Janssen Research & Development*

Clinical Protocol

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

Protocol CNTO148JIA3003; Phase 3
Amendment INT-4

SIMPONI® (golimumab) for Intravenous Use

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

Status:	Approved
Date:	16 December 2019
Prepared by:	Janssen Research & Development, LLC
EDMS No:	EDMS-ERI-71227414, 6.0

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	10 March 2014
Amendment 1	12 August 2014
Amendment 2	11 July 2016
Amendment 3	28 February 2017
Amendment 4	16 December 2019

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (16 December 2019)

The overall reason for the amendment: The overall reasons for this amendment are: 1) to allow continued treatment of subjects in the long-term extension (LTE) phase of the study (Week 52 through Week 252) that more closely resembles a real-world setting, collects critical safety information, and reduces the burden to subjects, and 2) to add details regarding an Extended Treatment Period (ETP) which allows subjects who are <18 years of age who are benefiting from treatment to continue to receive golimumab after Week 252 if the drug is not commercially available.

Applicable Section(s)	Description of Change(s)
Rationale: To change the collection of concomitant medications during the LTE to review and documentation of concomitant medications in source with update to the concomitant medications case report form (CRF) page to include only those medications that are associated with adverse events (AEs) and serious adverse events (SAEs). Corresponding text was updated in Section 8 (Prestudy and Concomitant Therapy).	
Time and Events Schedules Table 2 and 3	Concomitant medication collection has been updated to indicate that during the LTE, collection of concomitant medications is limited to only those medications associated with AEs and SAEs.
Footnote c.	**c. Review concomitant medications with subject and document in source; update concomitant medication CRF page to include only those medications that are associated with AEs and SAEs (ie, used to treat event or suspected in causing event).**
8. Prestudy and Concomitant Therapy	Prestudy JIA medications administered before the first dose of study agent must be recorded at screening. All concomitant therapies must be recorded ~~throughout~~ **through Week 52** of the study beginning with the administration of the first dose of the study drug. **After Week 52, the investigator will review concomitant medications with the subject and document in source, and record on the CRF page only those concomitant medications that are associated with AEs and SAEs (ie, used to treat event or suspected in causing event).** All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation and acupuncture) different from the study drug must be recorded in the CRF **through Week 52**. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study.

Applicable Section(s)	Description of Change(s)
Rationale: To change the frequency of review of systems, QuantiFERON®-TB Gold test, and the collection of vital signs before, during, and after an infusion in the LTE to at the discretion of the investigator to more closely follow standard medical practice. Corresponding text was updated in Section 9.4 (Safety Evaluations).	
Time and Events Schedules Table 2 and 3	Review of systems, QuantiFERON®-TB Gold test, and requirement for collection of vital signs before, during, and after the infusion have been updated to indicate that they are to be performed at the discretion of the investigator during the LTE.
~~Footnote d.~~	~~d. Vital signs should be taken pre-infusion; at 15 and 30 minutes (15-minute intervals during the infusion); and at 60 and 90 minutes (during the 1-hour observation period following the infusion).~~
~~Footnote f.~~	~~f. Testing is not required for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment~~
Time and Events Schedules Table 2 Footnote d.	**d. Perform at the discretion of the investigator.**
Time and Events Schedules Table 3 Footnote e.	**e. Perform at the discretion of the investigator.**
9.4. Safety Evaluations (Vital Signs)	Vital signs should be taken pre-infusion; at 15 and 30 minutes (15-minute intervals during the infusion); and at 60 and 90 minutes (during the 1-hour observation period following the infusion) **through Week 52**. **After Week 52, vital signs should be taken at the discretion of the investigator.**
9.4. Safety Evaluations (Physical Examination)	Physical examinations, including a skin exam at every physical examination and Tanner staging ~~at least every 6 months~~ for sexual maturity will be performed **(through Week 52 only)** according to the Time and Events Schedule. Review of systems will be performed at all visits **through Week 52** to evaluate for new symptomatology and if necessary, full physical examination may be performed at investigator discretion. **After Week 52, review of systems will 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.
9.4. Safety Evaluations (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 **through Week 252. After Week 252, TB evaluation will be carried out at investigator discretion and according to local and country guidelines for immunosuppressed patients.** The following series of questions is suggested for use during the evaluation.

Applicable Section(s)	Description of Change(s)
9.4. Safety Evaluations (Early Detection of Active Tuberculosis)	~~Annual~~ QuantiFERON®-TB Gold (and tuberculin skin) testing **at Week 52** is not required for subjects with a history of latent TB, and ongoing treatment for latent TB, or documentation of having completed adequate treatment for TB. **After Week 52, testing for latent TB should be performed at the discretion of the investigator and according to local and country guidelines.** Subjects who experience close contact with an individual with active TB during the conduct of the study ~~must~~ **should** have a repeat chest radiograph, a repeat QuantiFERON®-TB Gold test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB Gold test is not approved/registered, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. The QuantiFERON®-TB Gold test (and tuberculin skin test) does not need to be repeated for subjects with a history of latent TB, and ongoing treatment for latent TB, or documentation of having completed adequate treatment for TB. If the QuantiFERON®-TB Gold test result is indeterminate, the test should be repeated as outlined in Section 9.1.2. Subjects should be encouraged to return for all subsequent scheduled study visits according to the protocol.
Rationale: To remove Tanner staging during the LTE since this exam may place investigators and subjects in an unnecessary uncomfortable situation, may be particularly burdensome for subjects, and no safety concerns have been identified.	
Time and Events Schedules Table 2 Footnote e.	**e.** ~~e.~~ Includes skin examination at every physical examination ~~and Tanner staging approximately every 6 months~~.
Time and Events Schedules Table 3 Footnote f.	**f.** ~~e.~~ Includes skin exam ~~and Tanner staging~~.
Rationale: To decrease the frequency of routine laboratory analyses and antinuclear antibodies (ANA)/anti-dsDNA antibodies collected during the LTE. With decreased laboratory sampling, Footnote c. was added to Table 4 to indicate that the total volume of blood to be collected from each subject is decreased with the implementation of Protocol Amendment 4.	
Time and Events Schedules Table 2 and 3	The frequency of collection of routine laboratory analyses during the LTE has been decreased from every 24 weeks to once yearly. The collection of ANA/anti-dsDNA antibodies has been changed from occurring every 24 weeks to occurring only at the end of the LTE and at the final safety follow-up visit.
Table 4. Approximate Volume of Blood to be Collected From Each Subject Through Week 252 Footnote c.	**c. The approximate total volume is the maximum volume of blood collected from a subject during the study; with implementation of Protocol Amendment 4, the volume of blood collected will be decreased.**
Rationale: To change the frequency of collection of chest x-rays during the LTE to at the discretion of the investigator.	
Time and Events Schedules Table 2 Footnote g.	g. Chest x-ray screening **should be performed at the discretion of the investigator and** ~~as~~ per local and country regulations for ~~initiation of~~ **children with JIA who are receiving** immunosuppressive agents ~~in children with JIA~~ **and** who are at risk of TB.

Applicable Section(s)	Description of Change(s)
Time and Events Schedules Table 3 Footnote h.	**h.** ~~g.~~ Chest x-ray screening **should be performed at the discretion of the investigator and** ~~as~~ per local and country regulations for ~~initiation of~~ **children with JIA who are receiving** immunosuppressive agents ~~in children with JIA~~ **and** who are at risk of TB.
Rationale: To change the frequency of uveitis and slit lamp evaluations during the LTE to at the discretion of the investigator and per standard of care. Corresponding text was updated in Section 9.4 (Safety Evaluations) and Attachment 5 (Slit Lamp Evaluations).	
Time and Events Schedules Table 2 and 3	Evaluation of uveitis has been updated to indicate that the evaluation is to be performed at the discretion of the investigator during the LTE.
Time and Events Schedules Table 2 Footnote h.	h. Evaluations (based on physical examination and interview) should be performed ~~by~~ **at the discretion of** the investigator ~~at least every 6 months in all subjects~~. ~~In addition, all subjects are required to have s~~Slit lamp evaluations performed by an ophthalmologist/optometrist ~~during the study~~ at **the discretion of the investigator and per standard of care** ~~intervals (based on JIA subtype, ANA test results, age at JIA onset, and JIA duration) as specified in Attachment 5~~.
Time and Events Schedules Table 3 Footnote i.	**i.** ~~h.~~ Evaluations (based on physical examination and interview) should be performed ~~by~~ **at the discretion of** the investigator ~~at least every 6 months in all subjects~~. ~~In addition, all subjects are required to have s~~Slit lamp evaluations performed by an ophthalmologist/optometrist ~~during the study~~ at **the discretion of the investigator and per standard of care** ~~intervals (based on JIA subtype, ANA test results, age at JIA onset, and JIA duration) as specified in Attachment 5~~.
9.4. Safety Evaluations (Uveitis Evaluations)	All subjects will be assessed for new-onset uveitis at screening and at least every 6 months ~~thereafter~~ **through Week 52** by the investigator based on physical examination and interview. **After Week 52, uveitis evaluations will be performed at investigator discretion.** This consists of an assessment of signs and symptoms of uveitis, including, but not limited to, eye redness, light sensitivity, changes in vision, and floaters. ~~Based upon changing clinical standards, examinations may be more frequent.~~ In addition, all subjects are required to have slit lamp evaluations performed by an ophthalmologist/optometrist ~~during the study~~ **through Week 52** at intervals (based on JIA subtype, ANA test results, age at JIA onset, and JIA duration) as specified in Attachment 5. **After Week 52, slit lamp evaluations will be performed at the discretion of the investigator and per standard of care.**
Attachment 5: Slit Lamp Evaluations	**Through Week 52, a**~~A~~ll subjects are required to have slit lamp evaluations performed by an ophthalmologist/optometrist during the study at intervals (based on JIA subtype, ANA test results, age at JIA onset, and JIA duration) as specified in the table below. **After Week 52, slit lamp evaluations will be performed at the discretion of the investigator and per standard of care.** The date of the screening visit and the ANA test results during screening (as applicable depending on the JIA subtype) should be used to determine when the first slit lamp evaluation should be performed during the study. The interval for the slit lamp evaluations may be adjusted thereafter based on the subject's ANA test results and JIA disease duration after screening. However, once a subject tests positive for ANA at any time during the study (and regardless if the subject subsequently tests negative for ANA), the subject should be considered ANA positive when determining the frequency of slit lamp evaluations.

Applicable Section(s)	Description of Change(s)
Rationale: To change the length of infusion reaction evaluation from at least 60 minutes to at the discretion of the investigator. Corresponding text was updated in Section 9.4 (Safety Evaluations).	
Time and Event Schedules Table 2 Footnote j.	j. Subjects will be observed **at the discretion of the investigator** ~~for at least 60 minutes~~ after the administration of study agent for symptoms of an infusion reaction.
Time and Event Schedules Table 3 Footnote k.	**k.** ~~j.~~ Subjects will be observed **at the discretion of the investigator** ~~for at least 60 minutes~~ after the administration of study agent for symptoms of an infusion reaction.
9.4. Safety Evaluations (Infusion Reaction Evaluations)	An infusion reaction is any unfavorable or unintended sign that occurs during the infusion or within 1 hour of completion of the infusion. All subjects must be carefully observed for symptoms of an infusion reaction. **Through Week 52, s**~~S~~ubjects will be observed for at least 60 minutes after completion of the IV administration of study agent for symptoms of an infusion reaction. **After Week 52, subjects will be observed at the discretion of the investigator after completion of the IV administration of study agent for symptoms of an infusion reaction.** If an infusion reaction is observed, the subject should be treated at the investigator's discretion.
9.4 Safety Evaluations (Allergic Reactions)	Through~~out the study~~**Week 52**, all subjects must be observed carefully for symptoms of an allergic reaction (eg, urticaria, itching, hives) for at least 60 minutes after the completion of the infusion. **After Week 52, subjects must be observed carefully for symptoms of an allergic reaction at the discretion of the investigator after completion of the infusion.** If mild or moderate allergic reaction is observed, acetaminophen or NSAIDs and diphenhydramine at approved pediatric doses may be administered.
Rationale: To remove efficacy assessments from the LTE and add requirement for investigators to sign an annual attestation form regarding subject's receipt of continued benefit of treatment. The attestation form will be maintained in the subject's source documents. As no efficacy assessments will be collected during the LTE, instructions regarding Childhood Health Assessment Questionnaire (CHAQ) collection are no longer needed.	
Time and Event Schedules Table 2 and 3	All efficacy assessments have been removed from visits during the LTE.
Time and Event Schedules Table 2 Footnote k.	k. ~~JIA assessments include the following: Physician Global Assessment of Disease Activity, Childhood Health Assessment Questionnaire (CHAQ), and duration of morning stiffness.~~ **~~CHAQ should be completed before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions.~~ Investigator will complete an annual attestation form to document that subject is benefiting from treatment.**
Time and Event Schedules Table 3 Footnote l.	**l.** ~~k. JIA assessments include the following: Physician Global Assessment of Disease Activity, Childhood Health Assessment Questionnaire (CHAQ), and duration of morning stiffness.~~ **~~CHAQ should be completed before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions.~~ Investigator will complete an annual attestation form to document that subject is benefiting from treatment.**
Time and Event Schedules Table 2 and 3 ~~Footnote l.~~	~~l. CHAQ to be completed by the parent or caregiver; preferably the same parent or caregiver should complete at every visit. Subjects who are 15 to <18 years of age at study entry may complete the assessment jointly with the parent/caregiver.~~

Applicable Section(s)	Description of Change(s)
3.1.3. Week 52 through Week 252 (Long-term Extension)	During the LTE, all subjects will continue to receive golimumab q8w (±1 week) through Week 244. For children who have completed the full trial period of 252 weeks and for whom drug is proven beneficial but is not commercially available for pJIA indication (or patient does not qualify for insurance to pay for the drug) IV golimumab will continue to be provided by the Sponsor, as described in Section 3.1.4. Between Week 52 and Week 252, disease activity will be monitored and assessed **by investigators**, and **benefit of treatment will be documented in the subject's source documents by investigators on a yearly basis via an attestation form** ~~documented in the CRF every 16 weeks~~; infusions and safety measurements will be done ~~every 8 weeks~~ at the investigative site **according to the Time and Events Schedule**.
9.1.5. Long-Term Extension Phase: After Week 52 through Week 252	Subjects will have safety, ~~efficacy~~, PK, and immunogenicity evaluations performed according to the Time and Events Schedules (Table 2 and Table 3). **After Week 52, disease activity will be monitored and assessed by investigators. Investigators will fill out an annual attestation form to document that a subject is benefiting from treatment.** Subjects who discontinue study agent administration prior to Week 244 without withdrawing consent should return for a final safety follow-up visit approximately 8 weeks after their last study agent infusion (Section 10.2).
9.2.1. Evaluations	The Time and Events Schedule summarizes the frequency and timing of efficacy measurements applicable to this study (Table 1~~, Table 2, and Table 3~~). **After Week 52, investigators will complete an attestation form annually to document that the subject is benefiting from treatment.**
9.2.1.1. Evaluations (Joint Evaluation)	It is preferable 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 ~~244~~ **52**.
Rationale: To update the instructions regarding visits outside the recommended acceptable visit window after Week 52 in order to more closely resemble a real-world setting and reduce the burden to subjects.	
9.1.1. Overview	The Time and Events Schedules summarize the frequency and timing of efficacy, PK, immunogenicity, and safety measurements applicable to this study (Table 1, Table 2, and Table 3). All scheduled study visits should occur within ±3 days of the intended visit through Week 28 and ±1 week from Week 28 through Week 244. **Through Week 52, i**~~I~~f the recommended acceptable window cannot be observed, the Sponsor must be contacted before scheduling a visit. **After Week 52, if the recommended acceptable window cannot be observed, the reason for the deviation must be recorded in source documents. After Week 252, study procedures will be performed as described in Attachment 6.**
Rationale: To update the assessments performed at unscheduled visits based on the changes to Time and Events Schedule.	
9.1.1. Overview	At every unscheduled visit, the investigator will perform the following evaluations: • Review of systems **(after Week 52, at the discretion of the investigator)** • Vital signs **(after Week 52, at the discretion of the investigator)** • TB questionnaire • Adverse events • Review of concomitant medications **(after Week 52, medications should be reviewed and documented in source; medications used to treat or associated with AEs and SAEs should be recorded on the CRF)** • Safety laboratory evaluations **(after Week 52, at the discretion of the investigator)**

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the responsibilities of the investigator during the LTE based on the changes to Time and Events Schedule.	
9.1.5. Long-Term Extension Phase: After Week 52 through Week 252	**Review of systems, collection of vital signs, QuantiFERON®-TB Gold testing, uveitis evaluations (including slit lamp evaluations), and chest x-ray screening will be performed at the discretion of the investigator, refer to the Time and Events Schedules (Table 2 and Table 3). It is the responsibility of the investigator to carry out all assessments per standard of practice and to update the CRF with all information related to AEs and SAEs (eg, concomitant medications).**
Rationale: To update the assessments performed at the final safety follow-up visit based on the changes to Time and Events Schedule.	
Time and Events Schedules Table 2 Footnote b.	b. All subjects who discontinue study agent administration before Week 156 but do not withdraw consent must return to the study site for a final safety visit approximately 8 weeks after the last infusion (Section 10.2). **Collection of vital signs, review of symptoms, and uveitis evaluation are performed at the final safety follow-up visit at the discretion of the investigator.**
Time and Events Schedules Table 3 Footnote b.	b. All subjects who discontinue study agent administration before Week 244 but do not withdraw consent must return to the study site for a final safety visit approximately 8 weeks after the last infusion (Section 10.2). **Collection of vital signs, review of symptoms, and uveitis evaluation are performed at the final safety follow-up visit at the discretion of the investigator.**
10.2. Discontinuation of Study Treatment	Subjects who discontinue study agent infusions but do not terminate study participation will have the following assessments performed at the final safety follow-up visit: • Safety evaluation~~s~~ **including** ~~(vital signs, review of systems,~~ AE review, TB evaluation~~, uveitis evaluation~~ and the collection of a blood sample for routine laboratory analyses**,** ~~and~~ determination of the presence of ANA/anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies**,** and antibodies to golimumab~~).~~**; after Week 52, other safety evaluations are performed at the discretion of the investigator (vital signs, review of systems, uveitis evaluation).** • Concomitant medication review **(after Week 52, medications should be reviewed and documented in subject's source records; medications used to treat or associated with AEs and SAEs should be recorded in the source document as well as the CRF)**. • Efficacy evaluations (joint assessments, JIA assessments, and collection of blood sample for CRP) **through Week 52 only**. • Blood samples drawn for measurement of golimumab concentration for all subjects at the final safety follow-up visit.

Applicable Section(s)	Description of Change(s)
Rationale: To add an ETP in order to allow subjects <18 years of age who are demonstrating benefit from treatment with golimumab to continue treatment after Week 252 if the drug is not commercially available. An additional database lock at the end of the ETP is planned, which will be the final database lock for the study.	
Synopsis (Overview of Study Design)	All subjects will receive 80 mg/m^2 golimumab as an IV infusion (over 30±10 minutes) at Weeks 0, 4, and q8w (±3 days) through Week 28 and q8w (±1 week) thereafter (maximum single dose 240 mg [maximum body surface area (BSA) 3.0 m^2 x 80 mg/m^2]). Commercial MTX is to be administered at a stable dose of 10-30 mg/m^2/week in subjects with BSA <1.67 m^2 or a stable minimum dose of 15 mg/week in subjects with BSA ≥1.67 m^2 through Week 28 (unless lower doses of MTX are administered for documented safety reasons or unless documented country or site regulations prohibit dose of 15 mg/week or above in subjects with BSA ≥1.67 m^2). Subjects who complete the study at Week 52 will have the option to enter into the long-term extension (LTE) phase of the study. During the LTE, all subjects will continue to receive 80 mg/m^2 IV golimumab q8w (±1 week; maximum single dose 240 mg) through Week 244. All subjects who complete the Week 244 visit are expected to participate in the safety follow-up visit at Week 252. **Subjects <18 years of age who have completed the study through Week 252 and are benefiting from treatment, but for whom golimumab is not commercially available for the treatment of pJIA, will have the option to continue to receive golimumab (80 mg/m^2 q8w) in the Extended Treatment Period (ETP). The first dose of golimumab in the ETP is administered at Week 252 after all assessments have been completed.** ~~Golimumab after Week 252 (for subjects who have completed the full 252-week study before drug commercialization for pJIA indication has taken place) will be provided in the Extended Treatment Period until the drug will be is approved and marketed for use in pJIA in the country of the subject or for as long as proven beneficial to the child (in cases where commercial drug is not accessible to the subject).~~ Since this is an open-label study with all subjects receiving the same BSA-based dose of IV golimumab, an external Data Monitoring Committee will not be established. The end of the study is defined as the last follow-up assessment for the last subject in **the** ~~LTE~~**ETP**.
Synopsis (Dosage and Administration, Golimumab)	**During the ETP, subjects will continue to receive 80 mg/m^2 golimumab IV infusions q8w starting at Week 252.**
Time and Events Schedule Table 3 Footnote d.	**d. The ETP starts at Week 252. These procedures should only be completed for subjects who enter the ETP.**
3.1. Overview of Study Design	All subjects will receive 80 mg/m^2 golimumab (maximum single dose 240 mg) as an IV infusion given over 30±10 minutes at Weeks 0, 4, and every 8 weeks (q8w; ±3 days) through Week 28 and then q8w (±1 week) thereafter through Week 244. Body surface area will be calculated based on the subject's height and body weight measured at each visit, and the BSA-based dose of golimumab will be adjusted as needed to maintain the dose at 80 mg/m^2. Subjects will also receive commercial MTX weekly through Week 28 at the same BSA-based dosage (10 to 30 mg/m^2 per week of MTX in subjects with BSA <1.67 m^2, or a minimum of 15 mg/week in subjects with BSA ≥1.67 m^2) as at time of study entry as outlined in Section 6.2. **At Week 252, subjects who meet the inclusion criteria for the optional Extended Treatment Period (ETP) may continue treatment with golimumab (80 mg/m^2 q8w) after completion of the Week 252 assessments.**

Applicable Section(s)	Description of Change(s)
3.1.1. Week 0 through Week 28	After all subjects complete the Week 28 visit, the database will be locked to assess PK, safety and efficacy. An additional safety, efficacy, and PK database lock is currently planned for Week 52. ~~Final~~ **A** database lock will be performed at Week 252**, and a final database lock will be performed at the end of study**.
3.1.3. Week 52 through Week 252 (Long-term Extension)	~~The final~~ **A** database lock will **occur** ~~be~~ at Week 252.
3.1.4. After Week 252 (Extended Treatment Period)	**Subjects <18 years of age who complete the study through Week 252, and for whom drug is proven beneficial but is not commercially available for pJIA, will have the option to enter the ETP at Week 252, as described in Attachment 6.** **The final database lock will occur at the end of the ETP, as described in Attachment 6.**
3.1.5 End of Study Definition	The end of the study is defined as the last follow-up assessment for the last subject in the ~~long-term extension~~ **ETP.**
3.2.1. Blinding, Control, Study Phase/Periods, Treatment Groups	This is a single-arm, open-label study to evaluate the PK of IV golimumab in subjects with pJIA, with all subjects receiving the same BSA-based dose of IV golimumab through Week 52. Subjects who complete the study at Week 52 will have the option to enter into the LTE phase of this study through Week 252. **After Week 252, subjects who meet specific criteria (see Attachment 6) will have the opportunity to continue treatment with golimumab in the ETP.**
5. Treatment Allocation and Blinding	This is an open-label study. All subjects will receive golimumab 80 mg/m^2 at Week 0, Week 4, and q8w (± 3 days) through Week 28 and q8w (± 1 week) ~~up to Week 244~~ **after Week 28**.
4. Subject Population	**Eligibility criteria for the ETP are provided in Attachment 6. Prohibitions and restrictions during the ETP are also provided in Attachment 6.**
6.1. Golimumab	**During the ETP, golimumab will be administered as described in Attachment 6. The first dose of golimumab during the ETP will be at Week 252 after the subject has completed the Week 252 assessments.**
8. Prestudy and Concomitant Therapy	**After Week 252, concomitant medications are documented as described in Attachment 6.**
9.1.1. Overview	The Time and Events Schedules summarize the frequency and timing of efficacy, PK, immunogenicity, and safety measurements applicable to this study (Table 1, Table 2, and Table 3). All scheduled study visits should occur within ±3 days of the intended visit through Week 28 and ±1 week from Week 28 through Week 244. Through Week 52, if the recommended acceptable window cannot be observed, the Sponsor must be contacted before scheduling a visit. After Week 52, if the recommended acceptable window cannot be observed, the reason for the deviation must be recorded in source documents. **After Week 252, study procedures will be performed as described in Attachment 6.**
9.1.6. Extended Treatment Period	**9.1.6. Extended Treatment Period** **Subjects who enter the ETP after completion of the Week 252 assessments will continue to receive 80 mg/m^2 golimumab IV q8w.** **The frequency and timing of assessments during the ETP are provided in Attachment 6.**

Applicable Section(s)	Description of Change(s)
10. Subject Completion/ Withdrawal	**Subject completion/withdrawal during the ETP is described in Attachment 6.**
14.4. Preparation, Handling, and Storage	**Preparation, handling, and storage of study agent during the ETP is described in Attachment 6.**
14.5 Drug Accountability	**Drug accountability during the ETP is described in Attachment 6.**
Attachment 6. Extended Treatment Period	With the addition of the Extended Treatment Period, information was added to the protocol to detail the eligibility, requirements, and procedures of the Extended Treatment Period.
Rationale: To remove the use of a Data Review Committee as the study is open-label, golimumab has been marketed since 2009, and an internal Sponsor safety monitoring team reviews safety concerns in addition to routine medical monitoring.	
11.9. Data Monitoring Committee	This is an open-label study, with all subjects receiving the same dosage of IV golimumab. Therefore, an external Data Monitoring Committee will not be utilized. Safety data will be routinely evaluated by the study's medical monitor **and Sponsor's internal Safety Management Team as needed** ~~and an internal Data Review Committee as defined in the DRC charter~~. In addition, the data may be reviewed by the Steering Committee.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-3 (28 February 2017)

The overall reason for the amendment: 1) to change the inclusion criterion regarding C-reactive protein (CRP); 2) to provide clarification on the methotrexate (MTX) dose to be used during the study; 3) to modify the requirements and intervals for slit lamp evaluations; 4) to remove the term "emancipated" to describe a juvenile; 5) to remove unnecessary wording regarding blinding; 6) to indicate that a local laboratory may be used for the QuantiFERON®-TB Gold test.

Applicable Section(s)	Description of Change(s)
Rationale: With approximately half the planned number of subjects enrolled in the study to date, the study population exhibits a range of C-reactive protein (CRP) levels that would support the planned population pharmacokinetics (PK) analysis. At the same time, the Sponsor has received consistent feedback from the Steering Committee and investigators that otherwise qualified subjects have failed screening because their CRP was<0.1 mg/dL. Given these facts, the inclusion criterion has been revised to allow approximately 30% of the study population to have a screening CRP of <0.1 mg/dL in order to enhance enrollment in the study without affecting the Sponsor's ability to fulfill the objectives of the study.	
Synopsis, Objectives	The primary objective of this study is to assess the pharmacokinetics (PK) following intravenously administered golimumab in subjects (ages 2 to less than 18 years) with pJIA manifested by ≥5 joints with active arthritis ~~and C-reactive protein (CRP) of ≥0.1 mg/dL~~ despite methotrexate (MTX) therapy for ≥2 months.
Synopsis, Subject Population	Subjects must have ≥5 joints with active arthritis as defined by American College of Rheumatology (ACR) criteria at screening and enrollment.~~and must have a screening CRP of ≥0.1 mg/dL~~.
2.1 Objectives	The primary objective of this study is to assess the PK following intravenously administered golimumab in subjects (ages 2 to less than 18 years) with pJIA manifested by ≥5 joints with active arthritis~~ and CRP of ≥0.1 mg/dL~~ despite MTX therapy for ≥2 months.
4.1 Inclusion Criteria	6. Subjects must have a screening CRP of ≥0.1 mg/dL **with the exception of approximately 30% of the study population**.
Rationale: Text has been revised to clarify the appropriate MTX dose for subjects according to their body surface area (BSA) measurement.	
Synopsis, Overview of Study Design	Commercial MTX is to be administered at a **stable** dose of 10-30 mg/m^2/week **in subjects with BSA <1.67 m^2 or a stable minimum dose of 15 mg/week in subjects with BSA ≥1.67 m^2 through Week 28** (unless **lower doses of MTX are administered** for documented safety reasons **or unless documented country or site regulations prohibit dose of 15 mg/week or above in subjects with BSA ≥1.67 m^2**)~~, lower doses of MTX are administered~~) ~~through Week 28~~. ~~For patients with BSA greater than 1.67 m2, a minimum fixed dose of 15 mg/week is required~~.
Synopsis, Dosage and Administration	Subjects will receive commercial MTX **at least through Week 28** at the same BSA-based dose (10 to 30 mg/m^2 per week **for subjects with BSA <1.67 m^2 or at least 15 mg/week for subjects with BSA ≥1.67 m^2**) as at time of study entry ~~at least through Week 28~~.
3.1 Overview of Study Design	Subjects will also receive commercial MTX weekly **through Week 28** at the same BSA-based dosage (10 to 30 mg/m^2 per week of MTX **in subjects with BSA <1.67 m^2**, ~~with~~ **or** a minimum of 15 mg/**week** in subjects with BSA ≥1.67 m^2) as at time of study entry ~~through Week 28~~ as outlined in Section 6.2.
	……
(Legend for Figure 1)	All subjects receive 80 mg/m^2 golimumab IV infusion at Weeks 0, 4, and every 8 weeks thereafter through Week 244. **Subjects will receive**~~ and 10 to 30 mg/m^2 per week of~~ commercial methotrexate **at the same weekly dose as at time of study entry at least** through Week 28.

Applicable Section(s)	Description of Change(s)
4.1 Inclusion	7. Subjects must have active pJIA despite current use of oral, intramuscular, or subcutaneous MTX for ≥2 months before screening ~~at a weekly dose of ≥10 mg/m^2. Subjects currently on MTX must receive a stable dose (between 10 to 30 mg/m^2 per week) of MTX for ≥4 weeks before screening~~. **For subjects with BSA <1.67 m^2, the MTX dose must be between 10 to 30 mg/m^2 per week and stable for ≥4 weeks before screening. For s~~S~~**ubjects with BSA ≥1.67 m^2, **the MTX dose** must ~~receive a~~ **be a** minimum of 15 mg/week **and must be stable for ≥4 weeks before screening**. ~~of MTX unless documented country or site regulations prohibit use of 15 mg of MTX per week in subjects with BSA ≥1.67 m^2.~~ In situations where there is documented intolerance of doses >10 mg/m^2 weekly **(for subjects with BSA <1.67 m^2)** or ≥15 mg/week **(**for subjects with BSA ≥1.67 m^2**); or where documented country or site regulations prohibit use of ≥15 mg of MTX per week in subjects with BSA ≥1.67 m^2**, subjects may be entered into the trial on a lower dose of MTX.
6.2 Methotrexate	Subjects will receive commercial MTX **through Week 28** at the same BSA-based dose (10 to 30 mg/m^2 per week **for subjects with BSA <1.67 m^2 or at least 15 mg/week for subjects with BSA ≥1.67 m^2)**~~(10 to 30 mg/m^2 per week)~~ as at time of study entry~~through Week 28~~. Absolute dose should remain stable from baseline through Week 28. …… **After Week 28, changes in MTX administration are permitted (eg, increase or decrease in dosage, change in route of administration, or discontinuation).**
8. Prestudy and Concomitant Therapy	Subjects must have received MTX ~~at a weekly dose of ≥10 mg/m^2~~ for ≥2 months before screening. **For subjects with BSA <1.67 m^2, the MTX dose must be between 10 to 30 mg/m^2 per week and stable for ≥4 weeks before screening. For s~~S~~**ubjects with BSA ≥1.67 m^2 **the MTX dose must be** a minimum of 15 mg/week of MTX **and must be stable for ≥4 weeks before screening.** ~~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.~~
9.1.3. Treatment Phase: Week 0 through Week 28	Subjects will also receive commercial MTX weekly at the same BSA-based dosage ~~(10 to 30 mg/m2 per week)~~ as at time of study entry at least through Week 28 and commercial folic acid ≥5 mg weekly or folinic acid (at half the MTX dose) given the day after the MTX dose (Section 6.2). In children <12 years of age, the administration of folic acid or folinic acid will be at the discretion of the physician.
9.1.4. Treatment Phase: After Week 28 through Week 52	Subjects may also receive commercial MTX weekly at the same BSA-based dosage ~~(10 to 30 mg/m2 per week)~~ as at time of study entry and commercial folic acid ≥5 mg weekly or folinic acid if administered (at half the MTX dose; Section 6.2) given the day after the MTX dose; however, increases, decreases or discontinuations of MTX, other DMARDs, corticosteroids, and/or NSAIDs are permissible after Week 28.

Rationale: Text has been revised to clarify the nature of uveitis examinations and that, in addition to uveitis examinations performed at least every 6 months by the investigator, all subjects are required to have slit lamp evaluations performed by an ophthalmologist/optometrist during the study based on current clinical recommendations as specified in Attachment 5.

Applicable Section(s)	Description of Change(s)
Time & Events Schedules, Table 1	h. Evaluations **(based on physical examination and interview)** should be performed **by the investigator** at least every 6 months in all subjects. **In addition, all subjects are required to have slit lamp evaluations performed by an ophthalmologist/ optometrist during the study at intervals (based on JIA subtype, ANA test results, age at JIA onset, and JIA duration) as specified in Attachment 5.** ~~Subjects who test ANA positive at screening will be required to undergo slit lamp evaluation by a qualified ophthalmologist to evaluate for subclinical uveitis in the screening period, before first study drug administration, as well as at least every 3 months subsequent.~~
Time & Events Schedules, Table 2 and Table 3	h. Evaluations **(based on physical examination and interview)** should be performed **by the investigator** at least every 6 months in all subjects. **In addition, all subjects are required to have slit lamp evaluations performed by an ophthalmologist/ optometrist during the study at intervals (based on JIA subtype, ANA test results, age at JIA onset, and JIA duration) as specified in Attachment 5.** ~~Subjects who test ANA positive at screening will be required to undergo slit lamp evaluation by a qualified ophthalmologist at least every 3 months.~~
9.4 Safety Evaluations (Uveitis Evaluations)	All subjects will be ~~formally~~ assessed **for new-onset uveitis** at screening and at least every 6 months thereafter by the **investigator** ~~evaluation~~ **based on physical examination and interview.** ~~pertaining to new-onset uveitis on physical examination by the investigator and by interview.~~ **This consists of an assessment of signs and symptoms of uveitis, including, but not limited to, eye redness, light sensitivity, changes in vision, and floaters**. Based upon changing clinical standards, examinations may be more frequent. **In addition, all subjects are required to have slit lamp evaluations performed by an ophthalmologist/optometrist during the study at intervals (based on JIA subtype, ANA test results, age at JIA onset, and JIA duration) as specified in Attachment 5.** ~~Subjects who test antinuclear antibodies (ANA) positive at screening will be required to undergo slit lamp evaluation by a qualified ophthalmologist to evaluate for subclinical uveitis in screening period as well as at least every 3 months subsequent as specified in the Time and Events Schedules (Table 1, Table 2, and Table 3).~~ If a subject develops uveitis during the study, the subject's continued participation in the study is at the discretion of the investigator and Sponsor. ~~and a qualified ophthalmologist~~.
Attachment 5: Slit Lamp Evaluations	(Attachment added that outlines requirements and intervals for slit lamp evaluations based on JIA subtype, ANA test results, age at JIA onset, and JIA duration.)
Rationale: The term "emancipated" to describe a juvenile has been deleted because it does not have global application and text has been added to indicate that the CHAQ may be completed jointly with the parent/caregiver.	
Time & Events Schedules, Table 1, Table 2, and Table 3	l. CHAQ to be completed by the parent or caregiver; preferably the same parent or caregiver should complete at every visit. Subjects who are ~~emancipated juveniles (ages~~ 15 to <18 years **of age~~)~~** at study entry may complete the assessment~~s~~ **jointly with the parent/caregiver**~~themselves~~.
4.1 Inclusion Criteria	17. A parent or guardian ~~must~~ **should** accompany the subject to each study visit until the subject~~s~~ reaches the age of 18 years. ~~unless the subject is an emancipated juvenile.~~
9.2.1.4 Childhood Health Assessment Questionnaire (Parent/Subject Assessment of Overall Well-being)	Subjects who are ~~emancipated juveniles (ages~~ 15 to <18 years~~)~~ **of age** at study entry may complete ~~all~~ the CHAQ ~~assessments~~ **jointly with the parent/caregiver**~~themselves~~. Preferably, the same individual (eg, parent, caregiver, or subject) who completes the assessment~~s~~ at the start of the study should complete the assessment~~s~~ throughout the study.

Applicable Section(s)	Description of Change(s)
Rationale: Unnecessary text regarding blinding has been removed to avoid confusion.	
3.1 Overview of Study Design	~~Unblinded s~~**S**afety data will be routinely evaluated by the study's medical monitor.
5. Treatment Allocation and Blinding	As this is an open-label study, blinding procedures are not applicable. ~~Subjects and investigational study sites will remain unblinded. Sponsor personnel who will be involved with data analyses will be identified before the interim analyses.~~
11.9 Data Monitoring Committee	~~Unblinded s~~**S**afety data will be routinely evaluated by the study's medical monitor and an internal Data Review Committee as defined in the DRC charter.
Rationale: Wording was added to indicate that of a local laboratory may be used for the QuantiFERON®-TB Gold test.	
ATTACHMENT 1 QUANTIFERON®-TB GOLD TESTING	The central laboratory will analyze and report results for each subject, and sites will be informed of the results. **Under certain circumstances as approved by the Sponsor, a local laboratory may be used to process the QuantiFERON®-TB Gold test sample and/or analyze the results**.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-2 (11 July 2016)

The overall reason for the amendment: The overall reasons for the amendment are: 1) to change the criteria used to determine subject eligibility to enhance enrollment in the study; 2) to provide clarification and additional details regarding the efficacy and safety evaluations to be used during the study; 3) to clarify the timing of changes that can be made to background medications; 4) removal of the ultrasound substudy; and 5) inclusion of anticipated events due to progression of the disease in the overall safety analyses for the study.

Applicable Section(s)	Description of Change(s)
Rationale: Published Juvenile idiopathic arthritis (JIA) treatment guidelines such as the ACR guidelines (2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features) recommend the initiation of treatment with a TNFα inhibitor after 3 months of methotrexate (MTX) treatment for patients with active JIA despite MTX treatment. However, the Sponsor has received consistent feedback from the Steering Committee and investigators that this duration of MTX treatment is too long and is inconsistent with typical clinical practice. JIA is a cause of serious functional disability, and the goal of treatment for pediatric patients with the disease is to gain disease control as quickly as possible. The required duration of MTX therapy before screening was shortened from ≥3 months to ≥2 months to still allow adequate time for patients to demonstrate failure or inadequate response to MTX therapy, but to also provide this vulnerable patient population with an opportunity to enroll in a clinical trial and receive treatment that may provide symptomatic relief of their disease.	
Synopsis, Objectives and Hypothesis	The primary objective of this study is to assess the pharmacokinetics (PK) ~~of~~ **following** intravenously administered golimumab in subjects (ages 2 to less than 18 years) with ~~polyarticular JIA (~~pJIA~~)~~ manifested by ≥5 joints with active arthritis **and C-reactive (CRP) of ≥ 0.1 mg/dL** despite methotrexate (MTX) therapy for ≥~~3~~**2** months.
Synopsis, Subject Population	Subjects must have active pJIA despite current use of oral, intramuscular or subcutaneous MTX (for ≥~~3~~**2** months before screening) at a weekly dose of ≥10 mg/m^2.
2.1. Objectives, Primary Objective	The primary objective of this study is to assess the PK following intravenously administered golimumab in subjects (ages 2 to less than 18 years) with pJIA manifested by ≥5 joints with active arthritis and CRP of ≥0.1 mg/dL despite MTX therapy for ≥~~3~~**2** months.
4.1.Inclusion Criteria (Criterion #4)	Failure or inadequate response to at least a ~~3~~**2**-month course of MTX before screening.
4.1.Inclusion Criteria (Criterion #7)	Subjects must have active pJIA despite current use of oral, intramuscular, or subcutaneous MTX ~~(~~for ≥~~3~~**2** months before screening ~~and on a stable dose for 4 weeks as noted in Section 8)~~ at a weekly dose of ≥10 mg/m^2.
8.Prestudy and Concomitant Therapy	Subjects must have received MTX at a weekly dose of ≥10 mg/m^2 for ≥~~3~~**2** months before screening.

Applicable Section(s)	Description of Change(s)
Rationale: The secondary objectives were corrected to include PK evaluations.	
Synopsis, Objective and Hypothesis;	The secondary objectives of this study are to evaluate IV golimumab in subjects with pJIA with respect to **PK,** efficacy (relief of signs and symptoms, physical function, **and** quality of life), safety (**adverse events [**AEs**]**, **serious AEs [**SAEs**]**, and assessment of laboratory parameters), and immunogenicity (antibodies to golimumab).
2.1 Objectives, Secondary Objectives	The secondary objectives of this study are to evaluate IV golimumab in subjects with pJIA with respect to **PK**, efficacy (relief of signs and symptoms, physical function, **and** quality of life), safety (AEs, SAEs, and assessment of laboratory parameters) and immunogenicity (antibodies to golimumab).
Rationale: To align the description of the study design in the Synopsis with that in the body of the document.	
Synopsis, Overview of Study Design	This is a Phase 3, open-label, single-arm, multicenter study to evaluate the PK, safety, and efficacy of IV golimumab in subjects with active pJIA despite current treatment with MTX ~~and/or corticosteroids and/or non-steroidal anti-inflammatory agents and/or prior use of anti-TNFα agents (up to 30% of total population)~~.
Synopsis, Overview of Study Design	**Approximately** ~~At least~~ 120 subjects will be enrolled at Week 0 to ensure that **approximately** ~~at least~~ 100 subjects remain in the study at Week 52.
Rationale: The Synopsis was revised to clarify the evaluations and endpoints of the study and to align the presentation of this information with that in the body of the document.	
Synopsis	The efficacy evaluations/endpoints were separated from the PK evaluations/endpoints and clarified. The safety evaluations and analyses were moved and are now presented before the immunogenicity evaluations and analyses.
Rationale: To clarify the stable dose of MTX that subjects should be receiving for ≥4 weeks before screening.	
4.1.Inclusion Criteria (Criterion #7)	Subjects currently on MTX ~~(weekly 10 to 30 mg/m^2)~~, must receive a stable dose (**between 10 to 30 mg/m^2**) per week of MTX for ≥4 weeks before screening.
Rationale: To clarify that MTX is to be administered to subjects through Week 28 of the study.	
Synopsis, Overview of Study Design	All subjects will receive 80 mg/m^2 golimumab as an IV infusion (over 30 ±10 minutes) at Weeks 0, 4, and ~~every 8 weeks (~~q8w~~;~~ **(**± 3 days) through Week 28 and q8w (± 1 week) thereafter (maximum single dose 240 mg [maximum **body surface area (**BSA**)** 3.0 m^2 x 80 mg/m^2])~~, along with c~~**. C**ommercial MTX **is to be administered** at a dose of 10-30 mg/m^2/week (unless for documented safety reasons, lower doses of MTX are administered) **through Week 28**.
Rationale: Clarification that the MTX dose and route of administration should remain stable through the Week 28 "visit," not the Week 28 "safety and efficacy database lock."	
Synopsis, Dosage and Administration Methotrexate	Every effort should be made to ensure that subjects remain on the same dose and route of administration of MTX through the Week 28 **visit** ~~safety and efficacy database lock~~, unless intolerance or AEs due to MTX occur.
6.2. Methotrexate	Every effort should be made to ensure that subjects remain on the same dose and route of administration of MTX through the Week 28 **visit**~~safety and efficacy database lock~~, unless intolerance or AEs due to MTX occur (Section 8).

Applicable Section(s)	Description of Change(s)
Rationale: JADAS has been deleted from Time &Events schedules, Tables 1, 2, and 3, because it is not a specific assessment that the physician performs rather it is a calculation based on the Physician Global Assessment, parent/child ratings of well-being and pain, joint assessments, and CRP.	
Time and Events Schedules, Tables 1, 2, and 3	JADAS was removed from the Time and Events Schedules.
Rationale: The JADAS physician assessed remission was deleted from the efficacy endpoints because it is considered to be exploratory in nature and not necessary for the evaluation of efficacy in this study.	
9.2.1.6 Juvenile Arthritis Disease Activity Score (JADAS)	~~JADAS physician assessed remission is defined as a total JADAS score of ≤2.~~
9.2.2 Endpoints, Other Endpoints 11.3 Efficacy Analyses, Other Efficacy Endpoints	~~• The proportion of subjects who achieve JADAS 10, 27, and 71 remission over time.~~
Rationale: It has been decided not to initiate the exploratory ultrasound substudy as a result of concerns over the feasibility of enrolling a sufficient number of subjects in the substudy due to the lack of interest from sites participating in the substudy or the inability of sites to participate due to operational reasons.	
~~Synopsis, Ultrasound Substudy~~	~~Power Doppler Sonography (PDUS) is a non-invasive ultrasound technique to assess inflammation at the joint level in rheumatoid arthritis (RA). At selected sites, subjects over the age of 4 years who have been enrolled in the study and are currently receiving study treatment may undergo PDUS and High Frequency gray scale Ultrasound (HFUS) of the 2nd and 3rd metacarpophalangeal joints, wrist, knee and ankle. Up to 5 exams will be performed at Weeks 0, 4, 12, 24, and 52 using a standardized protocol, described in a separate manual. Reading of the PDUS and HFUS will be performed by a blinded independent central reader.~~
~~9.6 Ultrasound Substudy~~	~~At selected sites, a total of approximately 20 subjects over the age of 4 years who are enrolled in this study and are currently receiving study treatment may undergo power ultrasounds of their metacarpophalangeal 2 and 3 joints (examining dorsal and volar surfaces), wrist (dorsal long midline, tendons), knee (suprapatellar long and parapatellar images; entheseal evaluations), and ankle (tibula/talar, subtalar medial and lateral surfaces, tendon examinations). Up to 5 ultrasound assessments may be conducted at Weeks 0, 4, 12, 28, and 52. The primary objective of the substudy is to examine Power Doppler response measured as the Power Doppler Sum Score at 6 months compared with the score at baseline. Additional details will be presented in the ultrasound substudy Protocol.~~
15. Study-Specific Materials	~~• Ultrasound substudy (only for sites participating in the ultrasound substudy)~~

Applicable Section(s)	Description of Change(s)
Rationale: A footnote was added to the Time and Events schedules (Tables 1, 2, and 3) to describe when vital signs should be taken at visits when study agent infusion is administered. Corresponding text was added to Section 9.4 (Safety Evaluations).	
Time and Events Schedules, Tables 1, 2, and 3 Footnote d	**d. Vital signs should be taken pre-infusion; at 15 and 30 minutes (15-minute intervals during the infusion); and at 60 and 90 minutes (during the 1-hour observation period following the infusion).**
9.4 Safety Evaluations, Vital Signs	Pulse/**heart rate**, respiratory rate, temperature, and blood pressure measurements will be performed according to the Time and Events Schedules **(Table 1, Table 2, and Table 3).** **Vital signs should be taken pre-infusion; at 15 and 30 minutes (15-minute intervals during the infusion); and at 60 and 90 minutes (during the 1-hour observation period following the infusion).**
Rationale: Patients are excluded from the study if they had been treated with therapeutic agents that deplete B or T cells during the 12 months before the first study agent administration or have evidence of persistent depletion of the targeted lymphocyte after receiving any of these agents. Lymphocyte subset analyses were included in the Time and Events Schedule for subjects who received these agents >12 months prior to study entry. However, since these analyses are not performed by the central laboratory for this study, these have been removed from the Time and Events Schedule. If a subject is being considered for enrollment who previously received treatment with an agent that depletes B or T cells > 12 months before the first study agent administration, these tests can be performed at a local laboratory to confirm that the subject does not have persistent depletion. Footnote c was deleted accordingly.	
Time and Events Schedules, Table 1 ~~Footnote c.~~	~~c. For subjects who 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 the first study agent administration.~~
Rationale: Based on general knowledge about the tests for latent TB (QuantiFERON®-TB Gold and tuberculin skin tests), it is not recommended to repeat these tests in patients with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment. Therefore, a footnote has been added to Tables 1, 2, and 3 and text was added to Section 9.4 to indicate that QuantiFERON®-TB Gold (and tuberculin skin) testing does not need to be repeated during the study for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment.	
Time and Events Schedules, Tables 1, 2, and 3 Footnote-f.	**f. Testing is not required for subjects with a history of latent TB and ongoing treatment for latent TB, or documentation of having completed adequate treatment**.

Applicable Section(s)	Description of Change(s)
9.4 Safety Evaluations, Early Detection of Active Tuberculosis	**Annual QuantiFERON®-TB Gold (and tuberculin skin) testing is not required for subjects with a history of latent TB and ongoing treatment for latent TB, or documentation of having completed adequate treatment for TB.** Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON®-TB Gold test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB Gold test is not approved/registered, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. **The QuantiFERON®-TB Gold test (and tuberculin skin test) does not need to be repeated for subjects with a history of latent TB and ongoing treatment for latent TB, or documentation of having completed adequate treatment for TB.** If the QuantiFERON®-TB Gold test result is indeterminate, the test should be repeated as outlined in Section 9.1.2. Subjects should be encouraged to return for all subsequent scheduled study visits according to the protocol.
Rationale: The inclusion criterion for subjects who require a chest x-ray prior to the first administration of study agent has been modified to reflect that this is dependent on country or local guidelines rather than country and site guidelines. Similarly, Footnote f. in Tables 1, 2, and 3, has been modified to clarify that chest x-ray screening for each subject is to be conducted per local and country regulations, not per site and country regulations.	
Time and Events Schedules, Tables 1, 2, and 3 Footnote g.	**g** ~~f.~~ Chest x-ray screening as per ~~site~~ **local** and country regulations for initiation of immunosuppressive agents in children with JIA who are at risk of TB.
4.1 Inclusion Criteria, Criterion 10.g.	g. Unless country or ~~site~~**local** guidelines do not recommend a chest radiograph as a necessary screening process prior to initiation of anti-TNFα therapies, a chest radiograph (posterior-anterior view) must have been taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current active TB or old inactive TB.
Rationale: Visit windows were added to the Time and Events Schedules (Table 1, Table 2, and Table 3) to provide clarification of timing of study visits.	
Time and Events Schedules, Table 1, Table 2, and Table 3	In Table 1, -6 weeks was added to the Screening Period. A footnote was added to Table 1, Table 2 and Table 3 to indicate that the visit window from Week 0 through Week 28 is ±3 days of the intended visit and ±1 week after Week 28.
Rationale: A column was added to the Time and Events Schedules, Tables 1, 2, and 3, to specify the assessments that should be performed at the Final Safety Follow-up Visit.	
Time and Events Schedules, Table 1, Table 2, and Table 3	A final safety follow-up visit was added to each table and the following footnote was moved to the column: **b**. ~~a.~~ All subjects who discontinue study agent administration before Week 244 but do not withdraw consent must return to the study site for a final safety visit approximately 8 weeks after the last infusion (Section 10.2)**.**

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications were made to the Time and Events Schedules (Tables 1, 2, and 3), regarding the efficacy evaluations. Specifically, morning stiffness, the Physician Global Assessment of Disease Activity and CHAQ were grouped under "JIA assessments"; the footnote regarding the timing of PRO assessments was revised to clarify that the CHAQ should be conducted prior to any tests, procedures, or other consultations for that visit; and the redundant sentence in the footnote for the CHAQ was deleted.	
Time and Events Schedules, Tables 1, 2, and 3	Joint assessments~~/morning stiffness~~ ~~Physician Global Assessment of Disease Activity~~ **JIA assessments** ~~CHAQ~~
Time and Events Schedules, Tables 1, 2, and 3 Footnote k	~~k.All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions.~~ **k. JIA assessments include the following: Physician Global Assessment of Disease Activity, Childhood Health Assessment Questionnaire (CHAQ), and duration of morning stiffness. CHAQ should be completed before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions.**
Time and Events Schedules, Tables 1, 2, and 3 Footnote l	**l.** ~~i.~~ **CHAQ** to be completed by the parent or caregiver; preferably the same parent or caregiver should complete at every visit. Subjects who are emancipated juveniles (ages 15 to <18 years) at study entry may complete the assessments themselves. ~~Ideally the same individual (eg, parent, caregiver, or subject) who completes the assessments at the start of the study should complete the assessments throughout the study~~
Rationale: Change made to footnote o in Table 1 and text in Section 9.1.3 to clarify that the additional sample for evaluation of serum golimumab concentration must be collected at least 24 hours prior to or after study agent dosing and must not be collected at a regularly scheduled visit (eg. Week 8).	
Table 1. Footnote o	**o** ~~m.~~ One additional sample for serum golimumab concentration **for population PK** will be collected from all subjects at any time between Weeks 0 and 8 other than at the time of the Week 0, Week 4, and Week 8 visits; this sample must be collected at least 24 hours prior to or after a study agent administration **and must not be collected at a regularly scheduled visit (eg. Week 8).**
9.1.3 Treatment Phase: Week 0 through Week 28	~~In addition, 1~~**One** additional sample for serum golimumab concentration **for population PK** will be collected from all subjects at any time between Weeks 0 and 8 other than at the time of the Week 0, Week 4, and Week 8 visits; this sample must be collected at least 24 hours prior to or after a study agent administration **and must not be collected at a regularly scheduled visit (eg, Week 8)**.
Rationale: Figure 1 was revised to clarify that subjects will receive MTX through Week 28 instead of Week 52; after Week 28, changes in MTX are permitted.	
3.1. Overview of Study Design	Figure 1: Schematic Overview of the Study
Rationale: To be consistent in listing the background medications that may be used by subjects during the study.	
3.1.1. Week 0 through Week 28	No changes should be made to background medications (ie, **MTX, other** DMARDs, corticosteroids, and NSAIDs) in terms of increases or decreases in dosage beyond the parameters provided in Section 8 (eg, no more than 10 mg/day prednisone or no more than 0.20 mg/kg/day, whichever is lower) and/or route of administration between Weeks 0 and 28, unless there is a safety concern (eg, elevated liver function tests), which requires changes to background medications.

Applicable Section(s)	Description of Change(s)
Rationale: Editorial changes made to be consistent in listing the background medications that may be used by subjects during the study and to clarify that changes to these medications can be made after Week 28.	
3.1.2. Week 28 through Week 52	As noted ~~beginning at~~**after** Week 28, subjects will be permitted to change**/add MTX**, **other** DMARD**s**~~,~~ ~~(including agents besides MTX), MTX~~ corticosteroid**s**, and NSAID**s** ~~use~~ as outlined in Section 8.
Rationale: To clarify when subjects will be permitted to make changes to background medications (ie, after Week 28) during the long-term extension phase of the study; editorial changes have been made to be consistent in listing the background medications that may be used by subjects during each phase of the study; "approximately" has been added to indicate when the follow-up visit should occur (ie, approximately 8 weeks after the last administration of study agent to the subject).	
3.1.3. Week 52 through Week 252 (Long-term Extension)	As noted **above** ~~beginning at~~ **after** Week 28, subjects will be permitted to change**/add MTX, other** DMARD**s**, ~~MTX,~~ corticosteroid**s,** and NSAID**s** ~~use~~, including increases or decreases in BSA-based dosing (where appropriate) for these classes of agents as outlined in Section 8. Those subjects who discontinue study agent at any time before Week 244 are also expected to return for a safety follow-up visit **approximately** 8 weeks after the last administration of study agent.
Rationale: Clarification of how the PK and PD data collected during the study will be used. There are no changes to the primary endpoints/outcomes in this study.	
3.2.3. Rationale	The Sponsor will utilize PK~~/PD~~ data generated from the proposed open-label CNTO148JIA3003 study to extrapolate to adult PK ~~and efficacy~~ data from the CNTO148ART3001 study in RA, which was the pivotal study that served as the basis for approval of ~~intravenous~~**IV** golimumab (SIMPONI ARIA/~~ and~~ SIMPONI for Intravenous Use) for adult patients with RA. **Additionally, efficacy (PD) data will be collected to explore the assessment of supportive exposure-response.**
Rationale: Clarification of the definition of a joint with active arthritis when using ACR criteria to determine the number of joints with active arthritis.	
4.1 Inclusion Criteria, Criterion 5.	Subjects must have ≥5 joints with active arthritis at screening and at Week 0 as defined by ACR criteria **(ie, a joint with either swelling, or in the absence of swelling, limited range of motion associated with pain on motion or tenderness).**
Rationale: To correct the error in the stated inclusion criterion for the serum ALT upper limit of normal for the central laboratory for enrollment of boys 10 to 18 years of age.	
4.1 Inclusion Criteria, Criterion 15.e.	Serum transaminase levels not exceeding 1.2 x the upper limit of normal for the central laboratory: – Alanine aminotransferase (ALT) o ≤41 IU/L (girls, ages 2 to 18) o ≤41 IU/L (boys, ages 2 to <10) o ≤~~42~~ **52** IU/L (boys, ages 10 to 18)

Applicable Section(s)	Description of Change(s)
Rationale: Investigators have provided feedback that requiring subjects to present documentation of immunization may limit the opportunity for this vulnerable patient population to enroll in a clinical trial and receive treatment that may provide symptomatic relief of their disease. Therefore, the inclusion criterion has been modified to permit subjects without documentation of their immunizations with an opportunity to enroll in the trial provided that the investigator has evaluated the subject to confirm that the subject is up to date with all immunizations per the current local immunization guidelines for immunocompromised subjects.	
4.1 Inclusion Criteria, Criterion 16.	Subjects must be up to date with all immunizations in agreement with current local immunization guidelines for immunosuppressed subjects ~~prior to enrollment~~ **before Week 0.**~~, and must present documentation of immunizations (eg, medical record or vaccination card)~~.
17.4 Source Documentation	• ~~Subject verified report of vaccination or vaccination card~~
Rationale: Patients with JIA treated with a biologic medication may need to switch to another medication. Ideally, the first medication would be washed out prior to starting the second medication, since overlapping these types of treatments may result in increased risk of adverse events, such as infections. The Sponsor has received consistent feedback from investigators that the biologics washout periods in the CNTO148JIA3003 study are too long and are a deterrent to enrollment. The Sponsor has carefully assessed the half-lives of biologic agents that subjects may have previously been treated and has shortened the washout periods (ie, Criterion 6, Criterion 11, and Criterion 14), while at the same time, maintaining a long enough period of time between different administered medications to protect subjects from exposure to overlapping biologics.	
4.2 Exclusion Criteria, Criterion 6.	Subject has been treated with abatacept within ~~3 months~~ **8 weeks** before first study agent administration.
4.2 Exclusion Criteria, Criterion 11.	Subject has received IL-1ra (anakinra) within ~~4 weeks~~ **1 week** of the first study agent administration.
4.2 Exclusion Criteria, Criterion 14.	Subject has received ~~etanercept,~~ adalimumab, or certolizumab pegol within 6 weeks **or has received etanercept within 4 weeks** of the first dose of study agent.
Rationale: The target patient population for this study is patients with polyarticular JIA who have active disease despite MTX treatment. Anti-TNFα agents are typically the first biologic agent of choice after conventional DMARDs, however, other biologics may be used to treat the disease. The Sponsor has received consistent feedback that the prohibited medications are a deterrent to enrollment in the study. The Sponsor has carefully assessed the half-lives of known IL-12 and IL-23 inhibitors that subjects may have been treated and has modified Exclusion Criterion 3 to exclude only those subjects who have received a IL-12 or IL-23 inhibitor within 3 months before the first administration of study agent, while at the same time, maintaining a long enough period of time between the administration of this type of medication to protect subjects from exposure to overlapping biologics and from the risk of AEs, such as infections	
4.2 Exclusion Criteria, Criterion 3.	Subject has been treated with any therapeutic agent targeted at reducing IL-12 or IL-23, including but not limited to ustekinumab and ABT-874 **within 3 months before first study agent administration**.

Applicable Section(s)	Description of Change(s)
Rationale: The target patient population for this study is patients with polyarticular JIA who have active disease despite MTX treatment. Anti-TNFα agents are typically the first biologic agent of choice after conventional DMARDs, and published JIA treatment guidelines such as the ACR guidelines (2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features) recommend switching to a second anti-TNFα agent for patients who continue to have active JIA despite treatment with the first anti-TNFα agent. Factors besides lack of efficacy (including inconvenience and pain with administration) may also result in changes in treatment. The Sponsor has received consistent feedback that excluding patients who have received >1 anti-TNFα from this study is a deterrent to enrollment. Juvenile idiopathic arthritis is a cause of serious functional disability, and the goal of treatment for pediatric patients with the disease is to gain disease control as quickly as possible. Criterion 12 and Criterion 13 were modified to exclude patients who have been previously treated with more than 2 anti-TNFα agents. This change will provide this vulnerable patient population an opportunity to enroll in a clinical trial and receive treatment that may provide symptomatic relief of their disease.	
4.2 Exclusion Criteria, Criterion 12.	Subject~~s~~ has previously been treated with more than ~~1~~**2** therapeutic agent**s** targeted at reducing TNFα, including, but not limited to, infliximab, etanercept, adalimumab, or certolizumab pegol.
4.2 Exclusion Criteria, Criterion 13.	If a subject has been previously treated with ~~1~~**an** anti-TNFα agent, the reason for discontinuation of the anti-TNFα agent cannot have been a severe or serious adverse event consistent with the class of anti-TNFα agents.
8. Prestudy and Concomitant Therapy	Subjects may have been previously treated with no more than ~~1~~**2** therapeutic agents targeted at reducing TNFα prior to study entry per ~~Inclusion~~**Exclusion** Criterion ~~19~~**12** (Section ~~4.1~~**4.2**). Subjects may not have initiated or been treated with prohibited therapeutic agents as outlined in Exclusion Criteria 1 through 20 (Section 4.2).
Rationale: Previously, patients who were treated with a JAK inhibitor were not eligible for enrollment in the study, and the Sponsor has received feedback that this is a deterrent to enrollment. Subjects with JIA treated with a biologic medication may need to switch to another medication to gain disease control to prevent serious functional disability. The Sponsor has carefully assessed the half-lives of JAK inhibitors with which subjects may have been treated and has modified Exclusion Criterion 17 to exclude only those patients who have received a JAK inhibitor within 2 weeks of the first dose of study agent, while at the same time, maintaining a long enough period of time between the administration of this type of medication to protect subjects from exposure to overlapping treatments and from the risk of AEs, such as infections.	
4.2 Exclusion Criteria, Criterion 17.	Subject **has** ~~ever~~ received a Janus Kinase (JAK) inhibitor, including but not limited to tofacitinib**, within 2 weeks of the first dose of study agent.**
Rationale: Editorial changes were made to be consistent with the time period of prohibited sperm donation and pregnancy planning.	
4.3. Prohibitions and Restrictions, #4	If sexually active with a girl of childbearing potential and has not had a vasectomy, boys must use a double barrier method of birth control during the study and for 6 months after receiving the last administration of study agent, including the LTE phase of the study. Boys must not donate sperm and must agree not to plan a pregnancy or father a child **during the study** and ~~within~~ **for** 6 months following the last administration of study agent, including the LTE phase of the study.

Applicable Section(s)	Description of Change(s)
Rationale: A clarification was made to the collection of prior medications beginning at screening and concomitant medication collection beginning with the first dose of study drug.	
8. Prestudy and Concomitant Therapy	~~Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug to 8 weeks after the last dose of study drug.~~ **Prestudy JIA medications administered before the first dose of study agent must be recorded at screening. All concomitant therapies must be recorded throughout the study beginning with the administration of the first dose of the study drug.**
Rationale: Correction of the cross-reference made in text regarding the number of anti-TNFα agents that subjects are allowed to have been treated with prior to study entry which are in Exclusion Criterion 12 and Section 4.2.	
8. Prestudy and Concomitant Therapy	If using corticosteroids or NSAIDS, subjects must have been on stable doses of these medications prior to study entry per Inclusion Criteria 8 and 9 (Section 4.1). Subjects may have been previously treated with no more than ~~1~~**2** therapeutic agents targeted at reducing TNFα prior to study entry per ~~Inclusion~~**Exclusion** Criterion ~~1~~**9**~~1~~**2** (Section ~~4.1~~**4.2**). Subjects may not have initiated or been treated with prohibited therapeutic agents as outlined in Exclusion Criteria 1 through 20 (Section 4.2).
Rationale: For consistency, changes were made to list of background medications that may be adjusted and clarification added that these adjustments are allowed after Week 28.	
8. Prestudy and Concomitant Therapy	No changes should be made to background medications (ie, MTX, **other DMARDs,** corticosteroids, and NSAIDs) in terms of increases or decreases in dosage (eg, no more than 10 mg/day prednisone or no more than 0.20 mg/kg/day, whichever is lower) and/or route of administration between Weeks 0 and 28, unless there is a safety concern (eg, elevated liver function tests), which requires changes to background medications. ~~Beginning at~~**After** Week 28, subjects will be permitted to change/add **MTX,** ~~a new~~ **other** DMARD**s,** ~~MTX,~~ corticosteroid**s** and NSAID~~s use~~**s,** including increases or decreases in dosage, changes of route of administration, or discontinuations from these classes of agents.
Rationale: To clarify that the CHAQ is the PRO assessment that should be conducted prior to any tests, procedures, or other consultations for that visit	
9.1.1. Overview	**The Childhood Health Assessment Questionnaire** ~~All visit specific PRO assessments~~ **(CHAQ)** should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions. For additional details, refer to the PRO user manual.
Rationale: Clarification of the total volume of blood to be collected from each subject through the course of the study. The total blood volume that was reflected in Table 4 is the correct total blood volume. The total volume of blood in the text has been revised accordingly.	
9.1.1. Overview	The total blood volume to be collected from each subject for the study is approximately ~~146~~**149.4** mL (Table 4). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
Rationale: Added a cross-reference to Section 4.1 which includes the TB screening requirements.	
9.1.2. Screening Phase	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 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 **(see Section 4.1)**.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification regarding permissible changes in, or discontinuations of, other anti-rheumatic medications after Week 28 in subjects who continue to receive study agent through Week 52; clarification as to when subjects who discontinue or withdraw from study participation before Week 52 should return for a final safety follow-up visit after the last infusion of study agent.	
9.1.4. Treatment Phase: **After** Week 28 through Week 52	~~Beginning at~~ **After** Week 28, ~~eligible~~ subjects will **continue to** receive 80 mg/m^2 golimumab administered as IV infusions over 30±10 minutes ~~at Week 28 and~~ q8w (±1 week) through Week 52 (Section 6.1). Subjects may also receive commercial MTX weekly at the same BSA-based dosage (10 to 30 mg/m^2 per week) as at time of study entry ~~through Week 28~~ and commercial folic acid ≥5 mg weekly or folinic acid if administered (at half the MTX dose; Section 6.2) given the day after the MTX dose, however, increases, decreases or discontinuations of MTX, **other DMARDs,** corticosteroids and/or NSAIDs are permissible after Week 28. All changes and reasons for changes for these medications need to be documented in the eCRF.
Rationale: Clarification that end of treatment assessments should be obtained approximately 8 weeks after last infusion of study agent if a subject prematurely discontinues study treatment.	
9.1.4 Treatment Phase: **After** Week 28 through Week 52, End of Treatment/Early Withdrawal	If a subject discontinues study agent before Week 52, the subject should return **approximately** 8 weeks after the last administration of study agent for a **final** safety follow-up visit (Section 10.2). If a subject withdraws from study participation before Week 52, every effort should be made to obtain end-of-treatment assessments prior to the subject's withdrawal of consent.
10.2 Discontinuation of Study Treatment	If a subject discontinues study treatment before the end of the study, assessments should be obtained **approximately** 8 weeks after the last infusion of study agent.
10.3 Withdrawal from the Study	If a subject discontinues study treatment before the end of the study, end-of-treatment assessments should be obtained **approximately** 8 weeks after the last infusion of study agent **at the final safety follow-up visit.**
Rationale: Clarification that during the long-term extension phase of the study, subjects who discontinue before the end of the study without withdrawing consent should return for final evaluations within approximately 8 weeks after the last infusion of study agent.	
9.1.5. Long-Term Extension Phase: After Week 52 through Week 252	**Subjects who discontinue study agent administration prior to Week 244 without withdrawing consent should return for a final safety follow-up visit approximately 8 weeks after their last study agent infusion (Section 10.2).**
Rationale: Clarifications on the evaluations that should be performed at the Final Safety Follow-up visit.	
10.2 Discontinuation of Study Treatment	• Safety evaluations (vital signs, review of systems, AE review, ~~study agent infusion reaction evaluation~~, TB evaluation, uveitis evaluation, and the collection of a blood sample for routine laboratory analyses and determination of the presence of ANA/anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies and antibodies to golimumab). • Efficacy evaluations (~~eg~~ joint assessment**s**, ~~pain assessment, Parent/Subject Assessment of Overall Well-Being and Physician's Global Assessments of Disease Activity, and CHAQ~~, **JIA assessments, and collection of blood sample for CRP**).

Applicable Section(s)	Description of Change(s)
Rationale: Removed the subsection for the "Parent/Subject Assessment of Overall Well-being" in Section 9.2.1.2 and included it in Section 9.2.1.4, Childhood Health Assessment Questionnaire, since the "Parent/Subject Assessment of Overall Well-being" is part of the Childhood Health Assessment Questionnaire.	
9.2.1.2. American College of Rheumatology Pediatric Response ~~Parent/Subject Assessment of Overall Wellbeing~~	~~**Parent/Subject Assessment of Overall Well-being**~~ ~~The Parent/Subject Assessment of Overall Well-being is a 10-cm visual analog scale (VAS). Parents/subjects are to complete the VAS that asks them to consider all the ways arthritis impacts their child/themselves and then indicate how the child is doing. The anchors of the scale are "very well" to "very poor". Lower scores indicate better well-being. The process for including this measure in the core set of variables for the assessment of children has been captured in the literature.~~[5] ~~Subjects who are emancipated juveniles (ages 15 to <18 years) at study entry may complete the assessments themselves. The same individual (eg, parent, caregiver, or subject) who completes the assessments at the start of the study should complete the assessments throughout the study.~~
Rationale: Correction of the number scale units for the Physician's Global Assessment of disease activity for inactive disease.	
9.2.1.2. American College of Rheumatology Pediatric Response, Inactive Disease	• Physician~~'s~~ Global Assessment of ~~d~~**D**isease ~~a~~**A**ctivity indicating no active disease (<~~0.5 cm~~ **5 mm**)
Rationale: Correction of the number scale units for the visual analog scale (VAS) used in the Physician Global Assessment of Disease Activity.	
9.2.1.3. Physician Global Assessment of Disease Activity	The Physician Global Assessment of ~~d~~**D**isease ~~a~~**A**ctivity is a ~~10 cm~~**100 mm** VAS.
Rationale: Clarification of the construct and ordinal scores to be used to assess functioning and task performance with the Childhood Health Assessment Questionnaire (CHAQ); correction of the number scale units for the VAS used to assess the subject's pain and overall well-being; paragraph 1 of "Parent/Subject Assessment of Overall Well-being" was removed from Section 9.2.1.2 and was included in Section 9.2.1.4 since this assessment is a component of the CHAQ; paragraph 3 of Section 9.2.1.4, Childhood Health Assessment Questionnaire, was deleted because it was redundant to paragraph 2 which is now part of the subsection, "Parent/Subject Assessment of Overall Well-being."	
9.2.1.4. Childhood Health Assessment Questionnaire Parent/Subject Assessment of Pain Parent/Subject Assessment of Overall Well-being	The functional status of subjects will be assessed by the ~~Childhood Health Assessment Questionnaire (~~CHAQ~~)~~.[19] Parents/subjects **will** ~~are to~~ complete this **questionnaire** ~~20-question instrument~~ **to** ~~that~~ assess~~es~~ the degree of difficulty the **subject** ~~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~~ **as** 0~~, indicating "~~ **(W**~~W~~**without any** ~~ANY~~ difficulty)~~"~~, **1 (with some difficulty)**, **2 (with much difficulty)**, ~~to~~ 3 **(unable to do)**, **or 4 (not applicable).** ~~indicating "With MUCH Difficulty" 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~~. **Lower scores are indicative of improved functioning and task performance in specific functional areas.**

Applicable Section(s)	Description of Change(s)
	Additionally, the CHAQ includes 2 VAS questions—one used to assess the subject's level of pain, and one used to assess the subject's overall well-being. Properties of the **CHAQ**~~measure~~ have been evaluated and its validity assessed.[19] The CHAQ has been shown to be responsive to disease change.[19] A decrease of 0.188 has been determined to be a meaningful clinical improvement.[1] ~~Subjects who are emancipated juveniles (ages 15 to <18 years) at study entry may complete the assessments themselves. The same individual (eg, parent, caregiver, or subject) who completes the assessments at the start of the study should complete the assessments throughout the study.~~ **Parent/Subject Assessment of Pain** ~~Visual Analog Scale for p~~**P**ain will be assessed as average pain **experienced by the subject** during the past week **using** ~~on~~ a VAS~~. The~~ scale **that** ranges from "no pain" (0 **mm**~~cm~~) to "very severe pain" (10**0 mm**~~cm~~). This assessment should be completed by the parents **(caregiver)**/subjects prior to the tender and swollen joint examination. **Parent/Subject Assessment of Overall Well-being** **The Parent/Subject Assessment of Overall Well-being is a 0-100 mm VAS. Parents/subjects will complete the VAS that asks them to consider all the ways arthritis impacts their child/themselves and then indicate how the subject is doing. The anchors of the scale are "very well" (0 mm) to "very poor (100 mm)". Lower scores indicate better well-being. The process for including this measure in the core set of variables for the assessment of children has been captured in the literature.[5]** **Subjects who are emancipated juveniles (ages 15 to <18 years) at study entry may complete all the CHAQ assessments themselves. Preferably, the same individual (eg, parent, caregiver, or subject) who completes the assessments at the start of the study should complete the assessments throughout the study.**
Rationale: To align the text in Section 9.3.4 regarding the evaluation of samples for antibodies to golimumab for consistency with the Time and Events Schedule (Tables 1, 2, and 3).	
9.3.4. Immunogenicity Assessments (Antibodies to Golimumab)	Antibodies to golimumab will be evaluated in serum samples collected from all subjects according to the Time and Events Schedule (ie, Weeks 0, **4, 8,** 12, 28, 52, 100, 148, 196, and 244).
Rationale: Editorial changes only regarding subjects with severe infusion reactions that involve bronchospasms with wheezing and/or dyspnea.	
9.4 Safety Evaluations, Allergic Reactions	Subjects with severe reactions following an infusion ~~resulting~~ **that result** in bronchospasm~~s~~ with wheezing and/or dyspnea ~~requiring~~ **and require** ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm mercury (Hg), will not be permitted to receive any additional study agent infusions. In the case of such reactions, appropriate medical treatment should be administered.

Applicable Section(s)	Description of Change(s)
Rationale: Editorial changes made to clarify that the DRC charter defines how the DRC will review safety. The DRC charter does not define the Steering Committee's review of safety data.	
11.9. Data Monitoring Committee	Unblinded safety data will be routinely evaluated by the study's medical monitor and an internal Data Review Committee **as defined in the DRC charter. In addition, the data may be reviewed by** ~~as well as~~ **the Steering Committee** ~~as defined in DRC charter~~**.**
Rationale: Addition of language to clarify that events meeting the definition of a serious adverse event will be reported, as well as those events that are anticipated as related to the progression of the disease under study.	
12.3.1. All Adverse Events	All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. **Anticipated events will be recorded and reported as described in Attachment 4.**
Rationale: The Parent/Subject Assessment of Overall Well-being and the VAS for pain were removed from the list of assessments that are recorded into an electronic device because these are part of the CHAQ. Duration of morning stiffness was added as one of the assessments that are recorded into an electronic device. Text was added to clarify that these assessments should be not recorded on paper first.	
17.4. Source Documentation	• The following parent/subject- and investigator-completed scales and assessments designated by the Sponsor will be recorded **directly** into an electronic device and will be considered source data: joint assessments, CHAQ, ~~parent/subject assessment of overall well-being,~~ ~~p~~**P**hysician ~~g~~**G**lobal ~~a~~**A**ssessment of ~~d~~**D**isease ~~a~~**A**ctivity, **and duration of morning stiffness**.~~and visual analog scale for pain.~~ **These assessments should not be recorded on paper first**.
Rationale: Addition of language to include events that meet the definition of a serious adverse event, and anticipated events which may occur during the study as part of the safety analyses for the study; clarification of which anticipated events (drug or disease related) are to be captured in the Case Report Form (CRF), reported to the sponsor (serious or non-serious), may or may not be exempt for reporting to Health Authorities, the role of the Anticipated Event Review Committee, and analysis of anticipated events for safety evaluation and monitoring.	
ATTACHMENT 4 ANTICIPATED EVENTS	**An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.** **For the purposes of this study, the following events will be considered anticipated events:** • **Events related to the progression of the disease under study.** **These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.**

Applicable Section(s)	Description of Change(s)
	Anticipated Event Review Committee (ARC) **An ARC will be established to perform reviews of pre-specified events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.** **Statistical Analysis** **Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated event will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).**
Rationale: Minor errors were noted and corrected.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-1 (12 August 2014)

The overall reason for the amendment: The protocol has been revised to add safety information from golimumab studies in adults and pediatric patients and to address recommendations from PRINTO and PRCSG.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of approved therapies for pJIA has been made.	
Section 1.1.1 Juvenile Idiopathic Arthritis	~~Elevated levels of TNFα receptors have been found in the serum of JIA patients with systemic onset disease, and these levels correlate with disease state.~~ Currently approved biologic therapies for the treatment of polyarticular JIA (pJIA) include etanercept, adalimumab, abatacept, and tocilizumab; **canakinumab has been approved for systemic JIA.**
Rationale: Editorial changes were made.	
Section 1.1.2 Golimumab Clinical Studies in Rheumatoid Arthritis and Juvenile Idiopathic Arthritis	The results of the CNTO148ART3001 study of IV golimumab in adults ~~CNTO148JIA3001 study of SC golimumab in subjects with JIA~~ and the results of the CNTO148JIA3001 study of SC golimumab in subjects with JIA ~~CNTO148ART3001 study of IV golimumab in adults~~ are described below.
Rationale: Clarification of AEs and SAEs has been made	
Section 1.1.2.1 Intravenous Golimumab in Adult Rheumatoid Arthritis	**Through Week 16 (the placebo-controlled period prior to early escape) in CNTO148ART3001, 43.7% of subjects in the placebo group and 47.3% in the golimumab group had an AE; the highest incidence of AEs was in the infections and infestations SOC, 20.8% and 24.3% in the placebo and golimumab groups, respectively with upper respiratory tract infection (URTI) being the most frequently reported AE (5.6% and 5.1% in the placebo and golimumab groups, respectively). Through Week 112, 79.1% of golimumab-treated subjects had an AE; the highest incidence of AEs was in the infections and infestations SOC (50.5%) and URTI was the most frequently reported AE (11.5%).**

Applicable Section(s)	Description of Change(s)
	~~The proportion of subjects who reported an AE was comparable between the golimumab + MTX and placebo + MTX groups through Week 16 (47.3% compared with 43.7%, respectively) and Week 24 (52.9% compared with 49.2%, respectively). The most commonly reported system organ class AEs through Week 16 were Infections and infestations (24.3% and 20.8% in the golimumab + MTX and placebo + MTX groups, respectively), and were predominantly upper respiratory tract infection, urinary tract infection, and nasopharyngitis.~~ **Through Week 16 in CNTO148ART3001, 1.0% of subjects in the placebo group and 3.8% of subjects in the golimumab group had an SAE. The incidence of SAEs within each SOC was < 1.0%, and no SAE occurred in more than 1 subject. Through Week 112, 18.2% of golimumab-treated subjects had an SAE; the highest incidence of SAEs occurred in the infections and infestations SOC (5.5%) and musculoskeletal and connective tissue disorders SOC (3.4%) and the most frequently reported SAE was RA (2.1%).** ~~Serious adverse events (SAEs) through Week 24 in the golimumab + MTX group were higher (4.1%) compared with the placebo + MTX group (2.0%) and were predominantly serious infections (1.0% in the golimumab + MTX group and 0.0% in the placebo + MTX group).~~ ~~One subject in the placebo + MTX group died through Week 24 (presumed stroke due to hypertensive crisis; no autopsy performed).~~ **Through Week 24, 1 patient died in the CNTO148ART3001 study, this subject was randomized to treatment with placebo + MTX, had never received golimumab, and died of a presumed cerebrovascular accident (stroke). Through Week 112, an additional 5 subjects died in the CNTO148ART3001 study. Two subjects randomized to treatment with placebo + MTX died, both after switching to golimumab 2 mg/kg + MTX; cause of death was sudden death (n=1) and complications of severe dehydration, *Clostridium difficile* colitis, and atrial fibrillation (n=1). Three subjects randomized to treatment with 2 mg/kg golimumab + MTX died in the study; reported cause of death was acute abdominal syndrome (later diagnosed as peritoneal tuberculosis [TB], n=1), presumed myocardial infarction (MI, n=1), and septic shock secondary to a pyogenic lung abscess due to *Acinetobacter baumanii* (n=1).** **No malignancies were reported through Week 16 in CNTO148ART3001. Though not included in the tables which include only treatment-emergent events or the calculations of malignancy rates, there was 1 case of nontreatment-emergent lung adenocarcinoma reported in the placebo + MTX group before Week 16. Through the placebo-controlled period (Week 24), 1 malignancy (breast cancer) was reported in the golimumab group. Through Week 112, 5 additional malignancies basal cell carcinoma, chronic lymphocytic leukemia in a subject with a family history of chronic lymphocytic leukemia, cervix carcinoma in situ, Bowen's Disease and basal cell carcinoma) were reported. No lymphomas were reported through Week 112.**

Applicable Section(s)	Description of Change(s)
	Through Week 16 (the placebo-controlled period prior to early escape) in CNTO148ART3001, 43.7% of subjects in the placebo group and 47.3% in the golimumab group had an AE; the highest incidence of AEs was in the infections and infestations SOC, 20.8% and 24.3% in the placebo and golimumab groups, respectively with upper respiratory tract infection (URTI) being the most frequently reported AE (5.6% and 5.1% in the placebo and golimumab groups, respectively). Through Week 112, 79.1% of golimumab-treated subjects had an AE; the highest incidence of AEs was in the infections and infestations SOC (50.5%) and URTI was the most frequently reported AE (11.5%). ~~The proportion of subjects who reported an AE was comparable between the golimumab + MTX and placebo + MTX groups through Week 16 (47.3% compared with 43.7%, respectively) and Week 24 (52.9% compared with 49.2%, respectively). The most commonly reported system organ class AEs through Week 16 were Infections and infestations (24.3% and 20.8% in the golimumab + MTX and placebo + MTX groups, respectively), and were predominantly upper respiratory tract infection, urinary tract infection, and nasopharyngitis.~~ ~~Serious adverse events (SAEs) through Week 24 in the golimumab + MTX group were higher (4.1%) compared with the placebo + MTX group (2.0%) and were predominantly serious infections (1.0% in the golimumab + MTX group and 0.0% in the placebo + MTX group).~~ **No malignancies were reported through Week 16 in study CNTO148ART3001. There was 1 case of non-treatment-emergent lung adenocarcinoma reported in the placebo + MTX group prior to receiving study agent. Through the placebo-controlled period (Week 24), 1 malignancy (breast cancer) was reported in the golimumab group. Through Week 112, 5 additional malignancies were reported, including basal cell carcinoma, chronic lymphocytic leukemia in a subject with a family history of chronic lymphocytic leukemia, cervix carcinoma in situ, Bowen's Disease and basal cell carcinoma. No lymphomas were reported through Week 112.** Through Week 16 in CNTO148ART3001, 0.5% of subjects in the placebo group and 2.5% of subjects in the golimumab group had an infusion reaction. Through Week 112, 3.9% of golimumab-treated subjects had an infusion reaction and 0.4% of infusions were complicated by infusion reactions. It should be noted that all placebo infusions consisted of 0.9% normal saline alone rather than a true matched placebo. No serious infusion reactions requiring study agent discontinuation ~~or anaphylaxis~~ were noted. **There was a case of anaphylaxis which was not associated with study drug.** **For the most comprehensive nonclinical and clinical information regarding Simponi (golimumab), refer to the latest version of the Investigator's Brochure and Addenda for Simponi (golimumab).**

Applicable Section(s)	Description of Change(s)
	The median peak serum golimumab concentration (ie, post-infusion golimumab concentration) of 41.56 µg/mL was observed at Week 4 following IV administration of 2 mg/kg golimumab at Week 0, Week 4, followed by q8w (**±1 week**) administration. This peak is higher than that reported for SC golimumab administration of 50 mg every 4 weeks (q4w). The median trough serum golimumab concentration in subjects receiving IV golimumab at 2 mg/kg q8w with MTX was 0.28 µg/mL at Week 12 and 0.22 µg/mL at Week 20; these levels are similar to those reported with SC golimumab 50 mg. Overall exposure to golimumab in approximately 3 times that for SC golimumab 50 mg over a similar period of exposure.
Rationale: Major endpoints were not met and the study has been terminated and duly noted. Additionally, AEs have been described.	
Section 1.1.2.2 Subcutaneous Golimumab in Juvenile Idiopathic Arthritis	The baseline disease characteristics of the 173 enrolled subjects constituted a population with moderate to severe JIA comparable with other clinical studies of anti-TNFα agents in pJIA, with the exception of numerically lower mean and median CRP/**ESR** levels in CNTO148JIA3001. The study did not meet its primary and major secondary endpoints as the proportion of subjects who were **JIA** ACR 30 responders at Week 16 and did not experience a flare of disease between Week 16 and Week 48 was not significantly different in subjects randomized to continued golimumab treatment between Weeks 16 and 48 as compared with subjects randomized to receive placebo between Weeks 16 and 48 (59% versus 52.6%, p=0.41). All sensitivity analyses **and major secondary endpoints** demonstrated the lack of statistically significant differences between treatment groups. **The Sponsor terminated the long-term extension of the study early as pre-specified efficacy endpoints were not met.** With regards to immunogenicity, 40.1% of subjects developed antibodies to golimumab using the recently developed drug tolerant immunoassay analyses. The new drug tolerant immunoassay is more sensitive compared with assays used previously in adult golimumab RA studies and allows the detection of antibodies to golimumab despite detectable serum golimumab levels. Among subjects who were randomized and remained on golimumab 30 mg/m^2 SC + MTX, 30.8% developed antibodies to golimumab; antibody titers tended to be low. When evaluating the effects of immunogenicity on PK, efficacy, and safety, it was found that positive anti-golimumab antibody status ~~significantly~~ decreased steady-state trough golimumab concentrations when the titer levels were >1:100. However, the effect of antibodies on efficacy was less sensitive, requiring higher titers >1:1000 in order to correlate with apparent reductions in efficacy. Since only approximately 5% of subjects with JIA developed anti-golimumab antibodies with titers >**1:**1000, it was determined that immunogenicity was not a contributing factor to ~~not achieving~~ **lack of achievement of** the primary endpoint in CNTO148JIA3001. ~~Lastly,~~ **Additionally,** positive anti-golimumab antibody status did not appear to be associated with a higher incidence of injection-site reactions.

Applicable Section(s)	Description of Change(s)
	The proportion of subjects who reported an AE through Week 48 was 87.9%. The most commonly reported system organ class of AEs was Infections and infestations (67.1%), and were predominantly upper respiratory tract infections and nasopharyngitis. There was no marked difference in AEs reported between Week 16 and Week 48 for subjects randomized to placebo (82.9%) and those randomized to continued golimumab treatment (78.2%), **however it needs to be noted that all subjects in randomized withdrawal portion of the study were exposed to golimumab for 16 weeks before re-randomization.** Serious adverse events were reported by 13.3% of subjects. The most commonly reported SAE was worsening of JIA (6.4%). Serious infections were reported in 2.9% of subjects (pneumonia, urinary tract infection, herpes zoster, upper respiratory tract infection, and pyelonephritis), and there were no deaths, malignancies, or demyelination events through Week 48. There were no reports of active TB and no serious opportunistic infections. Through Week 48, the number of subjects with abnormal ALT measurements (**and no concomitant treatment for latent TB, which may affect LFTs**) ~~and no TB prophylaxis~~ was 29.5% (51/167), 39 of the 51 subjects had elevations < 3 X ULN. **There were two subjects with ALT elevation to > 8 X ULN but neither subject met the criteria for Hy's Law consistent with hepatotoxicity. Subjects were not receiving TB prophylaxis; one of the subjects had baseline ALT which was already abnormal. All subjects with LFT abnormalities were managed conservatively with changes in MTX dosing but one subject was discontinued for elevated LFTs.** **The incidence of injections with injection-site reactions through Week 48 was 0.8%; there was one SAE report of serum sickness-like reaction in a patient randomized to placebo who resumed golimumab treatment.** Although the CNTO148JIA3001 study did not meet its endpoints, when JIA ACR response rates were ~~presented~~ **analyzed** as observed data through Week 48 (using Week 0 as baseline and comparing drug/placebo effect at each visit through Week 48) the study showed the potential for ~~significant~~ efficacy that could be attained with SC golimumab in children with pJIA. Therefore, it lends support to the study of IV golimumab in subjects with pJIA who have an inadequate response to MTX.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of the primary objective has been made. Additionally, clarification on the prior use of agents has also been made.	
Section 1.2 Overall Rationale for the Study	The primary objective of this study is to characterize the PK of IV golimumab in pJIA, along with ~~simultaneous~~ evaluations of the safety and efficacy (r~~eflected in proportion of subjects with JADAS minimal disease activity at Week 28~~) of IV golimumab in these subjects. This study will also include subjects with multiple subtypes of JIA, including juvenile PsA, as well as subjects with prior anti-TNFα experience (up to ~~20~~ **30**% of the study population). The study is designed to obtain PK data in response to BSA-based (80 mg/m^2, which is expected to be equivalent to the 2 mg/kg dose in adult RA patients weighing 70 kg) IV golimumab for subjects with pJIA who have inadequate response to MTX treatment **as well as prior treatment with non-steroidal anti- inflammatory agents, corticosteroids and/or anti-TNFα agents,** with the intent to demonstrate its similarity to the response seen with weight-based (2 mg/kg) doses of IV golimumab in adult RA subjects who have inadequate response to MTX treatment. The 80 mg/m^2 dose for subjects with pJIA is based on the 2 mg/kg dose studied in CNTO148ART3001 in the adult RA population.
Rationale: Clarification of the primary objective has been made	
Section 2.1 Objectives Primary Objective	The primary objective of this study is to assess the PK ~~and JADAS minimal activity scores~~ following intravenously administered golimumab in subjects (ages 2 to less than 18 years) with pJIA manifested by ≥5 joints with active arthritis and CRP of ≥0.1 mg/dL despite MTX therapy for ≥3 months **at Week 28.**

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications of duration of disease for enrollment in study and maximum single dose have been made.	
Section 3.1 Overview of Study Design	This is a Phase 3, open-label, single-arm, multicenter study to evaluate the PK, safety, and efficacy of IV golimumab in subjects with active pJIA despite current treatment with MTX. The study population will be comprised of subjects with pJIA receiving MTX, ages 2 to less than 18 years, with at least a ~~6~~ **3**-month history of pJIA, and active arthritis in ≥5 joints. Approximately 120 subjects will be enrolled at Week 0 to ensure that approximately 100 subjects remain in the study at Week 52. Enrollment patterns are expected to yield a subject population of approximately 10% aged 2 to up to 6 years, approximately 20% aged 6 to up to 12 years, and approximately 70% aged 12 to less than 18 years. All subjects will receive 80 mg/m^2 golimumab (**maximum single dose 240 mg**) as an IV infusion given over 30±10 minutes at Weeks 0, 4, and every 8 weeks (q8w; ± **3 days**) through Week 28 and then q8w (± **1 week**) thereafter through Week 244. Body surface area will be calculated based on the subject's height and body weight measured at each visit, and the BSA-based dose of golimumab will be adjusted as needed to maintain the dose at 80 mg/m^2. Subjects will also receive commercial MTX weekly at the same BSA-based dosage (10 to 30 mg/m^2 per week of MTX, with a minimum of 15 mg in subjects with BSA ≥1.67 m^2) as at time of study entry through Week **28** as outlined in Section 6.2. Every effort should be made to maintain subjects at a dose of 80 mg/m^2 **of golimumab** based upon BSA, and decreases below or increases above 80 mg/m^2 or shortening of the dosing interval (eg, from 8 weeks to 6 weeks) will not be permitted at any visit. **The schematic overview of the study (Figure 1) has been revised to show the screening period (-6 Weeks to Week 0) and safety follow-up period (Week 244 to Week 252).**
Rationale: This subsection has been reorganized [Week 0 through Week 58 28] for clarity and therefore the deletion.	
Section 3.1.1 Week 0 through Week 28	Through Week 28 subjects will be monitored and disease activity and safety will be assessed at the investigative site every 4 weeks. ~~From Week 28 through Week 52, subjects will be monitored and disease activity and safety will be assessed at the investigative site every 8 weeks.~~ After all subjects complete the Week 28 visit, the database will be locked to assess PK, safety and efficacy. An additional safety, efficacy, and PK database lock is currently planned for Week 52. **Final data base lock will be performed at Week 252.** No changes should be made to background medications (ie, DMARDs, corticosteroids, and NSAIDs) in terms of increases or decreases in ~~BSA based~~ dosage beyond the parameters provided in Section 8 (eg, no more than 10 mg/**day** prednisone or no more than 0.20 mg/kg/day, whichever is lower) and/or route of administration between Weeks 0 and 28, unless there is a safety concern (eg, elevated liver function tests), which requires changes to background medications.

Applicable Section(s)	Description of Change(s)
Rationale: An additional subsection has been introduced as subsection 3.1.1 was re-organized for clarity	
Section 3.1.2 Week 28 through Week 52	**From Week 28 through Week 52, infusions will continue to be performed every 8 weeks (± 1 week), however subjects will be actively monitored at the investigative site and disease activity and safety will be assessed at the investigative site every 8 weeks rather than every 4 weeks as between Weeks 0 and 28. As noted beginning at Week 28, subjects will be permitted to change DMARD (including agents besides MTX), MTX, corticosteroid, and NSAID use as outlined in Section 8.**
Rationale: Clarifications of the availability of study agent have been made	
Section 3.1.3 Week 52 through Week 252 (Long-term extension)	During the long-term extension, all subjects will continue to receive golimumab q8w (± **1 week)** through Week 244. **For children who have completed the full trial period of 252 weeks and for whom drug is proven beneficial but the drug is not commercially available for JIA indication (or patient does not qualify for insurance to pay for drug) IV golimumab will continue to be provided by the Sponsor.** Between Week 52 and Week 252, disease activity will be monitored and assessed, and documented in the CRF every 16 weeks; infusions and safety measurements will be done every 8 weeks at the investigative site. As noted beginning at Week **28**, subjects will be permitted to change DMARD, MTX, corticosteroid, and NSAID use, including increases or decreases in BSA-based dosing (where appropriate) for these classes of agents as outlined in Section 8.
Rationale: Clarification of the visit window through Week 24 has been made	
Section 3.2.2 Dose Selection	~~In the CNTO148JIA3001 study, BSA based dosage of SC golimumab was utilized. After subjects with pJIA received golimumab 30 mg/m^2 SC q4w, median steady state trough golimumab levels were similar across different age groups (median 0.73 µg/mL to 1.25 µg/mL at Week 48). The median steady state concentrations in subjects with pJIA were also similar to or higher than those seen in adult subjects with RA who received golimumab 50 mg SC q4w (0.82 µg/mL at Week 76 and 1.17 µg/mL at Week 104 in C0524T06 using the same MSD ECLIA assay); both study populations were receiving concomitant MTX. The study results confirmed that BSA based doses achieved fairly even drug exposure in pediatric subjects at different ages and were comparable to the adult exposure.~~ Data from the Phase 3 IV study in adults with RA (CNTO148ART3001) through 24 weeks have shown that golimumab 2 mg/kg at Week 0, Week 4, and q8w **(±1 week)** thereafter is the optimal dose regimen for the treatment of RA in most adults. For a child, golimumab 80 mg/m^2 (2 mg/kg/1.73 m^2) would be approximately equivalent to 2 mg/kg for an adult subject weighing 70 kg (with a BSA of 1.73 m^2). Thus, in the current study (CNTO148JIA3003), a dose of golimumab 80 mg/m^2 has been chosen to evaluate the safety and efficacy of golimumab in the JIA population.
Rationale: Clarification of route of administration for Simponi Aria	
Section 3.2.3 Rationale	The Sponsor will utilize PK/PD data generated from the proposed open-label CNTO148JIA3003 study to extrapolate to adult PK and efficacy data from the CNTO148ART3001 study in RA, which was the pivotal study that served as the basis for approval of **intravenous golimumab** (SIMPONI ARIA and SIMPONI for Intravenous Use) for adult patients with RA.

Applicable Section(s)	Description of Change(s)
Rationale: Several inclusion criteria were revised per PRINTO/PRCSG recommendations	
Section 4.1 Inclusion criteria #1	~~Pediatric~~ Subjects **must be age** 2 years to less than 18 years with a body weight >15 kg at the time of **screening and at Week 0.**
Section 4.1 Inclusion criteria #3	Active JIA of one of the following subtypes: a. Rheumatoid factor positive or negative pJIA for ≥**3** months **prior to screening**, or b. Systemic JIA with no systemic symptoms **for ≥3 months** but with polyarthritis for ≥**3** months **prior to screening**, or c. Extended oligoarticular JIA ≥**3** months **prior to screening**, or d. Polyarticular juvenile psoriatic arthritis ≥**3** months **prior to screening**, or, e. Enthesitis related arthritis ≥**3** months **prior to screening**.
Inclusion criteria #4	**Failure or inadequate response to at least a 3-month course of MTX before screening.**
Inclusion criteria #7	Subjects must have active JIA despite current use of oral, intramuscular or subcutaneous MTX (for ≥3 months before screening **and on a stable dose for 4 weeks as noted in Section 8**) 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 MTX for ≥4 weeks before screening. Subjects with BSA ≥1.67 m^2 must receive a minimum of 15 mg/week of MTX unless documented country or site regulations prohibit use of 15 mg of MTX per week in subjects with BSA ≥1.67 m^2. In situations where there is documented intolerance of doses >10 mg/m^2 **weekly** or ~~for subjects with BSA ≥1.67 m^2 who do not tolerate~~ 15 mg/week **for subjects with BSA ≥1.67 m^2**, subjects may be entered into the trial on a lower dose of MTX.
Inclusion criteria #8	If using corticosteroids, must be on a stable dose of ≤10 mg/**day** prednisone equivalent or 0.20 mg/kg/day (whichever is lower) for ≥ **2** weeks before first administration of study agent (~~In extreme circumstances, a subject may receive <0.20 mg/kg/day if there is documented intolerance or AEs due to higher doses of corticosteroids~~). If currently not using corticosteroids, the subject must have not received corticosteroids for at least **2** weeks before the first dose administration. Subjects with systemic onset JIA **but without systemic symptoms** must be on a stable dose of corticosteroids for **at least** 3 days **screening.**
Inclusion criteria #9	If using NSAIDs, must be on a stable dose for ≥2 weeks before ~~the first administration of study agent~~ **screening**. If not currently using NSAIDs, must not have taken them for at least 2 weeks before ~~the first administration of study agent~~ **screening**.
Rationale: Several exclusion criteria were revised per PRINTO/PRCSG recommendations	
Section 4.2 Exclusion criteria #1	Subject has initiated DMARDs and/or immunosuppressive therapy (~~with the exception of MTX~~) within 4 weeks prior to first study agent administration.

Applicable Section(s)	Description of Change(s)
Exclusion criteria #9	Subject has received or is expected to receive any live viral or live bacterial vaccinations from **3** months before first study agent administration and up to **3** months after the last study agent administration.
Exclusion criteria #10	Subject has had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening **or is planned to receive BCG vaccination within 12 months following last study drug administration.**
Exclusion criteria #14	Subject has received ~~infliximab,~~ etanercept, adalimumab, or certolizumab pegol within 6 weeks of the first dose of study agent.
Exclusion criteria #15	Subject has received **infliximab or** tocilizumab within 8 weeks of the first administration of study agent.
Exclusion criteria #18	**Subject has received canakinumab within prior 4 months prior to first study dose administration.**
Exclusion criteria #31	Subject has 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 **not consistent with pJIA or systemic onset JIA without systemic symptoms.**
Exclusion criteria #35	Subject has a ~~past~~ history of macrophage activation syndrome.
Exclusion criteria #45	**Active uveitis within 3 months prior to screening**
Exclusion criteria #46	**Subject with BSA >3.0 m^2**
Rationale: Clarification of prohibitions and restrictions has been made.	
Section 4.3 Prohibitions and Restrictions #1	Subjects must not receive a live virus or live bacterial vaccination **3 months prior to screening,** during the study, or within 3 months after the last administration of study agent.
Prohibitions and Restrictions #2	Subjects must not receive a BCG vaccination for 12 months before ~~the study~~ **screening**, during the study or within 12 months after the last administration of study agent.
Prohibitions and Restrictions #5	Intramuscular administration of corticosteroids for the treatment of pJIA is not allowed during the study. Corticosteroids administered by bronchial or nasal inhalation for treatment of conditions other than pJIA may be given as needed throughout the course of the study. **For additional details, see Section 8.**
Prohibitions and Restrictions #6	**Subjects must not receive investigational drugs, other immunosuppressants (such as, but not exclusively, cyclophosphamide), or other biologics for pJIA during the study.**
Rationale: Clarification of the visit windows through Week 24 and through Week 244 has been made	
Section 5 Treatment Allocation and Blinding	This is an open-label study. Beginning at Week 0, all subjects will receive golimumab 80 mg/m^2 at Week 0, Week 4 and q8w (**± 3 days**) through Week 28 and q8w (**± 1 week**) up to Week 244.

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications on the maximum single dose have been made.	
Section 6.1 Dosage and Administration Golimumab	The study will have 1 active treatment group and all subjects will receive 80 mg/m^2 golimumab (**maximum single dose 240 mg**) IV infusions at Week 0, Week 4, and q8w **(±3 days) through Week 28 and q8w (±1 week)** thereafter through Week 244. The golimumab infusions will be prepared by a pharmacist under sterile conditions using golimumab 50 mg/4 mL liquid in vials and a 100 mL infusion bag of 0.9% saline. Subjects will receive 80 mg/m^2 golimumab IV infusions over 30±10 minutes. Infusions may be slowed down for evidence of infusion reactions as deemed appropriate by the investigator, and all changes in the infusion rate should be recorded in the CRF. Body surface area will be calculated at each visit and the dose of golimumab will be adjusted as needed to maintain the dose at 80 mg/m^2. Body surface area will be calculated using the Mosteller equation: BSA (m^2) = ([height (cm) x weight (kg)]/3600)$^{1/2}$. **For additional details, see the Site IP Manual.**
Rationale: Clarification on the use of the MTX has been made.	
Section 6.2 Dosage and Administration Methotrexate	Subjects will receive commercial MTX at the same BSA-based dose (10 to 30 mg/m^2 per week of MTX) as at time of study entry through Week **28**. ~~Body surface area will be calculated at each visit and the dose of MTX will be adjusted as needed to maintain the dose at the same mg/m^2 per week dose as the subject was receiving at time of study entry.~~ **Absolute dose should remain stable from baseline through Week 28.** Every effort should be made to ensure that subjects remain on the same BSA-based dose and route of administration of MTX through the Week **28** safety and efficacy database lock, unless intolerance or AEs due to MTX occur (Section 8). Guidelines for adjusting MTX dosage in the event of MTX toxicity are provided in the Trial Center File. Subjects will also receive **a total dose of** commercial folic acid ≥5 mg weekly or folinic acid (at half the MTX dose) given the day after the weekly MTX dose. **In children < 12 years of age, the administration of folic acid or folinic acid will be at the discretion of the physician.**

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications on the use of corticosteroids during participation in this study have been made	
Section 8 Prestudy and Concomitant Therapy	All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, and acupuncture ~~special diets, exercise regimens~~) different from the study drug must be recorded in the CRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study. If using corticosteroids or NSAIDs, subjects must have been on stable doses of these medications prior to study entry per Inclusion Criteria 8 and 9 (Section 4.1). Subjects may have been previously treated with no more than 1 therapeutic agent targeted at reducing TNFα prior to study entry per Inclusion Criterion 19 (Section 4.1). Subjects may not have initiated or been treated with prohibited therapeutic agents as outlined in Exclusion Criteria 1 through **20** (Section 4.2). 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. For exceptions to this rule, see Inclusion Criterion **7**. Subjects (**with the exception of those with sJIA**) receiving corticosteroids at the time of study entry must have been receiving a stable dose for ≥**2** weeks **before screening**, and that dose must have been ≤10 mg/**day** prednisone or prednisone equivalent or 0.20 mg/kg/day (whichever is lower). **Subjects with systemic onset JIA but without systemic symptoms for ≥3 months must be on stable corticosteroids for 3 days before screening and not exhibit systemic symptoms.** If receiving NSAID therapy, the dose must have been stable for ≥2 weeks before screening. No changes should be made to background medications (ie, ~~DMARDs,~~ MTX, corticosteroids, and NSAIDs) in terms of increases or decreases in ~~BSA-based~~ dosage (eg, no more than 10 mg/**day** prednisone or no more than 0.20 mg/kg/day, whichever is lower) and/or route of administration between Weeks 0 and **28**, unless there is a safety concern (eg, elevated liver function tests), which requires changes to background medications. Beginning at Week **28**, subjects will be permitted to change/**add new** DMARD, MTX, corticosteroid, and NSAID use, including increases **or decreases in dosage, changes of route of administration, or discontinuations** ~~in BSA-based dosage (where appropriate~~) for these classes of agents. Subjects may receive intra-articular injections of a corticosteroid, if clinically required, during the study **up to Week 52**. However, the number of intra-articular injections should be limited to 2 over any 24-week period. That is, if a subject has received 2 intra-articular injections and more than 24 weeks has elapsed, the subject may receive up to 2 additional intra-articular injections over another 24-week period. **After Week 52, the number of injected joints is no longer limited to 2 injections per 24 weeks.** 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).

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications regarding visit-specific PRO assessments have been made.	
Section 9.1.1 Overview	The Time and Events Schedules summarize the frequency and timing of efficacy, PK, immunogenicity, and safety measurements applicable to this study (Table 1, Table 2, and Table 3). **All scheduled study visits should occur within ±3 days of the intended visit through Week 28 and ± 1 week from Week 28 through Week 244. If the recommended acceptable window cannot be observed, the Sponsor must be contacted before scheduling a visit.** **All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions. For additional details, refer to the PRO user manual.** The total blood volume to be collected from each subject for the study is approximately **146.4 mL** (Table 4). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 4: Approximate Volume of Blood to be Collected From Each Subject Through Week 252

Type of Sample	Approximate Volume per Sample (mL)	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[a,b]
Safety (including screening and posttreatment assessments)			
- Hematology	1.2	~~18~~ **17**	~~21.6~~ **20.4**
- Serum chemistry	1.1	~~18~~ **17**	~~19.8~~ **18.7**
Serology (hepatitis B and hepatitis C)	2.0	1	2.0
Serum β-hCG pregnancy tests	1.1	1	1.1
- QuantiFERON®-TB Gold test	3.0	~~5~~ **6**	~~15.0~~ **18.0**
- Rheumatoid factor	1.1	1	1.1
- Anti-dsDNA antibody	1.1	~~16~~ **11**	~~17.6~~ **12.1**
- ANA antibodies	1.1	11	12.1
Efficacy (CRP)	1.1	24	26.4
PK and immunogenicity (antibodies to golimumab)	2.5	15	37.5
Approximate Total			~~154.2~~ **149.4**

a. Calculated as the number of samples multiplied by amount of blood per sample.
b. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
Note: An indwelling intravenous cannula may be used for blood sample collection.

Abbreviations: ANA = antinuclear antibodies; β-hCG = β-human chorionic gonadotropin; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid; PK = pharmacokinetic; TB = tuberculosis.

Rationale:	
Section 9.1.2 Screening Phase	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.

Applicable Section(s)	Description of Change(s)
Rationale: Reorganizations noted in Sections 3.1.1 and 3.1.2 resulted in the revisions in Sections 9.1.3	
Section 9.1.3 Treatment Phase: Week 0 through Week 28	Beginning at Week 0, eligible subjects will receive 80 mg/m^2 golimumab administered as IV infusions over 30±10 minutes at Weeks 0, 4 and q8w **(±3 days)** through Week **28** (Section 6.1). Subjects will also receive commercial MTX weekly at the same BSA-based dosage (10 to 30 mg/m^2 per week of MTX) as at time of study entry **at least** through Week **28** and commercial folic acid ≥5 mg weekly or folinic acid (at half the MTX dose) given the day after the MTX dose (Section 6.2). **In children <12 years of age, the administration of folic acid or folinic acid will be at the discretion of the physician.**
Rationale: Additional details have been as a result of reorganization noted in Sections 3.1.1 and 3.1.2	
Section 9.1.4 Treatment Phase: Week 28 through Week 52	**Beginning at Week 28, eligible subjects will receive 80 mg/m^2 golimumab administered as IV infusions over 30±10 minutes at Week 28 and q8w (±1week) through Week 52 (Section 6.1). Subjects may also receive commercial MTX weekly at the same BSA-based dosage (10 to 30 mg/m^2 per week of MTX) as at time of study entry through Week 28 and commercial folic acid ≥5 mg weekly or folinic acid (at half the MTX dose) given the day after the MTX dose, however, increases, decreases or discontinuations of MTX, corticosteroids and/or NSAIDs are permissible after Week 28. All changes and reasons for changes for these medications need to be documented in the eCRF.** **Subjects will have safety, efficacy, PK, and immunogenicity evaluations performed according to the Time and Events Schedule (Table 1).**
Rationale: Clarification of the visit windows from Week 52 through Week 244 has been made.	
Section 9.1.5 Long-Term Extension Phase: After Week 52 through Week 252	Subjects who enter the long-term extension after the Week 52 visit will continue to receive 80 mg/m^2 golimumab administered as IV infusions over 30±10 minutes q8w **(±1 week)** through Week 244.

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications for joint evaluations have been made.	
Section 9.2.1.1 Joint Evaluation	Each of 75 joints will be evaluated for tenderness, and 68 joints will be evaluated for swelling **and pain and limitation on motion** according to the standard PRINTO/PRCSG joint **evaluation**. 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. Training will be provided to a single consistent joint assessor from each site before the start of subject enrollment; the training is mandatory unless the site's joint assessor has taken certified training provided by PRINTO or PRCSG. 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 Sponsor **or PRINTO/PRCSG** 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. **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 **in the ePRO device**. 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).

Applicable Section(s)	Description of Change(s)
Rationale: The definition of CRP has been revised	
Section 9.2.1.2 American College of Rheumatology Pediatric Response	The **JIA ACR 30 response criteria**[4] is defined as a 30% improvement (ie, a decrease in score) from baseline in at least 3 of the following 6 components, with worsening of 30% or more in no more than 1 of the following components: • Physician's Global Assessment of disease activity • Parent/Subject 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) • CRP ~~(Improvement in CRP occurs when the CRP value changes from abnormal to normal or to lower levels within the abnormal range. Conversely, a worsening occurs when the CRP value changes from normal to abnormal or worsens within the abnormal range. Changes within the normal range are not considered improvements or worsening.)~~ The JIA ACR 50 response, the JIA ACR 70 response, and the JIA ACR 90 response are defined as a 50% improvement, a 70% improvement, and a 90% improvement from baseline, respectively, in at least 3 of the above 6 components, with worsening of 30% or more in no more than 1 of the above components. **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 CRP **(≤0.287 mg/dL for subjects without underlying inflammatory disease)** • Physician Global Assessment of disease activity indicating no active disease (<0.5 cm) • Duration of morning stiffness <15 minutes

Applicable Section(s)	Description of Change(s)
Rationale: As the VAS for pain is included in the CHAQ assessment, Sections 9.2.1.4 and 9.2.15 were merged. Clarification of very severe pain has also been made. CHAQ scoring has been aligned with the CHAQ questionnaire	
Section 9.2.1.4 Childhood Health Assessment Questionnaire	The functional status of subjects will be assessed by the Childhood Health Assessment Questionnaire.[18] Parents/subjects are to complete this 20-question instrument that assesses the degree of difficulty the 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.~~ **Responses in each functional area are scored from 0, indicating "Without ANY difficulty", to 3, indicating "With MUCH Difficulty" 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.[18] The CHAQ has been shown to be responsive to disease change.[18] A decrease of 0.188 has been determined to be a meaningful clinical improvement.[1] Visual Analog Scale for pain will be assessed as average pain during the past week on a VAS. The scale ranges from "no pain" (0 cm) to "**very severe pain**" (10 cm). This assessment should be completed by the parents/subjects prior to the tender and swollen joint examination.
Rationale: Clarifications on C-reactive protein evaluations has been made.	
Section 9.2.1.5 C-reactive Protein	C-reactive protein has been demonstrated to be useful as a marker of inflammation in patients with pJIA and is part of the **JIA** ACR 30 **core assessments.** C-reactive protein will be assayed **by a central laboratory** using a validated, high-sensitivity CRP assay.

Applicable Section(s)	Description of Change(s)
Rationale: An additional sectional on JADAS has been added.	
Section 9.2.1.6 Juvenile Arthritis Disease Activity Score (JADAS)	**Recently, a composite disease activity score for pJIA, the Juvenile Arthritis Disease Activity Score (JADAS), was developed; in validation analyses it was found to have good metrologic properties, including the ability to predict disease outcome. The JADAS (modified for using CRP) is computed by assessing the following variables: (1) physician global rating of overall disease activity, measured on a 10-cm horizontal visual analog scale (VAS) (0 no activity; 10 maximum activity for both VAS); (2) parent/child ratings of well-being and pain, assessed on a 21-Numbered Circle and 10-Centimeter Horizontal Line Visual Analog Scales[20]; (3) number of active joints, assessed in 71, 27, or 10 joints (JADAS 71, JADAS 27, and JADAS 10, respectively); and (4) CRP was truncated to a 0 scale according to the following formula: (CRP [mg/L]-10/10), similar to the truncated ESR used in JADAS-ESR. Before calculation, CRP values <10 mg/L are converted to 10 and CRP values >110 mg/L are converted to 110.[10]** **The JADAS is calculated as the sum of the scores of its 4 components, which yields a global score of 0–101, 0–57, and 0–40 for the JADAS 71, JADAS 27, and JADAS 10, respectively.** **The state of JADAS 10, 27, and 71 minimal disease activity[2,8] was defined as the presence of all of the following: physician's global assessment of disease activity of ≤3.5, parent's global rating of well-being of ≤2.5, and swollen joint count of ≤1 in patients with polyarthritis.** **JADAS physician assessed remission is defined as a total JADAS score of ≤2.** **The criteria for JADAS inactive disease is defined as a total JADAS score of ≤1.**

Applicable Section(s)	Description of Change(s)
Rationale: Clarification on major secondary and other endpoints have been made.	
Section 9.2.2 Endpoints	**Major Secondary Endpoints** Major secondary endpoints include: • **PK exposure at Week 52 (the trough concentrations at Week 52) and the Baysesian AUCss at Week 52 (from population PK modeling and simulation)** **Other endpoints** **Other endpoints include:** • The proportions of subjects who are **JIA ACR 30, 50, 70, and 90** responders over time • The change from baseline in CHAQ over time • CRP concentrations **over time** • The proportion of subjects who have inactive disease over time • The proportion of subjects in clinical remission on medication for pJIA **over time** • The improvement from baseline in the pJIA core set at each visit • The proportions of subjects who are **JIA ACR 30, 50, 70, and 90** responders by disease subtype, and/or age over time through Week 52 • **The change from baseline in JADAS 10, 27, and 71 scores over time** • **The proportion of subjects who achieve JADAS 10, 27, and 71 minimal disease activity over time** • **The proportion of subjects who achieve JADAS 10, 27, and 71 remission over time**
Rationale: No biomarker analyses will be done in this study.	
Section 9.3.1 Evaluations	Serum samples will be used to evaluate the PK, as well as the immunogenicity of golimumab (antibodies to golimumab). Venous blood samples will be collected and each serum sample will be divided into 3 aliquots (1 each for pharmacokinetics, antibodies to study drug, and a back-up). ~~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.~~ Subject confidentiality will be maintained. The sample should be drawn from a different arm than the IV line, or if using an IV line that is also being used to deliver medication, the line should be flushed and cleared of any residual medication that may be remaining prior to each PK sample being drawn. When using an IV line to draw PK samples, the first 1 mL of blood should be drawn and discarded prior to obtaining the sample. Intravenous line maintenance should be followed as per the standard of care. At visits where serum concentration and antibodies to golimumab will be evaluated, 1 blood draw of sufficient volume can be used.

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications on safety evaluations (physical examination and uveitis evaluations) have been made.	
Section 9.4 Safety Evaluations	**Serum Chemistry Panel** ~~cholesterol panel (total cholesterol and triglycerides)~~ **Physical Examination** Physical examinations, **including a skin exam at every physical examination and** Tanner staging **at least** every 6 months for sexual maturity ~~and a skin examination~~, will be performed according to the Time and Events Schedule. 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 at screening and **at least** every 6 months thereafter by evaluations pertaining to new-onset uveitis on physical examination by the investigator and by interview. **Based upon changing clinical standards, examinations may be more frequent.** Subjects who test antinuclear antibodies (ANA) positive at screening will be required to undergo slit lamp evaluation by a qualified ophthalmologist to evaluate for subclinical uveitis in screening period as well as **at least** every **3** months subsequent (Table 1, Table 2, and Table 3). If a subject develops uveitis during the study, the subjects' continued participation in the study is at the discretion of the investigator and a qualified ophthalmologist.
Rationale: Revisions to the number and time for the ultrasound assessments have been made.	
Section 9.6 Ultrasound Substudy	At selected sites, a total of approximately 20 subjects over the age of 4 years who are enrolled in this study and are currently receiving study treatment may undergo power ultrasounds of their metacarpophalangeal 2 and 3 joints (examining dorsal and volar surfaces), wrist (dorsal long midline, tendons), knee (suprapatellar long and parapatellar images; entheseal evaluations), and ankle (tibula/talar, subtalar medial and lateral surfaces, tendon examinations). Up to **5** ultrasound assessments may be conducted, at Weeks 0, 4, ~~8~~, 12, 28, and 52. The primary objective of the substudy is to examine Power Doppler response measured as the Power Doppler Sum Score at 6 months compared with the score at baseline. Additional details will be presented in the Ultrasound Substudy Protocol.

Applicable Section(s)	Description of Change(s)
Rationale: Uveitis evaluation has been added to the assessment to be performed for each subject who discontinue study agent administration but does not discontinue study participation.	
Section 10.2 Discontinuation of Study Treatment	Subjects who discontinue study agent infusions but do not terminate study participation, will have the following assessments performed at the final safety follow-up visit: • Safety evaluations (eg, vital signs, AE review, study agent infusion reaction evaluation, TB evaluation, **uveitis evaluation,** and the collection of a blood sample for routine laboratory analyses and determination of the presence of ANA/anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies and antibodies to golimumab).
Rationale: Clarification on major secondary and other endpoint analyses have been made.	
Section 11.3 Efficacy Analyses	**Primary Endpoint Analysis** No primary efficacy endpoint analysis is planned. ~~As the co-primary objective of this study is PK analyses of IV golimumab, the co-primary clinical evaluation is the proportion of subjects meeting JADAS minimal disease activity criteria at Week 28 the primary endpoint is not an efficacy endpoint (Section 11.4).~~ **Major Secondary Endpoints Analyses** **No major secondary efficacy endpoints analyses are planned.** **Other efficacy endpoints** The following will be summarized for all subjects enrolled in the study: • **The proportion of subjects who are JIA ACR 30, 50, 70, and 90 responders over time** • The proportion of subjects who have inactive disease over time • The proportion of subjects in clinical remission on medication for JIA (**ACR criteria**) over time • The improvement from baseline in the JIA core set over time • The proportions of subjects who are **JIA ACR 30, 50, 70, and 90** responders by disease subtype, and/or age over time through Week 52 • **The change from baseline in CHAQ over time** • CRP concentrations over time • **The change from baseline in JADAS 10, 27, and 71 scores over time** • **The proportion of subjects who achieve JADAS 10, 27, and 71 minimal disease activity over time** • **The proportion of subjects who achieve JADAS 10, 27, and 71 remission over time**

Applicable Section(s)	Description of Change(s)
Rationale: An additional PK analysis has been added	
Section 11.4 Pharmacokinetic Analyses	**Summary golimumab concentrations will be summarized and PK exposure will be evaluated through Week 52 and through the LTE.**
Rationale: Clarification on the DMC has been made	
Section 11.9 Data Monitoring Committee	This is an open-label study, with all subjects receiving the same dosage of IV golimumab. Therefore, an external Data Monitoring Committee will not be utilized. Unblinded safety data will be routinely evaluated by the study's medical monitor and an internal Data Review Committee **(DRC) as well as the Steering Committee as defined in DRC charter.**
Rationale: Clarification of time period for the reporting of serious adverse events has been made	
Section 12.3.1 All Adverse Events	All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days ~~after the last dose of study drug~~ **of the end of the study**, 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.
Rationale: The study-specific materials that will be provided to all study sites have been revised.	
Section 15 Study-specific Materials	The investigator will be provided with at least the following supplies: • Investigator Brochure • Trial Center File • Investigational Product Manual • Laboratory manual **and laboratory supplies** • ePRO device **and user manual** • Interactive voice/web response system manual • Electronic data capture (eDC) Manual (including on-line access) • Sample ICF and sample assent form • Subject participation cards (ie, wallet cards)

Applicable Section(s)	Description of Change(s)
Rationale: The storage time for samples collected in this study has been reduced from 15 to 2 years	
Section 16.2.5 Long-Term Retention of Samples for Additional Future Research	Samples collected in this study may be stored for up to **2** years (or according to local regulations) for additional research. Samples will only be used to understand golimumab, to understand pJIA, to understand differential drug responders, and to develop tests/assays related to SIMPONI for IV use and pJIA. The research may begin at any time during the study or the post-study storage period. Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research. ~~(refer to Section 10.3, Withdrawal From the Study (Withdrawal From the Use of Samples in Future Research).~~
Rationale: An incorrect reference has been deleted.	
Section 16.2.6 Country Selection	This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product. ~~unless explicitly addressed as a specific ethical consideration in Section 16.1, Study Specific Design Considerations.~~
Rationale: Data that will be entered into the CRF has been revised	
Section 17.4 Source Documentation	The following data (at a minimum) will be recorded directly into the CRF and will be considered source data where allowed by country regulations: • Race • History of smoking and all nicotine use (eg, cigarettes, cigars, chewing tobacco, patch, gum) • Blood pressure, pulse/heart rate, **temperature,** and respiratory rate • Height and weight • Details of physical examination • Limited range of motion and active joints • ~~PRO assessments: CHQ and CHAQ~~ • **The following parent/subject- and investigator-completed scales and assessments designated by the Sponsor will be recorded into an electronic device and will be considered source data: joint assessments, CHAQ, parent/subject assessment of overall well-being, physician global assessment of disease activity, and visual analog scale for pain.** ~~Subject and investigator-completed scales and assessments designated by the Sponsor will be recorded and will be considered source data.~~

Applicable Section(s)	Description of Change(s)
Rationale: Transmission of IWRS and ePRO data has been added.	
Section 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 sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory, **IWRS, and PRO data** into the Sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.
Section 17.11 Use of Information and Publication	The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain CRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory, **IWRS, and PRO data** into the Sponsor's database. 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 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 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.
Rationale: Clarifications to the Table of Events (Tables 1, 2, and 3) have been made	
Table 1: Screening Through Week 52	JADAS assessment has been added at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 36, 44, and 52. Antibodies to golimumab assessments have been added at Weeks 4 and 8 QuantiFERON TB Gold test has been added at Week 52 Uveitis evaluations were deleted at Weeks 24 and 52 and added to Weeks 20 and 44
Footnote b	Includes **skin examination at every physical examination and** Tanner staging every 6 months ~~and skin examination at every physical examination.~~
Footnote f	Evaluations should be performed **at least** every 6 months in all subjects. Subjects who test ANA positive at screening will be required to undergo slit lamp evaluation by a qualified ophthalmologist to evaluate for subclinical uveitis in the screening period, **before first study drug administration** as well as at least every **3** months subsequent.
Footnote i	To be completed by the parent or caregiver, preferably the same parent or caregiver should complete at every visit. Subjects who are emancipated juveniles (ages 15 to <18 years) at study entry may complete the assessments themselves. **Ideally** the same individual (eg, parent, caregiver, or subject) who completes the assessments at the start of the study should complete the assessments throughout the study. at least

Applicable Section(s)	Description of Change(s)
Footnote j	**All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions.** Parent/subject assessment of overall well-being has been deleted Visual analog scale for pain has been deleted CHQ assessments have been deleted. Checks for the following assessments during the screening period have been deleted: Parent/subject assessment of overall well-being, Physician Global Assessment of disease activity, and Visual analog scale for pain
Table 2: From Week 60 Through Week 156 (Long-term Extension)	JADAS assessment has been added at Weeks 68, 84, 100, 116, 132, and 148. Antibodies to golimumab assessments have been added at Weeks 4 and 8 QuantiFERON TB Gold test was deleted at Weeks 60 and 108 and has been added at Weeks 100 and 148. Uveitis evaluations were deleted at Weeks 76, 100, 124, and 148 and added to Weeks 68, 92, 116, and 140.
Footnote b	Includes **skin exam and** Tanner staging ~~every 6 months.~~
Footnote e	Evaluations should be performed **at least** every 6 months in all subjects. Subjects who test ANA positive at screening will be required to undergo slit lamp evaluation by a qualified ophthalmologist at least every **3** months.
Footnote h	To be completed by the parent or caregiver, preferably the same parent or caregiver should complete at every visit. Subjects who are emancipated juveniles (ages 15 to <18 years) at study entry may complete the assessments themselves. **Ideally** the same individual (eg, parent, caregiver, or subject) who completes the assessments at the start of the study should complete the assessments throughout the study.
Footnote i	**All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions.** Parent/subject assessment of overall well-being has been deleted Visual analog scale for pain has been deleted CHQ assessments have been deleted.

Applicable Section(s)	Description of Change(s)
Table 3: From Week 164 Through Week 252 (Long-term Extension – Continued)	JADAS assessment has been added at Weeks 164, 180, 196, 212, 228, and 244. Antibodies to golimumab assessments have been added at Weeks 4 and 8 QuantiFERON TB Gold test was deleted at Week 172 and has been added at Week 196 Uveitis evaluations were deleted at Weeks 172, 196, 220, and 244 and added to Weeks 164, 188, 212, 236, and 252.
Footnote b	Includes **skin exam and** Tanner staging ~~every 6 months.~~
Footnote e	Evaluations should be performed **at least** every 6 months in all subjects. Subjects who test ANA positive at screening will be required to undergo slit lamp evaluation by a qualified ophthalmologist at least every **3** months.
Footnote h	To be completed by the parent or caregiver, preferably the same parent or caregiver should complete at every visit. Subjects who are emancipated juveniles (ages 15 to <18 years) at study entry may complete the assessments themselves. **Ideally** the same individual (eg, parent, caregiver, or subject) who completes the assessments at the start of the study should complete the assessments throughout the study.
Footnote i	**All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions.** Parent/subject assessment of overall well-being has been deleted Visual analog scale for pain has been deleted CHQ assessments have been deleted.

Applicable Section(s)	Description of Change(s)
Rationale: Revisions were made to several sections of the synopsis to reflect the changes made in the protocol	
Synopsis Overview of Study Design	This is a Phase 3, open-label, single-arm, multicenter study to evaluate the PK, safety, and efficacy of IV golimumab in subjects with active pJIA despite current treatment with MTX **and/or corticosteroids and/or non-steroidal anti-inflammatory agents and/or prior use of anti-TNFα agents (up to 30% of total population).** The study population will be comprised of subjects with pJIA receiving MTX, ages 2 to less than 18 years, with at least a **3**-month history of pJIA, and active arthritis in ≥5 joints. At least 120 subjects will be enrolled at Week 0 to ensure that at least 100 subjects remain in the study at Week 52. Enrollment patterns are expected to yield a subject population of approximately 10% aged 2 to up to 6 years, approximately 20% aged 6 to up to 12 years, and approximately 70% aged 12 to less than 18 years. All subjects will receive 80 mg/m^2 golimumab as an IV infusion (**over 30 ±10 minutes)** at Weeks 0, 4, and every 8 weeks (q8w; ± **3 days) through Week 28 and q8w (± 1 week)** thereafter (**maximum single dose 240 mg [maximum BSA 3.0m^2 x 80 mg/m^2])**, along with commercial MTX at a dose of 10-30 mg/m^2/week (**unless for documented safety reasons, lower doses of MTX are administered). For patients greater than 1.67m^2, a minimum fixed dose of 15 mg/week is required.** Subjects who complete the study at Week 52 will have the option to enter into the long-term extension phase of the study. During the long-term extension, all subjects will continue to receive 80 mg/m^2 IV golimumab q8w (**±1 week**; **maximum single dose 240 mg**) through Week 244. All subjects who complete the Week 244 visit are expected to participate in the safety follow-up visit at Week 252. **Golimumab after Week 252 (for subjects who have completed the full 252 week study before drug commercialization for JIA indication has taken place) will be provided until the drug will be approved and marketed for use in JIA in the country of the subject or for as long as proven beneficial to the child (in cases where commercial drug is not accessible to the subject.**
Subject Population	The onset of disease must have been before the subject's 16th birthday, must be at least **3** months' duration, and must **have** active pJIA of one of the following subtypes: rheumatoid factor positive or negative pJIA; systemic JIA with no systemic symptoms ~~but with polyarthritis~~ for ≥**3** months but with polyarthritis **for ≥3 months**; extended oligoarticular JIA; **enthesitis related arthritis** or polyarticular juvenile psoriatic arthritis (PsA). Subjects must have ≥5 joints with active arthritis as defined by American College of Rheumatology (ACR) criteria **at screening and enrollment** and must have a screening C-reactive protein (CRP) of ≥0.1 mg/dL. Subjects must have active pJIA despite current use of oral, intramuscular or subcutaneous MTX (for ≥3 months before screening) at a weekly dose of ≥10 mg/m^2.
Dosage and Administration Golimumab	The study will have 1 active treatment group and all subjects will receive 80 mg/m^2 golimumab IV infusions at Week 0, Week 4, and q8w **± 3days through Week 28 and q8w ± 1 week** thereafter through Week 244. BSA will be calculated at each visit and the dose of golimumab will be adjusted as needed to maintain the dose at 80 mg/m^2. BSA will be calculated using the Mosteller equation: BSA (m^2) = ([height (cm) x weight (kg)]/3600).$^{1/2}$ **The maximum single dose will be golimumab 240 mg.**

Applicable Section(s)	Description of Change(s)
Methotrexate	Subjects will receive commercial MTX at the same BSA-based dose (10 to 30 mg/m^2 per week of MTX) as at time of study entry **at least** through Week **28**. ~~BSA will be calculated at each visit and the dose of MTX will be adjusted as needed to maintain the dose at the same mg/m^2 per week dose as the subject was receiving at time of study entry~~. Every effort should be made to ensure that subjects remain on the same ~~BSA based~~ dose and route of administration of MTX **at least** through the Week **28** safety and efficacy database lock, unless intolerance or AEs due to MTX occur. Subjects will also receive commercial folic acid ≥5 mg weekly or folinic acid (at half the MTX dose) given the day after the weekly MTX dose. **In children <12 years of age, the administration of folic acid or folinic acid will be at the discretion of the physician.**
Efficacy/Pharmacokinetic Evaluations and Endpoints	Efficacy evaluations include the following: • Joint evaluations (number of active joints and number of joints with limited range of motion) • Parent/Subject Assessment **of Overall Well-being** • Physician Global Assessment of disease activity • Visual Analog Scale for Pain • Childhood Health Assessment Questionnaire (CHAQ) • **JADAS 10, 27, and 71** • CRP The primary endpoint in this study is PK exposure at Week 28 (the trough concentrations at Week 28) and the Bayesian steady-state area under the curve [AUCss] over one dosing interval of 8 weeks (from population PK modeling and simulation). The major secondary endpoints **are as follows:** • **PK exposure at Week 52 (the trough concentrations at Week 52) and the Baysesian AUCss at Week 52 (from population PK modeling and simulation)** Other efficacy endpoints include: • The proportions of subjects who are JIA ACR 30, 50, 70, and 90 responders over time • The change from baseline in CHAQ over time • CRP concentrations over time • The proportion of subjects who have inactive disease over time • The proportion of subjects in clinical remission on medication for pJIA over time • The improvement from baseline in the pJIA core set at each visit • The proportions of subjects who are JIA ACR 30, 50, 70, and 90 responders by disease subtype, and/or age over time through Week 52 • The change from baseline in JADAS 10, 27, and 71 scores over time • The proportion of subjects who achieve JADAS 10, 27, and 71 minimal disease activity over time • The proportion of subjects who achieve JADAS 10, 27, and 71 remission over time

Applicable Section(s)	Description of Change(s)
	Serum golimumab concentration and/or efficacy measures **will be evaluated at Weeks 0, 4, 8, 12, 20, 28, 52, 100, 148, 196, and 244 and summarized over time. A population PK analysis with data through Week 28 will be performed to characterize the PK of golimumab as well as to identify important covariates of PK in the pediatric population with pJIA.** **Summary golimumab concentrations will be summarized and PK exposure will be evaluated through Week 52 and through the LTE.**
Immunogenicity Evaluations	Antibodies to golimumab will be evaluated in serum samples collected from all subjects at Weeks 0, **4, 8,** 12, 28, 52, 100, 148, 196, and 244.
Ultrasound substudy	**Power Doppler Sonography (PDUS) is a non-invasive ultrasound technique to assess inflammation at the joint level in RA. At selected sites, subjects over the age of 4 years who have been enrolled in the study and are currently receiving study treatment may undergo PDUS and High Frequency gray scale Ultrasound (HFUS) of the 2nd and 3rd metacarpophalangeal joints, wrist, knee and ankle. Up to 5 exams will be performed at Weeks 0, 4, 12, 24, and 52 using a standardized protocol, described in a separate manual. Reading of the PDUS and HFUS will be performed by a blinded independent central reader.**
Efficacy Analyses	The following will be summarized for all subjects enrolled in the study: • The proportion of subjects who are JIA ACR 30, 50, 70, and 90 responders over time • The proportion of subjects who have inactive disease over time • The proportion of subjects in clinical remission on medication for JIA (ACR criteria) over time • The improvement from baseline in the JIA core set over time • The proportions of subjects who are JIA ACR 30, 50, 70, and 90 responders by disease subtype, and/or age over time through Week 52 • The change from baseline in CHAQ over time • CRP concentrations over time • The change from baseline in JADAS 10, 27, and 71 scores over time • The proportion of subjects who achieve JADAS 10, 27, and 71 minimal disease activity over time • The proportion of subjects who achieve JADAS 10, 27, and 71 remission over time
Rationale: Minor errors were noted and corrected.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

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

Protocol Number: CNTO148JIA3003

Golimumab is a fully human monoclonal antibody (mAb) which binds to human tumor necrosis factor alpha (TNFα) with high affinity and specificity and neutralizes TNFα bioactivity. 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). SIMPONI® (golimumab) for intravenous (IV) use is being developed by the Sponsor to offer an alternative route of administration (compared with other available anti-TNFα agents) and a convenient dose regimen (ie, every 8 week [q8w] administration) for patients with polyarticular JIA (pJIA).

OBJECTIVES AND HYPOTHESIS

Primary Objective

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

Secondary Objectives

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

Hypothesis

No formal hypothesis testing is planned in this study.

OVERVIEW OF STUDY DESIGN

This is a Phase 3, open-label, single-arm, multicenter study to evaluate the PK, safety, and efficacy of IV golimumab in subjects with active pJIA despite current treatment with MTX. The study population will comprise subjects with pJIA receiving MTX, ages 2 to less than 18 years, with at least a 3-month history of pJIA, and active arthritis in ≥5 joints. Approximately 120 subjects will be enrolled at Week 0 to ensure that approximately 100 subjects remain in the study at Week 52. Enrollment patterns are expected to yield a subject population of approximately 10% aged 2 to up to 6 years, approximately 20% aged 6 to up to 12 years, and approximately 70% aged 12 to less than 18 years.

All subjects will receive 80 mg/m^2 golimumab as an IV infusion (over 30±10 minutes) at Weeks 0, 4, and q8w (±3 days) through Week 28 and q8w (±1 week) thereafter (maximum single dose 240 mg [maximum body surface area (BSA) 3.0 m^2 x 80 mg/m^2]). Commercial MTX is to be administered at a stable dose of 10-30 mg/m^2/week in subjects with BSA <1.67 m^2 or a stable minimum dose of 15 mg/week in subjects with BSA ≥1.67 m^2 through Week 28 (unless lower doses of MTX are administered for documented safety reasons or unless documented country or site regulations prohibit dose of 15 mg/week or above in subjects with BSA ≥1.67 m^2). Subjects who complete the study at Week 52 will have the option to enter into the long-term extension (LTE) phase of the study. During the LTE, all subjects will continue to receive 80 mg/m^2 IV golimumab q8w (±1 week; maximum single dose 240 mg) through Week 244. All subjects who complete the Week 244 visit are expected to participate in the safety follow-up visit at

Week 252. Subjects <18 years of age who have completed the study through Week 252 and are benefiting from treatment, but for whom golimumab is not commercially available for the treatment of pJIA, will have the option to continue to receive golimumab (80 mg/m^2 q8w) in the Extended Treatment Period (ETP). The first dose of golimumab in the ETP is administered at Week 252 after all assessments have been completed.

Since this is an open-label study with all subjects receiving the same BSA-based dose of IV golimumab, an external Data Monitoring Committee will not be established.

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

SUBJECT POPULATION

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

The onset of disease must have been before the subject's 16th birthday, must be of at least 3 months' duration, and must be active pJIA of one of the following subtypes: rheumatoid factor positive or negative pJIA; systemic JIA with no systemic symptoms for ≥3 months but with polyarthritis for ≥3 months; extended oligoarticular JIA; enthesitis-related arthritis or polyarticular juvenile psoriatic arthritis (PsA).

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

DOSAGE AND ADMINISTRATION

Golimumab

The study will have 1 active treatment group and all subjects will receive 80 mg/m^2 golimumab IV infusions at Week 0, Week 4, and q8w (± 3 days) through Week 28 and q8w (±1 week) thereafter through Week 244. BSA will be calculated at each visit and the dose of golimumab will be adjusted as needed to maintain the dose at 80 mg/m^2. BSA will be calculated using the Mosteller equation: BSA (m^2) = ([height (cm) x weight (kg)]/3600)^{½}. The maximum single dose will be golimumab 240 mg.

During the ETP, subjects will continue to receive 80 mg/m^2 golimumab IV infusions q8w starting at Week 252.

Methotrexate

Subjects will receive commercial MTX at least through Week 28 at the same BSA-based dose (10 to 30 mg/m^2 per week for subjects with BSA <1.67 m^2 or at least 15 mg/week for subjects with BSA ≥1.67 m^2) as at time of study entry. Every effort should be made to ensure that subjects remain on the same dose and route of administration of MTX through the Week 28 visit, unless intolerance or AEs due to MTX occur.

Subjects will also receive commercial folic acid ≥5 mg weekly or folinic acid (at half the MTX dose) given the day after the weekly MTX dose**.** In children <12 years of age, the administration of folic acid or folinic acid will be at the discretion of the physician.

EFFICACY EVALUATIONS AND ENDPOINTS

Efficacy evaluations include the following:

- Joint evaluations (number of active joints and number of joints with limited range of motion)
- Physician Global Assessment of Disease Activity

- Childhood Health Assessment Questionnaire (CHAQ; includes the Parent/Subject Assessment of Overall Well-being and Parent/Subject Assessment of Pain)
- CRP

No primary efficacy endpoint or major secondary endpoints are planned. Other efficacy endpoints include:

- The proportions of subjects who are JIA ACR 30, 50, 70, and 90 responders over time
- The change from baseline in CHAQ over time
- CRP concentrations over time
- The proportion of subjects who have inactive disease over time
- The proportion of subjects in clinical remission on medication for pJIA over time
- The improvement from baseline in the pJIA core set at each visit
- The proportions of subjects who are JIA ACR 30, JIA ACR 50, JIA ACR 70 and JIA ACR 90 responders by disease subtype, and/or age over time through Week 52
- The change from baseline in Juvenile Arthritis Disease Activity Score (JADAS) 10, 27, and 71 scores over time
- The proportion of subjects who achieve JADAS 10, 27, and 71 minimal disease activity over time

PHARMACOKINETIC EVALUATIONS AND ENDPOINTS

Serum golimumab concentration will be evaluated at Weeks 0, 4, 8, 12, 20, 28, 52, 100, 148, 196, and 244 and summarized over time. A population PK analysis with data through Week 28 will be performed to characterize the PK of golimumab as well as to identify important covariates of PK in the pediatric population with pJIA.

Golimumab concentrations will be summarized and PK exposure will be evaluated through Week 52 and through the LTE.

The primary endpoint in this study is PK exposure at Week 28 (the trough concentrations at Week 28) and the Bayesian steady-state area under the curve [AUCss] over one dosing interval of 8 weeks (from population PK modeling and simulation).

The major secondary PK endpoints include:

- PK exposure at Week 52 (the trough concentrations at Week 52) and Bayesian AUCss at Week 52 (from population PK modeling and simulation).

SAFETY EVALUATIONS

Safety evaluations include assessments of the following: AEs; infusion reactions; allergic reactions; clinical laboratory tests (hematology, chemistry, and pregnancy testing); vital signs; physical examination; height and body weight; uveitis; and early detection of tuberculosis.

IMMUNOGENICITY EVALUATIONS

Antibodies to golimumab will be evaluated in serum samples collected from all subjects at Weeks 0, 4, 8, 12, 28, 52, 100, 148, 196, and 244.

STATISTICAL METHODS

Subject Information

Demographics and baseline disease characteristics and prior medication data will be summarized for all subjects 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 1 administration of study agent. Efficacy analyses will be summarized for all subjects enrolled in the study. Safety assessments will be summarized for all treated subjects.

Sample Size

The sample size determination is not based on statistical considerations. The goal is to have a sample size that will be sufficient to build a population PK model and, if feasible, an exposure-response model. Additionally, a sample size that will provide reasonable safety assessments was also taken into consideration. With these considerations, a sample size of approximately 120 subjects has been chosen assuming that if 20 subjects drop out or if they do not provide PK samples, a sample size of approximately 100 subjects will remain in the study at Week 52. This sample size is thought to be sufficient to build a population PK model, given the sparse sampling of PK time points, as well as provide 1 year of safety data from approximately 100 subjects.

Efficacy Analyses

No primary efficacy endpoint analysis and no major secondary efficacy endpoint analyses are planned.

The following will be summarized for all subjects enrolled in the study:

- The proportion of subjects who are JIA ACR 30, 50, 70, and 90 responders over time
- The change from baseline in CHAQ over time
- CRP concentrations over time
- The proportion of subjects who have inactive disease over time
- The proportion of subjects in clinical remission on medication for pJIA (ACR criteria) over time
- The improvement from baseline in the pJIA core set over time
- The proportions of subjects who are JIA ACR 30, 50, 70, and 90 responders by disease subtype, and/or age over time through Week 52
- The change from baseline in JADAS 10, 27, and 71 scores over time
- The proportion of subjects who achieve JADAS 10, 27, and 71 minimal disease activity over time

Pharmacokinetic Analyses

The primary objective of this study is to characterize golimumab PK exposure (the trough concentrations at Week 28 and the Bayesian AUCss over a dosage interval of 8 weeks from population PK modeling and simulation) in the JIA population.

Serum golimumab concentrations will be summarized over time. In addition, a population PK analysis on data through Week 28 will be performed to characterize the PK of golimumab as well as to identify and quantify important covariates of PK in the pediatric population with JIA. Clearance and volume of distribution will be estimated using a nonlinear mixed effects modeling (NONMEM) approach.

Safety Analyses

Safety will be assessed by evaluating summaries of AEs, clinical laboratory tests, and vital signs findings through Week 252.

Immunogenicity Analyses

The occurrence and titers of antibodies to golimumab during the study will be summarized 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).

Pharmacokinetic/Pharmacodynamic Analyses

The relationships between serum golimumab concentration and efficacy will be explored. A suitable PK/pharmacodynamic (PD) model will be explored and developed to describe the exposure-response relationship.

TIME AND EVENTS SCHEDULES

Table 1: Screening Through Week 52

	Screen-ing Period (-6 weeks)	Week 0[a]	Week 4[a]	Week 8[a]	Week 12[a]	Week 16[a]	Week 20[a]	Week 24[a]	Week 28[a]	Week 36[a]	Week 44[a]	Week 52[a]	Final Safety Follow-up Visit[b]
Procedures and Evaluations													
Administrative													
Informed consent/Assent	X												
Medical history/demographic data	X												
Concomitant medications collection	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X											
Study Agent													
IV administration of study agent		X	X		X		X		X	X	X	X	
Safety													
Review of systems	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[c]	X			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[d]	X[d]	X	X[d]	X	X[d]	X	X[d]	X[d]	X[d]	X[d]	X
Routine laboratory analyses	X	X	X		X		X		X	X	X	X	X
Hepatitis B virus screening	X												

Table 1: Screening Through Week 52

	Screening Period (-6 weeks)	Week 0[a]	Week 4[a]	Week 8[a]	Week 12[a]	Week 16[a]	Week 20[a]	Week 24[a]	Week 28[a]	Week 36[a]	Week 44[a]	Week 52[a]	Final Safety Follow-up Visit[b]
Hepatitis C virus screening	X												
QuantiFERON®-TB Gold test[e]	X											X[f]	
TB evaluation (questionnaire)	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray[g]	X												
Uveitis evaluations[h]	X						X				X		X
Rheumatoid factor	X												
ANA/Anti-dsDNA antibodies	X							X				X	X
Pregnancy test (serum)[i]	X												
Pregnancy test (urine)[i]		X	X		X		X		X	X	X	X	
Infusion reaction evaluation[j]		X	X		X		X		X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy													
Joint assessments	X	X	X	X	X	X	X	X	X	X	X	X	X
JIA assessments[k, l]		X	X	X	X	X	X	X	X	X	X	X	X
CRP	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics													
Golimumab concentration[m, n]		2X	2X	X	2X		X		X			X	X
Population PK[o]		← X[o] →											

Table 1: Screening Through Week 52

	Screening Period (-6 weeks)	Week 0[a]	Week 4[a]	Week 8[a]	Week 12[a]	Week 16[a]	Week 20[a]	Week 24[a]	Week 28[a]	Week 36[a]	Week 44[a]	Week 52[a]	Final Safety Follow-up Visit[b]
Immunogenicity													
Antibodies to golimumab[n]		X	X	X	X				X			X	X

a. All scheduled visits should occur within ±3 days of the intended visit through Week 28 and ± 1 week after Week 28 through Week 52.

b. All subjects who discontinue study agent administration before Week 52 but do not withdraw consent must return to the study site for a final safety visit approximately 8 weeks after the last infusion (Section 10.2).

c. Includes skin examination at every physical examination and Tanner staging approximately every 6 months.

d. Vital signs should be taken pre-infusion; at 15 and 30 minutes (15-minute intervals during the infusion); and at 60 and 90 minutes (during the 1-hour observation period following the infusion).

e. Tuberculin skin tests should also be performed in countries where the QuantiFERON®-TB Gold test is not approved/registered in that country or the tuberculin skin test is mandated by local Health Authorities.

f. Testing is not required for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment.

g. Chest x-ray screening as per local and country regulations for initiation of immunosuppressive agents in children with JIA who are at risk of TB.

h. Evaluations (based on physical examination and interview) should be performed by the investigator at least every 6 months in all subjects. In addition, all subjects are required to have slit lamp evaluations performed by an ophthalmologist/optometrist during the study at intervals (based on JIA subtype, ANA test results, age at JIA onset, and JIA duration) as specified in Attachment 5.

i. All female subjects of childbearing potential (ie, post-menarche) must test negative for pregnancy during screening and at all visits prior to study drug administration.

j. Subjects will be observed for at least 60 minutes after the administration of study agent for symptoms of an infusion reaction.

k. JIA assessments include the following: Physician Global Assessment of Disease Activity, Childhood Health Assessment Questionnaire (CHAQ), and duration of morning stiffness. **CHAQ should be completed before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions**.

l. CHAQ to be completed by the parent or caregiver; preferably the same parent or caregiver should complete at every visit. Subjects who are 15 to <18 years of age at study entry may complete the assessment jointly with the parent/caregiver.

m. At the Weeks 0, 4, and 12 visits, 2 samples for serum golimumab concentrations (indicated by "2X" in the schedule above) will be collected: 1 sample will be collected immediately prior to the infusion and the other collected approximately 1 hour (eg, ± 10 minutes) after the end of the infusion. For each of the remaining visits, only 1 sample for serum golimumab will be collected, which should be collected prior to the infusion if an infusion of the study agent is administered at that visit. Post-infusion samples should be drawn from a different arm than the IV infusion line, or the IV infusion line must be flushed and cleared of any residual medication that may be remaining and 1 mL of blood should be drawn and discarded prior to obtaining the sample if using the same access line as was used for drug administration.

Table 1: Screening Through Week 52

	Screening Period (-6 weeks)	Week 0[a]	Week 4[a]	Week 8[a]	Week 12[a]	Week 16[a]	Week 20[a]	Week 24[a]	Week 28[a]	Week 36[a]	Week 44[a]	Week 52[a]	Final Safety Follow-up Visit[b]

n. 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.

o. One additional sample for serum golimumab concentration for population PK will be collected from all subjects at any time between Weeks 0 and 8 other than at the time of the Week 0, Week 4, and Week 8 visits; this sample must be collected at least 24 hours prior to or after a study agent administration and must not be collected at a regularly scheduled visit (eg, Week 8).

Abbreviations: ANA = antinuclear antibodies; CHAQ = Childhood Health Assessment Questionnaire; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid; IV = intravenous; PK = pharmacokinetic; TB = tuberculosis.

Table 2: From Week 60 Through Week 156 (Long-term Extension)														
	Week 60[a]	Week 68[a]	Week 76[a]	Week 84[a]	Week 92[a]	Week 100[a]	Week 108[a]	Week 116[a]	Week 124[a]	Week 132[a]	Week 140[a]	Week 148[a]	Week 156[a]	Final Safety Follow-up Visit[b]
Procedures and Evaluations														
Administrative														
Concomitant medications collection	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Study Agent														
IV administration of study agent	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety														
Review of systems	X[d]													
Physical examination[e]	X			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[d]													
Routine laboratory analyses						X							X	X
ANA/Anti-dsDNA antibodies														X
QuantiFERON®-TB Gold test	X[d,f]													
TB evaluation (questionnaire)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray	X[g]													
Uveitis evaluations	X[h]													
Pregnancy test (urine)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Infusion reaction evaluation[j]	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														
Annual attestation form	X[k]													

Table 2: From Week 60 Through Week 156 (Long-term Extension)

	Week 60[a]	Week 68[a]	Week 76[a]	Week 84[a]	Week 92[a]	Week 100[a]	Week 108[a]	Week 116[a]	Week 124[a]	Week 132[a]	Week 140[a]	Week 148[a]	Week 156[a]	Final Safety Follow-up Visit[b]
Pharmacokinetics														
Golimumab concentration[l]						X						X		X
Immunogenicity														
Antibodies to golimumab[l]						X						X		X

Note: All assessments at each study visit must be completed prior to study drug administration, unless otherwise specified.

a. All scheduled visits should occur ±1 week of the intended visit.

b. All subjects who discontinue study agent administration before Week 156 but do not withdraw consent must return to the study site for a final safety visit approximately 8 weeks after the last infusion (Section 10.2). Collection of vital signs, review of symptoms, and uveitis evaluation are performed at the final safety follow-up visit at the discretion of the investigator.

c. Review concomitant medications with subject and document in source; update concomitant medication CRF page to include only those medications that are associated with AEs and SAEs (ie, used to treat event or suspected in causing event).

d. Perform at the discretion of the investigator.

e. Includes skin examination at every physical examination.

f. Tuberculin skin tests should also be performed in countries where the QuantiFERON®-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local Health Authorities.

g. Chest x-ray screening should be performed at the discretion of the investigator and per local and country regulations for children with JIA who are receiving immunosuppressive agents and who are at risk of TB.

h. Evaluations (based on physical examination and interview) should be performed at the discretion of the investigator. Slit lamp evaluations performed by an ophthalmologist/optometrist at the discretion of the investigator and per standard of care.

i. All female subjects of childbearing potential (ie, post-menarche) must test negative for pregnancy at all visits prior to study drug administration.

j. Subjects will be observed at the discretion of the investigator after the administration of study agent for symptoms of an infusion reaction.

k. Investigator will complete an annual attestation form to document that subject is benefiting from treatment.

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.

Abbreviations: AE=adverse event; ANA=antinuclear antibodies; dsDNA=double-stranded deoxyribonucleic acid; IV=intravenous; SAE=serious adverse event; TB=tuberculosis.

Table 3: From Week 164 Through Week 252 (Continuation of Long-term Extension)

	Week 164[a]	Week 172[a]	Week 180[a]	Week 188[a]	Week 196[a]	Week 204[a]	Week 212[a]	Week 220[a]	Week 228[a]	Week 236[a]	Week 244[a]	Week 252[a]	Final Safety Follow-up Visit[b]
Procedures and Evaluations													
Administrative													
Concomitant medications collection	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Study Agent													
IV administration of study agent	X	X	X	X	X	X	X	X	X	X	X	X[d]	
Safety													
Review of systems	X[e]												
Physical examination[f]			X			X			X			X	
Body weight measurement	X	X	X	X	X	X	X	X	X	X	X	X[d]	
Height measurement	X	X	X	X	X	X	X	X	X	X	X	X[d]	
Vital signs	X[e]												
Routine laboratory analyses						X						X	X
ANA/Anti-dsDNA antibodies												X	X
QuantiFERON®-TB Gold test	X[e,g]												
TB evaluation (questionnaire)	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray	X[h]												
Uveitis evaluations	X[i]												
Pregnancy test (urine)[j]	X	X	X	X	X	X	X	X	X	X	X	X[d]	
Infusion reaction evaluation[k]	X	X	X	X	X	X	X	X	X	X	X	X[d]	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3: From Week 164 Through Week 252 (Continuation of Long-term Extension)

	Week 164[a]	Week 172[a]	Week 180[a]	Week 188[a]	Week 196[a]	Week 204[a]	Week 212[a]	Week 220[a]	Week 228[a]	Week 236[a]	Week 244[a]	Week 252[a]	Final Safety Follow-up Visit[b]
Efficacy													
Annual attestation form	X[l]												
Pharmacokinetics													
Golimumab concentration[m]					X						X		X
Immunogenicity													
Antibodies to golimumab[m]					X						X		X

Note: All assessments at each study visit must be completed prior to study drug administration, unless otherwise specified.

a. All scheduled visits should occur ± 1 week of the intended visit.

b. All subjects who discontinue study agent administration before Week 244 but do not withdraw consent must return to the study site for a final safety visit approximately 8 weeks after the last infusion (Section 10.2). Collection of vital signs, review of symptoms, uveitis evaluation are performed at the final safety follow-up visit at the discretion of the investigator.

c. Review concomitant medications with subject and document in source; update concomitant medication CRF page to include only those medications that are associated with AEs and SAEs (ie, used to treat event or suspected in causing event).

d. The ETP starts at Week 252. These procedures should only be completed for subjects who enter the ETP.

e. Perform at the discretion of the investigator.

f. Includes skin exam.

g. Tuberculin skin tests should also be performed in countries where the QuantiFERON®-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local Health Authorities.

h. Chest x-ray screening should be performed at the discretion of the investigator and per local and country regulations for children with JIA who are receiving immunosuppressive agents and who are at risk of TB.

i. Evaluations (based on physical examination and interview) should be performed at the discretion of the investigator. Slit lamp evaluations performed by an ophthalmologist/optometrist at the discretion of the investigator and per standard of care.

j. All female subjects of childbearing potential (ie, post-menarche) must test negative for pregnancy at all visits prior to study drug administration.

k. Subjects will be observed at the discretion of the investigator after the administration of study agent for symptoms of an infusion reaction.

l. Investigator will complete an annual attestation form to document that subject is benefiting from treatment.

m. 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: AE=adverse event; ANA=antinuclear antibodies; dsDNA=double-stranded deoxyribonucleic acid; ETP=Extended Treatment Period; IV=intravenous; SAE=serious adverse event; TB=tuberculosis.

ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ARC	Anticipated Event Review Committee
AS	ankylosing spondylitis
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guérin
β-hCG	β-human chorionic gonadotropin
BSA	body surface area
CHAQ	Childhood Health Assessment Questionnaire
CL/BSA	body surface area-normalized drug clearance
CL/F	apparent total systemic clearance
CRF	case report form
CRP	C-reactive protein
DAS	Disease Activity Index Score
DMARD	disease-modifying anti-rheumatic drug
DNA	deoxyribonucleic acid
dsDNA	double-stranded deoxyribonucleic acid
eDC	electronic data capture
ETP	Extended Treatment Period
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
HBsAg	HBV surface antigen
HBV	hepatitis B virus
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
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL-1β	Interleukin-1 beta
IL-6	interleukin-6
IRB	Institutional Review Board
JADAS	Juvenile Arthritis Disease Activity Score
JIA	juvenile idiopathic arthritis
LFT	liver function test
LTE	long-term extension
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamic(s)
PED	pediatric
pJIA	polyarticular juvenile idiopathic arthritis
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

q4w	every 4 weeks
q8w	every 8 weeks
RA	rheumatoid arthritis
RBC	red blood cell
RF	rheumatoid factor
SAE	serious adverse event
SC	subcutaneous
SF-36	36-item short form health survey
SI	International System of Units
SOC	system organ class
TB	tuberculosis
TNFα	tumor necrosis factor alpha
URTI	upper respiratory tract infection
US	United States
VAS	visual analog scale
vdH-S	van der Heijde Modified Sharp
V/F	apparent volume of distribution
Vss	volume of distribution at steady-state
WBC	white blood cell

1. INTRODUCTION

Golimumab is a fully human monoclonal antibody (mAb) with an immunoglobulin G1 heavy chain isotype (G1m[z] allotype) and a kappa light chain isotype. The molecular weight of golimumab ranges from 149,802 to 151,064 daltons. Golimumab binds to human tumor necrosis factor alpha (TNFα) with high affinity and specificity and neutralizes TNFα bioactivity.

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 anti-TNFα agents, can prevent the deleterious effects caused by excessive TNFα. SIMPONI® (golimumab) for intravenous (IV) use is being developed by the Sponsor to offer an alternative route of administration (compared with other available anti-TNFα agents) and a convenient dose regimen (ie, every 8 week [q8w] administration) for patients with polyarticular JIA (pJIA).

For the most comprehensive nonclinical and clinical information regarding SIMPONI® refer to the latest version of the Investigator's Brochure and Addenda for SIMPONI.

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

1.1.1. 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.[18] 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, rheumatoid factor [RF]-negative polyarthritis, RF-positive polyarthritis, enthesitis-related arthritis, psoriatic arthritis, undifferentiated arthritis) characterized by distinct clinical presentations and features.[16]

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.[18] 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 RF-positive polyarticular arthritis in older children, and HLA-B27 has been implicated in older boys with oligoarticular disease.[15,17]

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.[15] 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,[6] though the role of TNFα in systemic JIA is less convincing.[3]

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.[9,19,12,3,20] These studies have also found different cytokine profiles among patients with various JIA subgroups.

Juvenile idiopathic arthritis is an important cause of short-term and long-term disability in children,[14] but new advances in therapy have demonstrated clinically important steps forward. 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.[18] However, particularly serious complications of JIA include linear growth suppression, osteoporosis, local growth disturbances, macrophage activation syndrome and iridocyclitis.[18]

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 NSAIDs, intra-articular and systemic corticosteroids, methotrexate (MTX), and other DMARDs. The introduction of biological medications has provided an important new therapeutic option for the treatment of patients with JIA who are resistant to conventional anti-rheumatic agents.[18] Currently approved biologic therapies for the treatment of pJIA include etanercept, adalimumab, abatacept, and tocilizumab; canakinumab and tocilizumab have been approved for systemic JIA.

1.1.2. Golimumab Clinical Studies in Rheumatoid Arthritis and Juvenile Idiopathic Arthritis

Golimumab given as a SC injection has been demonstrated to be efficacious in adults with RA, PsA, ankylosing spondylitis (AS), and ulcerative colitis. Intravenous golimumab has also proven effective in adults with RA. Other anti-TNFα agents have been effective in the treatment of subjects with JIA. The Sponsor conducted a study of BSA-based dosages of SC golimumab (CNTO148JIA3001) to assess the benefits and risks associated with the use of SC golimumab in the treatment of multiple subtypes of JIA, including juvenile PsA.

The results of the CNTO148ART3001 study of IV golimumab in adults and the results of the CNTO148JIA3001 study of SC golimumab in subjects with JIA are described below.

1.1.2.1. Intravenous Golimumab in Adult Rheumatoid Arthritis

The primary objective of CNTO148ART3001, a randomized, placebo-controlled, multicenter, double-blind study, was to assess the clinical efficacy of IV administration of golimumab 2 mg/kg + MTX compared with MTX alone in adult subjects with active RA despite MTX therapy. Approximately 564 subjects were planned, and 592 were randomized.

Subjects were men or women 18 years of age or older with a diagnosis of RA for at least 3 months prior to screening who had active RA, defined as ≥6 tender and ≥6 swollen joints, at screening and at baseline, despite concurrent MTX therapy. At screening, subjects had to have C-reactive protein (CRP) measurement of ≥1.0 mg/dL (upper limit of normal=1.0 mg/dL) and be RF-positive.

Subjects randomized to golimumab received 2 mg/kg of golimumab intravenously over a 30±10 minute infusion time. Additionally, subjects were maintained on their stable dose of commercial MTX (between 15 mg and 25 mg/week) throughout the study.

Randomization was stratified based upon a screening CRP of <1.5 mg/dL or ≥1.5 mg/dL. Subjects were randomized 2:1 to golimumab + MTX or placebo + MTX at Week 0, Week 4, and every 8 weeks (q8w) thereafter. The duration of treatment for the entire study was 100 weeks with a 12 week safety follow-up period.

In total, 570 (96%) of 592 subjects completed the 24-week study. The remaining 22 (4%) subjects discontinued the study before Week 24. Most discontinuations were due to AEs: 9 [2.3%] subjects in the golimumab + MTX group and 2 [1.0%] subjects in the placebo + MTX group).

A significantly greater proportion of subjects in the golimumab + MTX group (58.5%) achieved the primary endpoint, an ACR 20 response at Week 14, compared with subjects in the placebo + MTX group (24.9%, p<0.001). The treatment effect was consistent in subjects with either a CRP ≥1.5 mg/dL or <1.5 mg/dL at screening. A significant difference in the proportion of ACR 20 responders between the golimumab + MTX and placebo + MTX groups was observed as early as Week 2. Major secondary efficacy endpoints were also achieved. A significantly greater proportion of subjects in the golimumab + MTX group had good or moderate Disease Activity Index Score (DAS)28 responses (using CRP) at Week 14 (81.3%) compared with subjects in the placebo + MTX group (40.1%, p<0.001).

There was a significantly greater improvement in Health Assessment Questionnaire Disability Index (HAQ-DI) disability scores at Week 14 in subjects in the golimumab + MTX group (0.500) compared with subjects in the placebo + MTX group (0.125, p<0.001). There was also a significant difference in clinically relevant improvements in HAQ-DI (≥0.25) in the golimumab + MTX group compared with the placebo + MTX group both at Week 14 (68.4% compared with 43.1%, respectively, p<0.001) and at Week 24 (67.6% compared with 45.2%, respectively, p<0.001). Subjects who received golimumab + MTX demonstrated significantly greater ACR 50

response rates at Week 24 (34.9%) compared with subjects who received placebo + MTX (13.2%, p<0.001).

A consistent treatment benefit was observed within subgroups of demography, baseline clinical characteristics, and prior exposure to medications for RA except for subgroups with small population size (ie, <15 subjects).

Statistically significant greater improvement in the mental and physical component summary scores of the 36-item short form health survey (SF-36) as well as all 8 scales of the SF-36 instrument were observed in golimumab + MTX treatment relative to placebo + MTX treatment at Week 12 (p<0.001 for all comparisons). These improvements were maintained through Week 24.

Through Week 16 (the placebo-controlled period prior to early escape) in CNTO148ART3001, 43.7% of subjects in the placebo group and 47.3% in the golimumab group had an AE; the highest incidence of AEs was in the Infections and infestations system organ class (SOC), 20.8% and 24.3% in the placebo and golimumab groups, respectively, with upper respiratory tract infection (URTI) being the most frequently reported AE (5.6% and 5.1% in the placebo and golimumab groups, respectively). Through Week 112, 79.1% of golimumab-treated subjects had an AE; the highest incidence of AEs was in the Infections and infestations SOC (50.5%) and URTI was the most frequently reported AE (11.5%).

Through Week 16 in CNTO148ART3001, 1.0% of subjects in the placebo group and 3.8% of subjects in the golimumab group had a serious adverse event (SAE). The incidence of SAEs within each SOC was <1.0%, and no SAE occurred in more than 1 subject. Through Week 112, 18.2% of golimumab-treated subjects had an SAE; the highest incidence of SAEs occurred in the infections and infestations SOC (5.5%) and musculoskeletal and connective tissue disorders SOC (3.4%) and the most frequently reported SAE was RA (2.1%).

Through Week 24, 1 patient died in the CNTO148ART3001 study; this subject was randomized to treatment with placebo + MTX, had never received golimumab, and died of a presumed cerebrovascular accident (stroke). Through Week 112, an additional 5 subjects died in the CNTO148ART3001 study. Two subjects randomized to treatment with placebo + MTX died, both after switching to golimumab 2 mg/kg + MTX; cause of death was sudden death (n=1) and complications of severe dehydration, *Clostridium difficile* colitis, and atrial fibrillation (n=1). Three subjects randomized to treatment with 2 mg/kg golimumab + MTX died in the study; reported cause of death was acute abdominal syndrome (later diagnosed as peritoneal tuberculosis [TB], n=1), presumed myocardial infarction (MI, n=1), and septic shock secondary to a pyogenic lung abscess due to *Acinetobacter baumannii* (n=1).

No malignancies were reported through Week 16 in study CNTO148ART3001. There was 1 case of nontreatment-emergent lung adenocarcinoma reported in the placebo + MTX group prior to receiving study agent. Through the placebo-controlled period (Week 24), 1 malignancy (breast cancer) was reported in the golimumab group. Through Week 112, 5 additional malignancies

were reported, including basal cell carcinoma, chronic lymphocytic leukemia in a subject with a family history of chronic lymphocytic leukemia, cervix carcinoma in situ, Bowen's Disease, and basal cell carcinoma. No lymphomas were reported through Week 112.

Through Week 16 in CNTO148ART3001, 0.8% of subjects in the golimumab group had a serious infection, including appendicitis, bacteremia, and (complications of) interstitial lung disease. No subjects in the placebo group had a serious infection. Through Week 112, 6.2% of golimumab-treated subjects had a serious infection. Serious infections occurring in more than one subject were pneumonia (n=5), UTI (n=4), and erysipelas (n=2).

Through Week 16 in CNTO148ART3001, 0.5% of subjects in the placebo group and 2.5% of subjects in the golimumab group had an infusion reaction. Through Week 112, 3.9% of golimumab-treated subjects had an infusion reaction and 0.4% of infusions were complicated by infusion reactions. It should be noted that all placebo infusions consisted of 0.9% normal saline alone rather than a true matched placebo. No serious infusion reactions requiring study agent discontinuation were noted. There was a case of anaphylaxis, which was not associated with study drug.

For the most comprehensive nonclinical and clinical information regarding golimumab, refer to the latest version of the Investigator's Brochure and Addenda for SIMPONI (golimumab).

The median peak serum golimumab concentration (ie, post-infusion golimumab concentration) of 41.56 µg/mL was observed at Week 4 following IV administration of 2 mg/kg golimumab at Week 0, Week 4, followed by q8w (±1 week) administration. This peak is higher than that reported for SC golimumab administration of 50 mg every 4 weeks (q4w). The median trough serum golimumab concentration in subjects receiving IV golimumab at 2 mg/kg q8w with MTX was 0.28 µg/mL at Week 12 and 0.22 µg/mL at Week 20; these levels are similar to those reported with SC golimumab 50 mg. Overall exposure to golimumab is approximately 3 times that for SC golimumab 50 mg over a similar period of exposure.

Data from the IV golimumab program demonstrated less radiographic progression in subjects treated with golimumab compared with subjects who received placebo. There was a significant difference in change from baseline in total van der Heijde Modified Sharp (vdH-S) score at Week 24 (placebo + MTX: 1.09 ± 3.194, golimumab 2 mg/kg + MTX: 0.03 ± 1.899 [$p<0.001$]) between the golimumab + MTX treatment group and placebo + MTX. Significant differences in favor of IV golimumab were also observed in changes from baseline in erosion and joint space narrowing scores. The proportion of subjects with radiographic progression based on the smallest detectable change was significantly lower for subjects treated with golimumab + MTX when compared with placebo + MTX for the total vdH-S score ($p<0.001$) as well as both erosion ($p=0.001$) and joint space narrowing measurements ($p=0.01$).

1.1.2.2. Subcutaneous Golimumab in Juvenile Idiopathic Arthritis

CNTO148JIA3001 was a randomized withdrawal, double-blind, placebo-controlled, parallel-group, multicenter study of BSA-based 30 mg/m^2 (up to a maximum 50 mg/dose) SC golimumab given every 4 weeks (q4w) in pediatric subjects with active pJIA despite current treatment with MTX. The study population comprised subjects with pJIA receiving MTX, ages 2 to less than 18 years, with at least a 6-month history of pJIA, and active arthritis in ≥5 joints. All subjects received SC golimumab in the active treatment portion of the study from Week 0 through Week 16. At Week 16, JIA ACR 30 responders were randomized to receive placebo or golimumab for 32 weeks; subjects randomized to placebo who experienced flares during this 32-week period had golimumab therapy re-instituted. The placebo-controlled period was through Week 48, and the long-term extension (LTE) was planned from Week 48 through Week 248.

Approximately 170 subjects were planned, and 173 subjects were enrolled into the study. All of the 173 subjects were included in the Week 48 efficacy and safety analyses. Nineteen of the 173 subjects discontinued study agent through Week 16 (due to: lack of efficacy [n = 14]; AEs [n = 4]; withdrawal of consent [n = 1]), and 154 subjects entered randomized withdrawal (76 to placebo and 78 continued golimumab).

The baseline disease characteristics of the 173 enrolled subjects constituted a population with moderate to severe JIA comparable with other clinical studies of anti-TNFα agents in pJIA, with the exception of numerically lower mean and median CRP/ESR levels in CNTO148JIA3001.

The proportion of subjects who were JIA ACR 30 responders at Week 16 was 87.3%. Additionally, the proportion of JIA ACR 50, JIA ACR 70, and JIA ACR 90 responders at Week 16 were 79.2%, 65.9%, and 36.4%, respectively.

The study did not meet its primary and major secondary endpoints as the proportion of subjects who were JIA ACR 30 responders at Week 16 and did not experience a flare of disease between Week 16 and Week 48 was not significantly different in subjects randomized to continued golimumab treatment between Weeks 16 and 48 as compared with subjects randomized to receive placebo between Weeks 16 and 48 (59% versus 52.6%, p=0.41). All sensitivity analyses and major secondary endpoints demonstrated the lack of statistically significant differences between treatment groups. The Sponsor terminated the LTE of the study early as pre-specified efficacy endpoints were not met.

Post-hoc analyses that evaluated flare rates based on Week 0 CRP levels ranging from 0.1-1.0 mg/dL demonstrated that, in general, among subjects with higher baseline CRP levels, the subjects who received continued golimumab therapy had significantly fewer flare episodes than subjects who were randomized to placebo at Week 16.

When JIA ACR response rates were analyzed based on observed data through Week 48 (using Week 0 as baseline and comparing drug/placebo effect at each visit through Week 48), JIA ACR 30 response rates of 89% to 95.9% and JIA ACR 90 response rates of 53.4% to 56.2% were achieved at Week 48. Improvements in the core sets through Week 48 were similar at all

visits in subjects randomized to golimumab at Week 16 as compared with subjects randomized to placebo at Week 16 and all represented clinically meaningful improvement in disease, eg, median percent improvement of 94.6% and 95.1% in Physician Global Assessment of Disease Activity, and median percent improvement of 90.9% and 100% in the number of active joints.

Pharmacokinetic (PK) and immunogenicity data were collected through Week 48 in CNTO148JIA3001. In subjects with pJIA who received golimumab 30 mg/m^2 SC and were randomized to stay on active treatment, median trough golimumab concentrations at Week 12, Week 24, and Week 48 were 1.16 µg/mL, 1.12 µg/mL, and 0.95 µg/mL, respectively, indicating that steady-state levels were maintained though Week 48. Furthermore, steady-state trough golimumab concentrations were similar across different age groups, body weight quartiles, body mass index quartiles, and body weight categories in subjects with pJIA. Overall, these concentrations were similar to the PK exposure observed in the adult active RA population (despite MTX) in C0524T06 treated with SC golimumab, and thus supported the hypothesis that the BSA-based golimumab regimen of 30 mg/m^2 SC q4w was sufficient to produce concentrations comparable to that seen in the adult RA population who received golimumab 50 mg SC q4w. Further, PK and efficacy analyses showed that similar efficacy (as measured by JIA ACR 30 response, and flare rates) were seen in subjects with pJIA in the 4 subgroups of steady-state trough golimumab concentration quartiles. Additionally, there were no apparent PK differences observed between subjects with and without flares.

With regards to immunogenicity, 40.1% of subjects developed antibodies to golimumab using the recently developed drug tolerant immunoassay analyses. The new drug tolerant immunoassay is more sensitive compared with assays used previously in adult golimumab RA studies and allows the detection of antibodies to golimumab despite detectable serum golimumab levels. Among subjects who were randomized and remained on golimumab 30 mg/m^2 SC + MTX, 30.8% developed antibodies to golimumab; antibody titers tended to be low. When evaluating the effects of immunogenicity on PK, efficacy, and safety, it was found that positive anti-golimumab antibody status decreased steady-state trough golimumab concentrations when the titer levels were >1:100. However, the effect of antibodies on efficacy was less sensitive, requiring higher titers >1:1000 in order to correlate with apparent reductions in efficacy. Since only approximately 5% of subjects with JIA developed anti-golimumab antibodies with titers >1:1000, it was determined that immunogenicity was not a contributing factor to lack of achievement of the primary endpoint in CNTO148JIA3001. Additionally, positive anti-golimumab antibody status did not appear to be associated with a higher incidence of injection-site reactions.

The proportion of subjects who reported an AE through Week 48 was 87.9%. The most commonly reported SOC of AEs was Infections and infestations (67.1%), and were predominantly URTIs and nasopharyngitis. There was no marked difference in AEs reported between Week 16 and Week 48 for subjects randomized to placebo (82.9%) and those randomized to continued golimumab treatment (78.2%); however, it needs to be noted that all subjects in randomized withdrawal portion of the study were exposed to golimumab for

16 weeks before re-randomization. Serious adverse events were reported by 13.3% of subjects. The most commonly reported SAE was worsening of JIA (6.4%). Serious infections were reported in 2.9% of subjects (pneumonia, urinary tract infection, herpes zoster, URTI, and pyelonephritis), and there were no deaths, malignancies, or demyelination events through Week 48. There were no reports of active TB and no serious opportunistic infections. Through Week 48, the number of subjects with abnormal alanine aminotransferase (ALT) measurements (and no concomitant treatment for latent TB, which may affect liver function tests [LFTs]) was 29.5% (51/167), 39 of the 51 subjects had elevations <3×ULN.

There were 2 subjects with ALT elevation to > 8×ULN but neither subject met the criteria for Hy's Law consistent with hepatotoxicity. Subjects were not receiving TB prophylaxis; one of the subjects had baseline ALT which was already abnormal. All subjects with LFT abnormalities were managed conservatively with changes in MTX dosing but one subject was discontinued for elevated LFTs.

The incidence of injections with injection-site reactions through Week 48 was 0.8%; there was one SAE report of serum sickness-like reaction in a subject randomized to placebo who resumed golimumab treatment.

For the most comprehensive nonclinical and clinical information regarding golimumab, refer to the latest version of the Investigator's Brochure and Addenda for SIMPONI (golimumab).

Although the CNTO148JIA3001 study did not meet its endpoints, when JIA ACR response rates were analyzed as observed data through Week 48 (using Week 0 as baseline and comparing drug/placebo effect at each visit through Week 48) the study showed the potential for efficacy that could be attained with SC golimumab in children with pJIA. Therefore, it lends support to the study of IV golimumab in subjects with pJIA who have an inadequate response to MTX.

1.2. Overall Rationale for the Study

Intravenous golimumab has been demonstrated to be efficacious in the treatment of adults with RA (Section 1.1.2.1). Other biologics, including anti-TNFα agents, have been shown to be effective in the treatment of subjects with pJIA. Though biologic infusion therapies are available for the treatment of pJIA, there are currently no approved intravenously administered anti-TNFα agents for this condition. The every 8 week, 30-minute infusion paradigm proposed in this study for children and studied in adults with RA may be appropriate for populations of patients where greater physician scrutiny of drug therapy may be needed or requested. Particularly in the pediatric population, the reduction in the number of drug administrations (ie, to an every 8 week maintenance schedule) could provide greater convenience and less pain (due to fewer IV administrations) compared with other biologic agents. In addition, switching to a different anti-TNFα agent in a patient in whom a previous anti-TNFα agent was not efficacious may provide further symptomatic relief of disease.

The primary objective of this study is to characterize the PK of IV golimumab in pJIA, along with evaluations of the safety and efficacy of IV golimumab in these subjects. This study will also include subjects with multiple subtypes of JIA, including juvenile PsA, as well as subjects with prior anti-TNFα experience (up to 30% of the study population).

The study is designed to obtain PK data in response to BSA-based (80 mg/m^2, which is expected to be equivalent to the 2 mg/kg dose in adult RA patients weighing 70 kg) IV golimumab for subjects with pJIA who have inadequate response to MTX treatment as well as prior treatment with non-steroidal anti- inflammatory agents, corticosteroids, and/or anti-TNFα agents, with the intent to demonstrate its similarity to the response seen with weight-based (2 mg/kg) doses of IV golimumab in adult RA subjects who have inadequate response to MTX treatment. The 80 mg/m^2 dose for subjects with pJIA is based on the 2 mg/kg dose studied in CNTO148ART3001 in the adult RA population.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

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

Secondary Objectives

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

2.2. Hypothesis

No formal hypothesis testing is planned in this study.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 3, open-label, single-arm, multicenter study to evaluate the PK, safety, and efficacy of IV golimumab in subjects with active pJIA despite current treatment with MTX. The study population will comprise subjects with pJIA receiving MTX, ages 2 to less than 18 years, with at least a 3-month history of pJIA, and active arthritis in ≥5 joints. Approximately 120 subjects will be enrolled at Week 0 to ensure that approximately 100 subjects remain in the study at Week 52. Enrollment patterns are expected to yield a subject population of approximately 10% aged 2 to up to 6 years, approximately 20% aged 6 to up to 12 years, and approximately 70% aged 12 to less than 18 years.

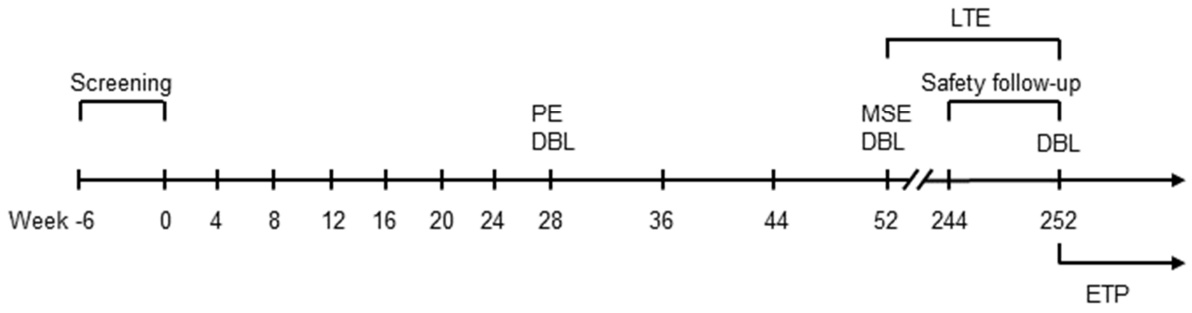
All subjects will receive 80 mg/m^2 golimumab (maximum single dose 240 mg) as an IV infusion given over 30±10 minutes at Weeks 0, 4, and every 8 weeks (q8w; ±3 days) through Week 28 and then q8w (±1 week) thereafter through Week 244. Body surface area will be calculated based on the subject's height and body weight measured at each visit, and the BSA-based dose of golimumab will be adjusted as needed to maintain the dose at 80 mg/m^2. Subjects will also receive commercial MTX weekly through Week 28 at the same BSA-based dosage (10 to 30 mg/m^2 per week of MTX in subjects with BSA <1.67 m^2, or a minimum of 15 mg/week in subjects with BSA ≥1.67 m^2) as at time of study entry as outlined in Section 6.2. At Week 252, subjects who meet the inclusion criteria for the optional Extended Treatment Period (ETP) may continue treatment with golimumab (80 mg/m^2 q8w) after completion of the Week 252 assessments.

Every effort should be made to maintain subjects at a dose of 80 mg/m^2 of golimumab based upon BSA, and decreases below or increases above 80 mg/m^2 or shortening of the dosing interval (eg, from 8 weeks to 6 weeks) will not be permitted at any visit.

This is an open-label study, with all subjects receiving the same BSA-based dose of IV golimumab. Safety data will be routinely evaluated by the study's medical monitor. Therefore, an external Data Monitoring Committee will not be established.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



DBL = Database lock ETP = Extended Treatment Period LTE = Long-term extension MSE = Major secondary endpoint PE = Primary endpoint

All subjects receive 80 mg/m^2 golimumab IV infusion at Weeks 0, 4, and every 8 weeks thereafter through Week 244. Subjects who meet inclusion criteria for the optional ETP may continue treatment with golimumab after completion of the Week 252 assessments. Subjects will receive commercial methotrexate at least through Week 28 at the same weekly BSA-based dose as at time of study entry.

3.1.1. Week 0 Through Week 28

Through Week 28, subjects will be monitored and disease activity and safety will be assessed at the investigative site every 4 weeks.

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

After all subjects complete the Week 28 visit, the database will be locked to assess PK, safety and efficacy. An additional safety, efficacy, and PK database lock is currently planned for Week 52. A database lock will be performed at Week 252, and a final database lock will be performed at the end of study.

No changes should be made to background medications (ie, MTX, other DMARDs, corticosteroids, and NSAIDs) in terms of increases or decreases in dosage beyond the parameters provided in Section 8 (eg, no more than 10 mg/day prednisone or no more than 0.20 mg/kg/day, whichever is lower) and/or route of administration between Weeks 0 and 28, unless there is a safety concern (eg, elevated LFTs), which requires changes to background medications.

If 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.

3.1.2. Week 28 Through Week 52

From Week 28 through Week 52, infusions will continue to be performed every 8 weeks (±1 week); however, subjects will be actively monitored at the investigative site and disease activity and safety will be assessed at the investigative site every 8 weeks rather than every 4 weeks as between Weeks 0 and 28. As noted above, after Week 28 subjects will be permitted to change/add MTX, other DMARD**s**, corticosteroids, and NSAIDs as outlined in Section 8.

3.1.3. Week 52 Through Week 252 (Long-term Extension)

Subjects who complete the study at Week 52 will have the option to enter into the LTE phase of this study. Subjects who opt not to enter the LTE will be encouraged to complete an additional 8-week safety follow-up visit following the last administration of study agent.

During the LTE, all subjects will continue to receive golimumab q8w (±1 week) through Week 244. For subjects who have completed the trial period of 252 weeks and for whom drug is proven beneficial but is not commercially available for pJIA indication (or patient does not qualify for insurance to pay for the drug) IV golimumab will continue to be provided by the Sponsor, as described in Section 3.1.4. Between Week 52 and Week 252, disease activity will be

monitored and assessed by investigators, and benefit of treatment will be documented in the subject's source documents by investigators on a yearly basis via an attestation form; infusions and safety measurements will be done at the investigative site according to the Time and Events Schedule.

As noted above, after Week 28, subjects will be permitted to change/add MTX, other DMARDs, corticosteroids, and NSAIDs, including increases or decreases in BSA-based dosing (where appropriate) for these classes of agents as outlined in Section 8.

All subjects who complete the Week 244 visit are expected to participate in the safety follow-up visit at Week 252. Those subjects who discontinue study agent at any time before Week 244 are also expected to return for a safety follow-up visit approximately 8 weeks after the last administration of study agent.

A database lock will occur at Week 252.

3.1.4. After Week 252 (Extended Treatment Period)

Subjects <18 years of age who complete the study through Week 252, and for whom drug is proven beneficial but is not commercially available for pJIA, will have the option to enter the ETP at Week 252, as described in Attachment 6.

The final database lock will occur at the end of the ETP, as described in Attachment 6.

3.1.5. End of Study Definition

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

3.2. Study Design Rationale

3.2.1. Blinding, Control, Study Phase/Periods, Treatment Groups

This is a single-arm, open-label study to evaluate the PK of IV golimumab in subjects with pJIA, with all subjects receiving the same BSA-based dose of IV golimumab through Week 52. Subjects who complete the study at Week 52 will have the option to enter into the LTE phase of this study through Week 252. After Week 252, subjects who meet specific criteria (see Attachment 6) will have the opportunity to continue treatment with golimumab in the ETP.

3.2.2. Dose Selection

Unlike adult drug doses, pediatric drug doses (parenteral) are commonly calculated individually as weight-based (mg/kg) or BSA-based (mg/m^2) doses to manage the PK variability observed in children across different ages as changes occur in their maturing organ systems.[10,22] 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 (eg, adalimumab and etanercept) supports the assumption that clinical responses to anti-TNFα agents in rheumatoid disease would be similar between adults and children. That is, after the PK differences inherent

between adults and children are accounted for, similar drug responses would be expected with similar drug exposure in both adults and children.

Data from the Phase 3 IV study in adults with RA (CNTO148ART3001) through 24 weeks have shown that golimumab 2 mg/kg at Week 0, Week 4, and q8w (±1 week) thereafter is the optimal dose regimen for the treatment of RA in most adults. For a child, golimumab 80 mg/m^2 (2 mg/kg/1.73 m^2) would be approximately equivalent to 2 mg/kg for an adult subject weighing 70 kg (with a BSA of 1.73 m^2). Thus, in the current study (CNTO148JIA3003), a dose of golimumab 80 mg/m^2 has been chosen to evaluate the safety and efficacy of golimumab in the pJIA population.

3.2.3. Rationale

The open-label study design for IV golimumab in the pJIA population is based on data from studies of other anti-TNFα agents in adult RA and pJIA, PK and efficacy data from the Sponsor's study of IV golimumab in adult RA (CNTO148ART3001), the Sponsor's experience with SC golimumab in pJIA (CNTO148JIA3001), and feedback from the Pediatric Rheumatology International Trials Organisation (PRINTO) and The Pediatric Rheumatology Collaborative Study Group (PRCSG).

The Sponsor will utilize PK data generated from the proposed open-label CNTO148JIA3003 study to extrapolate to adult PK data from the CNTO148ART3001 study in RA, which was the pivotal study that served as the basis for approval of IV golimumab (SIMPONI ARIA/SIMPONI for Intravenous Use) for adult patients with RA. Additionally, efficacy (PD) data will be collected to explore the assessment of supportive exposure-response.

4. SUBJECT POPULATION

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

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate Sponsor representative before enrolling a subject in the study.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Approximately 120 subjects will be enrolled in this study. Enrolled subjects who discontinue study treatment or withdraw from study participation will not be replaced with new subjects.

Retesting of an abnormal screening value that leads to exclusion is allowed only once using an unscheduled visit during the screening period to reassess eligibility. This should be considered only if there is no anticipated impact on subject safety.

Eligibility criteria for the ETP are provided in Attachment 6. Prohibitions and restrictions during the ETP are also provided in Attachment 6.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. Subjects must be age 2 years to less than 18 years with a body weight >15 kg at the time of screening and at Week 0.

2. Diagnosis must be made per JIA ILAR diagnostic criteria and the onset of disease must have been before the subject's 16th birthday.

3. Active JIA of one of the following subtypes:

    a. Rheumatoid factor positive or negative pJIA for ≥3 months prior to screening, or

    b. Systemic JIA with no systemic symptoms for ≥3 months, but with polyarthritis for ≥3 months prior to screening, or

    c. Extended oligoarticular JIA ≥3 months prior to screening, or

    d. Polyarticular juvenile psoriatic arthritis ≥3 months prior to screening, or,

    e. Enthesitis-related arthritis ≥3 months prior to screening.

4. Failure or inadequate response to at least a 2-month course of MTX before screening.

5. Subjects must have ≥5 joints with active arthritis at screening and at Week 0 as defined by ACR criteria (ie, a joint with either swelling, or in the absence of swelling, limited range of motion associated with pain on motion or tenderness).

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

7. Subjects must have active pJIA despite current use of oral, intramuscular, or subcutaneous MTX for ≥2 months before screening. For subjects with BSA <1.67 m^2, the MTX dose must be between 10 to 30 mg/m^2 per week and stable for ≥4 weeks before screening. For subjects with BSA ≥1.67 m^2, the MTX dose must be a minimum of 15 mg/week and must be stable for ≥4 weeks before screening. In situations where there is documented intolerance of doses >10 mg/m^2 weekly (for subjects with BSA <1.67 m^2) or ≥15 mg/week (for subjects with BSA ≥1.67 m^2); or where documented country or site regulations prohibit use of ≥15 mg of MTX per week in subjects with BSA ≥1.67 m^2, subjects may be entered into the trial on a lower dose of MTX.

8. If using corticosteroids, must be on a stable dose of ≤10 mg/day prednisone equivalent or 0.20 mg/kg/day (whichever is lower) for ≥2 weeks before first administration of study agent. If currently not using corticosteroids, the subject must have not received corticosteroids for at least 2 weeks before the first dose administration. Subjects with systemic onset JIA but without systemic symptoms must be on a stable dose of corticosteroids for at least 3 days prior to screening.

9. If using NSAIDs, must be on a stable dose for ≥2 weeks before screening. If not currently using NSAIDs, must not have taken them for at least 2 weeks before screening.

10. Subjects are considered eligible according to the following TB screening criteria:

    a. Have no history of latent or active TB prior to screening. An exception is made for subjects currently receiving treatment for latent TB with no evidence of active TB, or who have a history of latent TB and documentation of having completed appropriate treatment for latent TB within 3 years prior to the first administration of study agent. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculous 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 prior to the first administration of study agent.

    d. Within 6 weeks prior to the first administration of study agent, have a negative QuantiFERON®-TB Gold (Attachment 1) test result, or have a newly identified positive QuantiFERON®-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB (Section 9.1.2) has been initiated prior to the first administration of study agent. Within 6 weeks prior to the first administration of study agent, a negative tuberculin skin test (Attachment 2), or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study agent, is additionally

required if the QuantiFERON®-TB Gold test is not approved/registered in that country or the tuberculin skin test is mandated by local Health Authorities.

e. Indeterminate results should be handled as outlined in Section 9.1.2. Subjects with persistently indeterminate QuantiFERON®-TB Gold test results may be enrolled without treatment for latent TB, if active TB is ruled out, 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. This determination must be promptly reported to the Sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

f. The QuantiFERON®-TB Gold test and the tuberculin skin test are not required at screening for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; Subjects with documentation of having completed adequate treatment as described above **are not** required to initiate additional treatment for latent TB.

g. Unless country or local guidelines do not recommend a chest radiograph as a necessary screening process prior to initiation of anti-TNFα therapies, a chest radiograph (posterior-anterior view) must have been taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current active TB or old inactive TB. Chest radiographs (both posterior-anterior and lateral views) must be performed as part of the screening process in all cases when either the tuberculin skin test and/or QuantiFERON®-TB Gold testing for TB is positive.

11. Subjects must be 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.

12. Girls must be either:

- Not of childbearing potential: premenarchal; permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy,

  OR

- Of childbearing potential, and if sexually active, practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject and at the discretion of the investigator/per local regulations). Girls of

childbearing potential must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 6 months after receiving the last dose of study drug.

Note: If the childbearing potential changes after start of the study (eg, girl who is not heterosexually active becomes active, premenarchal girl experiences menarche) a girl must begin a highly effective method of birth control, as described above.

13. Girls of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) test at screening and a negative urine pregnancy test at each study visit where golimumab infusion is to take place.

14. Boys must practice abstinence, or if sexually active with a girl of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all boys must also not donate sperm during the study and for 6 months after receiving the last dose of study drug.

15. Subjects' 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:

       – Aspartate aminotransferase (AST)

          - ≤67 IU/L (girls, ages 2 to <4)
          - ≤58 IU/L (girls, ages 4 to <7)
          - ≤48 IU/L (girls, ages 7 to 18)
          - ≤83 IU/L (boys, ages 2 to <4)

- ≤71 IU/L (boys, ages 4 to <7)
- ≤48 IU/L (boys, ages 7 to 18)

– Alanine aminotransferase (ALT)

- ≤41 IU/L (girls, ages 2 to 18)
- ≤41 IU/L (boys, ages 2 to <10)
- ≤52 IU/L (boys, ages 10 to 18)

f. 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. Subjects must be up to date with all immunizations in agreement with current local immunization guidelines for immunosuppressed subjects before Week 0.

17. A parent or guardian should accompany the subject to each study visit until the subject reaches the age of 18 years.

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

19. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

20. Each subject (or their legally acceptable representative) must sign an ICF indicating that he or she understands 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 7 years of age and older and per local regulations) as described in Section 16.2.3, Informed Consent.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

Concomitant or previous medical therapies received:

1. Subject has initiated DMARDs and/or immunosuppressive therapy within 4 weeks prior to first study agent administration.

2. Subject has been treated with intra-articular, intramuscular or intravenous corticosteroids (including intramuscular corticotropin) during the 4 weeks before first study agent administration.

3. Subject has been treated with any therapeutic agent targeted at reducing IL-12 or IL-23, including but not limited to ustekinumab and ABT-874 within 3 months before first study agent administration**.**

4. Subject has 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 has evidence at screening of persistent depletion of the targeted lymphocyte after receiving any of these agents.

5. Subject has been treated with alefacept within 3 months before first study agent administration.

6. Subject has been treated with abatacept within 8 weeks before first study agent administration.

7. Subject has 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.

8. Subject has been treated with cytotoxic agents, including cyclophosphamide, nitrogen mustard, chlorambucil, or other alkylating agents.

9. Subject has received or is expected to receive any live viral or live bacterial vaccinations from 3 months before first study agent administration and up to 3 months after the last study agent administration.

10. Subject has had a BCG vaccination within 12 months of screening or is planned to receive BCG vaccination within 12 months following last study drug administration.

11. Subject has received IL-1ra (anakinra) within 1 week of the first study agent administration.

12. Subject has previously been treated with more than 2 therapeutic agents targeted at reducing TNFα, including, but not limited to, infliximab, etanercept, adalimumab, or certolizumab pegol.

13. If a subject has been previously treated with an anti-TNFα agent, the reason for discontinuation of the anti-TNFα agent cannot have been a severe or serious adverse event consistent with the class of anti-TNFα agents.

14. Subject has received adalimumab or certolizumab pegol within 6 weeks or has received etanercept within 4 weeks of the first dose of study agent.

15. Subject has received infliximab or tocilizumab within 8 weeks of the first administration of study agent.

16. Subject has ever received IV or SC golimumab.

17. Subject has received a Janus kinase (JAK) inhibitor, including but not limited to tofacitinib, within 2 weeks of the first dose of study agent.

18. Subject has received canakinumab within 4 months prior to first study dose administration.

19. Subject has current side effects related to MTX or conditions that 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.

20. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 3 months or 5 half-lives, whichever is longer, before the planned first dose of study drug or is currently enrolled in an investigational study.

Infections or predisposition to infections:

21. Subject has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. Refer to inclusion criterion (Section 4.1) for information regarding eligibility with a history of latent TB.

22. Subject tests positive for hepatitis B virus (Attachment 3).

23. Subject is seropositive for antibodies to hepatitis C virus (HCV).

24. Subject has a known history of infection with human immunodeficiency virus (HIV).

25. Subject has had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystis, or aspergillosis) within 6 months prior to screening.

26. Subject has a history of an infected joint prosthesis or has received antibiotics for a suspected infection of a joint prosthesis unless that prosthesis has been removed or replaced.

27. Subject has or has 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.

28. Subject has 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), open, draining, or infected skin wound, or ulcer.

29. Subject has a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB (if applicable).

Malignancy or increased potential for malignancy:

30. Subject has a known malignancy or a history of malignancy.

31. Subject has 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 not consistent with pJIA or systemic onset JIA without systemic symptoms.

Coexisting medical conditions or past medical history:

32. Subject has a history of severe progressive or uncontrolled liver or renal insufficiency; or significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, psychiatric, or metabolic disturbances.

33. Subject has known allergies, hypersensitivity, or intolerance to golimumab or its excipients (refer to Investigator's Brochure) or subject has known allergies, hypersensitivity, or intolerance to immunoglobulins.

34. Subject has or has had a substance abuse (drug or alcohol) problem.

35. Subject has a history of macrophage activation syndrome.

36. Subject has another inflammatory disease that might confound the evaluation of benefit from golimumab therapy, including but not limited to systemic lupus erythematosus or Lyme disease.

37. Subject is incapacitated, largely or wholly bedridden, or confined to a wheelchair, or has little or no ability for age-appropriate self-care.

38. Subject has a known history of demyelinating diseases such as multiple sclerosis.

39. Subject has a history of, or concomitant diagnosis of, congestive heart failure.

Other:

40. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

41. Subject is a girl who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study drug.

42. Subject is a boy who plans to father a child while enrolled in this study or within 6 months after the last dose of study drug.

43. Subject is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access.

44. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

45. Subject has active uveitis within 3 months prior to screening.

46. Subject with BSA >3.0 m^2.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Subjects must not receive a live virus or live bacterial vaccination 3 months prior to screening, during the study, or within 3 months after the last administration of study agent.

2. Subjects must not receive a BCG vaccination for 12 months before screening, during the study or within 12 months after the last administration of study agent.

3. If sexually active and of childbearing potential, girls must remain on a highly effective method of birth control during the study and for 6 months after receiving the last administration of study agent, including the LTE phase of the study. Girls must not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 6 months after receiving the last dose of study agent, including the LTE phase of the study.

4. If sexually active with a girl of childbearing potential and has not had a vasectomy, boys must use a double barrier method of birth control during the study and for 6 months after receiving the last administration of study agent, including the LTE phase of the study. Boys must not donate sperm and must agree not to plan a pregnancy or father a child during the study and for 6 months following the last administration of study agent, including the LTE phase of the study.

5. Intramuscular administration of corticosteroids for the treatment of pJIA is not allowed during the study. Corticosteroids administered by bronchial or nasal inhalation for treatment of conditions other than pJIA may be given as needed throughout the course of the study. For additional details, see Section 8.

6. Subjects must not receive investigational drugs, other immunosuppressants (such as, but not exclusively, cyclophosphamide), or other biologics for pJIA during the study.

5. TREATMENT ALLOCATION AND BLINDING

This is an open-label study. All subjects will receive golimumab 80 mg/m^2 at Week 0, Week 4, and q8w (± 3 days) through Week 28 and q8w (± 1 week) after Week 28.

As this is an open-label study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

6.1. Golimumab

The study will have 1 active treatment group and all subjects will receive 80 mg/m^2 golimumab (maximum single dose 240 mg) IV infusions at Week 0, Week 4, and q8w (±3 days) through Week 28 and q8w (±1 week) thereafter through Week 244. The golimumab infusions will be prepared by a pharmacist under sterile conditions using golimumab 50 mg/4 mL liquid in vials and a 100 mL infusion bag of 0.9% saline. Subjects will receive 80 mg/m^2 golimumab IV infusions over 30±10 minutes. Infusions may be slowed down for evidence of infusion reactions

as deemed appropriate by the investigator, and all changes in the infusion rate should be recorded in the CRF. Body surface area will be calculated at each visit and the dose of golimumab will be adjusted as needed to maintain the dose at 80 mg/m^2. Body surface area will be calculated using the Mosteller equation: BSA (m^2) = ([height (cm) x weight (kg)]/3600)$^{1/2}$. For additional details, see the Site IP Manual.

During the ETP, golimumab will be administered as described in Attachment 6. The first dose of golimumab during the ETP will be at Week 252 after the subject has completed the Week 252 assessments.

6.2. Methotrexate

Subjects will receive commercial MTX through Week 28 at the same BSA-based dose (10 to 30 mg/m^2 per week for subjects with BSA <1.67 m^2 or at least 15 mg/week for subjects with BSA ≥1.67 m^2) as at time of study entry. Absolute dose should remain stable from baseline through Week 28.

Every effort should be made to ensure that subjects remain on the same dose and route of administration of MTX through the Week 28 visit, unless intolerance or AEs due to MTX occur (Section 8). Guidelines for adjusting MTX dosage in the event of MTX toxicity are provided in the Trial Center File.

Subjects will also receive a total dose of commercial folic acid ≥5 mg weekly or folinic acid (at half the MTX dose) given the day after the weekly MTX dose. In children <12 years of age, the administration of folic acid or folinic acid will be at the discretion of the physician.

After Week 28, changes in MTX administration are permitted (eg, increase or decrease in dosage, change in route of administration, or discontinuation).

7. TREATMENT COMPLIANCE

The study site personnel will ensure compliance with the treatment assignments. Site personnel will administer the study infusion at each visit and record the amount of infusion given.

All subject 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 visits, will be recorded on the CRF. Subject charts will be reviewed and compared with the data entries on the CRFs to ensure accuracy.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy JIA medications administered before the first dose of study agent must be recorded at screening. All concomitant therapies must be recorded through Week 52 of the study beginning with the administration of the first dose of the study drug. After Week 52, the investigator will review concomitant medications with the subject and document in source, and record on the CRF

page only those concomitant medications that are associated with AEs and SAEs (ie, used to treat event or suspected in causing event).

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation and acupuncture) different from the study drug must be recorded in the CRF through Week 52. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study.

If using corticosteroids or NSAIDS, subjects must have been on stable doses of these medications prior to study entry per Inclusion Criterion 8 and 9 (Section 4.1). Subjects may have been previously treated with no more than 2 therapeutic agents targeted at reducing TNFα prior to study entry per Exclusion Criterion 12 (Section 4.2). Subjects may not have initiated or been treated with prohibited therapeutic agents as outlined in Exclusion Criteria 1 through 20 (Section 4.2).

Subjects must have received MTX for ≥2 months before screening. For subjects with BSA <1.67 m^2, the MTX dose must be between 10 to 30 mg/m^2 per week and stable for ≥4 weeks before screening. For subjects with BSA ≥1.67 m^2, the MTX dose must be a minimum of 15 mg/week of MTX and must be stable for ≥4 weeks before screening. For exceptions to this rule, see Inclusion Criterion 7. Subjects (with the exception of those with sJIA) receiving corticosteroids at the time of study entry must have been receiving a stable dose for ≥2 weeks before screening, and that dose must have been ≤10 mg/day prednisone or prednisone equivalent or 0.20 mg/kg/day (whichever is lower). Subjects with systemic onset JIA but without systemic symptoms for ≥3 months must be on stable corticosteroids for 3 days before screening and not exhibit systemic symptoms. If receiving NSAID therapy, the dose must have been stable for ≥2 weeks before screening.

No changes should be made to background medications (ie, MTX, other DMARDs, corticosteroids, and NSAIDs) in terms of increases or decreases in dosage (eg, no more than 10 mg/day prednisone or no more than 0.20 mg/kg/day, whichever is lower) and/or route of administration between Weeks 0 and 28, unless there is a safety concern (eg, elevated LFTs), which requires changes to background medications. After Week 28, subjects will be permitted to change/add MTX, other DMARDs, corticosteroids, and NSAIDs, including increases or decreases in dosage, changes of route of administration, or discontinuations from these classes of agents.

Intramuscular administration of corticosteroids for the treatment of pJIA is not allowed during the study. Corticosteroids administered by bronchial or nasal inhalation for treatment of conditions other than pJIA 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 pJIA, corticosteroid therapy should be limited to situations in which, in the opinion of the treating physician, there are no adequate alternatives and should be documented in the CRF.

Subjects may receive intra-articular injections of a corticosteroid, if clinically required, during the study up to Week 52. However, the number of intra-articular injections should be limited to 2 over any 24-week period. That is, if a subject has received 2 intra-articular injections and more than 24 weeks has elapsed, the subject may receive up to 2 additional intra-articular injections over another 24-week period.

After Week 52, the number of injected joints is no longer limited to 2 injections per 24 weeks. 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).

After Week 252, concomitant medications are documented as described in Attachment 6.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules summarize the frequency and timing of efficacy, PK, immunogenicity, and safety measurements applicable to this study (Table 1, Table 2, and Table 3). All scheduled study visits should occur within ±3 days of the intended visit through Week 28 and ±1 week from Week 28 through Week 244. Through Week 52, if the recommended acceptable window cannot be observed, the Sponsor must be contacted before scheduling a visit. After Week 52, if the recommended acceptable window cannot be observed, the reason for the deviation must be recorded in source documents. After Week 252, study procedures will be performed as described in Attachment 6.

The Childhood Health Assessment Questionnaire (CHAQ) should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions. For additional details, refer to the PRO user manual.

At every unscheduled visit, the investigator will perform the following evaluations:

- Review of systems (after Week 52, at the discretion of the investigator)
- Vital signs (after Week 52, at the discretion of the investigator)
- TB questionnaire
- Adverse events

- Review of concomitant medications (after Week 52, medications should be reviewed and documented in source; medications used to treat or associated with AEs and SAEs should be recorded on the CRF)
- Safety laboratory evaluations (after Week 52, at the discretion of the investigator)

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 at any time during the subject's participation in the study.

The total blood volume to be collected from each subject for the study is approximately 149.4 mL (Table 4). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 4: Approximate Volume of Blood to be Collected From Each Subject Through Week 252

Type of Sample	Approximate Volume per Sample (mL)	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[a,b]
Safety (including screening and posttreatment assessments)			
- Hematology	1.2	17	20.4
- Serum chemistry	1.1	17	18.7
Serology (hepatitis B and hepatitis C)	2.0	1	2.0
Serum β-hCG pregnancy tests	1.1	1	1.1
- QuantiFERON®-TB Gold test	3.0	6	18.0
- Rheumatoid factor	1.1	1	1.1
- Anti-dsDNA antibody	1.1	11	12.1
- ANA antibodies	1.1	11	12.1
Efficacy (CRP)	1.1	24	26.4
PK and immunogenicity (antibodies to golimumab)	2.5	15	37.5
Approximate Total[c]			149.4

a. Calculated as the number of samples multiplied by amount of blood per sample.
b. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
c. The approximate total volume is the maximum volume of blood collected from a subject during the study; with implementation of Protocol Amendment 4, the volume of blood collected will be decreased.

Note: An indwelling intravenous cannula may be used for blood sample collection.

Abbreviations: ANA = antinuclear antibodies; β-hCG = β-human chorionic gonadotropin; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid; PK = pharmacokinetic; TB = tuberculosis.

9.1.2. Screening Phase

After written informed consent/assent has been obtained (Section 16.2.3), and within a period of 6 weeks before Week 0, 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).

Girls of childbearing potential must have a negative serum β-hCG pregnancy test at screening and a negative urine pregnancy test prior to each administration of study agent. Sexually active subjects must consent to use a highly effective method of contraception and continue to use contraception for the duration of the study and for 6 months after receiving the last dose of study agent. 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 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 (Section 4.1).

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 or the tuberculin skin is mandated by local Health Authorities) are eligible to continue with screening procedures. Subjects with a newly identified positive QuantiFERON®-TB Gold (and/or tuberculin skin test) result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. 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 must be followed, or the subject will be excluded from the study.

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 active TB is ruled out, 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. This determination must be promptly reported to the Sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

Retesting of an abnormal screening value that leads to exclusion is allowed only once using an unscheduled visit during the screening period to reassess eligibility. This should only be considered if there is no anticipated impact on subject safety.

9.1.3. Treatment Phase: Week 0 Through Week 28

Beginning at Week 0, eligible subjects will receive 80 mg/m^2 golimumab administered as IV infusions over 30±10 minutes at Weeks 0, 4 and q8w (±3 days) through Week 28 (Section 6.1). Subjects will also receive commercial MTX weekly at least through Week 28 at the same BSA-based dosage as 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 (Section 6.2). In children <12 years of age, the administration of folic acid or folinic acid will be at the discretion of the physician.

Subjects will have safety, efficacy, PK, and immunogenicity evaluations performed according to the Time and Events Schedule (Table 1). One additional sample for serum golimumab concentration for population PK will be collected from all subjects at any time between Weeks 0 and 8 other than at the time of the Week 0, Week 4, and Week 8 visits; this sample must be collected at least 24 hours prior to or after a study agent administration and must not be collected at a regularly scheduled visit (eg, Week 8).

9.1.4. Treatment Phase: After Week 28 Through Week 52

After Week 28, subjects will continue to receive 80 mg/m^2 golimumab administered as IV infusions over 30±10 minutes q8w (±1 week) through Week 52 (Section 6.1). Subjects may also receive commercial MTX weekly at the same BSA-based dosage as at time of study entry and commercial folic acid ≥5 mg weekly or folinic acid if administered (at half the MTX dose; Section 6.2) given the day after the MTX dose; however, increases, decreases or discontinuations of MTX, other DMARDs**,** corticosteroids, and/or NSAIDs are permissible after Week 28. All changes and reasons for changes for these medications need to be documented in the eCRF.

Subjects will have safety, efficacy, PK, and immunogenicity evaluations performed according to the Time and Events Schedule (Table 1).

End of Treatment/Early Withdrawal

If a subject discontinues study agent before Week 52, the subject should return approximately 8 weeks after the last administration of study agent for a final safety follow-up visit (Section 10.2). If a subject withdraws from study participation before Week 52, every effort should be made to obtain end-of-treatment assessments prior to the subject's withdrawal of consent.

9.1.5. Long-Term Extension Phase: After Week 52 Through Week 252

Subjects who enter the LTE after the Week 52 visit will continue to receive 80 mg/m^2 golimumab administered as IV infusions over 30±10 minutes q8w (±1 week) through Week 244.

Subjects will have safety, PK, and immunogenicity evaluations performed according to the Time and Events Schedules (Table 2 and Table 3). After Week 52, disease activity will be monitored and assessed by investigators. Investigators will fill out an annual attestation form to document that a subject is benefiting from treatment. Subjects who discontinue study agent administration prior to Week 244 without withdrawing consent should return for a final safety follow-up visit approximately 8 weeks after their last study agent infusion (Section 10.2).

Review of systems, collection of vital signs, QuantiFERON®-TB Gold testing, uveitis evaluations (including slit lamp evaluations), and chest x-ray screening will be performed at the discretion of the investigator; refer to the Time and Events Schedules (Table 2 and Table 3). It is the responsibility of the investigator to carry out all assessments per standard of practice and to update the CRF with all information related to AEs and SAEs (eg, concomitant medications).

Subjects should continue to be evaluated for signs and symptoms of TB (Section 9.4).

9.1.6. Extended Treatment Period

Subjects who enter the ETP after completion of the Week 252 assessments will continue to receive 80 mg/m^2 golimumab IV q8w.

The frequency and timing of assessments during the ETP are provided in Attachment 6.

9.2. Efficacy

9.2.1. Evaluations

The Time and Events Schedule summarizes the frequency and timing of efficacy measurements applicable to this study (Table 1). After Week 52, investigators will complete an attestation form annually to document that the subject is benefiting from treatment.

9.2.1.1. Joint Evaluation

Each of 75 joints will be evaluated for tenderness, and 68 joints will be evaluated for swelling and pain and limitation on motion according to the standard PRINTO/PRCSG joint evaluation. 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.

Training will be provided to a single consistent joint assessor from each site before the start of subject enrollment; the training is mandatory unless the site's joint assessor has taken certified training provided by PRINTO or PRCSG. 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 Sponsor or PRINTO/PRCSG 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 preferable 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 52.

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 in the ePRO device 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).

9.2.1.2. American College of Rheumatology Pediatric Response

The JIA ACR 30 response criteria[5] is defined as a 30% improvement (ie, a decrease in score) from baseline in at least 3 of the following 6 components, with worsening of 30% or more in no more than 1 of the following components:

- Physician Global Assessment of Disease Activity
- Parent/Subject 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 CHAQ
- CRP

The JIA ACR 50 response, the JIA ACR 70 response, and the JIA ACR 90 response are defined as a 50% improvement, a 70% improvement, and a 90% improvement from baseline, respectively, in at least 3 of the above 6 components, with worsening of 30% or more in no more than 1 of the above components.

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 CRP (≤0.287 mg/dL for subjects without underlying inflammatory disease)
- Physician Global Assessment of Disease Activity indicating no active disease (<5 mm)
- 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.

9.2.1.3. Physician Global Assessment of Disease Activity

The Physician Global Assessment of Disease Activity is a 100 mm 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 less disease activity. The process for including this measure in the core set of variables for the assessment of children has been captured in the literature.[5]

9.2.1.4. Childhood Health Assessment Questionnaire

The functional status of subjects will be assessed by the CHAQ.[21] Parents/subjects will complete this questionnaire to assess the degree of difficulty the subject has in accomplishing tasks in 8 functional areas (dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area are scored as 0 (without any difficulty), 1 (with some difficulty), 2 (with much difficulty), 3 (unable to do), or 4 (not applicable). Lower scores are indicative of improved functioning and task performance in specific functional areas.

Additionally, the CHAQ includes 2 VAS questions—one used to assess the subject's level of pain, and one used to assess the subject's overall well-being. Properties of the CHAQ have been evaluated and its validity assessed.[21] The CHAQ has been shown to be responsive to disease change.[21] A decrease of 0.188 has been determined to be a meaningful clinical improvement.[1]

Parent/Subject Assessment of Pain

Pain will be assessed as average pain experienced by the subject during the past week using a VAS scale that ranges from "no pain" (0 mm) to "very severe pain" (100 mm). This assessment should be completed by the parents (caregiver)/subjects prior to the tender and swollen joint examination.

Parent/Subject Assessment of Overall Well-being

The Parent/Subject Assessment of Overall Well-being is a 0-100 mm VAS. Parents/subjects will complete the VAS that asks them to consider all the ways arthritis impacts their child/themselves and then indicate how the subject is doing. The anchors of the scale are "very well" (0 mm) to "very poor" (100 mm). Lower scores indicate better well-being. The process for including this measure in the core set of variables for the assessment of children has been captured in the literature.[5]

Subjects who are 15 to <18 years of age at study entry may complete the CHAQ jointly with the parent/caregiver. Preferably, the same individual (eg, parent, caregiver, or subject) who completes the assessment at the start of the study should complete the assessment throughout the study.

9.2.1.5. C-reactive Protein

C-reactive protein has been demonstrated to be useful as a marker of inflammation in patients with pJIA and is part of the JIA ACR 30 core assessments. C-reactive protein will be assayed by a central laboratory using a validated, high-sensitivity CRP assay.

9.2.1.6. Juvenile Arthritis Disease Activity Score (JADAS)

Recently, a composite disease activity score for pJIA, the Juvenile Arthritis Disease Activity Score (JADAS), was developed; in validation analyses it was found to have good metrologic properties, including the ability to predict disease outcome. The JADAS (modified for using CRP) is computed by assessing the following variables: (1) physician global rating of overall disease activity, measured on a 100-mm horizontal VAS (0 no activity; 100 maximum activity for both VAS); (2) parent/child ratings of well-being and pain, assessed on a 21-Numbered Circle and 100-Millimeter Horizontal Line Visual Analog Scales[4]; (3) number of active joints, assessed in 71, 27, or 10 joints (JADAS 71, JADAS 27, and JADAS 10, respectively); and (4) CRP was truncated to a 0 scale according to the following formula: (CRP [mg/L]-10/10), similar to the truncated ESR used in JADAS-ESR. Before calculation, CRP values <10 mg/L are converted to 10 and CRP values >110 mg/L are converted to 110.[13]

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

The state of JADAS 10, 27, and 71 minimal disease activity[2,11] was defined as the presence of all of the following: Physician Global Assessment of Disease Activity of ≤3.5, parent's global rating of well-being of ≤2.5, and swollen joint count of ≤1 in patients with polyarthritis.

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

9.2.2. Endpoints

Primary Endpoint

The primary endpoint in this study is PK exposure at Week 28 (the trough concentrations at Week 28) and the Bayesian AUCss over one dosing interval of 8 weeks (from population PK modeling and simulation).

Major Secondary Endpoints

Major secondary endpoints include:

- PK exposure at Week 52 (the trough concentrations at Week 52) and the Bayesian AUCss at Week 52 (from population PK modeling and simulation)

Other Endpoints

Other endpoints include:

- The proportions of subjects who are JIA ACR 30, 50, 70, and 90 responders over time
- The change from baseline in CHAQ over time
- CRP concentrations over time
- The proportion of subjects who have inactive disease over time
- The proportion of subjects in clinical remission on medication for pJIA over time
- The improvement from baseline in the pJIA core set at each visit
- The proportions of subjects who are JIA ACR 30, 50, 70, and 90 responders by disease subtype, and/or age over time through Week 52
- The change from baseline in JADAS 10, 27, and 71 scores over time
- The proportion of subjects who achieve JADAS 10, 27, and 71 minimal disease activity over time

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

Serum samples will be used to evaluate the PK, as well as the immunogenicity of golimumab (antibodies to golimumab). Venous blood samples will be collected and each serum sample will be divided into 3 aliquots (1 each for pharmacokinetics, antibodies to study drug, and a back-up). Subject confidentiality will be maintained. The sample should be drawn from a different arm than the IV line, or if using an IV line that is also being used to deliver medication, the line should be flushed and cleared of any residual medication that may be remaining prior to each PK sample being drawn. When using an IV line to draw PK samples, the first 1 mL of blood should be drawn and discarded prior to obtaining the sample. Intravenous line maintenance should be followed as per the standard of care. At visits where serum concentration and antibodies to golimumab will be evaluated, 1 blood draw of sufficient volume can be used.

9.3.2. Analytical Procedures

Pharmacokinetics

Serum samples will be analyzed to determine concentrations of golimumab using a validated, specific, and sensitive method by or under the supervision of the Sponsor.

Immunogenicity

The detection and characterization of antibodies to golimumab will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to golimumab will also be evaluated for golimumab serum concentration to enable interpretation of the antibody data.

9.3.3. Pharmacokinetic Parameters

Serum golimumab concentrations will be evaluated at Weeks 0, 4, 8, 12, 20, 28, 52, 100, 148, 196, and 244 and summarized over time.

Pre-infusion (immediately before infusion) and post-infusion (1 hour after infusion) samples will be drawn at Weeks 0, 4, and 12, and an additional random population PK sample will be drawn at any time between Weeks 0 and 8 other than at the time of the Week 0, Week 4, and Week 8 visits and collected at least 24 hours prior to or after study agent administration. For each of the remaining visits, only 1 sample for serum golimumab will be collected, which should be collected prior to the infusion if an infusion of the study agent is administered at that visit. Post-infusion samples should be drawn from a different arm than the IV infusion line, or the IV infusion line must be flushed and cleared of any residual medication that may be remaining and 1 mL of blood should be drawn and discarded prior to obtaining the sample if using the same access line as was used for drug administration.

A population PK analysis with data through Week 28 will be performed to characterize the PK of golimumab as well as to identify important covariates of PK in the pediatric population with pJIA. Additionally the population PK model will be used to assess the similarity of the PK in pediatrics and adults. The clearance and volume of distribution will be estimated using a NONMEM approach. In addition, an exposure-response analysis will be performed to explore and characterize the relationship between exposure and efficacy.

9.3.4. Immunogenicity Assessments (Antibodies to Golimumab)

Antibodies to golimumab will be evaluated in serum samples collected from all subjects according to the Time and Events Schedule (ie, Weeks 0, 4, 8, 12, 28, 52, 100, 148, 196, and 244). Additionally, serum samples should also be collected at the final visit from subjects who are discontinued from treatment or withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to golimumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to golimumab and/or further characterize the immunogenicity of golimumab.

The incidence of antibodies to golimumab during the study will be determined.

9.4. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal 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 Schedules:

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.

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 adverse event section of the CRF. The laboratory reports must be filed with the source documents.

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	
-alkaline phosphatase	-uric acid
-bicarbonate	-chloride

- Serum pregnancy testing for girls of childbearing potential will be conducted at screening.
- Urine pregnancy testing for girls of childbearing potential will be performed according to the Time and Events Schedules.
- 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.
- Serology for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc total) at screening.
- Serology for HCV antibody at screening.

Vital Signs

Pulse/heart rate, respiratory rate, temperature, and blood pressure measurements will be performed according to the Time and Events Schedules (Table 1, Table 2, and Table 3).

Vital signs should be taken pre-infusion; at 15 and 30 minutes (15-minute intervals during the infusion); and at 60 and 90 minutes (during the 1-hour observation period following the infusion) through Week 52. After Week 52, vital signs should be taken at the discretion of the investigator.

Physical Examination

Physical examinations, including a skin exam at every physical examination and Tanner staging for sexual maturity will be performed (through Week 52 only) according to the Time and Events Schedule. Review of systems will be performed at all visits through Week 52 to evaluate for new symptomatology and if necessary, full physical examination may be performed at investigator discretion. After Week 52, review of systems will 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.

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.

Uveitis Evaluations

All subjects will be assessed for new-onset uveitis at screening and at least every 6 months through Week 52 by the investigator based on physical examination and interview. After Week 52, uveitis evaluations will be performed at investigator discretion. This consists of an assessment of signs and symptoms of uveitis, including, but not limited to, eye redness, light sensitivity, changes in vision, and floaters.

In addition, all subjects are required to have slit lamp evaluations performed by an ophthalmologist/optometrist through Week 52 at intervals (based on JIA subtype, ANA test results, age at JIA onset, and JIA duration) as specified in Attachment 5. After Week 52, slit lamp evaluations will be performed at the discretion of the investigator and per standard of care.

If a subject develops uveitis during the study, the subject's continued participation in the study is at the discretion of the investigator and Sponsor.

Infusion Reaction Evaluations

Before an infusion is started, the appropriate personnel, medications (eg, epinephrine, inhaled beta agonists, antihistamines and corticosteroids), and other requirements to treat anaphylaxis should be available. The subject may be premedicated with prophylactic drugs (eg, diphenhydramine) prior to starting the infusion based on investigator's discretion but this is not mandatory. However, corticosteroids for prophylaxis are not allowed. Premedications should be recorded in the eCRF.

The investigator or qualified designee will evaluate the subject for infusion reactions according to the Time and Events Schedule.

An infusion reaction is any unfavorable or unintended sign that occurs during the infusion or within 1 hour of completion of the infusion. All subjects must be carefully observed for symptoms of an infusion reaction. Through Week 52, subjects will be observed for at least 60 minutes after completion of the IV administration of study agent for symptoms of an infusion reaction. After Week 52, subjects will be observed at the discretion of the investigator after completion of the IV administration of study agent for symptoms of an infusion reaction. If an infusion reaction is observed, the subject should be treated at the investigator's discretion.

The investigator will record the infusion reaction in the AE page. If no infusion reaction is observed, the investigator will note this in the subject's medical records (source data).

Allergic Reactions

Through Week 52, all subjects must be observed carefully for symptoms of an allergic reaction (eg, urticaria, itching, hives) for at least 60 minutes after the completion of the infusion. After Week 52, subjects must be observed carefully for symptoms of an allergic reaction at the discretion of the investigator after completion of the infusion. If mild or moderate allergic reaction is observed, acetaminophen or NSAIDs and diphenhydramine at approved pediatric doses may be administered.

Subjects with severe reactions following an infusion that result in bronchospasm with wheezing and/or dyspnea and require ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm mercury (Hg), will not be permitted to receive any additional study agent infusions. In the case of such reactions, appropriate medical treatment should be administered.

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 through Week 252. After Week 252, TB evaluation will be carried out at investigator discretion and according to local and country guidelines for immunosuppressed patients. 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.

QuantiFERON®-TB Gold (and tuberculin skin) testing at Week 52 is not required for subjects with a history of latent TB, and ongoing treatment for latent TB, or documentation of having completed adequate treatment for TB. After Week 52, testing for latent TB should be performed at the discretion of the investigator and according to local and country guidelines.

Subjects who experience close contact with an individual with active TB during the conduct of the study should have a repeat chest radiograph, a repeat QuantiFERON®-TB Gold test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB Gold test is not approved/registered, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. The QuantiFERON®-TB Gold test (and tuberculin skin test) does not need to be repeated for subjects with a history of latent TB, and ongoing treatment for latent TB, or documentation of having completed adequate treatment for TB. If the QuantiFERON®-TB Gold test result is indeterminate, the test should be repeated as outlined in Section 9.1.2. Subjects should be encouraged to return for all subsequent scheduled study visits according to the protocol.

9.5. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/WITHDRAWAL

Subject completion/withdrawal during the ETP is described in Attachment 6.

10.1. Completion

A subject will be considered to have completed the main study if he or she has completed assessments at Week 52. A subject will be considered to have completed the LTE if he or she has completed assessments at Week 252.

10.2. Discontinuation of Study 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, adverse event) it is in the best interest of the subject to discontinue study 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 infusion 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 congestive heart failure at any time during the trial.
- Demyelinating disease.
- The subject withdraws consent for administration of study agent.
- The initiation of protocol-prohibited medications.

- 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, and cannot or will not continue to undergo additional evaluation.
  - A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON®-TB Gold test result (or a positive tuberculin skin test result in countries in which the QuantiFERON®-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local Health Authorities), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of study agent and continued to completion. Indeterminate QuantiFERON®-TB Gold test results should be handled as in Section 9.1.2. Subjects with persistently indeterminate QuantiFERON®-TB Gold test results may continue without treatment for latent TB if active TB is ruled out, 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. This determination must be promptly reported to the Sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.
  - A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

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

Note: The visit that is approximately 8 weeks after the last study agent infusions 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 infusions but do not terminate study participation will have the following assessments performed at the final safety follow-up visit:

- Safety evaluation including AE review, TB evaluation, and the collection of a blood sample for routine laboratory analyses, determination of the presence of ANA/anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, and antibodies to golimumab; after Week 52, other safety evaluations are performed at the discretion of the investigator (vital signs, review of systems, uveitis evaluation).
- Concomitant medication review (after Week 52, medications should be reviewed and documented in subject's source records; medications used to treat or associated with AEs and SAEs should be recorded in the source document as well as the CRF).
- Efficacy evaluations (joint assessments, JIA assessments, and collection of blood sample for CRP) through Week 52 only.
- Blood samples drawn for measurement of golimumab concentration for all subjects at the final safety follow-up visit.

If a subject discontinues study treatment before the end of the study, assessments should be obtained approximately 8 weeks after the last infusion of study agent.

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

If a subject discontinues study treatment before the end of the study, end-of-treatment assessments should be obtained approximately 8 weeks after the last infusion of study agent at the final safety follow-up visit.

If a subject is lost to follow-up, every reasonable 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.

If a subject withdraws from the study before the end of the study, end-of-treatment assessments should be obtained prior to the withdrawal of consent.

11. STATISTICAL METHODS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

In general, 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 data.

11.1. Subject Information

All subjects who are enrolled in the study will have baseline descriptive statistics provided.

Subject baseline data, demographic and baseline disease characteristics will be summarized. The baseline measurement is defined as the closest measurement taken before the time of the Week 0 study agent administration.

Demographics and subject baseline disease characteristics and prior medication data will be summarized 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 1 administration of study agent. Efficacy analyses will be summarized for all subjects enrolled in the study unless otherwise specified. Safety assessments will be summarized for all treated subjects.

11.2. Sample Size Determination

The sample size determination is not based on statistical considerations. For the purpose of determining sample size of this study, the variability of PK in pediatric populations was considered. The goal is to have a sample size that will be sufficient to build a population PK and, if feasible, an exposure-response model. Additionally, a sample size that will provide reasonable safety assessments was also taken into consideration. With these considerations, a sample size of approximately 120 subjects has been chosen assuming that if 20 subjects were to drop out or if they do not provide PK samples, a sample size of approximately 100 subjects is thought to be sufficient to build a population PK model, given the sparse sampling of PK time points, as well as provide 1 year of safety data from approximately 100 subjects.

11.3. Efficacy Analyses

Primary Endpoint Analysis

No primary efficacy endpoint analysis is planned.

Major Secondary Endpoints Analyses

No major secondary efficacy endpoints analyses are planned.

Other Efficacy Endpoints

The following will be summarized for all subjects enrolled in the study:

- The proportion of subjects who are JIA ACR 30, 50, 70, and 90 responders over time
- The proportion of subjects who have inactive disease over time
- The proportion of subjects in clinical remission on medication for pJIA (ACR criteria) over time
- The improvement from baseline in the pJIA core set over time
- The proportions of subjects who are JIA ACR 30, 50, 70, and 90 responders by disease subtype, and/or age over time through Week 52
- The change from baseline in CHAQ over time
- CRP concentrations over time
- The change from baseline in JADAS 10, 27, and 71 scores over time
- The proportion of subjects who achieve JADAS 10, 27, and 71 minimal disease activity over time

11.4. Pharmacokinetic Analyses

The primary objective of this study is to characterize golimumab PK exposure (the trough concentrations at Weeks 28 and the Bayesian AUCss over a dosing interval of 8 weeks from population PK modeling and simulation) in the pJIA population.

Serum golimumab concentrations will be summarized over time. In addition, a population PK analysis on data through Week 28 will be performed to characterize the PK of golimumab as well as to identify and quantify important covariates of PK in the pediatric population with pJIA. Clearance and volume of distribution will be estimated using a NONMEM approach. Details will be provided in a population PK analysis plan and the results of the analysis will be presented in a separate report.

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

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

11.5. Immunogenicity Analyses

The occurrence and titers of antibodies to golimumab during the study will be summarized 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. Pharmacokinetic/Pharmacodynamic Analyses

The relationships between serum golimumab concentration and efficacy will be explored. A suitable PK/PD model will be explored and developed to describe the exposure-response relationship.

11.7. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

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 infusion reactions
- The occurrence of ANA and anti-dsDNA antibodies
- The occurrence of antibodies to golimumab
- The occurrence of markedly abnormal laboratory (hematology and chemistry) parameters

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Vital Signs

Descriptive statistics of pulse/heart rate, respiratory rate, temperature, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point in the Schedule of Events.

11.8. Interim Analysis

No interim analysis is planned.

11.9. Data Monitoring Committee

This is an open-label study, with all subjects receiving the same dosage of IV golimumab. Therefore, an external Data Monitoring Committee will not be utilized. Safety data will be routinely evaluated by the study's medical monitor and Sponsor's internal Safety Management Team as needed. In addition, the data may be reviewed by the Steering Committee.

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 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 adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 [ICH])

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 adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- 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
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that 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 other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For golimumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

For MTX, which has a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the package label supplied by the drug's manufacturer in that country.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event 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 adverse event 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 adverse event 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 adverse event 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).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a Sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study drug
- Suspected abuse/misuse of a Sponsor study drug
- Inadvertent or accidental exposure to a Sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a Sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a Sponsor study drug
- Medication error involving a Sponsor product (with or without subject/patient exposure to the Sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days of the end of the study, 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 events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 4.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, 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 adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

The Sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study 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.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate Sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events 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/status 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)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a subject in a study within 2 months of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy must be reported to the Sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Events of Special Interest

Any newly identified malignancy 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 12.3. 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 a serious adverse event.

12.5. 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, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from 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 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 study site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study site personnel must report the PQC to the Sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, 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

The test product, golimumab, will be supplied as a sterile liquid for IV infusion at a volume of 4 mL (50 mg, 12.5 mg/mL) in single-use vials. Each vial will contain golimumab in an aqueous medium of histidine, sorbitol and polysorbate 80 at pH 5.5. No preservatives are present. It will

be manufactured and provided under the responsibility of the Sponsor. Refer to the Investigator's Brochure for a list of excipients.

MTX (oral or injectable) will not be supplied by the Sponsor but rather must be acquired from a commercial pharmacy.

14.2. Packaging

The study drug will be packaged in individual subject kits. Each kit will consist of a single vial packaged within a carton. The packaging is not child-resistant. Both vials and cartons will have a booklet label containing local language translations as required for participating countries.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

Liquid study agent in glass vials will be supplied ready to use. At the study site, vials of golimumab solution must be stored in a secured refrigerator at controlled temperatures ranging from 2°C to 8°C (35.6°F to 46.4°F).

The study agent IV infusions will be prepared according to the subject's BSA. Details on the preparation and storage of study material are provided in the Pharmacy Manual.

Preparation, handling, and storage of study agent during the ETP is described in Attachment 6.

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. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the Sponsor's instructions. Study site personnel 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 must be stored at the study site 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 study site monitor during on-site monitoring visits. The return to the Sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, 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.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic 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.

Drug accountability during the ETP is described in Attachment 6.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with at least the following supplies:

- Investigator Brochure
- Trial Center File
- Investigational Product Manual
- Laboratory manual and laboratory supplies
- ePRO device and user manual
- Interactive voice/web response system manual
- Electronic data capture (eDC) Manual (including on-line access)
- Sample ICF and sample assent form
- Subject participation cards (ie, wallet cards)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They 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 who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects

and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The total blood volume to be collected is considered to be normal for this study population (ie, pediatric subjects with >15kg body weight) and does not exceed >1% of the subject's blood volume per visit.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (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 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 (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- 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 the 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, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, 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 (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF 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
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study 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 study conduct), the amendment and applicable ICF 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 study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or Sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

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 ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. 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 study site personnel 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 to not 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 personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease related treatments, or to obtain information about his or her survival status.

The subject or legally acceptable representative will be given sufficient time to read the ICF 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 ICF 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 ICF 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 7 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 to the subject's parent and/or legally acceptable representative.

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 fulfill the objectives of the 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 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/institution to allow direct access to his or her original medical records (source data/documents) 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. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 2 years (or according to local regulations) for additional research. Samples will only be used to understand golimumab, to understand pJIA, to understand differential drug responders, and to develop tests/assays related to SIMPONI for IV use and pJIA. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research.

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise 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 by the Sponsor. 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. 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 page(s) 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 study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, 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 (or sealed, where appropriate per local regulations) 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 study site personnel 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 principal 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)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- 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 study 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 subject identification and date of birth. In cases where the subject is not enrolled into the study, the date seen and date of birth will be used.

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 signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; 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.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study 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).

The following data (at a minimum) will be recorded directly into the CRF and will be considered source data where allowed by country regulations:

- Race
- History of smoking and all nicotine use (eg, cigarettes, cigars, chewing tobacco, patch, gum)
- Blood pressure, pulse/heart rate, temperature, and respiratory rate
- Height and weight
- Details of physical examination
- The following parent/subject- and investigator-completed scales and assessments designated by the Sponsor will be recorded directly into an electronic device and will be considered source data: joint assessments, CHAQ, Physician Global Assessment of Disease Activity, and duration of morning stiffness. These assessments should not be recorded on paper first.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

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

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the Sponsor within the timeframe agreed upon between the Sponsor and the study site. 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 subject's 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. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. 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 study site personnel 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:

- Study 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).
- Study site manager can generate a query for resolution by the study site personnel.
- Clinical data manager can generate a query for resolution by the study site personnel.

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 sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory, IWRS, and PRO data into the Sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study site 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 study database they will be verified for accuracy and consistency with the data sources.

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/institution 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 site visit log that will be kept at the study 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 study site personnel and are accessible for verification by the Sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

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 study site personnel. The Sponsor expects that, during monitoring visits, the relevant study site personnel 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 study assessment for the last subject participating in the study. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

The investigator may initiate study 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 a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the Sponsor's clinical quality assurance department may visit the study 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 study site personnel are responsible for being present and available for consultation during routinely scheduled study 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 he or she has 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 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 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 study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory, IWRS, and PRO data into the Sponsor's database. 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 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 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.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the Sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. 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, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), 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. PRINTO and PRCSG guidelines available on their respective websites should be followed.

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.

REFERENCES

1. Brunner HI, Klein-Gitelman MS, Miller MJ, et al. Minimal clinically important differences of the childhood health assessment questionnaire. J Rheumatol. 2005;32(1):150-161.
2. Consolaro A, Bracciolini G, Ruperto N, et al. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis. Arthritis Rheum. 2012;64(7):2366-2374.
3. De Benedetti F, Pignatti P, Gerloni V, et al. Differences in synovial fluid cytokine levels between juvenile and adult rheumatoid arthritis. J Rheumatol. 1997;24(7):1403-1409.
4. Filocamo G, Davì S, Pistorio A, et al. Evaluation of 21-numbered circle and 10-centimeter horizontal line visual analog scales for physician and parent subjective ratings in juvenile idiopathic arthritis. J Rheumatol. 2010;37(7):1534-1541.
5. Giannini EH, Ruperto N Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum. 1997; 40:1202-1209.
6. Grossman JM, Brahn E. Rheumatoid arthritis: current clinical and research directions. J Womens Health. 1997;6(6):627-638.
7. Heiligenhaus A, Minden K, Föll D, Pleyer U: Uveitis in juvenile idiopathic arthritis. Dtsch Arztebl Int. 2015; 112: 92–100. DOI: 10.3238/arztebl.2015.0092
8. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K; German Uveitis in Childhood Study Group. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology (Oxford). 2007;46(6):1015-1019.
9. Lepore L, Pennesi M, Saletta S, Perticarari S, Presani G, Prodan M. Study of IL-2, IL-6, TNF alpha, IFN gamma and beta in the serum and synovial fluid of patients with juvenile chronic arthritis. Clin Exp Rheumatol. 1994;12(5):561-565.
10. Levin RH, associate ed. Principles of drug disposition and therapy in neonates, infants, and children. In: Rudolph AM, ed; Hoffman JLE, co-ed; Axelrod S, assistant ed. Pediatrics. 18th ed. Norwalk, Ct: Appleton & Lange; 1987:781-792. Available upon request.
11. Magni-Manzoni S, Ruperto N, Pistorio A, et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. Arthritis Rheum. 2008;59(8):1120-1127.
12. Mangge H, Kenzian H, Gallistl S, et al. Serum cytokines in juvenile rheumatoid arthritis. Correlation with conventional inflammation parameters and clinical subtypes. Arthritis Rheum. 1995;38(2):211-220.
13. Nordal EB, Zak M, Aalto K, et al. Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population-based setting. Ann Rheum Dis. 2012;71(7):1122-1127.
14. Oen K. Long-term outcomes and predictors of outcomes for patients with juvenile idiopathic arthritis. Best Practice and Res Clin Rheumatol. 2002;16(3):347-360.
15. Petty RE, Cassidy JT. Oligoarthritis. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB. Textbook of Pediatric Rheumatology. 5th ed. Philadelphia, Pa: Elsevier Saunders; 2005b:274-290. Available upon request.
16. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390-392.
17. Prahalad S, Glass DN. Is juvenile rheumatoid arthritis/juvenile idiopathic arthritis different from rheumatoid arthritis? Arthritis Res 2002, 4(Suppl 3)**:**303-310. Available at: http://arthritis-research.com/content/4/S3/303. Accessed June 13, 2008.
18. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369(9563):767-778.
19. Rooney M, David J, Symons J, Di Giovine F, Varsani H, Woo P. Inflammatory cytokine responses in juvenile chronic arthritis. Br J Rheumatol. 1995;34(5):454-460.

20. Rooney M, Varsani H, Martin K, Lombard PR, Dayer JM, Woo P. Tumor necrosis factor alpha and its soluble receptors in juvenile chronic arthritis. Rheumatology. 2000;39(4):432-438.

21. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum. 1994;37(12):1761-1769.

22. Zenk KE. Methods of parenteral drug delivery. In: Rudolph AM, ed; Hoffman JLE, co-ed; Axelrod S, assistant ed. Pediatrics. 18th ed. Norwalk, Ct: Appleton & Lange; 1987:789-790. Available upon request.

ATTACHMENT 1 QUANTIFERON®-TB GOLD TESTING

The QuantiFERON®-TB Gold test is one of the interferon-γ (IFN-γ) based blood assays for TB screening (Cellestis, 2009). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON®-TB Gold assay measures the amount of IFN-γ produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN-γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON®-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of the QuantiFERON®-TB Gold test (standard format) in subjects with active TB, sensitivity has been shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QuantiFERON®-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON®-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN-γ-based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON®-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QuantiFERON®-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN-γ-based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

Performing the QuantiFERON®-TB Gold Test

The QuantiFERON®-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per subject, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000 g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the central laboratory. The central laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

The central laboratory will analyze and report results for each subject, and sites will be informed of the results. Under certain circumstances as approved by the Sponsor, a local laboratory may be used to process the QuantiFERON®-TB Gold test sample and/or analyze the results.

Subjects who have an indeterminate result should have the test repeated.

Adherence to Local Guidelines

Local country guidelines **for immunocompromised patients** should be consulted for acceptable anti-tuberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

In countries in which the QuantiFERON®-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required.

References

Barnes PF. Diagnosing latent tuberculosis infection: Turning glitter to gold [editorial]. Amer J Respir Crit Care Med. 2004;170:5-6.

Brock I, Weldingh K, Lillebaek T, et al. Comparison of tuberculin skin test and new specific blood test in tuberculosis contacts. Am J Respir Crit Care Med. 2004;170:65-69.

Cellestis. QuantiFERON-TB Gold clinicians guide and QuantiFERON-TB Gold In-Tube Method package insert. Downloaded from www.cellestis.com, February 2009.

Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-λ assay for the development of active tuberculosis disease after recent infection with mycobacterium tuberculosis. Am J Respir Crit Care Med. 2008;177:1164-1170.

Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. Lancet. 2003;361:1168-73.

Ferrara G, Losi M, Meacci M, et al. Routine hospital use of a new commercial whole blood interferon-γ assay for the diagnosis of tuberculosis infection. Am J Respir Crit Care Med. 2005; 172:631-635.

Higuchi K, Nobuyuki H, Mori T, Sekiya Y. Use of QuantiFERON-TB Gold to investigate tuberculosis contacts in a high school. Respirology. 2007;12:88-92.

Kobashi Y, Mouri K, Obase Y, et al. Clinical evaluation of QuantiFERON TB-2G test for immunocompromised patients. Eur Respir J. 2007; 30:945-950.

Matulis G, Jüni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a Mycobacterium tuberculosis antigen-specific interferon λ assay. Ann Rheum Dis. 2008;67:84-90

Mori T, Sakatani M, Yamagishi F, et al. Specific detection of tuberculosis infection: An interferon-γ-based assay using new antigens. Am J Respir Crit Care Med. 2004;170:59-64.

ATTACHMENT 2 TUBERCULIN SKIN TESTING

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Subjects should never be allowed to read their own tuberculin skin test results. If a subject fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a subject who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the subjects may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines **for immunocompromised patients** should be consulted for acceptable anti-tuberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). Tuberculosis, a comprehensive international approach. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

ATTACHMENT 3 HEPATITIS B VIRUS (HBV) SCREENING

Subjects must undergo screening for 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):

- Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) are ***eligible*** for this study.
- 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.
- Subjects who test **positive only** for **surface antibody** (anti-HBs+) are ***eligible*** for this study.
- Subjects who test **positive** for surface antigen (HBsAg+) are ***NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Subjects who test **positive only** for **core antibody** (anti-HBc+) are ***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.

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Include	—	—	—
	—	+	+
	—	+	—
Exclude	+	— *or* +	— *or* +
	—	—	+

ATTACHMENT 4: ANTICIPATED EVENTS

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study, the following events will be considered anticipated events:

- Events related to the progression of the disease under study.

These events will be captured on the CRF and in the database, and will be reported to the Sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets serious adverse event criteria will be reported to the Sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the Sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An ARC will be established to perform reviews of pre-specified events at an aggregate level. The ARC is a safety committee within the Sponsor's organization that is independent of the Sponsor's study team. The ARC will meet to aid in the recommendation to the Sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated event will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

ATTACHMENT 5: SLIT LAMP EVALUATIONS

Through Week 52, all subjects are required to have slit lamp evaluations performed by an ophthalmologist/optometrist during the study at intervals (based on JIA subtype, ANA test results, age at JIA onset, and JIA duration) as specified in the table below. After Week 52, slit lamp evaluations will be performed at the discretion of the investigator and per standard of care. The date of the screening visit and the ANA test results during screening (as applicable depending on the JIA subtype) should be used to determine when the first slit lamp evaluation should be performed during the study. The interval for the slit lamp evaluations may be adjusted thereafter based on the subject's ANA test results and JIA disease duration after screening. However, once a subject tests positive for ANA at any time during the study (and regardless if the subject subsequently tests negative for ANA), the subject should be considered ANA positive when determining the frequency of slit lamp evaluations.

If a subject develops uveitis during the study, the subject's continued participation in the study is at the discretion of the investigator and Sponsor, and slit lamp evaluations should be performed according to disease course.

Intervals for Slit Lamp Evaluations

JIA Subtype	ANA	Age at JIA onset (in years)	JIA duration (in years)	Slit Lamp Evaluation Interval (in months)
OA extended Polyarticular RF-negative Juvenile PSA	Positive (+)	≤6	≤4	≤3
			>4 and <7	≤6
			≥7	≤12
		>6	≤2	≤6
			>2	≤12
	Negative (-)	≤6	≤4	≤6
			>4	≤12
		>6	N/A	≤12
ERA	N/A	N/A	N/A	≤12
Polyarticular RF-positive Systemic with polyarticular course without systemic symptoms	N/A	N/A	N/A	≤12

ANA = antinuclear antibody; ERA = enthesitis-related arthritis; JIA= juvenile idiopathic arthritis; N/A = not applicable; OA = oligoarticular; PSA = psoriatic arthritis; RF = rheumatoid factor

Adapted from: Heiligenhaus et al, 2007[8] and Heiligenhaus et at, 2015[7]

ATTACHMENT 6: EXTENDED TREATMENT PERIOD

INTRODUCTION

As indicated in Section 3.1.4, subjects who have completed the full trial period of 252 weeks and for whom drug is proven beneficial but is not commercially available for the pJIA indication (or subject does not qualify for insurance to pay for the drug), will continue to be provided with IV golimumab by the Sponsor. This attachment outlines the procedures and assessments that should be followed, for provision of golimumab to eligible subjects after completion of the main study, in the ETP.

Eligible subjects are <18 years of age at the time of their Week 252 visit of the main study, have received the Week 244 infusion, and completed the Week 252 assessments. The investigator must confirm that the subject, in their opinion, will benefit from continued golimumab treatment, and it is not commercially available for the pJIA indication (or subject does not qualify for insurance to pay for the drug). The ETP begins at Week 252 of the main study and will continue until the subject either turns 18 years of age, is no longer benefiting from golimumab treatment, or marketing authorization is obtained for golimumab in the treatment of pJIA in the subject's respective country and subject qualifies for insurance to pay for the drug. Subjects may decide to stop golimumab treatment (withdraw consent) at any time.

Subjects will receive the same golimumab treatment (80 mg/m^2 every 8 weeks administered intravenously; maximum dose 240 mg) that they received prior to Week 252 in the main study.

Subject visits and monitoring (eg, laboratory evaluation, TB evaluation) should occur at the investigator's discretion and as per usual clinical practice for a subject with pJIA receiving a TNFα inhibitor. Physicians participating in this ETP must agree to take full responsibility for the use of this product.

Local regulations and guidelines related to participation in the ETP, including but not limited to period approvals, and re-approvals are the responsibility of the physician.

The physician must ensure that any local requirements for safety reporting to Health Authorities and/or Independent Ethics Committees/Institutional Review Boards, if appropriate, are met.

During the ETP, concomitant medications including those for pJIA will be administered at the discretion of the investigator for all subjects. During the course of the ETP, in situations where a departure from the protocol or standard of care is unavoidable, the investigator or other physician in attendance will contact the appropriate Sponsor (see Contact Information page[s] provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol or standard of care. 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 subject's medical records should reflect any departure from the protocol/standard of care.

ELIGIBILITY CRITERIA

The investigator must confirm and document in subject's medical records the necessity of continuing golimumab treatment in the ETP and that switching to another commercially available treatment is not in the best interest of the subject. Additionally, for subjects to be eligible for the ETP, the investigator must document that golimumab is not commercially available for the pJIA indication (and subject does not qualify for insurance to pay for the drug). Documentation should be done at the following timepoints:

- At Week 252, after the subject has completed participation in the study (ie, the Week 252 assessments have been completed)
- At each subsequent year the subject participates in the ETP (via attestation form).

Each subject must continue to satisfy specified inclusion and exclusion criteria as well as prohibitions and restrictions as noted in Sections 4.1, 4.2, and 4.3, respectively. For questions related to eligibility, the investigator should contact the Sponsor for clarification.

In addition, specific criteria for the ETP are noted below.

Inclusion Criteria

Each potential subject must satisfy the following criteria to continue to receive golimumab as part of the ETP. Criteria from Section 4.1 that apply are referenced below.

1. Subjects must be less than 18 years of age.

2. Subject has received the Week 244 infusion and completed the Week 252 assessments as outlined in Table 3 of the Time and Events Schedule of the Protocol.

3. Each subject (or their legally acceptable representative) must sign an ICF indicating that he or she understands the purpose of and the procedures required for the ETP. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older and per local regulations) as described in Section 16.2.3, Informed Consent.

4. Subjects must continue to have pJIA as specified in inclusion criterion #3 in Section 4.1. Subjects may remain in treatment if in remission, but if the diagnosis is thought to change from pJIA, treatment should be discontinued.

5. Subjects must continue to meet eligibility criteria for TB (Inclusion criterion #10 in Section 4.1)

6. Subjects must continue to avoid pregnancy (Inclusion criteria #12, #13, and #14 in Section 4.1).

Exclusion Criteria

The specific exclusion criteria listed in Section 4.2 that apply are noted below with the numbers referring to that section. If a subject meets these criteria, he/she will be excluded from continued participation in the ETP.

1. Pregnancy (in a female) or plans for pregnancy (in females or males) are exclusionary (Exclusion criteria #41 and #42 in Section 4.2).

2. Subjects with a BSA >3.0 m^2 (Exclusion criterion #46 in Section 4.2).

Prohibitions and Restrictions

All subjects must continue to comply with all the prohibitions and restrictions as noted in Section 4.3, with the exception of the prohibition regarding intramuscular corticosteroids. Contrary to the main study, subjects may receive intramuscular administration of corticosteroids for the treatment of pJIA as deemed necessary by the investigator in the ETP. However, these occurrences should be limited. If needed for ongoing control of pJIA, thought should be given to the need to change to a different medication and the subject stopping participation in the ETP.

PROCEDURES AND ACTIVITIES

Subjects who enter the ETP at the Week 252 visit will continue to receive 80 mg/m^2 golimumab (maximum dose 240 mg) administered as IV infusions over 30±10 minutes q8w (±1 week) until discontinuation of golimumab treatment, as described below.

The following procedures and activities must be performed by the investigator during the ETP:

- Completion of the attestation form to document that a subject is benefiting from treatment - annually.
- Record AEs considered to be related to golimumab, all SAEs (regardless of causality to golimumab), pregnancy, and events of special interest (ie, malignancy and TB) on the CRF. Refer to Section 12.3.1 for procedures for reporting these events.
- Record concomitant medications associated with or used to treat AEs and SAEs on the CRF.

Subject visits and monitoring (eg, laboratory evaluation, TB evaluation) should occur at the investigator's discretion and as per usual clinical practice for a subject with pJIA receiving a TNFα inhibitor. Physicians participating in this ETP must agree to take full responsibility for the use of this product.

GOLIMUMAB STORAGE, PREPARATION, DOSAGE, ADMINISTRATION, and ACCOUNTABILITY

Golimumab will be supplied by the Sponsor during the ETP. The first dose of golimumab in the ETP will be administered at Week 252 after completion of the Week 252 assessments. Subjects will receive 80 mg/m^2 golimumab (maximum dose 240 mg) IV infusions q8w. The q8w

(±1 week) dosing regimen should be adhered to and infusions may only be missed for safety reasons. Exceptions to the q8w (±1 week) dosing regimen should only be made if infusions are off-schedule for safety reasons. In these instances, the minimum time between infusions can be 4 weeks to enable the subject to resume the q8w dosing regimen.

Refer to Sections 14.1, 14.2, and 14.3 for details about the physical description, packaging, and labeling of golimumab, respectively.

Investigators will be responsible for ensuring that golimumab is stored according to the specifications outlined in Section 14.4.

Investigators/site personnel will also be responsible for scheduling golimumab infusions and ensuring correct administration.

Prior to preparing a dose for infusion, the subject's current weight and height should be used to obtain the subject's body surface area (BSA). The subject's BSA will be calculated prior to each infusion using the Mosteller equation and the dose of golimumab adjusted as needed to maintain the dose at 80 mg/m^2. A maximum dose of 240 mg cannot be exceeded in any circumstance, even if a subject's BSA is large enough to yield a higher calculated dose.

The golimumab infusions should be prepared and administered by a healthcare professional as noted in the Golimumab Preparation and Administration Instructions.

The investigator is responsible for ensuring that all golimumab received at the site is inventoried and accounted for throughout the ETP. All study drug should be stored and disposed of according to the Sponsor's instructions. Site personnel must not combine contents of the study drug containers.

Golimumab should be handled in strict accordance with the Golimumab Preparation and Administration Instructions and the container label and should be stored in a limited-access area or in a locked cabinet under appropriate environmental conditions. 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.

Potentially hazardous materials such as used ampules, 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.

Golimumab should be dispensed under the supervision of the investigator or a qualified member of the site personnel, or by a hospital/clinic pharmacist. Golimumab will be supplied only to subjects participating in the ETP. Golimumab returned to the site/IWRS stock must not be dispensed again, even to the same subject. Golimumab may not be relabeled or reassigned for use by other subjects.

CONCOMITANT MEDICATIONS

Concomitant medications including medications for pJIA may be administered and adjusted at the discretion of the investigator but should not violate any prohibitions and restrictions noted in Section 4.3, Prohibitions and Restrictions, with the exception noted in Section 4.3 concerning IM corticosteroids.

Concomitant medications associated with, or used to treat, AEs and SAEs should be recorded in the CRF.

Methotrexate will not be supplied by the Sponsor.

DISCONTINUATION OF GOLIMUMAB/TREATMENT WITHDRAWAL CRITERIA

The subjects may at any time withdraw consent and discontinue treatment with golimumab. If a subject's golimumab treatment is discontinued, this will result in automatic permanent withdrawal of the subject from the ETP. A subject's golimumab treatment provided via this ETP will be permanently discontinued when any of the following occur:

- The subject is no longer benefiting from golimumab treatment.
- The subject turns 18 years of age.
- Golimumab becomes commercially available in the subject's respective country and the subject's insurance will pay for the drug.

A subject's golimumab treatment should also be permanently discontinued if any of the criteria in Section 10.2. Discontinuation of Study Treatment, are met.

When a subject discontinues study treatment, a follow-up evaluation should occur approximately 8 weeks after the last infusion of study agent to ensure that there are no safety concerns.

ADVERSE EVENT REPORTING

AEs considered by the investigator to be related to study drug (as defined in Section 12.3.1), SAEs (as defined in Section 12.1.1), pregnancy, and events of special interest (ie, malignancy and TB) are required to be reported in the ETP on the CRF. Refer to the following sections for procedures for reporting these events: Section 12.3.1 for AEs, Section 12.3.2 for SAEs, Section 12.3.3 for pregnancy, and Section 12.4 for events of special interest.

PRODUCT QUALITY COMPLAINTS

Refer to Section 13 for definition of PQCs during the ETP. If a defect is combined with an SAE during the ETP, the study site personnel must report the PQC to the Sponsor according to the timelines and procedures for an SAE.

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.

ETHICAL ASPECTS

Refer to Section 16 for details regarding ethical aspects of the ETP.

Extended Treatment Period Considerations

Potential subjects will be fully informed of the risks and requirements of the ETP and, during the ETP, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the ETP 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 who are fully able to understand the risks, benefits, and potential adverse events of the ETP, and provide their consent voluntarily will be enrolled. For additional details regarding the ICF process, see Section 16.1.

ADMINISTRATIVE REQUIREMENTS

Protocol Amendments

If a modification to ETP is needed, a formal protocol amendment will be issued by the Sponsor. Refer to Section 17.1 for additional details about the procedures that will be followed for the implementation of a protocol amendment.

Documentation Required for Extended Treatment Period

At a minimum, the type and level of detail of subject's medical records available for a subject participating in the ETP should be consistent with that commonly recorded at the site as a basis for standard medical care. Subject records must be available for review of AEs considered to be related to study drug and SAEs. The author of an entry in the subject's medical records should be identifiable.

Record Retention

Refer to Section 17.7 for details regarding record retention during the ETP.

Monitoring

The Sponsor will perform on-site monitoring visits as necessary. The monitor will record dates of the visits in a site visit log that will be kept at the site. The nature and location of all subject's medical records will be identified to ensure that all sources of original data are known to the Sponsor and site personnel and are accessible for verification by the Sponsor site contact. If electronic records are maintained at the site, the method of verification must be discussed with the site personnel.

Direct access to subject's medical records must be allowed for the purpose of verification of the data reported to the Sponsor. Findings from this review of the subject's medical records will be discussed with the site personnel. The Sponsor expects that, during monitoring visits, the relevant site personnel will be available, the subject's medical records will be accessible, and a suitable environment will be provided for review of ETP-related documents. The monitor will

meet with the investigator as needed during the ETP to provide feedback on the administration of the ETP.

Extended Treatment Period Completion/Termination

Extended Treatment Period Completion

The ETP is considered completed when the youngest subject enrolled in the ETP is 18 years of age or the last subject participating in the ETP discontinues.

Extended Treatment Period Termination

The Sponsor reserves the right to close the study site or terminate the ETP at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed by the Sponsor upon ETP completion. Refer to Section 17.9.2 for further details regarding site closure and reasons for early closure of a site by the Sponsor.

Use of Information and Publication

Refer to Section 17.11 for details regarding the use of information and publication of data generated as a result of this ETP.

INVESTIGATOR AGREEMENT

SIMPONI® (golimumab) for Intravenous Use
Clinical Protocol CNTO148JIA3003 Amendment INT-4

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Elizabeth Hsia, MD

Institution: Janssen Research & Development

Signature: PPD Date: 17 Dec 2019
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 16 December 2019

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title

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

GO-VIVA

Protocol CNTO148JIA3003; Phase 3

SIMPONI® (golimumab) for Intravenous Use

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).]

Status: Approved
Date: 17 April 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-36793

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL CNTO148JIA3003 (EDMS-ERI-71227414)

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the Sponsor is providing options for study-related subjects management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If, at any time, a subject's safety is considered to be at unacceptable risk, study drug will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study drug, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation between the subject and investigator, and with the agreement of the Sponsor (see below).

The Sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a subject has tested positive for COVID 19, the investigator should contact the Sponsor's responsible medical officer to discuss plans for study drug and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the Sponsor and investigator to maintain continuity of subject care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:

    - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and subjects for study procedures e.g. those related to safety monitoring / efficacy evaluation / study drug storage and administration (including training where pertinent)

    - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed

    - other procedures, eg, imaging, may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study drug and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

    - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in CRFs and / or other study systems, as directed by detailed Sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.

- The Sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

- NOTES on COVID-related exclusion:

    1. The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Testing may be performed during the study if deemed necessary by the investigator and in accordance with current regulations / guidance from authorities / standards of care.

- Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those with a compromised immune system), follow guidance from local health authorities when weighing the potential benefits and risks of participation in the study.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Elizabeth Hsia, MD, MSCE

Institution: Janssen Research & Development

Signature: ELIZABETH HSIA Digitally signed by ELIZABETH HSIA DN: c=US, o=JNJ, ou=Subscribers, 0.9.2342.19200300.100.1.1=333795, cn=ELIZABETH HSIA Reason: I am approving this document. Date: 2020.04.19 16:58:17 -04'00' Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.