CLINICAL REVIEW

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Reviewer Name(s)	Rachel L. Glaser, MD
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Established Name	Golimumab
Trade Name	Simponi
Therapeutic Class	TNF Inhibitor
Applicant	Janssen Biotech, Inc
Formulation(s)	Subcutaneous
Dosing Regimen	No new dosing regimen is proposed with this submission
Indication(s)/ Intended Population(s)	No new indications/populations are proposed with this submission

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that the post-marketing requirement be considered fulfilled based on this submission. Section 8.4 of the label should be updated with information from Study CNTO148JIA3001.

1.2 Risk Benefit Assessment

Study CNTO148JIA3001 was conducted to fulfill a post-marketing requirement issued with the BLA 125289 approval letter dated 24April 2009 study to assess the pharmacokinetics, safety, immunogenicity, and efficacy of golimumab (GOL) in pediatric patients 2 to 16 years of age with active polyarticular juvenile idiopathic arthritis (PJIA). The study did not meet the primary or major secondary endpoints, and the Applicant (b) (4) .

The reasons that Study CNTO148JIA3001 failed are unclear. The American College of Rheumatology Pediatric 30 response (ACR Ped 30) to the initial open-label treatment period (87.3%) is similar to that seen with other biologic disease modifying anti-rheumatic drugs (bDMARDs) in randomized withdrawal studies (range 65-94% response to run-in period) that have demonstrated efficacy in PJIA (Appendix 2). However, at the end of the randomized withdrawal period, the ACR Ped 30 response rates were similar between the golimumab and placebo treatment groups (59.0% vs. 52.6%, respectively). The proportion of patients experiencing flares during the randomized withdrawal period was similar between treatment groups. A possible explanation, suggested by exploratory analyses, maybe that subjects enrolled in the study had an unexpectedly low inflammatory burden. Overall, the patients in CNTO148JIA3001 had fewer active joints and fewer joints with limitations in ROM, and lower inflammatory markers, than seen in several other JIA studies with bDMARDs. However, patients who did not enter the randomized withdrawal period, i.e. did not achieve an ACR Ped 30 response, may have had a higher inflammatory burden as evidenced by an increased number of joints with limited range of motion (ROM), increased number of joints with active arthritis, higher CHAQ scores, as well as somewhat higher inflammatory markers, suggesting a decrease in response in those patients with a higher inflammatory burden. In addition, the flare rate in the placebo group is similar to that observed for tocilizumab, a bDMARD which did demonstrate efficacy in PJIA in a randomized withdrawal study (47.4% in golimumab study, 48% in tocilizumab study), while the flare rate in the golimumab group is higher (41% vs. 26%). An exploratory analysis by CRP level shows a statistically significant treatment benefit to golimumab, however this analysis is based on evaluations of multiple subgroups

without control of overall type 1 error, and therefore, the observed benefit may be due to chance.

Dose selection must also be considered when evaluating reasons that Study CNTO148JIA3001 failed to meet its endpoints. Only a single dose was studied in PJIA. The dose selected for the study was based on the SC dosing regimen for adult patients with rheumatologic diseases and the Applicant's experience with infliximab in the pediatric population with JRA, an older nomenclature used to describe a patient population similar to PJIA. According to the Applicant, in the latter experience, body surface area (BSA)-normalized clearance and volume of distribution at steady state were constant across the studied age range (4 to 17 years). BSA-adjusted dosing was anticipated by the Applicant to achieve relatively similar exposure in pediatric patients of different ages. Thus, a BSA-adjusted dose of 30 mg/m^2 was selected to approximate the adult golimumab fixed dose of 50 mg for an adult subject weighing 60 kg (BSA 1.67 m^2). Despite the similar steady state trough golimumab concentrations between PJIA patients and adult RA patients, Study CNTO148JIA3001 did not meet its objectives. In the context of the limited dose-ranging and exposure-response data in the SC golimumab program in adults, it is possible that a dosing regimen in PJIA based on PK matching may not be adequately justified. Additional dose-ranging data to establish a dose-response relationship in PJIA may help address this uncertainty

The randomized withdrawal study design, in which all patients receive active treatment, presents limitations in assessment of safety, however, observed safety events were consistent with the known safety profile of golimumab. No new safety signals were identified. Adverse events (AEs) leading to discontinuation, serious adverse events (SAEs), and infections were higher in the group randomized to PBO+MTX, as compared to the GOL+MTX group through the end of the randomized withdrawal period. Serious infections were similar between treatment groups. While differences in study design, dosing regimens, and duration of follow-up limit direct comparison of frequencies of these events between JIA and RA populations, these are generally similar through Week 16, with a greater proportion of PJIA patients experiencing overall infections and injection site reactions.

In Type C written responses (17Dec2015), the Applicant was advised to conduct a controlled dose-ranging study in which they could consider using baseline CRP levels ≥ 1.0 mg/dL as an enrichment strategy which could potentially provide evidence of efficacy in PJIA to support an application for this indication. The Applicant was encouraged to discuss any proposed study design with the FDA prior to conducting the study. However, based on the feedback provided by the FDA, the Applicant has opted not to seek an indication for PJIA. In the current submission, the Applicant seeks an update to the USPI with the results of Study CNTO148JIA3001 in Section 8.4 and a determination that the post-marketing requirement has been fulfilled. In addition, the label has been updated to comply with the Pregnancy and Lactation Labeling Rule. Therefore, I recommend that the PMR be considered fulfilled based on completion of

Study CNTO148JIA3001 and labeling be updated with the results of the study in Section 8.4.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This supplement does not warrant postmarketing risk evaluation and management strategies (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

This supplement does not warrant new postmarketing requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Subcutaneous (SC) golimumab is a clear to opalescent, colorless to light yellow solution. In the 50 mg strength, 0.5 mL of Simponi® contains 50 mg of golimumab antibody, 0.44 mg of L-histidine and L-histidine monohydrochloride monohydrate, 20.5 mg of sorbitol, 0.08 mg of polysorbate 80, and Water for Injection. In the 100 mg strength, 1 mL of Simponi® contains 100 mg of golimumab antibody, 0.87 mg of L-histidine and L-histidine monohydrochloride monohydrate, 41.0 mg of sorbitol, 0.15 mg of polysorbate 80, and Water for Injection.

SC golimumab is currently approved in adults for treatment of moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate (MTX); active psoriatic arthritis (PsA), alone or in combination with MTX; active AS; and moderately to severely active ulcerative colitis (UC) in patients with an inadequate response to or intolerance of prior treatment or requiring continuous steroid therapy. It is administered as a subcutaneous injection via prefilled syringe (PFS) or autoinjector (AI) at a dose of 50 mg once monthly for treatment of RA, PsA, and AS. For treatment of UC, an induction regimen of 200 mg at Week 0, followed by 100 mg at Week 2 is administered, and then maintenance therapy is continued with 100 mg every 4 weeks.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently approved non-biologic and biologic systemic therapies for polyarticular juvenile idiopathic arthritis (PJIA) and the indications for which they are approved are

listed in Table 1. In addition, there are nonsteroidal anti-inflammatory drugs (NSAIDs), as well as glucocorticoids, that are approved for the treatment of juvenile rheumatoid arthritis. Available therapies may be approved for treatment of more than one condition.

Table 1: US-licensed Biologic and Non-biologic DMARDs for PJIA

Product Name (Trade Name) [Applicant] {year}	***Mechanism of Action***	**Approved Indications**					
		PJIA	**RA**	**PsA**	**AS**	**PsO**	**Other**
Sulfasalazine (AZULFIDINE) [Pfizer]{1950}	*Anti-inflammatory and/or immunomodulator*	X	X				UC
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple] {1953}	*Folate anti-metabolite*	X	X			X	Oncology indications
Etanercept (ENBREL) [Immunex/Amgen] {1998}	Fusion protein consisting of TNF-R and human IgG1 Fc *TNFα inhibitor*	X	X	X	X	X	
Adalimumab (HUMIRA) [Abbott] {2002}	Human IgG1 k mAb *TNFα inhibitor*	X	X	X	X	X	CD, UC, Pediatric CD, HS, Uveitis
Abatacept (ORENCIA) [Bristol Myers Squibb] {2005}	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor*	X	X				
Tocilizumab (ACTEMRA) [Genentech/Roche] {2010}	Humanized IgG1 k mAb *IL-6 receptor inhibitor*	X	X				SJIA
*Year = Year of first approval	UC=Ulcerative Colitis, CD=Crohn's Disease, SJIA= Systemic Juvenile Idiopathic Arthritis, HS=Hidradenitis Suppurativa						

2.3 Availability of Proposed Active Ingredient in the United States

Golimumab is an approved therapeutic biologic product that is available and marketed in the U.S. as a SC formulation (original BLA 125289, approved on April 24, 2009) and as an intravenous (IV) formulation (original BLA 125433, approved on July 18, 2013).

2.4 Important Safety Issues With Consideration to Related Drugs

Safety concerns associated with the use of TNF inhibitors are listed under the Warnings and Precautions section of the labels for these agents and include: increased susceptibility to serious infections such as opportunistic infections, tuberculosis, histoplasmosis, and reactivation of hepatitis B; increased risk for malignancies particularly lymphomas and hepatosplenic T-cell lymphoma; congestive heart failure, demyelinating disorders, autoimmune disorders, cytopenias, hepatotoxicity, hypersensitivity reactions, and injection-site reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

BLA 125289 for SC golimumab was initially approved for treatment of moderately to severely active rheumatoid arthritis in combination with MTX, active psoriatic arthritis alone or in combination with MTX, and active ankylosing spondylitis on 24April2009. A postmarketing study to assess the pharmacokinetics, safety, immunogenicity, and efficacy of golimumab in pediatric patients 2 to 16 years of age with active polyarticular juvenile idiopathic arthritis was required. The original final report submission date was October 2013. On 11Sept2013, a deferral extension until June 2017 was granted. In April 2015, golimumab was granted orphan drug designation for PJIA (0-16 years of age). In August 2016, the orphan designation was amended to expand the age range to PJIA in patients 0 to 18 years of age.

Type C written responses were communicated on 14May2013 regarding the need for additional clinical data to support the proposed weight based dosing rather than the body surface area used in Study CNTO148JIA3001, as well as the need for data to support with use of a proposed (b) (4) which was not used in the clinical study. A teleconference was subsequently requested for clarification and held on 25June2013. FDA informed Janssen that the clinical data was not sufficient to fulfil PREA without an age and dose-appropriate formulation. As the marketed prefilled syringe (PFS) did not have appropriate graduations to support pediatric dosing, Janssen proposed (b) (4) Janssen submitted an additional clarification request via email and written responses were communicated 07Jan2014 explaining that the proposed weight-tiered dosing regimen would require an additional controlled study with the new dosing regimen, as well as the planned PK and HF validation studies.

On 05March2014, Janssen notified FDA (b) (4) Following the submission of the clinical study report for CNTO148JIA3001 and additional analyses, Type C written responses were again requested and communicated on 17Dec2015. The Applicant asserted that the totality of the data support the efficacy of subcutaneous (SC) golimumab in PJIA, explaining the lack of observed benefit with golimumab treatment in CNTO148JIA3001 was due to the overall low rate of flares in the population which had a low inflammatory burden of disease, and noted that the response rates in the open label portion of the study were similar to those observed for other approved agents in randomized withdrawal studies. Additionally, in a pre-specified subgroup analysis, a difference in flare rates was observed in the randomized withdrawal period between the golimumab + MTX group as compared to the placebo + MTX group in those patients with higher baseline c-reactive protein (CRP) values. The Applicant maintained that the similar pharmacokinetic profiles in PJIA and adult RA patients, in which efficacy has previously been established, further supports the efficacy of golimumab in PJIA. The FDA did not

agree that the data from CNTO148JIA3001, which failed to meet its primary endpoint, would support an indication for golimumab in PJIA. The FDA expressed concern that the Applicant's conclusion that the study failed to meet the pre-specified endpoints because of low inflammatory burden was based on post-hoc analyses that were not controlled for Type 1 error and these analyses were considered exploratory; further that the use of PK extrapolation to support an indication was undermined by the failed clinical study. Janssen was advised to conduct a controlled dose-ranging study of relatively short duration to establish efficacy in patients with PJIA and establish a dose-response relationship that could support an application for a PJIA indication. The Applicant has decided not to conduct an additional study with golimumab in PJIA and is not seeking an indication for PJIA in this submission.

In the European Union, the Committee for Medicinal Products for Human Use issued a positive opinion on 26May2015 for a PJIA indication for SC golimumab and this was adopted by the EU Commission on 24June2016.

2.6 Other Relevant Background Information

SC golimumab was approved for UC in patients with an inadequate response to or intolerance of prior treatment or requiring continuous steroid therapy, on 15May2013. A clinical study in pediatric UC is currently ongoing. Additionally, IV golimumab is currently under investigation for treatment of PJIA in study CNTO148JIA3003.

Representatives of 2 pediatric rheumatology research networks, the Pediatric Rheumatology International Trials Organization (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG), which contributed to the recruitment for the study, submitted a letter in support of an indication for PJIA for subcutaneous golimumab in October 2015. The authors of the letter presented similar justification to support golimumab for PJIA as that presented by the Applicant in the briefing package for the Type C Written Responses in December 2015. They state that Study CNTO148JIA3001 provided open-label PK, effectiveness and safety data of similar type as to be provided for certolizumab and planned for intravenous golimumab in PJIA, and that golimumab offers an advantage over current therapies because of its monthly dosing and subcutaneous administration.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity of the study was good. The amount of missing data was small and did not interfere with reaching conclusions on safety and efficacy.

3.2 Compliance with Good Clinical Practices

The Applicant certifies that Study CNTO148JIA3001 was conducted in compliance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements. The study was monitored according to the Applicant's current Standard Operating Procedure for the Monitoring of Clinical Trials. Study protocol and amendments were reviewed by an Independent Ethics Committee or an Institutional Review Board. Written informed consent was obtained from subjects or their legally acceptable representatives after being informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.

3.3 Financial Disclosures

Financial disclosure certification was not included in this submission as the Applicant is not seeking indication claims. This was previously agreed upon with the Agency.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC information was submitted with this supplement. The relevant information was previously reviewed in the original BLA 125289.

4.2 Clinical Microbiology

No new clinical microbiology information was submitted with this supplement. The relevant information was previously reviewed in the original BLA 125289.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology information was submitted with this supplement. The relevant information was previously reviewed in the original BLA 125289.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Golimumab is a human monoclonal antibody, with an immunoglobulin G (IgG) 1 heavy chain isotype and a kappa light chain isotype, which binds both soluble and transmembrane forms of human TNFα, inhibiting the bioactivity of TNFα.

4.4.2 Pharmacodynamics

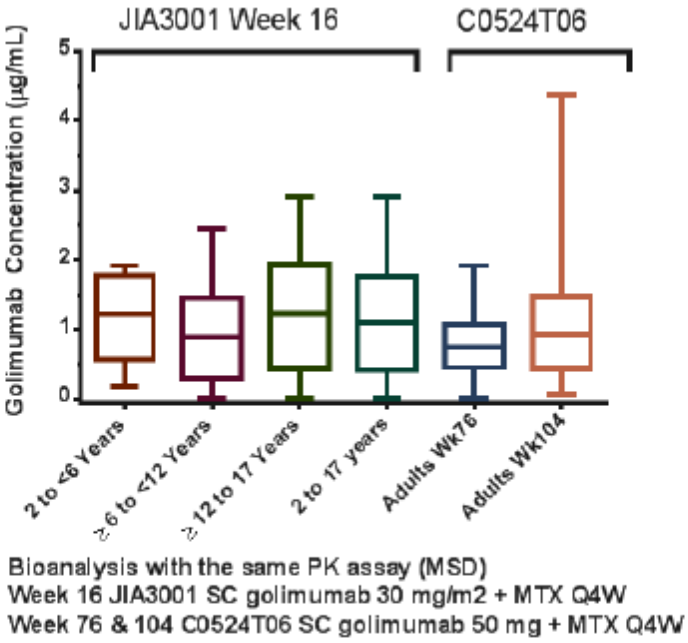
No new pharmacodynamics information was submitted with this supplement. In Study CNTO148JIA3001, pharmacodynamic responses to golimumab were measured in all patients ≥ 32 kg. Differential gene expression and protein profiling studies were utilized to identify genes or proteins linked to golimumab treatment in patients with JIA, and to determine which markers were most associated with changes in clinical measures after treatment. Pharmacodynamic data from Study CNTO148JIA3001 is to be provided in a separate technical report.

4.4.3 Pharmacokinetics

In Study CNTO148JIA3001, PK analyses were performed at Weeks 8, 16, and 48. An interim PK analysis, including population PK modeling, was performed at Week 8 on the first 30 enrolled patients. Pediatric patients in 3 age groups were evaluated including <6 years old (6 patients), ≥ 6 to < 12 years (9 patients), and ≥ 12 years (15 patients). The mean weights for the three age subgroups were 16, 30, and 57 kg, respectively. The serum mean trough golimumab concentrations were generally similar across the three age subgroups and were similar to mean concentrations in adult patients receiving golimumab 50 mg SC q4w in Study C0524T06. A population PK model found that simulations of golimumab concentrations in JIA patients were similar to observed serum golimumab concentrations in adult RA patients. The dosing regimen was felt by the applicant to be adequate to resume enrollment.

Based on Applicant analyses, an interim PK analysis on data from 121 patients at Week 16 confirmed similar serum golimumab concentrations across the age groups and BMI quartiles. Further assessment through Week 48 demonstrated that steady state levels of golimumab were maintained through Week 48 in the patients who continued on active treatment and decreased quickly for patients randomized to placebo + methotrexate (PBO+MTX). Median trough golimumab concentrations were similar over time for body weight quartiles, body weight categories (<20 kg, 20 kg to <40 kg, ≥ 40 kg), and baseline BMI. Median trough concentrations were higher and with greater variability for the lowest age group (0.92 to 1.77 µg/mL) as compared to the higher age groups (1.08 to 1.57 µg/mL and 0.73 to 1.25 µg/mL). Steady state trough concentrations of golimumab were similar to or slightly higher than those seen in adult RA patients who received 50 mg SC golimumab q4w in Study C0524T06 (Figure 1).

Figure 1: Comparison of steady-state trough GOL concentrations in PJIA in CNTO148JIA3001 and RA in C0524T06



MSD = Meso Scale Discovery; pJIA = polyarticular juvenile idiopathic arthritis; Q4W = every 4 weeks; RA = rheumatoid arthritis; SC = subcutaneous

Source: Clinical Overview Figure 1

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study ID	Design	Subjects	Treatments	Endpoints
CNTO148JIA3001	R, W, DB, PC, PG 12 wk OL 32 wk DB, RW 208 wk LTE	173 patients with active PJIA despite MTX enrolled, 154 patients randomized in DB portion	OL (Wk 0-12): • GOL 30mg/m^2 q4w + MTX DB (Wk 16-48): • GOL 30 mg/m^2 q4w + MTX • PBO	1: ACRp30 responders at Wk 16 without flare Wks 16-48 Major 2: • ACRp30 responders at Wk 16 with ACRp30 response at Wk 48 • Responders at Wk 16 with inactive disease at Wk 48 • Responders at Wk 16 in clinical remission while on medication for JIA at Wk 48

R = Randomized, W = Withdrawal, DB = Double Blind, PC = Placebo Controlled, PG = Parallel Group, OL = Open Label, LTE = Long Term Extension, GOL = Golimumab, MTX = Methotrexate, PBO = Placebo
ACRp30 = ACR Ped 30

5.2 Review Strategy

The supplemental BLA was reviewed for content, format, and overall data quality and integrity and found acceptable during the filing review.

The Applicant conducted a single randomized controlled study, CNTO148JIA3001, in pediatric patients, ages 2 to <18 years, with active polyarticular JIA, including rheumatoid factor (RF)-positive polyarthritis, RF-negative polyarthritis, extended oligoarthritis, juvenile psoriatic arthritis, or systemic JIA with no current systemic symptoms. Through Week 16, all patients received SC golimumab 30 mg/m^2 + MTX (GOL+MTX), and those patients who achieved an ACR Ped 30 response at Week 16 were randomized to blinded treatment with GOL+MTX or placebo + MTX (PBO+MTX). Patients receiving PBO+MTX who experienced a flare of their disease would be treated with GOL+MTX during or after the randomized withdrawal period (prior to and after Week 48). Efficacy analyses were conducted based on the intent to treat principle. Efficacy analyses up to Week 16 includes the "all enrolled patients" population, that includes all patients enrolled into the study at Week 0 who received at least 1 dose of study agent treatment. Efficacy analyses from Week 16 through Week 48 are conducted on the "all randomized patients" analysis set that includes all patients randomized into the randomized withdrawal portion of the study at Week 16. For analyses after Week 48 through Week 144, all randomized patients are included.

Safety data in this submission was also derived from Study CNTO148JIA3001. Safety analyses are based on all patients who received at least one study agent administration and are analyses based on actual treatment received. Safety data is presented for the following treatment groups in each period:

Through Week 16

- All enrolled patients
- Golimumab + MTX (GOL+MTX): patients randomized to receive GOL+MTX at Week 16
- Placebo + MTX (PBO+MTX): patients randomized to receive PBO+MTX at Week 16
- Enrolled patients who did not enter the randomized withdrawal period at Week 16

Week 16-48

- All randomized patients
- Golimumab + MTX: patients treated with GOL+MTX from Week 16 through Week 48
- PBO+MTX: patients treated with PBO+MTX from Week 16 through Week 48
- PBO+MTX→GOL+MTX: patients treated with PBO+MTX at Week 16 who switched to GOL+MTX prior to Week 48
- Combined: all patients treated with PBO+MTX at Week 16 including patients from the following groups: PBO+MTX, PBO+MTX→GOL+MTX prior to Week 48

Week 48-DBL

- All randomized patients
- Golimumab + MTX: patients treated with GOL+MTX at Week 16 who continued on GOL+MTX
- PBO+MTX: patients treated with PBO+MTX at Week 16 who continued on PBO+MTX
- PBO+MTX→GOL+MTX prior to Week 48: patients treated with PBO+MTX at Week 16 who switched to GOL+MTX prior to Week 48
- PBO+MTX→GOL+MTX at or after Week 48: patients treated with PBO+MTX at Week 16 who switched to GOL+MTX at or after Week 48
- Combined: all patients treated with PBO+MTX at Week 16 including patients from the following groups: PBO+MTX, PBO+MTX→GOL+MTX prior to Week 48, and PBO+MTX→GOL+MTX after Week 48

The randomized withdrawal study design limits comparison of safety events as all patients have been exposed to golimumab in the open-label period. Given that all patients received golimumab, it is difficult to determine if specific safety events may be related to this prior exposure event in patients receiving PBO+MTX after Week 16. Additionally, patients in the PBO+MTX group who were in clinical remission at Week 48 were discontinued from the study; the number of patients remaining in the PBO+MTX group after Week 48 is small. Therefore, the safety analysis will be presented by treatment groups described above in tabular form; however, the comparison of the GOL+MTX group to the Combined group is the comparison of primary interest.

5.3 Discussion of Individual Studies/Clinical Trials

Protocol: CNTO148JIA3001

Title: A Multicenter, Double-Blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab, a Human Anti-TNF-α Antibody, in Pediatric Subjects with Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy.

Dates Conducted: This study was started on December 1, 2010 and completed on May 27, 2014 (last patient last visit). The 48 Week database lock was September 18, 2013 and final database lock was July 7, 2014. The study was prematurely discontinued on March 31, 2014.

Objectives:
Primary Objective:
To assess the clinical efficacy of SC administration of golimumab in pediatric patients (ages 2 to less than 18 years) with PJIA manifested by ≥5 joints with active arthritis despite MTX therapy for ≥3 months

Secondary Objectives:
To evaluate golimumab in pediatric patients with PJIA with respect to:

- Safety (AEs, infections and serious infections, injection-site reactions, malignancies, laboratory parameters, vital signs, ANA and anti-dsDNA antibodies)
- Physical function
- Quality of life
- Disease activity status over time
- Pharmacokinetics and immunogenicity
- Pharmacodynamics

Overall Design:
Study CNTO148JIA3001 was a 256 week randomized-withdrawal, double-blind, placebo-controlled, parallel-group, multicenter study conducted at 33 global sites that included 173 patients, ages 2 to less than 18 years, with active polyarticular juvenile idiopathic arthritis despite treatment with MTX. All patients received golimumab SC 30 mg/m^2 q4w (maximum single dose 50 mg) in addition to a stable dose of methotrexate (10-30 mg/m^2/week) from Week 0 to Week 12. Body surface area was calculated at each visit and the dose of golimumab was adjusted accordingly. Patients also received commercial folic acid ≥ 5 mg weekly or folinic acid (at half the absolute MTX dose) on the day after the MTX dose.

Patients who achieved an ACR Ped 30 response by Week 16 were randomized 1:1 to receive:

- Golimumab 30 mg/m^2 SC q4w (maximum 50 mg) + MTX

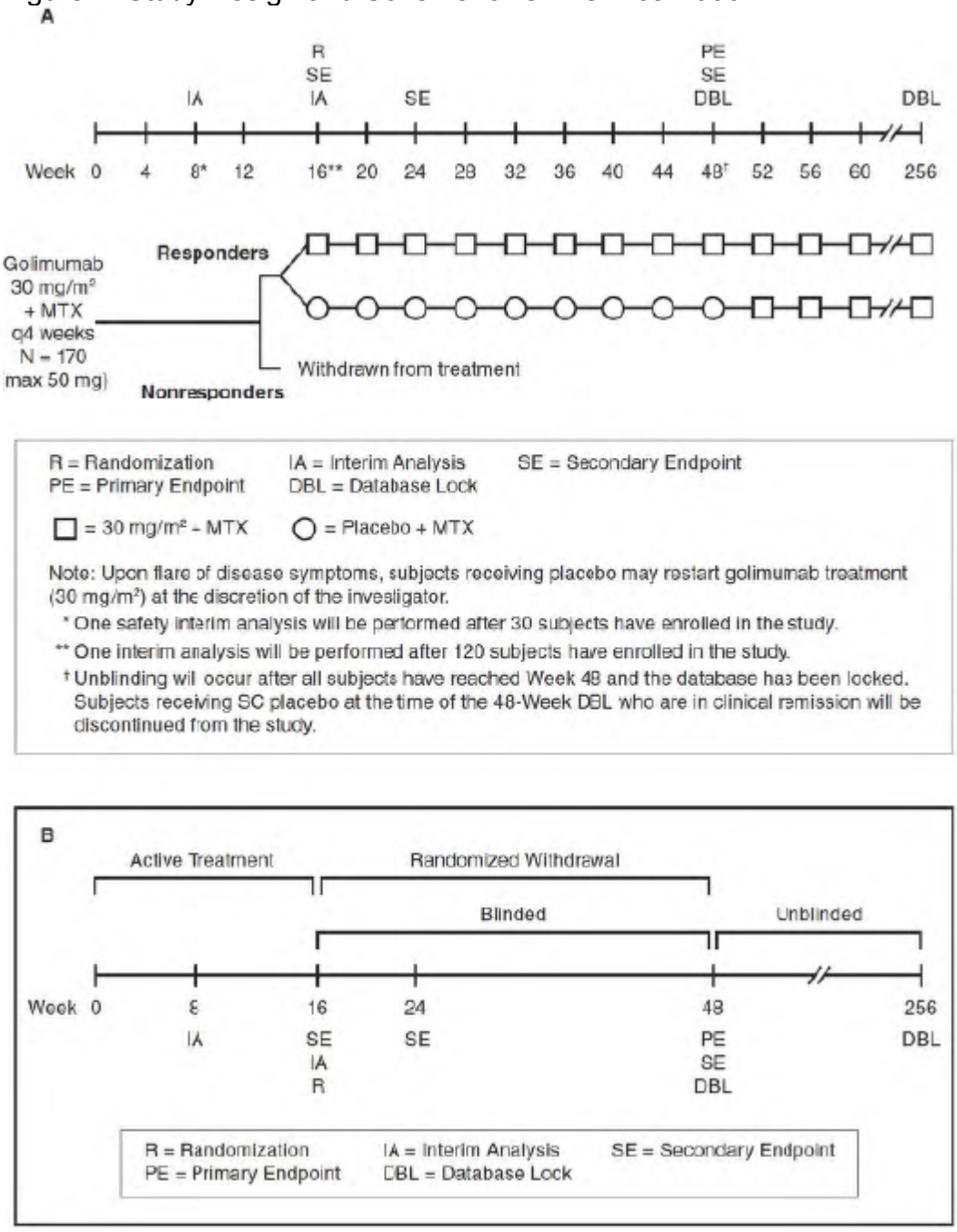
- Placebo SC injections q4w + MTX

Golimumab and placebo were supplied in prefilled syringes and transferred to a graduated syringe by a blinded pharmacist. Each PFS contained 100 mg of golimumab, L-histidine, sorbitol, and polysorbate 80 at pH 5.5. A matched placebo presentation was used without active drug.

Patients who experienced a flare while receiving placebo, were restarted on golimumab 30 mg/m^2 q4w (maximum 50 mg) at the next scheduled visit. Patients who experienced a flare while receiving golimumab remained on the same dose of golimumab. At Week 48, those patients who received placebo + MTX who were not in clinical remission were treated with blinded golimumab 30 mg/m^2. Upon unblinding of the site after the 48 week database lock, patients receiving SC placebo who were in clinical remission were discontinued from the study, while those receiving placebo who were not in clinical remission began golimumab 30 mg/m^2. A long term extension (LTE) phase with golimumab treatment from Week 48 through Week 248, and a final visit at Week 256, was planned.

The figure below details the study scheme.

Figure 2: Study Design and Scheme for CNTO148JIA3001



Source: 48 wk Clinical Study Report Figure 1

An interim analysis for PK, efficacy, and safety was conducted when the first 30 patients reached Week 8. If at least 8 of the first 30 patients were ACR Ped 30 responders at Week 8 and the PK analyses confirmed the dosing strategy, the study was continued.

A second interim analysis was performed after 121 patients completed the Week 16 visit to evaluate the response rate.

A flare of disease was defined according to the JIA pediatric criteria for flare and includes:

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

Inactive disease 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 ESR or CRP, Physician Global Assessment of disease activity indicating no active disease, and duration of morning stiffness < 15 minutes. Clinical remission while on medication for JIA is defined as inactive disease at each visit for a period of ≥ 6 months while on medication.

Study treatment was permanently discontinued for the following reasons: safety reasons, pregnancy, reaction resulting in bronchospasm with and without wheezing, and/or dyspnea requiring ventilator support, and/or symptomatic hypotension that occurs following study agent administration, reaction resulting in myalgia, arthralgia with fever and/or rash within 1 to 14 days after injection of study agent, opportunistic infection, malignancy, development of congestive heart failure, demyelinating disease, withdrawal of consent, initiation of protocol-prohibited medications, treatment assignment unblinded, and ineligibility according to tuberculosis (TB) screening criteria (symptoms, signs or diagnosis of active TB, or noncompliance with latent TB treatment). Patients who discontinued study agent injections during the study were followed for 8 weeks after the last administration.

Eligibility:

Major Inclusion Criteria:

1. Pediatric subject ages 2 to <18 years
2. Diagnosis of active JIA by JIA ILAR diagnostic criteria with onset prior to subject's 16th birthday. Active JIA of one of the following subtypes:
    a. Rheumatoid factor positive or negative polyarticular JIA for ≥6 months
    b. Systemic JIA with no systemic symptoms but polyarthritis for ≥6 months
    c. Extended oligoarticular JIA
    d. Polyarticular juvenile psoriatic arthritis
3. Disease duration ≥6 months prior to study entry
4. Must have ≥5 joints with active arthritis as defined by ACR criteria

5. Active JIA despite use of oral, intramuscular, or subcutaneous methotrexate (for ≥3 months) at a weekly dose of ≥10 mg/m^2. Subjects on MTX (weekly 10-30 mg/m^2) must receive stable dose for ≥4 weeks before screening
6. Subjects using NSAIDs must be on a stable dose for ≥2 weeks prior to first administration of study agent
7. If using corticosteroids, must be on stable dose of ≤10 mg/day prednisone equivalent or 0.20 mg/kg/day for ≥4 weeks before first administration of study agent. If currently not taking corticosteroids, subjects must have not received oral corticosteroids for at least 4 weeks prior to first administration
8. Subjects enrolled after the interim analysis of the first 30 subjects has been completed, may have been treated with no more than 1 TNFα inhibitor. The first 30 subjects should not have been previously treated with any TNFα inhibitors
9. Eligible based on the following tuberculosis (TB) screening criteria: no history of (H/O) latent or active TB prior to screening; no signs/symptoms suggestive of active TB upon medical history and/or physical exam; no recent close contact with a person with active TB or if such contact has occurred evaluation and appropriate treatment for latent TB (if warranted) prior to or simultaneously with first administration of study agent; must have a negative QuantiFERON-TB Gold (and negative TB skin test (TST) if QuantiFERON-TB Gold test is not approved/registered in that country) within 6 weeks prior to first administration of study agent, or if QuantiFERON-TB Gold or TST is positive, rule out active TB and initiate appropriate treatment for latent TB prior to or simultaneously with first administration of study agent; and a negative chest x-ray within 3 months prior to first administration of study agent with no evidence of current active TB or old, inactive TB as read by a qualified radiologist
10. Girls of childbearing potential must be incapable of pregnancy, abstinent, or practicing highly effective method of birth control. All girls of childbearing potential must have a negative serum pregnancy test at screening and urine pregnancy test at each study visit
11. Have the following screening lab test results: hemoglobulin ≥ 8.0 g/dL (girls and boys, ages 2-11), ≥ 8.5 g/dL (girls ages 12-18), ≥ 9.0 g/dL (boys ages 12-18); WBC≥ 3.0 x 10^3 cells/μL; neutrophils ≥ 1.5 x 10^3 cells/ μL; platelets ≥ 140 x 10^3 cells/μL; ALT and AST ≤ 1.2 x upper limits of normal (ULN); and serum creatinine ≤ 0.5 mg/dL (ages 2-5), ≤ 0.7 mg/dL (ages 6-10), ≤ 1.0 mg/dL (ages 11-12), ≤ 1.2 mg/dL (ages ≥ 13)
12. Must be up to date with immunizations as per local immunization guidelines for immunosuppressed subjects

Major Exclusion Criteria:

1. H/O hypersensitivity to human Ig proteins or other components of golimumab
2. Are pregnant or nursing, or planning pregnancy or fathering a child within 6 months after receiving last administration of study agent
3. H/O macrophage activation syndrome (MAS)
4. Treated with any investigational drug within the longer of 3 months or 5 half-lives of that drug prior to planned start of treatment or are current enrolled in an investigational study
5. Initiated DMARDs and/or immunosuppressive therapy within 4 weeks prior to study initiation
6. H/O inflammatory diseases such as systemic lupus erythematosus or Lyme disease that might confound evaluation of benefit from golimumab therapy
7. Are incapacitated, largely or wholly bedridden, or confined to a wheelchair, or have little or no ability for age-appropriate self-care

8. Received intra-articular, intra-muscular, or IV corticosteroids including adrenocorticotropic hormone during the 4 weeks prior to first study agent administration
9. Treated with therapeutic agent targeted at reducing IL-12 or IL-23, including ustekinumab and ABT-874
10. Received anakinra during the 4 weeks prior to first study agent administration
11. Received infliximab, etanercept, adalimumab, certolizumab pegol within 6 weeks of first dose of study agent
12. Received efalizumab, natalizumab, or therapeutic agents that deplete B or T cells within 12 months of first study agent administration, or have evidence at screening of persistent depletion of the targeted lymphocyte after receiving any of these agents
13. Received alefacept within the 3 months prior to the first study agent administration
14. Received abatacept within the 3 months prior to the first study agent administration
15. Received leflunomide within 4 weeks prior to the first study agent administration or received leflunomide from 4-12 weeks before first study agent administration and have not undergone a drug elimination procedure
16. Used cytotoxic agents such as chlorambucil., cyclophosphamide, nitrogen mustard, or other alkylating agents
17. Received or expected to receive any live virus or bacterial vaccination within 3 months prior to first study agent administration and up to 3 months after the last study agent administration
18. H/O latent or active granulomatous infection including histoplasmosis, or coccidioidomycosis prior to screening
19. Had bacilli Calmette-Guerin (BCG) vaccination within 12 months of screening
20. Chest X-ray within 3 months prior to first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection including TB
21. H/O nontuberculosis mycobacterial infection or opportunistic infection (e.g., cytomegalovirus, pneumocystosis, aspergillosis)
22. Have current side effects related to MTX that would preclude treatment with MTX including liver fibrosis, persistent elevations of ALT and AST (more than 3 of 5 tests elevated within 6 month 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
23. H/O infected joint prosthesis, or have received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced
24. H/O serious infection, hospitalization for an infection, or treatment with IV antibiotics for an infection within 2 months prior to first study agent administration
25. H/O or ongoing chronic/recurrent infectious disease (e.g., chronic renal infection, chronic chest infection, sinusitis, recurrent UTI, or open, draining or infected skin wound or ulcer)
26. H/O HIV, hepatitis C infection
27. Subjects must undergo screening for hepatitis B to include HBsAg, anti-HBs, and anti-HBc total. Subjects who test positive for surface antigen and those who test positive only for core antibody with positive HBV DNA are not eligible for the study
28. H/O demyelinating diseases such as multiple sclerosis
29. H/O or signs of lymphoproliferative disease
30. Known malignancy or h/o malignancy
31. H/O substance abuse
32. H/O (current or past) uveitis

33. H/O or concomitant diagnosis of CHF
34. H/o severe, progressive, or uncontrolled liver or renal insufficiency; or significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, psychiatric, or metabolic disturbances

Concomitant Medications:
Eligible patients were treated with MTX at a weekly dose of ≥ 10 mg/m^2 for ≥ 3 months prior to screening. The dose must have been stable between 10 to 30 mg/m^2 (or at least 15 mg/week in subjects with BSA ≥ 1.67 m^2) weekly for ≥ 4 weeks prior to screening. Patients receiving corticosteroids were required to be on a stable dose of the lesser of ≤ 10 mg prednisone or equivalent or 0.2 mg/kg/day, for ≥ 4 weeks prior to first study agent administration. If receiving NSAID therapy, the dose must have been stable for ≥ 2 weeks prior to first study agent administration. No changes in background medications were to be made between Week 16 and 48 in the randomized withdrawal period unless there was a documented flare or safety concern requiring change in background medication.

Intramuscular corticosteroids for treatment of JIA were not permitted during the study. Intraarticular steroids, up to 2 injections over a 24 week period, were permitted if clinically required. The joints affected by the procedure(s) are considered tender and swollen in subsequent data analyses from the data of the procedure through the 256 Week DBL. IV corticosteroids were to be avoided if possible; while, short courses (2 weeks or less) of oral or IV corticosteroids for prophylactic therapy prior to surgery or therapy for limited infections, exacerbation of asthma, or any condition other than JIA, were limited to situations in which there are no adequate alternatives. Corticosteroids administered by bronchial or nasal inhalation for treatment of other conditions could be given as needed.

Endpoints:
Primary efficacy endpoint:
The proportion of patients who were ACR Ped 30 responders at Week 16 and did not experience a flare of disease between Week 16 and Week 48

Major secondary endpoints:
- The proportion of ACR Ped 30 responders at Week 16 with ACR Ped 30 response at Week 48
- The proportion of patients who were responders at Week 16 and had inactive disease at Week 48
- The proportion of patients who were responders at Week 16 and were in protocol defined clinical remission while on medication for JIA at Week 48

Other efficacy endpoints:
- Proportion of ACR Ped 30 responders at Week 16

- Change from baseline in Childhood Health Assessment Questionnaire (CHAQ) at Week 16
- Change from Week 16 in CHAQ at each evaluation from Week 20 through Week 256
- Proportion of subjects with ACR Ped 30, 50, or 70 response
- Improvements in CRP concentrations
- Proportion of subjects who were responders at Week 16 and had inactive disease at Week 24
- Proportion of subjects who were responders at Week 16 and were in clinical remission on medication for JIA at Week 24
- For subjects in the OLE, the proportions of subjects with improvement in the JIA core set
- Time to flare of JIA disease from Week 16 through Week 48
- Change from baseline in physical function subscale score of CHQ at Week 48 in subjects who were ACR Ped 30 responders at Week 16
- Change from baseline in all subscale scores of the Child Health Questionnaire (CHQ)
- Percent improvement from baseline in the ACR Ped components through Week 16
- Percent improvement in the ACR Ped components from Week 16 through Week 256 in subjects who were responders at Week 16
- Proportion of subjects who were ACR Ped 30 responders at Week 48 and did not experience a flare of disease between Week 16 and Week 48
- Proportion of subjects who were ACR Ped 30, 50, and 70 responders by disease subtype, age, and treatment group

Other endpoints:

- Safety
- PK
- PD
- Immunogenicity

Statistical Analysis:

Efficacy analyses were compared and summarized using the intent-to-treat population. Safety assessments were summarized using the treated subject population. Based on sample size calculations, 134 patients who were responders at Week 16 were needed to enter the randomized withdrawal period to obtain 90% power to detect a significant difference between treatment groups.

The primary endpoint was evaluated by a Cochran-Mantel Haenszel test, stratified by JIA disease type, prior anti-TNF therapy, and age, and used for statistical testing at a 2-sided significance level of 0.05. A last observation carried forward (LOCF) procedure was used to impute the missing ACR Ped components if the patients had data for at

least one ACR component. If patients did not have data for all the ACR components at a certain timepoint, they were considered to have experienced a disease flare. In addition, patients were considered to have experienced a disease flare if they:

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

Patients who experienced a disease flare were considered non-responders for clinical response endpoints.

Major secondary endpoints were summarized by treatment group and compared between treatment groups. To account for multiplicity, the major secondary endpoints were to be tested sequentially if the primary endpoint was statistically significant. Nominal p-values were to be reported for secondary analyses.

Protocol Amendments & Study Conduct:
There were 9 amendments to the protocol. Amendments 1 through 5 and 1 administrative revision were adopted prior to initiation of study-related procedures. Key changes in protocol amendments 1-5 are as follows:

- At the Week 48 DBL subjects randomized to placebo who were not in clinical remission began receiving golimumab 30 mg/m^2 while those in clinical remission were discontinued from the study
- Clarification that flare of disease was based on comparison of criteria with Week 16 values
- Change from independent joint assessor (IJA) to consistent joint assessor as Applicant unable to obtain IJAs for all sites in a timely manner
- Inclusion criteria for use of MTX, prior use of TNFα inhibitors, immunizations, and TB screening criteria were revised. Exclusion criteria for chest radiographs and history of hepatitis B infections, hepatitis B testing, and use of TNFα inhibitors were added
- Use of MTX (dosage) during the study was clarified

The sixth amendment (07Mar2011) included clarifications of how concomitant medication would be adjusted for patients with worsening disease status from Weeks 0 to 16, clarification on the definition of clinical remission as it was thought unlikely any patient would stop all concomitant medications while in the study, clarification that the dose of golimumab would be adjusted by BSA for each patient for all q4w doses, and clarification on the reinstatement of golimumab treatment. In the seventh amendment (31May2012), clarifications were made on the use of corticosteroids and MTX after Week 16 or in the event of a flare, as well as the minimum weekly dosage of MTX for

patients ≥ 1.67 m^2. The number of joints to be evaluated was revised to include subtalar joints (1 in each foot) on the advice of the Pediatric Rheumatology International Trials Organisation/Pediatric Rheumatology Collaborative Study Group. In the eighth amendment (20Feb2013), the use of DMARDs, corticosteroids, and NSAIDs between Week 16 and 48 and the weekly MTX dosage were clarified. The ninth amendment (18June 2013), extended the long term extension by 104 weeks and included clarifications of the definition of inactive disease.

The protocol amendments and, specifically amendments 6 through 9 made after the initiation of the study, are unlikely to affect safety or efficacy results in an unbalanced manner.

6 Review of Efficacy

Efficacy Summary

A single study in patients with polyarticular juvenile idiopathic arthritis was conducted. Study CNTO148JIA3001 was conducted to fulfill Post-Marketing Requirement #1 issued with the BLA 125289 approval letter dated 24April 2009. The study did not meet the primary or major secondary endpoints, and the Applicant (b) (4)

6.1 Indication

Janssen is not seeking an indication for polyarticular JIA with this submission.

6.1.1 Methods

Efficacy analyses were based on the intent-to-treat population. Patients randomized to placebo who experienced a flare of disease were treated with GOL + MTX; these subjects were treated as ACR Ped 30 nonresponders in the analyses. Treatment failure rules, as defined in the statistical analysis plan, were as follows:

1. Initiated any DMARDS, biologics, or systemic immunosuppressives for JIA, or increase MTX dose above baseline.
2. Initiated treatment with oral, intravenous (IV), or intramuscular (IM) corticosteroids for JIA or non-JIA reasons, or increased the dose of oral corticosteroids for JIA above baseline dose.
3. Discontinued study agent injections due to lack of efficacy for JIA or an AE of worsening of JIA.

Data handling rules were implemented for all endpoints. Partially missing data were imputed using last observation carried forward and non-responder imputation was performed for responder/flare type dichotomous data that was completely missing.

A pre-specified interim efficacy analysis, performed when the first 30 patients completed Week 8, exceeded the specified criteria of 8 ACR Ped 30 responders to continue the study. At Week 8, 28 (93.3%) of the 30 enrolled patients were ACR Ped 30 responders. A second pre-specified interim analysis was performed after the initial 121 patients completed Week 16; at that time, 110 (90.9%) of 121 patients achieved an ACR Ped 30 response and the sample size was not adjusted.

6.1.2 Demographics

Baseline demographics were generally balanced between treatment groups (Table 2). The majority of patients were female (131 patients, 75.7%) and Caucasian (152 patients, 87.9%). The median age was 12.0 years and the median weight was 43.0 kg. The majority of the patients were pre-pubescent (Tanner stage I).

Table 2: Baseline Demographics

	Golimumab administered prior to randomization at Wk 16				
	Not randomized at Wk 16 N = 19 n (%)	GOL+MTX N = 78 n (%)	PBO+MTX N = 76 n (%)	All randomized patients N = 154 n (%)	All enrolled N =173 n (%)
Age, years					
Mean (SD)	11.8 (4.4)	11.1 (4.4)	11.1 (4.5)	11.1 (4.5)	11.2 (4.4)
Median	12.0	11.5	12.0	12.0	12
Gender, n(%)					
Female	15 (78.9)	59 (75.6)	57 (75.0)	116 (75.3)	131 (75.7)
Male	4 (21.1)	19 (24.4)	19 (25.0)	38 (24.7)	42 (24.3)
Race, n(%)					
Caucasian	17 (89.5)	68 (87.2)	67 (88.2)	135 (87.7)	152 (87.9)
Black	0	2 (2.6)	0	2 (1.3)	2 (1.2)
American ndian/Alaska Native	1 (5.3)	3 (3.8)	4 (5.3)	7 (4.5)	8 (4.6)
Other	1 (5.3)	3 (3.8)	3 (3.9)	6 (3.9)	7 (4.0)
Unknown	0	0	1 (1.3)	1 (0.6)	1 (0.6)
Height, cm					
Mean (SD)	145.4 (24.5)	144.3 (24.4)	143.9 (24.8)	144.1 (24.5)	144.3 (24.5)
Median	152.0	150.3	151.5	151.1	151.5
Weight, kg					
Mean (SD)	44.5 (20.6)	44.0 (21.8)	41.9 (18.5)	43.0 (20.2)	43.1 (20.2)
Median	46.0	43.0	41.8	42.7	43.0
Body Surface Area (m^2)					
Mean (SD)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
Median	1.4	1.4	1.3	1.3	1.4

Source: Adapted from 48 Week Clinical Study Report Table 6

Baseline disease characteristics were also generally balanced across the treatment groups (Table 3). The majority of patients had polyarticular rheumatoid factor (RF)-negative JIA (52.0%). The mean CRP at baseline was slightly lower in the group subsequently randomized to GOL+MTX, while the mean ESR was slightly higher in this group. The mean CHAQ scores at baseline were slightly lower in the group that was subsequently randomized to GOL+MTX, while the Parent Assessment of Pain was higher in the PBO + MTX group. The mean CRP and ESR, as well as the mean number of joints with limited range of motion and CHAQ scores were higher in the group that did not enter the randomized withdrawal period. There was also a small increase in the mean number of joints with active arthritis in this group, suggesting a higher inflammatory burden.

Table 3: Baseline Disease Characteristics

	Golimumab administered prior to randomization at Wk 16				
	Not randomized at Wk 16 N = 19 n (%)	GOL+MTX N = 78 n (%)	PBO+MTX N = 76 n (%)	All randomized patients N = 154 n (%)	All enrolled N = 173 n (%)
ILAR classification, N (%)					
Polyarticular RF neg	13 (68.4)	37 (47.4)	40 (52.6)	77 (50.0)	90 (52.0)
Polyarticular RF pos	3 (15.8)	18 (23.1)	13 (17.1)	31 (20.1)	34 (19.7)
Ol goarticular ext	1 (5.3)	12 (15.4)	9 (11.8)	21 (13.6)	22 (12.7)
JPsA	0	8 (10.3)	7 (9.2)	15 (9.7)	15 (8.7)
Systemic onset, polyarticular course with no systemic symptoms	2 (10.5)	3 (3.8)	7 (9.2)	10 (6.5)	12 (6.9)
Number of joints with active arthritis					
Mean (SD)	16.1 (10.7)	14.8 (9.2)	15.0 (10.6)	14.9 (9.9)	15 (10.0)
Median	12.0	13.0	11.5	12.0	12.0
Number of joints with limited ROM					
Mean (SD)	14.2 (12.8)	12.3 (9.9)	11.6 (10.9)	11.9 (10.3)	12.2 (10.6)
Median	11.0	9.0	8.0	8.0	8.0
Physician Global Assessment of Disease activity					
Mean (SD)	5.4 (2.5)	5.7 (1.8)	5.5 (2.0)	5.6 (1.9)	5.6 (2.0)
Median	5.7	5.7	4.9	5.4	5.4
Parent Assessment of Overall well-being					
Mean (SD)	4.7 (2.1)	4.3 (2.5)	4.5 (2.3)	4.4 (2.4)	4.4 (2.3)
Median	5.0	3.9	4.8	4.3	4.5
Parent Assessment of Pain	4.7 (2.7)	4.3 (2.8)	5.0 (2.4)	4.6 (2.6)	4.6 (2.6)
Mean (SD)	4.4	3.9	5.2	4.7	4.7
Median					
CHAQ					
Mean (SD)	1.2 (0.7)	0.9 (0.7)	1.0 (0.7)	1.0 (0.7)	1.0 (0.7)
Median	1.4	0.8	0.9	0.9	0.9
ESR (mm/h)					
Mean (SD)	23.9 (22.4)	21.8 (21.0)	20.8(18.2)	21.3 (19.6)	21.60(19.9)
Median	15.0	15.5	16.0	16.0	16.0
CRP (mg/dL)					
Mean (SD)	1.2 (2.1)	0.9 (1.9)	1.2 (2.4)	1.0 (2.2)	1.1 (2.2)
Median	0.4	0.2	0.1	0.2	0.2

Source: Adapted from 48 Week Clinical Study Report TSIMH2

Study CNTO148JIA3001 enrolled PJIA patients with moderately-severely active arthritis; however, median baseline inflammatory markers were low as compared to populations in JIA studies conducted with other approved biologics. The patients in CNTO148JIA3001 also had fewer active joints and fewer joints with limitations in ROM

than seen in several other JIA studies (Appendix 1). Patients who did not enter the randomized withdrawal period, ie did not achieve an ACR Ped 30 response, may have had a higher inflammatory burden as evidenced by an increased number of joints with limited range of motion, increased number of joints with active arthritis, higher CHAQ scores, as well as elevated inflammatory markers. This is of note in considering the Applicant's rationale that the study failed to meet the efficacy endpoints because of the low inflammatory burden of the enrolled patients.

Disease characteristics were generally similar between the patients randomized to PBO+MTX and GOL+MTX at Week 16. At Week 16, after receiving open-label golimumab treatment, the randomized patients had fewer joints with active arthritis (mean 3.1 and 2.3 in the PBO+MTX and GOL+MTX groups, respectively), fewer joints with limited range of motion (mean 3.3 and 2.9, respectively), and decreased mean inflammatory markers (ESR: 12.57 and 13.94, CRP 0.43 and 0.53, respectively) as compared to baseline. In addition, physician global assessment of disease activity, parent assessment of overall well-being and pain, and CHAQ scores were lower at Week 16 as compared to baseline.

Concomitant Medications
Eligible patients were taking stable doses of MTX (weekly 10-30 mg/m^2) for ≥ 4 weeks before screening. The dose and duration of prior exposure to MTX was generally similar across treatment groups. Sixty-seven (38.7%) of enrolled patients had previously taken DMARDs other than MTX, approximately 50% had taken systemic corticosteroids, and 91.9% had received NSAIDs. Twenty patients (11.6%) had prior exposure to anti-TNF therapies, primarily with etanercept (16 patients). Of the 20 patients previously exposed to anti-TNF treatment, 17 patients were subsequently randomized (9 patients in the PBO+MTX group, 8 in the GOL+MTX group).

Similar proportions of patients in each of the randomized treatment groups were on concomitant medications that could impact disease activity including oral corticosteroids and NSAIDs. Doses of oral corticosteroids and MTX were similar between randomized groups. The group of patients who were not randomized had the greatest proportion on oral corticosteroids and the highest mean corticosteroid dose, possibly reflecting the higher inflammatory burden in this group. Through Week 48, 1 patient in the PBO+MTX group, 1 patient in the GOL+MTX group, and 1 patient who was not randomized received a TNF-inhibitor (certolizumab, etanercept, and certolizumab, respectively). After Week 48, 1 patient (GOL+MTX) received leflunomide.

6.1.3 Subject Disposition

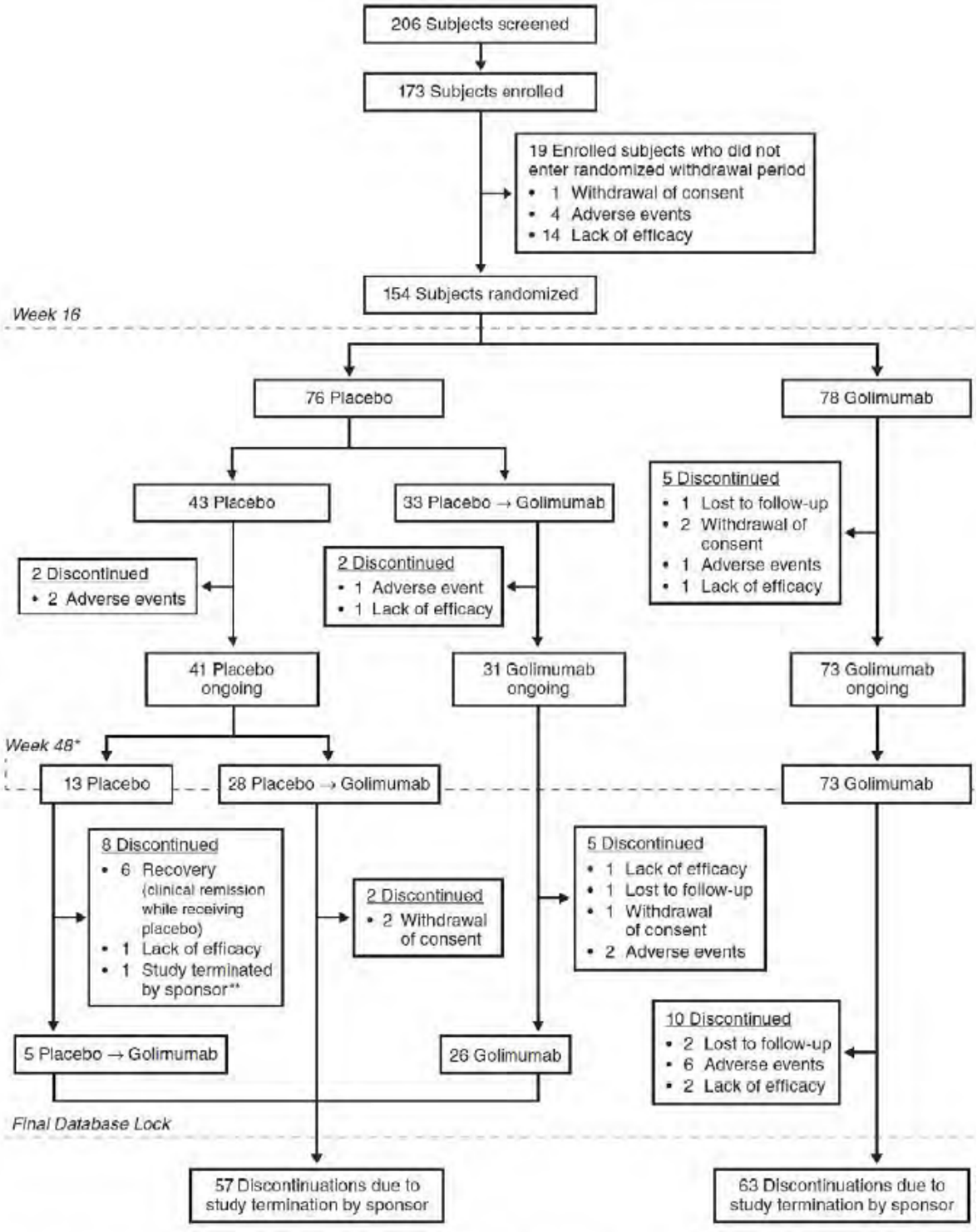
One hundred seventy three (173) patients were enrolled in 33 global sites. Thirty three patients were screening failures, most commonly related to not meeting eligibility criteria (29 patients). All of the enrolled patients received GOL+MTX at Week 0. As shown in Figure 3, 19 patients discontinued the study during the active treatment period; 14

patients withdrew due to lack of efficacy, 4 patients experienced adverse events, and 1 patient withdrew consent. Two patients who discontinued for lack of efficacy and one who withdrew consent were also lost to follow-up.

One hundred and fifty four patients were randomized at Week 16; 78 patients were randomized to GOL+MTX and 76 patients were randomized to PBO+MTX. From Weeks 16 through 48, 9 patients discontinued study agent, 4 (5.3%) patients in the PBO+MTX treatment group and 5 (6.4%) in the GOL+MTX. The most common reason for discontinuation was AE (Table 4). Thirty two patients (42.1%) randomized to PBO+MTX experienced a flare during the randomized withdrawal period and received GOL+MTX and one patient (0102-00147) who did not flare received GOL+MTX.

From Week 48 until the time of the final DBL, 15 patients in the PBO+MTX group discontinued study agent, 8 receiving PBO+MTX, 5 who received PBO+MTX → GOL+MTX during Week 16-48, and 2 who received PBO+MTX→GOL+MTX at or after Week 48. In the group randomized to GOL+MTX, 10 patients discontinued from Week 48 to the final DBL. Note, the reasons for discontinuation of 2 patients (1 PBO+MTX, 1 GOL+MTX) in the Week 48 to DBL period were incorrectly attributed to “Study termination by Sponsor”, rather than “Recovery” and “Lack of efficacy”, respectively. Of the 154 patients randomized at Week 16, 121 (78.6%) continued in the study until termination by the Applicant on 31March 2014. At the time of study discontinuation, 129 patients had completed through Week 96, 1 patient had completed through Week 168, and no patients completed the final Week 256 assessment.

Figure 3: Patient Distribution and Disposition through the Final DBL



* Note: All subjects remaining in the study received golimumab after the Week 48 database lock.
** The reason for discontinuation was incorrectly reported for this subject; the correct reason for discontinuation was Recovery.

Source: Final Clinical Study Report, Figure 2

Table 4: Patient Disposition

	Golimumab administered prior to randomization at Wk 16		
	Not randomized at Wk 16 N = 19 n (%)	PBO+MTX N = 76 n (%)	GOL+MTX N = 78 n (%)
Week 0-16			
Patients enrolled	19	76	78
Discontinued prior to or at Wk 16	19		
Reasons for discontinuation of study agent			
Lack of efficacy	14 (73.7)		
Adverse event	4 (21.0)		
ithdrawal of consent	1 (5.3)		
Week 16-48			
Randomized at Wk 16		76	78
Discontinued Wk 16-48		4 (5.3)	5 (6.4)
Reasons for discontinuation			
Adverse event		3 (3.9)	1 (1.3)
Lack of efficacy		1 (1.3)	1 (1.3)
Withdrawal of consent		--	2 (2.6)
Lost to follow-up		--	1 (1.3)
Week 48-DBL			
Continuing study agent at Wk 48		72	73
Discontinued Wk48-DBL		72 (94.7)	73 (93.6)
Reasons for discontinuation			
Study termination by Applicant		58 (76.3)	63 (80.8)
Adverse event		2 (2.6)	6 (7.7)
Recovery		6 (7.9)	--
Withdrawal of consent		3 (3.9)	--
Lack of efficacy		2 (2.6)	2 (2.6)
Lost to follow-up		1 (1.3)	2 (2.6)

Source: Adapted from 48 Week Clinical Study Report Table 5; Final Clinical Study Report Table 2
Reviewer JMP analysis using ADDS dataset, terms APERIODC, AVALC, TRT02P, USUBJ

No patients were unblinded through Week 48, and as per protocol, all sites were unblinded after the 48 week DBL on 10Oct2013. There were 109 major protocol deviations through the final DBL, balanced across the treatment groups (Table 5).

Table 5: Major Protocol Deviations through Final DBL (Randomized Patients)

	GOL+MTX N = 78 n (%)	Combined N = 76 n (%)	PBO+MTX N = 11 n (%)	PBO+MTX →GOL+MTX before W48 N = 32 n (%)	PBO+MTX →GOL+MTX at or after W48 N = 33 n (%)	All randomized N = 154 n (%)
Entered study but entry criteria not met	7 (9.0)	7 (9.2)	2 (18.2)	4 (12.5)	1 (3.0)	14 (9.1)
Met study withdrawal criteria but not withdrawn	1 (1.3)	0	0	0	0	1 (0.6)
Received wrong treatment or incorrect dose	8 (10.3)	6 (7.9)	0	2 (6.3)	4 (12.1)	14 (9.1)
Received disallowed concomitant treatment	2 (2.6)	1 (1.3)	0	0	1 (3.0	3 (1.9)
Other	49 (62.8)	54 (71.1)	8 (72.7)	25 (78.1)	21 (63.6)	103 (66.9)

Source: Adapted from Final Clinical Study Report TSIDEV1

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the proportion of patients who were ACR Ped 30 responders at Week 16 who did not experience a flare of disease between Week 16 and Week 48, based on the intent-to-treat population. Forty six patients (59.0%) in the GOL+MTX treatment group were ACR Ped 30 responders who did not experience flare between Week 16 and Week 48, while 40 patients (52.6%) in the PBO+MTX group met the primary endpoint (Table 6); the difference was not statistically significant (p-value 0.414).

Table 6: Primary and Major Secondary Endpoints (Randomized Patients)

	PBO+MTX N = 76 n (%)	GOL+MTX N = 78 n (%)	P value
ACRPed30 Responders at Wk 16 without flare through Wk 48	40 (52.6)	46 (59.0)	0.414
ACRPed30 Responders at Wk 16 with ACRPed30 Response at Wk 48	42 (55.3)	41 (52.6)	0.751
ACRPed30 Responders at Wk 16 with inactive disease at Wk 48	21 (27.6)	31 (39.7)	0.119
ACRPed30 Responders at Wk 16 in clinical remission while on medication for JIA at Wk 48	9 (11.8)	10 (12.8)	0.848

Source: Adapted from 48 Week Clinical Study Report Tables 11, 12, 13

Thirty three patients (43.4%) randomized to the placebo group received golimumab 30 mg/m^2 during the randomized withdrawal period, 32 of these patients experienced a flare. These patients were considered nonresponders for the efficacy analysis. Fifteen

patients (9.7%) had missing flare of disease data during at least one study visit that was imputed for the primary endpoint.

Of the 19 patients who did not enter randomized withdrawal, 18 patients met treatment failure criteria at Week 16, primarily due to lack of efficacy for JIA or an AE of worsening of JIA. From Weeks 16-48, 18.4% of patients in the PBO+MTX group and 9.0% in the GOL+MTX group met treatment failure criteria. The majority of treatment failures were due to initiation or increases in medications for JIA. Only the 3rd treatment failure criteria applied to analyses after Week 48. After Week 48 through the final DBL, 5.3% of patients in the PBO+MTX treatment group and 3.8% in the GOL+MTX group met treatment failure criteria.

Sensitivity analyses conducted (1) using a re-randomization test with the same data handling rules as the primary analysis, (2) considering patients with insufficient data to determine flare as having a flare, (3) considering patients with insufficient data as missing data, and (4) considering those who discontinue study agent after Week 16 through Week 48 due to any reason as having flared, were consistent with the results of the primary analysis.

6.1.5 Analysis of Secondary Endpoints(s)

Analysis of major secondary endpoints including the proportion of ACR Ped 30 responders at Week 16 with ACR Ped 30 response at Week 48, the proportion of patients who are responders at Week 16 and have inactive disease at Week 48, and the proportion of patients who are responders at Week 16 and are in protocol defined clinical remission while on medication for JIA at Week 48, showed similar response rates between treatment groups as seen in Table 6. Sensitivity analyses using a re-randomization test were consistent with the analysis for each of the major secondary endpoints.

6.1.6 Other Endpoints

ACR Responses
ACR responses were observed as early as Week 4. At Week 16, 151 (87.3%) patients were ACR Ped 30 responders, 137 (79.2%) were ACR Ped 50 responders, 114 (65.9%) were ACR Ped 70 responders, and 63 (36.4%) patients were ACR Ped 90 responders. The proportions of ACR 30/50/70/90 responders were stable in both the GOL+MTX and PBO+MTX groups from Weeks 16 to 48 when analyzing observed data, however the proportions of responders decreased over time, when data handling rules were applied. Data handling rules considered patients experiencing flares as nonresponders regardless of actual ACR core measurements. Table 7 presents the ACR Ped 30 Response rate by data handling rules and observed data. At Week 48, the proportions of ACR Ped 30, 50, 70 and 90 responders were similar between the GOL+MTX and PBO+MTX groups using either the data handling rules or observed data.

Table 7: ACR Ped 30 Responders from Week 16 through Week 48 (Randomized Patients)

	Data Handling Rules		Observed Data	
	PBO+MTX N = 76 n (%)	GOL+MTX N = 78 n (%)	PBO+MTX N = 76 n (%)	GOL+MTX N = 78 n (%)
ACR Ped 30				
Week 16	75 (98.7)	76 (97.4)	76 (100.0)	77 (98.7)
Week 20	66 (86.8)	74 (94.9)	67 (88.2)	74 (94.9)
Week 24	57 (75.0)	60 (76.9)	68 (89.5)	68 (87.2)
Week 28	51 (67.1)	53 (67.9)	70 (92.1)	67 (85.9)
Week 32	48 (63.2)	51 (65.4)	71 (93.4)	69 (88.5)
Week 36	45 (59.2)	49 (62.8)	73 (96.1)	67 (85.9)
Week 40	44 (57.9)	49 (62.8)	70 (92.1)	70 (89.7)
Week 44	42 (55.3)	46 (59.0)	71 (93.4)	71 (91.0)
Week 48	42 (55.3)	41 (52.6)	70 (92.1)	65 (83.3)

Source: Adapted from 48 wk Clinical Study Report TEFPEDACR2C
Reviewer JMP analysis, ADEF dataset using terms PARAM, AVISIT, AVAL, TRT02P

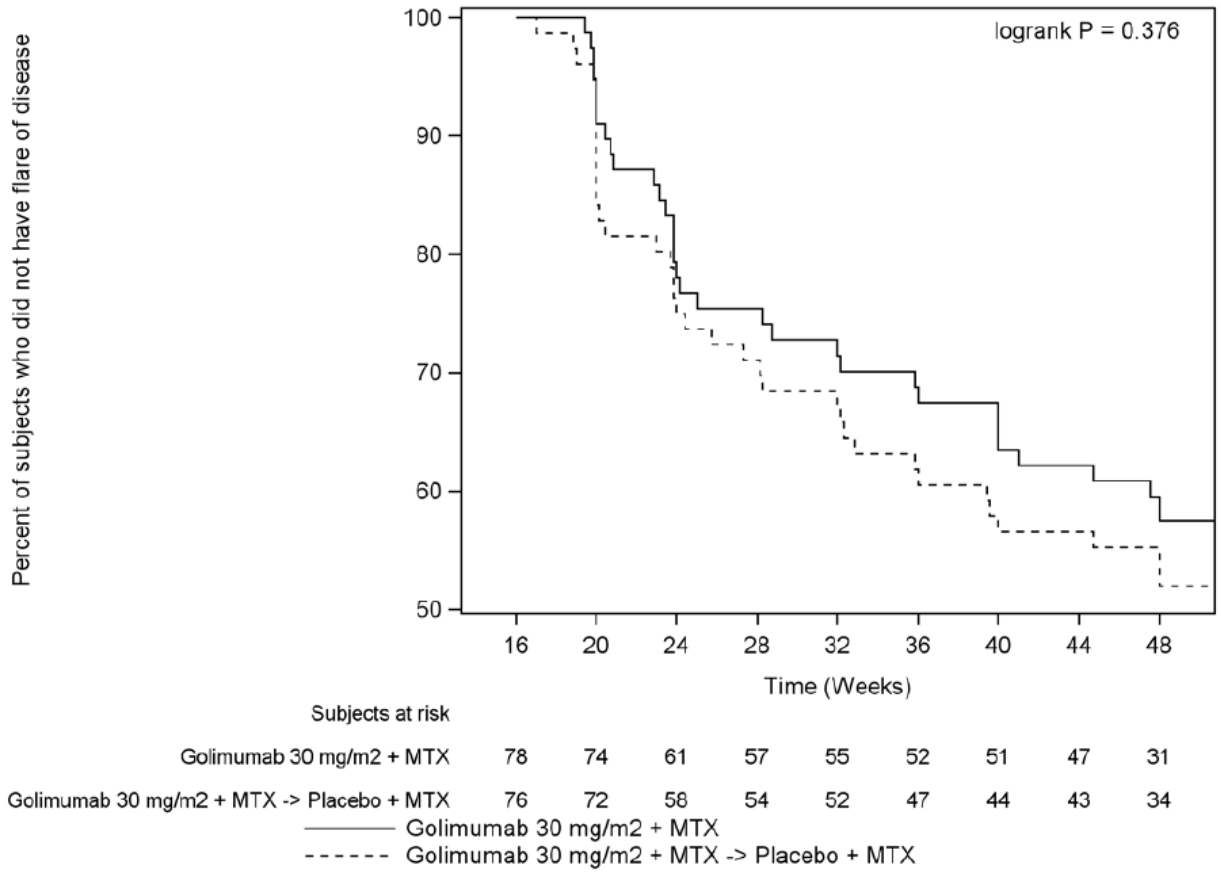
Median percent improvement from baseline in ACR Ped components was generally similar in both the GOL+MTX and PBO+MTX groups from Weeks 16-48. At Week 48, differences between the treatment groups in median percent improvement were observed for number of active joints (100.0% in GOL+MTX, 90.9% in PBO+MTX), physical function by CHAQ (54.9% in GOL+MTX, 78.4% in PBO+MTX), and ESR (26.3% in GOL+MTX and 37.5% in PBO+MTX).

The proportions of patients who were ACR Ped 30, 50, 70 and 90 responders increased from Week 48 through Week 84 in both treatment groups, based on reviewer analysis. Response rates at Week 96 were similar to those at Week 48 and subsequent assessment is limited by decreasing number of patients. Median percent improvement from baseline in ACR Ped components was generally similar between treatment groups through Week 96, with exception of increased CHAQ and ESR in the PBO+MTX group.

Flares

Through Week 16, 20 (11.6%) patients experienced a flare of disease. Of these, 18 patients did not enter the randomized withdrawal period, 1 patient was randomized to GOL+MTX, and 1 patient was randomized to PBO+MTX and later transitioned to GOL+MTX prior to Week 48. From Weeks 16-48, 32 (41.0%) patients randomized to GOL+MTX experienced flares, while 36 (47.4%) patients randomized to PBO+MTX experienced flares. Figure 4 presents a Kaplan Meier plot of time to first flare of disease from Week 16 through Week 48; the difference between the plots for each treatment group was not significant (p=0.376). A similar curve of time to first flare through the final DBL also does not show meaningful separation between the curves.

Figure 4: Kaplan Meier Plot of Time to First JIA Flare from Week 16 through Week 48 by Treatment Group (Randomized Patients)



Source: 48 Week Clinical Study Report, GEFFLARE4

After Week 48, 19 (24.4%) patients in the GOL+MTX group and 15 (19.7%) patients randomized to the PBO+MTX group experienced a flare. An increase in the proportions of patients with flare was observed in both treatment groups at Week 120 through the DBL, however, conclusions are limited by the smaller number of randomized patients participating in the study at these time points.

Inactive Disease and Clinical Remission

Inactive disease was defined as 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 ESR (<20 mm/hr) or CRP (<1.0 mg/dL or <10 mg/L), Physician Global Assessment of disease activity indicating no active disease (≤5 mm on the VAS), and duration of morning stiffness < 15 minutes. Clinical remission while on medication for JIA was defined as inactive disease at each visit for a period of ≥ 6 months while on medication.

By Week 16, 69 patients had inactive disease, 35 who were randomized to GOL+MTX, 32 randomized to PBO+MTX, and 2 patients who were not randomized. From Week 16 to 48, the proportions of patients with inactive disease at one or more visits was generally balanced between the treatment groups (47 (60.3%) GOL+MTX vs. 43 (56.6%) PBO+MTX). The Applicant has suggested that this demonstrates an increase in the proportions of patients with inactive disease over time, however fluctuations in JIA activity may occur as part of the natural course of disease. Given the similar increase in the PBO+MTX group, conclusions are limited.

By definition, patients could not be in clinical remission prior to Week 24. At Week 24, there were no patients in clinical remission. By Week 48, there were 19 patients in clinical remission (10 (12.8%) randomized to GOL+MTX, 9 (11.8%) randomized to PBO+MTX, based on reviewer analysis). The proportions of patients who met the criteria for inactive disease and clinical remission were generally balanced between treatment groups and did not demonstrate a benefit to treatment with GOL+MTX over PBO+MTX.

After Week 48 through the final DBL, the proportions of patients with inactive disease at one or more visits, were also balanced (52 (66.7%) GOL+MTX vs. 57 (75.0%) PBO+MTX). The proportions of patients in clinical remission at any time after Week 48, were similar in each treatment group (34 (43.6%) GOL+MTX vs. 33 (43.4%) PBO+MTX), and were similar at each visit with the exceptions of Weeks 60 and 72 which favored the GOL+MTX group (21.8% and 25.6%, respectively) over the PBO+MTX group (14.5% and 17.1%), based on reviewer analysis.

CRP

At Week 16, the mean and median CRP values were lower in the group randomized to PBO+MTX (median 0.04) as compared to the group randomized to GOL+MTX (median 0.06). At Week 48, the median CRP values were more similar at 0.06 in the PBO+MTX group as compared to 0.05 in the GOL+MTX. Changes in CRP values were small in magnitude and similar between treatment groups through the final DBL.

CHAQ

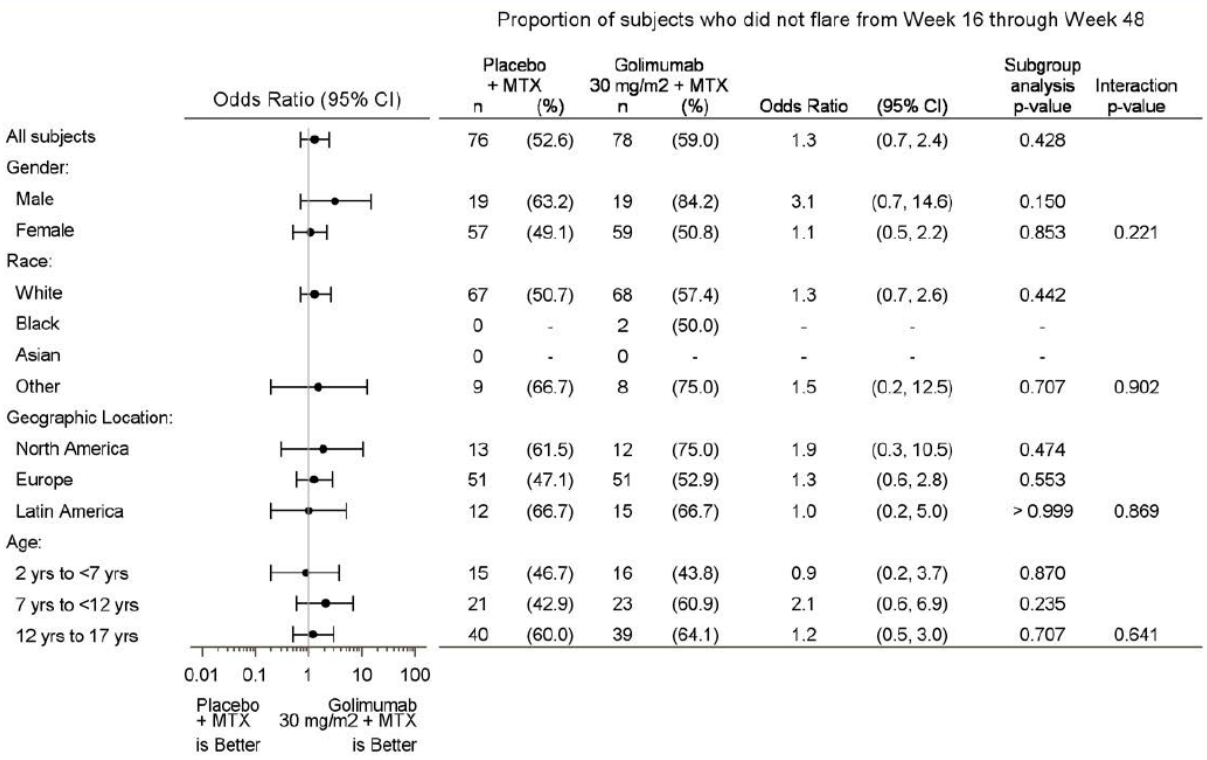
A decrease of 0.188 in CHAQ score is considered clinically meaningful improvement (Brunner, 2005). Through Week 16, median CHAQ scores decreased from baseline. At Week 16, median change in CHAQ score was -0.38 (GOL+MTX), -0.56 (PBO+MTX), and 0 (not randomized). At Week 48, a greater decrease in median CHAQ scores was observed in the PBO+MTX group (-0.25) as compared to the GOL+MTX group (-0.13). After Week 48, changes in CHAQ scores were similar between treatment groups as were proportions of patients with clinically meaningful improvement in CHAQ, numerically favoring the PBO+MTX group.

CHQ
At Week 48, median change from baseline in Physical Function subscale score in patients who were ACR Ped 30 responders at Week 16, was numerically greater in the PBO+MTX group (22, 28.9%) as compared to the GOL+MTX group (17, 21.8%). Median change from baseline in other subscales at Week 48 was generally similar between the treatment groups with the exceptions of Family Activities, Parental Impact-Emotional, and Role/Social Limitations – Physical, which favored the PBO+MTX treatment group. After Week 48, the median change from baseline in Physical Function subscale score remained numerically greater in the PBO+MTX group as compared to the GOL+MTX group. Other subscales that showed greater median change from baseline in the PBO+MTX group were Behavior, Family Activities, Mental Health, Role/Social Limitations-Physical, and Self Esteem, while Global Behavior Item, Parental Impact-Time, and Role/Social Limitations-Emotional/Behavioral showed greater median change in the GOL+MTX group, and the other subscales showed similar changes in each treatment group.

6.1.7 Subpopulations

To evaluate the consistency of the primary efficacy endpoint, subgroup analyses were performed to examine the impact of demographic and disease variables. As shown in Figure 5, the odds ratios by baseline demographics, including gender, age group, race, and geographic location were consistent with the primary analysis. Similarly, the odds ratios by weight groups, weight quartiles, and BSA quartiles did not favor either treatment group.

Figure 5: Proportion of Patients without Flare by Demography Categories (Randomized Patients)

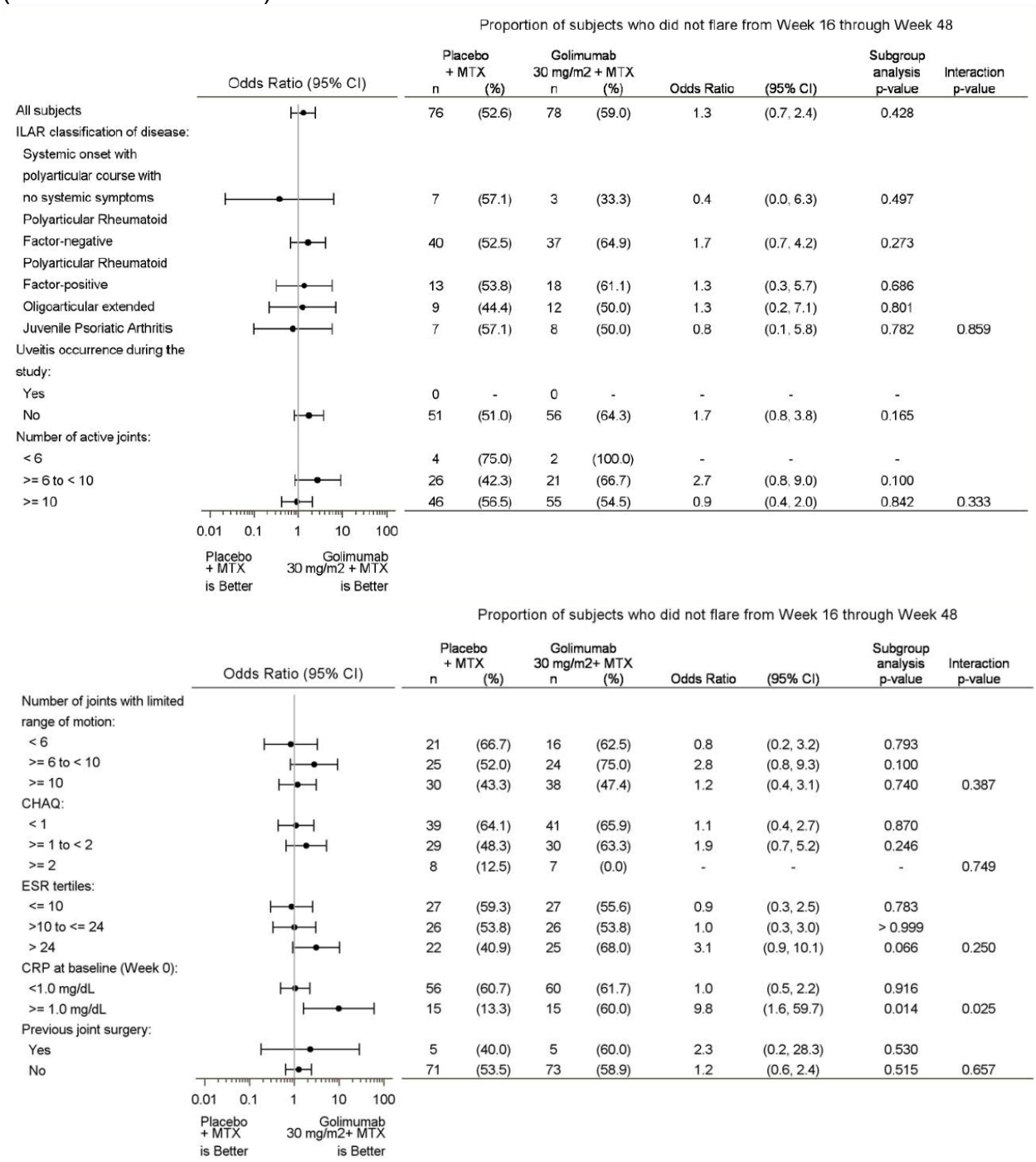


	Placebo + MTX n	Placebo + MTX (%)	Golimumab 30 mg/m2 + MTX n	Golimumab 30 mg/m2 + MTX (%)	Odds Ratio	(95% CI)	Subgroup analysis p-value	Interaction p-value
All subjects	76	(52.6)	78	(59.0)	1.3	(0.7, 2.4)	0.428	
Gender:								
Male	19	(63.2)	19	(84.2)	3.1	(0.7, 14.6)	0.150	
Female	57	(49.1)	59	(50.8)	1.1	(0.5, 2.2)	0.853	0.221
Race:								
White	67	(50.7)	68	(57.4)	1.3	(0.7, 2.6)	0.442	
Black	0	-	2	(50.0)	-	-	-	
Asian	0	-	0	-	-	-	-	
Other	9	(66.7)	8	(75.0)	1.5	(0.2, 12.5)	0.707	0.902
Geographic Location:								
North America	13	(61.5)	12	(75.0)	1.9	(0.3, 10.5)	0.474	
Europe	51	(47.1)	51	(52.9)	1.3	(0.6, 2.8)	0.553	
Latin America	12	(66.7)	15	(66.7)	1.0	(0.2, 5.0)	> 0.999	0.869
Age:								
2 yrs to <7 yrs	15	(46.7)	16	(43.8)	0.9	(0.2, 3.7)	0.870	
7 yrs to <12 yrs	21	(42.9)	23	(60.9)	2.1	(0.6, 6.9)	0.235	
12 yrs to 17 yrs	40	(60.0)	39	(64.1)	1.2	(0.5, 3.0)	0.707	0.641

Source:48 Week Clinical Study Report GEFFLARE1

Subgroup analysis based on baseline disease characteristics are presented in the Forest Plot in Figure 6. The odds ratios for the proportion of patients who were ACR Ped 30 responders at Week 16 and did not have a flare between Week 16 and 48 based on baseline disease characteristics, including ILAR subtype, presence of uveitis, number of active joints, number of joints with limited range of motion, CHAQ, ESR tertiles, and previous joint surgery were consistent with the primary analysis as well and did not favor either treatment group. For patients with a baseline CRP ≥ 1 mg/dL, a greater proportion of patients met the primary endpoint in the GOL+MTX group (60.0%), as compared to the PBO+MTX group (13.3%), with an odds ratio of 9.8 (95% CI 1.6, 59.7), while the response rate in each treatment group was similar in those patients with a baseline CRP < 1 mg/dL (GOL+MTX 61.7%, PBO+MTX 60.7%, odds ratio 1.0, 95% CI 0.5, 2.2). Response trended to GOL+MTX in those patients with an ESR in the highest tertile (>24 mm/hr), with an odds ratio of 3.1 (CI 0.9, 10.1); no difference was seen in the lower ESR tertiles. The odds ratios by baseline medicine use were also generally consistent with the primary analysis except for the subgroup in the tertile of MTX > 18 mg at baseline that favored GOL+MTX.

Figure 6: Proportion of Patients Without Flare by Baseline Disease Characteristics (Randomized Patients)



	Placebo + MTX n	Placebo + MTX (%)	Golimumab 30 mg/m2 + MTX n	Golimumab 30 mg/m2 + MTX (%)	Odds Ratio	(95% CI)	Subgroup analysis p-value	Interaction p-value
All subjects	76	(52.6)	78	(59.0)	1.3	(0.7, 2.4)	0.428	
ILAR classification of disease:								
Systemic onset with polyarticular course with no systemic symptoms	7	(57.1)	3	(33.3)	0.4	(0.0, 6.3)	0.497	
Polyarticular Rheumatoid Factor-negative	40	(52.5)	37	(64.9)	1.7	(0.7, 4.2)	0.273	
Polyarticular Rheumatoid Factor-positive	13	(53.8)	18	(61.1)	1.3	(0.3, 5.7)	0.686	
Oligoarticular extended	9	(44.4)	12	(50.0)	1.3	(0.2, 7.1)	0.801	
Juvenile Psoriatic Arthritis	7	(57.1)	8	(50.0)	0.8	(0.1, 5.8)	0.782	0.859
Uveitis occurrence during the study:								
Yes	0	-	0	-	-	-	-	
No	51	(51.0)	56	(64.3)	1.7	(0.8, 3.8)	0.165	
Number of active joints:								
< 6	4	(75.0)	2	(100.0)	-	-	-	
>= 6 to < 10	26	(42.3)	21	(66.7)	2.7	(0.8, 9.0)	0.100	
>= 10	46	(56.5)	55	(54.5)	0.9	(0.4, 2.0)	0.842	0.333
Number of joints with limited range of motion:								
< 6	21	(66.7)	16	(62.5)	0.8	(0.2, 3.2)	0.793	
>= 6 to < 10	25	(52.0)	24	(75.0)	2.8	(0.8, 9.3)	0.100	
>= 10	30	(43.3)	38	(47.4)	1.2	(0.4, 3.1)	0.740	0.387
CHAQ:								
< 1	39	(64.1)	41	(65.9)	1.1	(0.4, 2.7)	0.870	
>= 1 to < 2	29	(48.3)	30	(63.3)	1.9	(0.7, 5.2)	0.246	
>= 2	8	(12.5)	7	(0.0)	-	-	-	0.749
ESR tertiles:								
<= 10	27	(59.3)	27	(55.6)	0.9	(0.3, 2.5)	0.783	
>10 to <= 24	26	(53.8)	26	(53.8)	1.0	(0.3, 3.0)	> 0.999	
> 24	22	(40.9)	25	(68.0)	3.1	(0.9, 10.1)	0.066	0.250
CRP at baseline (Week 0):								
<1.0 mg/dL	56	(60.7)	60	(61.7)	1.0	(0.5, 2.2)	0.916	
>= 1.0 mg/dL	15	(13.3)	15	(60.0)	9.8	(1.6, 59.7)	0.014	0.025
Previous joint surgery:								
Yes	5	(40.0)	5	(60.0)	2.3	(0.2, 28.3)	0.530	
No	71	(53.5)	73	(58.9)	1.2	(0.6, 2.4)	0.515	0.657

Source: 48 Week Clinical Study Report GEFFLARE2

After Week 48, a greater proportion of patients were ACR Ped 30, 50, 70, and 90 responders in the PBO+MTX group with a baseline CRP < 1 mg/dL as compared to the

PBO+MTX group with a baseline CRP ≥ 1 mg/dL, while in the GOL+MTX group ACR Ped 70 and 90 response rates were greater in those patients with a baseline CRP < 1 mg/dL and generally similar regardless of baseline CRP subgroup for ACR Ped 30 and 50 responses. Patients who did not flare between Weeks 16 and 48, had higher ACR Ped 30, 50, 70, and 90 response rates after Week 48 through Week 120, after which time the small number of patients in the non-flare subgroup limits conclusions that can be drawn.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable. The Applicant is not seeking a new indication with this submission and thus there are no dosing recommendations. However, despite the similar steady state trough golimumab concentrations between PJIA patients and adult RA patients, Study CNTO148JIA3001 did not meet its objectives. In the context of the limited dose-ranging and exposure-response data in the SC golimumab program in adults, it is possible that a dosing regimen in PJIA based on PK matching may not be adequately justified in this case. Additional dose-ranging data to establish a dose-response relationship in PJIA may help address this uncertainty.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable. The primary analysis did not support efficacy. See Section 6.1.6 above for description of ACR Ped responses, components of ACR Ped response, and other efficacy assessments at later time points. Furthermore, a randomized withdrawal study is not designed to address persistence of efficacy.

6.1.10 Additional Efficacy Issues/Analyses

Given that primary and key secondary endpoints have failed, additional analyses are not detailed further.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data submitted include the safety results for patients in Study CNTO148JIA3001 from Week 0 to the final DBL.

7.1.2 Categorization of Adverse Events

Adverse Events (AEs) were defined as any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product, and does not necessarily have a causal relationship with the treatment. An AE could be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to that medicinal product (definition per International Conference on Harmonization). A serious adverse event (SAE) was any untoward medical occurrence that at any dose meets any of the following conditions: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any AE was considered a SAE if it was associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact. An Unexpected AE was an AE that is not listed in the Investigator's Brochure. Events of Special Interest were defined in the protocol as any newly identified malignancy, opportunistic infections, death, or active TB occurring after the first administration of study agent.

AEs were coded in accordance with the Medical Dictionary for Regulatory activities (MedDRA) Version 16.0, using the lower-level term (LLT), preferred term (PT), and the system organ class (SOC).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable. A single study has been completed with SC golimumab in PJIA.

7.2 Adequacy of Safety Assessments

Safety assessments included AEs, physical examination, vital signs, uveitis evaluations, laboratory studies and immunogenicity, and injection site evaluations as detailed in the Schedule of Assessments in Appendix 3 and Appendix 4. Vital signs, laboratory studies, TB questionnaires, AEs, and injection site evaluations were performed every 4 weeks during Week 0 to 48, and physical exams were conducted every 12 weeks. Hepcidin and anemia panels were performed in patients weighing ≥ 32 kg, as specified in the protocol.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

From Week 0 to 16, the median cumulative dose of golimumab was 163.0 mg. The median cumulative golimumab dose was somewhat higher in the group subsequently randomized to GOL+MTX, as compared to the group randomized to PBO+MTX at Week 16, as shown in Table 8. From Week 16 through 48, the median cumulative

doses of golimumab were 200.0 mg and 330.0 mg in the group randomized to PBO+MTX that transitioned to GOL+MTX, and the group randomized to GOL+MTX, respectively, while the group randomized to PBO+MTX did not receive additional golimumab. The average duration of follow-up for all randomized patients was similar across the treatment groups through the end of the randomized withdrawal period at Week 48. From Week 48 through the database lock, patients treated with PBO+MTX had a shorter duration of follow-up as compared to those patients randomized to PBO+MTX who transitioned to GOL+MTX, and those patients randomized to GOL+MTX; this is expected as by protocol, patients receiving PBO+MTX in clinical remission were discontinued from the study. As expected based on the study design, the median cumulative golimumab dose was highest in the group randomized to GOL+MTX (1030 mg), followed by those patients who transitioned from PBO+MTX to GOL+MTX before Week 48 (790 mg), and those who transitioned to GOL+MTX after Week 48 (655.0 mg), while those who remained on PBO+MTX through the study received a median cumulative dose of golimumab of 200.0 mg. The mean duration of follow-up through the entire study was similar in the GOL+MTX treatment group and the PBO+MTX groups that transitioned to GOL+MTX, while the overall follow-up was shorter in the PBO+MTX group, noting that this group consisted of only 10 patients by the end of the study.

Table 8: Mean Exposure to Golimumab by Treatment Group

		Golimumab administered prior to randomization at Wk 16					
	All enrolled	Not randomized at Wk 16	GOL+MTX	PBO+MTX	PBO+MTX →GOL+MTX before W48	PBO+MTX →GOL+MTX at or after W48	All randomized
Week 0-16	N = 173	N = 19	N = 78	N = 76	N = 78		N = 154
Median cumulative dose, mg	163.0	168.0	163.5	155.5			161.5
Mean duration of follow-up, weeks	16.1	16.1	16.0	16.2			16.1
Mean exposure, number of administrations	4.0	3.7	4.0	4.0			4.0
Week 16-48			N = 78	N = 43	N = 33		N = 154
Median cumulative dose, mg			330.0	0	200.0		213.0
Mean duration of follow-up, weeks			33.7	32.6	33.4		33.4
Avg exposure, number of administrations			7.7	7.8	7.9		7.8
Week 48-DBL				N = 78	N = 33	N = 33	N = 154
Median cumulative dose, mg			585.0	0	519.5	473.0	528.5
Mean duration of follow-up, weeks			60.3	44.3	59.3	63.9	59.8
Avg exposure, number of administrations			13.9	9.8	13.6	15.3	13.8
Week 0-DBL		N=19	N = 78	N = 10	N = 33	N = 33	N = 154
Median cumulative dose, mg		168.0	1030.0	200.0	790.0	655.0	821.5
Mean duration of follow-up, weeks		20.8	107.6	89.8	107.5	112.1	107.4
Avg exposure, number of administrations		3.7	25.6	20.9	25.5	27.3	25.6

Source: Adapted from 48 Wk Clinical Study Report Table 14, Table 15, TSFEXP3, TSFEXP3B, and Final Clinical Study Report Table 7, TSFEXP2, TSFEXP2B

Reviewer JMP analysis of ADSL dataset using terms CUMGO01, CUMGO02, CUMGO03, CUMGO, DURFUP01, DURFUP02, DURFUP03,DURFUP, TOTADM01, TOTADM02, TOTADM03, TOTADM. RANDFL, ARM, COLSF

7.2.2 Explorations for Dose Response

Not applicable, a single dose of golimumab was assessed in Study CNTO148JIA3001.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this submission.

7.2.4 Routine Clinical Testing

Clinical laboratory tests included hematology laboratory studies (hemoglobin, hematocrit, white blood cells, neutrophils, lymphocytes, eosinophils, monocytes, platelets) and chemistry studies (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, total bilirubin, calcium, chloride, creatinine, glucose, phosphate inorganic, potassium, sodium, total protein, and urea nitrogen).

7.2.5 Metabolic, Clearance, and Interaction Workup

No special metabolic, clearance and interaction workup studies were conducted for this application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Protocol-specified events of special interest include newly identified malignancy, opportunistic infections, death, or cases of active TB occurring after the first administration of study agent. Other adverse events, associated with use of golimumab or other members of the class of TNFα-inhibitors, include infections, serious infections, injection site reactions, and hepatobiliary events.

7.3 Major Safety Results

Table 9: Treatment Emergent AE Summary

	Enrolled subjects who did not enter randomized withdrawal period (N=19)		Golimumab 30 mg m2 + MTX (N=78)		Placebo + MTX -> Golimumab 30 mg m2 + MTX at or after W48 (N=33)		Placebo + MTX -> Golimumab 30 mg m2 + MTX prior to W48 (N=33)		Placebo + MTX only (N=10)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Patients with any TEAE	15	(78)	72	(92)	31	(93)	32	(96)	10	(100)
Patients with severe TEAE	5	(26)	5	(6)	1	(3)	1	(3)	0	(0)
Patients with any treatment emergent SAE	4	(21)	18	(23)	5	(15)	10	(30)	2	(20)
Patients with any TEAE leading to death	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Patients with any TEAE leading to permanent treatment discontinuation	3	(15)	7	(8)	0	(0)	3	(9)	2	(20)

Source: Reviewer analysis JMP Clinical

As stated above, the randomized withdrawal study design, in which all patients receive active treatment, presents limitations in a comparative assessment of safety. AEs by treatment group and study period are discussed further below. Further, differences in study design, dosing regimens, and duration of follow-up limit direct comparison of frequencies of events between the JIA and RA populations. Through Week 16, the proportion of patients reporting AEs and SAEs in Study CNTO148JIA3001 was similar to that reported by adult RA patients in Studies C0524T05, C0524T06, and C0524T11. Overall infections were more frequently reported in the PJIA population (38.7%) as compared to the RA patients (26.3%), however serious infections were similar (1.2% and 1.5%, respectively). Injection site reactions were more frequently reported by patients with PJIA than RA (5.8% vs. 4.5%). No new safety signals were identified.

7.3.1 Deaths

There were no deaths through the final DBL in CNTO148JIA3001.

7.3.2 Nonfatal Serious Adverse Events

Throughout Study CNTO148JIA3001, 71 SAEs were reported by 39 patients. SAEs were reported by 4 (21.1%) patients who were enrolled but not randomized, 18 (23.1%) patients randomized to GOL+MTX, and 17 (22.4%) patients randomized to PBO+MTX

(Combined group). One patient reported an SAE of dental caries prior to initiation of study agent.

Through Week 16, 8 (4.6%) patients reported treatment-emergent SAEs. Four of these patients did not enter the randomized withdrawal period (2 with JIA, 1 with cellulitis and herpes zoster, and 1 with pyelonephritis). Of the four patients who entered the randomized withdrawal period and experienced SAEs, 3 patients were randomized to the GOL+MTX group (1 event each of JIA, arthritis, and hepatitis toxic), while 1 patient receiving PBO+MTX reported an event of pain.

From Week 16 through Week 48, 18 (11.7%) randomized patients experienced at least 1 SAE, 8 (10.3%) in the GOL+MTX treatment group and 10 (13.2%) in the Combined group (PBO+MTX and PBO+MTX→GOL+MTX) as displayed in Table 10. The most frequently reported SAEs were JIA (5 patients in the Combined group vs. 3 patients in the GOL+MTX group), and arthritis (2 patients in the Combined group vs. 1 patient in the GOL+MTX group). There were few infectious SAEs reported and included single events of pneumonia and upper respiratory tract infection in the Combined group and pyelonephritis in the GOL+MTX group. An SAE of drug hypersensitivity was reported in a patient who received PBO+MTX and transitioned to GOL+MTX prior to Week 48. All other SAEs were also singular events and included immune thrombocytopenic purpura, vertigo, and pain (PBO+MTX), hepatic enzyme increased (PBO+MTX→GOL+MTX), and diabetes mellitus and constipation (GOL+MTX).

Table 10: Treatment Emergent Serious Adverse Events Weeks 16 through 48 Occurring in >1% of all Randomized Patients

	Golimumab administered prior to randomization at Wk 16				
System organ class Preferred term	GOL+MTX N = 78 n (%)	Combined N = 76 n (%)	PBO+MTX N = 43 n (%)	PBO+MTX →GOL+MTX N = 33 n (%)	All randomized patients N = 154 n (%)
Number of patients with SAEs	8 (10.3)	10 (13.2)	4 (9.3)	6 (18.2)	18 (11.7)
Musculoskeletal and connective tissue disorders	**4 (5.1)**	**7 (9.2)**	**2 (4.7)**	**5 (15.2)**	**11 (7.1)**
JIA	3 (3.8)	5 (6.6)	1 (2.3)	4 (12.1)	8 (5.2)
Arthritis	1 (1.3)	2 (2.6)	1 (2.3)	1 (3.0)	3 (1.9)
Infections and infestations	**1 (1.3)**	**2 (2.6)**	**0**	**2 (6.1)**	**3 (1.9)**
Pneumonia	0	1 (1.3)	0	1 (3.0)	1 (0.6)
Pyelonephritis	1 (1.3)	0	0	0	1 (0.6)
URTI	0	1 (1.3)	0	1 (3.0)	1 (0.6)
Psychiatric disorders	**1 (1.3)**	**1 (1.3)**	**1 (2.3)**	**0**	**2 (1.3)**
Depression	1 (1.3)	0	0	0	1 (0.6)
Somatoform disorder neurologic	0	1 (1.3)	1 (2.3)	0	1 (0.6)

JIA = Juvenile idiopathic arthritis; URTI = Upper respiratory tract infection
Source: Adapted from 48 Week Clinical Study Report Attachment TSFSAE1B
Reviewer JMP analysis, ADAE dataset using terms AESER, AEBODSYS, AEDECOD, COLSF, APERIODC, USUBJ

After Week 48, the proportion of all randomized patients reporting at least 1 SAE was 13.0%, 16.7% in the GOL+MTX group as compared to 9.2% in the Combined group (Table 11). The most common SAEs were JIA and arthritis. All other SAEs were singular events and included events of lymphoid tissue hyperplasia, eye pain, gallbladder oedema, hypoglycaemia, demyelination, anxiety, and tonsillar hypertrophy in the GOL+MTX treatment group, influenza like illness in the PBO+MTX→GOL+MTX prior to Week 48 group, and lower limb fracture in the PBO+MTX→GOL+MTX at or after Week 48 group.

Table 11: Treatment Emergent SAEs after Week 48, Occurring in >1% of all Randomized Patients

	Golimumab administered prior to randomization at Wk 16					
System organ class Preferred term	GOL+MTX N = 78 n (%)	Combined N = 76 n (%)	PBO+MTX N = 10 n (%)	PBO+MTX →GOL+MTX before W48 N = 33 n (%)	PBO+MTX →GOL+MTX at or after W48 N = 33 n (%)	All randomized N = 154 n (%)
Number of patients with SAEs	13 (16.7)	7 (9.2)	0	4 (12.1)	3 (9.1)	20 (13.0)
Musculoskeletal and connective tissue disorders	**7 (9.0)**	**2 (2.6)**	**0**	**2 (6.1)**	**0**	**9 (5.8)**
JIA	5 (6.4)	2 (2.6)	0	2 (6.1)	0	7 (4.5)
Arthritis	2 (2.6)	0	0	0	0	2 (1.3)
Arthralgia	1 (1.3)	0	0	0	0	1 (0.6)
Infections and infestations	**3 (3.8)**	**3 (3.9)**	**0**	**1 (3.0)**	**2 (6.1)**	**6 (3.9)**
Appendiceal abscess	0	1 (1.3)	0	0	1 (3.0)	1 (0.6)
Appendicitis	1 (1.3)	0	0	0	0	1 (0.6)
Otitis media	1 (1.3)	0	0	0	0	1 (0.6)
Peritonsillar abscess	0	1 (1.3)	0	1 (3.0)	0	1 (0.6)
Pneumonia	1 (1.3)	0	0	0	0	1 (0.6)
Scarlet fever	1 (1.3)	0	0	0	0	1 (0.6)
Skin bacterial infection	1 (1.3)	0	0	0	0	1 (0.6)
Tonsillitis	1 (1.3)	0	0	0	0	1 (0.6)
URTI	1 (1.3)	0	0	0	0	1 (0.6)
Wound infection	0	1 (1.3)	0	0	1 (3.0)	1 (0.6)
Gastrointestinal disorders	**0**	**2 (2.6)**	**0**	**1 (3.0)**	**1 (3.0)**	**2 (1.3)**
Constipation	0	1 (1.3)	0	1 (3.0)	0	1 (0.6)
Gastritis	0	1 (1.3)	0	0	1 (3.0)	1 (0.6)

JIA = Juvenile idiopathic arthritis; URTI = Upper respiratory tract infection
Source: Adapted from Final Clinical Study Report Attachment TSFSAE1
Reviewer JMP analysis, ADAE dataset using terms AESER, AEBODSYS, AEDECOD, COLSF, APERIODC, USUBJ

Overall, the most frequent SAEs were JIA and arthritis, which are not unexpected for a population of patients with active PJIA. During the randomized withdrawal period, SAEs of JIA and arthritis were reported in similar numbers of patients in the GOL+MTX treatment group (8 patients or 10.3%) as compared to the Combined group (7 patients or 9.2%); most of the patients in the Combined group received PBO+MTX and

transitioned to GOL+MTX prior to Week 48 (6 patients). JIA and arthritis were also the most common SAEs reported after Week 48, with increased frequency in the GOL+MTX group, however the absolute number of patients experiencing these SAEs were low. Infectious SAEs were balanced between the treatment groups; events were singular by preferred term, except for 2 patients with pyelonephritis. All other observed SAEs were singular events. The reported SAEs were consistent with the known safety profile of golimumab in adults.

7.3.3 Dropouts and/or Discontinuations

Fifteen patients discontinued study treatment due to treatment-emergent AEs as presented in Table 12. One patient developed uveitis prior to administration of study drug and discontinued treatment after a single open-label dose of golimumab. Through Week 16, 2 enrolled patients (1.2%) discontinued treatment due to AEs of JIA. From Weeks 16 through 48, 6 randomized patients (3.9%) discontinued treatment due to AEs including two patients (4.7%) receiving PBO+MTX who experienced arthritis (1 patient), JIA and affective disorder (1 patient), 3 patients (9.1%) receiving PBO+MTX who transitioned to GOL+MTX who experienced JIA (2 patients) and serum sickness reaction (1 patient), and 1 patient (1.3%) receiving GOL+MTX who experienced JIA.

After Week 48, 7 patients (4.5%) discontinued treatment with study agent, 6 patients in the GOL+MTX group (2 JIA, 1 ALT increased and AST increased, 1 positive TB test, 1 chest pain and gallbladder edema, and 1 demyelination) and 1 patient in the PBO+MTX who transitioned to GOL+MTX prior to Week 48 (JIA). Review of the narratives of the patient randomized to GOL+MTX who reported chest pain and gall bladder edema describes a patient who was hospitalized with retrosternal pain, with radiation to the left arm and nausea, noted to have gall bladder wall thickening without gallstones on abdominal imaging. Symptoms resolved with low fat diet and study drug was discontinued.

Table 12: Number of Patients with ≥1 Treatment-Emergent AEs Leading to Study Treatment Discontinuation by Treatment Group and Study Period

	Golimumab administered prior to randomization at Wk 16					
Period/ Preferred Term	Not randomized at Wk 16 N=19 n (%)	GOL+MTX N=78 n (%)	Combined N=76 n (%)	PBO+MTX[a] n (%)	PBO+MTX →GOL+MTX before W48 N=33 n (%)	PBO+MTX →GOL+MTX at or after W48 N=33 n (%)
Week 0-16	2 (10.5)	0	0	0	-	-
JIA	2 (10.5)	0	0	0	-	-
Week 16-48	-	1 (1.3)	5 (6.6)	2 (4.7)	3 (9.1)	-
JIA	-	1 (1.3)	3 (3.9)	1 (2.3)	2 (6.1)	-
Arthritis	-	0	1 (1.3)	1 (2.3)	0	-
Affective disorder	-	0	1 (1.3)	1 (2.3)	0	-
Serum sickness	-	0	1 (1.3)	0	1 (3.0)	-
Week 48-DBL	-	6 (7.7)	1 (1.3)	0	1 (3.0)	0
JIA	-	2 (2.6)	1 (1.3)	0	1 (3.0)	0
ALT increased	-	1 (1.3)	0	0	0	0
AST increased	-	1 (1.3)	0	0	0	0
Chest pain	-	1 (1.3)	0	0	0	0
Demyelination	-	1 (1.3)	0	0	0	0
Gallbladder oedema	-	1 (1.3)	0	0	0	0
TB test positive	-	1 (1.3)	0	0	0	0

[a] PBO+MTX: N= 43 for Week 16-48, N=10 for Week 48-DBL
JIA = Juvenile idiopathic arthritis
Source: Adapted from 48 Week Clinical Study Report TSFDCAE1, TSFDCAE1B , Final Clinical Study Report Attachment TSFDCAE1
Reviewer JMP analysis, ADAE dataset, terms AEACN 'drug withdrawn', AETRTEM 'Y', AEBODSYS, AEDECOD, COLSF, APERIODC, USUBJ

Sixteen patients had treatment with study drug interrupted due to AEs. From Week 0-16, 1 patient enrolled but not randomized and 1 patient in the GOL+MTX had study treatment interrupted for reasons of transaminases increased and JIA, respectively. In the randomized withdrawal period, study drug was interrupted in 3 patients in the GOL+MTX group for dermatitis and eye abscess, oral herpes, and tonsillitis, in 2 patients in the PBO+MTX→GOL+MTX prior to Week 48 for tonsillitis, and pain and chronic urticaria, and in 1 patient in the PBO+MTX→GOL+MTX at or after Week 48 for erythema infectiosum. After Week 48, study treatment was interrupted for 7 patients in the GOL+MTX group (varicella, bronchitis/cough/gastroenteritis viral/oral herpes/tonsillitis, lower respiratory tract infection/paronychia/upper respiratory tract infection, nasopharyngitis/sinusitis, influenza, respiratory tract infection/skin bacterial infection, and lymphoid tissue hyperplasia), 1 patient in the PBO+MTX group (foot fracture), 1 patient in the PBO+MTX→GOL+MTX prior to Week 48 (radius fracture,

tonsillitis, upper respiratory tract infection), and 1 patient in the PBO+MTX→GOL+MTX at or after Week 48 (nasopharyngitis). The most common AEs leading to study drug interruption were within the Infections and Infestations SOC and the most frequently reported preferred term was tonsillitis (reported by 3 patients). From Week 0 through the final DBL, 11 patients interrupted treatment with study drug due to AEs within the Infections and Infestations SOC, 8 patients randomized to GOL+MTX, and 3 patients randomized to PBO+MTX who subsequently transitioned to GOL+MTX treatment. See section 7.3.5 below for further discussion of infections.

Overall, the most common AE leading to discontinuation was JIA, which occurred with relatively balanced frequency across the treatment groups in the different phases of the study. Events of JIA and arthritis are expected AEs in this population. Singular events of serum sickness and demyelination were observed; these are labeled risks of golimumab treatment. The most common AEs leading to study drug interruption were in the Infections and Infestations SOC. These were relatively balanced through the end of the double blind portion of the study (Week 48), but were more frequently reported by patients in the GOL+MTX group after Week 48 as compared to the patients randomized to PBO+MTX. The AEs leading to study drug discontinuation and treatment interruption are labeled risks with golimumab treatment. Review of the treatment-emergent AEs leading to discontinuation and treatment interruption did not identify any new safety concerns.

7.3.4 Significant Adverse Events

Protocol-specified events of special interest include newly identified malignancy, opportunistic infections, death, or cases of active TB occurring after the first administration of study agent. The Applicant reports that in Study CNTO148JIA3001, there were no malignancies, opportunistic infections, deaths, or active tuberculosis reported through the final DBL. Reviewer analysis identifies 4 patients with herpes zoster (1 each in enrolled but not randomized, PBO+MTX, PBO+MTX→GOL+MTX prior to Week 48, PBO+MTX→GOL+MTX at or after Week 48). There were 2 patients with varicella (GOL+MTX), 3 patients with herpes simplex (1 GOL+MTX, 2 PBO+MTX→GOL+MTX after Week 48), and 3 patients with oral herpes (GOL+MTX). While there were no patients with active TB, there were two patients with latent TB (1 each in GOL+MTX, PBO+MTX→GOL+MTX at or after Week 48).

Twelve patients (6.9%) reported herpes virus infections, balanced between the GOL+MTX group (6 patients) and the Combined group (5 patients). Conclusions regarding the risk of herpes viral infections are limited by the study design where all patients were treated with GOL+MTX in the open label period.

7.3.5 Submission Specific Primary Safety Concerns

Other adverse events, associated with use of golimumab or other members of the class of TNF-inhibitors, include infections, serious infections, injection site reactions, and hepatobiliary events. Table 13 presents these significant adverse events by treatment group for Study CNTO148JIA3001.

Table 13: Treatment-Emergent Significant Adverse Events, Week 0-DBL

Number of patients with:	**Not randomized at Wk 16 N=19 n (%)**	**GOL+MTX N=78 n (%)**	**Combined N=76 n (%)**
Infections	11 (57.9)	62 (79.5)	62 (81.6)
Serious infections	2 (10.5)	4 (5.1)	5 (6.6)
Opportunistic infections	0	0	0
Malignancy	0	0	0
Demyelinating Events	0	1 (1.3)	0
TB (active/latent)	0	0/1 (1.3)	0/1 (1.3)
Hepatobiliary events	0	1 (1.3)	0
Hypersensitivity/Drug hypersensitivity	0	0	1 (1.3)
Anaphylaxis or serum-sickness	0	0	1 (1.3)
Injection site reactions	1 (5.3)	13 (16.7)	6 (7.9)

Source: Reviewer JMP analysis, ADAE dataset using terms AEBODSYS, AEDECOD, AEINF, AESER, CQ01NAM, CQ02NAM, CQ03NAM, CQ04NAM, COLSF, USUBJ

Infections

In analyzing infections, the Applicant used AEs identified as infections by the investigator on the eCRF. AEs identified as infections by the investigator that were not within the Infections and Infestations SOC include influenza like illness (8 patients), pyrexia (9 patients), respiratory disorder (1), but also terms less specific for infections such as cough (6 patients), oropharyngeal pain (7 patients), ear pain (1 patient), and others. For consistency with the other analyses, as well as to ensure inclusion of the largest number of potential infections, the analyses below include AEs of infections as identified by those events within the Infections and Infestations SOC. Over the entire study, the proportions of patients reporting treatment-emergent infections was similar between those patients randomized to GOL+MTX and the Combined group as shown in Table 9.

Through Week 16, 67 (38.7%) patients reported 1 or more infections. The proportion of patients who experienced infections was similar between each randomized treatment group (GOL+MTX: 32 patients, 41.0%; PBO+MTX: 26 patients 34.2%), as well as in the enrolled patients who did not enter the randomized withdrawal period (9 patients, 47.4%). The most commonly reported infections were nasopharyngitis, upper respiratory tract infection (URTI), and respiratory tract infection/viral respiratory tract infection; these infections occurred in 9.2%, 6.9% and 5.8% of all enrolled patients,

respectively. These were generally balanced across the treatment groups, including the enrolled patients who were not randomized.

From Week 16 to 48, 87 (56.5%) patients experienced at least 1 infection, including 2 patients who were enrolled and not randomized and reported events of gastroenteritis and paronychia. A greater proportion of patients experienced infections in the Combined group (63.2%) as compared to patients randomized to GOL+MTX (47.4%). The most commonly reported infections were URTI, nasopharyngitis, and gastroenteritis/viral gastroenteritis. These infectious AEs were more frequently reported by patients in the Combined treatment group as compared to the GOL+MTX group (URTI: 27.6% vs. 16.7%; nasopharyngitis: 11.8% vs. 7.7%; gastroenteritis/viral gastroenteritis: 7.9% vs. 3.8%).

From Week 48 through the DBL, patients with infections were balanced across the treatment groups (GOL+MTX: 51.3%; Combined: 53.9%). The proportions of patients reporting infections in the PBO+MTX group that transitioned to GOL+MTX before Week 48 was similar to that reported in patients in the PBO+MTX→GOL+MTX at or after Week 48 group (54.5% and 60.6% for transition before and after Week 48, respectively), while those patients remaining on PBO+MTX had the fewest infections (30.0%). This comparison is limited by the small number of patients remaining in the PBO+MTX group after Week 48. The most frequently reported infections after Week 48 were URTI, nasopharyngitis, respiratory tract infection/viral respiratory tract infection, and tonsillitis/streptococcal tonsillitis, and were generally balanced across the treatment groups, with the exception of tonsillitis/streptococcal tonsillitis that was reported in 11.5% of patients in the GOL+MTX group as compared to 6.6% in the Combined group.

Serious Infections
From Week 0 through the final DBL, 11 patients had a serious infection, balanced between the GOL+MTX (4 patients) and Combined treatment groups (5 patients), as well as 2 patients who were not randomized. Two (1.2%) patients who were not randomized experienced treatment-emergent serious infections, including cellulitis and herpes zoster in 1 patient and pyelonephritis in another patient, through Week 16. During the randomized withdrawal period, 3 patients (1.9%) experienced serious infections; pyelonephritis in 1 patient in the GOL+MTX group, and 1 patient each with pneumonia and URTI in the PBO+MTX→GOL+MTX prior to Week 48 group. Following Week 48, serious infections were observed in 6 (3.9%) patients, including 3 patients in the GOL+MTX group (appendicitis, scarlet fever, and tonsillitis in 1 patient; otitis media, URTI and skin bacterial infection in 1 patient; and pneumonia in 1 patient), 1 patient in the group who transitioned from PBO+MTX to GOL+MTX before Week 48 (peritonsillar abscess), and 2 patients in the PBO+MTX→GOL+MTX at or after Week 48 group (appendiceal abscess and wound infection in 1 patient each). The overall incidence of serious infections was low (6.9%). The most frequently reported serious infections were pyelonephritis, pneumonia, URTI, tonsillar disease, and appendiceal disease in 2 patients each. The USPI states that in clinical trials in patients with RA, PsA, and AS,

infections and serious infections were observed in 28% and 1.4%, respectively, of SIMPONI-treated patients through Week 16. While the observed overall infections are higher than that described in the USPI, the proportion of patients with serious infections through Week 16 in Study CNTO148JIA3001 was 1.2%, consistent with the risk seen in adult patients.

Anaphylaxis or Serum-sickness
One patient in the combined group (PBO+MTX →GOL+MTX prior to Week 48) experienced serum sickness-like reaction on Day 281, with symptoms of fever, chills, joint pain, and injection site reaction, and subsequently discontinued study agent. This patient also experienced 3 non-serious events of hypersensitivity in the randomized withdrawal period, as well as, events of drug hypersensitivity, urticaria, and chronic urticaria. There were no other reports of related anaphylactic or serum sickness-like reactions after Week 48. Hypersensitivity reactions are labeled risks of treatment with golimumab.

Demyelinating Disorders
One patient randomized to the GOL+MTX group reported a demyelination event after Week 48. She presented with a 3 month history of increasing headaches, as well as dizziness, and an MRI revealed multiple white matter lesions. The causality of the event was considered very likely to be related to study agent. Study treatment was discontinued. As reported in the narrative, the patient did not have other neurologic symptoms and, 1 month after the event, the headache was improved and the dizziness was resolved. Reviewer analysis of other reported preferred terms within the Nervous System Disorders SOC included: headache 42, dizziness 3, dizziness postural 3, restless legs syndrome 2, and 1 event each of migraine, paresthesia, temporal lobe epilepsy, dysgeusia, demyelination, and dysphonia psychogenic. Events of headaches were numerically greater from Week 16-48 and Week 48-DBL, as well as occurring more frequently in patients treated with GOL+MTX and PBO+MTX →GOL+MTX after Week 48.

Demyelinating disorders are described risks of use of TNFα inhibitors. Based on the information in the USPI, there have been rare reports of central demyelination, multiple sclerosis, optic neuritis, and peripheral demyelinating polyneuropathy in patients treated with golimumab. Review of the reported neurologic events does not raise additional concerns for demyelinating events.

Hepatobiliary Events
One 6 year old patient in the GOL+MTX treatment group experienced hepatitis toxic with an elevated ALT and AST ≥ 5x ULN on Day 23. She was hospitalized with symptoms of vomiting, and ALT increased to 698 U/L and AST to 484 U/L. Testing for viral hepatitis was negative. She was treated with ursodeoxycholic acid and ademetionine, and subsequently recovered. The Investigator considered the causality between the event and the study agent to be possible; the patient continued treatment

with study drug. Approximately 6 weeks after the resolution of this event, the patient had events of nasopharyngitis and gallbladder disorder, thought not to be related to study agent, and both events resolved without change in dose of study agent.

The term hepatobiliary event was not defined in the protocol. No additional hepatobiliary events were reported by the Applicant, however reviewer analysis of AEs within the hepatobiliary disorders SOC included PTs of hepatomegaly (1 patient in GOL+MTX, 1 patient not randomized), and gall bladder edema (1 patient in GOL+MTX). Additionally AEs of liver function test or bilirubin abnormalities were reported by 25 patients (15 GOL+MTX, 5 PBO+MTX→GOL+MTX prior to Week 48, 2 PBO+MTX→GOL+MTX after Week 48, 1 PBO+MTX, and 2 patients who were not randomized). Four (2.3%) patients in Study CNTO148JIA3001 experienced AEs within the hepatobiliary disorders SOC. All of the patients were exposed to both golimumab and methotrexate, limiting definitive conclusions that can be drawn regarding potential risk of hepatobiliary events with golimumab treatment in PJIA, however events were rare.

Injection-site reactions
The placebo presentation used in the study included the same excipients as the golimumab presentation. Through the study, 20 patients reported 24 AEs of injection-site reactions (Table 14). None of the ISRs were severe or serious. There were 2 moderate ISRs (serum-sickness like reaction and application site erythema); the remainder were mild in intensity. From Week 0-16, when all enrolled patients received golimumab and methotrexate, the proportion of patients reporting ISR was similar across treatment groups. After Week 16, the proportions of patients reporting ISR is higher in the GOL+MTX group as compared to the PBO+MTX group. There were greater numbers of patients with ISR in the Combined group as compared to the GOL+MTX group before Week 48, but fewer patients with ISR in the Combined group after Week 48.

Table 14: Proportion of Patients with Injection-site Reactions by Treatment Group

	Golimumab administered prior to randomization at Wk 16						
Periods	Not randomized at Wk 16 N=19 n (%)	GOL+MTX N=78 n (%)	Combined N=76 n (%)	PBO+MTX[a] n (%)	PBO+MTX →GOL+MTX before W48 N=33 n (%)	PBO+MTX →GOL+MTX at or after W48 N=33 n (%)	All randomized N=154 n (%)
Week 0-16	1 (5.3)	5 (6.4)	-	4 (5.3)	-	-	9 (5.8)
Week 16-48	-	2 (2.6)	3 (3.9)	2 (0.6)	1 (3.0)	-	5 (3.2)
Week 48-DBL	-	6 (7.7)	1 (1.3)	0	0	1 (3.0)	7 (4.5)
Week 0-DBL	1 (5.3)	13 (16.7)	6 (7.9)	--	1 (3.0)	5 (15.2)	19 (12.3)

[a] PBO+MTX: N= 43 for Week 16-48, N=10 for Week 48-DBL
Source: Adapted from 48 Week Clinical Study Report Attachment TSFINJ1, TSFINJ1B ; Adapted from Final Clinical Study Report Attachment s TSFINJ1, TSFINJ1B

Overall, rates of injection-site reactions (ISR) were low. The number of patients remaining on placebo + MTX after Week 16 through the end of the study was limited to 10 patients, providing a limited comparison for proportion of patients with ISR over the entire study. As may be expected, a similar proportion of patients in each group experienced ISR during the open-label period. A greater proportion of patients in the GOL+MTX treatment group experienced ISR after Week 16 as compared to the PBO+MTX and the Combined treatment groups. The observed proportion of patients with ISR during Week 0-16, 5.3% in the Combined group and 6.4% in the GOL+MTX group, and from Week 48-DBL in the GOL+MTX group is consistent with that observed in patients with RA, PsA, and AS as described in the USPI (6%). The proportion of patients with ISR during the randomized withdrawal period was lower than that described in the USPI, however interpretation is limited by the prior treatment with GOL in all groups from Week 0-16, as well as the relatively small number of ISR. ISR were not associated with the presence of ADA. Based on reviewer analysis, of the 20 patients with ISR, 9 of them had detectable ADA, however only 3 (15%) had ADA detected on or about the time of the ISR.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Thirty six patients experienced 45 AEs prior to administration of study drug. Events occurring in greater than 1 patient include: C-reactive protein increased and nasopharyngitis (3 patients each), bronchitis, cough, latent tuberculosis, oropharyngeal pain, pyrexia, and vomiting (2 patients each). Proportions of patients with treatment-emergent AEs were generally balanced across the randomized treatment groups

(GOL+MTX: 92.3%, Combined: 96.1%), and somewhat less in the patients who were enrolled, but not randomized (78.9%) as shown in Table 9.

Through Week 16,118 patients (68.2%) experienced 331 AEs, as shown in Table 18. AEs events were generally balanced across the treatment groups. The SOCs in which the greatest proportion of patients experienced TEAEs through Week 16 were: Infections and Infestations (38.7%), Gastrointestinal Disorders (19.7%), and General Disorders and Administration Site Conditions (12.1%). A greater proportion of patients who did not enter randomized withdrawal experienced TEAEs in the Infections and Infestations SOC (47.4%), as compared to the groups later randomized to GOL+MTX (41.0%) and PBO+MTX (34.2%). The most common reported preferred terms in the Infections and Infestations SOC were nasopharyngitis, URTI, and respiratory tract infection. In the Gastrointestinal Disorders SOC, a greater proportion of patients subsequently randomized to the GOL+MTX group reported TEAEs (23.1%) as compared to the patients who did not enter the randomized withdrawal period (21.1%) and the group subsequently randomized to PBO+MTX (15.8%). Differences between groups were due to small numeric differences in reported TEAEs of nausea, abdominal pain, and vomiting.

During the randomized withdrawal period from Week 16 through Week 48, 124 randomized patients reported TEAEs (Table 19). The proportion of patients experiencing TEAEs was generally balanced across the treatment groups, with the highest proportion in the PBO+MTX→GOL+MTX group. The proportion of patients with TEAEs within the Infections and Infestations SOC was higher in the Combined treatment group (63.2%) as compared to the GOL+MTX treatment group (47.4%); this was largely due to increased URTIs in the Combined group. More patients in the Combined treatment group had TEAEs within the Gastrointestinal Disorders SOC, with an increased number of patients with abdominal pain, diarrhea, vomiting, and abdominal pain upper as compared to the GOL+MTX group, however the differences between treatment groups are due to a small number of patients. SOCs in which there were a greater proportion of patients with AEs in the GOL+MTX group include the Skin and Subcutaneous Tissue Disorders, Nervous System Disorders, and Vascular disorders SOCs, however differences were due to small numbers of patients. In all other SOCs, a greater proportion of patients in the Combined treatment group reported AEs as compared to the GOL+MTX group. AEs that occurred in ≥ 5% of all randomized patients include URTI, JIA, nasopharyngitis, pyrexia, headache, and abdominal pain.

After Week 48 through the final DBL, the proportion of patients experiencing TEAEs was similar in each treatment group (GOL+MTX: 75.6%, Combined: 73.7%, All randomized: 74.7%). The SOCs with the highest incidence of AEs were similar to those with the highest AEs in the randomized withdrawal period and include: Infections and Infestations (52.6%), Gastrointestinal Disorders (26.6%), Musculoskeletal and Connective Tissue Disorders (24.0%), Skin and Subcutaneous Tissue Disorders (14.9%), General Disorders and Administration Site Conditions (13.6%), Injury

Poisoning and Procedural Complications (13.0%), and Respiratory, Thoracic, and Mediastinal disorders (12.3%). The most frequently reported TEAEs by preferred term were nasopharyngitis, URTI, JIA, vomiting, and tonsillitis. The events by preferred terms reported with a frequency ≥ 5% in all randomized patients from Week 48-DBL were balanced between the GOL+MTX and Combined groups for all PTs except for JIA (GOL+MTX 16.7%, Combined 7.9%), cough (GOL+MTX 12.8%, Combined 1.3%), rhinitis (GOL+MTX 9.0%, Combined 2.6%), and conjunctivitis (GOL+MTX 7.7%, Combined 2.6%).

All TEAEs reported in ≥ 5% of randomized patients throughout Study CNTO148JIA3001 are presented in Table 15 below. The SOCs and PTs reported with the greatest frequency are consistent with those seen in each of the study periods. From Week 0 through the final DBL, similar proportions of patients experienced TEAEs in the Combined and GOL+MTX treatment groups for the SOCs with the exception of Investigations; patients in the GOL+MTX group more frequently reported ALT and AST elevations as compared to patients in the Combined treatment group. Adverse events that occurred in ≥ 10% of all randomized patients by preferred term include URTI (31.2%), nasopharyngitis (27.3%), headache (16.2%), vomiting (16.2%), pyrexia (15.6%), nausea (13.0%), respiratory tract infection (12.3%), JIA (12.3%), abdominal pain (11.0%), and diarrhoea (10.4%). URTI, nasopharyngitis, vomiting, nausea, respiratory tract infection, and diarrhoea were reported with similar frequency in the GOL+ MTX and Combined treatment groups; pyrexia and abdominal pain were more frequently reported in the Combined group, while headache and JIA were more frequently reported in the GOL+MTX group. Preferred terms that were reported with a frequency of ≥ 5% in the GOL+MTX group as compared to the Combined group include rhinitis, influenza, gastroenteritis viral, JIA, cough, ALT increased, and AST increased.

Upper respiratory tract infection (including nasopharyngitis, pharyngitis, laryngitis, and rhinitis), viral infections (including influenza), bronchitis, sinusitis, as well as increases in ALT and AST are described as adverse drug reactions that occurred with a higher incidence in Simponi-treated patients than placebo-treated patients in clinical studies in patients with RA, PsA, and AS in the USPI. The preferred terms reported with > 5% frequency in the GOL+MTX group as compared to the Combined group are described in the USPI as adverse drug reactions with the exceptions of JIA and cough. Review of the TEAEs is consistent with the known safety profile of golimumab and does not raise new safety concerns in the pediatric population.

Table 15: Number of Patients with ≥1 TEAEs occurring in ≥5% of Randomized Patients by SOC and PT by Treatment Group, Week 0-DBL

	Golimumab administered prior to randomization at Wk 16					
System organ class Preferred term	GOL+MTX N = 78 n (%)	Combined N = 76 n (%)	PBO+MTX N = 10 n (%)	PBO+MTX →GOL+MTX before W48 N = 33 n (%)	PBO+MTX →GOL+MTX at or after W48 N = 33 n (%)	All Randomized N = 154 n (%)
Total patients with ≥1 TEAEs	**72 (92.3)**	**73 (96.1)**	**10 (100.0)**	**32 (97.0)**	**31 (93.9%)**	**145 (94.2)**
Infections and infestations	62 (79.5)	62 (81.6)	7 (70.0)	29 (87.9)	26 (78.8)	124 (80.5)
URTI	20 (25.6)	28 (36.8)	3 (30.0)	14 (42.4)	11 (33.3)	48 (31.2)
Nasopharyngitis	21 (26.9)	21 (27.6)	3 (30.0)	10 (30.3)	8 (24.2)	42 (27.3)
Respiratory tract infection	10 (12.8)	9 (11.8)	0	3 (9.1)	6 (18.2)	19 (12.3)
Gastroenteritis	8 (10.3)	7 (9.2)	1 (10.0)	3 (9.1)	3 (9.1)	15 (9.7)
Pharyngitis	9 (11.5)	6 (7.9)	0	4 (12.1)	2 (6.1)	15 (9.7)
Sinusitis	8 (10.3)	7 (9.2)	0	4 (12.1)	3 (9.1)	15 (9.7)
Tonsillitis	9 (11.5)	6 (7.9)	0	5 (15.2)	1 (3.0)	15 (9.7)
Rhinitis	10 (12.8)	4 (5.3)	0	2 (6.1)	2 (6.1)	14 (9.1)
Otitis media	6 (7.7)	5 (6.6)	0	3 (9.2)	2 (6.1)	11 (7.1)
Bronchitis	6 (7.7)	4 (5.3)	0	2 (6.1)	2 (6.1)	10 (6.5)
nfluenza	7 (9.0)	2 (2.6)	0	2 (6.1)	0	9 (5.8)
Gastroenteritis ral	2 (2.6)	6 (7.9)	0	3 (9.1)	3 (9.1)	8 (5.2)
Gastrointestinal disorders	33 (42.3)	36 (47.4)	3 (30.0)	19 (57.6)	14 (42.4)	69 (44.8)
omiting	12 (15.4)	13 (17.1)	0	8 (24.2)	15 (15.2)	25 (16.2)
Nausea	11 (14.1)	9 (11.8)	2 (20.0)	3 (9.1)	4 (12.1)	20 (13.0)
Abdominal pain	7 (9.0)	10 (13.2)	2 (20.0)	5 (15.2)	3 (9.1)	17 (11.0)
Diarrhoea	7 (9.0)	9 (11.8)	0	5 (15.2)	4 (12.1)	16 (10.4)
Abdominal pain upper	2 (2.6)	10 (13.2)	0	3 (9.1)	7 (21.2)	12 (7.8)
Constipation	3 (3.8)	5 (6.6)	0	3 (9.1)	2 (6.1)	8 (5.2)
Musculoskeletal and connective tissue disorders	30 (38.5)	29 (38.2)	4 (40.0)	17 (51.5)	8 (24.2)	59 (38.3)
J A	21 (26.9)	15 (19.7)	2 (20.0)	11 (33.3)	2 (6.1)	36 (23.4)
Arthralgia	8 (10.3)	7 (9.2)	1 (10.0)	6 (18.2)	0	15 (9.7)
Pain in extremity	6 (7.7)	4 (5.3)	1 (10.0)	3 (9.1)	0	10 (6.5)
General disorders and administration	25 (32.1)	26 (34.2)	1 (10.0)	11 (33.3)	14 (42.4)	51 (33.1)

site conditions						
Pyrexia	9 (11.5)	15 (19.7)	0	9 (27.3)	6 (18.2)	24 (15.6)
Influenza like illness	0	9 (11.8)	0	4 (12.1)	5 (15.2)	9 (5.8)
Skin and subcutaneous tissue disorders	27 (34.6)	23 (30.3)	2 (20.0)	11 (33.3)	10 (30.3)	50 (32.5)
Urticaria	6 (7.7)	4 (5.3)	0	3 (9.1)	1 (3.0)	10 (6.5)
Acne	2 (2.6)	4 (5.3)	1 (10.0)	1 (3.0)	2 (6.1)	6 (3.9)
Injury, poisoning and procedural complications	18 (23.1)	19 (25.0)	5 (50.0)	8 (24.2)	6 (18.2)	37 (24.0)
Respiratory, thoracic, and mediastinal disorders	19 (24.4)	18 (23.7)	2 (20.0)	8 (24.2)	8 (24.2)	36 (24.0)
Cough	10 (12.8)	3 (3.9)	0	2 (6.1)	1 (3.0)	13 (8.4)
Oropharyngeal pain	2 (2.6)	9 (11.8)	2 (20.0)	2 (6.1)	5 (15.2)	11 (7.1)
Nervous system disorders	19 (24.4)	13 (17.1)	0	6 (18.2)	7 (21.2)	32 (20.8)
Headache	15 (19.2)	10 (13.2)	0	4 (12.1)	6 (18.2)	25 (16.2)
Investigations	19 (24.4)	11 (14.5)	1 (10.0)	6 (18.2)	4 (12.1)	30 (19.5)
ALT increased	8 (10.3)	3 (3.9)	0	2 (6.1)	1 (3.0)	11 (7.1)
Hepatic enzyme ncreased	6 (7.7)	4 (5.3)	1 (10.0)	3 (9.1)	0	10 (6.5)
AST increased	7 (9.0)	1 (1.3)	0	1 (3.0)	0	8 (5.2)
Eye disorders	13 (16.7)	9 (11.8)	1 (10.0)	2 (6.1)	6 (18.2)	22 (14.3)
Conjunctivitis	7 (9.0)	5 (6.6)	0	2 (6.1)	3 (9.1)	12 (7.8)
Blood and lymphatic system disorders	10 (12.8)	11 (14.5)	0	4 (12.1	7 (21.2)	21 (13.6)
Ear and labyrinth disorders	5 (6.4)	7 (9.2)	1 (10.0)	2 (6.1)	4 (12.1)	12 (7.8)
Psychiatric disorders	4 (5.1)	7 (9.2)	2 (20.0)	1 (3.0)	4 (12.1)	11 (7.1)
Vascular disorders	6 (7.7)	4 (5.3)	0	1 (3.0)	3 (9.1)	10 (6.5)

Adapted from Final CSR Attachment TSFAE1B

7.4.2 Laboratory Findings

Hematology
During the open label treatment period from Weeks 0-16, mean changes from baseline in hematology parameters included mean decrease in neutrophils of -0.9 x 10^9/L, decrease in platelets of -30.9 x 10^9/L, and mean decrease in ESR of -8.0 mm/h. The hematology parameters most frequently observed to be abnormal were increase in eosinophils (76 patients, 43.9%), decrease in hematocrit (46 patients, 26.6%), decrease in hemoglobin (37 patients, 21.4%), and decrease in WBC (32 patients, 18.5%). A greater proportion of patients who did not enter the randomized withdrawal period reported a markedly abnormal decrease in hemoglobin and hematocrit, elevations in WBC, and decreases in lymphocytes, however, the numbers of patients in this group was small. Changes in hematology parameters were generally balanced between groups later randomized to PBO+MTX and GOL+MTX.

Elevation in eosinophils was also the most frequently reported abnormal value in the randomized withdrawal treatment period, reported in 47 (61.8%) patients in the Combined group and 51 (65.4%) patients in the GOL+MTX group. Decreased hemoglobin and hematocrit were observed in 27.3% and 34.4% of the randomized patients, respectively; decrease in hemoglobin occurred less commonly in the GOL+MTX group, while decrease in hematocrit was similar across the Combined and GOL+MTX groups. Decrease in WBC occurred more commonly in the Combined group (27.6%) compared to the GOL+MTX group (20.5%), with a similar number of patients with decreased absolute neutrophil counts in each group. Decrease in platelets occurred in 3.9% of the randomized patients, 2.6% of the GOL+MTX group and 5.3% of the Combined group. Mean change in eosinophil count was small in both treatment groups (GOL+MTX: -0.002 x 10^9/L; Combined group: 0.0002 x 10^9/L). Mean changes from baseline in ESR (-7.9 mm/h), hemoglobin (3.6 g/L), hematocrit (0.008), leukocytes (-0.57 x 10^9/L) and platelets (-35.3 x 10^9/L) were similar between treatment groups

Similarly, following Week 48, elevation in eosinophils was the most frequently reported abnormal value, reported in 50.7% of the patients in the Combined group and 53.5% of patients in the GOL+MTX group. There were more patients with abnormal decreases in WBC in the GOL+MTX group (22.5%) as compared to the other treatment groups (Combined 13.7%) and more patients in the Combined group with decreased hematocrit, however decrease in hemoglobin was similar across the treatment groups. Mean change from baseline in eosinophils was small (GOL+MTX: 0.0051 x 10^9/L, Combined: -0.0097 x 10^9/L). Mean changes in ESR, hemoglobin, hematocrit, leukocytes, and platelets were similar between the treatment groups.

In Study CNTO148JIA3001, the mean change from baseline in hematology parameters, and the proportions of patients with abnormal hematology labs, was generally similar in the GOL+MTX as compared to the Combined treatment groups.

Chemistry
In each period of the study, elevation of non-fasting glucose was the most frequently reported abnormal value occurring in 35.3% of patients (Week 0-16), 46.1% of patients (Week 16-48), and 49.3% (Week 48-DBL). Decreases in glucose were also observed in 19.1%, 23.4%, and 24.3% of patients in each of the study periods, respectively. Elevated glucose was more frequently reported by patients in the GOL+MTX group compared to the Combined group in the randomized withdrawal (GOL+MTX 51.3%, Combined 40.8%) and after Week 48 (GOL+MTX 53.5%, Combined 45.2%) periods of the study. Mean change from baseline in glucose in the randomized withdrawal and after week 48 periods were 0.08 and 0.11 mmol/L, and somewhat higher in the group originally randomized to PBO+MTX.

Elevations in ALT were reported in 18.5%, 23.4%, and 20.8% of patients across the treatment periods, while elevations in AST were reported in 14.5%, 16.9%, and 15.3%, respectively. From Week 0-16, the proportion of patients with abnormal post baseline ALT and AST levels were higher in the group later randomized to GOL+MTX (21.8% and 16.7%, respectively) as compared to the PBO+MTX group (14.5% and 11.8%, respectively). From Weeks 16-48, the proportion of patients with abnormal post baseline ALT and AST levels were higher in the GOL+MTX group (29.5% and 20.5%, respectively) as compared to the Combined group (17.1% and 13.2%, respectively). From Week 48-DBL, AST and ALT abnormalities were again more frequently reported by patients in the GOL+MTX group (29.6% and 21.1%) as compared to the Combined group (12.3% and 9.6%). Mean change from baseline in ALT in the Week 0-16 period was greater in the group later randomized to GOL+MTX (3.7 U/L) as compared to that of the group later randomized to PBO+MTX (1.7 U/L). Changes in AST values were similar. In the randomized withdrawal period, mean changes in ALT were 0.049 U/L in the GOL+MTX group and 1.55 U/L in the PBO+MTX arm, while changes in AST were -1.02 U/L in the GOL+MTX group and 0.93 U/L in the PBO+MTX arm. In the final period of the study, mean changes in ALT were 0.11 U/L in the GOL+MTX group and 1.75 U/L in the Combined group, while changes in AST were -0.96 U/L in the GOL+MTX group and 0.63 U/L in the Combined group.

ALT values ≥ 3x ULN were observed in 18 patients on 24 occasions, 7 patients in the open-label period, 6 in the randomized withdrawal period, and 6 patients after Week 48. Elevations in ALT values ≥ 3x ULN were more commonly reported by patients receiving GOL+MTX (10 patients, 12.8%), as compared to patients originally randomized to PBO+MTX (6 patients, 7.9%) and patients who were not randomized (2 patients, 10.5%). Three patients experienced bilirubin levels ≥ 2x ULN, however none of these patients had concomitant ALT values ≥ 3x ULN. The patients with bilirubin levels ≥ 2x ULN were all originally randomized to PBO+MTX, and experienced elevated bilirubin in the randomized withdrawal period (1 patient) and after Week 48 (2 patients).

Other frequently reported lab abnormalities from Week 0-16, Week 16-48, and Week 48-DBL include elevated calcium levels and elevated phosphate levels. Elevated

calcium levels were reported in 13.3% of enrolled patients (GOL+MTX: 14.1%, PBO+MTX: 11.8%) from Week 0-16, 16.9% of randomized patients from Week 16-48 (GOL+MTX: 14.1%, Combined: 19.7%), and 9.7% of randomized patients from Week 48-DBL (GOL+MTX: 9.9%, Combined: 9.6%). Elevated phosphate levels were reported in 10.4% of enrolled patients (GOL+MTX: 9.0%, PBO+MTX: 13.2%) from Week 0-16, 17.5% of randomized patients from Week 16-48 (GOL+MTX: 14.1%, Combined: 21.1%), and 11.8% of randomized patients from Week 48-DBL (GOL+MTX: 8.5%, Combined: 15.1%). Mean change from baseline in calcium and phosphate levels were small in magnitude and similar across treatment groups.

In Study CNTO148JIA3001, elevations in glucose, AST and ALT were more frequently observed in the GOL+MTX treatment group as compared to the Combined group, which includes those patients randomized to PBO+MTX at Week 16 who subsequently transitioned to GOL+MTX. The magnitude of mean changes from baseline was generally small. Increases in ALT values ≥ 3x ULN were observed more frequently in patients in the GOL+MTX group and occurred throughout the study. Other changes were overall balanced across the treatment groups, however, it is difficult to make an informed comparison as all patients received open label golimumab during the initial open-label period. In the golimumab USPI, liver enzyme elevations are described in the adverse reaction section; ALT elevations ≥ 3x ULN occurred in 2% of SIMPONI-treated patients in controlled studies in RA, PsA, and AS through Week 16. The observed rate of ALT elevations ≥ 3x ULN through Week 16 in the current study was 4.0%. Differences in these rates may be due to differences in the patient diseases, concomitant medications, and study designs. The observed laboratory abnormalities do not raise additional safety concerns.

7.4.3 Vital Signs

Median weight and body surface areas were similar across treatment groups with BSA 1.5 in the GOL+MTX group as compared to 1.4 in the Combined group. Temperature, heart rate, and respiratory rate were obtained at baseline only, while blood pressure was monitored through the study. Abnormal systolic blood pressure measurements were observed in139 patients (80.3%) through Week 48, including 63 patients (82.9%) in the Combined group and 64 patients (82.1%) in the GOL+MTX group. Abnormal diastolic blood pressure values were observed in 96 patients (55.5%), 48 patients (63.2%) in the Combined group and 43 patients (55.1%) in the GOL+MTX group. After Week 48, 120 patients (82.8%) had an abnormal systolic blood pressure, 57 (78.1%) in the Combined group and 63 (87.5%) in the GOL+MTX group; while 88 (60.7%) patients had an abnormal diastolic blood pressure, 45 (61.6%) in the combined groups and 43 (59.7%) in the GOL+MTX treatment group. Based on reviewer analysis, median change from baseline in systolic and diastolic blood pressures was 0 in the GOL+MTX and Combined groups from Weeks 0-48. Median change in systolic blood pressure after Week 48 was similar in each treatment group (GOL+MTX: 1; Combined: 2 mm Hg), while there was no median change in diastolic blood pressure. None of the

abnormal blood pressure values were reported as SAEs nor did they have hemodynamic consequences. Hypertension is included as an adverse drug reaction in the golimumab USPI. In the current study, similar proportions of patients had abnormal blood pressures in each treatment group and median blood pressure changes from baseline were minimal.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in Study CNTO148JIA3001.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies with golimumab were submitted in the sBLA.

7.4.6 Immunogenicity

A drug-tolerant, enzyme immunoassay (EIA) method was used to screen, titer, and confirm specificity of antibodies to golimumab in human serum in the presence of golimumab. This new assay has approximately 16-fold higher sensitivity for detection of antibodies to golimumab with improved drug tolerance as compared to the original EIA used in the adult rheumatology and UC studies. Thus, comparisons to immunogenicity in previous studies described in labeling are limited and can be misleading. Samples were collected at baseline, Weeks, 4, 12, 24, and 48. Samples that were positive for antibodies to golimumab were further tested to determine if the antibodies were neutralizing antibodies. The Applicant presents the incidence of antibody formation in the randomized population, however, antibody formation in the enrolled population by treatment group is discussed below.

At baseline, 1 patient (0703-00176) was positive for ADA. Over the course of the study, ADA were detected in 81 patients, in a greater proportion of patients in the Combined treatment group as compared to the GOL+MTX group (Table 16). ADA were detected in 38 (22.1%) and 69 (40.1%) of 172 golimumab treated patients with appropriate samples through Week 12 and Week 48, respectively (Table 16). Throughout the study, the incidence of ADA was lower in the patients randomized to GOL+MTX (41.0%), as compared to the patients in the Combined group (52.6%). The majority of the antibody positive patients had titers < 1:1000. The overall incidence of neutralizing antibodies was 42.0%, based on reviewer analysis. The incidence of neutralizing antibodies was similar across the treatment groups.

Table 16: Immunogenicity Week 0-DBL

		Golimumab administered prior to randomization at Wk 16				
	Not randomized at Wk 16 N = 19[a] n (%)	PBO+MTX[b] n (%)	Combined N = 76 n (%)	GOL+MTX N = 78 n (%)	All randomized patients N = 154 n (%)	All subjects N = 172* n (%)
ADA positive at any time through Week 12	8 (44.4)	16 (21.1)	16 (21.1)	14 (17.9)	30 (19.5)	38 (22.1)
ADA positive at any time through Week 48	9 (47.4)	20 (46.5)	37 (48.7)	24 (30.8)	61 (39.6)	69 (40.1)
ADA positive at any time through DBL	9 (47.4)	3 (30.0)	40 (52.6)	32 (41.0)	72 (46.8%)	81 (47.1)
nAb positive through DBL[c]	4 (44.4)	--[d]	16 (40.0)	14 (43.8)	30 (41.7)	34 (42.0)

[a] One patient without appropriate sample
[b] PBO+MTX: N= 43 for Week 16-48, N=10 for Week 48-DBL
[c] Denominator when calculating proportion of patients with nAb is number of patients ADA positive
[d] None of the 3 patients receiving PBO+MTX with ADA were nAb positive
Source: Adapted from 48 Wk CSR Table 9, Attachment TSFPKATSA1A, Attachment TPKNAB1; Final CSR Table 4
Reviewer JMP analysis using ADXA dataset and terms PARAM, AVALC, AVISIT, COLSF, ARM, USUBJ

Serum golimumab concentrations were lower in patients who developed ADA, particularly when titer level was >1:100, than in those patients who were ADA negative. In the patients with positive ADA, the proportions of ACR Ped 30 responders at Week 16 (72 patients, 88.9%) and proportions of patients without flare through Week 48 (51 patients, 62.9%) were similar to the overall population. There was no association between positive ADA and injection site reactions. As discussed above, one patient in the Combined group experienced a serum sickness-like reaction; there were no other reports of anaphylactic or serum sickness-like reactions.

The incidence of ADA is higher than the reported immunogenicity of golimumab in the USPI of 2% in RA, PsA, and AS patients treated with concomitant MTX, however this is consistent with the increased sensitivity of the newer assay. The Applicant has previously submitted data comparing the older assay with the newer drug-tolerant assay. When ADA were assessed in samples from the phase 3 rheumatologic studies, the incidence of ADA through Week 52 was 31.7%, similar to the observed rate in the GOL+MTX group through Week 48 in CNTO148JIA3001. (b) (4)

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Golimumab 30 mg/m^2 q4 weeks was the single dose of golimumab studied in Study CNTO148JIA3001.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

Safety analyses based on demographic characteristics were not conducted by the Applicant. The discussion below is based on Reviewer analysis of the ADAE dataset using JMP software.

SAEs
Of the 39 patients who reported SAEs, the majority were female (89.7%), and Caucasian (92.3%), reflecting the demographics of the enrolled patients of whom 75% were female and 87.9% were Caucasian. The mean age of patients with SAEs was 9.8 years (SD 5.0) and the median age was 10 years.

AEs leading to discontinuation
Fifteen patients reported AEs leading to drug discontinuation. Twelve (80.0%) patients were female and 3 (20.0%) were male, 14 were Caucasian and 1 was black or African American. The mean and median ages of patients with AEs leading to discontinuation was 13.1 (SD 3.6) and 14, respectively.

AEs
One hundred and sixty patients reported 1444 TEAEs. One hundred and twenty three (76.9%) patients were female and 37 (23.1%) were male, and the majority were Caucasian (140 patients, 87.5%). The mean and median ages of patients reporting TEAEs were 11.0 (SD 4.5) and 12 years, respectively.

Analysis of TEAEs, SAEs, and AEs leading to discontinuation by demographic subgroups was similar to the safety profile of the overall study population. This analysis is limited by the small number of non-Caucasian and non-female patients enrolled in the study.

7.5.4 Drug-Disease Interactions

Study CNTO148JIA3001 enrolled JIA patients of the following subtypes: polyarticular RF-negative arthritis (52.0% of enrolled patients), polyarticular RF-positive arthritis (19.7%), extended oligoarticular arthritis (12.7%), psoriatic arthritis (8.7%), and systemic

arthritis without evidence of systemic symptoms (6.9%). The proportion of patients reporting ≥1 TEAEs, including AEs, SAEs, infections, and ISRs through Week 48 were evaluated by disease subgroup (
Table 17). In the polyarticular RF-negative arthritis subgroup, a greater proportion of patients in the Combined group experienced AEs and infections compared to the GOL+MTX group, while the frequencies of SAEs and ISRs were similar through Week 48. In the RF-positive arthritis subgroup, AEs and infections occurred with greater frequency in the GOL+MTX group vs. the Combined group; SAEs and ISRs were rare. In the extended oligoarticular subgroup, an increased number SAEs occurred in the GOL+MTX group, but this difference was driven by a very small number of patients. In the psoriatic arthritis subgroup, there were proportionally more AEs and infections in the Combined group and more SAEs in the GOL+MTX group, however interpretation is limited by the very small numbers in each treatment group with psoriatic arthritis. Finally, systemic arthritis, without systemic symptoms, rates of AEs were the same between treatment groups, while rates of SAEs and infections were higher in the Combined treatment group, but this is again limited by the very small numbers in each treatment group. The overall frequencies of AEs, SAEs, infections, and ISR through Week 48 in each disease subgroup, as defined by ILAR classification, were similar to the frequencies in the overall patient population. The frequency of events in the largest disease subgroups, polyarticular RF-negative arthritis and polyarticular RF-positive arthritis, were generally similar by treatment group (Combined vs. GOL+MTX). While conclusions are limited by the small numbers of patients with extended oligoarticular arthritis, psoriatic arthritis, and systemic arthritis without evidence of systemic symptoms, across all of the disease subgroups, there was no consistent increase in events in either the Combined or GOL+MTX groups.

Table 17: Patients with ≥ 1 TEAEs through Week 48 by Disease Subgroup

	Golimumab administered prior to randomization at Wk 16						
System organ class Preferred term	Enrolled patients not entering randomized withdrawal N = 19 n (%)	PBO+MTX N = 43 n (%)	PBO+MTX →GOL+MTX N = 33 n (%)	Combined N = 76 n (%)	GOL+MTX N = 78 n (%)	All Randomized N = 154 n (%)	All patients N = 173 n (%)
All subjects							
N	19	43	33	76	78	154	173
AEs	15 (78.9)	39 (90.7)	32 (97.0)	71 (93.4)	66 (84.6)	137 (89.0)	152 (87.9)
SAEs	4 (21.1)	4 (9.3)	6 (18.2)	10 (13.2)	9 (11.5)	19 (12.3)	23 (13.3)
Infections	10 (52.6)	27 (62.8)	29 (87.9)	56 (73.7)	47 (60.3)	103 (66.9)	113 (65.3)
ISR	1 (5.3)	5 (11.6)	1 (3.0)	6 (7.9)	7 (9.0)	13 (8.4)	14 (8.1)
Systemic Arthritis without systemic symptoms							
N	2	3	4	7	3	10	12
AEs	2 (100.0)	3 (100.0)	4 (100.0)	7 (100.0)	3 (100.0)	10 (100.0)	12 (100.0)
SAEs	0	0	1 (25.0)	1 (14.3)	0	1 (10.0)	1 (8.3)
Infections	2 (100.0)	2 (66.7)	4 (100.0)	6 (85.7)	2 (66.7)	8 (80.0)	10 (83.3)
ISR	0	0	0	0	0	0	0
Polyarticular RF-positive Arthritis							
N	3	7	6	13	18	31	34
AEs	2 (66.7)	5 (71.4)	5 (83.3)	10 (76.9)	16 (88.9)	26 (83.9)	28 (82.4)
SAEs	2 (66.7)	1 (14.3)	1 (16.7)	2 (15.4)	0	2 (6.5)	4 (11.8)
Infections	1 (33.3)	2 (28.6)	4 (66.7)	6 (46.2)	12 (66.7)	18 (58.1)	19 (55.9)
ISR	0	1 (14.3)	0	1 (7.7)	1 (5.6)	2 (6.5)	2 (5.9)
Polyarticular RF-negative Arthritis							
N	13	25	15	40	37	77	90
AEs	11 (84.6)	23 (92.0)	15 (100.0)	38 (95.0)	30 (81.1)	68 (88.3)	79 (87.8)
SAEs	2 (15.4)	3 (12.0)	2 (13.3)	5 (12.5)	4 (10.8)	9 (11.7)	11 (12.2)
Infections	7 (53.8)	17 (68.0)	15 (100.0)	32 (80.0)	19 (51.4)	51 (66.2)	58 (64.4)
ISR	1 (7.7)	4 (16.0)	0	4 (10.0)	4 (10.8)	8 (10.4)	9 (10.0)
Extended Oligoarticular Arthritis							
N	1	4	5	9	12	21	22
AEs	0	4 (100.0)	5 (100.0)	9 (100.0)	11 (91.7)	20 (95.2)	20 (90.9)
SAEs	0	0	1 (20.0)	1 (11.1)	3 (25.0)	4 (19.0)	4 (18.2)
Infections	0	2 (50.0)	5 (100.0)	7 (77.8)	10 (83.3)	17 (81.0)	17 (77.3)
ISR	0	0	1 (20.0)	1 (11.1)	2 (16.7)	3 (14.3)	3 (13.6)
Psoriatic Arthritis							
N	0	4	3	7	8	15	15
AEs	-	4 (100.0)	3 (100.0)	7 (100.0)	6 (75.0)	13 (86.7)	13 (86.7)
SAEs	-	0	1 (33.3)	1 (14.3)	2 (25.0)	3 (20.0)	3 (20.0)
Infections	-	4 (100.0)	1 (33.3)	5 (71.4)	4 (50.0)	9 (60.0)	9 (60.0)
ISR	-	0	0	0	0	0	0

Source: Adapted from 48 Week Clinical Study Report Attachment TSFAESUB1A

7.5.5 Drug-Drug Interactions

Not applicable for this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Lymphoma and other malignancies have been reported in children and adolescent patients treated with TNF-inhibitors as described in a boxed warning in the USPI for golimumab. There were no malignancies observed during Study CNTO148JIA3001.

7.6.2 Human Reproduction and Pregnancy Data

The Applicant submitted a literature review on 21Oct2016 to support the proposed PLLR labeling submitted with this supplement on 22Aug2016. Nine identified publications that involved cases of golimumab exposure in pregnancy were reviewed by the Applicant; 5 described AEs with exposure to TNF-antagonists, 4 of which were specifically linked to golimumab exposure. Of the 4 publications, 2 were published by the Applicant based on cases reported to the safety database and the other 2 publications did not identify new safety information.

A golimumab Pregnancy Research Initiative study is ongoing. As of 2015, five golimumab-exposed pregnancies were reported in national registers and no adverse birth outcomes have been reported. One infant required hospitalization for infection during the first year of life.

The Applicant also identified 478 cases of golimumab exposure during pregnancy or lactation in the global safety database through 31Aug2016. Of the 151 pregnancy cases with a reported outcome, 65.6% of the cases reported live births, of which 90% resulted in births with no reported AEs, while 35 (23.2%) reported spontaneous/missed abortions, 14 (9.3%) reported elective/induced abortions, 2 (1.3%) reported abortion unspecified, and 1 (0.7%) reported a ruptured ectopic pregnancy. The Applicant notes that the rate of missed/spontaneous abortions is slightly higher than the background rate of 15-20%, but the observed cases were confounded by advanced maternal age, concomitant use of other medications known to cause fetal death and/or teratogenic effects, and/or inflammatory bowel disease, which is associated with increased risks of adverse maternal and fetal outcomes. Twenty child cases were identified and 16 of these were reported as serious. Of the serious cases, 7 reported PTs were identified as congenital anomalies including congenital anomaly (2), anencephaly, atrial septal defect, fetal malformation, heart disease congenital, and Turner's syndrome. Overall, 4.6% of the identified pregnancy cases with reported outcomes were linked to child cases with reported congenital anomaly; assessment of several of these cases was

confounded by maternal ulcerative colitis, family history, or concomitant methotrexate use.

Five child cases described infants exposed to golimumab during breast feeding; 2 of these were described as serious. In the first case, reported PTs and outcomes included Sepsis (recovered), Exposure during breast feeding (outcome not reported), premature baby (outcome not reported), Fungal infection (recovering), Milk allergy (outcome not reported), Low birth weight baby (outcome not reported), and Foetal exposure during pregnancy (outcome not reported). In the second serious case, PTs of Foetal exposure during pregnancy (recovered) and Colitis ulcerative (outcome not reported). These infants were also exposed to golimumab in utero, and, therefore, conclusions cannot be made regarding risk associated with golimumab exposure via breast milk.

See review by pharmacology/toxicology reviewer/team leader Dr. Timothy Robison for discussion of updated PLLR labeling.

7.6.3 Pediatrics and Assessment of Effects on Growth

Study CNTO148JIA3001 was conducted in a pediatric population of patients with polyarticular JIA. Assessment of effects on growth was not included in this study.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable to this submission.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

There is no available postmarketing data in the indication of PJIA.

9 Appendices

9.1 Literature Review/References

Brunner HI, Klein-Gitelman MS, Miller MJ, et al. Minimal clinically important differences of the childhood health assessment questionnaire. J Rheum. 2005, 32(1): 150-161.

USPI Simponi (golimumab). January 2016.

9.2 Labeling Recommendations

At the time of this review, labeling discussions are ongoing regarding PLLR formatting and changes to Section 8.4.

9.3 Advisory Committee Meeting

This supplemental application does not seek any additional indications or claims; thus no Advisory Committee meeting was warranted.

Appendix 1: Comparison of Baseline Characteristics to Other PJIA Studies

Table 16: Comparison of baseline disease characteristics across pJIA studies with biologics[4]

	Golimumab	Tocilizumab[4]	Adalimumab[8]	Etanercept[7]	Abatacept[9,11]
Sample Size (OL/RW)	173/154	188/163	85/80*	69/51	190/122
Active joints	12	20	15	28	15
Limited ROM joints	8	18	8	10	14
CHAQ	0.9	1.4	0.9	1.4	1.2
Parent Assessment of Disease (cm)	4.5	5.3	4.3	5.0	4.0
Physician Assessment of Disease (cm)	5.4	6.1	5.8	7.0	5.3
ESR (mm/hr)	16	35	-	35	30
CRP (median)	0.17 mg/dL (20.5% of subjects with CRP > 1.0 mg/dL)	78% of subjects with CRP >1.0 mg/dL	0.7-0.8 mg/dL	3.5 mg/dL	3.2 mg/dL

CHAQ = Childhood Health Assessment Questionnaire; CRP= C-reactive protein; ESR = erythrocyte sedimentation rate; OL/RW= Open label/randomized withdrawal; pJIA = polyarticular juvenile idiopathic arthritis; ROM = range of motion; SC = subcutaneous

* Adalimumab + MTX cohort

Values presented for golimumab and etanercept are median values; those for tocilizumab, adalimumab, and abatacept are mean values, unless otherwise noted

Source: IND 9925, Type C Meeting package, 17Dec2015

Appendix 2: Comparison of Response Rates to Other PJIA Studies

Table 17: Comparison of ACR Response across pJIA studies with biologics[4]

Study Drug	Study Duration	Patient and Disease Characteristics	Number of Subjects Randomized	JIA ACR Response Lead in Phase	Flare Rates	JIA ACR Response Withdrawal Period (Active/PBO)	Qualifications
Etanercept[7]	Phase 1: 12 weeks Phase 2: 16 weeks	Children 4 to 17 years with MTX-IR active JIA (oligoarticular, polyarticular, systemic)	Phase 1: 69 Phase 2: 51	ACR 30 = 74% ACR 50 = 64% ACR 70 = 36%	ETN = 28% PBO = 81%	ACR 30: 80%/35% ACR 50: 72%/23% ACR 70: 44%/19%	Enrolled systemic subjects. Allowed flare subjects to be counted as ACR responders Monotherapy only
Abatacept[11]	Phase 1: 16 weeks Phase 2: 24 weeks	Children 6 to 17 years with DMARD-IR active JIA (oligoarticular, polyarticular, systemic)	Phase 1: 190 Phase 2: 122	ACR 30 = 65% ACR 50 = 50% ACR 70 = 28% ACR 90 = 13%	ABA = 20% PBO = 53%	ACR 30: 82%/69% ACR 50: 77%/52% ACR 70: 53%/31% ACR 90: 40%/16%	Enrolled systemic subjects. Allowed flare subjects to be counted as ACR responders. Mono and combination therapy.
Adalimumab*[8]	Phase 1: 16 weeks Phase 2: 32 weeks	Children 4 to 17 years with MTX-IR and MTX-naïve NSAID-IR active pJIA (extended oligoarticular and polyarticular)	Phase 1: 83** Phase 2: 75**	ACR 30 = 94% ACR 50 = 91% ACR 70 = 71% ACR 90 = 28%	ADA = 37% PBO = 65%	ACR 30: 63%/38% ACR 50: 63%/38% ACR 70: 63%/27% ACR 90: 42%/27%	Flare subjects categorized as ACR non-responders. Data from subjects receiving concurrent MTX presented.

Table 17: Comparison of ACR Response across pJIA studies with biologics[4]

Study Drug	Study Duration	Patient and Disease Characteristics	Number of Subjects Randomized	JIA ACR Response Lead in Phase	Flare Rates	JIA ACR Response Withdrawal Period (Active/PBO)	Qualifications
Tocilizumab[1]	Phase 1: 16 weeks Phase 2: 24 weeks	Children 2 to 17 years with MTX-IR active pJIA (extended oligoarticular and polyarticular)	Phase 1: 188 Phase 2: 163	ACR 30 = 89% ACR 50 = 83% ACR 70 = 62% ACR 90 = 26%	TCZ = 26% PBO = 48%	ACR 30: 74%/54% ACR 50: 73%/52% ACR 70: 65%/42% ACR 90: 45%/23%	Flare subjects categorized as ACR non-responders. Mono and combination therapy.
Golimumab	Phase 1: 16 weeks Phase 2: 32 weeks	Children 2 to 17 years of age with MTX-IR active pJIA. (polyarthritis, extended oligoarthritis, systemic JIA without current systemic symptoms, JPsA)	Phase 1: 173 Phase 2: 154	ACR 30 = 87.3% ACR 50 = 79.2% ACR 70 = 65.9% ACR 90 = 36.4%	GLM = 41% PBO = 47.4%	ACR 30: 55%/52% ACR 50: 54%/51% ACR 70: 47%/47% ACR 90: 32%/38%	Flare subjects were categorized as ACR nonresponders. Combination therapy with MTX only.

ABA = abatacept; ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; ETN = etanercept; IR = immediate-release; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drugs; PBO = placebo; pJIA = polyarticular JIA; TCZ = tocilizumab; GLM = golimumab

* Data was presented as monotherapy and MTX combination therapy. Given the fact that the abatacept and tocilizumab data is not presented in this way, only the results of the MTX combination population are presented here. Details of monotherapy are presented in the manuscript listed in the references.
** Subjects that received MTX + adalimumab only

Appendix 3: Schedule of Assessments Screening through Week 48

Table 1: From Screen through Week 48

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

Table 1: From Screen through Week 48

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

Source: IND 9925 submission Study CNTO148JIA3001 protocol version 9

Appendix 4: Schedule of Assessments Week 52 through Week 100

Table 2: From Week 52 through Week 100

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

Table 2: From Week 52 through Week 100

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

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

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

Source: IND 9925 submission Study CNTO148JIA3001 protocol version 9

For the Schedules of Assessments for Week 104 through Week 148, Week 152 through Week 196, Week 200 through Week 256, see the Study CNTO148JIA3001 protocol \\cdsesub1\evsprod\ind009925\0995\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rheumatoid-arthritis\5351-stud-rep-contr\cnto148jia3001\cnto148jia3001-protocol.pdf

Appendix 5: Additional Safety Tables

Table 18: Number of Patients with ≥1 TEAEs occurring in ≥ 2% of all Patients by SOC and PT by Treatment Group, Week 0-16

	Golimumab administered prior to randomization at Wk 16				
System organ class Preferred term	Not randomized at Wk 16 N = 19 n (%)	GOL+MTX N = 78 n (%)	PBO+MTX N = 76 n (%)	All randomized N = 154 n (%)	All enrolled N = 173 n (%)
Total patients with ≥1 TEAEs	**13 (68.4)**	**56 (71.8)**	**49 (64.5)**	**105 (68.2)**	**118 (68.2)**
Infections and infestations	9 (47.4)	32 (41.0)	26 (34.2)	58 (37.7)	67 (38.7)
Nasopharyngitis	2 (10.5)	8 (10.3)	6 (7.9)	14 (9.1)	16 (9.2)
URTI	1 (5.3)	4 (5.1)	7 (9.2)	11 (7.1)	12 (6.9)
Respiratory tract nfection	1 (5.3)	3 (3.8)	4 (5.3)	7 (4.5)	8 (4.6)
Pharyngitis	0	2 (2.6)	3 (3.9)	5 (3.2)	5 (2.9)
Gastroenteritis	1 (5.3)	1 (1.3)	2 (2.6)	3 (1.9)	4 (2.3)
Otitis media	0	2 (2.6)	2 (2.6)	4 (2.6)	4 (2.3)
Urinary tract infection	0	4 (5.1)	0	4 (2.6)	4 (2.3)
Gastrointestinal disorders	4 (21.1)	18 (23.1)	12 (15.8)	30 (19.5)	34 (19.7)
Nausea	2 (10.5)	5 (6.4)	3 (3.9)	8 (5.2)	10 (5.8
Abdominal pain	0	6 (7.7)	2 (2.6)	8 (5.2)	8 (4.6)
omiting	0	4 (5.1)	3 (3.9)	7 (4.5)	7 (4.0)
Abdominal pain upper	0	0	6 (7.9)	6 (3.9)	6 (3.5)
Diarrhoea	0	2 (2.6)	4 (5.3)	6 (3.9)	6 (3.5)
General disorders and administration site conditions	2 (10.5)	9 (11.5)	10 (13.2)	19 (12.3)	21 (12.1)
Pyrexia	0	2 (2.6)	6 (7.9)	8 (5.2)	8 (4.6)
Skin and subcutaneous tissue disorders	5 (26.3)	6 (7.7)	9 (11.8)	15 (9.7)	20 (11.6)
Urticaria	2 (10.5)	1 (1.3)	1 (1.3)	2 (1.3)	4 (2.3)
Musculoskeletal and connective tissue disorders	3 (15.8)	9 (11.5)	7 (9.2)	16 (10.4)	19 (11.0)
J A	3 (15.8)	3 (3.8)	0	3 (1.9)	6 (3.5)
Investigations	4 (21.1)	7 (9.0)	3 (3.9)	10 (6.5)	14 (8.1)
ALT increased	0	5 (6.4)	1 (1.3)	6 (3.9)	6 (3.5)
AST increased	0	4 (5.1)	0	4 (2.6)	4 (2.3)
Nervous system disorders	1 (5.3)	6 (7.7)	7 (9.2)	13 (8.4)	14 (8.1)
Headache	1 (5.3)	4 (5.1)	5 (6.6)	9 (5.8)	10 (5.8)
Respiratory, thoracic, and mediastinal disorders	2 (10.5)	3 (3.8)	8 (10.5)	11 (7.1)	13 (7.5)
Oropharyngeal pain	0	2 (2.6)	4 (5.3)	6 (3.9)	6 (3.5)

Injury, poisoning and procedural complications	1 (5.3)	5 (6.4)	5 (6.6)	10 (6.5)	11 (6.4)
Eye disorders	2 (10.5)	4 (5.1)	2 (2.6)	6 (3.9)	8 (4.6)
Conjunctivitis	1 (5.3)	2 (2.6)	1 (1.3)	3 (1.9)	4 (2.3)

Source: Adapted from 48 Week CSR Attachment TSFAE1

Table 19: Number of Patients with ≥1 TEAEs occurring in ≥ 2% of Randomized Patients by SOC and PT by Treatment Group, Week 16-48

	Golimumab administered prior to randomization at Wk 16				
System organ class Preferred term	GOL+MTX N = 78 n (%)	Combined N = 76 n (%)	PBO+MTX N = 43 n (%)	PBO+MTX →GOL+MTX N = 33 n (%)	All randomized patients N = 154 n (%)
Total patients with ≥1 TEAEs	**61 (78.2)**	**63 (82.9)**	**32 (74.4)**	**31 (93.9)**	**124 (80.5)**
Infections and infestations	37 (47.4)	48 (63.2)	25 (58.1)	23 (69.7)	85 (55.2)
URTI	13 (16.7)	21 (27.6)	10 (23.3)	11 (33.3)	34 (22.1)
Nasopharyngitis	6 (7.7)	9 (11.8)	3 (7.0)	6 (18.2)	15 (9.7)
Rhinitis	3 (3.8)	4 (5.3)	2 (4.7)	2 (6.1)	7 (4.5)
Gastroenteritis	2 (2.6)	4 (5.3)	3 (7.0)	1 (3.0)	6 (3.9)
Tonsillitis	4 (5.1)	2 (2.6)	0	2 (6.1)	6 (3.9)
Respiratory tract nfection	2 (2.6)	3 (3.9)	3 (7.0)	0	5 (3.2)
Bronchitis	2 (2.6)	2 (2.6)	1 (2.3)	1 (3.0)	4 (2.6)
Gastrointestinal disorders	12 (15.4)	22 (28.9)	11 (25.6)	11 (33.3)	34 (22.1)
Abdominal pain	1 (1.3)	7 (9.2)	4 (9.3)	3 (9.1)	8 (5.2)
Nausea	3 (3.8)	4 (5.3)	3 (7.0)	1 (3.0)	7 (4.5)
Diarrhoea	1 (1.3)	5 (6.6)	2 (4.7)	3 (9.1)	6 (3.9)
omiting	1 (1.3)	5 (6.6)	1 (2.3)	4 (12.1)	6 (3.9)
Abdominal pain upper	1 (1.3)	4 (5.3)	3 (7.0)	1 (3.0)	5 (3.2)
Constipation	3 (3.8)	1 (1.3)	0	1 (3.0)	4 (2.6)
Musculoskeletal and connective tissue disorders	14 (17.9)	17 (22.4)	4 (9.3)	13 (39.4)	31 (20.1)
J A	10 (12.8)	10 (13.2)	1 (2.3)	9 (27.3)	20 (13.0)
Arthralgia	1 (1.3)	5 (6.6)	1 (2.3)	4 (12.1)	6 (3.9)
Pain in extremity	2 (2.6)	3 (3.9)	1 (2.3)	2 (6.1)	5 (3.2)
Arthritis	1 (1.3)	3 (3.9)	1 (2.3)	2 (6.1)	4 (2.6)
Skin and subcutaneous tissue disorders	14 (17.9)	12 (15.8)	8 (18.6)	4 (12.1)	26 (16.9)
Acne	2 (2.6)	3 (3.9)	3 (7.0)	0	5 (3.2)
Urticaria	2 (2.6)	3 (3.9)	1 (2.3)	2 (6.1)	5 (3.2)
General disorders and administration site conditions	7 (9.0)	16 (21.1)	7 (16.3)	9 (27.3)	23 (14.9)
Pyrexia	4 (5.1)	11 (14.5)	4 (9.3)	7 (21.2)	15 (9.7)
Respiratory, thoracic, and mediastinal	7 (9.0)	12 (15.8)	7 (16.3)	5 (15.2)	19 (12.3)

disorders					
Oropharyngeal pain	0	5 (6.6)	4 (9.3)	1 (3.0)	5 (3.2)
Cough	1 (1.3)	3 (3.9)	1 (2.3)	2 (6.1)	4 (2.6)
Injury, poisoning and procedural complications	7 (9.0)	10 (13.2)	6 (14.0)	4 (12.1)	17 (11.0)
Ligament sprain	2 (2.6)	3 (3.9)	1 (2.3)	2 (6.1)	5 (3.2)
Nervous system disorders	8 (10.3)	6 (7.9)	5 (11.6)	1 (3.0)	14 (9.1)
Headache	6 (7.7)	6 (7.9)	5 (11.6)	1 (3.0)	12 (7.8)
Blood and lymphatic system disorders	5 (6.4)	5 (6.6)	3 (7.0)	2 (6.1)	10 (6.5)
Neutropenia	2 (2.)	3 (3.9)	1 (2.3)	2 (6.1)	5 (3.2)
Investigations	5 (6.4)	5 (6.6)	3 (7.0)	2 (6.1)	10 (6.5)
Hepatic enzyme ncreased	3 (3.8)	3 (3.9)	1 (2.3)	2 (6.1)	6 (3.9)
Eye disorders	3 (3.8)	6 (7.9)	5 (11.6)	1 (3.0)	9 (5.8)
Conjunctivitis	1 (1.3)	3 (3.9)	2 (4.7)	1 (3.0)	4 (2.6)
Vascular disorders	3 (3.8)	2 (2.6)	2 (4.7)	0	5 (3.2)
Ear and labyrinth disorders	2 (2.6)	2 (2.6)	2 (4.7)	0	4 (2.6)
Psychiatric disorders	1 (1.3)	3 (3.9)	3 (7.0)	0	4 (2.6)

Source: Adapted from 48 Week CSR Attachment TSFAE1B

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/s/

RACHEL GLASER
05/18/2017

NIKOLAY P NIKOLOV
05/18/2017