks later for WD4. *If the investigator withdraws a patient due to sJIA flare or fever attributable to sJIA, t*he visit at which JIA flare assessment shows flare of disease may be used as the study completion/early termination visit.

See Appendix 1 for the Schedule of Assessments performed at the study completion/early termination visit *for Part 1 and 2*.

4.4.2.4 Follow-Up Assessments

Patients who terminate study participation by withdrawing consent will not be required to return for any follow-up assessments.

Patients and/or parents/legal guardians who discontinue study drug infusions for adverse events or other reasons and have not withdrawn consent should complete all withdrawal visits.

After the study completion/early termination visit, adverse events should be followed as outlined in Section 5.5 and Section 5.6 *for Part 1 and Part 2 of the study.*

See Appendix 1 for the Schedule of Follow-Up Assessments (visits WD1–WD4).

4.5 PATIENT, STUDY, AND SITE DISCONTINUATION

4.5.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time *(Part 1 and 2).* In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following*:*

- Patient/guardians may request withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Lost to follow up
- Death

4.5.1.1 Discontinuation from Study Drug

Patients must discontinue *the* study drug if they experience any of the following *at any time (Part 1 and 2):*

- Pregnancy
- Anaphylaxis or serious hypersensitivity as per Section 5.1.1.6
- *s*JIA flare *(Part 2 only and at the discretion of the investigator)*
- MAS
- Fever attributable to sJIA *(Part 2 only and at discretion of investigator)*

Patients who discontinue study drug prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 4.4.2.3) and may undergo follow-up assessments (see Section 4.4.2.4). The primary reason for premature study drug discontinuation should be documented on the appropriate page of the eCRF. Patients who discontinue study drug prematurely will not be replaced.

4.5.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study *in both Part 1 and Part 2. Parents/guardians should be asked if they can still be*

contacted for further information. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

If lost to follow-up, the investigator should contact the patient's parents/guardian or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF. The patient should, if possible, not be withdrawn from the study but only the study drug and if possible, the patient should be followed until the adverse event has resolved (see Section 5.5).

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

4.5.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for GCP

The investigator may also withdrawal a patient from the study at any time. Reasons for withdrawing a patient from the study may include, but are not limited to, the following:

- Non-compliance with the requirements of the study
- Any adverse event that in the opinion of the investigator or the Sponsor precludes further study participation
- It is in the best interest of the patient

When applicable, parents/guardians should be informed of circumstances under which their child's participation may be terminated by the investigator without the parent's/guardian's consent. The investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure, or any reason where it is felt by the investigator that it is in the best interest of the patient to be discontinued from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient and/or parent/legal guardian.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety of patients *in Part 1 and Part 2 of the study* will be assessed by physical examination, assessment of vital signs, screening for TB and treatment as applicable, laboratory assessments (see Section 4), and the collection of adverse events.

5.1.1 *Risks associated with TCZ Therapy and Risk Mitigation Strategies*

This section describes the known and potential risks of TCZ therapy, and risk mitigation strategies that should be followed during this study (Part 1 and Part 2).
Adherence to the planned dose regimen of TCZ is required unless an adjustment is necessary for safety reasons. The following risk mitigation and dose modification rules apply to patients receiving the study drug *in Part 1 and 2 of the study.*
Recommendations for vigilance with signs and symptoms of particular safety events of interest are summarized in the following sections. For study visits *(Part 1 and Part 2)* at which the study drug dose is held due to toxicity, all other study assessments should be performed as per study schedule. For management of neutropenia, thrombocytopenia, and elevated liver enzymes in the study, see Section 3.1.2.

5.1.1.1 Opportunistic Infections and Serious Infections

Physicians should exercise caution when considering the use of TCZ in patients with a history of recurring infection or with underlying conditions (e.g., diabetes) that may predispose patients to infections. TCZ should not be administered to patients with active infection. The effects of TCZ on CRP, neutrophils, and the signs and symptoms of infection should be considered when evaluating a patient for a potential infection.

Vigilance for timely detection of serious infection is recommended for patients receiving biologic agents as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reaction. Patients/legal guardians must be instructed to contact their child's physician immediately when any symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment. If a patient develops a serious infection, administration of TCZ is to be interrupted until the infection is controlled. The physician must consider the benefit – risk before resuming treatment with TCZ.

5.1.1.2 Gastrointestinal Perforations

Although uncommon in the pediatric population, patients/legal guardians should be made aware of the symptomatology potentially indicative of diverticular disease, and they should be instructed to alert their healthcare provider as soon as possible if these symptoms arise. Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticulitis and thus reduce the risk of GI perforations. In patients with a history of symptomatic diverticulosis, diverticulitis or chronic ulcerative lower GI disease, such as Crohn's disease, ulcerative colitis, or other chronic lower GI conditions that might predispose the patient to GI perforations, the physician should consider the benefit-risk before using TCZ. Discontinuation of TCZ is recommended for patients who develop GI perforations.

5.1.1.3 Demyelinating Disorders

The impact of treatment with TCZ on demyelinating disorders is not known; events were reported rarely in adult RA patients. Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders. Physicians should exercise caution in considering the use of TCZ in patients with pre-existing or recent-onset demyelinating disorders. Treatment with TCZ should be interrupted during assessment of a potential demyelination event and only resumed if the benefit of continuing study drug is favorable.

5.1.1.4 Cardiovascular Events and Elevated Lipids

Patients with RA have an increased risk for cardiovascular disorders; therefore, risk factors for cardiovascular disease (e.g., hypertension, hyperlipidemia) should be managed as part of their standard of care. For pediatric patients that are at higher risk for cardiovascular disease with an LDL cholesterol $\geq$ 130 mg/dL, the National Cholesterol Education Program (NCEP) guidelines for children and adolescents recommends changes in diet with nutritional counseling and other lifestyle interventions, such as increased physical activity. For patients 8 years and older with an LDL cholesterol of $\geq$ 190 mg/dL (or LDL $\geq$ 160 mg/dL with a family history of early heart disease or 2 additional risk factors present or LDL $\geq$ 130 mg/dL if diabetes mellitus is present), pharmacologic intervention should be considered.

It is worth noting that the same values are used for all children, from 2 to 18 years of age. After 18 years of age, the concentrations presented in the NCEP report for adults would be used (Daniels et al. 2008).

5.1.1.5 Malignancies

The impact of immunosuppression on the development of malignancies is not known. No imbalance of malignancies was observed in controlled clinical trials of TCZ. It is recognized that identification of such events in TCZ-treated patients may require a longer period of surveillance.

5.1.1.6 Hypersensitivity or Anaphylaxis

An infusion/dose reaction is defined as an adverse event occurring during and within 24 hours after the infusion of TCZ. This may include hypersensitivity reactions or anaphylactic reactions. Signs of a possible hypersensitivity reaction include but are not limited to:

- Fever, chills, pruritus, urticaria, angioedema, and skin rash
- Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension

Healthcare professionals administering TCZ infusions should be trained in the appropriate administration procedures, be able to recognize the symptoms associated with potential anaphylactic or hypersensitivity reactions, and have the appropriate medication available for immediate use in case of anaphylaxis or hypersensitivity reaction during or after administration of TCZ. Healthcare professionals should also instruct patients to seek medical attention if they experience symptoms of a hypersensitivity reaction outside of the clinic. If a patient has symptoms of anaphylaxis or serious hypersensitivity, or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity, administration of TCZ must be discontinued permanently. The patient should be treated according to the standard of care for management of the hypersensitivity reaction. A blood sample for the presence of anti-TCZ antibodies should be obtained (refer to the schedule of assessments). The patient must be withdrawn from *Part 1 or 2 of* the study.

*Samples for a*nti-TCZ antibodies, *TCZ PK, and sIL-6R* will be collected for all study patients to evaluate immunogenicity of TCZ at baseline *and Week 24 for patients on Q2W in Part 1; baseline*, Week 6*, 12, 24, 36, and 48* (for patients on Q3W dosing *in Part 2*) *and at baseline, 8 weeks, and 12 weeks after switching to Q4W* for patients on Q4W dosing *in Part 2* and at the last study visit, or at the time of early withdrawal from the study (visit WD1*) for Part 1 or Part 2*. Event-driven sampling (at the time of the event and also at least 6 weeks after the last dose) will occur for all patients experiencing serious infusion-related or allergic reactions or any hypersensitivity event (including non-serious events) leading to treatment withdrawal *in Part 1 or Part 2*.

5.1.2 Laboratory Test Abnormalities

Laboratory test results *in Part 1 and Part 2 of the study* will be recorded on the laboratory results e-form of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable. Any laboratory result abnormality fulfilling the criteria for a serious adverse event should be reported as such, in addition to being recorded as an adverse event in the eCRF. Any treatment-emergent abnormal laboratory result that is clinically significant (i.e., meeting one or more of the following conditions) should be recorded as a single diagnosis on the adverse event e-form in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study drug (e.g., dose interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study drug, which falls outside the laboratory reference range and meets the clinical significance criteria. This does not apply to any abnormal laboratory result that falls outside the laboratory reference range but does not meet the clinical significance criteria (these will be analyzed and reported as laboratory abnormalities); those that are considered adverse events of the type explicitly exempted by the protocol; or those which are a result of an adverse event that has already been reported.

The following laboratory abnormalities are considered exempt from the above, and should not be recorded as adverse events in the eCRF: serum amyloid A, serum ferritin, hsCRP *and ESR*.

5.1.2.1 Laboratory Test Abnormalities Suggestive of MAS

Special attention will be taken to the early reporting and identification of MAS-related features or MAS-like events to Roche.

The occurrence of laboratory findings or clinical criteria suggestive of MAS or MAS-like events with or without unusual features should be reported to Roche as a serious adverse event (see Section 5.2.2). Specific information about these events will be collected to obtain a complete description of the event.

Any patients with the clinical findings and supporting laboratory evidence of MAS (see Appendix 3) should have TCZ treatment interrupted and be treated appropriately for MAS. These patients will be withdrawn from the study. Please see Section 3.1.3.

The definition of MAS (see Appendix 3) was developed to assist physicians to distinguish between active sJIA and MAS. It should be noted that some of the laboratory features associated with TCZ administration and related to its blocking of IL-6 action are similar to some of the laboratory features often associated with the diagnosis of MAS (features such as a decline in WBC count, neutrophil count, platelet count, serum fibrinogen, and ESR, all of which occur most notably within the week following TCZ administration). Ferritin levels frequently decrease with TCZ administration, but often increase with MAS and, therefore, can be a useful differential laboratory analysis. Characteristic clinical findings of MAS (CNS dysfunction, hemorrhages, and hepatosplenomegaly) should accompany laboratory findings when establishing the diagnosis of MAS in the context of IL-6 inhibition. Clinical experience and clinical status of the patient and timing of the laboratory specimens in relation to TCZ administration must guide interpretation of these laboratory data and their potential significance. Please refer to the latest Roche TCZ Investigator's Brochure for more information about MAS (Tocilizumab [RO4877533] Investigator's Brochure).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

To further evaluate the adverse events of special interest, detailed information about these events should be documented and reported. The documentation and reporting requirements for such adverse events will be described in a separate document (ACTEMRA® [Tocilizumab] events of special interest guidance document).

As noted in Section 5.2.2, investigators will submit reports of all reportable serious adverse events, regardless of attribution, all protocol-defined events of special interest

(including events of special interest), and pregnancies to the Roche Drug Safety within 24 hours of learning of the event. For initial serious adverse event and protocol-defined events of special interest reports (including events of special interest), investigators should record all case details that can be gathered within 24 hours on an adverse event eCRF and submit the report through the electronic data capture (EDC) system.

All adverse events of special interest are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

Adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6
- Suspected transmission of an infectious agent by the study drug. *Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.).*
- *Adverse events of special interest for Actemra in this study are provided in the current AESI guidance document.*

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 through Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient*, parent or guardian,* or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies*; see Section 5.4.2 for instructions for reporting serious adverse events*).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 3 months after the last dose of study drug. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 7 provides guidance for assessing adverse event severity.

Table 7 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving *TCZ in* combination *with other* therapies, causality *to TCZ* will be assessed *for TCZ* individually.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the adverse event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the adverse event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this. *If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.*

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF. Abnormalities in vital signs will be interpreted in reference to age and gender specific normal values.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor within 24 hours after learning of the event, either as a serious adverse event or a adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of sJIA.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of sJIA, "sJIA progression" should be recorded on the Adverse Event eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of sJIA

Medical occurrences or symptoms of deterioration that are anticipated as part of sJIA do not need to be recorded as an adverse event.

JIA flares as assessed and notified by the external collaborative groups will be recorded in the relevant flare eform in the eCRF. Fever attributable to sJIA as assessed by the investigator will be recorded in the relevant flare eform in the eCRF.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

Hospitalization for a preexisting condition, provided that all of the following criteria are met:

- The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
- The patient has not suffered an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Elective hospitalizations or surgical procedures that are the result of a patient's pre-existing condition(s) and which have not worsened since receiving study drug. Examples may include, but are not limited to: joint replacement surgery, physical therapy rehabilitation, and diagnostic testing. Such events must still be recorded as adverse events in the eCRF.
- Hospitalization to receive study drug such as infusions of TCZ unless it is prolonged (more than 24 hours) due to safety issues.
- *Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.*

5.3.5.11 *Adverse Events Associated with an* Overdose *or Error in Drug Administration*

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment

in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report the following events to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events *(see Section 5.4.2 for further details)*
- *A*dverse events of special interest *(see Section 5.4.2 for further details)*
- Pregnancies *(see Section 5.4.3 for further details)*

The investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

MEDICAL MONITOR (ROCHE MEDICAL RESPONSIBLE) CONTACT INFORMATION

Primary Contact

Medical Monitor: Dr. [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: Dr. [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be

available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information and List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

For reports of serious adverse events and adverse events of special interest, investigators should record all case details that can be gathered within 24 hours on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system (ACTEMRA® [Tocilizumab] events of special interest guidance document).

To further evaluate the adverse events of special interest, detailed information about these events should be documented and reported. The documentation and reporting requirements for such adverse events will be described in a separate document (ACTEMRA® [Tocilizumab] events of special interest guidance document).

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Adverse Event of Special Interest Case Report Form and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the event, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information and List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.2.1 *Events That Occur after Study Drug Initiation*

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 3 months after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or 90 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. *Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.*

In the event that the EDC system is unavailable*, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.*

5.4.3.2 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data

verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

At the study completion/early termination visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any death, serious adverse event, or other adverse event of concern occurring at any time after a patient has discontinued study participation if the event is believed to be related to prior study drug treatment or study procedures. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information and List of Investigators").

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- TCZ Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Full details of all statistical issues and planned statistical summaries will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to locking of the study database.

All data to be presented will be descriptive and no hypothesis testing will be performed.

Analysis Populations will be defined as follows:

- All TCZ population: All patients who have received at least one dose of study drug.
- Safety population: All patients who have received at least one dose of study drug and who have at least one post-baseline assessment of safety.

Safety data will be presented for the safety population and efficacy data will be presented for the all TCZ population. All patients *in Part 1 will commence treatment with the TCZ Q2W regimen; all patients in Part 2* will commence treatment with a Q3W dosing frequency regimen.

Basic safety reporting will occur for Part 1 of the study and full reporting (including PK, PD, and efficacy assessments) will occur for Part 2.

Separate subgroup summaries may be presented for the patients who enter into a Q4W dosing frequency regimen during the study, if sufficient data exists. In addition, dependent on sufficient data, data by dose group (8 mg/kg $\geq$30 kg or 12 mg/kg $<$30 kg) may be presented.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is to explore the efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity of TCZ in a reduced dosing frequency regimen in patients with adequately controlled sJIA who have experienced a predefined resolved laboratory abnormality on TCZ Q2W dosing. This is a non-powered, descriptive study.

Part 2 of the study will enroll patients already receiving TCZ who have experienced a predefined laboratory abnormality on Q2W TCZ. A sample size of approximately 20 patients in Part 2 who complete 5 consecutive Q3W treatments up to Week 12 has been deemed adequate for the objectives of this study. In addition, 20 patients in Part 2 would ensure 95% probability of observing at least one adverse event when the underlying incidence of that event is ≥14%.

In addition to the 6 patients enrolled in Part 2 as of May 2015 (under Protocol Version 2), approximately an additional 65 patients will be enrolled into Part 1 of the

study (under Protocol Version 3). On investigation of Study WA18221 data, it was found that 46% (52 of 112) of patients experienced a resolved laboratory abnormality on TCZ Q2W, per the Part 2 entry criteria at any point during the study: 25% (28 of 112) of TCZ naive patients during the study from 0-6 months, and 31% (32 of 102) of TCZ non-naive patients between Months 12 and 18 in the study. Based on these percentages, 65 patients enrolled in the run-in period of this study (Part 1) will result in approximately 16-20 TCZ naive/non-naive patients eligible for Part 2, which when added to the 6 patients currently enrolled in Part 2, will result in approximately 20 patients in Part 2, even taking into account the JADAS (and absence of fever attributable to sJIA) entry requirement for Part 2, and the possibility of withdrawals.

6.2 SUMMARIES OF CONDUCT OF STUDY

The conduct and integrity of the study will be assessed based on all descriptive data provided. Blinding and major protocol violations affecting analysis populations are not applicable to this study.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

No formal assessment of treatment group comparability will be performed. All patients will receive TCZ, dose determined based on weight (8 mg/kg ≥ 30 kg or 12 mg/kg < 30 kg) and given *TCZ Q2W (Part 1), and then TCZ* Q3W *(Part 2)* and Q4W (for those patients who experience a repeat laboratory abnormality *during Part 2*). All baseline data, including demographics, baseline characteristics, patient disposition, infusion data, and concurrent treatment, will be summarized. No testing of baseline characteristics will be performed.

Part 1 Baseline is defined as the first dose of TCZ received in *Part 1 of* the study. *Part 2 baseline is defined as the first dose of TCZ received in Part 2 of the study (see Appendix 1 for the schedule of assessments).*

6.4 EFFICACY ANALYSES

No formal hypothesis testing is planned for this study. All efficacy data will be presented descriptively. Summaries by visit will be presented for the all TCZ population (all patients to commence treatment with a Q3W dosing frequency regimen at baseline *of Part 2* [Week 0]). In addition, separate subgroup summaries for patients moving on to a Q4W dosing frequency regimen during the study will be produced if sufficient data exists. Data will be summarized from the first Q4W dosing visit. All summaries will be based on observed case data. No imputation of missing data will be performed.

Full details of all planned efficacy analyses will be provided in the SAP.

Assessment of efficacy will be based on JADAS-71 during *Part 2 of* the study and assessment of fever *(attributable to sJIA).*

JIA flare relative to *Part 2* baseline will be assessed at each visit *in Part 2* to determine if a patient should be withdrawn based on lack of efficacy *at the discretion of the investigator*. Component scores in the assessment of JIA flare (physician global assessment of disease activity [100 mm horizontal VAS], patient/parent global assessment of overall well-being [100 mm horizontal VAS], number of joints with active arthritis [0–71], number of joints with limitation of movement, CHAQ, and ESR) will be summarized or listed as appropriate.

6.5 SAFETY ANALYSES

Safety will be assessed based on reporting of adverse events, vital signs, clinical laboratory assessments, concomitant medications, and physical examination *(for Part 1 and Part 2 of the study separately)*. All safety data will be reported based on the safety population and will be listed or summarized descriptively as appropriate. Full details of all safety reporting will be provided in the SAP.

Verbatim terms for adverse events reported during the study will be mapped to the appropriate thesaurus level. All adverse events will be coded and tabulated by body system and preferred term for individual events within each body system and will be presented in descending frequency. Adverse events will also be tabulated by severity and relationship to study drug. Serious adverse events and adverse events leading to withdrawal will be presented separately.

Vital signs data will be summarized or listed, as appropriate. Values outside the normal ranges and marked abnormalities will be flagged. Concomitant medications will be presented in listings or summary tables as appropriate.

Clinical laboratory data will be summarized or listed as appropriate. Values outside normal ranges will be flagged.

6.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Nonlinear mixed effects modeling (using NOMMEM software) (Beal et al. 1992) will be used to analyze the serum TCZ concentration-time data collected in this study *in Part 2 of the study*. The current PK model developed for sJIA patients from previous studies (Studies MRA316JP, LRO320, and WA18221) will be used to analyze the serum TCZ concentration-time data.

The following systemic exposure parameters will be estimated for all patients who provide adequate PK samples:

- AUCτ during a dosing interval at week 12 *of Part 2*; $\tau = 3$ weeks for Q3W and $\tau = 4$ weeks for Q4W
- C_{max} post infusion at Week 12 *of Part 2*
- C_{min} at end of a dosing interval at Week 12 *of Part 2*

TCZ serum concentrations and computed PK parameters will be listed and summarized descriptively. Mean and median serum concentrations versus time will be plotted on linear scales.

Serum concentration of PD markers will be summarized descriptively by dose frequency. Mean and median serum concentrations versus time will be presented graphically

TCZ serum concentration response relationship (PD markers and efficacy parameters) will be explored.

6.7 PATIENT-REPORTED OUTCOMES

PROs in this study include the CHAQ questionnaire (see Section 4.4.1.10.1 and Appendix 2) and the patient/parent global assessment of overall well-being 100 mm horizontal VAS. The left-hand extreme of the line should be described as “very well” (symptom-free and no arthritis symptoms) and the right-hand extreme as “very poor” (maximum arthritis disease activity), which are *all* part of the 6 core *JIA* American College of Rheumatology components. Data will be summarized or listed as appropriate.

6.8 INTERIM ANALYSES

Interim analyses may be performed at the discretion of the sponsor, for regulatory reporting purposes.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor’s standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system’s audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor’s standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and a have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the

electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data, Informed Consent Forms/informed assent forms, laboratory test results, and medication inventory records, must be retained by the principal investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the EU/ European Environment Agency (EEA) will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients or their legally authorized representatives must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Informed Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the principal investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the

local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

The study will be overseen by a Steering Committee who will monitor the conduct of the study to ensure that expectations for study outcomes can be met and to provide a method for delivering recommendations and actions regarding conduct and management of trials as they evolve. Periodically, dependent on enrollment, the Steering Committee may evaluate the conduct of trials according to GCP guidelines and assess data for expectedness including demographics, efficacy, and safety. Upon study completion, the committee will review the Clinical Study Report. Further details are provided in the Steering Committee Charter.

A central laboratory will be used to analyze the majority of samples detailed in Section 4.4.1.9 and results will be made available to the investigational sites.

An IXRS vendor will be used to enroll the patients into the study.

External collaborative groups will confirm the JIA flare and JADAS-71 calculations to the investigational sites as required.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement *(with the Paediatric Rheumatology International Trials Organisation (PRINTO at www.printo.it) and the Pediatric Rheumatology Collaborative Study Group (PRCSG at www.prcsg.org)* and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

APPENDIX 1-A: PART 1/RUN-IN PHASE (≤24 WEEKS)																		
	Part 1 Visits (Run-in Phase)														*Withdrawal Visits*			
VISIT	*Screening Evaluation 1*	*Baseline 1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*WD1*[a]	*WD2*[a]	*WD3*[a]	*WD4*[a]
Weeks from Baseline for Part 1 (±3 days)	*≤4 weeks*	*0*	*2*	*4*	*6*	*8*	*10*	*12*	*14*	*16*	*18*	*20*	*22*	*24*	*2 wks after last study drug*	*2 wks after WD1*	*4 wks after WD2*	*4 wks after WD3*
Informed consent [b]	*x*	*x*																
Inclusion/exclusion	*x*	*x*																
Medical history	*x*	*x*																
Demographics	*x*																	
Concomitant medication	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
TB screening (e.g., PPD [c]*)*	*x*																	
CXR [d]	*x*																	
TCZ infusions [e, f]		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*				
Adverse events	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Vital signs and temperature [g]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*				
Height and weight	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*			*x*
Screening labs [h]	*x*																	
Hematology	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Pregnancy (urine) [i, j]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*				
Blood chemistry	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

Appendix 1
Schedule of Assessments (cont.)

APPENDIX 1-A: PART 1/RUN-IN PHASE (≤24 WEEKS)																	
	Part 1 Visits (Run-in Phase)														Withdrawal Visits			
VISIT	Screening Evaluation 1	Baseline 1	2	3	4	5	6	7	8	9	10	11	12	13	WD1[a]	WD2[a]	WD3[a]	WD4[a]
Weeks from Baseline for Part 1 (±3 days)	≤4 weeks	0	2	4	6	8	10	12	14	16	18	20	22	24	2 wks after last study drug	2 wks after WD1	4 wks after WD2	4 wks after WD3
Physical examination	x	x													x	x	x	x
Anti-TCZ antibodies [l]		x													x			

CXR =chest X-ray; ESR =erythrocyte sedimentation rate; HgbA1c =hemoglobin A1c; hsCRP =high-sensitivity C-reactive protein; PPD =purified protein derivative; Q2W =every 2 weeks; TB =tuberculosis; TCZ =tocilizumab; WD =withdrawal visit.

[a] *All 4 withdrawal visits to be performed after premature withdrawal from or on completion of Part 1 (and are not eligible for Part 2). Patients who are entering Part 2 should successfully complete Screening Evaluation 2 before completing Part 1 WD1 and then transferring to Part 2. Patients who have fulfilled entry requirements for Part 2 Screening Evaluation 2 do not need to complete WD2, WD3, and WD4. No infusion is given at withdrawal visits. If a patient permanently discontinues study drug at any time during Part 1, Part 1 WD1 should be performed approximately 2 weeks after last infusion of study drug, followed by WD2 assessments 2 weeks later, followed by WD3 assessments 4 weeks later, and WD4 4 weeks later.*

[b] *The parent (or patient if he or she has reached the legal age of consent and if applicable at the site) must sign and date an Informed Consent Form before any study-related activities can occur.*

[c] *PPD or equivalent (e.g., Quantiferon gold) must be interpreted based on local guidelines for immunosuppressed patients.*

[d] *If a patient's TB testing is positive at screening and the patient has not previously received TB treatment, then a chest radiograph is required at screening. A chest radiograph obtained within 90 days of baseline can be utilized for screening purposes, if consistent with local practices.*

[e] *All assessments (safety, clinical, laboratory) except as noted should be completed prior to start of infusion. If a patient has symptoms of anaphylaxis or serious hypersensitivity, or requires interruption of study drug because of symptoms of anaphylaxis or hypersensitivity (serious or non-serious), administration of TCZ must be permanently discontinued; a blood sample to assess anti-TCZ antibodies, TCZ PK and sIL-6R levels should be obtained at the time of the event and 6 weeks later.*

Appendix 1
Schedule of Assessments (cont.)

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[f] *Patients will receive TCZ Q2W for ≤ 24 weeks until they experience a laboratory abnormality as specified in inclusion criteria (Section 4.1.1). Following the occurrence and resolution of this laboratory abnormality, patients who have a successful screening evaluation (Screening Evaluation 2) and who fulfil all the Inclusion/Exclusion criteria for Part 2, may enter Part 2 of the study.*

[g] *Vital signs must be taken pre-infusion, every 30 minutes during infusion, and 30 minutes after end of infusion (as stated in the main body of the protocol).*

[h] *Screening laboratories include hepatitis B surface antigen, hepatitis C antibody, HgbA1c, hsCRP, fibrinogen, Epstein-Barr virus titer, varicella IgG testing, and ESR.*

[i] *Urine pregnancy test for patients in Tanner stages ≥ 2 or above only or onset of menarche.*

[j] *Dipstick urinalysis and pregnancy test on fresh voided urine sample. May be performed at any visit at the investigator's discretion for symptoms.*

[l] *Samples for anti-TCZ antibodies, TCZ PK, and sIL-6R will be collected at baseline and WD1. In addition to the scheduled samples listed for patients who withdraw because of anaphylaxis or serious or non-serious hypersensitivity reactions, a sample for assessment of anti-TCZ antibodies and PK (TCZ) and PD (sIL-6R) assessments will be drawn at the time of event and also at least 6 weeks after the last dose.*

Appendix 1
Schedule of Assessments (cont.)

APPENDIX 1-B: PART 2/MAIN STUDY															
	Part 2 Visits (Main Study)											Withdrawal Visits			
VISIT	Screening *Evaluation* 2 [a]	Baseline [b]	2	3	4	5	6	7	8	9	Infusion Visits	WD1 [c]	WD2 [c]	WD3 [c]	WD4 [c]
Weeks from Baseline *for Part 2* (±3 days)	≤4 weeks	0	1	2	3	6	9	10	11	12	Q3W or Q4W [d]	2 wks after last study drug	2 wks after WD1	4 wks after WD2	4 wks after WD3
Informed consent [e]	x														
Inclusion/exclusion	x	x													
Medical history [f]	x	x													
Demographics [g]	x														
Concomitant medications	x	x			x	x	x			x	x	x	x	x	x
TB screening (e.g., PPD) [h]	x														
CXR [i]	x														
TCZ infusions [j, k, l]		x			x	x	x			x	x				
Height/weight	x	x			x	x	x			x	x	x			x
Physical examination	x	x			x [m]	x [m]	x [m]			x [m]	x [m]	x [m]	x [m]	x [m]	x [m]
Joint count	x	x			x	x	x			x	x	x			
Patient/parent global (VAS)	x	x			x	x	x			x	x	x			

Appendix 1
Schedule of Assessments (cont.)

APPENDIX 1-B: PART 2/MAIN STUDY															
	Part 2 Visits (Main Study)											Withdrawal Visits			
VISIT	Screening *Evaluation* 2 [a]	Baseline [b]	2	3	4	5	6	7	8	9	Infusion Visits	WD1 [c]	WD2 [c]	WD3 [c]	WD4 [c]
Weeks from Baseline *for Part 2* (±3 days)	≤4 weeks	0	1	2	3	6	9	10	11	12	Q3W or Q4W [d]	2 wks after last study drug	2 wks after WD1	4 wks after WD2	4 wks after WD3
Physician global (VAS)	x	x			x	x	x			x	x	x			
CHAQ	x	x			x	x	x			x	x	x			
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Screening laboratories [n]	x														
Hematology	x	x			x	x	x			x	x	x	x	x	x
Pregnancy (urine) [o, p]	x	x			x	x	x			x	x				
Blood chemistry	x	x [q]			x [q]	x	x			x	x	x [q]	x	x	x
Immunology profile (IgG, IgM, IgA)		x										x			
Urinalysis dipstick [p]		x										x			
Fibrinogen/D-Dimer		x			x	x	x			x	x	x			
Lipid profile		x [q]			x [q]							x [q]			
Acute phase reactants (hsCRP, serum ferritin, C4, C3, ESR) [r]		x [s]	x [t]	x [t]	x [s]	x [s]	x [s]	x [t]	x [t]	x [s]	x [s]	x [t]			

Appendix 1
Schedule of Assessments (cont.)

APPENDIX 1-B: PART 2/MAIN STUDY															
	Part 2 Visits (Main Study)											Withdrawal Visits			
VISIT	Screening *Evaluation* 2 [a]	Baseline [b]	2	3	4	5	6	7	8	9	Infusion Visits	WD1 [c]	WD2 [c]	WD3 [c]	WD4 [c]
Weeks from Baseline *for Part 2* (±3 days)	≤4 weeks	0	1	2	3	6	9	10	11	12	Q3W or Q4W [d]	2 wks after last study drug	2 wks after WD1	4 wks after WD2	4 wks after WD3
PK/PD: TCZ, IL6 sIL-6R [u, v]		x [u, w]	x [t, x]	x [t, x]	x [u, w]	x [u, w]	x [u, w]	x [t, x]	x [t, x]	x [u]	x [y, z]	x [u]			
Anti-TCZ antibodies [l, v, s]		x [s]				x [s]				x [s]	x [y, z]	x [s]			
Vital signs and temperature [aa]	x	x			x	x	x			x	x	x	x	x	x

CHAQ = Childhood Health Assessment Questionnaire; CXR = chest X-ray; eCRF = electronic Case Report Form; ESR = erythrocyte sedimentation rate; hsCRP = high-sensitivity C-reactive protein; IL = interleukin; JIA = juvenile idiopathic arthritis; PD = pharmacodynamic; PK = pharmacokinetic; PPD = purified protein derivative; Q3W = every three weeks; Q4W = every 4 weeks; sIL-6 = soluble interleukin-6; TB = tuberculosis; TCZ = tocilizumab; VAS = visual analogue scale; WD = withdrawal visit.

[a] *TCZ infusions may continue to be received during the Screening Evaluation 2, but there must be at least 10 days clear between the last TCZ infusion during screening and the first study TCZ infusion received at baseline.*

[b] *Numbering for visits for Part 2 commence from baseline visit for Part 2.*

[c] *Withdrawal visit: All 4 withdrawal visits to be performed after premature withdrawal or when the patient completes Part 2. No infusion is given at withdrawal visits. If a patient permanently discontinues study drug at any time during the study, the first Withdrawal visit (WD1) should be performed approximately 2 weeks after last infusion of study drug, followed by WD2 assessments 2 weeks later, followed by WD3 assessments 4 weeks later, followed by WD4 assessments 4 weeks later. Samples for anti-TCZ antibodies, TCZ PK, and sIL-6R will be collected at the WD1.*

Appendix 1
Schedule of Assessments (cont.)

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[d] *Patients on Q3W who do not meet all requirements to switch to Q4W may continue on Q3W up to 52 weeks. Patients on Q4W will remain on this dose until the end of Part 2 (up to 52 weeks).*

[e] The parent (or patient if he or she has reached the legal age of consent, and if applicable at the site) must sign and date an Informed Consent Form before any study related activities can occur. *Informed Consent for Part 2 is not required for patients entering from Part 1.*

[f] Medical history to include information on prior immunization/vaccines. *Adverse events ongoing from Part 1 should be entered as an ongoing condition in the medical history for Part 2.*

[g] *Demographics for Part 2 is not required for patients entering from Part 1.*

[h] PPD (or equivalent, e.g., Quantiferon gold) must be interpreted based on local guidelines for immunosuppressed patients. *TB screening does not need to be repeated for patients entering from Part 1.*

[i] *If a patient's TB testing is positive at screening and the patient has not previously received TB treatment, then a chest radiograph is required at screening. A chest radiograph obtained within 90 days of baseline can be utilized for screening purposes, if consistent with local practices. TB screening test and chest x-ray does not need to be repeated for patients entering from Part 1.*

[j] All assessments (safety, clinical, laboratory) except as noted should be completed prior to start of infusion. If *a patient has symptoms of anaphylaxis or serious hypersensitivity, or requires interruption of study drug because of symptoms of anaphylaxis or hypersensitivity (serious or non-serious), administration of* TCZ *must be permanently discontinued. A blood sample to assess for anti-TCZ antibodies, TCZ PK, and sIL-6R must be taken at the time of the event and 6 weeks later.*

[k] Patients must continue on Q3W dosing for a minimum of *5* consecutive infusions *(at least 12 weeks)*. After *5* consecutive Q3W infusions, if a patient experiences any of the laboratory abnormalities outlined in Section 3.1.2 and has maintained adequate disease control *(JADAS ≤ 3.8 and no fever attributable to sJIA),* they will switch to Q4W dosing upon restarting treatment with TCZ. Patients experiencing a JIA flare or fever attributable to sJIA will be withdrawn from the study *at the discretion of the investigator.*

[l] For patients on Q4W dosing, please refer to Appendix 1-C for timing of these assessments.

[m] Focused physical examination (examination may be limited to appropriate organ systems based on relevance to any ongoing adverse events). Focused laboratory assessments may be appropriate depending on reason for discontinuation of study drug administration.

[n] Screening labs include hepatitis B surface antigen, hepatitis C antibody, HgbA1c, hsCRP, fibrinogen, Epstein-Barr virus titer, varicella IgG testing and ESR.

[o] Urine pregnancy test for patients in Tanner stages ≥ 2 or above only or onset of menarche.

[p] Dipstick urinalysis, pregnancy test on fresh voided urine sample. May be performed at any visit at the investigator's discretion for symptoms.

[q] Fasting labs for glucose and lipids should be obtained after minimum 8-hour fast.

[r] *All samples taken pre-dose unless otherwise specified.* ESR performed locally and required for the JIA flare assessment.

[s] Pre-dose samples will be collected.

[t] Can be obtained at any timepoint during the day that is convenient for patient and site unless the visit is designated as a fasting visit.

[u] Pre-dose *samples for* PK (TCZ concentrations) and PD (IL-6, and sIL-6R concentrations) will be obtained from a single specimen obtained at indicated timepoints in Schedule of Assessments. See laboratory manual for directions on handling of these specimens.

[v] In addition to the scheduled samples listed, for patients who withdraw from *Part 2* because of anaphylaxis or serious *or non-serious* hypersensitivity reactions, a sample for assessment of anti-TCZ antibodies and PK (TCZ) and PD (sIL-6R) will be drawn at the time of event and also at least 6 weeks after the last dose.

[w] Post-dose PK/PD samples (obtained within 15 minutes following saline flush marking end of infusion) from opposite arm.

[x] Home nursing may be used for collection of samples at non-dosing visits.

[y] PK/PD and immunogenicity assessments for first 12 weeks of Q4W regimen are to be taken as specified in the Schedule of Assessments–PK/PD and immunogenicity assessments for Q4W regimen (Appendix 1-*C*).

[z] After Week12, pre-dose PK/PD and immunogenicity samples to be taken at Weeks 24, 36, and 48 only *for patients on Q3W.*

[aa] *Vital signs must be taken pre-infusion, every 30 minutes during infusion, and 30 minutes after end of infusion (as stated in the main body of the protocol.*

Appendix 1
Schedule of Assessments (cont.)

APPENDIX 1-C: PK/PD AND IMMUNOGENICITY ASSESSMENTS FOR Q4W REGIMEN IN PART 2										
Weeks from first dosing of Q4W (±3 days)	*Part 2* Visit									
	0	1	2	3	4	8	9	10	11	12
TCZ Infusion	x				x	x				x
PK/PD: TCZ, IL-6, sIL-6R [a]	x [b,c]	x [d]	x [d]	x [d]	x [b,c]	x [b,c]	x [d]	x [d]	x [d]	x [b]
Adverse Events	x	x	x	x	x	x	x	x	x	x
Acute Phase Reactants (hsCRP, serum ferritin, C4, C3, ESR)	x [e]	x [d,f]	x [d,f]	x [d,f]	x [e]	x [e]	x [d,f]	x [d,f]	x [d,f]	x [e]
Anti-TCZ Antibodies [a]	x [e]					x [e]				x [e]

ESR = erythrocyte sedimentation rate; hsCRP = high-sensitivity C-reactive protein; IL = interleukin; JIA = juvenile idiopathic arthritis; PD = pharmacodynamic; PK = pharmacokinetic; Q4W = every 4 weeks; sIL-6 = soluble interleukin-6; sJIA = systemic Juvenile Idiopathic Arthritis; TCZ = tocilizumab.

[a] In addition to the scheduled samples listed, for patients who withdraw from the study *(Part 2)* or who withdraw because of anaphylaxis or hypersensitivity reactions, a sample for assessment of anti-TCZ antibodies and PK (TCZ) and PD (sIL-6R) assessments will be drawn at the time of event and also at least 6 weeks after the last dose.

[b] Pre-dose PK (TCZ concentrations) and PD (IL-6, and sIL-6R concentrations) will be obtained from a single specimen obtained at indicated timepoints in Schedule of Assessments for Q4W dosing. Anti-TCZ antibodies will be obtained from a separate specimen at indicated timepoints in Schedule of Assessments. See laboratory manual for directions on handling of these specimens.

[c] Post dose PK/PD samples (obtained within 15 minutes following saline flush marking end of infusion) from opposite arm.

[d] Can be obtained at any timepoint during the day that is convenient for patient and site

[e] *Pre-dose samples will be collected.*

[f] Home nursing may be used for collection of samples at non-dosing visits.

Appendix 2
Childhood Health Assessment Questionnaire (CHAQ)
(Example Only–Not for Use)

CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE (CHAQ)	
SUBJECT ID: __ __ __ __ __	
DATE OF VISIT (dd/mmm/yyyy): ____/____/_____	Month 5 visit

In this section we are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the back of this page. In the following questions, please check the one response that best describes your child's usual activities (averaged over an entire day) **OVER THE PAST WEEK**. **ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS THAT ARE DUE TO ILLNESS**. If most children at your child's age are not expected to do a certain activity, please mark it as "Not Applicable". **For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but not because he/she is RESTRICTED BY ILLNESS, please mark it as "NOT Applicable".**

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
DRESSING & GROOMING					
Is your child able to:					
- Dress, including tying shoelaces and doing buttons?	☐	☐	☐	☐	☐
- Shampoo his/her hair?	☐	☐	☐	☐	☐
- Remove socks?	☐	☐	☐	☐	☐
- Cut fingernails?	☐	☐	☐	☐	☐
ARISING					
Is your child able to:					
- Stand up from a low chair or floor?	☐	☐	☐	☐	☐
- Get in and out of bed or stand up in a crib?	☐	☐	☐	☐	☐
EATING					
Is your child able to:					
- Cut his/her own meat?	☐	☐	☐	☐	☐
- Lift up a cup or glass to mouth?	☐	☐	☐	☐	☐
- Open a new cereal box?	☐	☐	☐	☐	☐
WALKING					
Is your child able to:					
- Walk outdoors on flat ground?	☐	☐	☐	☐	☐
- Climb up five steps?	☐	☐	☐	☐	☐

*** Please check any AIDS or DEVICES that your child usually uses for any of the above activities:**

Cane	☐	Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)	☐
Walker	☐	Built up pencil or special utensils	☐
Crutches	☐	Special or built up chair	☐
Wheelchair	☐	Other (Specify:_____)	☐

*** Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

Dressing and Grooming	☐	Eating	☐
Arising	☐	Walking	☐

Appendix 2
Childhood Health Assessment Questionnaire
(Example Only–Not for Use) (cont.)

CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE (CHAQ) (page 2 of 2)

SUBJECT ID: __ __ __ __ __

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
HYGIENE					
Is your child able to:					
- Wash and dry entire body?	☐	☐	☐	☐	☐
- Take a tub bath (get in and out of tub)?	☐	☐	☐	☐	☐
- Get on and off the toilet or potty chair?	☐	☐	☐	☐	☐
- Brush teeth?	☐	☐	☐	☐	☐
- Comb/brush hair?	☐	☐	☐	☐	☐
REACH					
Is your child able to:					
- Reach and get down a heavy object such as a large game or books from just above his/her head?	☐	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor?	☐	☐	☐	☐	☐
- Pull on a sweater over his/her head?	☐	☐	☐	☐	☐
- Turn neck to look back over shoulder?	☐	☐	☐	☐	☐
GRIP					
Is your child able to:					
- Write or scribble with pen or pencil?	☐	☐	☐	☐	☐
- Open car doors?	☐	☐	☐	☐	☐
- Open jars that have been previously opened?	☐	☐	☐	☐	☐
- Turn faucets on and off?	☐	☐	☐	☐	☐
- Push open a door when he/she has to turn a door knob?	☐	☐	☐	☐	☐
ACTIVITIES					
Is your child able to:					
- Run errands and shop?	☐	☐	☐	☐	☐
- Get in and out of a car or toy car or school bus?	☐	☐	☐	☐	☐
- Ride bike or tricycle?	☐	☐	☐	☐	☐
- Do household chores (e.g. wash dishes, take out trash, vacuuming, yard work, make bed, clean room)?	☐	☐	☐	☐	☐
- Run and play?	☐	☐	☐	☐	☐

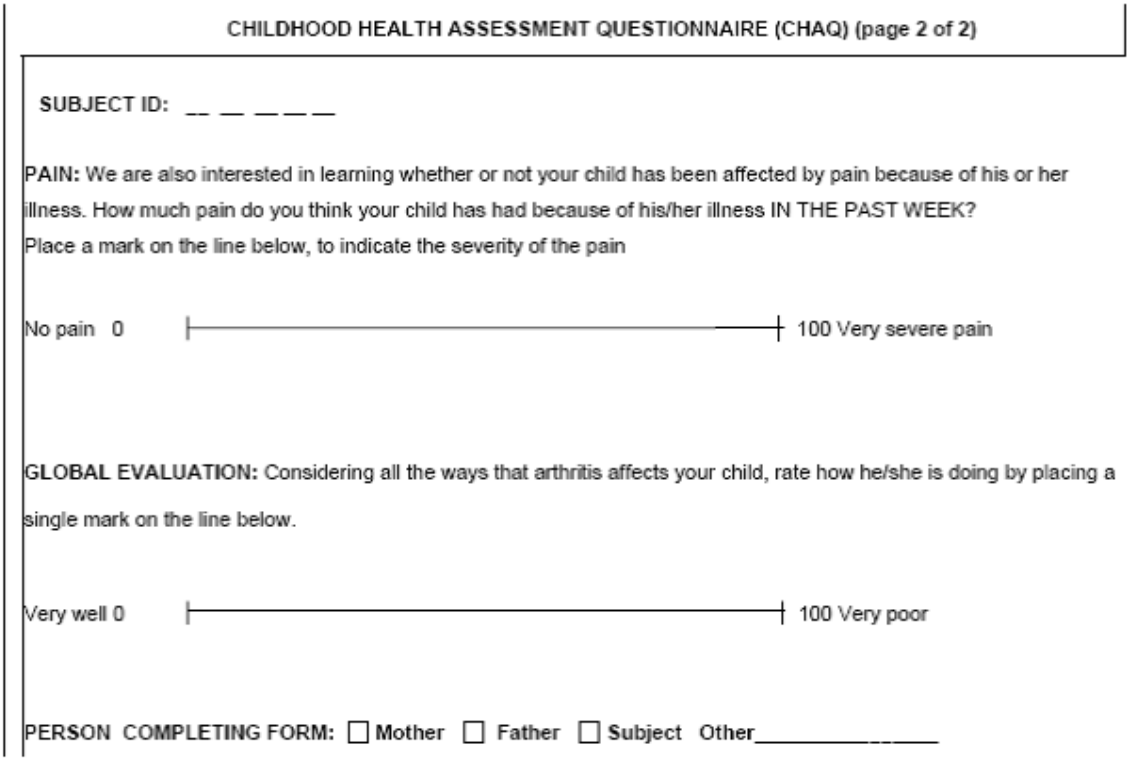
*** Please check any AIDS or DEVICES that your child usually uses for any of the above activities:**

Raised toilet seat	☐	Bathtub bar	☐
Bathtub seat	☐	Long-handled appliances for reach	☐
Jar opener (for jars previously opened)	☐	Long-handled appliances in bathroom	☐

*** Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

Hygiene	☐	Gripping and opening things	☐
Reach	☐	Errand and chores	☐

Appendix 2
Childhood Health Assessment Questionnaire
(Example Only–Not for Use) (cont.)



CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE (CHAQ) (page 2 of 2)

SUBJECT ID: __ __ __ __ __

PAIN: We are also interested in learning whether or not your child has been affected by pain because of his or her illness. How much pain do you think your child has had because of his/her illness IN THE PAST WEEK?
Place a mark on the line below, to indicate the severity of the pain

No pain 0 ——————————— 100 Very severe pain

GLOBAL EVALUATION: Considering all the ways that arthritis affects your child, rate how he/she is doing by placing a single mark on the line below.

Very well 0 ——————————— 100 Very poor

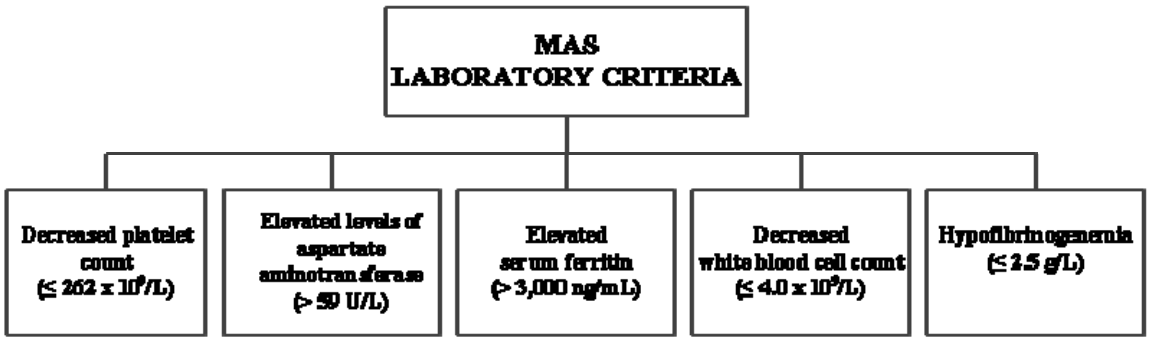
PERSON COMPLETING FORM: ☐ Mother ☐ Father ☐ Subject Other_____

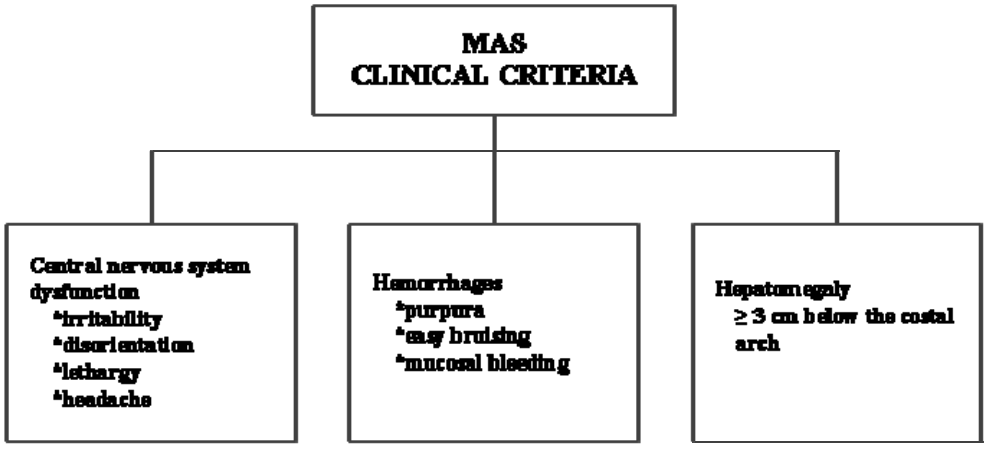
References:

Ruperto N, Martini A, for the Paediatric Rheumatology International Trials Organisation (PRINTO). Quality of life in juvenile idiopathic arthritis patients compared to healthy children. Clin Exp Rheumatol 2001; 19 (suppl.23):S1-S172.

Ruperto N, Ravelli A, Pistorio A, et al., for the Paediatric Rheumatology International Trials Organisation (PRINTO): Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. Clin Exp Rheumatol 2001; 19 (Suppl. 23): S1-9.

Appendix 3
Definition of MAS (Macrophage Activation Syndrome)





Recommendations:

The aforementioned criteria are of value only in patients with active tocilizumab (sJIA). The thresholds of laboratory criteria are provided by way of example only.

Please refer to Section 5.1.2.1 of the protocol for more detailed information on establishing the diagnosis of MAS within the context of tocilizumab (TCZ) administration.

Comments:

The clinical criteria are *more* useful as a classification criteria rather than diagnostic criteria because often they can occur late in the presentation.

Other abnormal clinical features to include: *nonremitting high fever* (different from the sJIA pattern), splenomegaly, generalized lymphadenopathy, and paradoxical improvement of signs and symptoms of arthritis.

Appendix 3
Definition of MAS (Macrophage Activation Syndrome) (cont.)

Other abnormal laboratory findings: anemia, falling Erythrocyte Sedimentation Rate, increased bilirubin, elevated liver enzymes, elevated LDH, hypertriglyceridemia, low sodium levels, decreased albumin, increase fibrin degradation products and hyperferritinemia.

Reference

Ravelli A, Magni-Mazoni S, Pistorio A, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr 2005;146:598-604.