Janssen Research & Development*

Clinical Protocol

A Multicenter, Double-Blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab, a Human Anti-TNFα Antibody, in Pediatric Subjects with Active Polyarticular Course Juvenile Idiopathic Arthritis (JIA) Despite Methotrexate Therapy

Protocol CNTO148JIA3001; Phase 3
AMENDMENT 9

SIMPONI™ (golimumab)

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER: 2009-015019-42

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Amendment 1: 19 Apr 2010
Original Protocol: 01 Feb 2010

Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

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SYNOPSIS

A Multicenter, Double Blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab, a Human Anti-TNFα Antibody, in Pediatric Subjects with Active Polyarticular Course Juvenile Idiopathic Arthritis (JIA) Despite Methotrexate Therapy

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Golimumab is a human anti-tumor necrosis factor alpha (TNFα) monoclonal antibody (mAb) developed to offer flexibility in route of administration, a convenient dose regimen, and to demonstrate equivalent or superior efficacy to other anti-TNFα agents in treating inflammatory disease while maintaining an acceptable safety profile. TNFα is a key inflammatory mediator, with high levels of TNFα implicated in the pathophysiology of diseases such as rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). Blocking TNFα activity as demonstrated in clinical studies of infliximab and other anti-TNF agents can prevent the deleterious effects caused by excessive TNFα.

OBJECTIVE

Primary Objectives

The primary objective of this study is to assess the clinical efficacy of SC administration of golimumab in pediatric subjects (ages 2 to less than 18 years) with JIA manifested by ≥ 5 joints with active arthritis despite methotrexate (MTX) therapy for ≥ 3 months.

Secondary Objectives

The secondary objectives of this study are to evaluate golimumab in pediatric subjects with JIA with respect to:

1. Safety.
2. Physical function.
3. Quality of life.
4. Disease activity status over time.
5. Pharmacokinetics and immunogenicity.
6. Pharmacodynamics.

Hypothesis

Pediatric subjects with JIA who have responded at Week 16 to golimumab administered subcutaneously every 4 weeks and continue to receive golimumab treatment through Week 48 will exhibit fewer flares of disease (defined below) from Week 16 through Week 48 compared with subjects who responded to golimumab at Week 16 and began receiving placebo at Week 16.

Flare of disease is defined as the worsening from Week 16 by 30% or more in 3 of the 6 ACR (American College of Rheumatology) Ped (pediatric) Core Set Variables with no more than 1 of the 6 ACR Ped Core Set Variable improving by more than 30% at the time of the flare.

OVERVIEW OF STUDY DESIGN

This is a randomized withdrawal, double-blind, placebo-controlled, parallel-group, multicenter study of SC golimumab in pediatric subjects with active JIA despite current treatment with MTX. At least 170 subjects will be enrolled at Week 0 to ensure that at least 134 subjects are randomized into the randomized withdrawal portion of the study.

All subjects will receive 30 mg/m^2 golimumab SC injection (maximum 50 mg) at Week 0, and every 4 weeks thereafter through Week 12. BSA will be calculated at each visit and the dose of golimumab will be adjusted accordingly. Subjects will also receive commercial MTX weekly at the same numerical (mg/week of MTX) dose as at time of study entry.

Two interim analyses will be performed during the course of this study.

Week 8 interim analysis

An interim analysis will be performed at the Week 8 timepoint, when 30 subjects have completed the Week 8 visit, after receiving 2 golimumab administrations at Weeks 0 and 4. This interim analysis will be performed to ensure that 8 or more subjects are American College of Rheumatology (ACR) Pediatric (Ped 30) responders by the Week 8 visit. Pharmacokinetic (PK), efficacy and safety assessments will be reviewed after 30 subjects have completed the Week 8 visit. All new screening will stop pending completion of this initial interim analysis.

Week 16 Interim Analysis (120 subjects completed at Week 16)

After approximately 120 subjects complete the Week 16 visit, another interim analysis will be performed. The response rates of subjects at Week 16 will be evaluated to ensure that 134 subjects would participate in the randomized withdrawal portion of the study. If the response rates at the interim analysis indicate that < 134 responders would enter the randomized withdrawal portion of the study, the total number of subjects enrolled into the study at Week 0 will be increased.

In addition, a population PK analysis, combined with an assessment of efficacy and safety, will explore the potential benefit and risk of tiered fixed doses based on pediatric weight ranges. Based on these analyses, tiered fixed dosing may be utilized after the Week 48 DBL during the long-term extension of the study.

At Week 16, each subject will be evaluated to determine if they have achieved an ACR Ped 30 response ("responders") compared with baseline. Responders will be randomized at Week 16 in a 1:1 ratio to either continue to receive golimumab 30 mg/m^2 (to 50 mg maximum) injections every 4 weeks or to begin receiving placebo injections every 4 weeks up to Week 48. BSA will be calculated at each visit and the dose of golimumab will be adjusted accordingly. Subjects will be monitored every 4 weeks for disease activity. Subjects randomized to placebo that experience flare of disease between Weeks 16 and 48 will restart receiving golimumab (30 mg/m^2) at the time that the flare is detected and will continue on that dose to Week 48. No changes should be made to background medications (ie, DMARDs, corticosteroids, and NSAIDs) in terms of dosage and route of administration between Weeks 16 and 48 in the randomized withdrawal period, unless the subject has a documented flare or there is a safety concern (eg, elevated LFTs), which require changes to background medications. Doses of methotrexate, corticosteroids, or non-steroidal anti-inflammatory agents should not be reduced between Weeks 16 and 48, even if subjects have shown good improvement in signs and symptoms. For subjects randomized to continue receiving golimumab at Week 16, the golimumab dose will remain the same as that received from Week 0 to Week 12 (ie, 30 mg/m^2).

At Week 48, subjects who received placebo + MTX who are not in clinical remission while on medication for JIA will begin receiving golimumab 30 mg/m^2 SC in a blinded fashion. Beginning at Week 48, subjects will be permitted to change DMARD, corticosteroid, and NSAID use. Golimumab dose decreases or increases below or above 30 mg/m^2 based upon BSA measured at the specific visit will not be permitted. After the 48-Week DBL and site unblinding, investigators will begin golimumab 30 mg/m^2 SC for subjects receiving SC placebo who are not in clinical remission while on medication for JIA (Section 9.2.1.3). Subjects who were still receiving SC placebo at the time of the 48-Week DBL and who are in clinical remission while on medication for JIA will be discontinued from the study. Subjects will continue active treatment after Week 48 in a long-term extension until Week 248, with safety follow-up through Week 256. Investigative study sites and subjects will remain blinded to treatment assignment until the last subject enrolled completes the Week 48 evaluations and the database is locked.

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

An Independent DMC has been commissioned for this study.

STUDY POPULATION

The study population will include subjects with active JIA with the following subtypes: 1) polyarticular (rheumatoid factor positive), 2) polyarticular (rheumatoid factor negative), 3) extended oligoarticular JIA, 4) systemic JIA, without systemic symptoms but with polyarthritis, or 5) juvenile psoriatic arthritis (JPsA). All subjects must have ≥ 5 active joints at the time of screening and disease duration of ≥ 6 months prior to study entry. Diagnosis must be made per JIA International League of Associations for Rheumatology (ILAR) diagnostic criteria and the onset of disease must have been before the subject's 16th birthday. Active disease at the time of screening and before first injection is defined by the presence of polyarticular disease with ≥ 5 joints with active arthritis as defined by ACR criteria (ie, presence of swelling, or if no swelling is present, limitation of motion accompanied by pain, tenderness, or both). Subjects with exposure to only 1 prior anti-TNF agent before entering screening for this study will be permitted to enroll in the study but will be limited to no more than 20% of the total number of subjects. These subjects will be allowed to enter the study after the first interim analysis at Week 8 is completed.

DOSAGE AND ADMINISTRATION

The study will have 1 active treatment group. The test products, golimumab and placebo, will be prepared by a blinded pharmacist from a prefilled syringe (PFS) and transferred to a graduated syringe under sterile conditions. Subjects will receive 30 mg/m^2 golimumab SC injection to a maximum dose of 50 mg. Subjects will also receive commercial MTX weekly at their fixed dose at time of study entry and commercial folic acid ≥ 5 mg weekly or folinic acid (at half the MTX dose) given the day after the MTX dose.

EFFICACY EVALUATIONS

The primary efficacy endpoint is the proportion of subjects who are ACR Ped 30 responders at Week 16 and do not experience a flare of disease between Week 16 and Week 48.

The major secondary analyses endpoints are as follows:

1. The proportion of ACR Ped 30 responders at Week 16 with ACR Ped 30 response at Week 48 will be summarized by treatment group and compared between treatment groups.

2. The proportion of subjects who are responders at Week 16 and have inactive disease at Week 48 will be summarized by treatment group and compared among treatment groups.

3. The proportion of subjects who are responders at Week 16 and are in protocol defined clinical remission while on medication for JIA at Week 48 will be summarized by treatment group and compared among treatment groups.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Venous blood samples of 2 mL will be generally collected for determination of serum golimumab concentrations and antibodies to golimumab at the time points presented in the Time and Events Schedule.

Serum golimumab concentrations will be summarized for each treatment group over time. If feasible, a population PK analysis will be performed to characterize the PK of golimumab as well as to identify and quantify important covariates of PK using a nonlinear mixed effects modeling (NONMEM) approach.

To assess the immunogenicity of golimumab, detection of antibodies to golimumab will be performed using a validated immunoassay. All samples collected for detection of antibodies to golimumab will also be evaluated for golimumab serum concentration to enable interpretation of the antibody data. The occurrences and titers of antibodies to golimumab will be summarized by treatment group over time.

PHARMACODYNAMIC EVALUATIONS

Changes in the concentration of individual serum and urine markers, from baseline to the selected after treatment time points, will be summarized. Additional analyses may be performed following evaluation of the data. RNA analyses and additional analyses will be summarized in a separate technical report.

SAFETY EVALUATIONS

Safety will be assessed by monitoring AEs, clinical laboratory tests, vital signs, physical examinations, concomitant medication review, injection-site evaluations, allergic reactions, and early detection of TB.

STATISTICAL METHODS

Descriptive statistics, such as mean, median, standard deviation, interquartile range, minimum and maximum for continuous variables, and counts and percentages for categorical variables will be used to summarize most data.

Analyses suitable for categorical data (eg, chi-square test, Cochran-Mantel-Haenszel [CMH] test) will be used to compare the proportion of subjects achieving selected endpoints. Continuous data will be compared using an analysis of variance (ANOVA) on the van der Waerden normal scores. All statistical procedures will be performed 2-sided at a significance level of 0.05. In addition to statistical analyses, graphical summaries of the data may be used.

Subject baseline data, demographic and baseline disease characteristic, including earlier JIA therapies, will be summarized. The baseline measurement is defined as the closest measurement taken before the time of the Week 0 injection.

The study is designed to maintain a Type I error of 0.05 or less for the primary analyses.

Nominal p-values will be reported for secondary analyses.

TIME AND EVENTS SCHEDULE

Table 1: From Screen through Week 48

Phase	Screen	Active Treatment/Randomized Withdrawal												
Week		0	4	8	12	16	20	24	28	32	36	40	44	48
Procedures and Evaluations														
Administrative														
Informed consent	X													
Medical history/demographic data	X													
Concomitant medications collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X												
Randomization						X								
Study Agent														
SC administration of study agent		X	X	X	X	X	X	X	X	X	X	X	X	X
Safety														
Physical examination[a]	X				X			X			X			X
Review of systems	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Uveitis evaluations[b]	X							X						X
Chest x-ray[c]	X													
Routine laboratory analyses	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepcidin[d,e]		X	X			X				X				X
Anemia panel[d,e]		X	X			X				X				X
QuantiFERON® - TB Gold test[f]	X													
TB evaluation (questionnaire)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: From Screen through Week 48

Phase	Screen	Active Treatment/Randomized Withdrawal												
Week		0	4	8	12	16	20	24	28	32	36	40	44	48
Procedures and Evaluations														
Pregnancy test (serum)[g]	X													
Pregnancy test (urine)[g]		X	X	X	X	X	X	X	X	X	X	X	X	X
Injection-site evaluation[h]		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
Efficacy														
Efficacy evaluations[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP[j]		X	X	X	X	X	X	X	X	X	X	X	X	X
ESR	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CHQ[k]		X			X			X						X
CHAQ[k]		X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics														
Golimumab concentration[l,j]		X	X	X	X	X	X	X						X
Population PK[m]		← X →												
Immunogenicity														
Antibodies to golimumab[l]		X	X		X			X						X
ANA/anti-dsDNA antibodies		X						X						X
Pharmacodynamics														
Rheumatoid factor	X							X						X
CCP	X							X						X
Biomarkers														
RNA analysis[n,e]		X				X								
Sample collection for serum biomarkers[e]		X	X			X								
Sample collection urine biomarkers		X	X			X								

Table 1: From Screen through Week 48

a. Includes Tanner staging every 6 months.
b. Evaluations should be performed every 6 months in all subjects. Slit lamp examinations are required every 6 months in subjects who are ANA positive.
c. Chest x-ray screening as per site and country regulations for initiation of immunosuppressive agents in children with JIA who are at risk of TB.
d. Anemia panel includes serum iron, total iron binding capacity, ferritin, transferring receptor, reticulocyte count, and EPO (erythropoietin). In addition, hepcidin levels will be determined in serum (Weeks 0, 4, 16, 32, and 48) and urine. First morning urine (in all subjects regardless of weight) will be collected for the urinary hepcidin assay at Weeks 0, 4, 16, 32, and 48.
e. Only to be performed in children ≥ 32 kg.
f. PPD should also be performed in countries where Quantiferon TB-Gold testing is not approved.
g. All female subjects of childbearing potential (ie, post-menarche) must test negative for pregnancy before enrolling in the trial and at all visits through Week 48.
h. Subjects will be observed for at least 30 minutes after the SC administration of study agent for symptoms of an injection-site reaction.
i. Evaluations at all time points will include standard joint counts, physician global assessment, parent assessment of overall wellbeing, pain assessment, except at Screening when only the standard joint count will be performed.
j. For the first 30 subjects in the study, additional PK and CRP samples will be obtained on Day 4 ± 1 day and Day 15 ± 2 days.
k. To be completed by the parent or caregiver, preferably the same parent of caregiver should complete at every visit.
l. The same serum samples may be used for the measurement of golimumab concentration and detection of antibodies to golimumab. For visits with study agent administration, all blood samples for assessing golimumab concentration and antibodies to golimumab MUST be collected BEFORE the administration of the study agent.
m. One additional PK sample for serum golimumab concentration will be collected from all subjects at any time between Weeks 0 and 12 other than at the time of the Week 0, Week 4, Week 8, and Week 12 visits; this sample must be collected at least 24 hours before or after a study agent injection.
n. It is a requirement for sites and subjects to participate in this study. Samples will be collected for RNA analysis at Weeks 0 and 16.

Abbreviations: ANA = antinuclear antibodies; CCP = cyclic citrullinated peptide; CHAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; IVRS = interactive voice response system; PK = pharmacokinetic; RNA = ribonucleic acid; SC = subcutaneous; TB = tuberculosis.

Table 2: From Week 52 through Week 100

Phase	Long-term Extension												
Week	52	56	60	64	68	72	76	80	84	88	92	96	100
Procedures and Evaluations													
Administrative													
Concomitant medications collection	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Agent													
SC administration of study agent	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety													
Physical examination[a]	X			X		X							X
Body weight measurement	X	X	X	X	X	X	X	X	X	X	X	X	X
Height measurement	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine laboratory analyses	X		X			X			X			X	
QuantiFERON® - TB Gold test[b]	X												
TB evaluation (questionnaire)	X	X	X	X	X	X	X	X	X	X	X	X	X
CXR[c]	X												
Uveitis evaluations[d]						X						X	
Pregnancy test (urine)[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection-site evaluation[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
Efficacy													
Efficacy evaluations[g]			X			X			X			X	
CRP			X			X			X			X	
ESR	X		X			X			X			X	
CHQ			X			X			X			X	
CHAQ			X			X			X			X	

Table 2: From Week 52 through Week 100

Phase	Long-term Extension												
Week	52	56	60	64	68	72	76	80	84	88	92	96	100
Pharmacokinetics													
Golimumab concentration[h]						X						X	
Immunogenicity													
Antibodies to golimumab[h]						X						X	
ANA/anti-dsDNA												X	

a. Includes Tanner staging every 6 months.
b. PPD should also be performed in countries where Quantiferon TB-Gold testing is not approved.
c. Chest x-ray screening as per site and country regulations for initiation of immunosuppressive agents in children with JIA who are at risk of TB.
d. Evaluations should be performed every 6 months in all subjects. Slit lamp examinations are required every 6 months in subjects who are ANA positive.
e. All female subjects of childbearing potential (ie, post-menarche) must test negative for pregnancy at all visits.
f. Subjects will be observed for at least 30 minutes after the SC administration of study agent for symptoms of an injection-site reaction.
g. Evaluation includes standard joint counts, physician global assessment, parent assessment of overall wellbeing, pain assessment.
h. The same serum samples may be used for the measurement of golimumab concentration and detection of antibodies to golimumab. For visits with study agent administration, all blood samples for assessing golimumab concentration and antibodies to golimumab MUST be collected BEFORE the administration of the study agent.

Abbreviations: ANA = antinuclear antibodies; CHAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire; CRP = C-reactive protein; CXR = chest x-ray; ESR = erythrocyte sedimentation rate; SC = subcutaneous; TB = tuberculosis.

Table 3: From Week 104 through Week 148

Phase	Long Term Extension											
Week	104	108	112	116	120	124	128	132	136	140	144	148
Procedures and Evaluations												
Administrative												
Concomitant medications collection	X	X	X	X	X	X	X	X	X	X	X	X
Study Agent												
SC administration of study agent	X	X	X	X	X	X	X	X	X	X	X	X
Safety												
Physical examination[a]	X				X						X	
Body weight measurement	X	X	X	X	X	X	X	X	X	X	X	X
Height measurement	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Routine laboratory analyses		X			X			X			X	
QuantiFERON® - TB Gold test[b]		X										
TB evaluation (questionnaire)	X	X	X	X	X	X	X	X	X	X	X	X
CXR[c]	X											
Uveitis evaluations[d]					X						X	
Pregnancy test (urine)[e]	X	X	X	X	X	X	X	X	X	X	X	X
Injection-site evaluation[f]	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
Efficacy												
Efficacy evaluations[g]		X			X			X			X	
CRP		X			X			X			X	
ESR		X			X			X			X	
CHQ					X						X	
CHAQ		X			X			X			X	

Table 3: From Week 104 through Week 148

Phase	Long Term Extension											
Week	104	108	112	116	120	124	128	132	136	140	144	148
Pharmacokinetics												
Golimumab concentration[h]					X						X	
Immunogenicity												
Antibodies to golimumab[h]					X						X	

a. Includes Tanner staging every 6 months. Cursory physical examinations as per site protocol may be performed at visits where full physical examinations are not mandated.
b. PPD should also be performed in countries where Quantiferon TB-Gold testing is not approved.
c. Chest x-ray screening as per site and country regulations for initiation of immunosuppressive agents in children with JIA who are at risk of TB.
d. Evaluations should be performed every 6 months in all subjects. Slit lamp examinations are required every 6 months in subjects who are ANA positive.
e. All female subjects of childbearing potential (ie, post-menarche) must test negative for pregnancy at all visits.
f. Subjects will be observed for at least 30 minutes after the SC administration of study agent for symptoms of an injection-site reaction.
g. Evaluation includes standard joint counts, physician global assessment, parent assessment of overall wellbeing, pain assessment.
h. The same serum samples may be used for the measurement of golimumab concentration and detection of antibodies to golimumab. For visits with study agent administration, all blood samples for assessing golimumab concentration and antibodies to golimumab MUST be collected BEFORE the administration of the study agent.

Abbreviations: ANA = antinuclear antibodies; CHAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire; CRP = C-reactive protein; CXR = chest x-ray; ESR = erythrocyte sedimentation rate; SC = subcutaneous; TB = tuberculosis.

Table 4: From Week 152 through Week 196

Phase	Long Term Extension											
Week	152	156	160	164	168	172	176	180	184	188	192	196
Procedures and Evaluations												
Administrative												
Concomitant medications collection	X	X	X	X	X	X	X	X	X	X	X	X
Study Agent												
SC administration of study agent	X	X	X	X	X	X	X	X	X	X	X	X
Safety												
Physical examination[a]					X						X	
Body weight measurement	X	X	X	X	X	X	X	X	X	X	X	X
Height measurement	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Routine laboratory analyses		X			X			X			X	
QuantiFERON® - TB Gold test[b]		X										
TB evaluation (questionnaire)	X	X	X	X	X	X	X	X	X	X	X	X
CXR[c]		X										
Uveitis evaluations[d]					X						X	
Pregnancy test (urine)[e]	X	X	X	X	X	X	X	X	X	X	X	X
Injection-site evaluation[f]	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
Efficacy												
Efficacy evaluations[g]					X						X	
CRP					X						X	
ESR					X						X	
CHQ					X						X	
CHAQ					X						X	

Table 4: From Week 152 through Week 196

Phase	Long Term Extension											
Week	152	156	160	164	168	172	176	180	184	188	192	196
Pharmacokinetics												
Golimumab concentration[h]					X						X	
Immunogenicity												
Antibodies to golimumab[h]					X						X	
ANA/anti-dsDNA antibodies											X	

a. Includes Tanner staging every 6 months. Cursory physical examinations as per site protocol may be performed at visits where full physical examinations are not mandated.
b. PPD should also be performed in countries where Quantiferon TB-Gold testing is not approved.
c. Chest x-ray screening as per site and country regulations for initiation of immunosuppressive agents in children with JIA who are at risk of TB.
d. Evaluations should be performed every 6 months in all subjects. Slit lamp examinations are required every 6 months in subjects who are ANA positive.
e. All female subjects of childbearing potential (ie, post-menarche) must test negative for pregnancy at all visits.
f. Subjects will be observed for at least 30 minutes after the SC administration of study agent for symptoms of an injection-site reaction.
g. Evaluation includes standard joint counts, physician global assessment, parent assessment of overall wellbeing, pain assessment.
h. The same serum samples may be used for the measurement of golimumab concentration and detection of antibodies to golimumab. For visits with study agent administration, all blood samples for assessing golimumab concentration and antibodies to golimumab MUST be collected BEFORE the administration of the study agent.

Abbreviations: ANA = antinuclear antibodies; CHAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire; CRP = C-reactive protein; CXR = chest x-ray; ESR = erythrocyte sedimentation rate; SC = subcutaneous; TB = tuberculosis.

Table 5: From Week 200 through Week 256

Phase	Long Term Extension													
Week	200	204	208	212	216	220	224	228	232	236	240	244	248	256
Procedures and Evaluations														
Administrative														
Concomitant medications collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Agent														
SC administration of study agent	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety[a]														
Physical examination[b]					X						X			X
Body weight measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine laboratory analyses		X			X			X			X			X
QuantiFERON® - TB Gold test[c]		X									X			
TB evaluation (questionnaire)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CXR[d]	X													
Uveitis evaluations[e]					X						X			
Pregnancy test (urine)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection-site evaluation[g]	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
Efficacy														
Efficacy evaluations[h]					X						X			X
CRP					X						X			X
ESR					X						X			X
CHQ					X						X			X
CHAQ					X						X			X

Table 5: From Week 200 through Week 256

Phase	Long Term Extension													
Week	200	204	208	212	216	220	224	228	232	236	240	244	248	256
Pharmacokinetics														
Golimumab concentration[1]					X						X			X
Immunogenicity														
Antibodies to golimumab[1]					X						X			X
ANA/anti-dsDNA antibodies														X

a. All subjects who discontinue study agent administrations before Week 248, must return to the study site for a final safety visit approximately 8 weeks after the last injection administered (Section 10.2).
b. Includes Tanner staging every 6 months. Cursory physical examinations as per site protocol may be performed at visits where full physical examinations are not mandated.
c. PPD should also be performed in countries where Quantiferon TB-Gold testing is not approved.
d. Chest x-ray screening as per site and country regulations for initiation of immunosuppressive agents in children with JIA who are at risk of TB.
e. Evaluations should be performed every 6 months in all subjects. Slit lamp examinations are required every 6 months in subjects who are ANA positive.
f. All female subjects of childbearing potential (ie, post-menarche) must test negative for pregnancy at all visits.
g. Subjects will be observed for at least 30 minutes after the SC administration of study agent for symptoms of an injection-site reaction.
h. Evaluation includes standard joint counts, physician global assessment, parent assessment of overall wellbeing, pain assessment.
i. The same serum samples may be used for the measurement of golimumab concentration and detection of antibodies to golimumab. For visits with study agent administration, all blood samples for assessing golimumab concentration and antibodies to golimumab MUST be collected BEFORE the administration of the study agent.

Abbreviations: ANA = antinuclear antibodies; CHAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire; CRP = C-reactive protein; CXR = chest x-ray; ESR = erythrocyte sedimentation rate; SC = subcutaneous; TB = tuberculosis.

ABBREVIATIONS

ACR	American College of Rheumatology
ACTH	intramuscular corticotropin
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANOVA	analysis of variance
AS	ankylosing spondylitis
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guérin
β-hCG	β-human chorionic gonadotropin
BSA	body surface area
CDM	clinical data management
CHAQ	Childhood Health Assessment Questionnaire
CHF	congestive heart failure
CHQ	Child Health Questionnaire
CL/BSA	body surface area-normalized drug clearance
CL/F	apparent total systemic clearance
CL/WT	Body weight-normalized drug clearance
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
DBL	database lock
DCF	data correction form
DMARD	disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
dsDNA	double-stranded DNA
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EMEA	European Medicines Evaluation Agency
EPO	erythropoietin
ESR	erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
Fc	fragment crystalizable
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HLA-B27	human leukocyte antigen B27
HLA-DR4	human leukocyte antigen DR4
HLA-DR5	human leukocyte antigen DR5
HLA-DR8	human leukocyte antigen DR8
IAC	Interim Analysis Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG1κ	immunoglobulin G1κ
IL-1β	Interleukin-1 beta
IL-6	interleukin-6

ILAR	International League of Associations for Rheumatology
IM	intramuscular
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
JIA	juvenile idiopathic arthritis
JPsA	juvenile psoriatic arthritis
JRA	juvenile rheumatoid arthritis
LDL	low-density lipoprotein
LOCF	last observation carried forward
LQC	lowest quantifiable concentration
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MED	minimum effective dose
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NONMEM	nonlinear mixed effects modeling
NSAID	nonsteroidal anti-inflammatory drug
PD	Pharmacodynamic(s)
PED	pediatric
PFS	prefilled syringe
PK	pharmacokinetic
PQC	Product Quality Complaint
PPD	purified protein derivative
PRCSG	The Pediatric Rheumatology Collaborative Study Group
PRINTO	Pediatric Rheumatology INternational Trials Organisation
PRO	patient-reported outcome(s)
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RBC	red blood cell
RF	rheumatoid factor
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SI	International System of Units
SM	site manager
TB	tuberculosis
TNFα	tumor necrosis factor alpha
US	United States
VAS	visual analog scale
V/F	apparent volume of distribution
Vss	volume of distribution at steady state
VSS/BSA	body surface area-normalized volume of distribution at steady state
V/WT	body weight-normalized volume of distribution
WBC	white blood cell
WT	weight

1 INTRODUCTION

Golimumab is a human anti-tumor necrosis factor alpha (TNFα) monoclonal antibody (mAb) developed by the Sponsor to offer flexibility in route of administration, a convenient dose regimen, and efficacy similar or superior to other anti-tumor necrosis factor agents while maintaining an acceptable safety profile. TNFα is a key inflammatory mediator, with high levels of TNFα implicated in the pathophysiology of diseases such as rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). Blocking TNFα activity as demonstrated in clinical studies of infliximab and other anti-TNF agents can prevent the deleterious effects caused by excessive TNFα.

The term Sponsor used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1 Background

Juvenile Idiopathic Arthritis

Juvenile Idiopathic Arthritis is a diagnosis of exclusion that encompasses all forms of arthritis that begin before the age of 16 years, persist for more than 6 weeks and are of unknown cause (Ravelli and Martini, 2007). It is the most common chronic rheumatic disease in children and is categorized according to the International League of Associations for Rheumatology [ILAR] classification into 7 subtypes (systemic arthritis, oligoarthritis, RF-negative polyarthritis, RF-positive polyarthritis, enthesitis-related arthritis, psoriatic arthritis, undifferentiated arthritis) characterized by distinct clinical presentations and features (Petty et al, 2004).

JIA is an important cause of short-term and long-term disability in children (Oen et al, 2002). In the past 10 years, studies have shown that 40% to 60% of patients have inactive disease or clinical remission while on medication for JIA at follow-up. Functional outcome has improved in the last decade, with 2.5% to 10% of patients with serious functional disability (Ravelli and Martini, 2007). Particularly serious complications of JIA include linear growth suppression, osteoporosis, local growth disturbances, macrophage activation syndrome and iridocyclitis (Ravelli and Martini, 2007).

The heterogeneity of JIA indicates that multiple factors contribute to the etiology and pathogenesis of the disease, and both genetic and environmental factors have been implicated. These include implicating infection as a triggering mechanism, links between human leukocyte antigen (HLA) and non-HLA molecules and disease development, and immunological abnormalities leading to tissue inflammation and joint destruction. The role of infection in disease development is still unproven (Ravelli and Martini, 2007). However, in JIA, HLA-DR5 and HLA-DR8 locus antigens have been implicated as associated contributory elements in young

girls with oligoarticular arthritis, whereas HLA-DR4 has been implicated in rheumatoid factor-(RF) positive polyarticular arthritis in older children, and HLA-B27 has been implicated in older boys with oligoarticular disease (Petty et al, 2005b; Cassidy and Petty, 2005a; Prahalad and Glass, 2002).

Although the etiology and pathogenesis of JIA are still unclear, the same cell types and underlying mechanisms that play a role in the progression of adult RA are probably involved (Cassidy and Petty, 2005a). The cellular entities involved include macrophages that elaborate a number of inflammatory cytokines and mediators of inflammation. Macrophage-derived cytokines, such as TNFα, appear to play a critically important role in the induction and perpetuation of chronic inflammatory processes in the joints of patients with RA as well as in the systemic manifestations of this disease (Grossman and Brahn, 1997), though the role of TNFα in systemic JIA is less convincing (De Benedetti and Martini, 2005).

Some studies have shown that levels of inflammatory cytokines (eg, interleukin-1 beta [IL-1β], interleukin-6 [IL-6], and TNFα) elevated in adults with RA are also elevated in the synovial fluid and serum of patients with JIA (Lepore et al, 1994; Rooney et al, 1995; Mangge et al, 1995; De Benedetti et al, 1997; Rooney et al, 2000). These studies have also found different cytokine profiles among patients with various JIA subgroups. Elevated levels of TNF receptors have been found in the serum of JIA patients with systemic-onset disease, and these levels correlate with disease state (Mangge et al, 1995; Gattorno et al, 1996).

The aim of treatment in JIA is to obtain complete control of the disease, to preserve the physical and psychological integrity of the child and to prevent any long-term consequence related to the disease or its therapy. The mainstays of treatment in JIA have been nonsteroidal anti-inflammatory drugs (NSAID[s]), intraarticular and systemic corticosteroids, methotrexate and other disease-modifying antirheumatic drugs (DMARDs). The introduction of biological medications has provided a very important new therapeutic option for the treatment of patients with JIA who are resistant to conventional antirheumatic agents (Ravelli and Martini, 2007). While there are no current data on the use of golimumab in the pediatric population, there are abundant, relevant data available on the use of golimumab in the adult population with rheumatic diseases, and on the use of other anti-TNF agents such as infliximab, etanercept, and adalimumab in both the adult and pediatric populations with rheumatic diseases.

Infliximab

Infliximab is a recombinant immunoglobulin Gκ (IgG1)κ, human-murine chimeric mAb produced by the Sponsor that specifically and potently binds and neutralizes soluble TNFα and its membrane-bound precursor. A study of infliximab in JRA was conducted in 122 subjects

between 4 and 17 years of age with active JRA unresponsive to MTX therapy. Subjects were randomized to receive placebo plus MTX, or infliximab 3 mg/kg plus MTX, at Weeks 0, 2, and 6. Subjects in the placebo group then received infliximab 6 mg/kg every 8 weeks; subjects in the infliximab 3 mg/kg continued receiving infliximab 3 mg/kg every 8 weeks. This study has been the only study of an anti-TNF in JRA/JIA that has included a placebo control group.

At Week 14, the proportion of subjects achieving the primary endpoint (American College of Rheumatology [ACR] pediatric [Ped] 30 response) was 65% in the infliximab treatment group and 48% in the placebo treatment group ($p = 0.055$). An indication for infliximab in the treatment of JRA was not pursued.

Safety findings in this study were generally consistent with what has been seen with the use of anti-TNF agents in adults. During the placebo-controlled portion of the study, SAEs were observed in 13% of subjects in the infliximab 3 mg/kg treatment group compared with 5% of subjects in the placebo treatment group. Infusion reactions, antibodies to infliximab, and high antibody titers were reported more frequently in subjects receiving infliximab 3 mg/kg than in subjects receiving infliximab 6 mg/kg.

Etanercept

Etanercept is a recombinant soluble dimeric fusion protein which binds to circulating TNF and inhibits its attachment to endogenous TNF cell surface receptors, thereby rendering TNF inactive and inhibiting TNF-mediated mechanisms of inflammation (Enbrel Summary of Product Characteristic, 2009). The pivotal study of etanercept in JRA was conducted in 69 children between 4 and 17 years of age, with active polyarticular JRA intolerant or minimally responsive to MTX. All subjects were receiving MTX at baseline; subjects had MTX withdrawn and twice weekly SC etanercept begun, followed by randomized withdrawal after 3 months of treatment. After 3 months of treatment, 74% of subjects fulfilled criteria for an ACR Ped 30 response; during randomized withdrawal, 28% of etanercept-treated subjects and 81% of placebo-treated subjects experienced a flare of disease activity (Lovell et al, 2000). Safety findings were consistent with the profile in adults. Etanercept is now approved in patients, ages 4 to 17 years, with active polyarticular-course JIA who have had an inadequate response to MTX.

Adalimumab

Adalimumab is a recombinant human IgG1 mAb against TNFα. The adalimumab JIA study included 171 children between the ages of 4 and 17 years with polyarticular-course JIA and at least 5 active joints and 3 joints with limitation of motion at baseline. Adalimumab was administered subcutaneously every 2 weeks with and without MTX for a total of 16 weeks;

subjects demonstrating a Pediatric ACR 30 response were then randomized to continue adalimumab or to start placebo (HUMIRA® [US package insert]; Lovell et al, 2006).

At Week 16, 83% of the 133 subjects who completed the open-label portion of the study achieved an ACR Ped 30 response. In randomized withdrawal, fewer subjects treated with adalimumab than subjects treated with placebo (37% versus 65% with MTX and 43% versus 71% without MTX) experienced flares of disease activity. Safety findings were generally similar to those seen in adults. Creatine phosphokinase (CPK) was elevated in 15% of subjects treated with adalimumab; CPK levels decreased or returned to normal in all subjects. Adalimumab is now approved for the treatment of active polyarticular JIA in adolescents, ages 13 to 17 years, who have had an inadequate response to one or more DMARDs (Lovell et al, 2006, HUMIRA® [US package insert]).

Clinical Studies

Efficacy of Golimumab in Adult Rheumatologic Diseases

For registration golimumab has been studied in 5 ongoing Phase 3 studies in adults with rheumatologic disease; including RA (3 studies; 1 in MTX-naïve subjects, 1 in subjects with active disease, despite MTX, and 1 in subjects previously treated with anti-TNF agents), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Indications for the golimumab 50 mg dose have been granted in RA, PsA, and AS in the United States, the European Union, and Canada. Of the 5 studies, the results from the study of subjects with active RA despite MTX and the study of subjects with PsA are discussed below. Pediatric subjects similar to these adult populations are planned for inclusion in this study.

C0524T06 is a multicenter, randomized, double-blind, placebo-controlled (through Week 52) study of golimumab 50 mg and 100 mg administered SC every 4 weeks alone or in combination with oral MTX in 444 subjects with active RA despite ongoing MTX therapy. In this study, currently continuing in a long-term extension, significantly greater proportions of subjects achieved an ACR 20 response at Week 14 (a coprimary endpoint) in the golimumab 50 mg + MTX group (55.1%; $p = 0.001$) and golimumab 100 mg + MTX group (56.2%; $p < 0.001$) compared with the placebo + MTX group (33.1%) and this significant difference was maintained at Week 24. Median improvement in the HAQ score at Week 24 (the other coprimary endpoint) was significantly greater in the combined golimumab + MTX group compared with the placebo + MTX group (0.4375 compared with 0.1250; $p < 0.001$) as was each golimumab dose group (0.3750 and 0.5 for the 50 mg and 100 mg dose groups, respectively; $p < 0.001$ for each comparison). This study was not powered to detect changes in radiographic scores, and such changes from baseline to Week 24 were minimal in all groups; therefore no statistically significant difference versus placebo was noted with golimumab. These and other efficacy

findings persisted through follow-up. The benefit appeared to be similar regardless of dose (Keystone et al, 2009).

C0524T08 is a multicenter, randomized, double-blind, placebo-controlled (through Week 24) study designed to assess the efficacy, safety, and clinical pharmacology of golimumab 50 mg or 100 mg administered as SC injections every 4 weeks in 405 adult subjects with active PsA. In this study, currently continuing in a long-term extension, the proportion of subjects achieving an ACR 20 response at Week 14 (coprimary endpoint) was significantly greater in the combined golimumab group than in the placebo group (47.9% versus 8.8%; $p < 0.001$); significant differences from placebo were also noted in the golimumab 50 mg and 100 mg dose groups (50.7% and 45.2% for the golimumab 50 mg and 100 mg dose groups respectively; $p < 0.001$ for each comparison) (Kavanaugh et al, 2009). In addition, the coprimary endpoint of change from baseline in total modified van der Heijde Sharp score at Week 24 was significant for both the combined golimumab group and the golimumab 50 mg group, but not for the golimumab 100 mg dose group. The change from baseline in vdH-S score was 0.27 ± 1.259 for the placebo group, -0.09 ± 1.315 ($p = 0.015$) for the combined golimumab group, -0.16 ± 1.309 ($p = 0.011$) for the golimumab 50 mg group, and -0.02 ± 1.322 ($p = 0.086$) for the golimumab 100 mg group. Efficacy findings persisted through follow-up (Kavanaugh et al, 2009).

Safety of Golimumab in Adult Rheumatologic Diseases

In studies of golimumab in adult rheumatologic diseases, the types of adverse events reported have been similar to those reported with established anti-TNFα agents. Tuberculosis and invasive fungal and other opportunistic infections have been reported. Other infections have also been noted, ranging from upper respiratory tract infections (the most frequently reported infection) to more serious infections, including sepsis. Hepatic enzyme elevations have been noted, but have generally been mild and transient. Dizziness and paresthesia have been reported in 2.0 to 3.9% of treated subjects, and demyelinating disorders (a known class effect) have also been seen but in < 1% of subjects.

The incidence of malignancies has been similar between golimumab and placebo treatment groups in studies in rheumatologic indications, although the incidence of lymphoma in golimumab-treated subjects has been higher than expected in the general population. In the rheumatoid arthritis population, particularly in patients previously treated with another anti-TNF agent, lymphoma has been reported with a greater frequency in subjects receiving golimumab 100 mg than golimumab 50 mg.

Of note, in the Phase 2b study of severe, persistent asthma, 8 malignancies were reported, all in golimumab-treated subjects with a greater number in higher (100 and 200 mg SC Q4 weeks) than in lower dose groups.

In golimumab clinical studies, injection-site reactions have been reported in approximately 6% of golimumab-treated subjects compared with 2% of placebo-treated subjects through the common placebo-controlled period. The majority of injection-site reactions were mild and the most frequent manifestation was injection-site erythema.

For the most accurate and current information regarding the efficacy and safety of golimumab, refer to the latest version of the Investigator's Brochure for golimumab.

1.2 Overall Rationale for the Study

Golimumab has recently been demonstrated to be efficacious in adults with RA, PsA, and AS. Other anti-TNF agents have been effective in the treatment of pediatric subjects with juvenile idiopathic arthritis. Golimumab has been shown to be effective as a monthly injection; all other anti-TNF agents approved in juvenile arthritis require more frequent dosing. Particularly in the pediatric population, the reduction in the number of injections could provide substantial benefit to patients compared with other anti-TNF agents. In addition, none of the commercially available anti-TNF agents have been proven to be efficacious in all JIA subjects; switching to a different anti-TNF agent in a patient in whom the first anti-TNF agent was not efficacious may provide greater symptomatic relief of disease. This study is being conducted to assess the benefit and risk associated with the use of golimumab in the treatment of multiple subtypes of JIA, including juvenile psoriatic arthritis.

2 OBJECTIVES

Primary Objective(s)

The primary objective of this study is to assess the clinical efficacy of SC administration of golimumab in pediatric subjects (ages 2 to less than 18 years) with JIA manifested by ≥ 5 joints with active arthritis despite MTX therapy for ≥ 3 months (Section 9.2.1.3).

Secondary Objectives

The secondary objectives of this study are to evaluate golimumab in pediatric subjects with JIA with respect to:

- Safety
- Physical function
- Quality of life

- Disease activity status over time
- Pharmacokinetics and immunogenicity
- Pharmacodynamics

Hypothesis: Pediatric subjects with JIA who have responded (Section 9.2.1.3) at Week 16 to golimumab administered subcutaneously every 4 weeks and continue to receive golimumab treatment through Week 48 will exhibit fewer flares of disease (defined below) from Week 16 through Week 48 compared with subjects who responded to golimumab at Week 16 and began receiving placebo at Week 16.

Flare of disease is defined as the worsening from Week 16 by 30% or more in 3 of the 6 ACR Ped Core Set Variables with no more than 1 of the 6 ACR Ped Core Set Variable improving by more than 30% at the time of the flare.

3 OVERVIEW OF STUDY DESIGN

This is a randomized-withdrawal, double-blind, placebo-controlled, parallel-group, multicenter study of SC golimumab in pediatric subjects with active JIA despite current treatment with MTX. The study population will be comprised of subjects with JIA receiving MTX, ages 2 to less than 18 years, with at least a 6-month history of arthritis, and active arthritis in $\geq$ 5 joints. A target of 170 subjects will be enrolled in this study.

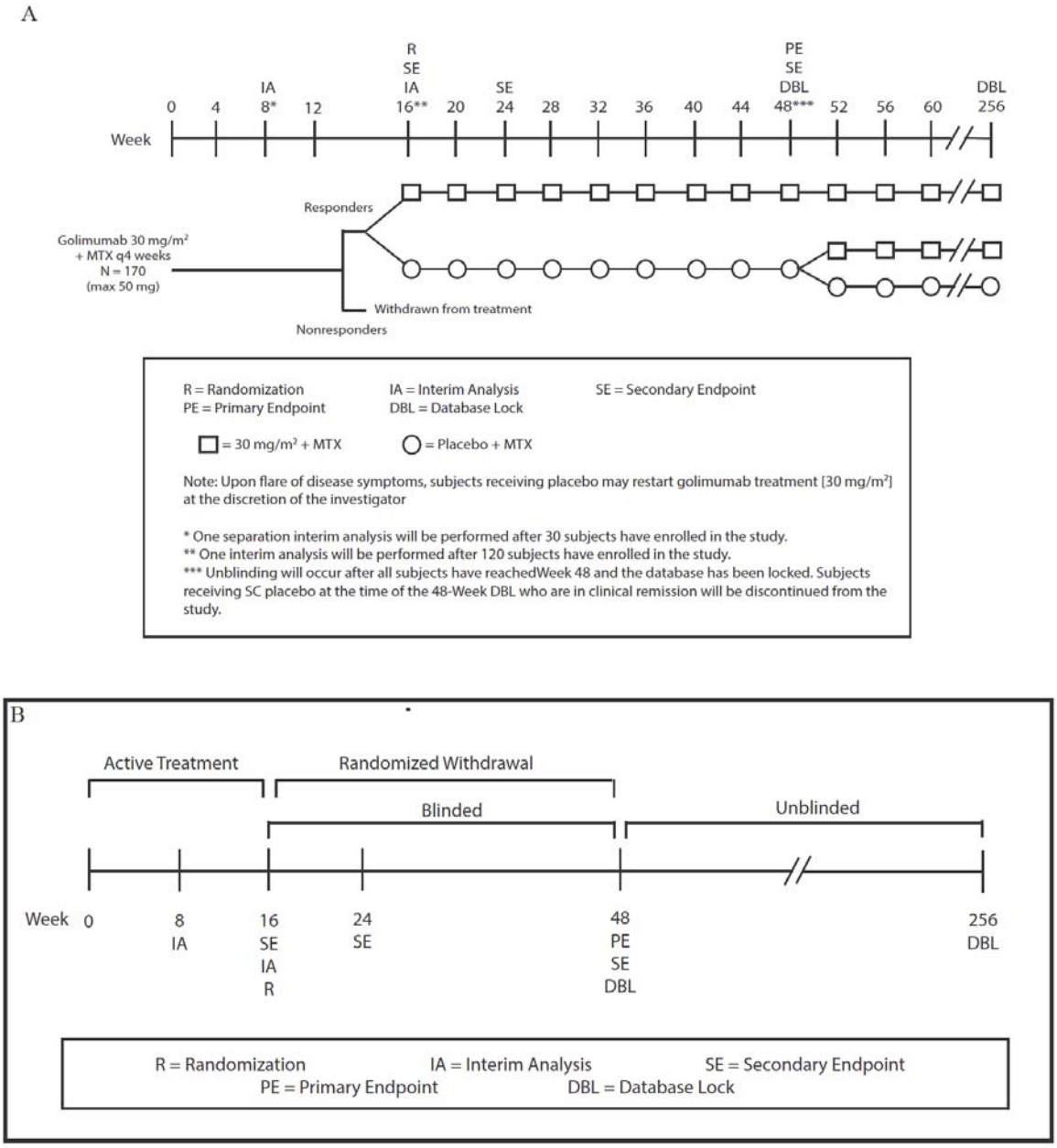
An Independent DMC has been commissioned for this study. See Section 11.10, Data Monitoring Committee, for details.

3.1 Study Design

The study design is provided in Panel A of

Figure 1 and the study timelines are provided in Panel B of Figure 1.

Figure 1: Study Design and Timelines for CNTO148JIA3001



3.1.1 Active Treatment (Week 0 Through Week 12)

At least 170 subjects will begin receiving golimumab administered subcutaneously at a dose of 30 mg/m^2 every 4 weeks (maximum 50 mg) beginning at Week 0 and continuing through Week 12. BSA will be calculated at each visit and the dose of golimumab will be adjusted accordingly. Subjects will also receive commercial MTX weekly at the same numerical (mg/week of MTX) dose as at time of study entry.

3.1.1.1 Interim Analysis: Response at Week 8

If fewer than 8 of the first 30 subjects enrolled in the trial are ACR Ped 30 responders at Week 8, the study will be discontinued. If 8 or more of the 30 subjects are responders, the study will continue.

Pharmacokinetic (PK), efficacy and safety assessments will be reviewed after 30 subjects have completed the Week 8 visit. All new screening will stop pending completion of this initial interim analysis.

3.1.1.2 Interim Analysis at Week 16

After approximately 120 subjects complete the Week 16 visit, another interim analysis will be performed. The response rates of subjects at Week 16 will be evaluated to ensure that 134 subjects would participate in the randomized withdrawal portion of the study. Section 11.3 summarizes the requirements for a sample size increase.

A population PK analysis, combined with an assessment of efficacy and safety, will explore the potential benefit and risk of tiered fixed doses based on pediatric weight ranges. Based on these analyses, which will use data obtained through the Week 16 visit for each of the first 120 subjects, tiered fixed dosing may be utilized after the Week 48 database lock (DBL) during the long-term extension of the study.

Subjects who have a worsening of clinical status between Weeks 0 and 16, but do not require changes in their concomitant medications, could still qualify for randomization at Week 16 if they have achieved ACR Ped 30 at Week 16.

Nonresponders Between Week 0 and Week 16

Subjects who have worsening of their clinical status between Week 0 and Week 16 and who require the addition of new DMARDs, corticosteroids or NSAIDs or increases in dosing due to worsening clinical status will be considered treatment failures and will not be randomized.

3.1.2 Treatment Week 16 Through Week 48

BSA will be calculated at each visit and the dose of golimumab will be adjusted accordingly. At Week 16, responders (based on ACR Ped 30 criteria) will be randomized in a 1:1 ratio in a blinded fashion to one of two treatment groups.

Treatment Group I (n = approximately 67): Subjects will continue receiving golimumab 30 mg/m^2 SC injection (maximum 50 mg) at Week 16, and every 4 weeks thereafter through Week 48. Subjects will also receive commercial MTX weekly at the same numerical (mg/week of MTX) dose as at the time of study entry (Section 6).

Treatment Group II (n = approximately 67): Subjects will receive placebo as a SC injection at Week 16 and every 4 weeks thereafter through Week 48 unless they experience a flare of disease (see Section 9.2.1.3 for definition of flare) at which time golimumab 30 mg/m^2 SC injections (maximum 50 mg) will be resumed. Subjects will also continue to receive commercial MTX weekly at the same numerical (mg/week of MTX) dose as at the time of study entry (Section 6).

Subjects will be monitored every 4 weeks for safety and efficacy and to identify flares of disease.

For responders receiving placebo at the time of a flare of disease, treatment with golimumab 30 mg/m^2 every 4 weeks will be reinitiated at the next scheduled visit. For responders receiving golimumab 30 mg/m^2 at the time of a flare of disease, the golimumab dose will not change.

When a flare of disease is documented at either a scheduled or unscheduled visit, concomitant medications may then be adjusted by the investigator, regardless of study treatment. If the flare of disease is documented at a scheduled visit, SC study agent will be adjusted the same day. If the flare of disease is documented at an unscheduled visit, SC study agent will be adjusted at the next scheduled visit. No adjustment to SC study agent will be permitted if a subject is already on active treatment. No changes should be made to background medications (ie, DMARDs, corticosteroids, and NSAIDs) in terms of dosage and route of administration between Weeks 16 and 48 in the randomized withdrawal period, **unless** the subject has a documented flare or there is a safety concern (eg, elevated LFTs), which require changes to background medications. Doses of methotrexate, corticosteroids, or non-steroidal anti-inflammatory agents should not be reduced between Weeks 16 and 48, even if subjects have shown good improvement in signs and symptoms.

Nonresponders at Week 16

Nonresponders at Week 16 will not participate in the randomized withdrawal portion of the study and will be withdrawn from treatment and discontinued from the study after a safety follow-up.

3.1.3 Week 48 to Week 256 (Long-term Extension)

Investigators will be permitted to change background DMARD, corticosteroid, and NSAID use after the Week 48 visit. Golimumab dose will be adjusted by BSA for each subject for all doses every 4 weeks. Golimumab dose decreases or increases below or above 30 mg/m^2 based upon BSA measured at the specific visit will not be permitted. Subjects will continue active treatment after Week 48 in a long-term extension until Week 248, with safety follow-up through Week 256. At Week 48, subjects who received placebo + MTX who are not in clinical remission while on medication for JIA will begin receiving golimumab 30 mg/m^2 SC in a blinded fashion. After the 48-week DBL and site unblinding, investigators will begin golimumab 30 mg/m^2 SC for subjects receiving SC placebo who are not in clinical remission while on medication for JIA (Section 9.2.1.3). Subjects who were still receiving SC placebo at the time of the 48-Week DBL and who are in clinical remission while on medication for JIA will be discontinued from the study.

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

3.2 Study Design Rationale

This study to support SC golimumab use in the pediatric population is a single study investigating PK, safety, and efficacy. The randomized withdrawal design is used because, given the seriousness of the disease and the availability of approved therapies, it is felt that a placebo control for a protracted period of time could not be employed ethically. This double-blind, randomized withdrawal study design is congruent with the designs of the pivotal etanercept and adalimumab JRA studies.

Dose Selection

The dose selection for golimumab development in the pediatric population with JIA is based on the established dosing regimen of SC golimumab in adults with rheumatic diseases and the Sponsor's experience with infliximab in the pediatric population with JRA (C0168T32).

Unlike adult drug doses, pediatric drug doses (parenteral) are commonly calculated individually on a weight-adjusted (mg/kg) or body surface area- (BSA) adjusted basis (mg/m^2) to manage the pharmacokinetic variability observed in children across different ages as changes occur in their maturing organ systems (Levin et al, 1987; Zenk et al, 1987). The successful outcome of dose extrapolation from adults to pediatric subjects through weight-based or BSA-based dose

normalization for other approved anti-TNFα agents (adalimumab and etanercept) supports the assumption that clinical responses to anti-TNFα agents in rheumatoid disease would be similar between adults and children. In other words, after the pharmacokinetic differences inherent between adults and children are accounted for, similar drug responses would be expected with similar drug exposure in both adults and children.

Currently, no golimumab PK data are available for the pediatric population. However, the PK of infliximab, an anti-TNFα chimeric mAb has been investigated in pediatric patients with JRA. Population PK analysis of infliximab in pediatric subjects showed that weight-normalized clearance (CL) and volume of distribution at steady state (Vss) of infliximab (ie, CL/WT and body weight-normalized volume of distribution [V/WT]) decreased with increasing age from age 4 to ages 10 to 12 yrs, then became stabilized in adolescents (age 12 to 17 yrs); whereas BSA-normalized infliximab CL and Vss values (ie, body surface area-normalized drug clearance [CL/BSA] and Vss/BSA) were constant across the whole age range (age 4 to 17 yrs). This suggests that compared with weight, BSA would have been a better predictor of infliximab CL and Vss in children across different age groups. Since golimumab and infliximab have the same fragment crystalizable (Fc) fragment and the same target, the interaction for these 2 products with neonatal Fc receptor (FcRn), which primarily determines the elimination rate of a mAb, is expected to be similar. It is anticipated that a BSA-adjusted dosing regimen for SC golimumab would achieve relatively similar drug exposure in pediatric subjects at different ages.

Data from the Phase 2 dose-finding study in adults with RA and the 5 Phase 3 SC studies in adults with RA, PsA, or AS through 24 weeks have shown that golimumab 50 mg every 4 weeks is the optimal dosing regimen for the treatment of RA and PsA in most adults. For a child, golimumab 30 mg/m^2 (50 mg/1.67 m^2) would be approximately equivalent to 50 mg, for an adult subject weighing 60 kg (with BSA of 1.67 m^2). Thus in the current study (CNTO148JIA3001), a dose of golimumab 30 mg/m^2 has been chosen to evaluate the safety and efficacy of golimumab in the JIA population. The every 4 week dosing schedule proposed is identical to that studied in adults.

Golimumab 50 mg SC every 4 weeks is considered the minimum effective dose (MED) in adult subjects with RA, PsA, or AS. Therefore, a dose of 30 mg/m^2 every 4 weeks (to a maximum 50 mg/dose) would be expected to be the MED for juvenile subjects.

Fixed doses and body size-adjusted doses have been used for monoclonal antibody therapies in adults (Wang et al, 2009). Due to the desired convenience and less risk of dosing error for tiered fixed dosing, a population PK approach will be used to explore the possibility of tiered fixed doses based on pediatric weight ranges using data from the first approximately 120 subjects

through Week 16. If this is feasible, fixed doses may be administered to subjects during the long-term extension of the study.

4 STUDY POPULATION

The study population will include subjects with active polyarticular course JIA (rheumatoid factor positive or negative) ≥ 6 months before study entry, extended oligoarticular, systemic JIA with no current systemic symptoms but with polyarthritis for ≥ 6 months before study entry, or polyarticular JPsA). Active disease at the time of screening and before first injection must be present and is defined by the presence of polyarticular disease involving ≥ 5 joints (Brewer et al, 1977) with active arthritis as defined by ACR criteria (ie, presence of swelling, or if no swelling is present, limitation of motion accompanied by pain, tenderness, or both). Subjects with exposure to only 1 prior anti-TNF agent before entering screening for this study will be permitted to enroll in the study but will be limited to no more than 20% of the total number of subjects. These subjects will be allowed to enter the study after the first interim analysis at Week 8 is completed.

4.1 General Considerations

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate Sponsor representative before enrolling the subject in the study.

For a discussion of the statistical considerations, refer to Section 11.3, Sample Size Determination.

4.2 Inclusion Criteria

Potential subjects must satisfy all of the following criteria to be enrolled in the study:

1. Pediatric subject ages 2 to less than 18 years of age. Age must not be a factor in the ability to continue follow-up with the investigator through the end of the study.
2. Diagnosis must be made per JIA ILAR diagnostic criteria and the onset of disease must have been before the subject's 16th birthday

   Active JIA of one of the following subtypes:

   a. rheumatoid factor positive or negative polyarticular JIA for ≥ 6 months, or
   b. systemic JIA with no systemic symptoms but with polyarthritis for ≥ 6 months, or
   c. extended oligoarticular JIA, or
   d. polyarticular juvenile psoriatic arthritis.

3. Disease duration of at least 6 months before study entry.
4. Must have ≥ 5 joints with active arthritis as defined by ACR criteria.
5. Active JIA despite current use of oral, intramuscular or subcutaneous methotrexate (for ≥ 3 months before screening) at a weekly dose of ≥ 10 mg/m^2. Subjects currently on MTX (weekly 10 to 30 mg/m^2), must receive a stable dose of methotrexate for ≥ 4 weeks before screening. Subjects with BSA ≥ 1.67 m^2 must receive a minimum of 15 mg/week of MTX.
6. If using corticosteroids; must be on a stable dose of ≤ 10 mg prednisone equivalent or 0.20 mg/kg/day (whichever is less) for ≥ 4 weeks before first administration of study agent. If currently not using corticosteroids, the subject must have not received corticosteroids for at least 4 weeks before the first dose administration.
7. If using NSAIDs, must be on a stable dose for ≥ 2 weeks before the first administration of study agent. If not currently using NSAIDs, the subject must not have taken them for at least 2 weeks before the first administration of study agent.
8. Are considered eligible according to the following TB screening criteria:
    a. Have no history of latent or active TB before screening. An exception is made for subjects who have a history of latent TB (defined for the purposes of this study as having had a positive result from either the tuberculin skin test or the QuantiFERON-TB Gold test prior to screening) and documentation of having completed an adequate treatment regimen for latent TB within 3 years prior to the first administration of study agent under this protocol. Adequate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local guidelines for immunocompromised patients exist, US guidelines must be followed. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.
    b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
    c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before or simultaneously with the first administration of study agent.
    d. Within 6 weeks before the first administration of study agent, have a negative QuantiFERON-TB Gold test result (Attachment 1) (in countries where the QuantiFERON-TB Gold test is not approved, the Tuberculin Skin Test [Attachment 2] should be performed in addition to the QuantiFERON (QFT)-Gold test for screening for latent TB) or have a newly identified positive TB screening test (QuantiFERON –TB Gold test or TST) result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either before or simultaneously with the first administration of study agent (Section 9.1.2).

e. Have a chest radiograph (both posterior-anterior and lateral views), taken within 3 months before the first administration of study agent and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB if country or site guidelines include CXR as necessary screening process prior to initiation of anti-TNF therapies. Chest radiographs must be performed as part of screening process in all cases when either PPD and/or QuantiFERON Gold testing for TB is positive.

9. Medically stable on the basis of physical examination, medical history, and vital signs performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population.

10. Girls of childbearing potential must be:

    a. Incapable of pregnancy,

    b. Abstinent (at the discretion of the investigator/per local regulations), or

    c. If sexually active, practicing a highly effective method of birth control (eg, prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel], male partner sterilization) as local regulations permit, before entry, and must agree to continue to use the same method of contraception throughout the study.

11. All girls of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening; and a negative urine pregnancy test at each study visit.

12. Boys must practice abstinence or agree to use a double barrier method of birth control and to not donate sperm during the study and for 6 months after receiving the last dose of study drug.

13. Willing/able to adhere to the prohibitions and restrictions specified in this protocol.

14. Subjects (or their legally-acceptable representatives) must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. Assent is also required of children capable of understanding the nature of the study (typically 10 years of age and older) as described in Section 16.2.3, Informed Consent.

15. Screening laboratory tests must meet the following criteria:

    a. Hemoglobin: ≥ 8.0 g/dL (SI: ≥ 80 g/L; girls and boys, ages 2 to 11)

    ≥ 8.5 g/dL (SI: ≥ 85 g/L; girls, ages 12 to 18)

    ≥ 9.0 g/dL (SI: ≥ 90 g/L; boys, ages 12 to 18)

b. White blood cells (WBCs) ≥ 3.0 x 10^3 cells/μL (SI: ≥ 3.0 x 10^9 cells/L)

c. Neutrophils ≥ 1.5 x 10^3 cells/μL (SI: ≥ 1.5 x 10^9 cells/L)

d. Platelets ≥ 140 x 10^3 cells/μL (SI: ≥ 140 x 10^9 cells/L)

e. Serum transaminase levels not exceeding 1.2 x the upper limit of normal for the central laboratory:

f. AST: ≤ 72 IU/L (girls and boys, ages 2 to 11)
≤ 54 IU/L (girls and boys, ages 12 to 18)

g. ALT: ≤ 54 IU/L (girls and boys, ages 2 to 18)

h. Serum creatinine not to exceed:

0.5 mg/dL (SI: 44 μmol/L; ages 2 to 5)
0.7 mg/dL (SI: 62 μmol/L; ages 6 to 10)
1.0 mg/dL (SI: 88 μmol/L; ages 11 to 12)
1.2 mg/dL (SI: 106 μmol/L; ages ≥ 13)

16. Must be up to date with all immunizations in agreement with current local immunization guidelines for immunosuppressed subjects before enrollment.

17. A parent or guardian must accompany the subject to each study visit.

18. The subject and his/her parent must be able to adhere to the study visit schedule, and understand and comply with other protocol requirements.

19. May have been previously treated with no more than 1 therapeutic agent targeted at reducing TNFα, including, but not limited to, infliximab, etanercept, adalimumab, certolizumab pegol. The first 30 subjects, should not have had been previously treated with any anti-TNF agents.

20. If previously treated with anti-TNF agent, must have previously:

a. Received at least an 8-week dosage regimen (including a dose at Week 8) of etanercept, adalimumab, or certolizumab pegol or

b. Received at least a 14-week dosage regimen (including a dose at Week 14) of infliximab

c. This inclusion criterion ONLY applies to subjects enrolled after the interim analysis of the first 30 subjects has been completed.

4.3 Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

1. Have known allergies, hypersensitivity, or intolerance to golimumab or other immunoglobulins or its excipients (refer to Section 14.1, Physical Description of Study Drug[s]).

2. Are pregnant or breast-feeding, or planning a pregnancy or fathering a child within 6 months after the last study agent administration.
3. Have a past history of macrophage activation syndrome (MAS).
4. Have received an investigational drug (including vaccines) or used an investigational medical device within 3 months or 5 half lives, whichever is longer, before the planned start of treatment or are currently enrolled in an investigational study.
5. Have initiated DMARDS and/or immunosuppressive therapy within 4 weeks prior to study initiation.
6. Have other inflammatory disease that might confound the evaluation of benefit from golimumab therapy, including but not limited to systemic lupus erythematosus or Lyme disease.
7. Are incapacitated, largely or wholly bedridden, or confined to a wheelchair, or have little or no ability for age-appropriate self care.
8. Have been treated with intra-articular, intramuscular or intravenous corticosteroids (including intramuscular corticotropin [ACTH]) during the 4 weeks before first study agent administration.
9. Have been treated with any therapeutic agent targeted at reducing IL-12 or IL-23, including but not limited to ustekinumab and ABT-874.
10. Have been treated with natalizumab, efalizumab, or therapeutic agents that deplete B or T cells (eg, rituximab, alemtuzumab, or visilizumab) during the 12 months before first study agent administration, or have evidence at screening of persistent depletion of the targeted lymphocyte after receiving any of these agents.
11. Have been treated with alefacept within 3 months before first study agent administration.
12. Have been treated with abatacept within 3 months before first study agent administration.
13. Have been treated with leflunomide within 4 weeks before first study agent administration (irrespective of undergoing a drug elimination procedure), or have received leflunomide from 4 to 12 weeks before first study agent administration and have not undergone a drug elimination procedure.
14. Have been treated with cytotoxic agents, including cyclophosphamide, nitrogen mustard, chlorambucil, or other alkylating agents.
15. Have received or are expected to receive any live viral or bacterial vaccinations from 3 months before first study agent administration and up to 3 months after the last study agent administration.
16. Have a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to inclusion criterion (Section 4.2) for information regarding eligibility with a history of latent TB.
17. Have had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.

18. If applicable, have a chest radiograph within 3 months before the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB.
19. Have had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystis, or aspergillosis).
20. Have current side effects related to MTX which would preclude treatment with MTX, including but not limited to liver cirrhosis, liver fibrosis, persistent elevations of ALT and AST; more than 3 of 5 tests elevated within 6-months period), MTX pneumonitis, severe mucosal ulcers, intractable nausea, vomiting/diarrhea, evidence of clinically significant bone marrow suppression, severe headaches, severe bone pain, or traumatic fractures.
21. Have a history of an infected joint prosthesis or have received antibiotics for a suspected infection of a joint prosthesis unless that prosthesis has been removed or replaced.
22. Have or have had a serious infection (including but not limited to hepatitis, pneumonia, or pyelonephritis), or have been hospitalized or received IV antibiotics for an infection during the 2 months before first study agent administration.
23. Have a history of or ongoing chronic or recurrent infectious disease, including, but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis or chronic nonremitting cystitis), open, draining, or infected skin wound, or ulcer.
24. Have a known history of infection with HIV.
25. Have a known history of hepatitis C infection.
26. Have a known history of demyelinating diseases such as multiple sclerosis.
27. Have a history of lymphoproliferative disease, including lymphoma, or signs suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location, or clinically significant splenomegaly.
28. Have a known malignancy or have a history of malignancy.
29. Have or have had a substance abuse (drug or alcohol) problem.
30. Are unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access.
31. Have history (current or past) of uveitis.
32. Have a history of or concomitant diagnosis of CHF.
33. Have a history of severe progressive or uncontrolled liver or renal insufficiency; or significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, psychiatric, or metabolic disturbances.
34. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements.

35. Are employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.
36. Have received IL-1ra (anakinra) within 4 weeks of the first study agent administration.
37. Have received infliximab, etanercept, adalimumab, certolizumab pegol within 6 weeks of the first dose of study agent.
38. Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):
    a. Subjects who test **positive** for surface antigen (HBsAg+) ***are not eligible*** for this study, regardless of the results of other hepatitis B tests.
    b. Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this study.
    c. Subjects who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study.
    d. Subjects who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the patient ***is not eligible*** for this study. If the HBV DNA test is **negative**, the patient ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the subject ***is not eligible*** for this study.

For subjects who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

5 TREATMENT ALLOCATION

Randomization and Blinding

At Week 0, all subjects will be administered golimumab 30 mg/m^2 every 4 weeks up to Week 12. At Week 16, subjects who are responders will be randomized in a 1:1 ratio in a blinded fashion to either continue with golimumab SC injections or to begin placebo SC injections.

Dynamic central randomization will be implemented in conducting this study. During the randomized withdrawal portion subjects will be randomized to placebo or golimumab treatment regimens based on an algorithm implemented in the IVRS before the study. Dynamic central randomization minimizes the imbalance in the distribution of the number of subjects across treatment groups within the levels of the stratification factor: geographic region (Europe, North America, Latin America, Asia, and Australasia), JIA disease type (JPsA versus other non-JPsA), prior anti-TNF therapy, and age (2 to < 7, 7 to < 12, and 12 to 17 years old). Based on the algorithm, the IVRS will assign a unique treatment code, which will dictate the treatment

assignment and matching study drug kit for the subject. The randomization method will be minimization with a biased-coin assignment.

Subjects and investigational study sites will remain blinded through all interim analyses. Sponsor personnel who will be involved with data analyses will be identified before the interim analyses.

Randomization codes will be maintained within the IVRS, which has the functionality to allow the investigator to break the blind for an individual subject.

At the 48-Week DBL, the data will be unblinded for analysis. Identification of Sponsor personnel who will have access to the unblinded subject-level data at Week 48 will be documented before unblinding. Investigative study sites and subjects will remain blinded to treatment assignment until the last subject enrolled completes the Week 48 evaluations and the database is locked.

Data that may potentially unblind the treatment assignment (ie, study agent serum concentrations, antibodies to study agent, study agent preparation/accountability data, treatment allocation, specific laboratory data), will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

Under normal circumstances, the blind should not be broken for individual subjects until the 48-Week DBL and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by telephoning the IVRS. It is recommended that the investigator contact the Sponsor or its designee if possible to discuss the particular situation. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented by the IVRS, and in the source document. The investigator is also advised not to reveal the study treatment assignment to the study site or Sponsor personnel.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations.

6 DOSAGE AND ADMINISTRATION

Both test products, golimumab and placebo, will be supplied in a prefilled syringe (PFS) and transferred to a graduated syringe by a blinded pharmacist under sterile conditions. To maintain the blind, all study agent administrations will consist of 1 SC injection. Subjects receiving golimumab 30 mg/m^2 will receive 1 injection of golimumab; subjects receiving placebo will receive 1 injection of placebo at the same volume as if golimumab were being administered. Subjects in both treatment groups will also receive commercial MTX weekly at their fixed dose at time of study entry and commercial folic acid ≥ 5 mg weekly or folinic acid (at half the absolute MTX dose) given the day after the MTX dose.

7 TREATMENT COMPLIANCE

Treatments will be administered by appropriately licensed and authorized health professionals, allowing compliance with the treatment assignments to be controlled by study site personnel. All subjects' CRFs will be monitored by a site monitor designated by the Sponsor. During these monitoring visits, all procedures will be evaluated for compliance with the protocol. Treatments that are administered outside of the scheduled windows, as well as missed injections or visits, will be recorded on the CRF.

8 PRESTUDY AND CONCOMITANT THERAPY

Subjects must have received MTX at a weekly dose of ≥ 10 mg/m^2 for ≥ 3 months before screening. Subjects with BSA ≥ 1.67 m^2 must receive a minimum of 15 mg/week of MTX. The dose must have been stable and between 10 to 30 mg/m^2 weekly (or at least 15 mg/week in subjects with BSA ≥ 1.67 m^2) for ≥ 4 weeks before screening. Subjects receiving corticosteroids at the time of study entry must have been receiving a stable dose for ≥ 4 weeks before first study agent administration, and that dose must have been ≤ 10 mg prednisone or prednisone equivalent or 0.2 mg/kg/day (whichever is less). If receiving NSAID therapy, the dose must have been stable for ≥ 2 weeks before first study agent administration. No changes should be made to background medications (ie, DMARDs, corticosteroids, and NSAIDs) in terms of dosage and route of administration between Weeks 16 and 48 in the randomized withdrawal period, **unless** the subject has a documented flare or there is a safety concern (eg, elevated LFTs), which require changes to background medications. Doses of methotrexate, corticosteroids, or non-steroidal anti-inflammatory agents should not be reduced between Weeks 16 and 48, even if subjects have shown good improvement in signs and symptoms.

Intramuscular administration of corticosteroids for the treatment of JIA is not allowed during the study. Corticosteroids administered by bronchial or nasal inhalation for treatment of conditions other than JIA may be given as needed throughout the course of the study.

Every attempt should be made to avoid the use of IV corticosteroids. For subjects requiring short courses (2 weeks or less) of oral or IV corticosteroids for reasons such as prophylactic therapy prior to surgery (stress-dose corticosteroids) or therapy for limited infections, exacerbation of asthma, or for any condition other than JIA, corticosteroid therapy should be limited to situations in which, in the opinion of the treating physician, there are no adequate alternatives.

Subjects may receive an intra-articular injection of a corticosteroid, if clinically required, during the study. However, the number of intra-articular injections should be limited to 2 over a 24-week period. The joint(s) affected by the procedure(s) will be considered tender and swollen in the data analyses from the date of the procedure onward through the 256-Week database lock.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered (Section 4.3).

9 STUDY EVALUATIONS

9.1 Study Procedures

9.1.1 Overview

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy, PK, immunogenicity, pharmacodynamic (PD), and safety measurements applicable to this study (Table 1, Table 2, Table 3, Table 4, and Table 5). All post-baseline visits may occur at the scheduled visit ± 7 days with the exception of visits at Weeks 16 and 48 which should occur within ± 3 days of the scheduled visit. In addition, the Day 4 and Day 15 visits for PK and CRP sampling in the first 30 subjects will only allow a window of ± 1 and ± 2 days, respectively. If the recommended acceptable window cannot be observed, the Sponsor must be contacted before scheduling a visit.

At every unscheduled visit between Weeks 16 and 48, the investigator will perform evaluations:

- Review of systems
- Vital signs
- TB questionnaire
- Adverse events
- Efficacy evaluations
- ESR
- CHAQ

All visit-specific Patient Reported Outcome (PRO) assessments during a visit should be conducted before any tests, procedures, or other consultations for that visit.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy throughout the study.

The total blood volume to be collected from each subject in 256 weeks will be approximately 333 mL. This volume of blood excludes blood that may be drawn for retesting. To prevent collecting > 1% of the total blood volume of a subject at a single visit (assuming 80 mL per kg bodyweight), samples for biomarkers, RNA, Hepcidin testing and the anemia panel will not be collected for subjects weighing < 32 kg.

Table 6 and Table 7 summarize the estimated blood volume to be drawn during the study. Total blood volume to be collected will be approximately 333 mL (339.5 mL first 30 subjects).

Table 6: Estimated Blood Volume Drawn Per Subject From Screening Through Week 48

Scheduled Visit	Total Maximum Volume of Blood (mL) per visit[a]
Screening	15.5
Week 0	25.5
PK sample: Between Week 0 and Week 12 (first 30 subjects)	9[b]
PK sample: Between Week 0 and Week 12 (all except first 30 subjects)	2.5
Week 4	20.5
Week 8	9
Week 12	9
Week 16	23.5
Week 20	9
Week 24	11
Week 28	6.5
Week 32	14
Week 36	6.5
Week 40	6.5
Week 44	6.5
Week 48	19.5

a. See Schedule of Events. Subjects < 32 kg will have limited pharmacodynamic testing.

b. These samples will be collected at Day 4 and Day 15.

Abbreviations: PK = pharmacokinetic

Table 7: Estimated Blood Volume Drawn Per Subject From Week 52 Through Week 256

Scheduled Visit	Total Maximum Volume of Blood (mL) per Visit
Week 52	9
Week 56	0
Week 60	6.5
Week 64	0
Week 68	0
Week 72	9
Week 76	0
Week 80	0
Week 84	6.5
Week 88	0
Week 92	0
Week 96	11
Week 100	0
Week 104	0
Week 108	9.5
Week 112	0
Week 116	0
Week 120	9
Week 124	0
Week 128	0
Week 132	4.5
Week 136	0
Week 140	0
Week 144	9
Week 148	0
Week 152	0
Week 156	7
Week 160	0
Week 164	0
Week 168	9
Week 172	0
Week 176	0
Week 180	4
Week 184	0
Week 188	0
Week 192	11
Week 196	0
Week 200	0
Week 204	7
Week 208	0
Week 212	0
Week 216	9
Week 220	0
Week 224	0
Week 228	4

Table 7: Estimated Blood Volume Drawn Per Subject From Week 52 Through Week 256

Scheduled Visit	Total Maximum Volume of Blood (mL) per Visit
Week 232	0
Week 236	0
Week 240	12
Week 244	0
Week 248	0
Week 256	11

9.1.2 Screening Phase

After written informed consent has been obtained and within a period of 6 weeks before enrollment, all screening evaluations establishing subject eligibility will be performed. Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study. Every effort should be made to adhere to the study Time and Events Schedule for each subject (Table 1, Table 2, Table 3, Table 4, and Table 5).

Girls of childbearing potential must have a negative serum β–hCG pregnancy test at screening and a negative urine test before enrollment. Sexually active subjects must consent to use a highly effective method of contraception and continue to use contraception for the duration of the study. The method(s) of contraception used by each subject must be documented.

Subjects must undergo testing for TB (Attachment 1 and Attachment 2) at screening and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

Subjects with a negative QuantiFERON-TB Gold test result and a negative tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered, are eligible to continue with prerandomization procedures. Subjects with a newly identified positive QuantiFERON-TB Gold or tuberculin skin test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB before the first dose. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines (CDC, 2000) must be followed. A subject whose first QuantiFERON-TB Gold test result is indeterminate must have the test repeated. In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the subject may be enrolled without treatment for latent TB if

their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the subject has no additional risk factors for TB as determined by the investigator and medical monitor. In countries where the QuantiFERON-TB Gold test is not approved, the Tuberculin Skin Test (Attachment 2) should be performed in addition to the QFT-Gold test for screening for latent TB.

9.1.3 Weeks 0 to 12 Open Label

Treatment Period: Week 0 to Week 12

At Week 0 and every 4 weeks thereafter through Week 12, eligible subjects will have safety and efficacy assessments performed and have golimumab 30 mg/m^2 (maximum 50 mg) administered as SC injections (Section 6).

9.1.4 Double-blind Treatment Phase

Treatment Period: Week 16 to Week 48

After randomization, subjects will have efficacy and safety assessments performed and study agent administered at Week 16 and every 4 weeks through Week 48. Subjects who experience a flare of disease between scheduled visits will have efficacy study assessments performed as an unscheduled visit (Section 3.1.2 and Section 9.1.1).

9.1.5 Long Term Extension

Treatment Period: Week 48 to Week 256

Safety assessments will be performed at Week 48 and every 4 weeks through Week 256 with the exception of Week 252. Efficacy assessments will be performed every 12-24 weeks. The final efficacy assessments will be performed at Week 256 and the final safety assessments will be performed at Week 256.

Early detection of active tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (refer to Time and Events Schedule) or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation

- "Has your child had a new cough of > 14 days' duration or a change in a chronic cough?"
- "Has your child had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"

- "Has your child had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a subject may have TB reactivation or new TB infection, study agent administration should be interrupted and an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised subjects may present as disseminated disease or with extrapulmonary features. Subjects with evidence of active TB must immediately discontinue study agent and should be referred for appropriate treatment.

Subjects who experience close contact with an individual with active TB during the conduct of the study must immediately discontinue further administration of study agent and be encouraged to return for all subsequent scheduled study visits.

9.2 Efficacy

9.2.1 Efficacy Evaluations

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy measurements applicable to this study (Table 1, Table 2, Table 3, Table 4, and Table 5).

All visit-specific PRO assessments during a visit should be conducted before any tests, procedures, or other consultations for that visit.

9.2.1.1 Joint Evaluation

Each of 75 joints will be evaluated for tenderness, and 68 joints will be evaluated for swelling. A consistent joint assessor, with at least 1 year of experience in performing joint assessment, will be designated at each study center to perform all joint assessments.

The consistent joint assessor should try to have minimal contact with the subject besides the joint assessment once the subject is randomized if feasible, may be the treating physician, should limit discussing the subject's clinical status with the subject during the joint assessment or with other site personnel as much as possible, and is permitted to review the subject's medical records, the CRF, or any previous joint assessments, if medically necessary.

The Sponsor will provide mandatory training to a single consistent joint assessor from each site before the start of subject enrollment. If a consistent joint assessor was trained by the Sponsor in a previous clinical study, he or she may receive a waiver for this training. Documentation of this

training will be maintained in the Trial Center File. If possible, the consistent joint assessor for the study should not be changed during the study. However, the assessor from each site who attends the consistent joint assessor training provided by the Sponsor may train 1 additional assessor at the site for coverage during their absences. It is expected that any additional consistent joint assessors who are trained will also have 1 or more years of experience as joint assessors or be approved by the Sponsor. If the designated consistent joint assessor from the site trains any additional assessors at the site, a letter documenting the training should be filed in the site's Trial Center File. In addition, if more than 1 consistent joint assessor at a site performs joint assessments during the study, the names of all consistent joint assessors performing the joint evaluation at the site at each visit must be listed in the Trial Center File and documented in the source document.

It is recommended that the consistent joint assessor who performs the baseline joint assessments for a subject also performs the joint assessments for that subject for all subsequent visits through the final efficacy assessment at Week 256.

9.2.1.2 Nonevaluable Joints

While it may be reasonable in clinical practice to identify as "nonevaluable" any joint which in the past or during study participation has been surgically altered (ie, prosthesis placement) or medically treated (ie, intra-articular injection), the designation of "nonevaluable" for the purposes of this study is slightly different. Joints should only be designated as "nonevaluable" by the consistent joint assessor on the Joint Assessment Worksheet if it is physically impossible to assess the joint (ie, joint inaccessible due to a cast, joint not present due to an amputation, joint deformed so as to make it impossible to assess).

9.2.1.3 American College of Rheumatology Ped 30 Response

ACR Ped 30 response (Giannini, et al, 1997) is defined as a 30% improvement from baseline in at least 3 of the following 6 components:

- Physicians global assessment of disease,
- Subject/parent global assessment of overall well-being,
- Number of active joints (defined as either swelling, or in absence of swelling, limited range of motion associated with pain on motion or tenderness),
- Number of joints with limited range of motion,
- Physical function by Childhood Health Assessment Questionnaire (CHAQ),
- Erythrocyte Sedimentation Rate (performed at site),

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.

Flare of Disease

Flare according to the JIA pediatric criteria for flare (all criteria must be met):

- ≥ 30% worsening in at least 3 of the 6 PED ACR categories and ≥ 30% improvement in not more than 1 of the 6 ACR response components from Week 16.
- If the Physician or Parent Global Assessment is one of the 3 ACR response components used to define flare, worsening of ≥ 20 mm from Week 16 must be present,
- If the number of active joints or joints with limitation of motion is one of the 3 ACR response components used to define flare, worsening in ≥ 2 joints from Week 16 must be present.

Inactive Disease

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

- No joints with active arthritis,
- No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA,
- No active uveitis,
- Normal erythrocyte (ESR; < 20 mm/hr) or C-reactive protein (CRP; < 20 mm/hr)
- Physician Global Assessment of disease activity indicating no active disease.
- Duration of morning stiffness < 15 minutes

Clinical remission while on medication for JIA

Clinical remission while on medication for JIA is defined as inactive disease at each visit for a period of ≥ 6 months while on medication.

9.2.1.4 Parent's Visual Analog Scale for Overall Wellbeing

The Parent Assessment of Overall Wellbeing is a 10 cm visual analog scale (VAS). Parents are to complete the VAS that asks them to consider all the ways arthritis impacts their child and then indicate how their child is doing. The anchors of the scale are "very well" to "very poor". Lower scores indicate improvement. The process for including this measure in the core set of variables for the assessment of children has been captured in the literature (Giannini et al, 1997).

9.2.1.5 Physician's Visual Analog Scale for Disease Activity

The Physician Global Assessment of Disease Activity is a 10 cm VAS. Physicians are to complete the VAS that has them assess the patient's current arthritis activity. The anchors of the scale are "no arthritis activity" to "extremely active arthritis". Lower scores indicate improvement. The process for including this measure in the core set of variables for the assessment of children has been captured in the literature (Giannini et al, 1997).

9.2.1.6 Visual Analog Scale for Pain

Pain will be assessed as average pain during the past week on a VAS. The scale ranges from "no pain" (0 cm) to "the worst possible pain" (10 cm). This assessment should be completed by the parents prior to the tender and swollen joint examination. The validity of this assessment has been evaluated and reviewed extensively as it is a component of the ACR response score (Felson et al, 1993; Hawley and Wolfe, 1992).

9.2.1.7 Child Health Questionnaire

The Child Health Questionnaire™ (CHQ) is a family of generic quality of life instruments that have been designed and normalized for children up to 18 years of age. Parents are to complete the CHQ that measures 15 unique, physical and psychosocial concepts including general health, physical functioning, bodily pain/discomfort, limitations in school, work, and activities with friends due to physical problems, and self-esteem. Previous research has demonstrated improvements in the CHQ among JIA patients treated with MTX. These improvements were most pronounced in the physical health aspects of the measure (Céspedes-Cruz et al, 2008).

Profile scores may be analyzed separately, or combined to derive an overall physical and psychosocial score. Higher scores indicate a better quality of life. The CHQ has been culturally validated in a variety of languages in subjects with or without JIA.

9.2.1.8 Childhood Health Assessment Questionnaire

The functional status of subjects will be assessed by the CHAQ (Singh et al, 1994). Parents are to complete this 20-question instrument that assesses the degree of difficulty a child 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 from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area (lower scores are indicative of better functioning) with an unable to do and not applicable response options as well. Properties of the measure have been evaluated and its validity assessed (Singh et al, 1994). The CHAQ has been shown to be responsive to disease change (Singh et al, 1994). A decrease of 0.188 has been determined to be a meaningful improvement (Brunner et al, 2005).

9.2.2 Criteria

The primary endpoint is the proportion of subjects who are ACR Ped 30 responders (as defined in Section 9.2.1.3) at Week 16 and do not experience a flare of disease between Week 16 and Week 48.

The major secondary endpoints are as follows:

1. The proportion of ACR Ped 30 responders at Week 16 with ACR Ped 30 response at Week 48.
2. The proportion of subjects who are responders at Week 16 and have inactive disease at Week 48.
3. The proportion of subjects, who are responders at Week 16 and are in clinical remission while on medication for JIA (as defined in Section 9.2.1.3) at Week 48.

9.3 Pharmacokinetics and Immunogenicity

Serum samples will be used to evaluate the pharmacokinetics, as well as the immunogenicity of golimumab (antibodies to golimumab). Sera collected for golimumab serum concentration and antibodies to golimumab analyses may additionally be used to evaluate biomarkers of safety or efficacy aspects that address concerns that arise during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained. Sera for the measurement of both golimumab concentration and antibodies to golimumab can be derived from the same blood draw.

Instructions for the collection, handling, and shipment of these samples are found in the Laboratory Reference Manual provided by the Sponsor.

9.3.1 Sample Collection and Handling

Venous blood samples of 2 mL will be collected for determination of serum golimumab concentrations and antibodies to golimumab at the timepoints presented in the Time and Events Schedule. For the first 30 subjects in the study, additional PK and CRP samples will be obtained on Day 4 ± 1 day and Day 15 ± 2 days. An additional PK sample for serum golimumab concentration will be collected from all subjects at any time between Weeks 0 and 12 other than at the time of the Week 0, Week 4, Week 8, and Week 12 visits; this sample must be collected at least 24 hours before or after a study agent injection.

Note that if a subject is to receive an injection of study agent at that visit, the samples for serum concentration and antibodies to golimumab will be collected before study agent administration. The exact dates and times of blood sampling must be recorded in the laboratory requisition form and accurately record the date/time of each administration of the study agent. Subjects who

terminate study participation before completing the study should have final visit samples collected at the time of termination.

9.3.2 Analytical Procedure

Serum samples will be analyzed to determine serum golimumab concentration or antibodies to golimumab using validated, specific, and sensitive immunoassay methods under the supervision of the Sponsor's or CRO's bioanalytical facility.

The Sponsor, or its designee, under conditions in which the subjects' identity remains blinded, will assay these samples.

To minimize the potential impact of inter-assay variability on model-based analysis, serum samples used in the Week 8 interim PK analyses will be re-analyzed for the subsequent population PK interim analysis using data from the first 120 subjects.

9.3.3 Pharmacokinetic Evaluations

Serum golimumab concentrations will be summarized for each treatment group over time. In addition, if feasible, a population PK analysis 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. The apparent total systemic clearance (CL/F) and apparent volume of distribution (V/F) will be estimated using a nonlinear mixed effects modeling (NONMEM) approach.

9.3.4 Immunogenicity Assessments (Antibodies to Golimumab)

Serum samples collected for immunogenicity assessment will be screened for antibody binding to golimumab and the titer of confirmed positive samples will be reported. All samples collected for detection of antibodies to golimumab will also be evaluated for golimumab serum concentration to enable interpretation of the antibody data. The incidence of antibodies to golimumab during the study will be determined. Other analyses may be performed to further characterize the immunogenicity of golimumab.

9.4 Pharmacodynamic Evaluations

Pharmacodynamic responses to golimumab will be measured in all subjects ≥ 32 kg at Weeks 0, 4, and 16. Differential gene expression and protein profiling studies may be utilized to identify genes or proteins linked to golimumab treatment in JIA subjects, and to determine those markers most associated with changes in clinical measures after treatment.

Four mL of blood will be collected from all subjects and analyzed for biomarkers associated with JIA and response to anti-TNFα therapy at the times shown in the Schedule of Events. In addition, a urine sample (10 mL) will be collected from all subjects at the specified time points.

Markers associated with tissue remodeling, bone metabolism, and inflammation may be analyzed.

9.4.1 Serum-based Biomarkers

Blood samples for serum-based biomarker analyses will be collected from all subjects ≥ 32 kg at Weeks 0, 4, and 16. Assays to be performed may include the following: measurement of cytokines associated with inflammation (IL-6, IL-2) and anti-inflammatory effects (tissue inhibitors of metalloproteinase (TIMP1, TIMP-2), IL-10), the recruitment of antigen-presenting cells (MCP-1, MIP), and markers associated with tissue injury or repair (MMP-3, MMP-9, MMP-12), markers associated with bone growth/resorption (BSAP, Osteocalcin), and markers associated with cartilage degradation (COMP). Other markers associated with inflammation or treatment may also be tested.

9.4.2 Urine-based Biomarkers

Urine samples for urine-based biomarker analyses will be collected from all subjects at Weeks 0, 4, and 16. Assays to be performed may include the following: measurement of markers associated with bone resorption (DPD, CTX-1) and cartilage degradation (CTX-II). Other markers associated with inflammation or treatment may also be tested.

9.4.3 RNA Profiling

RNA profiling will be performed in subjects ≥ 32 kg to examine changes in gene expression before and after treatment with golimumab. Blood samples for RNA analysis will be collected from all subjects ≥ 32 kg at the times shown in the Times and Events Schedule.

9.5 Safety Evaluations

Details regarding the Independent Data Monitoring Committee are provided in Section 11.10. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached. The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule.

Adverse Events:

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Injection-site Evaluations:

The investigator or qualified designee will evaluate the injection site according to the Time and Events Schedule.

An injection site reaction is any unfavorable or unintended sign that occurs at the study agent injection site. All subjects must be carefully observed for symptoms of an injection site reaction. Subjects will be observed for at least 30 minutes after the SC administration of study agent for symptoms of an injection-site reaction. If an injection site reaction is observed, the subject should be treated at the investigator's discretion.

The investigator will indicate the site of injection and evaluate the injection-site for the categories of redness, pain, swelling, and induration. The evaluation will be recorded using a rating scale of 0 to 3, with 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The score > 0 (1 to 3) for redness, pain, swelling or induration will be recorded as an AE in the electronic CRF.

If no injection-site reaction is observed, the investigator will note this in the subject's medical records (source data).

Anemia

Anemia is common in JIA patients with systemic arthritis. In these patients the anemia is microcytic in nature and more severe than that seen in adult RA (Ravelli and Martin, 2007). Blood testing will only be performed in subjects $\geq$ 32 kg. Each subject's anemia status will be monitored by scheduled blood draws at Wk 0, 4, 16, 32, and 48. The anemia panel run by the central laboratory includes serum iron, total iron binding capacity, ferritin, transferring receptor, reticulocyte count, and EPO (erythropoietin). In addition, hepcidin levels will be determined in serum (Weeks 0, 4, 16, 32, and 48) and urine. First morning urine (in all subjects regardless of weight) will be collected for the urinary hepcidin assay at Weeks 0, 4, 16, 32, and 48. This assay quantifies the concentration of urinary hepcidin normalized to urinary creatinine. The method compensates for the variable dilution of urine, a result of varying diet, fluid intake and medications.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The following tests will be performed by the central laboratory.

- **Hematology Panel**

-hemoglobin	-WBC (neutrophils, lymphocytes, monocytes, eosinophils, basophils [%, absolute])
-hematocrit	-platelet count
-RBC	-mean corpuscular volume
-mean corpuscular hemoglobin	-mean corpuscular hemoglobin concentration
-RBC morphology	-WBC morphology (if present)

- **Serum Chemistry Panel**

-sodium	-total bilirubin
-potassium	-bilirubin (direct and indirect)
-urea nitrogen	-calcium
-creatinine	-phosphorous
-glucose	-albumin
-AST	-total protein
-ALT	-cholesterol panel (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides)
-alkaline phosphatase	-uric acid
-bicarbonate	-chloride

- Serum Pregnancy Testing for women of childbearing potential will be conducted at screening.
- Urine Pregnancy Testing for women of childbearing potential will be performed according to the Time and Events Schedule.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy throughout the study.
- Urine samples (non pregnancy testing) will be waived for subjects too young to provide a sample on demand.
- Serology for HBV antibody, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc total).

Vital Signs

Pulse, respiratory rate, and blood pressure will be performed according to the Time and Events Schedule.

Height and Body Weight

Height will be measured at screening, and all timepoints specified in the Time and Events Schedule. Weight will be measured at the timepoints specified in the Time and Events Schedule,

using a calibrated scale at each weight measurement. Subjects will be instructed to remove shoes and outdoor apparel and gear.

Physical Examination

Physical examinations including Tanner staging for sexual maturity will be performed according to the Time and Events Schedule that follows the Synopsis. Review of systems will be performed at all visits to evaluate for new symptomatology and if necessary, full physical examination may be performed at investigator discretion. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Uveitis Evaluations

All subjects will be formally assessed every 6 months following enrollment by evaluations pertaining to new-onset uveitis. Subjects who test antinuclear antibodies (ANA) positive at screening will be required to undergo slit lamp evaluation by qualified ophthalmologist to evaluate for subclinical uveitis in screening period as well as every 6 months subsequent.

Safety will be monitored by an independent DMC. Details regarding the Independent Data Monitoring Committee are provided in Section 11.10.

10 SUBJECT COMPLETION/WITHDRAWAL

10.1 Completion

A subject will be considered to have completed the study if he or she has completed assessments at Week 256.

10.2 Discontinuation of Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be permanently discontinued if any of the following occur:

- The investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject to stop treatment.
- The subject becomes pregnant.
- Reaction resulting in bronchospasm (both new onset study agent-related and severe exacerbation of pre-existing asthma) with and without wheezing, and/or dyspnea requiring ventilatory support, and/or symptomatic hypotension that occurs following a study agent administration.

- Reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study agent. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- Opportunistic infection.
- Malignancy.
- The subject develops CHF at any time during the trial.
- Demyelinating disease.
- The subject withdraws consent for administration of study agent.
- The initiation of protocol-prohibited medications.
- Treatment assignment unblinded.
- Subject is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB.
  - A subject undergoing continued evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB Gold test result and/or a positive tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered and/or an indeterminate QuantiFERON-TB Gold test result on repeat testing with an additional TB risk factor as determined by the medical monitor and investigator.
  - A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

All subjects who discontinue study agent injections during the study will be followed for approximately 8 weeks after the last injection is administered.

Note: The visit that is approximately 8-weeks after the last study agent injection is referred to as the "final safety follow-up visit," which may occur at a scheduled or an unscheduled visit.

Subjects who discontinue study agent injections but do not terminate study participation, will have the following assessments performed at scheduled visits through the final safety follow-up visit:

- Safety evaluations (eg, vital signs, AE review, study agent injection-site evaluation, TB evaluation, and the collection of a blood sample for routine laboratory analyses and determination of the presence of ANA/anti-dsDNA antibodies and antibodies to golimumab).
- Concomitant medication review.
- Efficacy evaluations (eg, joint assessment, pain assessment, Subject/Parent's assessment of overall wellbeing, and Physician's Global Assessments of Disease Activity).
- Blood samples drawn for measurement of antibodies to golimumab and golimumab concentration for all subjects at the final safety follow-up visit.

Subjects whose final safety follow-up visit occurs at an unscheduled visit will have the following assessments performed:

- AE review.
- Concomitant medication review.
- Golimumab concentration.
- Blood samples drawn for measurement of antibodies to golimumab.

10.3 Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Withdrawal of consent.
- Death.

In case a subject is lost to follow-up, every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

11 STATISTICAL METHODS

Descriptive statistics, such as mean, median, standard deviation, interquartile range, minimum and maximum for continuous variables, and counts and percentages for categorical variables will be used to summarize most data.

Analyses suitable for categorical data (eg, chi-square test, Cochran-Mantel-Haenszel [CMH] test) will be used to compare the proportion of subjects achieving selected endpoints (eg, proportion

of subjects with an ACR Ped 30 response). Continuous data will be compared using an analysis of variance (ANOVA) on the van der Waerden normal scores. All statistical procedures will be performed 2-sided at a significance level of 0.05. Data permitting, analyses will be performed stratified by JIA disease type, prior anti-TNF therapy, and age. In addition to statistical analyses, graphical summaries of the data may be used (see Section 5).

Subject baseline data, demographic and baseline disease characteristics, including earlier JIA therapies, will be summarized. The baseline measurement is defined as the closest measurement taken before the time of the Week 0 injection.

The study is designed to maintain a Type I error of 0.05 or less for the primary analyses.

Nominal p-values will be reported for secondary analyses.

11.1 Subject Information

Demographics and subject baseline disease characteristics and earlier medication data will be described for all subjects who have been enrolled in the study, whether or not they have received study agent administration.

Pharmacokinetic data will be summarized for all subjects who had received at least one administration of study agent.

Efficacy analyses will be compared and summarized using the intent-to-treat population. Subjects will be summarized within the treatment group to which they were assigned, regardless of the treatment they received.

Safety assessment will be summarized using the treated subject population. Subjects must have received at least one administration of study agent to be included in the safety assessment. Some safety assessments may also be summarized for all subjects who have signed an inform consent form.

11.2 Efficacy Analyses

11.2.1 Primary Analyses

The primary endpoint is the proportion of subjects who are ACR Ped 30 responders (as defined in Section 9.2.1.3) at Week 16 and do not experience a flare of disease between Week 16 and Week 48.

The proportion of subjects who are responders at Week 16 and do not experience a flare of disease between Weeks 16 and 48 in the golimumab treatment groups will be compared with the proportion of subjects in the placebo treatment group. A CMH test, stratified by JIA disease type, prior anti-TNF therapy, and age (see Section 5 for categories), will be used for statistical testing at a 2-sided significance level of 0.05. If cell sizes are too small, pooling may be performed to facilitate the stratified analyses.

As a primary efficacy analysis, subjects will be evaluated for flare of disease every 4 weeks from Week 16 through Week 48.

A last observation carried forward (LOCF) procedure will be used to impute the missing ACR Ped components if the subjects have data for at least one ACR component. If the subjects do not have data for all the ACR components at a certain timepoint, the subjects will be considered to have experienced a flare of disease. In addition, after a full physical examination and the completion of flare evaluation, subjects who meet any one of the following criteria will be considered to have not achieved the primary endpoint, ie, subjects will be considered to have experienced a flare of disease:

- Initiate any DMARDs, biologics, or systemic immunosuppressives for JIA or increase MTX dose above baseline level before the time point being evaluated for flare of disease.
- Initiate treatment with oral, IV or IM corticosteroids for JIA, or increase the dose of oral corticosteroids for JIA above baseline dose before the time point being evaluated for flare of disease.
- Discontinue study agent injections due to lack of efficacy for JIA or an AE of worsening of JIA before the time point being evaluated flare of disease.

11.2.2 Major Secondary Analyses

The major secondary analyses are as follows:

- The proportion of ACR Ped 30 responders at Week 16 with ACR Ped 30 response at Week 48 will be summarized by treatment group and compared between treatment groups.
- The proportion of subjects who are responders at Week 16 and have inactive disease (Section 9.2.1.3) at Week 48 will be summarized by treatment group and compared among treatment groups.
- The proportion of subjects who are responders at Week 16 and are in protocol defined clinical remission while on medication for JIA at Week 48 will be summarized by treatment group and compared among treatment groups.

11.2.3 Other Efficacy Analyses

Other efficacy analyses include:

- The proportion of ACR Ped 30 responders at Week 16 will be summarized.
- The change from baseline in CHAQ at Week 16 will be summarized.
- The change from Week 16 in CHAQ at each evaluation from Week 20 through Week 256 will be summarized by treatment group.
- The proportions of subjects with an ACR Ped 30, 50, or 70 response (Section 9.2.1.3) will be summarized over time by treatment group.
- CRP concentrations will be summarized over time by treatment group.
- The proportion of subjects who are responders at Week 16 and have inactive disease at Week 24 will be summarized by treatment group and compared among treatment groups.
- The proportion of subjects who are responders at Week 16 and are in clinical remission on medication for JIA at Week 24 will be summarized by treatment group and compared among treatment groups.
- For subjects participating in the open-label extension, the proportions of subjects with improvement in the JIA core set (ACR Ped 30 Section 9.2.1.3) will be summarized over time by treatment group.
- The time to flare of disease in JIA disease from Week 16 through Week 48 will be summarized by treatment group and compared between treatment groups.
- The change from baseline in physical function subscale score of CHQ in subjects who are ACR Ped 30 responders at Week 16 will be compared between treatment groups and summarized by treatment groups at Week 48.
- The change from baseline in all subscale scores of CHQ will be summarized over time by treatment groups.
- The percent improvement from baseline in the ACR Ped components will be summarized through Week 16.
- The percent improvement in ACR Ped components in subjects who are responders at Week 16 will be summarized by treatment groups from Week 16 through Week 256.
- The proportion of subjects in clinical remission on medication for JIA (see Section 9.2.1.3) will be summarized at Week 16.
- The proportion of subjects who are ACR Ped 30 responders at Week 48 and do not experience a flare of disease between Week 16 and Week 48 will be summarized by treatment group.
- The proportion of subjects who are ACR Ped 30, 50, and 70 responders will be summarized by disease subtype, age, and treatment group over time.

11.3 Sample Size Determination

The study is powered to detect significant treatment differences in the primary endpoint between treatment groups.

Power calculations were performed using a chi-squared test with flare of JIA disease as the response variable and treatment group as the dependent variable.

Assuming 65% and 37% subjects experiencing a flare of disease from Week 16 through Week 48 for the placebo + MTX, and 30 mg/m^2 + MTX treatment groups respectively, 134 subjects who are responders at Week 16 (67 subjects from each treatment group) will be required to enter the randomized withdrawal portion of the study to obtain 90% power to detect a significant difference between treatment groups. These percentages of disease flares were observed in the adalimumab study in JRA (Lovell et al, 2008).

In addition, the power arising from different randomization ratios of subjects entering the randomized withdrawal portion of the study was also examined. There is no marked difference in power based on the results observed.

Table 8 shows fluctuations in the power to detect a significant difference between treatment groups when different disease flare rates are assumed.

Table 8: The power to detect a significant difference in at least one treatment group when different flare of disease rates is assumed

Placebo + MTX flare rate	30 mg/m^2 + MTX flare rate	Power
0.6	0.25	98.69
0.6	0.37	75.76
0.6	0.45	40.22
0.6	0.55	8.45
0.65	0.25	99.77
0.65	0.37	90.36
0.65	0.45	63.6
0.65	0.55	21.19
0.7	0.25	99.98
0.7	0.37	97.3
0.7	0.45	83.39
0.7	0.55	43.31

Assuming an 85% response rate at Week 16, the 95% confidence interval for the response rate would be (79%, 91%). Using the lower bound of the 95% confidence interval, 170 subjects will be required to be initiated into the study at Week 0.

Interim Analysis at Week 8

The study will continue if 8 or more subjects of 30 subjects enrolled are responders at Week 8. Assuming a response rate of 62% (as was seen in the C0168T32 trial of infliximab in JRA), there is a > 99.9% probability that 8 or more subjects will be responders at Week 8.

Interim Analysis When 120 Subjects Have Completed at Week 16

An interim analysis will be performed at Week 16 to ensure 134 subjects who are responders will enter the randomized withdrawal portion of the study. The sample size for the study was calculated assuming response rate of 85% at Week 16.

If the response rate observed at the interim analysis is greater than or equal to 81.7%, the probability of obtaining 134 responders out of 170 subjects at Week 16 is > 95%. Therefore, the sample size will only be increased if the observed response rate is < 81.7% ie, if fewer than 98 out of 120 subjects are responders.

At the interim analyses, the total number of subjects required to be enrolled at Week 0 is calculated assuming the response rate observed minus one standard error.

11.4 Pharmacokinetics

Data will be listed for all subjects with available serum concentrations per treatment. All concentrations below the lowest quantifiable concentration (LQC) in a sample or missing data will be labeled as such in the concentration data listings. Concentrations below the LQC in a sample will be treated as zero in the summary statistics and for the calculation of pharmacokinetic parameters. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each dose group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for the golimumab serum concentrations at each sampling time of golimumab.

Serum golimumab concentrations will be summarized for each treatment group over time. In addition, if feasible, a population PK analysis 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. The apparent total systemic clearance (CL/F) and apparent volume of distribution (V/F) will be estimated using a nonlinear mixed effects modeling (NONMEM) approach.

11.5 Immunogenicity Analyses (Antibodies to Golimumab)

The occurrence and titers of antibodies to golimumab during the study will be summarized by treatment group over time for all subjects who receive an administration of golimumab and have appropriate samples collected for detection of antibodies to golimumab (ie, subjects with at least 1 sample obtained after their first golimumab administration).

11.6 Pharmacodynamic Analyses

Changes in the concentration of individual serum and urine markers from baseline to the selected post-treatment time points will be summarized. Additional analyses may be performed following evaluation of the data. RNA analyses and additional analyses will be summarized in a separate technical report.

11.7 Pharmacokinetic and Pharmacodynamic Analyses

If data permit, the relationships between serum golimumab concentration and efficacy may be analyzed graphically. If any visual trend is observed, a suitable PK/PD model may be developed to describe the exposure-response relationship.

11.8 Safety Analyses

Adverse Events

The original terms used in the CRFs by investigators to identify AEs will be coded using the MedDRA. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs) will be included in the analysis. For each AE, the percentage of subjects who experienced at least 1 occurrence of the given event will be summarized by treatment group.

Special attention will be given to those subjects who died, or who discontinued treatment due to an AE, or who experienced a severe AE or a SAE (eg, summaries, listings, and narrative preparation may be provided, as appropriate).

The following analyses will be used to assess the safety of subjects in this trial.

- The occurrence and type of AEs.
- The occurrence and type of SAEs.
- The occurrence and type of reasonably related AEs.
- The occurrence of injection-site reactions.
- The occurrence of ANA and anti-dsDNA antibodies.

- The occurrence of antibodies to golimumab.
- The laboratory (hematology and chemistry) parameters and change from baseline in these laboratory parameters.
- The occurrence of markedly abnormal laboratory (hematology and chemistry) parameters.

11.9 Interim Analysis

Two interim analyses will be performed during the course of this study.

An Interim Analysis Committee (IAC) will be established to review the interim data and formulate recommended decisions/actions in accordance with the objectives of the interim analysis. The IAC consists of a clinician, pharmacokineticist, and a statistician, one of whom will chair the committee, and other members as required by the nature of the interim analysis. In addition, the DMC members will be recruited to be involved in the interim analyses as needed.

Week 8 Interim Analyses

The first interim analysis will be performed at the Week 8 timepoint, when 30 subjects have completed the Week 8 visit, after receiving 2 golimumab administrations at Weeks 0 and 4. All new screening will stop after the 30th subject receives the Week 0 dose, until completion of the interim analysis. This interim analysis will be performed to ensure that 8 or more subjects are American College of Rheumatology (ACR) Pediatric (Ped 30) responders by the Week 8 visit. If 8 or more out of 30 subjects are responders, the study will continue. If fewer than 8 subjects are responders then the study will be discontinued.

Week 16 Interim Analysis

After approximately 120 subjects complete the Week 16 visit, another interim analysis will be performed. The response rates of subjects at Week 16 will be evaluated to ensure that 134 subjects would participate in the randomized withdrawal portion of the study. If the response rates at the interim analysis indicate that less than 134 responders would enter the randomized withdrawal portion of the study, the total number of subjects enrolled into the study at Week 0 will be increased. Section 11.3 summarizes the requirements for a sample size increase.

In addition, a population PK analyses, combined with an assessment of efficacy and safety, will explore the potential benefit and risk of tiered fixed doses based on pediatric weight ranges. Based on these analyses, which will use data obtained through the Week 16 visit for each of the first 120 subjects, tiered fixed dosing may be utilized after the Week 48 DBL during the long-term extension of the study.

11.10 Data Monitoring Committee

An independent DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. Thereafter, the committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study. The details will be provided in a separate DMC charter.

The DMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

12 ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

12.1 Definitions

12.1.1 Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The Sponsor collects AEs starting with the signing of the informed consent form (refer to Section 12.2.1, All AEs for time of last AE recording).

Serious Adverse Event

A SAE as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above (eg, suspected transmission of an infectious agent by a medicinal product is considered a SAE). Any AE is considered a SAE if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An unlisted AE, the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure. For a comparator product with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the golimumab product information sheet.

Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is by the definitions listed in Section 12.1.2.

12.1.2 Attribution Definitions

Not related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.2 Procedures

12.2.1 All Adverse Events

All AEs, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure (may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days of the last dose of study drug, must be reported using the Serious Adverse Event Form. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the name of the investigational study drug, the study number, the investigator's name and excluded concomitant medications.

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The Sponsor will also report to the investigator all SAEs that are unlisted (unexpected) and associated with the use of the drug. The investigator (or Sponsor where

required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

12.2.2 Serious Adverse Events

All SAEs occurring during clinical studies must be reported to the appropriate Sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of a SAE should be made by facsimile (fax). All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The occurrence of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a SAE. Suspected transmission of an infectious agent by a medicinal product should be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a SAE, except hospitalizations for the following:

- Social reasons in absence of an AE
- Surgery or procedure planned before entry into the study (must be documented in the CRF)

12.2.3 Pregnancy

All initial reports of pregnancy must be reported to the Sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered SAEs and must be reported using the

Serious Adverse Event Form. Any subject who becomes pregnant during the study must promptly discontinue further study treatment, and be followed for duration of the pregnancy. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Because the study drug may have an effect on sperm, or if the effect is unknown, pregnancies in partners of male subjects included in the study should be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

12.2.4 Events of Special interest

Any newly identified malignancy, opportunistic infections, death, or case of active TB occurring after the first administration of study agent(s) in subjects participating in this clinical study must be reported by the investigator according to the procedures in Section 12.2.2. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

12.3 Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13 PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, and reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

13.1 Procedures

All initial PQCs must be reported to the Sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with a SAE, the investigational staff must report the PQC to the Sponsor according to the SAE reporting timelines (refer to Section 12.2.2, Serious Adverse

Events). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

13.2 Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14 STUDY DRUG INFORMATION

14.1 Physical Description of Study Drug(s)

Golimumab is a human IgG1κ mAb to human TNFα, with an approximate molecular weight of 149,700 daltons. It is produced using a murine myeloma cell line in continuous perfusion cell culture, followed by a 7-stage purification and formulation process that includes 4 independent virus removal/inactivation steps. The resulting formulated bulk is stored frozen and shipped to the fill site.

SC golimumab drug product is supplied as a single-use, sterile solution containing golimumab in a glass syringe. The target composition of golimumab PFS is presented in Table 9.

Table 9: Target composition of golimumab Pre-filled Syringe

Component	Golimumab Pre-filled Syringe: 100 mg dose
Golimumab	100 mg
Sorbitol	41.0 mg
L-histidine	0.87 mg
Polysorbate 80	0.15 mg
Water for injection qs	1.0 mL

The golimumab and corresponding placebo product for this study will be supplied as a 1 mL single-use PFS for SC administration. No preservatives are present.

Placebo will employ the same product presentation without the presence of active drug. These doses will be BSA-adjusted and administered subcutaneously.

14.2 Packaging

SC golimumab drug product is supplied as a single-use, sterile solution containing golimumab in a glass syringe. The PFS is a Type I glass syringe with Fluorotec® coated rubber stopper, plunger handle, and a dry natural rubber (a derivative of latex) needle shield.

14.3 Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4 Preparation, Handling, and Storage

All study agents must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C). Study drug must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions.

Refer to the Pharmacy Manual for additional guidance on study drug preparation and handling.

14.5 Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. Site staff must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the Sponsor's site monitor during on-site monitoring visits. The return to the Sponsor of unused study drug, or used returned study drug for destruction, will be documented on the Drug Return Form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the Drug Return Form.

Hazardous materials such as used ampoules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic blinded pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the Sponsor.

15 STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Pharmacy manual.
- Worksheet binder.
- Online access to electronic CRFs.

- Trial Center File.
- Laboratory manual.
- IVRS manual.
- Subject study participation card.
- PRO assessments.

16 ETHICAL ASPECTS

16.1 Study-Specific Design Considerations

Potential subjects or their legally-acceptable representative will be fully informed of the risks and requirements of the study and, during the study, subjects or their legally-acceptable representative will be given any new information that may affect their decision to continue participation. They or their legally-acceptable representative will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects or their legally-acceptable representative who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected will be approximately 333 mL (339.5 mL first 30 subjects), will not exceed the ethically allowed maximum of 3 % of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time, as per the pediatric guidelines related to Directive 2001/20/EC of the European Commission.

16.2 Regulatory Ethics Compliance

16.2.1 Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2 Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments.
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects).
- Investigator's Brochure (or equivalent information) and amendments.
- Sponsor-approved subject recruiting materials.
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB).
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects.
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments.
- Revision(s) to informed consent form and any other written materials to be provided to subjects.
- If applicable, new or revised subject recruiting materials approved by the Sponsor.
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable.
- Investigator's Brochure amendments or new edition(s).
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted, and associated with the investigational drug.

- New information that may adversely affect the safety of the subjects or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects.
- Report of deaths of subjects under the investigator's care.
- Notification if a new investigator is responsible for the study at the site.
- Development Safety Update Report and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The re-approval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct).

At the end of the study, the investigator (or Sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3 Informed Consent

Each subject (or a legally-acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form and assent form that is used must be approved by both the Sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects or their legally-acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate, will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized

Sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject or legally-acceptable representative is authorizing such access, and agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The subject or legally-acceptable representative will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally-acceptable representative's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject or legally-acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject or legally-acceptable representative is obtained.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally-acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 10 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and the subject's parent and/or legally-acceptable representative.

When prior consent of the subject is not possible and the subject's legally-acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally-acceptable representative must be informed about the study as soon as possible and give consent to continue.

Subject (or a legally-acceptable representative) who have given written consent or provided assent, may come to their regularly scheduled visits without their legally-acceptable representative for all study-related assessments.

16.2.4 Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject or his or her legally-acceptable representative includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

16.2.5 Country Selection

Unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations, this study will only be conducted in those countries where the intent is to help ensure access to the developed product.

17 ADMINISTRATIVE REQUIREMENTS

17.1 Protocol Amendments

Neither the investigator nor the Sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the Sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the Sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate Sponsor representative (see Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2 Regulatory Documentation

17.2.1 Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2 Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the investigator.
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the investigator, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the Sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).
- Photocopy of the site signature log, describing delegation of roles and responsibilities at the start of the study.
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3 Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by anonymous initials, subject ID, and date of birth only.

The investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4 Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs; and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.5 Case Report Form Completion

Case report forms are provided for each subject in printed or electronic format.

Electronic Data Capture (eDC) will be used for this study. It is recommended that the study data will be transcribed by study personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the Sponsor within 2 days of the subject's visit. The electronic file will be considered to be the CRF. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subjects' source documentation. All data relating to the study must be recorded in CRFs prepared by the Sponsor. Data must be entered into CRFs in English. Designated site personnel must complete CRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

Every effort should be made to ensure that all subjective measurements (eg, pain scale information or other questionnaires) to be recorded in the CRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Site manager (SM) can generate a query (field DCF) for resolution by the investigational staff.
- Clinical data manager (CDM) can generate a query for resolution by the investigational staff.

17.6 Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's data base. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study.

The Sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy.

17.7 Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

17.8 Monitoring

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the Sponsor and

investigational staff and are accessible for verification by the Sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the investigational staff. The Sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9 Study Completion/Termination

17.9.1 Study Completion

The study is considered completed with the last visit of the last subject participating in the study. The final data from the investigational site will be sent to the Sponsor (or designee) after completion of the final subject visit at that site, in the time frame specified in the Clinical Trial Agreement.

17.9.2 Study Termination

The Sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further drug development.

17.10 On-Site Audits

Representatives of the Sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records,

including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11 Use of Information and Publication

All information, including but not limited to information regarding golimumab or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the investigator and not previously published, and any data, including pharmacogenomic research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the Sponsor in connection with the continued development of golimumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain CRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomics analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of pharmacogenomics results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

The Sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the

manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, results may need to be published in a given sequence (eg, substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The Sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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