Janssen Research & Development *

Statistical Analysis Plan

A Multicenter, Open-Label Trial of Intravenous Golimumab, a Human Anti-TNFα Antibody, in Pediatric Subjects with Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy GO-VIVA

Protocol CNTO148JIA3003; Phase 3

Simponi® (golimumab)

Status:	Approved
Date:	1 August 2018
Prepared by:	Janssen Research & Development, LLC
Document No.:	EDMS-ERI-112318522; 2.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

AMENDMENT HISTORY

SAP Version	Date
Original SAP	11 December 2017
Amendment 1	01 August 2018

ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibodies
AST	aspartate aminotransferase
AUCss	steady state AUC
BMI	body mass index
BSA	body surface area
CHAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
CRP	C-reactive protein
DBL	database lock
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic case report form
GCP	Good Clinical Practice
IV	intravenous
IWRS	interactive web response system
JADAS	Juvenile Arthritis Disease Activity Score
JIA	juvenile idiopathic arthritis
LLOQ	lower limit of quantification
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NSAID	non-steroidal anti-inflammatory drug
pJIA	polyarticular JIA
PK	pharmacokinetics
PKE	pharmacokinetics evaluable
q8w	every 8 weeks
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SOP	Standard Operating Procedure
TB	tuberculosis
TNFα	tumor necrosis factor alpha
VAS	visual analogue scale
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the analysis of pharmacokinetics (PK), efficacy, safety, and immunogenicity in the CNTO148JIA3003 study.

1.1. Trial Objectives

Primary Objective

The primary objective of this study is to assess the PK following intravenously administered golimumab in subjects (ages 2 to less than 18 years) with polyarticular JIA (pJIA) manifested by ≥5 joints with active arthritis despite methotrexate (MTX) therapy for ≥2 months.

Secondary Objectives

The secondary objectives of this study are to evaluate IV golimumab in subjects with pJIA with respect to PK, efficacy (relief of signs and symptoms, physical function, quality of life), safety (AEs, SAEs, and assessment of laboratory parameters), and immunogenicity (antibodies to golimumab).

1.2. Trial Design

This is a Phase 3, open-label, single arm, multicenter study to evaluate the PK, safety, and efficacy of IV golimumab in subjects with active pJIA despite current treatment with MTX. Approximately 120 subjects will be enrolled at Week 0 to ensure that approximately 100 subjects remain in the study at Week 52.

All subjects will receive 80 mg/m^2 golimumab (maximum single dose 240 mg [maximum BSA 3.0 m^2 x 80 mg/m^2]) as an IV infusion (over 30 ±10 minutes) at Weeks 0, 4, and q8w (± 3 days) through Week 28 and then q8w (± 1 week) thereafter through Week 52. Subjects will also receive commercial MTX weekly through Week 28 at the same BSA-based dosage (10 to 30 mg/m^2 per week of MTX in subjects with BSA <1.67 m^2, or a minimum of 15 mg/week in subjects with BSA ≥1.67 m^2) as at time of study entry. Subjects who complete the study at Week 52 will have the option to enter into the long-term extension phase of the study (from Week 52 to Week 252). All subjects who complete the Week 244 visit are expected to participate in the safety follow-up visit at Week 252.

Since this is an open-label study with all subjects receiving the same BSA-based dose of IV golimumab, an external Data Monitoring Committee will not be established. Instead, an internal Janssen Data Review Committee (DRC) will be formed in its place.

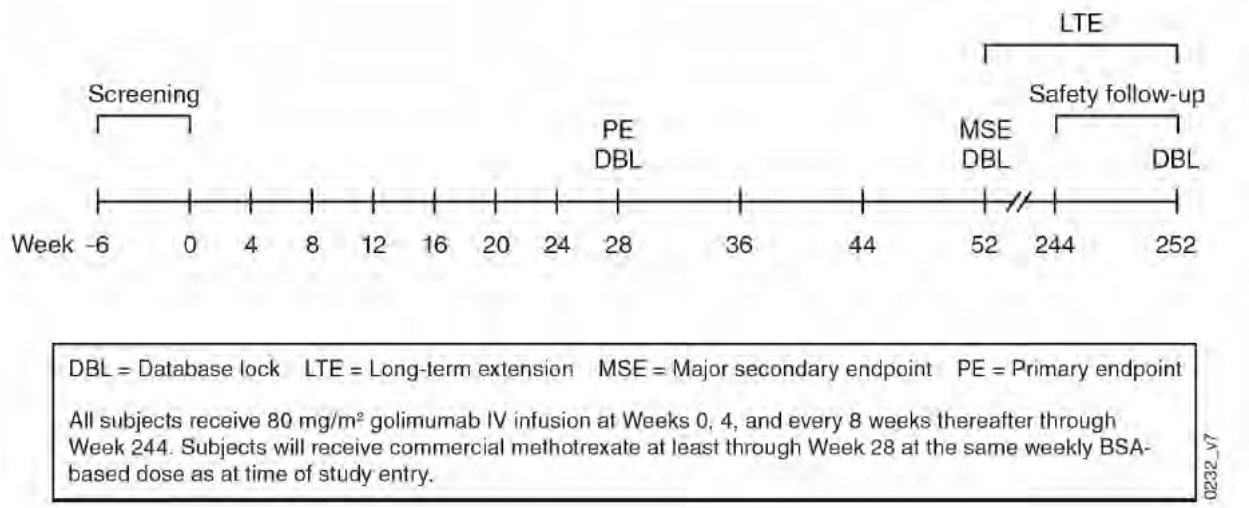
The end of the study is defined as the last follow-up assessment for the last subject in the long-term extension.

Database locks (DBL) are scheduled for Weeks 28, 52 and 252 (Section 1.2.3).

If <50% of the study population achieves an adequate response to the treatment (American College of Rheumatology Pediatric 30% [JIA ACR 30] response) at the Week 28 DBL, the study will be discontinued.

Figure 1 depicts the schematic overview of the study.

Figure 1: Schematic overview of the study



1.2.1. Subject Population

Subjects must meet the inclusion and exclusion criteria of the study.

Subjects must be 2 to less than 18 years of age with a body weight >15 kg at the time of enrollment.

The onset of disease must have been before the subject's 16th birthday, must be of at least 3 months'

duration, and must be active pJIA of one of the following subtypes: rheumatoid factor positive or negative pJIA; systemic JIA with no systemic symptoms for ≥3 months but with polyarthritis for ≥3 months; extended oligoarticular JIA; enthesitis-related arthritis or polyarticular juvenile psoriatic arthritis (PsA).

Subjects must have ≥5 joints with active arthritis as defined by American College of Rheumatology (ACR) criteria at screening and enrollment. Subjects must have active pJIA despite current use of oral, intramuscular, or subcutaneous MTX (for ≥2 months before screening) at a weekly dose of ≥10 mg/m^2.

Subjects must have a screening CRP of ≥0.1 mg/dL with the exception of approximately 30% of the study population.

Screening for eligible subjects will be performed within 6 weeks before administration of the study agent.

1.2.2. Dosage and Administration

The study will have 1 active treatment group.

All subjects will receive 80 mg/m^2 golimumab (maximum single dose 240 mg) IV infusions at Week 0, Week 4, and q8w (±3 days) through Week 28 and q8w (±1 week) thereafter through Week 244. BSA will be calculated using the Mosteller equation:

BSA (m^2) = ([height (cm) x weight (kg)]/3600)$^{1/2}$.

All infusions will be completed over 30±10 minutes.

In addition, subjects will receive commercial MTX at the same BSA-based dose (10 to 30 mg/m^2 per week for subjects with BSA <1.67 m^2 or at least 15 mg/week for subjects with

BSA ≥1.67 m^2) as at time of study entry through Week 28. Absolute dose should remain stable from baseline through Week 28.

1.2.3. Database Locks

Database locks are scheduled at Weeks 28, 52 and 252. The Week 28 and Week 52 database locks will include all data collected up to the Week 28 and Week 52 visits, respectively. The final database lock at Week 252 will include all data collected.

1.3. Statistical Hypotheses for Trial Objectives

No formal hypothesis testing is planned for this study.

1.4. Sample Size Justification

The sample size determination is not based on statistical considerations. For the purpose of determining sample size of this study, the variability of PK in pediatric populations was considered. The goal is to have a sample size that will be sufficient to build a population PK and, if feasible, an exposure-response model. Additionally, a sample size that will provide information about the safety profile of golimumab IV in children was also taken into consideration.

With these considerations, a sample size of approximately 120 subjects has been chosen assuming that if 20 subjects were to drop out or if they do not provide PK samples, a sample size of approximately 100 subjects is thought to be sufficient to build a population PK model, given the sparse sampling of PK time points, as well as provide 1 year of safety data from approximately 100 subjects.

Assuming that inter-subject coefficient of variation (CV%) of concentration is about 50% (moderate – large variation), a sample size of 100 subjects will be able to provide a 95% confidence interval (CI) with the length about 20% of the mean concentration, i.e., 95% CI ≈ Mean×(1±10%).

The table below provides the length of 95% CI of mean concentration using sample size of 100 subjects with various CV% from 30% (small variation) to 70% (larger variation).

Table 1: Length of 95% CI with Sample Size 100 Subjects

CV %	95% CI
30%	Mean×(1± 5.9%)
40%	Mean×(1± 7.8%)
50%	Mean×(1± 9.8%)
60%	Mean×(1±11.8%)
70%	Mean×(1±13.7%)

1.5. Randomization and Blinding

1.5.1. Randomization

All subjects will receive 80 mg/m^2 golimumab and commercial MTX, therefore randomization of subjects to treatment is not needed.

1.5.2. Treatment Supply and Allocation

Golimumab will be supplied as a sterile liquid for IV infusion at a volume of 4 mL (50 mg, 12.5 mg/mL) in single-use vials. Normal saline will be supplied as a sterile liquid for IV infusion in single-use infusion bags.

Treatment (golimumab vials) allocation will be performed by using a centralized, interactive web response system (IWRS) provided by Parexel International Corporation. After the informed consent has been obtained and the subject has been successfully screened, sites will enroll a subject at Week 0 via the IWRS. Vial numbers will be assigned to the subject. One or more golimumab vials can be assigned at each visit. The assigned vial numbers will be provided via fax to the pharmacist and will be stored electronically in the IWRS database. The IV study agent for infusion will be prepared according to the subject's BSA.

In the event that a vial of treatment is not available at the site or a problem with the vial or vial contents are noted, an alternate vial number will be provided via IWRS to the pharmacist. The sponsor will be alerted in order to promptly address the deficient clinical supply issue. The assignment of the new vial will be recorded in the electronic case report form.

1.5.3. Maintenance of the Blind

This is an open label study with one treatment group, therefore maintenance of blinding is not necessary.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

All scheduled study visits should occur within ±3 days of the intended visit through Week 28 and ± 1 week from Week 28 through Week 244.

Unless otherwise specified, actual scheduled visits will be used for the summaries and listings over time with no visit windows applied.

For PK analyses, if a subject has an infusion more than ± 3 days of the scheduled dosing date through Week 28, the concentration data collected between such a dosing visit and the subsequent dosing visit will be excluded from the by-visit data analyses. For the visits after Week 28, if the PK sampling time deviates more than ± 7 days of the scheduled date, the PK concentration at this visit will be excluded from the by-visit data analyses.

2.2. Pooling Algorithm for Analysis Centers

Data from all investigational centers/sites will be pooled for analyses.

2.3. Analysis Sets

2.3.1. Pharmacokinetics Analysis Set

The pharmacokinetics evaluable (PKE) analysis set includes treated subjects (who received at least 1 infusion) who have sufficient PK samples for analysis.

Pharmacokinetics analyses will be performed using the PKE analysis set.

2.3.2. Full Analysis Set

The full analysis set includes all enrolled subjects who received at least 1 infusion.

This analysis set will be used for efficacy analysis and safety analysis, unless otherwise specified.

2.4. Definition of Subgroups

2.4.1. Subgroups for the Summary of Concentrations

To evaluate the consistency in the concentrations over demographics, baseline characteristics. The subgroups described below are for the concentrations.

The following demographic subgroups will be used for concentration summary:

a. Age: 2 years to <6 years, ≥6 years to <12 years, ≥12 years to <18 years
b. Baseline body weight: quartiles
c. Baseline BMI: quartiles
d. Baseline BSA: quartiles
e. Baseline CRP quartiles, CRP categories (<1.0 mg/dL, ≥1.0 mg/dL) and CRP categories (<0.1 mg/dL, ≥0.1 mg/dL)

2.4.2. Subgroups for the Summary of Other Efficacy Endpoints

In addition to demographic subgroups of age, gender, race, geographic region, weight, BMI, and BSA the following subgroups will also be used for the summary of JIA ACR30 (Section 5.4.1.1). The subgroups for efficacy analyses include, but are not limited to, the following:

Baseline disease characteristics subgroups

a. ILAR classification of disease (Systemic onset with polyarticular course with no systemic symptoms, Polyarticular Rheumatoid Factor-negative, Polyarticular Rheumatoid Factor-positive, Oligoarticular extended, Juvenile Psoriatic Arthritis, and Enthesitis-related JIA)
b. Number of active joints (<6, ≥6 to <10, ≥10)
c. Number of joints with limited range of motion (<6, ≥6 to <10, ≥10)
d. CHAQ (<1, ≥1 to <2, ≥2)
e. CRP (<1.0 mg/dL, and ≥1.0 mg/dL at baseline (Week 0))
f. CRP (<0.1 mg/dL, and ≥0.1 mg/dL at baseline (Week 0))
g. Previous joint surgery (yes, no)
h. Disease duration (<6 months, ≥6 months to <1 year, ≥1 year to <3 years, ≥3 years)

Medication use subgroups:

a. Prior anti-TNF therapy (yes, no)
b. Oral corticosteroids (yes, no)
c. NSAIDs (yes, no)
d. MTX dose: tertiles
e. Duration of MTX therapy (<1 year, ≥1 year to <3 years, ≥3 years)
f. Prior DMARDs excluding MTX (0, 1, 2, ≥3)
g. Concomitant conventional DMARDs use at baseline, excluding MTX (0, 1, 2, ≥3)
h. Prior biologics, excluding anti-TNFs (yes, no)
i. Prior JAK inhibitors (yes, no)

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

3.1. Interim Analysis

No interim analyses are planned for this study.

3.2. Data Review Committee

An internal DRC will periodically review and assess safety data during the study to ensure subject safety while participating in the study. DRC review will commence when 20 subjects have been enrolled into the study and then will meet at least once annually as well as on an ad hoc basis upon the request of the study team, until the Week 252 DBL. The content of safety summaries, DRC roles and responsibilities, and the general procedures (including

communications) are defined and documented in the DRC Charter. Statistical output will be provided by Parexel International Corporation.

The safety data summary package prepared by Parexel International Corporation includes summaries and listings of all adverse event (AEs), SAEs, infections, infusion reactions, and lab parameter data. Following the review, the DRC will make a formal, written recommendation regarding the conduct of the study to the study team.

4. SUBJECT INFORMATION

Subject information will be summarized for PKE analysis set unless otherwise specified.

4.1. Demographics and Baseline Characteristics

The baseline measurement is defined as the closest measurement taken prior to the first study agent administration (Week 0) unless otherwise stated.

Subjects' demographic data including age, race, gender, height, weight, BSA, and BMI at baseline will be summarized. Baseline disease characteristics including duration of disease and baseline JIA efficacy assessments will be summarized.

Baseline TB information and medication usage will also be summarized.

The number of subjects will also be summarized by geographic region, country, and investigational site.

4.2. Disposition Information

The number of subjects screened, enrolled, and treated will be summarized. Subjects who discontinued study agent through Week 28, and 52, and 252, and the reasons for discontinuation will also be summarized. Likewise, subjects who terminated study participation and the reasons for termination will also be summarized.

4.3. Treatment Compliance

Subjects will be summarized by the study agent lot(s) received.

Treatment compliance will be assessed by summarizing the total number of infusions actually received, interrupted infusions, and incorrect (± 15% of calculated dose in mg) infusions.

4.4. Extent of Exposure

The cumulative dose of golimumab (mg/m^2) and MTX dose (mg and mg/week) received will be summarized through Week 28, 52 and 252. The length of infusions will be summarized and subjects with <20 and >40 minutes infusion durations will be listed.
The number of administrations will be summarized.

The average follow-up time will also be summarized in the safety tables.

4.5. Protocol Deviations

Major protocol deviations will be tabulated separately and presented for the following categories:

- Subjects who entered the study but did not satisfy entry criteria,
- Subjects who received the incorrect dose
- Subjects who received disallowed medication, and other.

Besides these major deviations, other deviations may be summarized. Subjects with protocol deviations in study agent administration will be summarized by type of deviations.

All protocol deviations will be summarized through Week 28, through Week 52, and through Week 252 for the full analysis set.

4.6. Prior and Concomitant Medications

Medications taken by subjects prior to starting the study will be summarized. These include medications for JIA such as MTX, other DMARDs, oral corticosteroids, and NSAIDs.

Concomitant medications will be summarized through Week 28, 52 and 252 for all subjects who belong in the full analysis set.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

No statistical testing will be performed.

5.1.2. Data Handling Rules

No data handling rules will be applied to all individual endpoints and composite endpoints that are not dichotomous. Observed data will be summarized.

For a dichotomous composite endpoint, subjects who have completely missing data (ie, all components of the composite endpoint are missing) will be assumed to be a non-responder. When at least 1 of the components is non-missing, last observation carried forward (LOCF) will be used for imputing the components with missing data.

5.1.3. Joint Evaluability

For subjects who have a joint injection or surgical procedure prior to the date of enrollment, the affected joints will be analyzed according to the impact of the joint injection or joint surgical procedure on the evaluability of the involved joints. See Attachment 1 for details. If a joint is considered nonevaluable at baseline, then all post-baseline joint evaluations will also be considered as nonevaluable; furthermore, this nonevaluability overrides any other documented, post baseline joint assessments. For subjects undergoing joint injections and/or procedures during the study for reasons not related to JIA, joint evaluability is summarized in Attachment 2.

For subjects undergoing a joint procedure/injection for the treatment of JIA, the corresponding joint(s) will be counted as swollen, having active arthritis, and having limited range of motion from the date of procedure onward.

5.1.4. Adjusted Joint Counts Rules

For subjects who have an incomplete set of evaluable joints, the joint count will be adjusted to a 69 joint count for joints with limited range of motion and 73 joint count for active joints for JIA ACR endpoints. This is done by dividing the number of affected joints by the number of evaluable joints and multiplying by 69 and 73, respectively.

5.2. Primary Efficacy Endpoint

No primary efficacy endpoint is planned.

5.3. Major Secondary Endpoints

No major secondary efficacy endpoints are planned.

5.4. Other Efficacy Variable(s)

5.4.1. Definition of other efficacy endpoints

5.4.1.1. JIA ACR Response

JIA ACR responses are composite endpoints measured by the 6 pediatric ACR categories. These are as follows:

1. Physician's global assessment of disease activity, (0 = No arthritis activity, 100 = Extremely arthritis activity) (0-100 mm VAS)
2. Parent/subject assessment of overall well-being, (0 = Very well, 100 = Very poor) (0-100 mm VAS)
3. Number of active joints (defined as either swelling, or in absence of swelling, limited range of motion associated with pain on motion or tenderness), (0-73)
4. Number of joints with limited range of motion, (0-69)
5. Physical function by Childhood Health Assessment Questionnaire, (0-3) (See Section 5.4.1.4 for details)
6. CRP (unit = mg/dL)

JIA ACR 30 response[4] is defined as ≥30% improvement from baseline in at least 3 of the 6 components with worsening of 30% or more in no more than 1 of the above noted components. Improvement in each of the individual components is indicated by a decrease in score.

If a subject's baseline value for a component is zero (ie, no disease activity as measured by that component), the subject should be considered as not achieving 30% improvement from baseline for that component since there is no room for improvement.

JIA ACR 50, 70 and 90 responses are similarly defined using the corresponding threshold for improvement from baseline and with worsening of 30% or more in no more than 1 of the above noted components.

5.4.1.2. Inactive Disease

Inactive disease is indicated by the presence of all of the following:

1. No joints with active arthritis
2. No fever, rash, serositis, splenomegaly, hepatomegaly or generalized lymphadenopathy attributable to JIA
3. No active uveitis
4. Normal CRP (≤ 0.287 mg/dL for subjects without underlying inflammatory disease)
5. Physician Global Assessment of disease activity indicating no active disease (≤5 mm VAS)
6. Duration of morning stiffness <15 minutes

5.4.1.3. Clinical Remission While on Medication

Clinical remission while on medication for JIA is defined as inactive disease (Section 5.4.1.2) at each non-missed visit for a period of ≥6 months (24 weeks) while on medication. All subjects are assumed to be on medication.

For a given visit, the determination of clinical remission while on mediation for JIA will be based on the period of 24 weeks prior to the visit. To be considered clinical remission, all the visits encompassing at least 24 weeks prior to the visit will have to meet the inactive disease criteria.

5.4.1.4. Childhood Health Assessment Questionnaire (CHAQ)

The functional status of subjects will be assessed by the CHAQ. Parents are to complete this questionnaire to assess the degree of difficulty the subject has in accomplishing tasks in 8 functional areas (dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area are scored as 0 = without difficulty, 1 = with some difficulty, 2 = with much difficulty, 3 = unable to do, or 4 = not applicable response options. If aids or devices are used or assistance is required, the minimal score for the corresponding area is 2. The CHAQ has been shown to be responsive to disease change.[1] A decrease of 0.188 has been determined to be a meaningful clinical improvement.[6]

The disability index is calculated as the mean of the 8 domains and yields a score between 0 (no disability) and 3 (most severe disability). The disability index is not computed if the subject does not have scores for at least 6 categories.

5.4.1.5. Juvenile Arthritis Disease Activity Score (JADAS)

The JADAS (modified for using CRP) is computed by assessing the following variables:

(1) Physician global rating of overall disease activity, measured on a 100-mm horizontal VAS (0 no activity; 100 maximum activity);

(2) Parent/child ratings of well-being and pain, assessed on a 100-mm Horizontal Line Visual Analog Scales,[3]

(3) Number of active joints, assessed in 71, 27, or 10 joints (JADAS 71, JADAS 27, and JADAS 10, respectively); and

(4) CRP was truncated to a 0-10 scale according to the following formula: ((CRP [mg/L]-10)/10), similar to the truncated ESR used in JADAS-ESR. Before calculation, CRP values <10 mg/L are converted to 10 and CRP values >110 mg/L are converted to 110.[5]

JADAS-71 includes the entire number of joints. The JADAS-27 includes the following joints: cervical spine, elbows, wrists, meta-carpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles. JADAS-10 is based on the count of any active joint, irrespective of its type, up to a maximum of 10 joints.

The JADAS is calculated as the sum of the scores of its 4 components, which yields a global score of 0–101, 0–57, and 0–40 for the JADAS 71, JADAS 27, and JADAS 10, respectively.

JADAS 10, 27, and 71 minimal disease activity[2,5] is defined as the presence of all of the following:

(1) Physician's global assessment of disease activity of ≤3.5,

(2) Parent's global rating of well-being of ≤2.5, and

(3) Swollen joint count of ≤1 in patients with polyarthritis.

JADAS inactive disease is defined as a total JADAS score of ≤1.

5.4.2. Analysis Methods

Unless otherwise specified, the analysis population will be the full analyses set defined in Section 2.3.2.

Summaries over time will be for all visits data was collected through Week 28, 52, and 252, if the visit of the endpoint is not specified. Simple descriptive summary statistics, such as n, mean, SD, median, IQ range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

The following endpoints will be summarized over time.

1. The proportion of subjects who are JIA ACR 30, 50, 70, and 90 responders
2. The proportion of subjects who have inactive disease
3. The proportion of subjects in clinical remission on medication for pJIA
4. The improvement from baseline in the JIA ACR core set of components
5. The proportions of subjects who are JIA ACR 30, 50, 70, and 90 responders by disease subtype, and/or age through Week 52
6. The change from baseline in CHAQ
7. CRP concentrations
8. The change from baseline in JADAS 10, 27, and 71 scores
9. The proportion of subjects who achieve JADAS 10, 27, and 71 minimal disease activity

6. SAFETY

Safety will be assessed by summarizing the occurrences and type of AEs, and examining the changes in the laboratory parameters.

Subjects who received at least 1 IV study agent administration will be included in the analysis (full analysis set).

6.1. Safety Table(s) Presentation

If a subject discontinues study participation, the follow-up time will stop at the day of study participation discontinuation.

The safety summary tables will be presented through the following periods:

1. Through Week 28
2. Through Week 52
3. Through Week 252

6.2. Adverse Events

Treatment-emergent AEs will be summarized by system organ class and preferred term defined by MedDRA.

The following treatment-emergent AE summary tables will be provided for this study:

- Any AEs
- SAEs

- AEs with severe intensity
- AEs and SAEs that are reasonably related to study agent
- AEs leading to discontinuation of study agent
- Infusion reactions
- Infections and infections requiring oral or parenteral anti-microbial treatment
- Serious infections

In addition to the summary tables, a listing of subjects who died and listings of subjects with the following AEs will be presented: SAEs, AEs leading to discontinuation of study agent(s), anaphylactic reactions or serum sickness reactions, malignancy, tuberculosis, clinically important hepatobiliary events (defined as ALT $\geq$ 3×ULN and either bilirubin $\geq$ 2×ULN or occurrence of a serious adverse event in the hepatobiliary system-organ class), and demyelination.

Infusion reactions and infection:

- An infusion reaction is identified as any unfavorable or unintended sign that occurs during the infusion or within 1 hour of completion of the infusion. Infusion reactions are captured in the eCRF.
- An infection is identified as any AE that was recorded as an infection by the investigator on the eCRF.

Since safety should be assessed relative to exposure, the following summaries will be presented:

- Proportion of subjects receiving scheduled IV study agent administrations at each study agent administration visit.
- Summary of cumulative golimumab dose.

In addition, all AE summary tables will include average weeks of follow-up and average number of IV infusions.

6.3. Clinical Laboratory Tests

The laboratory parameters include but are not limited to the following:

Hematology: hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, platelets, and WBC count.

Chemistry: BUN/urea, creatinine, total bilirubin, alkaline phosphatase, ALT/SGPT, AST/SGOT, bicarbonate, sodium, potassium, calcium, albumin, chloride, phosphate, glucose, uric acid and total protein.

Laboratory results will be graded according to NCI-CTCAE version 4.03 or later. Note that toxicity grading for creatinine increase will be based on the NCI CTC v4.03 or later criteria, but limited only to the part based on the upper limit of normal (ULN), the other part, that is based on change from baseline, will not be used for toxicity grading. Generic normal ranges will be applied whenever reference ranges are not available.

NCI-CTCAE grades will be used in the summary of laboratory data (Grade 0 – 4). The proportion of subjects for select laboratory parameters with maximum Grades will be presented. In addition, the proportion of subjects with markedly abnormal laboratory results will also be provided. The subjects' maximum post-baseline ALT and AST will also be summarized by TB prophylaxis (TB prophylaxis, or no TB prophylaxis).

Levels of laboratory values that are considered to be markedly abnormal have been defined for each laboratory parameter in Attachment 3.

Boxplots will be used to describe the selected laboratory analyte at baseline and at each scheduled time point. The selected laboratory analytes are: WBC counts, neutrophils, hemoglobin, platelets, ALT, and AST.

6.4. Vital Signs and Physical Examination Findings

Vital signs including heart rate, respiratory rate, temperature, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized by visit.

6.5. Electrocardiogram

This section does not apply to this study.

6.6. Antinuclear (ANA)/ Anti-dsDNA antibodies

Blood samples will be collected at Weeks 0, 24, 52, 76, 100, 124, 148, 172, 196, 220 and 244 to determine the presence of antinuclear (ANA)/ anti-dsDNA antibodies.

Subjects' baseline ANA and anti-dsDNA status and proportion of subjects who change ANA and anti-dsDNA status during the trial will be summarized.

7. PHARMACOKINETICS/PHARMACODYNAMICS AND IMMUNOGENICITY

7.1. Pharmacokinetics

7.1.1. Primary PK Endpoints

The primary endpoints in this study are PK exposure at Week 28 (the trough concentrations at Week 28) and the Bayesian AUC_{ss} over one dosing interval of 8 weeks (from population PK modeling and simulation).

7.1.1.1. Definition

$C_{trough,wk28}$: Serum golimumab trough concentration at Week 28

AUC_{ss}: Area under the curve at steady-state over a dosing interval

7.1.1.2. Analyses Methods

Summary golimumab concentrations will be summarized and PK exposure will be evaluated through Week 52 and through the LTE (Week 252).

A population PK analysis with data through Week 28 will be performed to characterize the PK of golimumab as well as to identify and quantify important covariates of PK in the pediatric population with JIA. Clearance and volume of distribution will be estimated using a nonlinear mixed effects modeling (NONMEM) approach. Details will be provided in a population PK analysis plan and the results of the analysis will be presented in a separate report.

Measures of PK exposure will be graphically evaluated in the pediatric populations after administration of IV golimumab (including but not limited to steady-state C_{max}, C_{min} and AUC) and compared to PK exposure from adults in CNTO148ART3001. Similarity between pediatric and adult subjects will be assessed by the generation of box plots from the population PK modeling via visual inspection in addition to the descriptive statistics of the observed concentrations.

7.1.2. Major Secondary PK Endpoints

Major secondary endpoints include PK exposure at Week 52 (the trough concentrations at Week 52) and the Bayesian AUCss at Week 52 (from population PK modeling and simulation).

7.1.2.1. Definition

$C_{trough,wk52}$: Serum golimumab concentration at Week 52.

7.1.2.2. Analyses Methods

The analysis of the major secondary PK endpoint will be performed via population PK modeling using NONMEM as described in Section 7.1.1.2.

7.1.3. General PK Summaries

PK samples for measuring serum golimumab concentrations will be collected from all subjects at the specified visits as shown in the schedule of events of the protocol. Samples will be collected at Weeks 0, 4, 8, 12, 20, 28, 52, 100, 148, 196 and 244. Two samples, one pre-infusion and another post-infusion, will be collected at Weeks 0, 4, and 12. An additional random PK sample for serum golimumab concentration will be collected from all subjects at any time between Weeks 0 and 8 other than at the time of the Week 0, 4 and 8 visits; this sample must be collected at least 24 hours before or after a study agent infusion.

All PK evaluations will be based on the subjects who receive at least 1 infusion of golimumab (PKE analysis set).

No imputation for missing concentration data will be performed. Pre and post infusion serum concentrations will be summarized separately.

The data analysis of serum golimumab concentrations includes the following:

- Summary of serum golimumab concentrations at each visit
- Summary of serum golimumab concentrations at each visit by body weight quartiles.
- Summary of serum golimumab concentrations at each visit by BMI quartiles.

- Summary of serum golimumab concentrations at each visit by BSA quartiles.
- Summary of serum golimumab concentrations at each visit by age (2 to <6 years, 6 to <12 years, 12 to <18 years).
- Summary of serum golimumab concentrations at each visit by CRP quartiles and CRP categories (<0.1 mg/dL, ≥0.1 mg/dL; <1.0 mg/dL, ≥1.0 mg/dL).
- Proportion of subjects without detectable serum golimumab concentration at each visit.
- Summary of serum golimumab concentrations at each visit by antibodies to golimumab status.
- Median serum golimumab concentrations plotted over time.

In addition, the relationship between serum golimumab concentrations and antibody to golimumab status, safety and efficacy may be explored using graphical displays. Median serum golimumab concentrations will be plotted. Box plots of serum golimumab concentrations will be plotted by percentage subjects who achieved JIA ACR 30 responses.

For summary statistics of serum golimumab concentrations, concentration values below the lower limit of quantification will be treated as zero. Once a subject meets one of the following dosing deviation criteria, the subject's data will be excluded from the by-visit data analyses from that point onwards.

Dosing deviation criteria:

- Discontinue IV study agent administrations.
- Skipped an IV administration.
- Received an incomplete / incorrect IV dose.
- Received an additional IV dose.

In addition, if a subject has an administration more than 7 days earlier or later than the scheduled dosing date, the concentration data collected between such a dosing visit and the subsequent dosing visit will be excluded from the by-visit data analyses. For visits prior to Week 28, if the PK sampling time deviates more than 3 days earlier or later than the scheduled date, the PK concentration at this visit will be excluded from the by-visit data analyses. Additional exclusions for incongruous PK data to be implemented based on Janssen SOP-07948v2.

Population PK analyses will be performed to characterize the population PK parameters based on the available golimumab concentration data obtained through the Week 28 visit. The population pharmacokinetic approach will also be used to identify and quantify any significant covariates such as demographic characteristics (including but not limited to body weight, sex, and age).

PK analyses will be summarized through the following time periods:

- Through Week 28
- Through Week 52
- Through Week 244

7.2. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum golimumab concentrations and efficacy measures may be explored, and the results will be reported in a separate technical report.

7.3. Immunogenicity

Blood samples will be collected to examine the formation of antibodies to golimumab at the specified visits as shown in the schedule of events of the protocol. For subjects who discontinue IV study agent administrations, samples will be collected at their safety follow-up visit.

The data analysis of antibodies to golimumab includes the following:

- The antibody status (positive, negative) of subjects will be summarized. For subjects who discontinue IV study agent administrations and complete safety follow-up, a listing of their antibody status will be presented.
- The relationship between antibody to golimumab status and efficacy and safety will be assessed at major assessment time points (Weeks 28, 52 and 252). JIA ACR 30 responses by antibody to golimumab status; infusion reactions by antibody to golimumab status.
- The relationship between antibody to golimumab status at Week 28 and antibody to golimumab status at Week 52 will be explored.
- The onset of antibody to golimumab formation will be summarized
- The duration of antibody to golimumab will be summarized.
- The serum golimumab concentrations by antibody to golimumab status will be presented graphically.

8. HEALTH ECONOMICS

This section does not apply to this study.

REFERENCES

1. Brunner HI, Klein-Gitelman MS, Miller MJ, et al. Minimal clinically important differences of the childhood health assessment questionnaire. J Rheumatol. 2005; 32(1):150-161.
2. Consolaro A, Bracciolini G, Ruperto N, et al. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis. Arthritis Rheum. 2012; 64(7):2366-2374.
3. Filocamo G, Davì S, Pistorio A, et al. Evaluation of 21-numbered circle and 10-centimeter horizontal line visual analog scales for physician and parent subjective ratings in juvenile idiopathic arthritis. J Rheumatol. 2010; 37(7):1534-1541.
4. Giannini EH, Ruperto N Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum. 1997; 40:1202-1209.
5. Magni-Manzoni S, Ruperto N, Pistorio A, et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. Arthritis Rheum. 2008; 59(8):1120-1127.
6. Nordal EB, Zak M, Aalto K, et al. Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population-based setting. Ann Rheum Dis. 2012; 71(7):1122-1127.
7. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum. 1994; 37(12):1761-1769.

ATTACHMENT

Attachment 1: Analytical considerations on joints with joint procedure/injection prior to study [a]

Procedures/Injection	***Impact on Joint Count Outcome***
Synovectomy	Not evaluable
Arthrodesis	Not evaluable
Joint replacement	Not evaluable
Amputation	Not evaluable
Arthrocentesis	Evaluable if happened > 3 months prior to baseline
Excision / Resection	Not evaluable
Arthrotomy	Not evaluable
Arthroscopy – surgical	Evaluable if happened > 3 months prior to baseline visit, otherwise not evaluable
Arthroscopy – diagnostic	Evaluable if happened > 4 weeks prior to baseline visit, otherwise not evaluable
Chondroplasty	Evaluable if happened > 4 weeks prior to baseline visit, otherwise not evaluable
Synovial cyst aspiration	Evaluable if happened > 4 weeks prior to baseline visit, otherwise not evaluable
Needle biopsy – synovium	Evaluable if happened > 3 months prior to baseline visit, otherwise not evaluable
Osteotomy	Not evaluable
Radio synovectomy	Not evaluable
Tendon surgery	Not evaluable
Bursal surgery	Not evaluable
Fracture reduction	Not evaluable
Steroid injection (IA, tendon, sheath, bursa)	Evaluable if happened > 3 months prior to baseline visit, otherwise not evaluable
Other injection	Not evaluable

[a] The joint assessors may mark a joint as not evaluable based on his clinical judgment, which is not included in this table.

Attachment 2: Analytical considerations on joints with injection and/or joint surgery for reasons NOT related to JIA during the study [a]

Procedures/Injection	***Impact on Joint Count Outcome***
Synovectomy	Not evaluable from procedure date onward
Arthrodesis	Not evaluable from procedure date onward
Joint replacement	Not evaluable from procedure date onward
Amputation	Not evaluable from procedure date onward
Arthrocentesis	Not evaluable from procedure date onward
Excision / Resection	Not evaluable from procedure date onward
Arthrotomy	Not evaluable from procedure date onward
Arthroscopy – surgical	Evaluable if happened > 3 months prior to evaluation, otherwise not evaluable
Arthroscopy – diagnostic	Evaluable if happened > 4 weeks prior to evaluation, otherwise not evaluable
Chondroplasty	Evaluable if happened > 4 weeks prior to evaluation, otherwise not evaluable
Synovial cyst aspiration	Evaluable if happened > 4 weeks prior to evaluation, otherwise not evaluable
Needle biopsy – synovium	Evaluable if happened > 3 months prior to evaluation, otherwise not evaluable
Osteotomy	Not evaluable from procedure date onward
Radio synovectomy	Not evaluable from procedure date onward
Tendon surgery	Not evaluable from procedure date onward
Bursal surgery	Not evaluable from procedure date onward
Fracture reduction	Not evaluable from procedure date onward
Steroid injection (IA, tendon, sheath, bursa)	Evaluable if happened > 3 months prior to evaluation, otherwise not evaluable
Other injection	Not evaluable from procedure date onward

[a] The joint assessors may mark a joint as not evaluable based on his clinical judgment, which is not included in this table.

Attachment 3: Markedly Abnormal Laboratory Parameter Criteria

Table 3 Markedly abnormal criteria for laboratory parameters	
Hematology Test	**Criteria for Markedly Abnormal Status**
Hemoglobin (g/L)	Decrease > 20.0 **AND** Value < 100.0
Hematocrit (%)	Value < 0.27
Total WBC ($x10^9$/L)	Value < 2.0 **OR** Value > 20.0
Neutrophils, absolute ($x10^9$/L)	Percent decrease ≥33 **AND** Value < 1.5
Lymphocytes, absolute ($x10^9$/L)	Percent decrease ≥ 33 **AND** Value < 1.5
Eosinophils, absolute ($x10^9$/L)	Percent increase ≥ 100 **AND** Value > 1.3
Platelet count ($x10^9$/L)	Percent decrease ≥50 **AND** Value < 75
Chemistry Test	**Criteria for Markedly Abnormal Status**
Alkaline phosphatase (U/L)	Percent increase ≥ 100 **AND** Value > 500
ALT (U/L)	Percent increase ≥100 **AND** Value > 150
AST (U/L)	Percent increase ≥ 100 **AND** Value > 150
Total bilirubin (umol/L)	Percent increase ≥ 100 **AND** Value > 51.3
Sodium (mmol/L)	(Increase ≥10 **AND** Value > 150) **OR** (Decrease ≥ 10 **AND** Value < 120)
Potassium (mmol/L)	(Increase ≥ 0.8 **AND** Value > 5.5) **OR** (Decrease ≥ 0.8 **AND** Value < 3.0)
Chloride (mmol/L)	Value < 85 **OR** Value > 120
BUN/Urea (mmol/L)	Percent increase ≥ 66 **AND** Value > 14.28
Creatinine (umol/L)	Percent increase ≥ 66 **AND** Value > 132.6
Albumin (g/L)	Decrease ≥ 10.0 **AND** Value < 30.0
Total protein (g/L)	Value < 45 **OR** Value > 100
Calcium (mmol/L)	(Increase ≥ 0.37 **AND** Value > 2.62) **OR** (Decrease ≥0.37 **AND** Value < 1.87)