26 May 2016
EMA/CHMP/404217/2016
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Simponi

International non-proprietary name: golimumab

Procedure No. EMEA/H/C/000992/II/0063

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# Table of contents

**1. Background information on the procedure ..... 4**
1.1. Type II variation ..... 4
1.2. Steps taken for the assessment of the product ..... 4

**2. Scientific discussion ..... 5**
2.1. Introduction ..... 5
2.2. Non-clinical aspects ..... 6
2.2.1. Ecotoxicity/environmental risk assessment ..... 6
2.3. Clinical aspects ..... 6
2.3.1. Introduction ..... 6
2.3.2. Pharmacokinetics ..... 8
2.3.3. PK/PD modelling ..... 9
2.3.4. Discussion on clinical pharmacology ..... 16
2.3.5. Conclusions on clinical pharmacology ..... 17
2.4. Clinical efficacy ..... 18
2.4.1. Main study ..... 18
2.4.2. Discussion on clinical efficacy ..... 35
2.4.3. Conclusions on the clinical efficacy ..... 37
2.5. Clinical safety ..... 37
2.5.1. Discussion on clinical safety ..... 44
2.5.2. Conclusions on clinical safety ..... 45
2.5.3. PSUR cycle ..... 45
2.6. Risk management plan ..... 45
2.7. Update of the Product information ..... 61
2.7.1. User consultation ..... 61

**3. Benefit-Risk Balance ..... 62**

**4. Recommendations ..... 64**

**5. EPAR changes ..... 65**

# List of abbreviations

| | |
|---|---|
| ACR | American College of Rheumatology |
| ADR | adverse drug reaction |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AS | ankylosing spondylitis |
| AST | aspartate aminotransferase |
| AxSpA | axial spondyloarthritis |
| CHAQ | Childhood Health Assessment Questionnaire |
| CHQ | Child Health Questionnaire |
| CRP | C-reactive protein |
| DBL | database lock |
| ECLIA | electrochemiluminescent immunoassay |
| EIA | enzyme immunoassay |
| ERA | enthesitis related arthritis |
| ESR | erythrocyte sedimentation rate |
| ILAR | International League of Associations for Rheumatology |
| ITT | Intent-to-treat |
| JIA | juvenile idiopathic arthritis |
| JPsA | juvenile psoriatic arthritis |
| LTE | long-term extension |
| MSD | Meso Scale Discovery |
| MTX | methotrexate |
| NAbs | neutralizing antibodies |
| nr-AxSpA | non-radiographic axial spondyloarthritis |
| PDCO | Paediatric Committee |
| PIP | Pediatric Investigational Plan |
| pJIA | polyarticular juvenile idiopathic arthritis |
| PK | pharmacokinetic |
| PsA | psoriatic arthritis |
| q4w | every 4 weeks |
| RA | rheumatoid arthritis |
| RF | rheumatoid factor |
| RMP | Risk Management Plan |
| SAE | serious adverse event |
| SC | subcutaneous |
| sJIA | systemic JIA |
| SmPC | Summary of Product Characteristics |
| SOC | system organ class |
| TB | tuberculosis |
| TNFα | tumor necrosis factor alpha |
| UC | ulcerative colitis |
| ULN | upper limit of normal |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen Biologics B.V. submitted to the European Medicines Agency on 7 January 2015 an application for a variation.

The following variation was requested:

| Variation requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I and IIIB |

Update of the SmPC sections 4.2 and 5.1 in order to reflect the data from a multicentre, placebo-controlled, double-blind, randomised-withdrawal, parallel group study (GO KIDS) in children (2 to 17 years of age) with active polyarticular juvenile idiopathic arthritis (pJIA). The Package leaflet is proposed to be updated accordingly. This procedure includes also an update to the RMP.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

### *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0226/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0226/2014 was completed.

The PDCO issued an opinion on compliance for the PIP P/0226/2014.

### *Information relating to orphan market exclusivity*

### *Similarity*

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Scientific advice*

The applicant did not seek Scientific Advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur appointed by the CHMP and the evaluation teams was:

Rapporteur: Kristina Dunder

| Timetable | Actual dates |
|---|---|
| Submission date | 7 January 2015 |
| Start of procedure: | 25 January 2015 |
| CHMP Rapporteur Assessment Report | 27 February 2015 |
| PRAC Rapporteur Assessment Report | 27 February 2015 |
| Committees comments on PRAC Rapp Advice | 5 March 2015 |
| PRAC Rapporteur Updated Assessment Report | 20 March 2015 |
| PRAC Meeting, adoption of PRAC Assessment Overview and Advice | 12 March 2015 |
| CHMP comments | 16 March 2015 |
| 1st Request for supplementary information (RSI) | 26 March 2015 |
| PRAC Rapporteur Assessment Report | 19 October 2015 |
| CHMP Rapporteur Assessment Report | 19 October 2015 |
| Committees comments on PRAC Rapp Advice | 23 October 2015 |
| PRAC Meeting, adoption of PRAC Assessment Overview and Advice | 6 November 2015 |
| CHMP comments | 9 November 2015 |
| 2nd Request for supplementary information (RSI) | 19 November 2015 |
| CHMP Rapporteur Assessment Report | 2 March 2016 |
| PRAC Rapporteur Assessment Report | 2 March 2016 |
| Committees comments on PRAC Rapp Advice | 9 March 2016 |
| PRAC Meeting, adoption of PRAC Assessment Overview and Advice | 17 March 2016 |
| CHMP comments | 21 March 2016 |
| 3rd Request for supplementary information (RSI) | 1 April 2016 |
| PRAC Rapporteur Assessment Report | 2 May 2016 |
| CHMP Rapporteur Assessment Report | 11 May 2016 |
| PRAC Meeting, adoption of PRAC Assessment Overview and Advice | 13 May 2016 |
| CHMP comments | 17 May 2016 |
| Opinion | 26 May 2016 |

# 2. Scientific discussion

## *2.1. Introduction*

Golimumab is a human monoclonal IgG antibody. Golimumab binds to both soluble and transmembrane forms of tumor necrosis factor alpha (TNFα) and inhibits TNFα bioactivity. Other members of this therapeutic class include infliximab, etanercept, adalimumab, and certolizumab pegol. Simponi is currently approved for use in the adult therapeutic indications RA, PsA, AS, nr-AxSpA, and UC.

Juvenile idiopathic arthritis (JIA) refers to arthritis of at least 6 weeks duration of unknown aetiology that begins in children less than 16 years old. JIA has an annual incidence of 0.008-0.226 per 1000 children and a prevalence of 0.07-4.01 per 1000 children. Children of all age groups may be affected although onset during the first year of life is rare and restricted predominantly to systemic JIA.

Rheumatoid arthritis, axial spondyloarthritis (AxSpA), and PsA are diseases in adults that correspond most closely to individual categories of JIA with similar clinical manifestations and underlying immunologic mechanisms (ie, polyarticular JIA, enthesitis related arthritis [ERA], and juvenile psoriatic arthritis [JPsA], respectively).

The Applicant has conducted a Phase 3 clinical study (CNTO148JIA3001 [GO-KIDS]; EudraCT No: 2009-015019-42) to assess the efficacy, safety, pharmacokinetics (PK), and immunogenicity of golimumab in paediatric subjects ≥2 to <18 years of age with polyarticular JIA.

## *2.2. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

The applicant did not submit any environmental risk assessment (ERA) studies in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) which states that proteins are unlikely to result in significant risk to the environment.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

**GCP**

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| Study Type | | | | | |
|---|---|---|---|---|---|
| Study ID<br>EudraCT Number<br>First Patient First Visit / Completion date<br>(day Month year)<br>Study Status | Country(ies):<br>Number of Centers | Phase<br>Study Description/Design,<br>Study Population,<br>Primary Objective(s) | Total Number of Subjects | Study Drug(s):<br>Formulation (Route of Administration)<br>Dose Regimen<br>Duration of Treatment | Number of Subjects Treated<br>(by Treatment Group) |
| **Efficacy and Safety Controlled Clinical Study** | | | | | |
| CNTO148JIA3001<br><br>Synopsis<br><br>2009-015019-42<br><br>1 Dec 2010<br><br>27 May 2014<br><br>Terminated | AUT, BEL, BRA, CAN, FIN, DEU, LTU, MEX, NLD, POL, RUS, USA: 33 | Phase 3<br><br>A multicenter, double-blind, randomized-withdrawal study.<br><br>Pediatric subjects between 2 to less than 18 years of age, with active polyarticular juvenile idiopathic arthritis (pJIA) per JIA ILAR diagnostic criteria for at least 6 months and with onset of disease occurring before the subject's 16th birthday.<br><br>Assess the clinical efficacy of SC administration of golimumab in pediatric subjects (ages 2 to less than 18 years) with pJIA manifested by ≥5 joints with active arthritis despite methotrexate (MTX) therapy for ≥3 months | Planned: 170<br><br>Treated with golimumab: 173 | Single-use, sterile solution in a 1 mL pre-filled syringe (PFS) for subcutaneous (SC) administration<br><br>**Active Treatment (Week 0 Through Week 12):**<br><br>All subjects: SC golimumab 30 mg/m$^2$ every 4 weeks (maximum 50 mg) beginning at Week 0 and continuing through Week 12. Body surface area (BSA) was calculated at each visit and based upon height and weight, the dose of golimumab was adjusted accordingly. In addition, subjects received commercial MTX weekly at the who were still receiving SC placebo at the time of the 48-Week DBL and who were in clinical remission while on medication for JIA were discontinued from the study. BSA was calculated at each visit and based upon height and weight, the dose of golimumab was adjusted accordingly. In addition, subjects received commercial MTX weekly at the same dose as at time of study entry. | Treatment group 1: Golimumab 30 mg/m$^2$ + MTX: 78<br><br>Treatment Group 2: Placebo + MTX: 76 |

Abbreviations: PFS = pre-filled syringe; MTX = methotrexate; pJIA = polyarticular juvenile idiopathic arthritis; ILAR = International League of Associations for Rheumatology; SC = subcutaneous; BSA = body surface area.

## 2.3.2. Pharmacokinetics

In study CNTO148JIA3001 (see Section 2.4.1 for detailed description of the study), samples for the measurement of serum golimumab concentrations were collected at Weeks 0, 4, 8, 12, 16, 20, 24, 48, 72, 96, 120, and 144. For the first 30 subjects in the study, additional PK samples were drawn at Day 4 and Day 15.

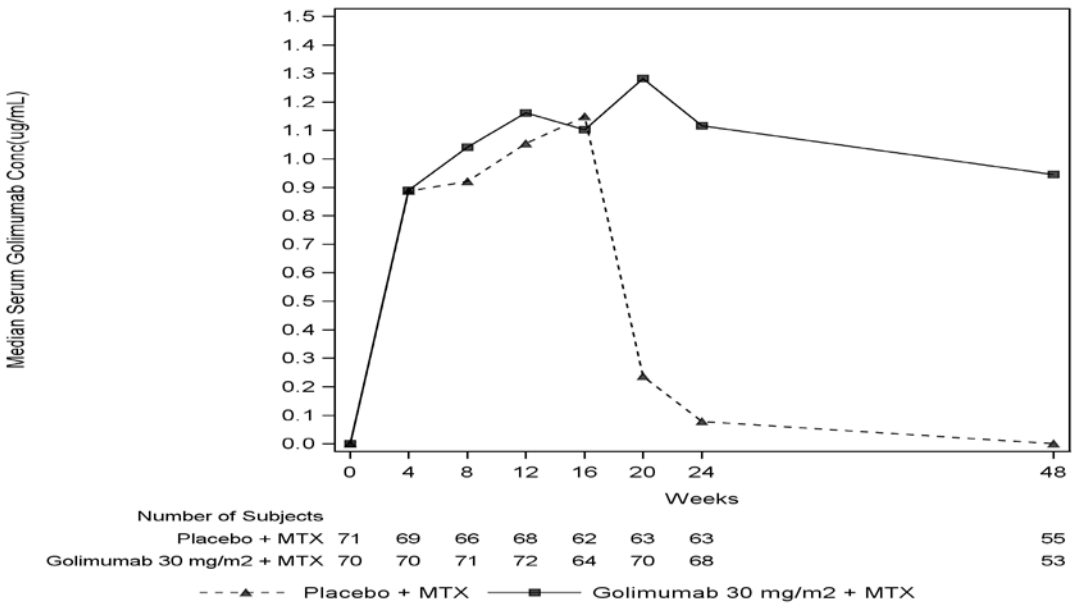
Interim PK analyses including population PK analyses were performed after 30 subjects reached Week 8 (with a pause in enrolment for confirmation of dosing strategy after the 30th subject was enrolled) and after 121 subjects reached Week 16 to evaluate the PK and develop the population PK model.

The Week 8 population PK analysis demonstrated that paediatric subjects had similar mean serum trough golimumab concentrations (ranging from 0.99 to 1.10 µg/mL across 3 age subgroups [2 to 6, ≥6 to 12, ≥12 years] at Week 8). Furthermore, these concentrations in subjects with JIA were also similar to the mean concentrations (0.82 µg/mL at Week 76; 1.17 µg/mL at Week 104) observed in an adult RA population of MTX-inadequate responders who received golimumab 50 mg SC q4w + MTX in the study C0524T06 where the same MSD ECLIA method was used at Weeks 76 and 104 for the measurement of serum golimumab concentrations (results from this study were evaluated during EMEA/H/C/II/0009).

Another interim PK analysis was performed with data from 121 subjects that had completed their Week 16 visit. Serum golimumab concentrations that were observed through Week 8 were maintained through Week 16 and were similar across the age groups as well as across the BMI quartiles.

Median trough golimumab concentrations through Week 48 for the two groups of JIA subjects who were randomized at Week 16 to receive either placebo or golimumab (30 mg/m2 q4w) after the 16-week open-label treatment with golimumab (30 mg/m2 q4w) are presented in **Figure 1**.

**Figure 1.** Median trough serum golimumab concentration (µg/mL) through Week 48; treated subjects who were randomized at Week 16




Median trough concentrations were similarly maintained through Week 144 of the study (data not shown).

Immunogenicity Evaluation

Samples for antibody to golimumab assessment were collected at baseline (Week 0), Week 4, Week 12, Week 24, Week 48, Week 72, Week 96, Week 120, and Week 144 and evaluated with a drug-tolerant EIA method. Subjects who were positive for antibodies to golimumab were further tested for NAbs.

Antibodies to golimumab were detected in 69 (40.1%) of 172 golimumab treated subjects with appropriate samples through Week 48. The majority of the antibody positive subjects had low titers, 38 of 69 subjects had a titer lower than 1:100 and 61 of 69 subjects had a titer lower than 1:1000. The highest titer was 1:3072.

The effect of immunogenicity on PK, efficacy and safety was further evaluated by titer groups. It was found that subjects with positive anti-golimumab antibody status and golimumab titers >1:100 had decreased steady-state trough golimumab levels; however, an apparent reduction in efficacy was not seen until the titers of antibodies to golimumab were >1:1000. In addition, there was no association between positive status for antibodies to golimumab and injection site reactions.

Overall, of the subjects positive for antibodies to golimumab, 25 (38.5%) were positive for NAbs.

## 2.3.3. PK/PD modelling

**Population PK model**

Population pharmacokinetic modelling was performed with the First Order Conditional Estimation method. A one-compartment model with first-order absorption parameterised in terms of apparent clearance (CL/F), apparent volume of distribution (V/F) and the absorption rate constant (ka) was used to describe the time course of serum golimumab concentrations. The inter-individual random effects on the parameters were modelled.

Potential covariate effects evaluated using the Stepwise Covariate Method (SCM) were (i) body weight, age, white blood cell count, serum albumin, C-reactive protein, creatinine clearance, sex and immune response on clearance, and (ii) body weight on volume of distribution.

PK samples for serum golimumab concentration were collected from all subjects in study CNTO148JIA3001 at visits at Weeks 0, 4, 8, 12, 16, 20, 24 and 48. An additional PK sample was collected from all subjects at any time between Weeks 0 and 12 other than the time of the Week 0, Week 4, and Week 8 visits and collected at least 24 hours before or after a study agent injection. For the first 30 subjects in the study, additional PK and CRP samples were obtained on Day 4 and Day 15.

From the 1478 pharmacokinetic observations included in the dataset, 17 (1.15%) duplicate records, 1 (0.07%) pre-dose record, and 358 (24.2%) records below the quantifiable limit (BQL) were excluded from the analysis. After exclusions of the unusable data, there were a total of 1102 pharmacokinetic observations from 169 subjects that were included in the population PK analysis.

Final model parameter estimates and covariate effects are included in Table 2 (see below). All fixed effect parameters were estimated with good precision, with the %RSE less than 19%, except for the estimate of additive residual error which was 54%. Inter-individual random effects were also estimated with good precision, with %RSE less than 25%, with the exception of ka, which was 48.2%. Although the shrinkage for ka, was relatively high (63.2%), it was not found to be an issue since no covariates were evaluated on that parameter.

**Table 1**. Parameter estimates form the population PL model for golimumab

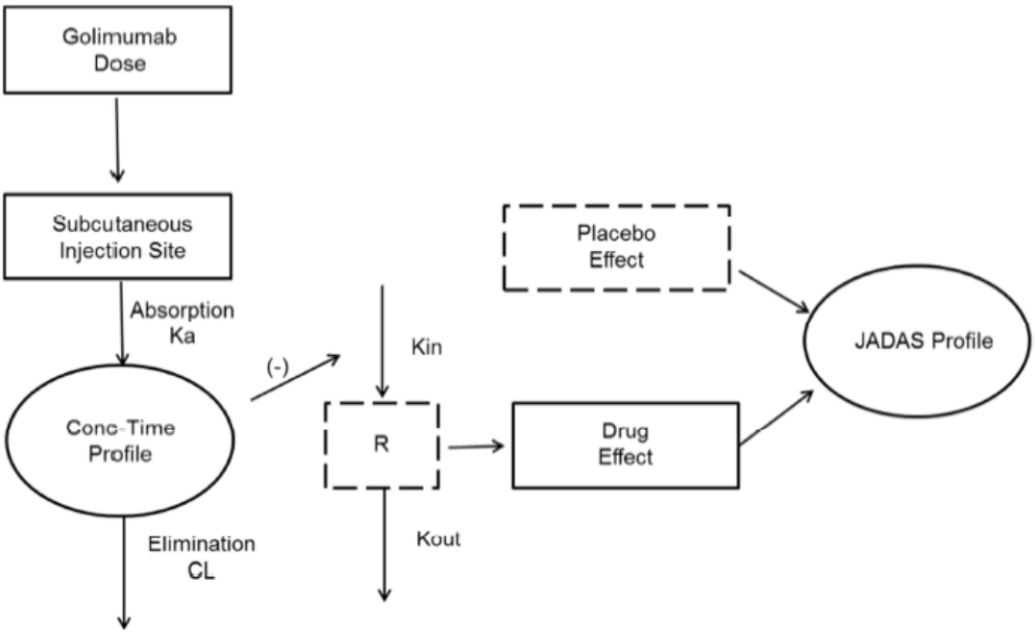
| Parameter | Estimate | Relative SE (%) | BSV (CV%) |
|---|---|---|---|
| $\theta_1$: V/F (L) | 12.2 | 4.10 | 28.7 |
| $\theta_2$: CL/F (L/day) | 0.605 | 3.80 | 31.2 |
| $\theta_3$: $k_a$ (1/day) | 1.02 | 14.9 | 81.2 |
| $\theta_4$: Proportional Residual Error ($\sigma$) | 0.259 | 10.1 | |
| $\theta_5$: Additive Residual Error ($\sigma$, µg/mL) | 0.0466 | 54.0 | |
| $\theta_6$: Serum Albumin at Baseline~CL/F | -1.57 | 16.8 | |
| $\theta_7$: Immune Response Status~CL/F | 0.308 | 18.5 | |
| $\theta_8$: Body Weight~CL/F | 0.889 | 6.60 | |
| $\theta_9$: Body Weight~V/F | 1.09 | 7.90 | |
| | | | Shrinkage (%) |
| $\omega^2$: V/F | 0.083 | 24.7 | 38.6 |
| $\omega^2$: CL/F | 0.098 | 19.2 | 10.1 |
| $\omega^2$: V/F~CL/F[a] | 0.049 | 1.60 | |
| $\omega^2$: $k_a$ | 0.659 | 48.2 | 63.2 |
| [a]Correlation between random effects of V/F~CL/F = r = 0.54 | | | |

Based on the estimated parameters of the final model, a subject with body weight corresponding to the 10th percentile (16 kg) of the population in the PK analysis would be expected to have CL/F and V/F values that are 39% and 32%, respectively, than those of a subject with median body weight of 46 kg. Conversely, CL/F and V/F in a subject with body weight at the 90th percentile (67 kg) are predicted to be 39% and 51% higher than that of a subject with median body weight, respectively.

**Exposure-response model**

An analysis of Juvenile Arthritis Disease Activity Score (JADAS) response in paediatric patients with juvenile idiopathic arthritis receiving 30 mg/m2 SC golimumab q4w was performed using an indirect response population PK/PD model. Data for this analysis were obtained from study CNTO148JIA3001, which was a randomized withdrawal study in children aged 2 to less than 18 years. The individual PK parameters obtained from the final population PK model were then used to describe each subject's full PK profile, which was used as a driver for the JADAS PK/PD model. The natural log of the raw JADAS scores was the dependent variable for the analysis.

The semi-mechanistic PK/PD model used to characterize the time course of log-transformed JADAS scores is illustrated in the figure below.




The final PK/PD model for log-transformed JADAS had between-subject variability terms on Kout, Pmax, and IC50. No covariate effects were found to be statistically significant during testing.

Visual predictive checks were in good agreement with the observed data for all treatment groups with the exception of the non-responders that withdrew after Week 16. The VPCs of the non-responders at Week 16 were based on a small number of subjects (19 out of 173 subjects, 11%), which makes the interpretation of VPC quality difficult in the group of non-responders.

From the Juvenile Arthritis Disease Activity Score (JADAS) PK/PD analysis using the M3 model for the PK characterization, the golimumab concentration required for a typical individual to reach EC50 was 0.412 ug/mL. The calculated EC80 and EC90 for a typical individual were 1.648 ug/mL and 3.708 ug/mL.

The percentage of patients with a steady state average plasma concentration (Css,av) above EC50, EC80 and EC90 was derived from the PKPD model of JADAS. Approximately 91% of the patients <40 kg (receiving BSA-based dose) and 76% of the patients ≥ 40 kg (receiving a fixed 50 mg dose) had a Css,av > EC80. The corresponding percentages for Css,av > EC90 were approximately 22% and 12% for the <40 kg and ≥ 40 kg groups, respectively. The difference is likely to be a result of individualized dosing (BSA based) vs. fixed dosing rather than an effect of the actual body weight.

**Exposure simulations**

The final population PK model was used to perform simulations in order to evaluate steady-state area-under-the-curve (AUCss) and minimum golimumab concentration (Cmin,ss) in paediatric subjects resulting from the proposed golimumab dose regimens of:

- 30 mg/m2 q4wk in children weighing < 40 kg.
- 50 mg q4w in children weighing ≥ 40 kg.

The impacts of age, weight, and dose rounding on exposure were explored by simulating the following paediatric populations:

- Age: 2-5 years, 6-11 years, 12-17 years, and all pediatrics.
- Weight: <40 kg, ≥40 kg, and all pediatrics.

For purposes of comparison, exposures in lighter weight adults receiving golimumab 50 mg q4w were also simulated for the following populations: weight <60 kg and weight <80 kg.

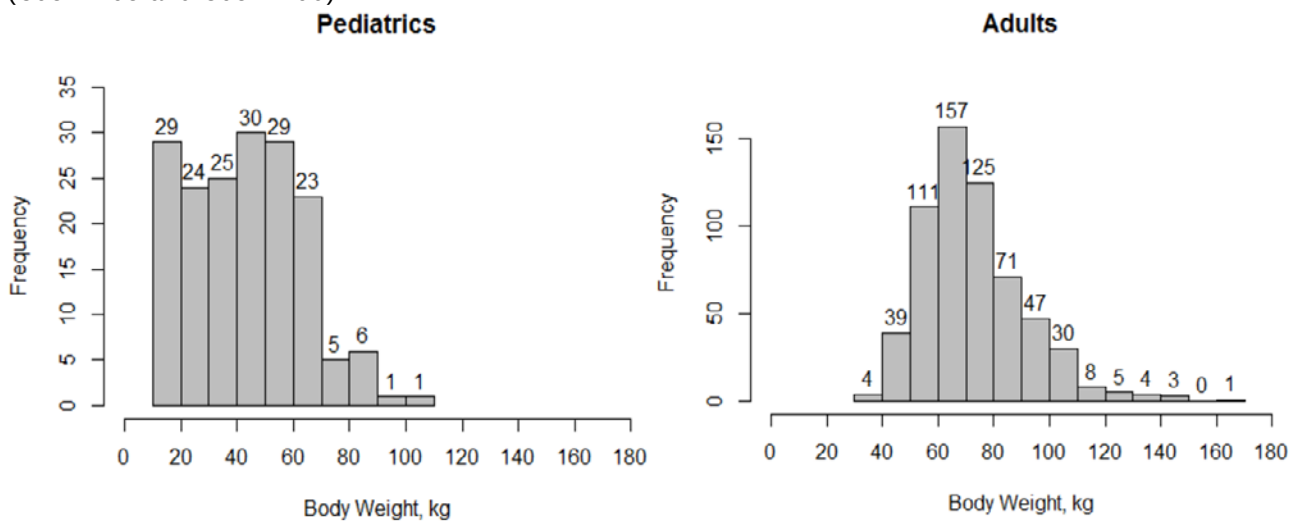
All simulation cohorts (scenarios) were comprised of 1000 simulated subjects. Height and weight values for simulated paediatric subjects were sampled from CDC growth chart data using the following scheme:

- Age records within the growth chart tables were sampled with replacement.
- Within each age record, height and weight values were sampled from a normal distribution with mean equal to the median reported in the table and standard deviation (SD) imputed from table values for median and 75th percentile (Q75) using the following formula: SD = (Q75 – median)/Z75, where Z75 is the 75th percentile of a standard normal distribution.

Values for serum albumin in simulated pediatric subjects were sampled with replacement from the baseline values from all 173 pediatric subjects who participated in Study CNTO148JIA3001.

This approach was deemed appropriate following exploration of the available paediatric demographic data, which did not reveal any appreciable correlation between albumin and other covariates of interest. All demographic data for simulated adult subjects was sampled with replacement from the demographic data from Studies C0524T05 and C0524T06 (initially submitted and evaluated through EMEA/H/C/000992/II/0055), which were contributed by a total of 279 subjects. Originally only demographic data from C0524T06 were planned; however, C0524T05 was included to increase the numbers of adults with lower body weights for comparison to the paediatric population. Body weight data from studies C0524T05 and C0524T06 were used to compare the exposure of paediatrics and adults with body weight <60kg as well as <80kg. The body weight distributions of the paediatrics and adults used in the simulations are shown in (**Figure 2**).

**Figure 2**. A histogram of body weight distributions of the paediatrics (CNTO148JIA3001) and adults (C0524T05 and C0524T06)




Individual values for AUCss were computed from the simulation output using the individual dose and clearance values for each simulated subject (AUCss = Dose/CL). Simulated trough concentrations at Week 48 were used as estimates of Cmin,ss. These derived PK parameters were then displayed as side-by-side box-and-whisker plots for all simulation scenarios (**Figures 3** and **4**). Bold lines are

drawn at data medians. Box edges are drawn at the medians of the upper and lower halves of the data. Whiskers are drawn at the most extreme observations to fall within 1.5x the interquartile range.

**Figure 3.** Boxplots of simulated Cmin,ss values in paediatric subjects by weight category with adult reference populations.

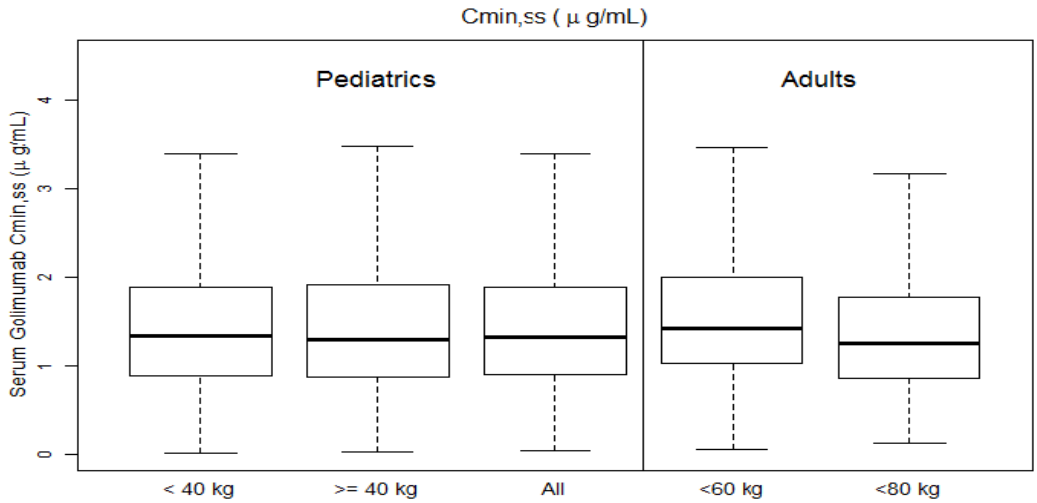
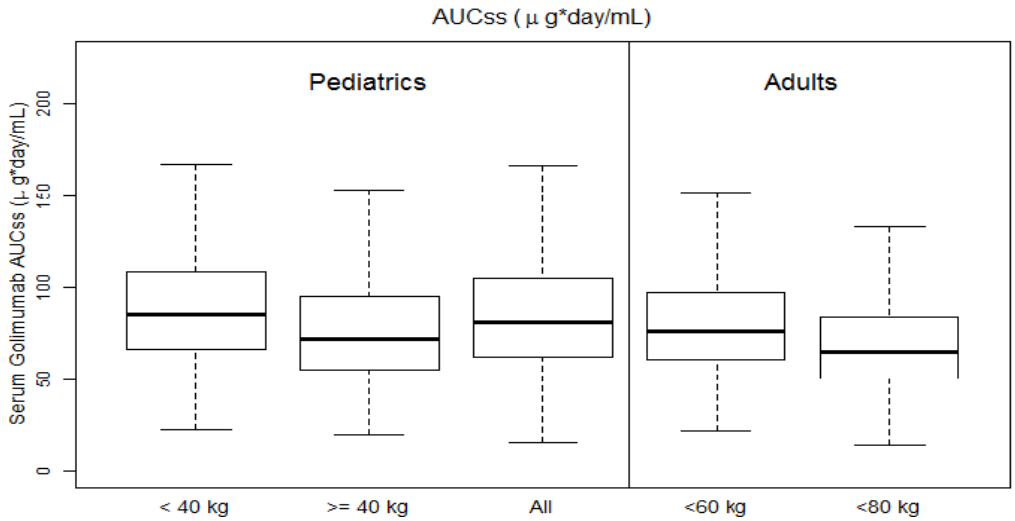



**Figure 4**. Boxplots of simulated AUCss values in paediatric subjects by weight category with adult reference populations. Bold lines are drawn at data medians.




Due to the large number of pharmacokinetic observations below the quantification limit and in order to minimise the risk of BQL-induced bias in parameter estimates and facilitate evaluation of non-linear PK, the Applicant submitted an updated model in which the M3 method (Bergstrand et al., 2009) was applied handle the BQL data. Boxplots from this updated model are presented in **Figures 5**, **6, 7** and **8**.

**Figure 5**: Boxplots of simulated Cmin,ss values in paediatric subjects by age group with adult reference populations (M3)

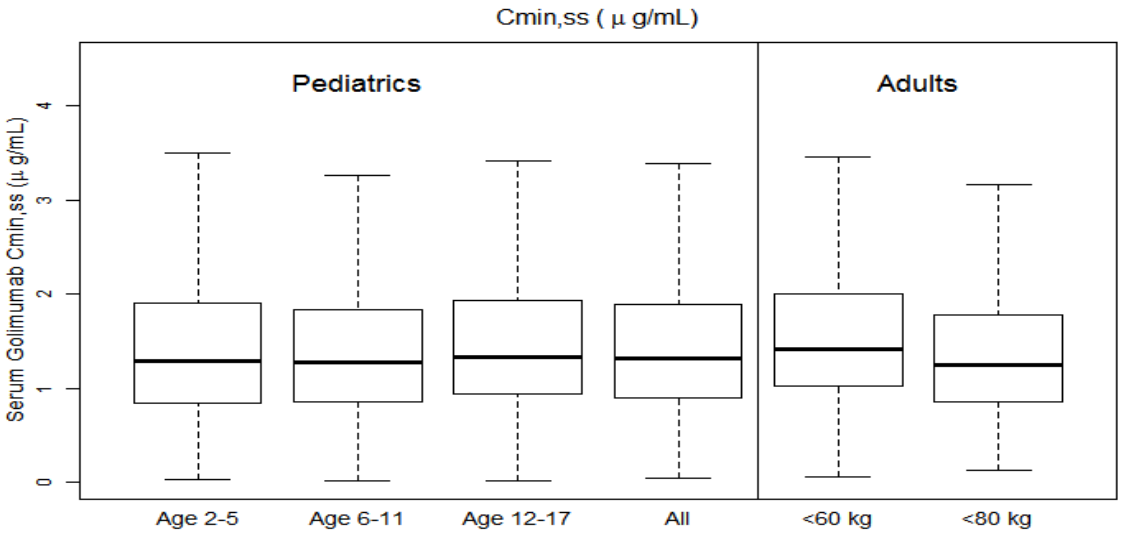



**Figure 6.** Boxplots of simulated AUCss values in paediatric subjects by age group with adult reference populations (M3)

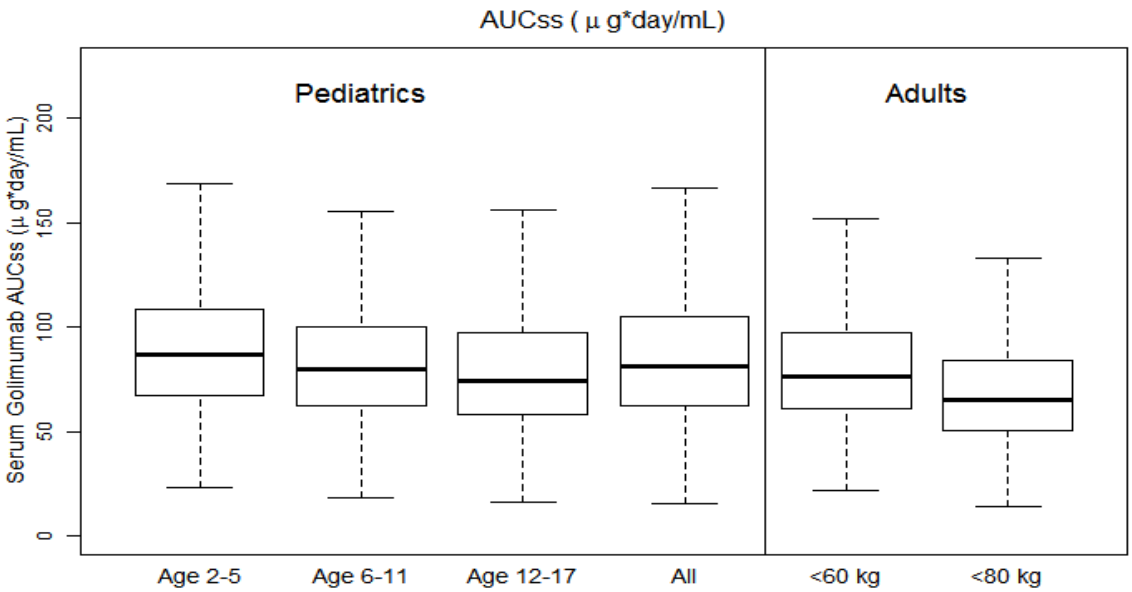


**Figure 7**: Boxplots of simulated Cmin,ss values in paediatric subjects by weight category with adult reference populations (M3)

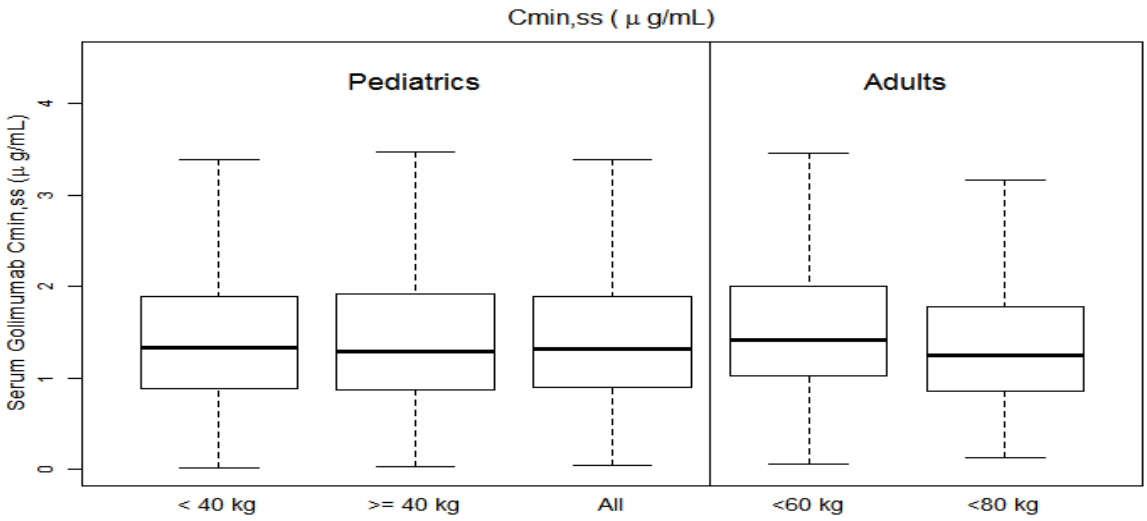
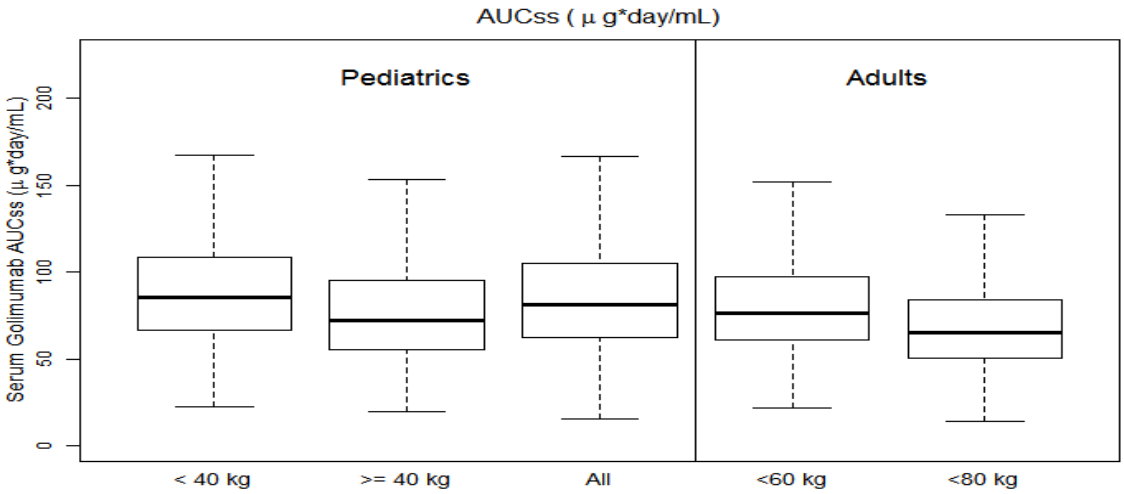



**Figure 8.** Boxplots of simulated AUCss values in paediatric subjects by weight category with adult reference populations (M3)

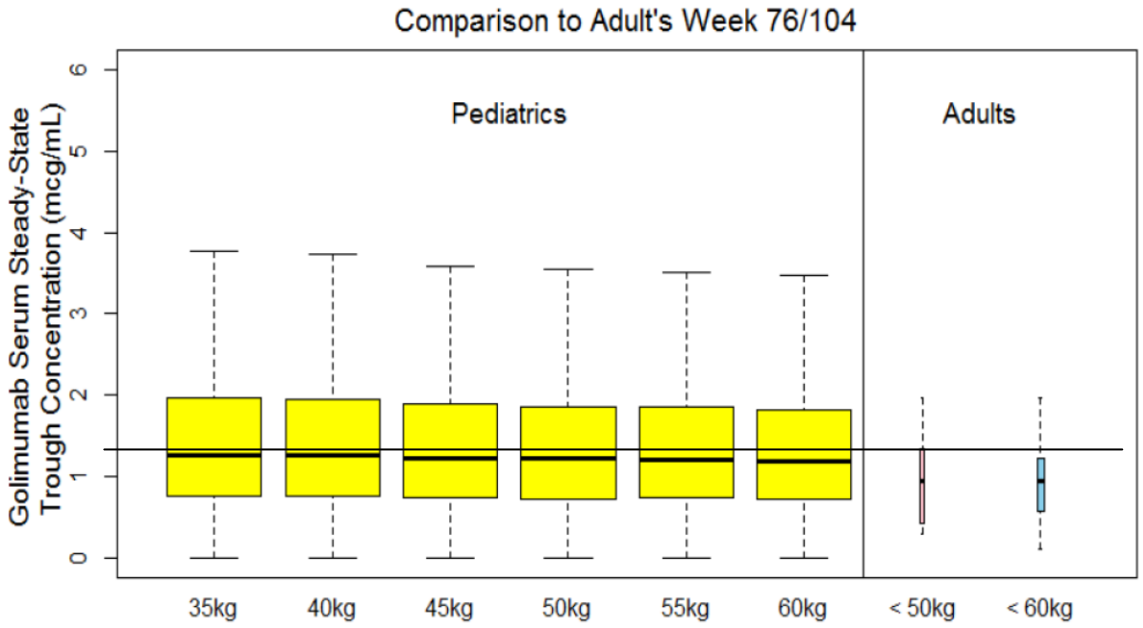



To further support the weight cut-off selection with historical adult data for the dosing posology of golimumab in pJIA, PK simulations to evaluate the effect of various weight cut-offs were performed, which were then compared with historical adult exposures from study C0524T06 to optimize the weight cut-off selection.

For the historical adult exposure, the previously established adult RA population PK model could not be used for comparison with the pJIA data since golimumab concentrations through Week 24 for the corresponding adult RA study (C0524T06) were evaluated with a different assay platform compared to that used in study CNTO148JIA3001. Therefore, observed trough concentrations from study C0524T06 at Week 76 and Week 104 were used because these concentrations were measured using the same platform as in study CNTO148JIA3001. The data at Week 76 and Week 104 were combined since both values were at steady-state. In addition, the data from the 50 mg q4w and 100 mg q4w treatment arms were included in order to increase the pool of observed historical adult trough concentrations with body weight <50 kg and <60 kg. Since golimumab PK is approximately dose proportional, the exposure from the 100 mg q4w was divided in half for combination with data from the 50 mg q4w treatment group. Of note, the sample size from the adult historical data was low (<50kg: n = 13; <60kg: n = 49).

Target exposure distributions were evaluated by comparing the resulting overall paediatric steady-state trough serum golimumab concentrations of 10,000 paediatric virtual subjects by various weight cut-off values with the distribution of the historical adult target exposures (**Figure 9**).

**Figure 9.** Comparison of Simulated Paediatric and Observed Adult Steady-state Trough Serum Golimumab Concentrations (Grouped by Cut-off Scenario)




## 2.3.4. Discussion on clinical pharmacology

For subjects with JIA who received golimumab 30 mg/m2 q4w throughout the study, median trough golimumab concentrations at Week 12, Week 24, and Week 48 were 1.16, 1.12, and 0.95 µg/mL respectively. Steady-state trough golimumab levels in JIA subjects at 30 mg/m2 q4w SC were similar across different age groups (2 to 6, ≥6 to 12, ≥12 years), body weight quartiles, BMI quartiles and body weight categories and were also similar to or slightly higher than those seen in adult subjects who received 50 mg SC golimumab q4w.

Median trough on active treatment golimumab concentrations were maintained over time for subjects who continued on active treatment. Conversely for subjects who were randomized to placebo at Week

16 these quickly dropped to low concentrations. Since placebo subjects switched to golimumab upon disease flare, detectable low golimumab concentration at Weeks 24 and 48 were expected in this group of subjects.

The population PK analysis at Week 8 confirmed that the dosing strategy was adequate and enrolment in the study recommenced. The Week 16 population PK analysis was considered appropriate for characterizing the population PK and confirming the dosing strategy for SC golimumab in JIA.

To further support the rationale of selecting of 40 kg as the body weight cut-off for children to transition from BSA based dosing to the adult fixed dose of 50 mg every 4 weeks the MAH also provided a comparison of simulated exposure for different values for the body weight cut-off (35 kg to 60 kg in steps of 5 kg). Regardless of weight cut-off, the medians and range were very similar or slightly higher than the historical observed adult data and were well within the observed paediatric data seen in study CNTO148JIA3001. Comparison of the medians and difference from the adults for the 40 and 45 kg weight cuts showed that the 40 kg cut-off would have a 34% difference from the historical adult data while the 45 kg weight cut-off would have a 30% difference. However, the precision of these estimations is limited due to the small sample size for the historical adult target exposure distributions.

Exposure data in adults was considered to be comparable to that in children, especially as this comparison was based on historical PK data in adult patients which were generated with the same bioassay as the paediatric data. However, as a presentation that can be dosed per body area is not yet available, use of the product in pJIA will be limited to the population that can use the currently available formulation i.e. children with a body weight of at least 40 kg.

The PKPD analysis of ACR was not considered sufficient to draw conclusions about exposure-response. Instead, the PKPD model of Juvenile Arthritis Disease Activity Score (JADAS) constitutes the support for claims of efficacy and dosing regimen in children with pJIA weighing at least 40 kg. The posology is considered adequate based on simulations of the proportion of patients that achieve mean exposure above the modeled EC50.

Higher incidences of antibodies to golimumab were expected with the new drug-tolerant EIA method compared to the previous EIA method due to the high sensitivity and improved drug tolerance of the new method. This was also observed in the adult RA C0524T06 study where results from the original EIA and the drug-tolerant EIA methods were compared.

The overall incidence of antibodies to golimumab in JIA subjects was 40.1% (69 of 172 subjects) when using a newly developed drug-tolerant immunoassay which was highly sensitive in detecting low titer/weak immunogenic responses. Positive antibody to golimumab status decreased steady-state trough levels when titer levels were >1:100; however, the effect of ADA on efficacy was less sensitive requiring titers >1:1000 in order to show apparent efficacy reduction. Due to the low numbers of subjects with high titers, there was no overall effect of antibodies to golimumab on efficacy or safety and therefore does not represent any new safety signal.

### 2.3.5. Conclusions on clinical pharmacology

The results indicate that the PK profile of golimumab in adult patients is similar to that in children with JIA. Considering the effect of weigh on exposure, the proposed used of golimumab in children with a body weight of 40 kg or more is considered appropriate.

## *2.4. Clinical efficacy*

### 2.4.1. Main study

#### *CNTO148JIA3001*

A Multicentre, Double-Blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab, a Human Anti-TNFα Antibody, in Paediatric Subjects with Active Polyarticular Course Juvenile Idiopathic Arthritis (pJIA) Despite Methotrexate Therapy (GO KIDS).

***Methods***

***Study participants***

Main inclusion criteria

1. Paediatric subject ages 2 to less than 18 years of age. Age must not be a factor in the ability to continue follow-up with the investigator through the end of the study.

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

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

3. Disease duration of at least 6 months before study entry.

4. Must have ≥ 5 joints with active arthritis as defined by ACR criteria.

5. Active JIA despite current use of oral, intramuscular or subcutaneous methotrexate (for ≥ 3 months before screening) at a weekly dose of ≥10 mg/m2. Subjects currently on MTX (weekly 10 to 30 mg/m2), must receive a stable dose of methotrexate for ≥ 4 weeks before screening. Subjects with BSA≥1.67 m2 must receive a minimum of 15 mg/week of MTX.

6. If using corticosteroids; must be on a stable dose of ≤10 mg prednisone equivalent or 0.20 mg/kg/day (whichever is less) for ≥4 weeks before first administration of study agent. If currently not using corticosteroids, the subject must have not received corticosteroids for at least 4 weeks before the first dose administration.

7. If using NSAIDs, must be on a stable dose for ≥2 weeks before the first administration of study agent. If not currently using NSAIDs, the subject must not have taken them for at least 2 weeks before the first administration of study agent.

Main exclusion criteria

1. Have known allergies, hypersensitivity, or intolerance to golimumab or other immunoglobulins or its excipients.

2. Are pregnant or breast-feeding, or planning a pregnancy or fathering a child within 6 months after the last study agent administration.

3. Have a past history of macrophage activation syndrome (MAS).

4. Have received an investigational drug (including vaccines) or used an investigational medical device within 3 months or 5 half-lives, whichever is longer, before the planned start of treatment or are currently enrolled in an investigational study.

5. Have initiated DMARDS and/or immunosuppressive therapy within 4 weeks prior to study initiation.

6. Have other inflammatory disease that might confound the evaluation of benefit from golimumab therapy, including but not limited to systemic lupus erythematosus or Lyme disease.

7. Are incapacitated, largely or wholly bedridden, or confined to a wheelchair, or have little or no ability for age-appropriate self care.

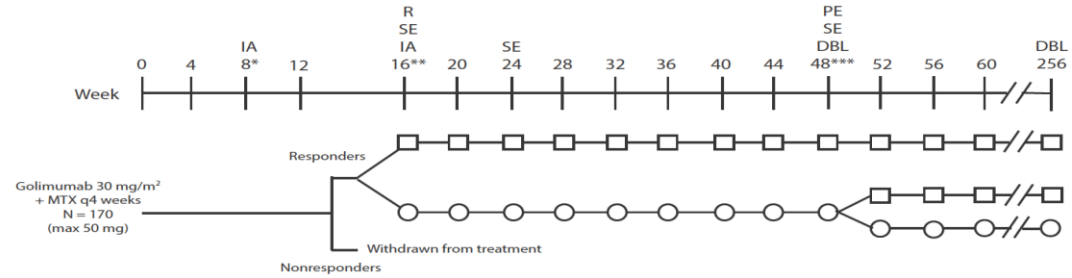
8. Have been treated with intra-articular, intramuscular or intravenous corticosteroids (including intramuscular corticotropin [ACTH]) during the 4 weeks before first study agent administration.

***Treatments***

All subjects received SC golimumab 30 mg/m2 (maximum 50 mg) q4w + MTX in the active treatment portion of the study from Week 0 through Week 12, followed by randomisation of ACR Ped 30 responders at Week 16 to receive placebo + MTX or golimumab 30 mg/m2 (maximum 50 mg) + MTX. The primary study was through Week 48.

The study design and timelines of study CNTO148JIA3001 is depicted in **Figure 10**.

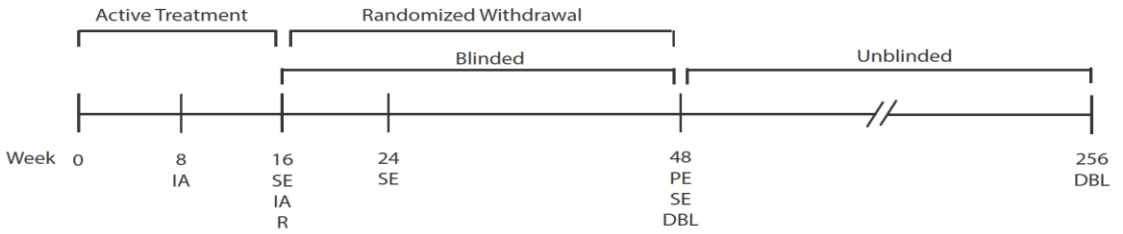
**Figure 10.** Study design and timeline of study CNTO148JIA3001




R = Randomization
PE = Primary Endpoint
IA = Interim Analysis
DBL = Database Lock
SE = Secondary Endpoint
□ = 30 mg/m² + MTX
○ = Placebo + MTX

Note: Upon flare of disease symptoms, subjects receiving placebo may restart golimumab treatment [30 mg/m²] at the discretion of the investigator

* One separation interim analysis will be performed after 30 subjects have enrolled in the study.
** One interim analysis will be performed after 120 subjects have enrolled in the study.
*** Unblinding will occur after all subjects have reachedWeek 48 and the database has been locked. Subjects receiving SC placebo at the time of the 48-Week DBL who are in clinical remission will be discontinued from the study.




R = Randomization IA = Interim Analysis SE = Secondary Endpoint
PE = Primary Endpoint DBL = Database Lock

***Objectives***

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

The secondary objectives of this study were to evaluate golimumab in paediatric subjects with JIA with respect to:

- Safety
- Physical function
- Quality of life
- Disease activity status over time
- Pharmacokinetics and immunogenicity
- Pharmacodynamics

***Outcomes/endpoints***

The primary endpoint is the proportion of subjects who were American College of Rheumatology Paediatric (ACR Ped) 30 responders at Week 16 and did not experience a flare of disease between Week 16 and Week 48.

**ACR Ped 30, 50, 70 and 90 responses**

ACR Ped response and flare of disease are composite endpoints measured by the 6 paediatric ACR categories. These are as follows:

- Physicians global assessment of disease, (Visual Analogue Scale, 0-100mm)
- Subject/parent global assessment of overall wellbeing, (Visual Analogue Scale, 0-100 mm)
- Number of active joints (defined as either swelling, or in absence of swelling, limited range of motion associated with pain on motion or tenderness), (0-73)
- Number of joints with limited range of motion, (0-69)
- Physical function by Childhood Health Assessment Questionnaire (CHAQ, 0-3)
- Erythrocyte Sedimentation Rate (ESR, performed at site), (unit = mm/h)

ACR Ped 30 response is defined as ≥30% improvement from baseline in at least 3 of the 6 components with worsening of 30% or more in no more than 1 of the above noted components.

ACR Ped 50, 70 and 90 responses are also defined as 50%, 70%, and 90% improvement respectively in a minimum of three core set criteria with worsening of one variable by no more than 30%.

ACR Ped 30, 50, 70 and 90 were also assessed throughout the open-label phase of the study.

**Flare of Disease**

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

- ≥30% worsening in at least 3 of the 6 ACR PED components and ≥30% improvement in not more than 1 of the 6 ACR response components from Week 16.
- If the Physician or Subject/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.
- If ESR was used in flare definition, the worsening in ESR had to be to a level above the upper limit of normal (ULN, 20 mm/h). If CRP was used in flare definition, the worsening in CRP had to be to a level above the ULN, 1.0 mg/dL or 10 mg/L.

Flare was assessed at each visit or reported at an unscheduled visit. Therefore, it was possible for a subject to have multiple flares over time. For flare of JIA disease determination prior to Week 16 study agent administration, the baseline was the value measured at Week 0. After Week 16 study agent administration, the baseline for flare of disease calculation was the measurement at Week 16. Baseline for observed ACR Ped response calculations were the component measurements at Week 0.

A subject was considered to have a flare of disease if there was at least one occurrence of flare of disease (as defined above) anytime between Week 16 and Week 48.

There were 3 major secondary endpoints. The major secondary analyses in order of importance are as follows:

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

**Inactive disease**

Inactive disease was defined as the presence of all of the following:

1. No joints with active arthritis;
2. No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA;
3. No active uveitis;
4. Normal erythrocyte sedimentation rate (ie, <20 mm/hour[h]) or CRP (<1.0 mg/dL or <10 mg/L),
5. Physician Global Assessment of disease activity indicating no active disease (≤5 mm on the VAS).
6. Duration of morning stiffness <15 minutes.

***Sample size***

Power calculations were performed using a chi-squared test with flare of JIA disease as the response variable and treatment group as the dependent variable. Assuming 65% and 37% of subjects experienced a flare of disease from Week 16 through Week 48 for the placebo + MTX, and 30 mg/m2 + MTX treatment groups respectively, 134 subjects who were responders at Week 16 (67 subjects from each treatment group) would be required to enter the randomized withdrawal portion of the study to obtain 90% power to detect a significant difference between treatment groups. These percentages of disease flares were observed in the adalimumab study in juvenile rheumatoid arthritis (JRA).
In addition, the power arising from different randomization ratios of subjects entering the randomized withdrawal portion of the study was also examined. There was no marked difference in power based on the results observed.

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

Recruitment was stopped when 30 subjects were enrolled. When these 30 subjects reached Week 8, interim analyses for PK (including the population PK analyses), efficacy and safety were performed; if more than 8 of the first 30 subjects enrolled in the study were ACR Ped 30 responders at Week 8 and the PK analyses confirmed the dosing strategy, the study was permitted to continue.

After approximately 120 subjects completed the Week 16 visit, another interim analysis was performed. The response rate of subjects at Week 16 was evaluated to ensure the likelihood that at least 134 subjects would participate in the randomized withdrawal portion of the study. To qualify for randomized withdrawal, subjects had to be ACR Ped 30 responders at Week 16. Subjects with a transient worsening of clinical status between Weeks 0 and 16 and not requiring changes in their concomitant medications could still qualify for randomization at Week 16 if they were ACR Ped 30 responders at Week 16

***Randomisation and blinding***

At Week 16, subjects who achieved an ACR Ped 30 response were randomized in a 1:1 ratio in a

blinded fashion to 1 of 2 treatment groups:

Golimumab: Subjects received golimumab 30 mg/m2 SC injection (maximum 50 mg) at Week 16, and q4w thereafter through Week 48. Subjects also received commercial MTX weekly at the same numerical (mg/week of MTX) dose as at the time of study entry.

Placebo: Subjects received placebo as a SC injection at Week 16 and q4w thereafter through Week 48 unless they experienced a flare of disease at which time golimumab 30 mg/m2 SC injections (maximum 50 mg) were resumed. Subjects also continued to receive commercial MTX weekly at the same numerical (mg/week of MTX) dose as at the time of study entry.

For subjects receiving placebo at the time of a flare of disease, treatment with golimumab 30 mg/m2 q4w was reinitiated at the next scheduled visit. For subjects receiving golimumab 30 mg/m2 at the time of a flare of disease, the golimumab dose did not change.

Subjects were planned to continue active treatment after Week 48 in the LTE until Week 248, with follow-up through Week 256. At Week 48, subjects who received placebo + MTX who were not in clinical remission while on medication for JIA were to begin receiving golimumab 30 mg/m2 SC in a blinded fashion. After the Week 48 DBL and site unblinding, investigators were to begin administering golimumab 30 mg/m2 SC to subjects receiving SC placebo who were not in clinical remission. After the Week 48 DBL and site unblinding, subjects who were still receiving SC placebo and who were in clinical remission while on medication for JIA, were to be discontinued from the study.

**Statistical methods**

All efficacy analyses were based on an intent-to-treat (ITT) principle. Therefore, the efficacy data for each subject were analysed according to the assigned treatment regardless of the actual treatment received. To maintain the Type I error rate among the primary and major secondary endpoints, the endpoints were tested sequentially.

The data handling rules for the ITT population include LOCF (last observation carried forward) of partial data, non-responder imputation of completely missing data, and treatment failure rules.

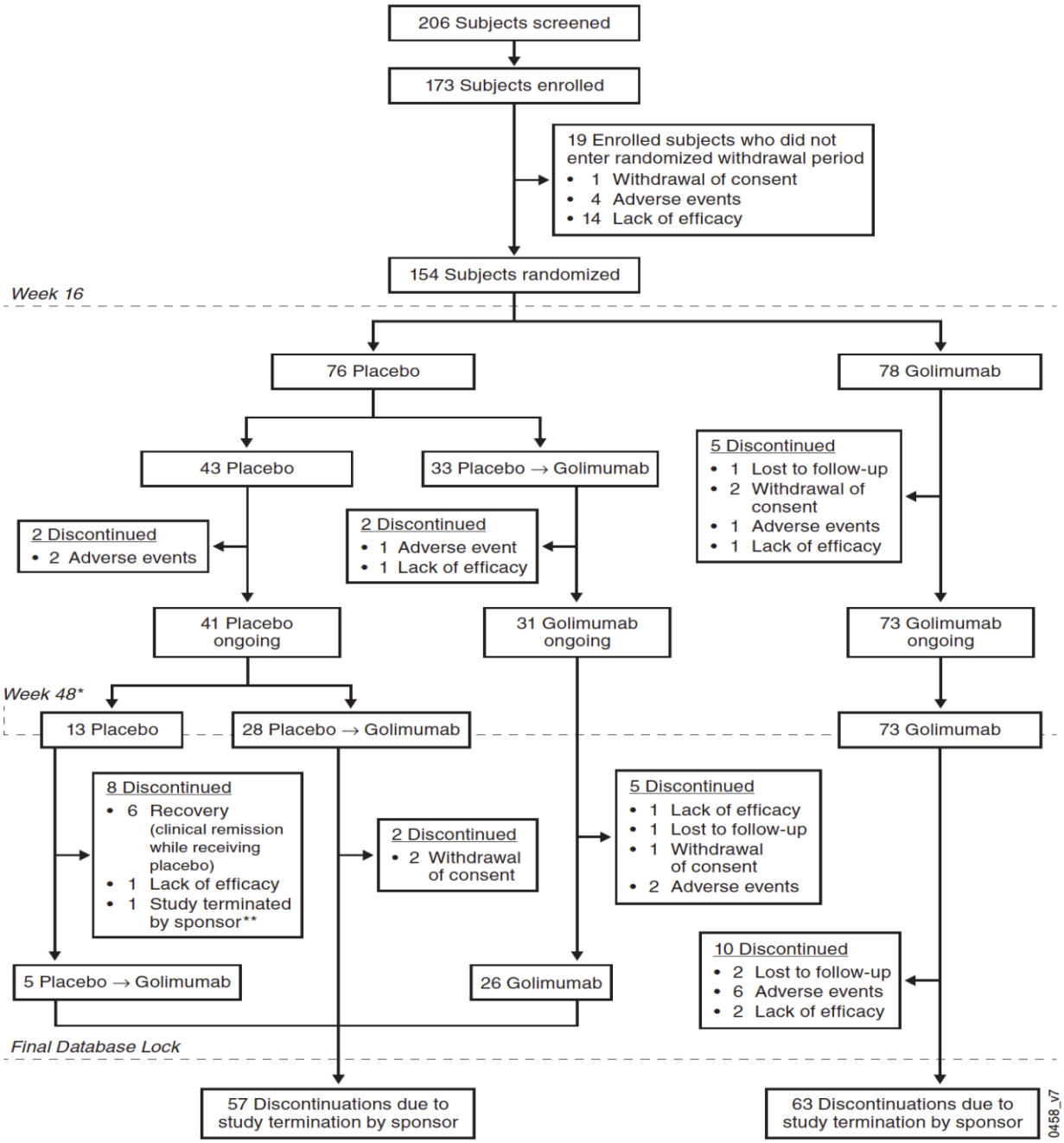
For subjects who were terminated due to the Applicant decision, no data imputation was performed after the termination date.

In addition to the ITT analyses, after the Week 48 DBL, selected efficacy data was also summarized using observed data alone, without any data manipulation. No imputation was performed when data was missing.

Safety, PK and immunogenicity data were summarized for all subjects who received at least one (full or partial) administration of study agent.

***Results***

**Participant flow**




* 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.

At Week 0, 173 subjects enrolled and received golimumab + MTX, and by Week 16, 19 subjects discontinued the study. Of the 154 remaining subjects, 78 subjects were randomized to golimumab + MTX, and 76 subjects were randomized to placebo + MTX at Week 16 (**Table 2**).

Per protocol, subjects who experienced a flare of disease while receiving placebo could resume golimumab 30 mg/m2 SC injections (maximum 50 mg), and of the 76 subjects in the placebo + MTX group, 44 (57.9%) remained on placebo + MTX and 32 (42.1%) received golimumab + MTX for flare. One subject in the placebo + MTX group received golimumab 30 mg/m2 + MTX, but never flared.

**Table 2.** Number of subjects through Week 48 by study treatment assigned vs study treatment received; randomised subjects

| | Golimumab Administered Prior to Randomization at Week 16 | | |
|---|---|---|---|
| | Placebo + MTX | | |
| | Placebo + MTX | Placebo + MTX → Golimumab 30 mg/m$^2$ + MTX | Golimumab 30 mg/m$^2$ + MTX |
| Subjects randomized | 44 | 32 | 78 |
| Subjects treated | 44 | 32 | 78 |
| Treatment received | | | |
| Placebo + MTX | | | |
| Placebo + MTX only | 43 (97.7%) | 0 | 0 |
| →Golimumab 30 mg/m$^2$ | 1 (2.3%) | 32 (100.0%) | 0 |
| Golimumab 30 mg/m$^2$ + MTX | 0 | 0 | 78 (100.0%) |

***Recruitment***

The study was conducted at 33 sites globally and enrolled 173 subjects. For this report, data were locked at Week 48.

The study was planned to continue to Week 256; however, the primary and major secondary efficacy endpoints at Week 48 were not met, and the applicant decided to discontinue the study prematurely. The last dose of study agent was administered on 31 Mar 2014, and the last subject last visit was 27 May 2014. Of the 154 subjects randomized at Week 16, 121 (78.6%) remained in the study until it was prematurely discontinued by the Applicant on 31 Mar 2014. At the time of study discontinuation, 129 subjects had completed through Week 96, 1 subject had completed through Week 168, and no subjects completed the final Week 256 assessment.

***Conduct of the study***

There were 9 amendments to the protocol. None of these protocol amendments impacted the validity of the study results.

97 subjects had protocol deviations, categorized as follows:

- Entered study, but study entry criteria not met: 18 (10.4%)
- Met study withdrawal criteria, but not withdrawn: 1 (0.6%)
- Received wrong treatment or incorrect dose: 9 (5.2%)
- Received disallowed concomitant treatment: 3 (1.7%)
- Other: 85 (49.1%)

The number of deviations was balanced across the combined placebo + MTX and golimumab + MTX groups (data not shown).

***Baseline data***

Demographic characteristics of enrolled subjects at baseline are presented in **Table 3**.

**Table 3.** Summary of demographics at baseline in study CNTO148JIA3001

| | | Golimumab Administered Prior to Randomization at Week 16 | | | |
|---|---|---|---|---|---|
| | Enrolled Subjects Who Did Not Enter Randomized Withdrawal Period | Placebo + MTX | Golimumab 30 mg/m$^2$ + MTX | All Randomized Subjects | All Enrolled Subjects |
| Subjects enrolled | 19 | 76 | 78 | 154 | 173 |
| Sex | | | | | |
| N | 19 | 76 | 78 | 154 | 173 |
| Male | 4 (21.1%) | 19 (25.0%) | 19 (24.4%) | 38 (24.7%) | 42 (24.3%) |
| Female | 15 (78.9%) | 57 (75.0%) | 59 (75.6%) | 116 (75.3%) | 131 (75.7%) |
| Race | | | | | |
| N | 19 | 76 | 78 | 154 | 173 |
| Black | 0 | 0 | 2 (2.6%) | 2 (1.3%) | 2 (1.2%) |
| Caucasian | 17 (89.5%) | 67 (88.2%) | 68 (87.2%) | 135 (87.7%) | 152 (87.9%) |
| Other | 2 (10.5%) | 9 (11.8%) | 8 (10.3%) | 17 (11.0%) | 19 (11.0%) |
| Age (yrs) | | | | | |
| N | 19 | 76 | 78 | 154 | 173 |
| Mean (SD) | 11.8 (4.40) | 11.1 (4.51) | 11.1 (4.43) | 11.1 (4.46) | 11.2 (4.44) |
| Median | 12.0 | 12.0 | 11.5 | 12.0 | 12.0 |
| IQ range | (9.0; 16.0) | (7.5; 15.0) | (8.0; 15.0) | (8.0; 15.0) | (8.0; 15.0) |
| Range | (2; 17) | (2; 17) | (2; 17) | (2; 17) | (2; 17) |
| Weight (kg) | | | | | |
| N | 19 | 76 | 78 | 154 | 173 |
| Mean (SD) | 44.48 (20.582) | 41.94 (18.499) | 43.97 (21.804) | 42.97 (20.200) | 43.13 (20.188) |
| Median | 46.00 | 41.75 | 43.00 | 42.70 | 43.00 |
| IQ range | (27.30; 55.00) | (26.10; 56.35) | (25.00; 59.20) | (25.00; 57.60) | (26.80; 56.80) |
| Range | (12.1; 96.1) | (11.2; 83.0) | (12.5; 109.8) | (11.2; 109.8) | (11.2; 109.8) |
| Height (cm) | | | | | |
| N | 19 | 76 | 78 | 154 | 173 |
| Mean (SD) | 145.44 (24.490) | 143.88 (24.787) | 144.31 (24.445) | 144.10 (24.534) | 144.25 (24.462) |
| Median | 152.00 | 151.50 | 150.25 | 151.05 | 151.50 |
| IQ range | (121.90; 161.40) | (129.25; 162.60) | (127.00; 164.80) | (127.50; 163.10) | (127.50; 162.90) |
| Range | (97.4; 186.9) | (83.0; 183.2) | (87.0; 179.6) | (83.0; 183.2) | (83.0; 186.9) |
| Body Surface Area (m$^2$) | | | | | |
| N | 19 | 76 | 78 | 154 | 173 |
| Mean (SD) | 1.321 (0.4184) | 1.280 (0.3943) | 1.304 (0.4359) | 1.292 (0.4147) | 1.295 (0.4140) |
| Median | 1.400 | 1.300 | 1.350 | 1.300 | 1.400 |
| IQ range | (1.000; 1.600) | (0.950; 1.600) | (1.000; 1.600) | (1.000; 1.600) | (1.000; 1.600) |
| Range | (0.60; 2.20) | (0.50; 2.00) | (0.60; 2.30) | (0.50; 2.30) | (0.50; 2.30) |

Baseline clinical disease characteristics are summarised in **Table 4**.

The enrolled subjects who did not respond had a higher median number of joints with a limited range of motion (11.0) and a higher CHAQ (1.38) than those subjects who were ACR 30 responders at Week 16. Additionally, all treatment groups had median ESR levels in the normal range, <20 mm/h, and median CRP levels in the normal range, <1.0 mg/dL. By the ILAR classification, the majority (52.0%) of enrolled subjects had polyarticular RF-negative JIA, and 15 (8.7%) subjects had JPsA.

All enrolled subjects had joints with active arthritis, and 52.6% to 64.5% of the subjects across the treatment groups had morning stiffness greater than 15 minutes.

Across treatment groups, 85.7% to 100% of subjects had received prior corticosteroid injections and 14.3% to 17.4% of subjects had undergone prior arthrocentesis.

Baseline CHQ subscale scores indicated that enrolled subjects with JIA showed impaired health-related quality of life with values below the mean of generally healthy populations in CHQ scale scores, especially in the general health, bodily pain/discomfort, parent impact - emotional and parent impact – time scales.

**Table 4.** Summary of disease characteristics at Week 0 and Week 16 in study CNTO148JIA3001; randomised subjects

| | Week 0 | Week 16 |
|---|---|---|
| Subjects randomized | 154 | 154 |
| Number of joints with active arthritis | | |
| N | 154 | 154 |
| Mean (SD) | 14.9 (9.90) | 2.7 (5.29) |
| Median | 12.0 | 1.0 |
| IQ range | (8.0; 18.0) | (0.0; 3.0) |
| Range | (4; 58) | (0; 39) |
| Number of joints with limited range of motion | | |
| N | 154 | 154 |
| Mean (SD) | 11.9 (10.33) | 3.1 (5.88) |
| Median | 8.0 | 1.0 |
| IQ range | (6.0; 15.0) | (0.0; 4.0) |
| Range | (0; 56) | (0; 39) |
| Physician's global assessment of disease activity (VAS 0-10 cm) | | |
| N | 154 | 154 |
| Mean (SD) | 5.58 (1.884) | 1.02 (1.426) |
| Median | 5.40 | 0.50 |
| IQ range | (3.90; 7.00) | (0.10; 1.30) |
| Range | (2.2; 10.0) | (0.0; 7.7) |
| Parent assessment of overall well-being (VAS 0-10 cm) | | |
| N | 154 | 154 |
| Mean (SD) | 4.41 (2.355) | 1.62 (2.021) |
| Median | 4.30 | 0.90 |
| IQ range | (2.80; 6.10) | (0.30; 2.30) |
| Range | (0.1; 9.4) | (0.0; 9.8) |
| Parent assessment of pain (VAS 0-10 cm) | | |
| N | 154 | 154 |
| Mean (SD) | 4.63 (2.633) | 1.51 (1.833) |
| Median | 4.70 | 0.90 |
| IQ range | (2.50; 6.60) | (0.30; 1.80) |
| Range | (0.0; 9.6) | (0.0; 9.0) |
| CHAQ | | |
| N | 153 | 154 |
| Mean (SD) | 0.96 (0.708) | 0.42 (0.523) |
| Median | 0.88 | 0.25 |
| IQ range | (0.38; 1.50) | (0.00; 0.75) |
| Range | (0.0; 3.0) | (0.0; 2.6) |

A medication or therapy was considered concomitant at baseline if it had been used both prior to and after the first study agent administration. The proportions of subjects at baseline taking oral corticosteroids or NSAIDs specifically for JIA were generally similar in both randomised groups

The median dose of prednisone was the same in all groups (data not shown).

***Numbers analysed***

Through Week 16, all subjects received golimumab 30 mg/m2 + MTX. At Week 16, subjects were randomised 1:1 to receive golimumab 30 mg/m2 + MTX or placebo + MTX. Efficacy analyses for the primary and major secondary endpoints are based on the intent-to-treat population and are reported for the 2 randomized treatment groups, golimumab + MTX and placebo + MTX. Subjects remained on placebo unless they experienced a flare of disease at which time golimumab administrations were resumed. Of the 76 subjects randomized to placebo, 33 (43.4%) subjects received golimumab 30 mg/m2 + MTX. The subjects were treated as ACR Ped non-responders for analysis purposes and, thus, could not be deemed to have inactive disease or qualify for clinical remission while on medication.

***Outcomes and estimation***

*Primary endpoint*

The primary endpoint was the proportion of subjects who were ACR Ped 30 responders at Week 16 and did not experience a flare of disease between Week 16 and Week 48, and these results are summarised in **Table 5**.

**Table 5.** Number of subjects who did not flare from Week 16 through Week 48 in study CNTO148JIA3001; randomised subjects

| | Golimumab Administered Prior to Randomization at Week 16 | |
|---|---|---|
| | Placebo + MTX | Golimumab 30 mg/m$^2$ + MTX |
| Subjects randomized | 76 | 78 |
| Subjects who did not flare | | |
| N | 76 | 78 |
| Non-flare subjects | 40 (52.6%) | 46 (59.0%) |
| p-value | | 0.414 |

*Major Secondary Endpoints*

The proportion of randomised subjects who achieved an ACR Ped 30 response at Week 16 with ACR Ped 30 response at Week 48 was 52.6% (41) subjects in the golimumab group compared with the placebo group 55.3% (41; p = 0.751). In addition, 51%, 47%, and 39% of patients in the golimumab + MTX group were, ACR Ped 50, ACR Ped 70, and ACR Ped 90 responders, respectively

The proportion of randomised subjects who achieved an ACR Ped 30 response at Week 16 and had inactive disease at Week 48 was 39.7% (31) subjects in the golimumab group compared with the placebo group 27.6% (21; p = 0.119).

The proportion of randomised subjects who achieved an ACR Ped 30 response at Week 16 and were in clinical remission while on medication for JIA at Week 48 was 12.8% (10) subjects in the golimumab group compared with the placebo group 11.8% (n=9, p = 0.848).

*Subgroup analysis by CRP levels*

The median baseline (Week 0) CRP in the CNTO148JIA3001 study (0.17 mg/dL) was low and within the normal range of the assay used (≤1.0 mg/dL). Pre-specified subgroup analyses of the primary endpoint by baseline CRP (≥1 mg/dL vs <1 mg/dL) demonstrated higher flare rates in placebo + MTX vs golimumab + MTX treated subjects among subjects with baseline CRP ≥1 mg/dL (87% vs 40%, p=0.0068).

Additional post-hoc analysis was performed to evaluate the primary and secondary endpoints in subgroups of patients by baseline CRP levels (≥0.02 to ≥ 1.0 mg/dL). Results from this analysis are presented in **Table 6** and **Figures 11** and **12** for all randomised subjects, those with ACR Ped 30 response at week 48 and those with inactive disease at week 48 respectively.

**Table 6.** Number of subjects who did not flare from Week 16 through Week 48 by CRP levels at baseline in study CNTO148JIA3001; randomised subjects

| | Golimumab Administered Prior to Randomization at Week 16 | | |
|---|---|---|---|
| | Placebo + MTX | Golimumab 30 mg/m$^2$ + MTX | p-value |
| Subjects randomized | 76 | 78 | - |
| Subjects who did not flare | | | |
| baseline CRP >= 0.02 mg/dL | 37/72 (51.4%) | 46/75 (61.3%) | 0.196 |
| baseline CRP >= 0.1 mg/dL | 14/38 (36.8%) | 27/44 (61.4%) | 0.020 |
| baseline CRP >= 0.2 mg/dL | 12/33 (36.4%) | 20/36 (55.6%) | 0.100 |
| baseline CRP >= 0.3 mg/dL | 10/30 (33.3%) | 19/33 (57.6%) | 0.050 |
| baseline CRP >= 0.4 mg/dL | 6/26 (23.1%) | 17/28 (60.7%) | 0.003 |
| baseline CRP >= 0.5 mg/dL | 5/25 (20.0%) | 15/26 (57.7%) | 0.003 |
| baseline CRP >= 0.6 mg/dL | 5/22 (22.7%) | 14/23 (60.9%) | 0.005 |
| baseline CRP >= 0.7 mg/dL | 4/20 (20.0%) | 13/20 (65.0%) | 0.004 |
| baseline CRP >= 0.8 mg/dL | 2/18 (11.1%) | 12/19 (63.2%) | 0.001 |
| baseline CRP >= 0.9 mg/dL | 2/17 (11.8%) | 11/18 (61.1%) | 0.004 |
| baseline CRP >= 1.0 mg/dL | 2/15 (13.3%) | 9/15 (60.0%) | 0.007 |

CRP = C-reactive protein

**Figure 11.** Number of subjects who are ACR Ped responders at week 16 with ACR Ped 30 response at week 48 by CRP levels at baseline in study CNTO148JIA3001; randomised subjects

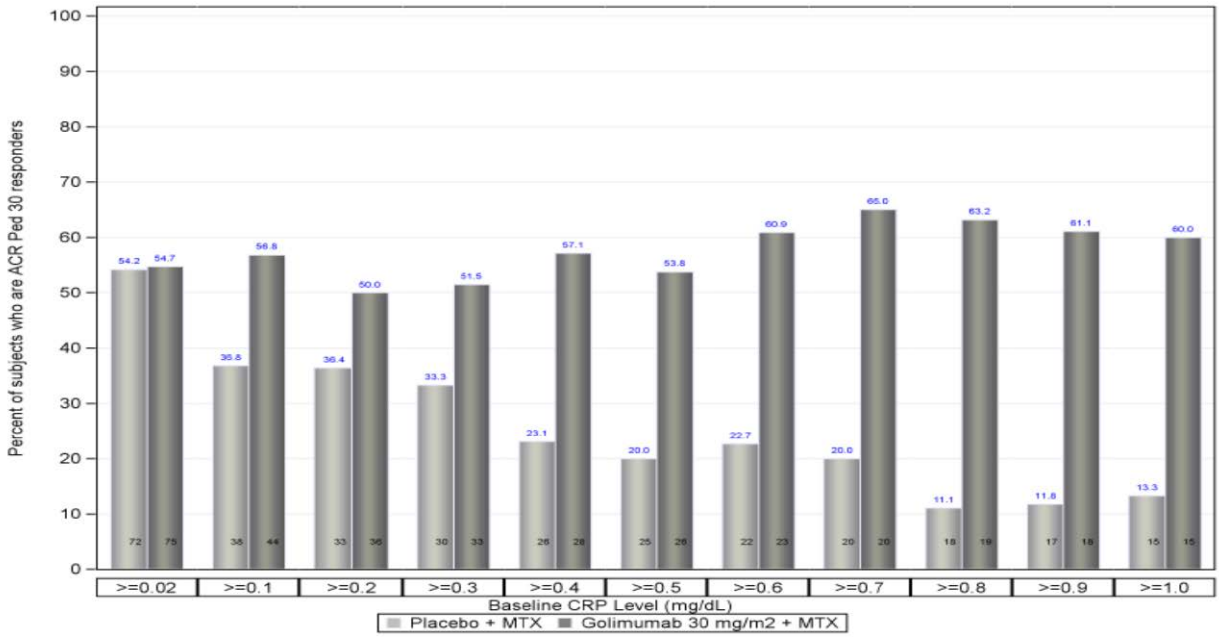
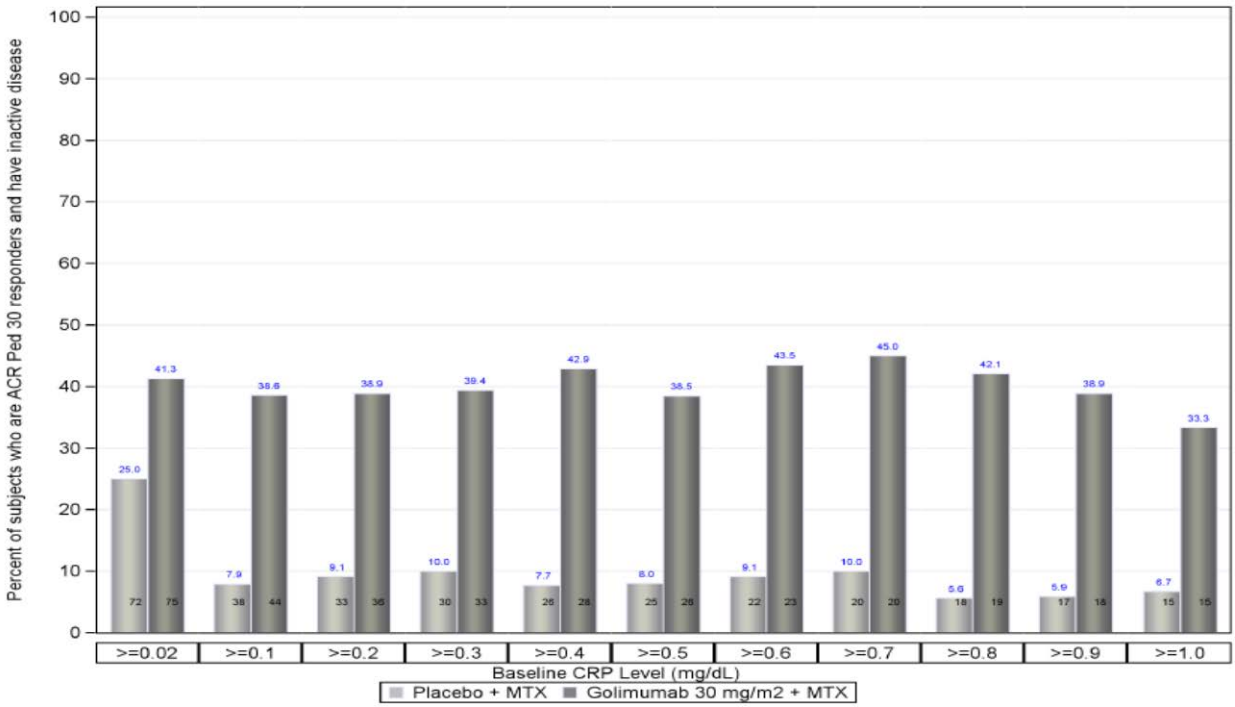


**Figure 12.** Number of subjects who are ACR Ped responders at week 16 and had inactive disease at week 48 by CRP levels at baseline in study CNTO148JIA3001; randomised subjects




*Open label phase of the study*

High ACR Ped responses were seen in the open-label treatment phase to Week 16 (**Table 7**).

**Table 7**. Number of subjects who are ACR Ped 30, 50, 70, or 90 responders through Week 16 in study CNTO148JIA3001; subjects enrolled

| | | Golimumab Administered Prior to Randomization at Week 16 | | | |
|---|---|---|---|---|---|
| | Enrolled Subjects Who Did Not Enter Randomized Withdrawal Period | Placebo + MTX | Golimumab 30 $mg/m^2$ + MTX | All Randomized Subjects | All Enrolled Subjects |
| Subjects enrolled | 19 | 76 | 78 | 154 | 173 |
| Week 4 | | | | | |
| N | 19 | 76 | 78 | 154 | 173 |
| ACR Ped 30 responders | 7 (36.8%) | 53 (69.7%) | 63 (80.8%) | 116 (75.3%) | 123 (71.1%) |
| ACR Ped 50 responders | 4 (21.1%) | 38 (50.0%) | 42 (53.8%) | 80 (51.9%) | 84 (48.6%) |
| ACR Ped 70 responders | 2 (10.5%) | 19 (25.0%) | 23 (29.5%) | 42 (27.3%) | 44 (25.4%) |
| ACR Ped 90 responders | 0 | 7 (9.2%) | 9 (11.5%) | 16 (10.4%) | 16 (9.2%) |
| Week 8 | | | | | |
| N | 19 | 76 | 78 | 154 | 173 |
| ACR Ped 30 responders | 9 (47.4%) | 66 (86.8%) | 71 (91.0%) | 137 (89.0%) | 146 (84.4%) |
| ACR Ped 50 responders | 4 (21.1%) | 59 (77.6%) | 57 (73.1%) | 116 (75.3%) | 120 (69.4%) |
| ACR Ped 70 responders | 2 (10.5%) | 41 (53.9%) | 46 (59.0%) | 87 (56.5%) | 89 (51.4%) |
| ACR Ped 90 responders | 1 (5.3%) | 17 (22.4%) | 27 (34.6%) | 44 (28.6%) | 45 (26.0%) |
| Week 12 | | | | | |
| N | 19 | 76 | 78 | 154 | 173 |
| ACR Ped 30 responders | 7 (36.8%) | 73 (96.1%) | 70 (89.7%) | 143 (92.9%) | 150 (86.7%) |
| ACR Ped 50 responders | 4 (21.1%) | 66 (86.8%) | 64 (82.1%) | 130 (84.4%) | 134 (77.5%) |
| ACR Ped 70 responders | 1 (5.3%) | 49 (64.5%) | 48 (61.5%) | 97 (63.0%) | 98 (56.6%) |
| ACR Ped 90 responders | 1 (5.3%) | 23 (30.3%) | 28 (35.9%) | 51 (33.1%) | 52 (30.1%) |
| Week 16 | | | | | |
| N | 19 | 76 | 78 | 154 | 173 |
| ACR Ped 30 responders | 0 | 75 (98.7%) | 76 (97.4%) | 151 (98.1%) | 151 (87.3%) |
| ACR Ped 50 responders | 0 | 67 (88.2%) | 70 (89.7%) | 137 (89.0%) | 137 (79.2%) |
| ACR Ped 70 responders | 0 | 57 (75.0%) | 57 (73.1%) | 114 (74.0%) | 114 (65.9%) |
| ACR Ped 90 responders | 0 | 29 (38.2%) | 34 (43.6%) | 63 (40.9%) | 63 (36.4%) |

ACR Ped = American College of Rheumatology Pediatric ; MTX = methotrexate

The improvement from baseline in ACR Ped components through week 16 are summarised in **Table 8**.

**Table 8.** Summary of percent improvement from baseline in ACR Ped components through Week 16 in study CNTO148JIA3001; subjects enrolled

| | Enrolled Subjects Who Did Not Enter Randomized Withdrawal Period | Golimumab Administered Prior to Randomization at Week 16 | | | |
|---|---|---|---|---|---|
| | | Placebo + MTX | Golimumab 30 mg/m$^2$ + MTX | All Randomized Subjects | All Enrolled Subjects |
| | 19 | 76 | 78 | 154 | 173 |
| **Physicians global assessment of disease (VAS 0-10 cm)** | | | | | |
| Mean (SD) | 24.32 (37.601) | 84.74 (19.417) | 80.88 (20.401) | 82.79 (19.951) | 76.37 (28.951) |
| Median | 13.04 | 91.72 | 87.04 | 89.66 | 88.00 |
| IQ range | (6.90; 57.14) | (78.17; 100.00) | (73.02; 96.83) | (73.33; 98.44) | (68.42; 97.50) |
| Range | (-33.3; 97.5) | (15.9; 100.0) | (18.9; 100.0) | (15.9; 100.0) | (-33.3; 100.0) |
| **Subject/parent global assessment of overall well-being (VAS 0-10 cm)** | | | | | |
| Mean (SD) | 6.62 (35.566) | 51.75 (62.293) | 59.13 (45.112) | 55.49 (54.223) | 50.12 (54.613) |
| Median | 5.45 | 70.64 | 74.51 | 71.61 | 66.67 |
| IQ range | (-15.38; 28.89) | (38.05; 89.73) | (37.25; 96.00) | (37.25; 93.33) | (28.57; 90.41) |
| Range | (-64.0; 76.2) | (-275.0; 100.0) | (-100.0; 100.0) | (-275.0; 100.0) | (-275.0; 100.0) |
| **Number of active joints** | | | | | |
| Mean (SD) | 39.03 (45.013) | 83.93 (20.757) | 86.74 (19.249) | 85.35 (19.992) | 80.26 (27.903) |
| Median | 30.77 | 91.61 | 95.10 | 93.54 | 92.31 |
| IQ range | (0.00; 78.57) | (75.00; 100.00) | (77.78; 100.00) | (76.92; 100.00) | (72.22; 100.00) |
| Range | (-50.0; 100.0) | (20.0; 100.0) | (0.0; 100.0) | (0.0; 100.0) | (-50.0; 100.0) |
| **Number of joints with limited range of motion** | | | | | |
| Mean (SD) | 9.42 (70.499) | 70.75 (36.876) | 74.04 (30.734) | 72.42 (33.833) | 65.50 (43.916) |
| Median | 7.14 | 85.36 | 86.61 | 85.71 | 80.00 |
| IQ range | (-5.13; 63.64) | (50.00; 100.00) | (57.14; 100.00) | (54.55; 100.00) | (42.86; 100.00) |
| Range | (-200.0; 100.0) | (-100.0; 100.0) | (0.0; 100.0) | (-100.0; 100.0) | (-200.0; 100.0) |
| **Physical function by Childhood Health Assessment Questionnaire (CHAQ)** | | | | | |
| Mean (SD) | 1.17 (35.678) | 42.49 (87.709) | 49.89 (45.498) | 46.23 (69.474) | 41.29 (68.017) |
| Median | 0.00 | 55.84 | 51.67 | 54.20 | 50.00 |
| IQ range | (-20.00; 25.00) | (12.50; 100.00) | (0.00; 100.00) | (10.00; 100.00) | (0.00; 100.00) |
| Range | (-66.7; 58.4) | (-600.0; 100.0) | (-50.0; 100.0) | (-600.0; 100.0) | (-600.0; 100.0) |
| **ESR (mm/h)** | | | | | |
| Mean (SD) | -7.73 (90.502) | 21.96 (51.199) | 9.93 (77.264) | 15.87 (65.771) | 13.27 (68.992) |
| Median | 0.00 | 33.33 | 38.76 | 33.33 | 33.33 |
| IQ range | (-18.42; 55.36) | (0.00; 55.59) | (-17.65; 68.75) | (-9.52; 61.11) | (-11.96; 59.70) |
| Range | (-250.0; 80.8) | (-166.7; 95.0) | (-223.1; 93.2) | (-223.1; 95.0) | (-250.0; 95.0) |

Patients at the end of the open label phase of the study, who had inactive disease are summarised in **Table 9**.

**Table 9.** Number of subjects who have inactive disease at Week 16 in study CNTO148JIA3001using observed data only; enrolled subjects

| | | Golimumab Administered Prior to Randomization at Week 16 | | | |
|---|---|---|---|---|---|
| | Enrolled Subjects Who Did Not Enter Randomized Withdrawal Period | Placebo + MTX | Golimumab 30 mg/m$^2$ + MTX | All Randomized Subjects | All Enrolled Subjects |
| Subjects enrolled | 19 | 76 | 78 | 154 | 173 |
| Week 16 | | | | | |
| N | 18 | 76 | 78 | 154 | 172 |
| Subjects with inactive disease | 1 (5.6%) | 27 (35.5%) | 31 (39.7%) | 58 (37.7%) | 59 (34.3%) |

***Efficacy analysis***

***Comparison of golimumab with other biologics authorised for pJIA***

Of the TNF-inhibitors, Enbrel and Humira are approved for the pJIA indication. The studies supporting this indication had generally the same design as the Simponi study. Baseline characteristics in those trials and main results are presented in **Tables 10** and **11**.

**Table 10.** Comparison of baseline disease characteristics across pJIA studies with biologics

| | Golimumab | Tocilizumab | Adalimumab | Etanercept | Abatacept |
|---|---|---|---|---|---|
| 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. | | | | | |
| * Adalimumab + MTX cohort | | | | | |
| Values presented for golimumab and etanercept are median values; those for tocilizumab, adalimumab, and abatacept are mean values, unless otherwise noted | | | | | |

**Table 11.** Comparison of ACR Response across pJIA studies with biologics

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

| Study Drug | Trial Duration | Patient and Disease Characteristics | Number of Patients Randomized | JIA ACR Response Lead in Phase | Flare Rates | JIA ACR Response Withdrawal Period (Active/PBO) | Qualifications |
|---|---|---|---|---|---|---|---|
| Tocilizumab | Phase 1: 16 weeks<br>Phase 2: 24 weeks | Children 2 to 17 years with MTX-IR active pJIA (extended oligoarticular and polyarticular) | Phase 1: 188<br>Phase 2: 163 | ACR 30 = 89%<br>ACR 50 = 83%<br>ACR 70 = 62%<br>ACR 90 = 26% | TCZ = 26%<br>PBO = 48% | ACR 30: 74%/54%<br>ACR 50: 73%/52%<br>ACR 70: 65%/42%<br>ACR 90: 45%/23% | Flare patients categorized as ACR non-responders. Mono and combination therapy. |
| Golimumab | Phase 1: 16 weeks<br>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<br>Phase 2: 154 | ACR 30 = 87.3%<br>ACR 50 = 79.2%<br>ACR 70 = 65.9%<br>ACR 90 = 36.4% | GLM = 41%<br>PBO = 47.4% | ACR 30: 55%/52%<br>ACR 50: 54%/51%<br>ACR 70: 47%/47%<br>ACR 90: 32%/38% | Flare patients 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.
** Patients that received MTX + adalimumab only

***Efficacy and Antibodies to golimumab***

In study CNTO148JIA3001, subjects were evaluated for having a positive or negative status for antibodies to golimumab with the drug-tolerant enzyme immunoassay (EIA) method.

When immunogenicity was evaluated at the time of flare, 33.3% of subjects on placebo + MTX and 25.0% of subjects on golimumab 30 mg/m2 + MTX had antibodies to golimumab. The range of titers between the 2 groups was also similar. Additionally, the incidence of antibodies of golimumab in those who continued on golimumab and flared (28.1%; 9/32) was similar to those who continued golimumab and did not flare (32.6%; 15/46).

## 2.4.2. Discussion on clinical efficacy

**Design and conduct of clinical studies**

Golimumab 30 mg/m2 SC q4w was evaluated in a single, randomized-withdrawal, double-blind, placebo-controlled study (CNTO148JIA3001) to determine its efficacy and safety in treating paediatric subjects (2 to 17 years of age) with pJIA.

The study consisted of a 16-week open label portion with golimumab administration q4w + MTX administered weekly for 12 weeks followed by a randomized withdrawal portion comparing placebo + MTX administered weekly and golimumab administration q4w + MTX administered weekly for 32 weeks. The demographic characteristics of the study population at Week 0 and at Week 16 were well balanced across treatment groups. The baseline characteristics of this population were consistent with moderate to severe disease activity in subjects with pJIA with a median joint count of 12 joints with active arthritis, a median joint count of 8 joints with limited range of motion and visual analogue scores ranging from 4.5 to 5.4 cm. Subjects had mild to moderate disability as reflected in the median CHAQ score at baseline of 0.94. Baseline levels of inflammation by ESR (median 16 mm/h; normal <20 mm/h) and CRP (median 0.17 mg/dL; normal <1.0 mg/dL) were within the normal range.

**Efficacy data and additional analyses**

Responses in the open label period

After 16 weeks of open label golimumab treatment, the proportions of subjects achieving ACR Ped 30, 50, 70, and 90 responses were robust (ACR Ped 30: 87.3%, ACR Ped 50: 79.2%, ACR Ped 70: 65.9%, ACR Ped 90: 36.4%) as was the proportion of subjects with inactive disease (37.7%). These results indicate a positive effect of golimumab on active pJIA and are comparable to what has been reported for other TNF inhibitors (74-94% ACR Ped 30).

In addition, evaluation of the individual ACR Ped components for all enrolled subjects demonstrated clinically important changes, particularly for the number of joints with active arthritis, the number of joints with limited range of motion, and physician's global assessment of disease activity (VAS 0-10 cm).

The proportions of treated subjects with inactive disease also increased over time and at Week 16 was 34% of all the enrolled subjects. Improvements in physical function and health related quality of life, as measured by the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ), respectively, were also observed during the open label period A decrease of 0.188 in CHAQ score has been determined to be a meaningful improvement. At Week 16, median

improvement in CHAQ score was 0.38 in all enrolled subjects.

Randomised withdrawal phase

The randomized withdrawal portion of the study did not demonstrate a difference in flare rates between subjects randomized to the golimumab + MTX group (59.0%) and the placebo + MTX group (52.6%, p=0.414). There are several potential reasons which could explain this lack of differentiation between the different arms in this trial.

Neither inadequate serum trough concentrations nor immunogenicity seem to have been important contributing factors to the lack of statistical significance between the 2 randomised groups for the primary and major secondary endpoints.

The most plausible explanation is an inadequate inflammatory burden in subjects randomised in the study at baseline. The median baseline (Week 0) CRP in study CNTO148JIA3001 (0.17 mg/dL) was low and within the normal range of the assay used. This was in contrast to baseline values in studies performed over the past 10 years in JRA and JIA with different anti TNFα and non-anti-TNFα biologics in which the median baseline CRP levels were higher than observed in the current study.

Pre-specified subgroup analyses of the primary endpoint by baseline CRP (⩾1 mg/dL vs <1 mg/dL) demonstrated higher flare rates in placebo + MTX vs golimumab + MTX treated subjects among subjects with baseline CRP ⩾1 mg/dL (87% vs 40%). Additionally, post-hoc analyses evaluated flare rates based upon Week 0 CRP levels ranging from 0.1 to 1.0 mg/dL. These analyses demonstrated that, in general, among subjects with baseline CRP levels >0.1 mg/dL, subjects who received continued golimumab + MTX therapy had significantly fewer flare episodes than subjects who were randomized to placebo + MTX at Week 16.

Among golimumab-treated subjects with CRP >0.7 mg/dL, 35% in the golimumab group and 80% in the placebo group experienced a flare from week 16 through week 48 (p=0.004). This is in line with a previous adalimumab in pJIA study, where median CRP at baseline was 0.7-0.8 mg/dL, and the flare rates were 37% and 65% respectively. The flare rate in the placebo group in the adalimumab study was in turn lower than for etanercept, which included subjects with higher baseline median CRP than adalimumab (3.2mg/dL vs 0.7-0.8mg/dL). The average number of active joints at baseline was also considerably higher in the etanercept study. These figures support the hypothesis that higher inflammatory activity at baseline concurred with a higher flare rate in the placebo group, although they should be interpreted with caution, since these are comparisons between studies.

Another possible explanation is that the level of disease suppression achieved in the first 16 weeks of open label drug administration may have led to prolonged suppression of disease that might not have been fully elucidated in a 32-week randomized withdrawal period. This is supported to some extent by literature reports (Lovell DJ et al, *Pediatric Rheumatology 2014*) which have shown that anti-TNFs have a prolonged therapeutic effect on JIA control that lasts beyond their pharmacological half-life. Even though for the agents included in this study an effect was seen within the time period of the randomised withdrawal phase in study CNTO148JIA3001, it cannot be excluded that the level of suppression of the disease by golimumab may require an even longer time period before a negative effect of the treatment withdrawal can be demonstrated.

The median percent improvements from baseline in ACR Ped components at Week 48 continued to show pronounced improvement in disease activity in both randomized treatment groups. At Week 48, 53%, 51%, 47%, and 39% of patients in the golimumab + MTX group were ACR Ped 30, ACR Ped 50, ACR Ped 70, and ACR Ped 90 responders, respectively), and 40% achieved inactive disease.

Consistent results were also observed in the major secondary endpoints, when analysed by baseline CRP as a greater proportion of subjects achieved ACR Ped 30 response, as well as inactive disease, in the golimumab + MTX group compared with the placebo + MTX group in subjects with higher baseline CRP.

After Week 48 through the final DBL, with a median follow-up of approximately 2 years, efficacy responses were generally similar over time in subjects continuing golimumab.

### 2.4.3. Conclusions on the clinical efficacy

The totality of the data from study CNTO148JIA3001 support that golimumab in combination with MTX is efficacious in the treatment of pJIA. ACR Ped 30, 50, 70, and 90 responses at Week 16 were high and demonstrated that clinically meaningful improvements in disease activity were experienced by subjects during the open-label period.

The subgroup analyses demonstrating that for a subpopulation with elevated CRP at baseline, more similar to the population studied for the successful studies of etanercept and adalimumab, the primary endpoint was met, further supports this conclusion.

## *2.5. Clinical safety*

**Patient exposure**

A total of 173 subjects were enrolled at Week 0 and received at least 1 dose of golimumab. One hundred fifty-four (154) of the 173 subjects entered the randomized withdrawal period at Week 16. The summaries of safety data presented are based on the 154 randomized subjects who received at least 1 dose of study agent during this study. The average duration of follow-up for all randomized patients was 107 weeks or 26 administrations of golimumab and the average exposure to golimumab was 22 administrations of golimumab. The total subject-years of follow-up was 318. For all randomized subjects through the final DBL, the median cumulative dose of golimumab was 821.50 mg (range: 142.0-2045.0 mg.
Data sets were analysed for the following treatment groups:

- Placebo + MTX: Subjects who were treated with golimumab from Week 0 to Week 12, and who received placebo + MTX at Week 16 and continued on placebo + MTX.
- Placebo + MTX → Golimumab 30 mg/m2 + MTX prior to W48: Subjects who were treated with golimumab from Week 0 to Week 12, and who received placebo + MTX at Week 16 and switched to golimumab 30 mg/m2 + MTX prior to Week 48 and remained on golimumab through the end of study.
- Placebo + MTX → Golimumab 30 mg/m2 + MTX at or after W48: Subjects who were treated with golimumab from Week 0 to Week 12, and who received placebo + MTX at Week 16 and switched to golimumab 30 mg/m2 + MTX at or after Week 48 and remained on golimumab through end of study.
- Combined Placebo: All subjects who were treated with placebo + MTX at Week 16, which includes subjects from the following groups:
    - Placebo + MTX

- Placebo + MTX → Golimumab 30 mg/m2 + MTX prior to Week 48
- Placebo + MTX → Golimumab 30 mg/m2 + MTX at or after Week 48

❖ Golimumab 30 mg/m2 + MTX: Subjects who were treated with golimumab from Week 0 to Week 12, and who received golimumab 30 mg/m2 + MTX at Week 16 and continued on golimumab 30 mg/m2 + MTX through end of study.

❖ All Randomized Subjects: Subjects who were treated with either placebo or golimumab 30 mg/m2 + MTX at Week 16

**Adverse events**

Through Week 48, the proportion of subjects experiencing at least 1 AE was comparable in the treatment groups:

- All subjects: 87.9%
- Golimumab + MTX: 84.6%
- Combined Placebo: 93.4%

The system organ classes (SOCs) with the highest proportion of enrolled subjects experiencing at least 1 AE during the open-label phase of the Study (through Week 16) were:

- Infections and infestations: 38.7%
- Gastrointestinal disorders: 19.7%
- General disorders and administration site conditions: 12.1%
- Skin and subcutaneous tissue disorders: 11.6%
- Musculoskeletal and connective tissue disorders: 11.0%

The SOCs with the highest incidence of AEs for all subjects through Week 48 were:

- Infections and infestations: 67.1%
- Gastrointestinal disorders: 31.8%
- Musculoskeletal and connective tissue disorders: 24.9%
- General disorders and administration site conditions: 24.3%
- Skin and subcutaneous tissue disorders: 22.5%
- Respiratory, thoracic, and mediastinal disorders: 17.3%
- Injury poisoning, and procedural complications: 15.0%

Adverse events that occurred in ≥5% of all subjects included URTI (23.1%), nasopharyngitis (16.2%), JIA (15.0%), pyrexia (12.1%), headache (11.6%), nausea (9.2%), abdominal pain (8.7%), oropharyngeal pain and vomiting (6.9% each), abdominal pain upper, diarrhoea, gastroenteritis, and respiratory tract infection (6.4% each), and urticaria (5.2%). The number of subjects with AEs was generally similar in the golimumab + MTX and combined placebo groups.

There was no new adverse drug reaction identified based on the analyses of safety in study CNTO148JIA3001 after week 48 through to the final DBL.

**Serious adverse event / deaths / other significant events**

From Week 0 through the final DBL, the proportion of randomized subjects experiencing at least 1 SAE was comparable among the treatment groups.

- All randomized subjects: 22.7%
- Golimumab 30 mg/m2 + MTX: 23.1%
- Combined placebo + MTX: 22.4%

The SOCs with the highest incidence of SAEs for all randomized subjects through the final DBL were Musculoskeletal and connective tissue disorders (12.3%) and Infections and infestations (5.8%).

The most common SAEs were:

- JIA: 15 (9.7%) subjects in the all randomized subjects groups, 8 (10.3%) subjects in the golimumab 30 mg/m2 + MTX group and 7 (9.2%) subjects in the combined placebo + MTX group.
- Arthritis: 4 (2.6%) in the all randomized subjects groups, 2 (2.6%) subjects in the golimumab 30 mg/m2 + MTX group and 2 (2.6%) subjects in the combined placebo + MTX group.
- Pneumonia: 2 (1.3%) in the all randomized subjects groups, 1 (1.3%) subject in the golimumab 30 mg/m2 + MTX group and 1 (1.3%) subject in the combined placebo + MTX group.
- Upper respiratory tract infection: 2 (1.3%) in the all randomized subjects groups, 1 (1.3%) subject in the golimumab 30 mg/m2 + MTX group and 1 (1.3%) subject in the combined placebo + MTX group.

All other SAEs were singular events, including an event of demyelination, which was reported through the final DBL. There was also clinically important hepatobiliary event (hepatitis toxic) through the final DBL which resolved while the subject continued golimumab treatment.

There were no malignancies, active tuberculosis infections, or opportunistic infections observed in the CNTO148JIA3001 pJIA study through the final DBL.

The incidence of SAEs per hundred subject-years of follow-up through the final DBL was 20.44 (95% confidence interval [CI]: 15.77, 26.05) for all randomized subjects.

No deaths were reported through the final DBL.

**Discontinuation due to adverse events**

The subjects who discontinued the study due to an adverse event are summarised in **Table 12**.

**Table 12.** Number of Subjects Who Discontinued Study Agent Because of 1 or More Adverse Events through the Final DBL in CNTO148JIA3001 by MedDRA System-organ Class and Preferred Term; Treated Subjects Who Were randomised

| | pJIA Study (CNTO148JIA3001) | | | | | |
|---|---|---|---|---|---|---|
| | Golimumab Administered Prior to Randomization at Week 16 | | | | | |
| | Placebo + MTX | | | | | |
| | Placebo + MTX | Placebo + MTX → Golimumab 30 mg/m² + MTX prior to W48 | Placebo + MTX → Golimumab 30 mg/m² + MTX at or after W48 | Combined | Golimumab 30 mg/m² + MTX | All Randomized Subjects |
| Treated subjects who were randomized | 10 | 33 | 33 | 76 | 78 | 154 |
| Avg duration of follow-up (weeks) | 89.76 | 107.51 | 112.07 | 107.15 | 107.62 | 107.39 |
| Avg exposure (number of administrations) | 20.90 | 25.55 | 27.27 | 25.68 | 25.59 | 25.64 |
| Subjects who discontinued study agent due to 1 or more adverse events | 2 (20.0%) | 3 (9.1%) | 0 | 5 (6.6%) | 7 (9.0%) | 12 (7.8%) |
| System-organ class/preferred term | | | | | | |
| Musculoskeletal and connective tissue disorders | 2 (20.0%) | 2 (6.1%) | 0 | 4 (5.3%) | 3 (3.8%) | 7 (4.5%) |
| Juvenile idiopathic arthritis | 1 (10.0%) | 2 (6.1%) | 0 | 3 (3.9%) | 3 (3.8%) | 6 (3.9%) |
| Arthritis | 1 (10.0%) | 0 | 0 | 1 (1.3%) | 0 | 1 (0.6%) |
| Investigations | 0 | 0 | 0 | 0 | 2 (2.6%) | 2 (1.3%) |
| Alanine aminotransferase increased | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 (0.6%) |
| Aspartate aminotransferase increased | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 (0.6%) |
| Mycobacterium tuberculosis complex test positive | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 (0.6%) |
| General disorders and administration site conditions | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 (0.6%) |
| Chest pain | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 (0.6%) |
| Hepatobiliary disorders | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 (0.6%) |
| Gallbladder oedema | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 (0.6%) |
| Immune system disorders | 0 | 1 (3.0%) | 0 | 1 (1.3%) | 0 | 1 (0.6%) |
| Serum sickness-like reaction | 0 | 1 (3.0%) | 0 | 1 (1.3%) | 0 | 1 (0.6%) |
| Nervous system disorders | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 (0.6%) |
| Demyelination | 0 | 0 | 0 | 0 | 1 (1.3%) | 1 (0.6%) |
| Psychiatric disorders | 1 (10.0%) | 0 | 0 | 1 (1.3%) | 0 | 1 (0.6%) |
| Affective disorder | 1 (10.0%) | 0 | 0 | 1 (1.3%) | 0 | 1 (0.6%) |

**Comparison of safety data between adult patients and children with JIA exposed to golimumab**

Five Phase 3 pivotal studies formed the basis for approval of Simponi in the rheumatologic indications. Three studies were conducted in subjects with RA (C0524T05, C0524T06, and C0524T11), 1 in subjects with PsA (C0524T08), and 1 in subjects with AS (C0524T09). Safety displays through Week 16 represent the longest common placebo-controlled period prior to early escape for the 5 adult rheumatologic Phase 3 studies. At Week 16 in 4 of the 5 studies (C0524T06, C0524T11, C0524T08, and C0524T09), placebo subjects were allowed to “escape” to active treatment with golimumab 50 mg q4w, and golimumab 50 mg subjects were allowed to escape to treatment with golimumab 100 mg q4w (in study C0524T05, the early escape was available at Week 28). All placebo subjects who did not enter early escape at Week 16 crossed over to active golimumab treatment at Week 24 in studies C0524T06, C0524T08, C0524T09, and C0524T11, and most placebo subjects crossed over to golimumab at Week 52 in study C0524T05.

Safety analyses included all randomized subjects who received at least 1 administration of study agent, and were summarized by actual treatment received:

- Placebo: Subjects treated with placebo at Week 0 through Week 16.
- Golimumab 50 mg: Subjects treated with golimumab 50 mg at Week 0 through Week 16.
- Golimumab 100 mg: Subjects treated with golimumab 100 mg at Week 0 through Week 16.
- Combined (golimumab): All subjects treated with golimumab (50 mg and 100 mg) at Week 0 through Week 16.

In general, the frequency, type, and severity of the adverse reactions seen in children in pJIA study CNTO148JIA3001 were comparable to those observed in adults in the RA and rheumatology studies and no new safety events were observed in CNTO148JIA3001.

Through Week 16 of the studies, 68.2% of subjects in the pJIA study (all enrolled subjects) and 67.7% in the adult RA studies (50 mg group) and 67.9% of the adult rheumatologic studies (50 mg group) experienced at least 1 AE. **(Table 13)**.

**Table 13**. Overall comparison of golimumab paediatric and adult safety data through Week 16 of rheumatology studies

| | Ped<br>All enrolled | Adult RA Studies<br>GOL 50 mg | Adult Rheumatologic Studies<br>GOL 50 mg | Adult RA Studies<br>Combined GOL | Adult Rheumatologic Studies<br>Combined GOL |
|---|---|---|---|---|---|
| N | 173 | 399 | 683 | 1089 | 1659 |
| Average duration of follow-up (wks) | 16.13 | 16.0 | 16.0 | 15.9 | 15.9 |
| Subjects with adverse events | 68.2% | 67.7% | 67.9% | 66.4% | 66.6% |
| Most common SOCs | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders |
| Most Common AEs | Nasopharyngitis 9.2%, URTI 6.9% | URTI 6.3%, Nausea 6.0% | URTI 7.5%, Nasopharyngitis 5.4% | URTI 6.8%, Nausea 5.7% | URTI 7.2%, Nasopharyngitis 5.5% |
| Subjects with SAEs | 4.6% | 5.5% | 4.4% | 4.4% | 3.9% |
| Most common SOC | Musculoskeletal and connective tissue disorders | Infections and infestations | Infections and infestations | Infections and infestations | Infections and infestations |
| Subjects with AEs leading to discontinuation | 1.2% | 3.0% | 2.6% | 2.3% | 2.2% |
| Most common SOCs | Musculoskeletal and connective tissue disorders (both JIA) | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders |
| Subjects with any infection | 38.7% | 26.3% | n/a | 26.5% | n/a |
| Most common infections | Nasopharyngitis 8.7%<br>URTI, 6.9%<br>Respiratory tract infection, 4.6% | URTI, 6.0%,<br>Nasopharyngitis, 2.8%<br>Bronchitis, 2.3% | n/a | URTI, 6.7%<br>Nasopharyngitis, 3.0%<br>Bronchitis, 2.0% | n/a |
| Subjects with serious infections | 1.2% | 1.5% | 1.0% | 1.9% | 1.4% |
| Most common serious infections | Cellulitis and herpes zoster infections (1); pyelonephritis (1) | All singular | All singular | Sepsis, pneumonia, cellulitis | Sepsis, pneumonia, |
| Injections with injection-site reactions | 1.5% | 0.8% | 0.8% | 1.3% | 1.2% |
| Subjects with ≥1 injection-site reaction | 5.8% | 4.5% | 4.7% | 6.7% | 5.8% |

AE = adverse event; CI = confidence interval; GOL = golimumab; n/a = not available; Ped = pediatric; RA = rheumatoid arthritis; SAE = serious adverse event; SOC = system organ class; URTI = upper respiratory tract infection

*Notes*:
Ped Study = CNTO148JIA3001
Adult RA Studies = C0524T05, C0524T06, C0524T11
Adult Rheumatologic Studies = C0524T05, C0524T06, C0524T11, C0524T08, C0524T09

A similar comparison was also performed between paediatric and adult patients for the total duration of the studies in which they had participated (**Table 14**).

**Table 14.** Overall comparison of golimumab paediatric and adult safety data through the end of the rheumatology studies

| | Ped<br>All enrolled | Adult RA Studies<br>GOL 50 mg | Adult Rheumatologic Studies<br>GOL 50 mg | Adult RA Studies<br>Combined GOL | Adult Rheumatologic Studies<br>Combined GOL |
|---|---|---|---|---|---|
| N | 173 | 399 | 683 | 1089 | 1659 |
| Average duration of follow-up (wks) | 16.13 | 16.0 | 16.0 | 15.9 | 15.9 |
| Subjects with adverse events | 68.2% | 67.7% | 67.9% | 66.4% | 66.6% |
| Most common SOCs | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders |
| Most Common AEs | Nasopharyngitis 9.2%, URTI 6.9% | URTI 6.3%, Nausea 6.0% | URTI 7.5%, Nasopharyngitis 5.4% | URTI 6.8%, Nausea 5.7% | URTI 7.2%, Nasopharyngitis 5.5% |
| Subjects with SAEs | 4.6% | 5.5% | 4.4% | 4.4% | 3.9% |
| Most common SOC | Musculoskeletal and connective tissue disorders | Infections and infestations | Infections and infestations | Infections and infestations | Infections and infestations |
| Subjects with AEs leading to discontinuation | 1.2% | 3.0% | 2.6% | 2.3% | 2.2% |
| Most common SOCs | Musculoskeletal and connective tissue disorders (both JIA) | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders | Infections and infestations, Gastrointestinal disorders |
| Subjects with any infection | 38.7% | 26.3% | n/a | 26.5% | n/a |
| Most common infections | Nasopharyngitis 8.7%<br>URTI, 6.9%<br>Respiratory tract infection, 4.6% | URTI, 6.0%,<br>Nasopharyngitis, 2.8%<br>Bronchitis, 2.3% | n/a | URTI, 6.7%<br>Nasopharyngitis, 3.0%<br>Bronchitis, 2.0% | n/a |
| Subjects with any infection | 79.2% | 74.6% | 74.2% | 77.6% | 76.8% |
| Most common infections | URTI 29.9%, Nasopharyngitis 22.7% | URTI, Bronchitis, Nasopharyngitis | URTI, Bronchitis, Nasopharyngitis | URTI, Bronchitis, Nasopharyngitis | URTI, Bronchitis, Nasopharyngitis |
| Subjects with serious infections (%) | 6.5% | 10.4% | 7.5% | 12.5% | 9.9% |
| Most common serious infections | Pneumonia (2); Others were singular events | Pneumonia | Pneumonia | Pneumonia | Pneumonia |
| Incidence (CI) of serious infections[a] | 4.40 (2.41, 7.39) | 3.72 (2.72, 4.96) | 2.48 (1.89, 3.20) | 4.30 (3.77, 4.88) | 3.29 (2.92, 3.69) |
| Injections with injection-site reactions | 0.6% | 0.4% | 0.7% | 0.7% | 0.7% |
| Subjects with ≥1 injection-site reaction | 12.3% | 9.9% | 11.0% | 12.6% | 12.8% |

AE = adverse event; CI = confidence interval; GOL = golimumab; n/a = not available; JIA = juvenile idiopathic arthritis; Ped = pediatric; RA = rheumatoid arthritis; SAE = serious adverse event; SOC = system organ class; URTI = upper respiratory tract infection

[a] Incidence provided when available for both pediatric and adult subjects.

*Notes*:
Ped Study = CNTO148JIA3001
Adult RA Studies = C0524T05, C0524T06, C0524T11
Adult Rheumatologic Studies = C0524T05, C0524T06, C0524T11, C0524T08, C0524T09

Incidence rates (per 100 subject-years) were also compared between paediatric and adult patients in these indications, up to 16 weeks of treatments (**Table 15**) and till the end of the studies (**Table 16**).

**Table 15.** Overall Summary of Golimumab Pediatric and Adult Safety Data Through Week 16 of Studies Using Incidence Rates (Per 100 Subject-years); Enrolled Subjects in CNTO148JIA3001 and Treated Subjects in Phase 3 SC Rheumatology Studies

| | Ped | Adult RA Studies | Adult Rheumatologic Studies | Adult RA Studies | Adult Rheumatologic Studies |
|---|---|---|---|---|---|
| | All enrolled | GOL 50 mg | GOL 50 mg | Combined GOL | Combined GOL |
| N | 173 | 399 | 683 | 1089 | 1659 |
| Avg duration of follow-up (wks) | 16.1 | 16.0 | 16.0 | 15.9 | 15.9 |
| Total subject-years of follow-up | 53.65 | 122.67 | 209.71 | 333.42 | 508.70 |
| Median subject-years of follow-up | 0.31 | 0.31 | 0.31 | 0.31 | 0.31 |
| Adverse events (per 100 subject-years) | 616.92 | 591.01 | 630.88 | 590.25 | 615.49 |
| SAEs (per 100 subject-years) | 18.64 | 20.38 | 17.17 | 18.60 | 16.32 |
| AEs leading to discon (per 100 subject-years) | 5.59 | 13.04 | 13.83 | 10.50 | 10.81 |
| Infections (per 100 subject-years) | 201.29 | 114.13 | 123.51 | 122.07 | 127.97 |
| Serious infections (per 100 subject-years) | 5.59 | 4.89 | 3.34 | 7.80 | 5.70 |
| Injections with injection-site reactions (per 100 subject-years) | 20.50 | 24.46 | 26.23 | 39.29 | 35.19 |

AE = adverse event; GOL = golimumab; n/a = not available; Ped = pediatric; RA = rheumatoid arthritis; SAE = serious adverse event
Notes:
Ped Study = CNTO148JIA3001
Adult RA Study = C0524T05, C0524T06, C0524T11
Adult Rheumatologic Studies = C0524T05, C0524T06, C0524T11, C0524T08, C0524T09

**Table 16.** Overall Summary of Golimumab Pediatric and Adult Safety Data Through the End of the Studies Using Incidence Rates (Per 100 Subject-years); Treated Subjects Who Were Randomized in CNTO148JIA3001 and Treated Subjects in Phase 3 SC Rheumatology Studies

| | Ped | Adult RA Studies | Adult Rheumatologic Studies | Adult RA Studies | Adult Rheumatologic Studies |
|---|---|---|---|---|---|
| | All randomized | GOL 50 mg | GOL 50 mg | Combined GOL | Combined GOL |
| N | 154 | 374 | 671 | 1481 | 2228 |
| Avg duration of follow-up (wks) | 107.4 | 172.0 | 184.0 | 196.9 | 203.2 |
| Total subject-years of follow-up | 318.04 | 1237.16 | 2374.79 | 5606.50 | 8704.37 |
| Median subject-years of follow-up | 2.00 | 4.16 | 4.62 | 4.71 | 4.85 |
| Adverse events (per 100 subject-years) | 437.05 | 293.57 | 307.82 | 299.21 | 301.50 |
| SAEs (per 100 subject-years) | 20.44 | 16.73 | 12.80 | 17.84 | 14.85 |
| AEs leading to discon (per 100 subject-years) | 5.03 | 7.19 | 5.60 | 6.42 | 5.48 |
| Infections (per 100 subject-years) | 166.33 | 86.73 | 84.64 | 82.19 | 82.75 |

| | | | | | |
|---|---|---|---|---|---|
| Serious infections (per 100 subject-years) | 4.40 | 4.12 | 2.69 | 4.91 | 3.73 |
| Injections with injection-site reactions (per 100 subject-years) | 7.23 | 7.44 | 14.23 | 13.86 | 14.58 |

AE = adverse event; GOL = golimumab; n/a = not available; Ped = pediatric; RA = rheumatoid arthritis; SAE = serious adverse event
Notes:
Ped Study = CNTO148JIA3001
Adult RA Study = C0524T05, C0524T06, C0524T11
Adult Rheumatologic Studies = C0524T05, C0524T06, C0524T11, C0524T08, C0524T09

The nature of infections between paediatric and adult subjects was different, with respiratory tract infection, tonsillitis, gastroenteritis, otitis media, pyrexia, conjunctivitis, rhinitis, and influenza-like illness the most commonly type of infections reported in the pJIA study. Pneumonia and urinary tract infection were more commonly reported in the adult RA studies (data not shown).

### 2.5.1. Discussion on clinical safety

Of the 173 subjects who were enrolled in the pJIA study at Week 0 and received at least 1 dose of golimumab, 154 entered the randomized withdrawal period at Week 16.

The majority (68%) of the enrolled subjects experienced at least 1 AE during the first 16 weeks, and most (92%) experienced at least 1 AE through the end of the study. This was in line with previously conducted adult RA studies with golimumab.

During the open label part of the study, 39% of the subjects experienced an infection however the paediatric population is known to be particularly susceptible to infections. In addition, infections are a known identified risk for golimumab as described in the Risk Management Plan. Other SOCs with high proportions of AEs during the first 16 weeks were gastrointestinal disorders (20%), general disorders and administration site conditions (12%), skin and subcutaneous tissue disorders (12%) and musculoskeletal and connective tissue disorders (11%). The reported PTs within these groups were also in line with the known safety profile of golimumab.

The same pattern of events to the open label phase of the study was reported through the DBL.

Of the serious adverse events reported, other than infections and events related to the treated condition in the study, there was 1 case of demyelination which is a known ADR for golimumab. A case of toxic hepatitis was also reported, which resolved during treatment, thus a correlation with golimumab was considered to be unlikely.

The higher incidence of all AEs in children appears to be largely driven by the higher incidence of infections in children. Children are known to have generally increased susceptibility to infections compared to adults. A key reason for this is limited previous exposure to diseases, resulting in no developed immunity to these diseases whilst environmental issues can also play a role. Children in day care and school circulate infections and take them home to siblings. This, combined with higher potential for poor hygiene practices, increases exposure and susceptibility to infections. The types of infections most commonly reported in the trials for children was different to those in adults and representative of typical infections in this population. Importantly however, incidences of serious infections between the paediatric and adult populations were similar.

The SmPC contains extensive warnings in relation to Sections 4.4 and 4.8 from the information available from the adult population and these are considered applicable and sufficient to minimise the risk in the paediatric population as well. Furthermore, as there are limited data on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients

receiving anti-TNF therapy it is recommended in the SmPC that prior to initiating golimumab therapy, paediatric patients, are brought up to date with all immunisations in agreement with current immunisation guidelines. In addition, monitoring of the long-term safety of golimumab in the treatment of JIA will be done through a registry included in the Risk Management Plan, focusing especially on serious infections including opportunistic infections and tuberculosis, lymphoma (excluding HSTCL), autoimmune processes, skin cancer and malignancies.

Overall, the safety profile of golimumab in combination with MTX in the JIA population, including the type and frequency of the adverse reactions seen, was consistent with the known safety profile of golimumab in the studied RA, PsA, and AS adult populations. Even if indirect comparisons between different studies and populations included are difficult to interpret, the incidence of the adverse events of interest appear to support a similar safety profile for golimumab between paediatric and adult patients.

### 2.5.2. Conclusions on clinical safety

The safety profile of golimumab is well characterised through a number of clinical trials in the adult population. The study in children with JIA did not reveal any new safety concerns to those which had been previously identified from studies with adults. Warnings in the SmPC and studies included in the RMP are considered adequate to minimise the known risks and further characterise the use of golimumab in paediatric patients.

### 2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The PSUR cycle for the medicinal product should follow a 3-yearly cycle until otherwise agreed by the CHMP.

The next data lock point will be 07 April 2017.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

## *2.6. Risk management plan*

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 13.3 is acceptable.

The CHMP endorsed this advice with some minor amendments on the safety concerns which will be addressed through the JIA Registry.

The applicant implemented the changes in the RMP as requested by CHMP.

The CHMP endorsed the Risk Management Plan version 13.4 with the following content:

***Safety concerns***

| | |
|---|---|
| Important identified risks | • Serious infections including opportunistic infections and TB<br>• Demyelinating disorders<br>• Hypertension<br>• Lymphoma (excluding HSTCL)<br>• Hepatitis B virus reactivation<br>• Congestive heart failure<br>• Autoimmune processes<br>• Haematologic reactions<br>• Serious systemic hypersensitivity (including anaphylactic reaction)<br>• Vasculitis<br>• Psoriasis (new onset or worsening of pre-existing)<br>• Skin cancer<br>• Leukaemia<br>• Sarcoidosis/sarcoid-like reaction |
| Important potential risks | • Malignancy<br>• Serious hepatotoxicity<br>• Exposure during pregnancy<br>• Serum sickness<br>• Maladministration/administration error<br>• Serious depression including suicidality<br>• Colon cancer/dysplasia (in UC)<br>• HSTCL<br>• Medication error (wrong dose related to different strengths) |
| Missing information | • Use in paediatric patients with ulcerative colitis<br>• Use in patients with hepatic impairment<br>• Use in patients with renal impairment<br>• Use in patients with a past history of latent or active TB<br>• Use in patients with concurrent malignancy or a history of malignancy<br>• Use in patients with active infections including HIV, hepatitis B, hepatitis C<br>• Use in patients with recent prior use of other biologics excluding anti-TNFα agents<br>• Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF<br>• Use in patients with history of demyelinating disease<br>• Use in patients with a history of lupus or lupus-like syndrome<br>• Use in patients after recent vaccination with live bacterial or viral vaccine<br>• Long-term safety in adult patients<br>• Long-term safety in paediatric patients |

***Pharmacovigilance plan***

| Study/activity type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| P04480<br>(non-interventional cohort, category 3) | Evaluate the long term safety of biologics. A minimum follow-up period of 5 years is planned in golimumab. | • Serious infections including opportunistic infections and TB<br>• Demyelinating disorders<br>• Lymphoma (excluding HSTCL)<br>• Congestive heart failure<br>• Haematologic reactions<br>• Serious systemic hypersensitivity (including anaphylactic reaction)<br>• Skin cancer<br>• Malignancy<br>• Serum sickness<br>• Long-term safety in adult patients | Ongoing | Interim reports: planned annually<br>Final report:<br>December 2018 |
| CNTO148ART4003<br>(non-interventional cohort, category 3) | Using Swedish and Danish National (whole population) medical and pharmaceutical data sets to collect characteristics, disease features, adverse events, and serious adverse events of RA, PsA, and AS patients treated with golimumab, other biologics or non-biologics to allow physicians to gain a better understanding of the relative risks and/or any treatment outcomes of golimumab. | • Serious infections including opportunistic infections and TB<br>• Demyelinating disorders<br>• Hypertension<br>• Lymphoma (excluding HSTCL)<br>• Hepatitis B virus reactivation<br>• Congestive heart failure<br>• Autoimmune processes<br>• Serious systemic hypersensitivity (including anaphylactic reaction)<br>• Vasculitis<br>• Psoriasis (new onset or worsening of pre-existing)<br>• Skin cancer<br>• Malignancy<br>• Serious hepatotoxicity<br>• Serious depression including suicidality<br>• Sarcoidosis/ sarcoid-like reaction<br>• Use in patients with hepatic impairment<br>• Use in patients with renal impairment<br>• Use in patients with a past history of latent or active TB<br>• Use in patients with concurrent malignancy or a history of malignancy<br>• Use in patients with active infections including HIV, hepatitis B, hepatitis C | Ongoing | Interim reports: planned annually<br>Final report:<br>February 2016 |

| Study/activity type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| | | • Use in patients with recent prior use of other biologics excluding anti-TNFα agents<br>• Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF<br>• Use in patients with a history of demyelinating disease<br>• Use in patients with a history of lupus or lupus like syndrome<br>• Long-term safety in adult patients | | |
| CNTO148ART4002<br>(non-interventional cohort, category 3) | Using a large US health insurance claims database to evaluate the incidence rate of selected outcomes of interest in a cohort of patients with RA, PsA, or AS initiating golimumab, other biologics or non-biologics. The risks in the golimumab cohort will be compared to those in similar patients in the control cohorts. | • Serious infections including opportunistic infections and TB<br>• Demyelinating disorders<br>• Hypertension<br>• Lymphoma (excluding HSTCL)<br>• Hepatitis B virus reactivation<br>• Congestive heart failure<br>• Autoimmune processes<br>• Haematologic reactions<br>• Serious systemic hypersensitivity (including anaphylactic reaction)<br>• Leukaemia<br>• Malignancy<br>• Serious hepatotoxicity<br>• Exposure during pregnancy<br>• Serum sickness<br>• Serious depression including suicidality<br>• Use in patients with hepatic impairment<br>• Use in patients with a past history of latent or active TB<br>• Use in patients with concurrent malignancy or a history of malignancy<br>• Use in patients with active infections including HIV, hepatitis B, hepatitis C<br>• Use in patients with recent prior use of other biologics excluding anti-TNFα agents<br>• Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF<br>• Use in patients with a history of demyelinating disease<br>• Use in patients with a history of lupus or lupus-like syndrome<br>• Long-term safety in adult patients | Ongoing | Interim reports:<br>Planned annually after 1000 patient years have been accrued in the SIMPONI-exposed RA cohort.<br>Final report:<br>September 2018 |

| Study/activity type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| CNTO148ART4001<br>(non-interventional cohort category 3) | Using the Swedish, Danish, and Finnish medical birth registers to collect and analyse information pertaining to pregnancy outcomes of women exposed to golimumab during pregnancy and the health status during the first year following delivery of their infants, relative to the background risk in patients treated with other biologics, non-biologic systemic therapy, and general population controls. | • Exposure during pregnancy | Ongoing | Interim reports planned annually<br>Final report:<br>February 2017 |
| MK-8259-013<br>(non-interventional cohort, category 3) | TBD | • Additional data regarding both continuation of treatment and interruption of treatment<br>• Colon cancer/dysplasia (in UC)<br>• HSTCL<br>• Long-term safety in adult patients in UC for colon cancer/dysplasia and HSTCL | Planned | TBD |

| Study/activity type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| C0524T18<br>(randomised, controlled, category 3) | To evaluate the efficacy of 2 SC administered regimens of golimumab in maintaining clinical response through Week 54 in subjects with moderately to severely active UC induced into clinical response with golimumab in the induction trials C0524T16 or C0524T17. Additionally, to evaluate the efficacy of golimumab in maintaining clinical remission at Weeks 30 and 54, to evaluate the efficacy of golimumab in maintaining mucosal healing at Weeks 30 and 54, to evaluate the efficacy of golimumab in maintaining clinical remission at Weeks 30 and 54 for subjects in clinical remission at Week 0, and to evaluate the efficacy of golimumab in achieving clinical remission and eliminating corticosteroid use at Week 54 among subjects receiving concomitant corticosteroids at Week 0. | • Long-term safety in adult patients | Ongoing | February 2016 |
| CNTO148UCO1001<br>(open label, category 3) | To evaluate the pharmacokinetics and safety of golimumab in paediatric subjects aged 2 through 17 years with moderately to severely active UC. Additionally, to evaluate the efficacy of golimumab induction (ie, short-term therapy) in these paediatric subjects. | • Use in paediatric patients with ulcerative colitis | Ongoing | August 2018 |

| Study/activity type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| MK-8259-042<br><br>(non-interventional observational study, category 3) | TBD | • Colon cancer/dysplasia (in UC)<br>• HSTCL<br>• Long-term safety in adult patients in UC for cancer/dysplasia and HSTCL | Planned | TBD |
| MK-8259-050<br><br>(non-interventional cohort using the German Biologics JIA Registry (BiKeR), category 3) | An observational post-authorisation safety study to investigate long-term safety of golimumab in pJIA subjects. | • Serious infections including opportunistic infections and TB<br>• Malignancies<br>• Autoimmune disorders<br>• Outcome of any pregnancies that occur during maternal exposure to study drugs<br><br>Secondary objectives will be to describe crude incidence rates of<br><br>• Demyelinating disorders<br>• Congestive heart failure<br>• Hypertension<br>• Serious hepatotoxicity<br>• Vasculitis<br>• Haematologic reactions<br>• Serious systemic hypersensitivity (including anaphylactic reaction)<br>• Serum sickness<br>• Hepatitis B virus reactivation<br>• Serious depression including suicidality<br>• Maladministration/ administration error<br>• Medication error (wrong dose related to different strengths)<br>• Psoriasis (new onset or worsening of pre-existing)<br>• Sarcoidosis/sarcoid- like reaction | Planned | TBD |

***Risk minimisation measures***

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| **Important identified risks:** | | |
| Serious infections including opportunistic infections and TB | The SmPC contraindicates the use of golimumab in patients with active TB or other severe infections such as sepsis, and opportunistic infections.<br>Serious infections including opportunistic infections and TB are specifically addressed in the Contraindications (4.3), Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC.<br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | • Educational Programme<br>• Patient Alert Card |
| Demyelinating disorders | Demylinating disorders are addressed in the Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8) sections of the SmPC.<br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed. |
| Hypertension | Hypertension is addressed in the Undesirable Effects (4.8) section of the SmPC.<br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Lymphoma (excluding HSTCL) | Lymphoma is specifically addressed in the Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC.<br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Hepatitis B virus reactivation | Hepatitis B reactivation is specifically addressed in the Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8) sections of the SmPC.<br>Guidance is provided on monitoring for hepatitis B infection as well as the management of hepatitis B infection.<br><br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | • Educational Programme<br>• Patient Alert Card |
| Congestive heart failure | The SmPC contraindicates the use of golimumab in patients with moderate or severe heart failure (NYHA class III/IV).<br><br>CHF is specifically addressed in the Special Warnings and Precautions and for Use (4.4) and the Undesirable Effects (4.8) sections of the SmPC.<br>Guidance is provided for patients with mild heart failure (NYHA class I/II) and new or worsening symptoms of heart failure.<br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | • Educational Programme<br>• Patient Alert Card |
| Autoimmune processes | Autoimmune processes are addressed in the Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8) sections of the SmPC.<br><br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed**.** |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Haematologic Reactions | Haematologic reactions are addressed in the Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8) sections of the SmPC.<br><br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Serious systemic hypersensitivity (including anaphylactic reaction) | The SmPC contraindicates the use of golimumab in patients with hypersensitivity to golimumab or to any of the excipients and provides medical advice on how to deal with these reactions.<br><br>Serious systemic hypersensitivity (including anaphylactic reaction) is specifically addressed in the Contraindications (4.3), Special Warnings and Precautions for Use (4.4), and the Undesirable Effects (4.8) sections of the SmPC.<br><br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | Educational Programme |
| Vasculitis | Vasculitis is included in the Undesirable Effects (4.8) section of the SmPC.<br><br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Psoriasis (new onset or worsening of pre-existing) | Psoriasis (new onset or worsening of pre-existing) is included in the Undesirable Effects (4.8) section of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Skin Cancer | Guidance about the overall risk of skin cancers, including melanoma and Merkel cell carcinoma and the need to perform periodic skin examinations is provided in the Special Warnings and Precautions for Use (4.4) section of the SmPC.<br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | Educational Programme |
| Leukaemia | Leukaemia is addressed in the Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8) sections of the SmPC.<br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk. Therefore, no additional risk minimisation activities are proposed. |
| Sarcoidosis/sarcoid-like reaction | Sarcoidosis is included in the Undesirable Effects (4.8) section of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| **Important potential risks:** | | |
| Malignancy | Guidance about the overall risk of malignancy, including paediatric malignancy, is provided in the Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8) sections of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed for the malignancy in general. |
| Serious hepatotoxicity | Hepatic disorders are included in the Undesirable Effects (4.8) section of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Exposure during pregnancy | Guidance is provided in the Fertility, Pregnancy, and Lactation (4.6) section of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed |
| Serum sickness | Guidance on serious systemic hypersensitivity reactions, including serum sickness, is provided in the Contraindications (4.3), Special Warnings and Precautions for Use (4.4), and the Undesirable Effects (4.8) sections of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | Educational Programme |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Maladministration/administration error | Detailed instructions on the proper technique of administering golimumab to minimise the risk of injury and assure proper drug delivery is provided in the Posology (4.2) and Method of Administration and Special Precautions for Disposal and Other Handling (6.6) sections of the SmPC, and the Instruction for Use section of the Package Leaflet.<br><br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | Educational Programme |
| Serious depression including suicidality | Depression is included in the Undesirable Effects (4.8) section of the SmPC.<br><br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Colon cancer/dysplasia (in UC) | Colon cancer/dysplasia (in UC) is addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC.<br><br>Medicinal product subject to restricted medical prescription.<br><br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of UC. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| HSTCL | Guidance about the overall risk of malignancy is in the Special Warnings and Precautions for Use (4.4) section of the SmPC.<br><br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Medication error (wrong dose related to different strengths) | Medication error (wrong dose related to different strengths) is addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC.<br>A separate SmPC for each strength is available.<br>The Applicant has minimised this potential for medication error by developing a packaging design that clearly differentiates the 2 strengths (50 mg and 100 mg). This will serve to ensure that the different presentations are distinct enough for healthcare professionals and patients to distinguish between and reduce any potential medication errors related to the injection of the wrong strength.<br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| **Missing information** | | |
| Use in paediatric patients with ulcerative colitis | The Posology and Method of Administration (4.2) section in the SmPC indicates that safety in patients aged less than 18 for indications other than pJIA have not been established. The Special Warnings and Precautions for Use (4.4) section provides information about the risk of malignancy in paediatric patients.<br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Use in patients with hepatic impairment | This safety concern is included in the Special Warnings and Precautions for Use (4.4) section of the SmPC.<br>Medicinal product subject to restricted medical prescription.<br>SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Use in patients with renal impairment | This safety concern is included in the Special Warnings and Precautions for Use (4.4) section of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Use in patients with a past history of latent or active TB | Guidance is provided in the Contraindications (4.3), and Special Warnings and Precautions for Use (4.4) sections of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Use in patients with concurrent malignancy or a history of malignancy | This safety concern is included in the Special Warnings and Precautions for Use (4.4) section of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Use in patients with active infections including HIV, hepatitis B, hepatitis C | Guidance is provided in the Contraindications (4.3), and Special Warnings and Precautions for Use (4.4) sections of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Use in patients with recent prior use of other biologics excluding anti-TNFα agents | Guidance is provided in the Special Warnings and Precautions for Use (4.4) and the Interactions with Other Medicinal Products and Other Forms of Interaction (4.5) sections of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF | Guidance is provided in the Contraindications (4.3), and Special Warnings and Precautions for Use (4.4) sections of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Use in patients with history of demyelinating disease | This safety concern is included in the Special Warnings and Precautions for Use (4.4) section of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Use in patients with a history of lupus or lupus-like syndrome | This safety concern is included in the Special Warnings and Precautions for Use (4.4) section of the SmPC.<br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Use in patients after recent vaccination with live bacterial or viral vaccine | Guidance is provided in the Special Warnings and Precautions for Use (4.4), Interactions with Other Medicinal Products and Other Forms of Interaction (4.5), and Fertility, Pregnancy, and Lactation (4.6) sections of the SmPC.<br><br>Medicinal product subject to restricted medical prescription. SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, PsA, AS, nr-Axial SpA, UC, or pJIA. | The Sponsor considers that the language included in the SmPC is sufficient to minimise the risk.<br>Therefore, no additional risk minimisation activities are proposed. |
| Long-term safety in adult patients | None proposed | None proposed |
| Long-term safety in paediatric patients | None proposed | None Proposed |

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Luxemburg.

### 2.7.1. User consultation

A justification for not performing a user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- The contents of the package leaflet have not significantly changed compared to the currently approved package leaflet
- These changes are limited to Sections 1, 2 and 3 of the package leaflet which have been revised to include a relatively small amount of information on the Juvenile Idiopathic Arthritis indication and the dosing in children and are comparable with the approved adult indications wording.

# 3. Benefit-Risk Balance

***Benefits***

**Beneficial effects**

Clinically meaningful efficacy was observed with golimumab + MTX treatment in all disease parameters during the open-label phase of the study through Week 16. This included ACR Ped responses which were observed as early as Week 4 and the proportions of treated subjects with ACR Ped 30, 50, 70, and 90 responses increased over time through Week 16. The proportion of subjects who were ACR Ped responders at Week 16 were high (ACR Ped 30: 87.3%, ACR Ped 50: 79.2%, ACR Ped 70: 65.9%, ACR Ped 90: 36.4%)

In ACR Ped components through Week 16 there were substantial clinically important improvements. Median percent improvements were 92% in number of active joints; 80% in number of joints with limited range of motion; 88% in physician global assessment of disease; 67% in parent assessment of overall well-being; 50% in physical function by CHAQ; and 33% in ESR.

The proportions of treated subjects with inactive disease increased over time and at Week 16 was 34% in all enrolled subjects.

**Uncertainty in the knowledge about the beneficial effects**

The primary and major secondary endpoints were not met; however analyses showed that the unexpectedly low inflammatory burden of the enrolled population (in comparison to studies performed over the past 10 years in JIA with different anti-TNFα) could potentially explains these findings.

This is supported by a differentiation in non-flare rates between subjects continuing treatment with golimumab + MTX versus placebo + MTX from Week 16 through Week 48 in the pre-specified subgroup analysis of subjects with baseline CRP of at least 1.0 mg/dL and post-hoc subgroup analyses among subjects with CRP levels >0.1 mg/dL at baseline. Placebo subjects in the higher CRP subsets experienced more flares compared with the placebo subjects in the entire population, with placebo flare rates in the higher CRP subsets more consistent with those observed in previous pJIA studies.

***Risks***

**Unfavourable effects**

Overall, the safety profile of golimumab which is known for studies in other rheumatological conditions in adults such as RA, PsA, and AS were also confirmed in the pJIA population. Through Week 48, the proportion of subjects experiencing at least 1 AE was comparable in the treatment groups, 84.6% in the Golimumab + MTX group and 93.4% in the combined Placebo group. . Adverse events that occurred in ⩾5% of all subjects included URTI (23.1%), nasopharyngitis (16.2%), JIA (15.0%), pyrexia (12.1%), headache (11.6%), nausea (9.2%), abdominal pain (8.7%), oropharyngeal pain and vomiting (6.9% each), abdominal pain upper, diarrhea, gastroenteritis, and respiratory tract infection (6.4% each), and urticaria (5.2%). There were no meaningful differences noted between treatment arms.

Comparisons to safety results in earlier Adult RA studies showed that paediatric incidences were similar to adult incidences for serious infections. Paediatric incidences were lower than adult incidences for AEs leading to discontinuation and for injections with injection-site reactions. Paediatric incidences were

higher than adults for AEs, serious adverse events (SAE), and infections. The higher incidence of all AEs in children appears to be largely driven by the higher incidence of infections in children. Given that children have an increased susceptibility to infections compared to adults, the higher infection rate in the paediatric population is not unexpected.

**Uncertainty in the knowledge about the unfavourable effects**

Exposure to golimumab in paediatric patients with pJIA is limited, and therefore the long term safety effects of golimumab in this population are not extensively characterised. This will be addressed through a registry which will allow the collection of further long term data through evaluation of the risk of serious infections, malignancies and autoimmune disorders in this population and which has been included in the Risk Management Plan of Simponi.

***Effects Table***

**Table 17**. Effects Table for golimumab in pJIA

| Effect | Short Description | Unit | GOL +MTX | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|
| **Favourable Effects** | | | | | |
| Responders at week 16 | ACR Ped 30 | % | 87.3 | Uncontrolled data, but in line with historical data for other anti-TNFs<br><br>Primary and major secondary endpoints of the trial failed at week 48, possibly due to significant suppression of inflammatory burden achieved at week 16<br><br>Extrapolation of efficacy in pJIA from adults in RA | All enrolled subjects in CNTO148JIA3001 |
| Inactive disease at week 16 | No joint with active arthritis, normal ESR. CPR and PGA | | 34.3 | | |
| **Unfavourable Effects** | | | | | |
| Infections | All<br>Serious | % | 79.2<br>6.5 | Other serious known effects of golimumab not observed, possibly due to limited size of safety database but can be expected from known safety profile in adults | All randomised subjects in CNTO148JIA3001 |

*ACR Ped: American College of Rheumatology Pediatric; N/A: Not applicable; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PGA: Physicians Global Assessment*

***Benefit-Risk Balance***

**Importance of favourable and unfavourable effects**

Clinically relevant short-term efficacy of golimumab in the treatment of pJIA has been shown. The most relevant safety concerns of identified so far are related to infections. Appropriate measures to minimise this risk are included in the SmPC and further information on this issue will be collected as described in the RMP. Additional evidence of efficacy and safety can be extrapolated from relevant data

in adult patients.

**Benefit-risk balance**

**Discussion on the Benefit-Risk Balance**

The evolution of knowledge of pJIA has established that there is sufficient similarity between adult rheumatoid arthritis and paediatric pJIA in terms of disease progression and response to anti-TNFα agents. In this context, the open-label efficacy data from study CNTO148JIA3001 are considered sufficient to demonstrate the significant benefit of golimumab in pJIA. In addition, drug exposure in children using the proposed dosing appears to be similar to adults treated with Simponi 50mg q4w and PK-modelling indicates a dose response relationship. Given that disease progression and response to anti-TNFα therapy are believed to be similar between children and adults, the pharmacokinetic data, exposure-response modelling, and clinical efficacy through Week 16 would be considered sufficient evidence of benefit in the framework of extrapolation.

No new safety signals have emerged from the study in pJIA. The safety profile of golimumab in paediatric patients appears consistent with that in adults.

The totality of available data from study CNTO148JIA3001, together with the reasonable extrapolation of efficacy, PK and safety from the adult to the paediatric population confirms the positive benefit-risk balance for golimumab in pJIA in children with a body weight of at least 40 kg, who have responded inadequately to previous therapy with MTX.

# 4. Recommendations

***Outcome***

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Extension of indication to add a new indication for Simponi in the treatment of polyarticular juvenile idiopathic arthritis in combination with methotrexate in children with a body weight of at least 40 kg, who have responded inadequately to previous therapy with methotrexate; consequently, SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 have been revised to include new efficacy, PK and safety information. The Package Leaflet and RMP have been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.0.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

***Paediatric data***

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0226/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

***Scope***

Extension of indication to add a new indication for Simponi in the treatment of polyarticular juvenile idiopathic arthritis in combination with methotrexate in children with a body weight of at least 40 kg, who have responded inadequately to previous therapy with methotrexate; consequently, SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 have been revised to include new efficacy, PK and safety information. The Package Leaflet and RMP have been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.0.

***Summary***

Please refer to the scientific discussion Simponi EMEA/H/C/00993/II/0063.