13 December 2018
EMA/898638/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Simponi

International non-proprietary name: golimumab

Procedure No. EMEA/H/C/000992/0000/X/0083/G

Note

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

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List of abbreviations

ACR	American College of Rheumatology
ADR	adverse drug reaction
AE	adverse event
AS	ankylosing spondylitis
ATC	Anatomical Therapeutic Chemical
AUCss	area under the curve steady-state
AxSpA	axial spondyloarthritis
BPS	Baxter Pharmaceutical Solutions
BSA	body surface area
CDC	Center for Disease Control and Prevention
CHAQ	Childhood Health Assessment Questionnaire
CHMP	Committee for Medicinal Products for Human Use
CHQ	Child Health Questionnaire
CL/F	apparent clearance
Cmin,ss	steady-state trough serum concentrations
CRP	C-reactive protein
CV%	percentage coefficient of variance
DBL	database lock
DP	Drug Product
DS	Drug Substance
ER	exposure-response
ERA	enthesitis related arthritis
ESR	erythrocyte sedimentation rate
EU	European Union
FB	Formulated bulk
IgG1κ	human immunoglobulin G1κ monoclonal antibody
ILAR	International League of Associations for Rheumatology
JADAS	Juvenile Arthritis Disease Activity Score
JIA	juvenile idiopathic arthritis
JPsA	juvenile psoriatic arthritis
ka	absorption rate constant

LTE	long-term extension
MTX	methotrexate
PD	pharmacodynamics
PDCO	Pediatric Committee
PFP	prefilled pen
PFS	prefilled syringe
PFS-V	Assembly of the PFS into the VarioJect device
PIP	Pediatric Investigational Plan
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetics
PL	Package Leaflet
PsA	psoriatic arthritis
q4w	every 4 weeks
QRD	Quality Review of Documents
RA	rheumatoid arthritis
RF	rheumatoid factor
RMP	risk management plan
SAE	serious adverse event
SC	subcutaneous
SOC	system-organ classes
sJIA	systemic juvenile idiopathic arthritis
SmPCs	Summary of Product Characteristics
TB	tuberculosis
TNFα	tumor necrosis factor alpha
V/F	apparent volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

Janssen Biologics B.V. submitted on 23 March 2018 a group of variations consisting of an extension of the marketing authorisation and the following variations:

Variations requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	IB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	IB

Extension application to add a new strength of 100 mg/ml solution for injection for paediatric use.
C.I.6.a - Extension of indication to include paediatric patients from the age of 2 years and older for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) with Simponi 100 mg/ml solution for injection. As a consequence, sections 4.1, 4.2, 5.1 and section 4.1 of the 50mg strength have been updated accordingly.
C.I.11.z - To update the RMP to version 18.0 to delete the following safety concerns: vasculitis, psoriasis (new onset or worsening of pre-existing), and sarcoidosis/sarcoid like reaction. This change has been agreed by the CHMP in the outcome of variation Type II/068.
C.I.11.z - To update the RMP to version 18.0 to change the due date of the category 3 study MK-8259-050. This change has been agreed by the CHMP in the outcome of MEA033.
In addition, the marketing authorisation holder took the opportunity to:
- update the Product Information in line with the latest QRD template (version 10);
- implement the recommendations stated in the revised Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' with regards to the excipient Sorbitol (E420);
- add a statement in Section 4.4 of the SmPC to record the name and the batch number of the administered product, in line with Good Pharmacovigilance Practice (GVP) Module PII: Biological medicinal products.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

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 MAH 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 MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

The application was received by the EMA on	23 March 2018
The procedure started on	24 May 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	9 July 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 September 2018
The MAH submitted the responses to the CHMP consolidated List of Questions on	12 October 2018
The Rapporteur circulated the Assessment Report on the responses to the List of Questions to all CHMP members on	13 November 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 November 2018
The Rapporteur circulated the updated Assessment Report to all CHMP members on	6 December 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Simponi on	13 December 2018

2. Scientific discussion

2.1. Problem statement

In this application the MAH propose to introduce a new presentation for paediatric use, 45 mg/0.45 ml in pre-filled pen, and to broadening the pJIA indication from children with a body weight of at least

40kg to children 2 years of age or older. The clinical data supporting this change is derived from study CNTO148JIA3001, together with the reasonable extrapolation of efficacy, PK and safety from the adult to the paediatric population. This data was previously assessed confirming the positive benefit-risk balance for golimumab in pJIA in children in procedure variation EMEA/H/C/000992/II/63. However, as that time a presentation that can be dosed per body area was not yet available and therefore, the use of the product in pJIA was limited to the population that can use the available formulation i.e. children with a body weight of at least 40 kg.

2.1.1. Disease or condition

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.

2.1.2. Epidemiology

JIA has an annual incidence of 2 to 20 cases per 100,000 population and a prevalence of 16 to 150 cases per 100,000 population. JIA is less common than RA in adults but it is one of the most common systemic autoimmune diseases in children and adolescents.

2.1.3. Biologic features

Although the aetiology and pathogenesis of JIA are not fully understood, it is known that JIA shares many of the pathological abnormalities that have been identified in RA. At the same time multiple differing pathogenesis and phenotypic features exist between the JIA categories. Increased production of cytokines in different forms of JIA (e.g.interleukin-1ß and interleukin-6 in sJIA, tumor necrosis factor-alpha (TNF-α) in polyarticular JIA) in conjunction with osteoclastic cell activation leads to degradation of adjacent cartilage and bone.

2.1.4. Clinical presentation, diagnosis

Chronic arthritis in childhood is a heterogeneous group of diseases. The International League of Associations for Rheumatology (ILAR) introduced a nomenclature and classification for JIA. The currently used ILAR classification distinguishes the following JIA categories:

- Systemic JIA (sJIA)
- Polyarthritis rheumatoid factor (RF) negative
- Polyarthritis RF positive
- Oligoarticular arthritis (2 subcategories based on joint count after 6 months)
    - Persistent (not more than 4 joints)
    - Extended (more than 4 joints)
- Psoriatic arthritis (JIA-PsA)
- Enthesitis related arthritis (ERA)
- Undifferentiated arthritis

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 (i.e., polyarticular JIA, enthesitis related arthritis [ERA], and juvenile psoriatic arthritis [JPsA], respectively).

2.1.5. Management

For JIA, NSAIDs are the usual first-line treatment, since they are considered to be the least toxic agent in children. They provide symptomatic relief, but are not considered to be disease-modifying. Methotrexate (MTX) is considered to have an acceptable level of toxicity relative to its efficacy; most children demonstrate at least some response to MTX therapy, although remission is rare. Other types of traditional medications commonly used to treat rheumatoid arthritis (RA) in adults are less preferable for use in paediatric subjects. Five biologic agents including golimumab are approved for the treatment of pJIA. Besides golimumab, 2 of these are TNF-inhibitors, dosed once weekly and q2w respectively.

About the product

Golimumab is a human monoclonal IgG antibody that binds to human tumor necrosis factor alpha (TNFα), thereby neutralizing the biological activity of TNFα. Simponi is an immunomodulator whose mechanism of action is inhibition of TNFα.

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, and UC and in children with a body weight of at least 40 kg in pJIA.

This new presentation, Simponi 45 mg/0.45 mL solution for injection in pre-filled pen (VarioJect), is intended for paediatric use and SC administration. The pre-filled pen delivers volumes ranging from 0.10 – 0.45 mL with 0.05 mL increments.

The identical pre-filled syringe (PFS) and formulation (100 mg/ml), as used in the already approved Simponi 50 mg presentations in pre-filled syringe and pre-filled pen, is used for the assembly into the VarioJect pre-filled pen.

The following paediatric indication was approved for Simponi 50 mg solution for injection in pre filled pen and pre filled syringe (Variation EMEA/H/C/000992/II/63):

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Simponi in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children with a body weight of at least 40 kg, who have responded inadequately to previous therapy with MTX.

At the time of assessment of this variation the CHMP concluded as follows:

"*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."

Type of Application and aspects on development

At the time of the CHMP's positive opinion of Variation EMEA/H/C/000992/II/63, the pJIA indication could not yet be registered for those subjects who require a dose less than 50 mg, as an age appropriate presentation was still being developed. The indication was therefore approved for those subjects weighing at least 40 kg as they could use a dose of 50 mg.

A new presentation of golimumab for paediatric use has now been developed. The new product, Simponi 45 mg/0.45 ml is presented in a single use pre-filled pen (VarioJect) intended for SC administration in the dose range 0.1 to 0.45 ml. This new formulation would allow dosing in children weighing less than 40kg, who can now be dosed by body surface area (BSA). The proposed dosing is every fourth week, which would be of benefit in the targeted population.

The MAH sought the following indication for this new presentation:

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Simponi in combination with methotrexate (MTX) is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

In addition, the MAH proposed to change the indication for the 50 mg solution for injection in pre filled pen and pre filled syringe as follows:

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Simponi in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older ~~with a body weight of at least 40 kg~~, who have responded inadequately to previous therapy with MTX.

Since the pivotal study CNTO148JIA3001 included children aged 2-17 years, no additional data was submitted with the current application.

2.2. Quality aspects

2.2.1. Introduction

A new strength of golimumab for paediatric use has been developed. The new strength, Simponi 45 mg/0.45 ml is presented as a solution for injection in a single use pre-filled pen (VarioJect) intended for subcutaneous (SC) administration. The currently approved Simponi presentations include:

- Simponi 50 mg solution for injection in pre filled pen (SmartJect)
- Simponi 50 mg solution for injection in pre filled syringe
- Simponi 100 mg solution for injection in pre filled pen (SmartJect)
- Simponi 100 mg solution for injection in pre filled syringe

The proposed finished product is presented as a solution for injection in a pre-filled pen (VarioJect), containing 45 mg/0.45 ml of golimumab as active substance. The pre-filled syringe (PFS) and formulation used for the assembly into the VarioJect pre-filled pen are identical to those used in the already approved Simponi 50 mg presentations in pre-filled syringe and pre-filled pen.

Other ingredients are: histidine, sorbitol, polysorbate 80 (PS 80) and water for injections. The product is available in the pack size of 1 pre-filled pen as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Golimumab is a human immunoglobulin G1κ (IgG1κ) monoclonal antibody that binds to human tumor necrosis factor alpha (TNF α), thereby neutralizing the biological activity of TNF α. Simponi is an immunomodulator whose mechanism of action is inhibition of TNF α.

There is no 3.2.S provided with this application. The golimumab active substance used for the manufacture of the Simponi 45 mg/0.45 ml strength will be manufactured and tested according to the currently approved Marketing Authorisation.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The new Simponi 45 mg/0.45 ml strength applied for in this line extension is supplied as a sterile solution in a single-use, pre-filled pen (VarioJect). The finished product is filled in a pre-filled syringe (PFS), which is further assembled into the VarioJect delivery device which allows dosing in the range 0.10-0.45 ml (0.05 ml increments). The PFS is composed of a 1-mL long syringe with a fixed needle, stoppered with a grey plunger stopper. The 50 mg (0.5 mL) prefilled syringe as used in the already approved Simponi 50 mg presentations in pre-filled syringe and pre-filled pen is identical to that used for the assembly into the VarioJect.

The excipients are shown in Table 2 below.

Table 1: Excipients used in the Simponi PFS

Material	Function	Grade
L-Histidine	Buffer	USP/EP
L-Histidine monochloride monohydrate	Buffer	EP
Sorbitol	Stabilizer/Tonicifier	NF/EP
PS 80	Surfactant	NF/EP
WFI	Solvent	USP/EP

The VarioJect (PFS-V) is a pre-filled pen for single use which allows variable doses with 0.05 ml increments in the range 0.1 to 0.45 ml. The PFS-V is not currently approved for marketing.

According to the SmPC guideline, when the amount to be given is calculated on the basis of the patient's weight or body surface or other variable ('partial use'), the quantity of active substance(s) should be stated per ml. However in this case the strength of the product is declared as 45 mg/0.45 ml i.e. the maximum dose. Although the proposed expression of strength may be misinterpreted that the dose is always the total volume of 0.45 ml, the applicant's rationale for the chosen way of declaring the strength of the product, highlighting the importance of making a clear distinction between the 3 strengths available in the EU, is acknowledged and was found acceptable. In particular, the risk of mix-up between the 100 mg strength and the new strength, if expressed as 100 mg/ml, was noted.

The VarioJect is the drug delivery device component of the drug-device combination intended to be marketed. The VarioJect is a pre-filled, manually-operated, variable dose, single use, disposable, needle safety, drug delivery device for the subcutaneous administration of liquid biologic drug products. The VarioJect is a clean (not sterile) device with no direct contact with the drug product.

It is designed for and pre-assembled with a standard 1-mL long syringe with a fixed, 27 gauge (G) ½-inch stainless steel needle. The syringe is pre-filled with 0.5 mL of finished product solution and then assembled with the VarioJect.

The PFS-V allows for the administration of 1 of 8 different user-selected volumes ranging from 0.10 to 0.45 mL in 0.05 mL increments.

Comprehensive technical information on the VarioJect Device has been provided.

The container closure integrity following the assembly of the PFS into the VarioJect device and the shipment has been addressed. It has been acceptably demonstrated that the assembly process did not have an impact on the integrity of the primary package.

The information about the development of the VarioJect and compliance with relevant criteria is found acceptable. Consideration has been given to relevant guidance and requirements pertaining to medical devices during the development. Documentation has been provided supporting that the essential requirements of the Medical Device Directive apply for safety and performance-related device features. The applicant has also provided a review to demonstrate compliance with relevant ISO standards. A risk analysis according to ISO 14971:2012 was conducted to identify, evaluate and control risks during the defined development phases. This is found acceptable.

The manufacturing process development of the device assembly process has been described. The devices are received as subassemblies consisting of 2 parts: the Dose Unit subassembly and the Syringe Unit subassembly. A failure mode and effect analysis (FMEA) was performed according to ICH Q9 and ISO 14971 Medical devices - Application of Risk Management to Medical Devices. Process parameters are in place to ensure the process produces the desired quality.

Furthermore, an assessment of the biocompatibility of the patient contacting materials in accordance with the ISO 10993-1, Biological Evaluation of Medical Devices was performed. It has been sufficiently demonstrated that the materials selected for the VarioJect are biocompatible.

Manufacture of the product and process controls

All manufacturers of relevance for the manufacturing, testing and release of the new presentation 45 mg/0.45 ml in pre-filled pen (VarioJect) are already approved for the currently registered Simponi presentations. Batch release is performed at Janssen Biologics B.V., The Netherlands.

The VarioJect subassemblies are received from qualified suppliers and are stored in quarantine until release. The finished product is manufactured ready for assembly with the VarioJect subassemblies and the assembled product is referred to as PFS-V.

The assembly, labelling, and secondary packaging processes are not to exceed the cumulative validated hold time exposure to room temperature for these processes.

An acceptable overview of the manufacturing process, critical steps and in-process controls (IPCs) has been provided. The control strategy has been acceptably addressed.

The process validation of the final assembly of the pre-filled syringe in the VarioJect (PFS-V) consisted of the production and evaluation of batches of finished product and placebo. Compliance with process controls or IPCs was confirmed and the validation results for the validation batches demonstrate compliance with the finished product specification.

Product specification, analytical procedures, batch analysis

Release and shelf-life specifications for the pre-filled syringe are the same as for currently approved products and therefore not further addressed here.

Release and shelf-life specifications are in place for the assembled PFS-V to ensure the functionality of the device and include appearance, functionality testing before and after actuation, needle protrusion length, delivered volume, and cover sleeve defeat force.

The specifications are considered adequate to control the functionality of the PFS-V.

The methods are found acceptably validated and suitable for its intended use.

The acceptance criteria for the control of delivered volume complies with ISO 11608-1. For the lower doses (0.10 to 0.40 mL) the dose accuracy limits are even tighter than specified by the ISO standard to fulfil the USP requirements. The proposed acceptance criteria are found acceptably justified from a clinical safety point of view. Taken together, the applicant has satisfactory justified the proposed acceptance criteria for the control of delivered volume.

The specification limit for cover sleeve defeat force has been acceptably justified. Also the acceptance criterion for needle protrusion length is found acceptably justified taken into account the chosen needle length (4.5 mm).

Batch analysis

All batch results for the test of finished product are well within specification and confirm acceptable reproducibility in relation to the functionality of the finished product.

Stability of the product

In line with the currently approved Simponi presentations in pre-filled syringe and pre-filled pen, using the identical pre-filled syringe (PFS) with the same formulation, a shelf life of 22 months when stored at 2-8 °C and protected from light is proposed.

To support this claim the Applicant has provided data from on-going functional stability studies. All results comply with the specification.

The approach referring to the established shelf life of the pre-filled syringe and only focusing on a functional stability study of the assembled pre-filled pen (VarioJect) is acceptable taking into account the data demonstrating that the assembly process has no impact on the quality of the finished product solution in the PFS.

The data provided does not indicate any significant difference in stability trend compared to the currently approved Simponi presentations.

Although the biochemical stability study is still on-going the claimed shelf life (22 months at 2-8 °C) for the finished product (PFS-V) is found acceptably justified.

Adventitious agents

No new information has been provided in relation to adventitious agents. This is acceptable since the manufacture of the active substance and the pre-filled syringe used for the assembly of the finished product is identical to the currently approved Simponi presentations.

Regional information, Medical device issues

The VarioJect is the delivery device component of the combination product applied for and is intended for the subcutaneous administration of a single dose in the range of 0.10 to 0.45 mL in 0.05 mL increments.

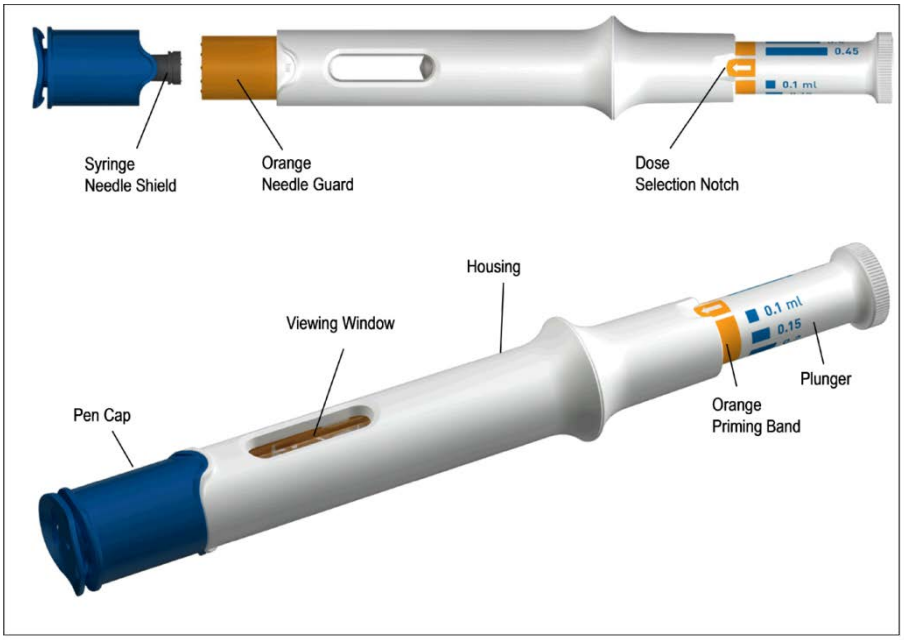
Risk related to the VarioJect is being managed according to ISO 14971:2012 Medical Devices - Application of Risk Management to Medical Devices. Comprehensive technical information about the VarioJect's design, performance characteristics, and manufacture, including results from relevant studies (summative human factors, formative, ethnographic) are provided in 3.2.R.2, Medical Devices, VarioJect. This information also includes a completed Essential Requirements checklist demonstrating that the PFS-V and the applicant are in conformance with Annex I, Essential Requirements of the Medical Device Directive.

Design verification testing was guided by the FDA draft guidance on injectors and relevant ISO standards, including IS0 11608-1:2014 Needle-based injection systems for medical use -Requirements and test methods – Part 1, to confirm that the performance specifications for the PFS-V were met.

Comprehensive information about device development and verification, performance characteristics and assembly operation has been provided.

An overview of the studies conducted to support the usability of the Varioject has also been provided in this section. This is further commented in the clinical part.

Figure 1: ***VarioJect Schematic***



2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure a multidisciplinary major objection was raised about the dose accuracy of the pen. In response the applicant satisfactorily justified adherence to the ISO 11608-1. For the lower doses (0.10 to 0.40 mL) the dose accuracy limits are even tighter than specified by the ISO standard to fulfil the USP requirements. In addition, the proposed acceptance criteria were further justified from a clinical safety point of view. Taken together, the responses were considered satisfactory and the acceptance criteria are considered justified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

No new clinical data have been submitted in this application.

2.3.1. Ecotoxicity / environmental risk assessment

Since golimumab is an antibody (i.e. a protein), the product is not expected to pose a risk to the environment when used according to the labelling. Therefore, it is considered acceptable that no formal ERA according to the EMA 2006 Guideline (corr. 2) is needed for golimumab.

2.3.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application. This is considered acceptable in the paediatric population.

2.3.3. Conclusion on the non-clinical aspects

is considered acceptable to the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

The proposed extension of indication is based on the data submitted and assessed by the CHMP as part of the variation EMEA/H/C/000992/II/63. No new PK, efficacy and safety data were submitted as part of this application. Therefore, a summary of these data is included in the sections below. Reference to the CHMP AR for variation EMEA/H/C/000992/II/63 is made for the full assessment of the data.

- Tabular overview of clinical studies submitted as part of variation EMEA/H/C/000992/II/63

Study Type					
Study ID EudraCT Number First Patient First Visit / Completion date (day Month year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)
Efficacy and Safety Controlled Clinical Study					
CNTO148JIA3001 Synopsis 2009-015019-42 1 Dec 2010 27 May 2014 Terminated	AUT, BEL, BRA, CAN, FIN, DEU, LTU, MEX, NLD, POL, RUS, USA: 33	Phase 3 A multicenter, double-blind, randomized-withdrawal study. 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. 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 Treated with golimumab: 173	Single-use, sterile solution in a 1 mL pre-filled syringe (PFS) for subcutaneous (SC) administration **Active Treatment (Week 0 Through Week 12):** 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 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.

2.4.2. Pharmacokinetics

No new studies were submitted to support the current application; the pharmacokinetics of golimumab in children with pJIA aged 2-17 was assessed in variation EMEA/H/C/000992/II/63. A summary of the PK in children with pJIA is presented below.

The PK and immunogenicity data of golimumab were evaluated in paediatric (2 to 17 years) subjects with pJIA in study CNTO148JIA3001. Samples for PK and immunogenicity assessments were taken through Week 144 of the study.

In study CNTO148JIA3001, subjects received BSA adjusted doses (mg/m2) to manage the PK variability observed in children across different ages. The 30 mg/m2 (up to a maximum dose of 50 mg) SC golimumab q4w + MTX treatment regimen studied in study CNTO148JIA3001 was selected to be equivalent to the adult subject's with RA SC golimumab 50 mg q4w + MTX treatment regimen. Therefore, the observed concentrations were compared between the 30 mg/m2 paediatric pJIA treatment regimen in study CNTO148JIA3001 and the 50 mg SC adult treatment regimen in study C0524T06, a Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Rheumatoid Arthritis Despite Methotrexate Therapy, (after Week 76 with the same PK assay) on the Meso Scale Discovery platform and is presented in the figure below.

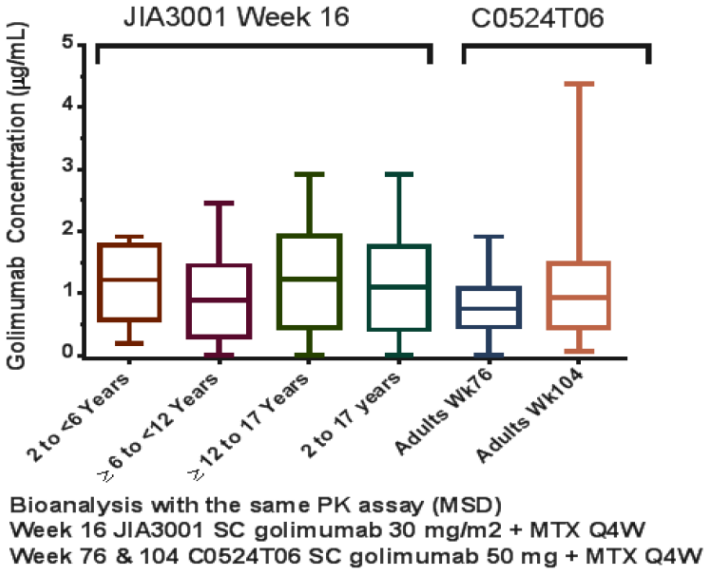


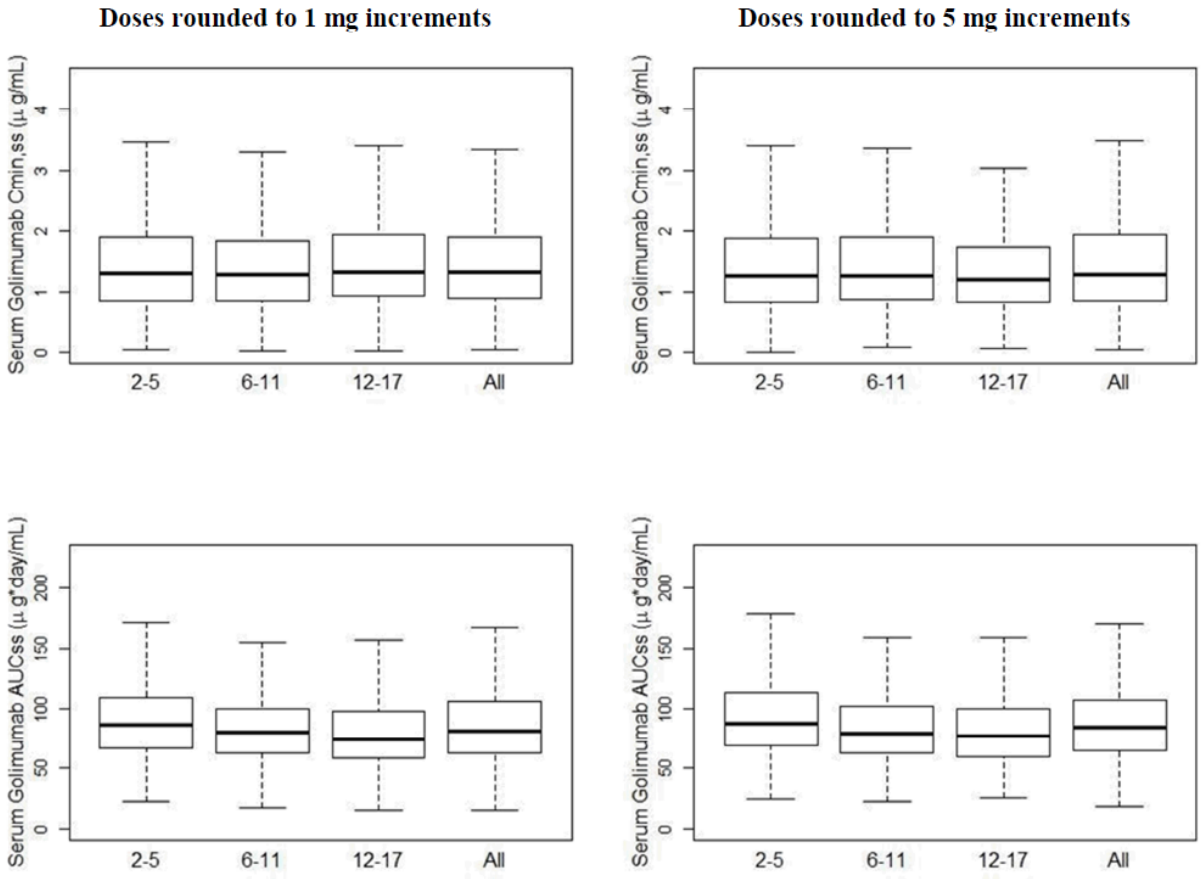
Figure 2 Comparison of Steady-State Trough Golimumab Concentrations (µg/mL) in Pediatric Subjects with pJIA in Study CNTO148JIA3001 and Adult Subjects with RA in C0524T06.

Overall, following the BSA-based dosing (30 mg/m2 with a maximum dose of 50 mg q4w) steady-state serum concentrations obtained in subjects with pJIA appeared to be within the range of those previously observed in adult RA subjects. Steady-state trough golimumab levels in pJIA 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 concentrations were similarly maintained through Week 144 of the long-term extension (LTE).

Justification for the Proposed Posology for the pJIA Indication for Subjects Below 40 kg

To support the proposed presentation deliver golimumab in 5 mg (0.05 mL) increments, comparisons of simulated exposures given 5 mg or 1 mg increments, respectively, have been provided. A dataset for 1000 subjects based on the Center for Disease Control and Prevention growth chart was created and the PK model was used to provide exposure metrics. The simulated $C_{min,ss}$ and AUC_{ss} values are presented in the figure below. The PK simulation indicates that rounding doses in increments of 5 mg

has minimal impact on the PK exposure in the context of the inherent inter-subject PK variability (percentage coefficient of variance [CV%]=31% for CL/F) for SC golimumab.



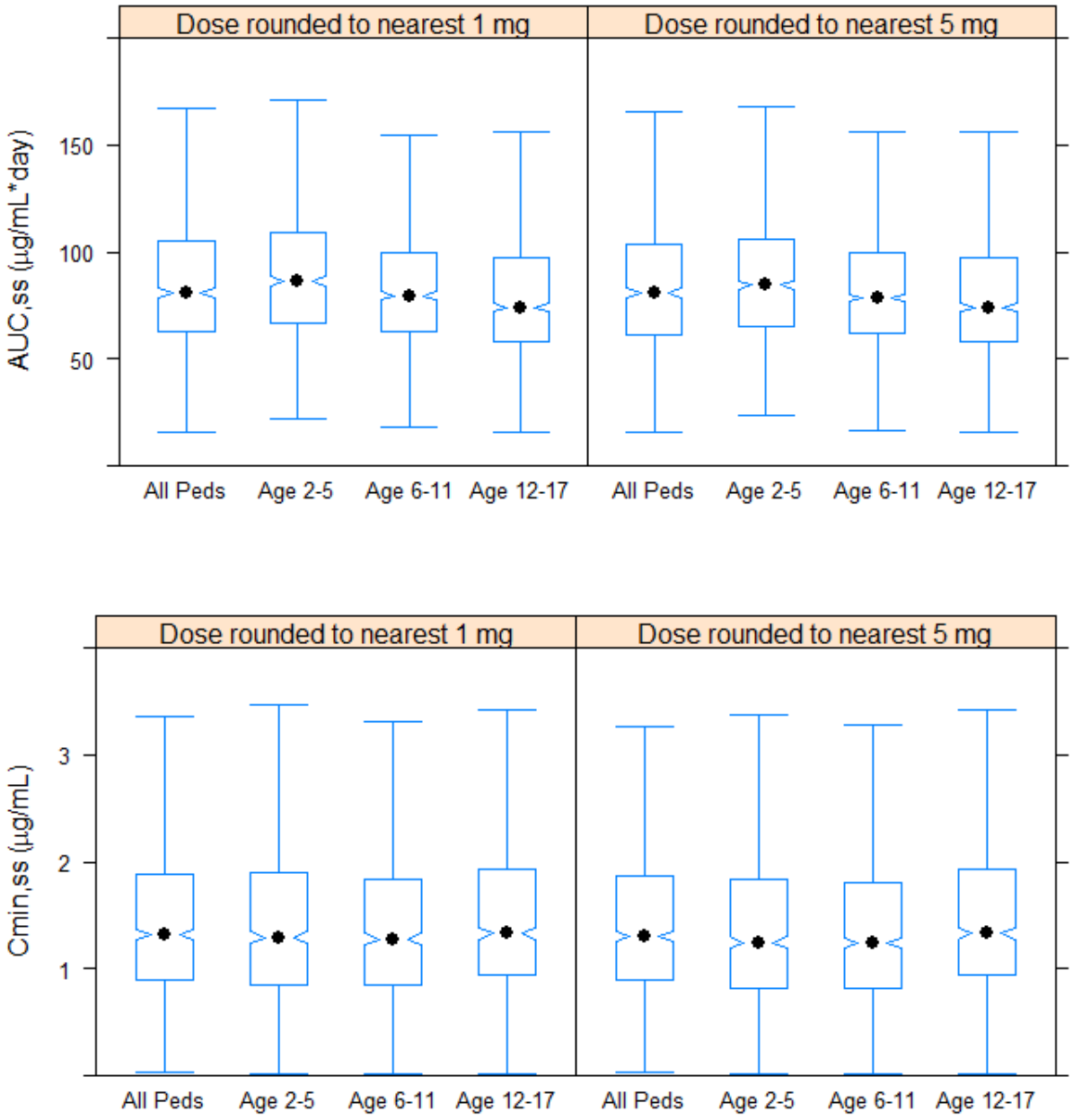
Note: Notches are drawn at data medians. Box edges are drawn at the medians of the upper and lower halves of the data. Whiskers are drawn at the most extreme observations to fall within 1.5x the inter-quartile range.
Key: AUC_{ss}=area under the curve steady-state; $C_{min,ss}$=steady-state trough serum concentrations; pJIA= polyarticular juvenile idiopathic arthritis.

Figure 3 Simulation of Cmin,ss and AUCss for pJIA Subjects for Doses Rounded to the Nearest 1 mg (Left Panels) or in 5 mg Increments (According to the Dosing Chart; Right Panels)

The MAH was asked to further justify from a clinical safety point of view the acceptance criteria for the control of delivered volume of the pre-filled pen.

The MAH has therefore provided background history on the development of the paediatric presentation. Due to the complexity of calculating BSA, a paediatric presentation that could deliver 3 tiered-fixed doses was in 2013 discussed at a meeting at the MPA. The advice received was to further personalize the doses by 5mg increments, based on a BSA-based dosing regimen.

To justify the currently proposed 5 mg dosing increment, simulations performed with the population PK model developed from CNTO148JIA3001 has been provided (figure below). It is acknowledged that steady-state golimumab exposures are expected to be similar when rounding the nearest 1mg or 5 mg in all age groups.



Notches 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 inter-quartile range (IQR).

Figure 4 Simulation of Cmin,ss and AUCss for pJIA Subjects for Doses Rounded to the Nearest 1 mg or 5 mg

The MAH also presented PK-simulations to justify the proposed acceptance criteria showing simulated serum golimumab concentrations through Week 48 (figure below), using the example where a dose of 0.25 mL may be in the range up to 0.3mL. This shows small differences in drug exposure with overlapping overall PK-concentrations. The variability was shown to be similar to adults <60kg and <80 kg.

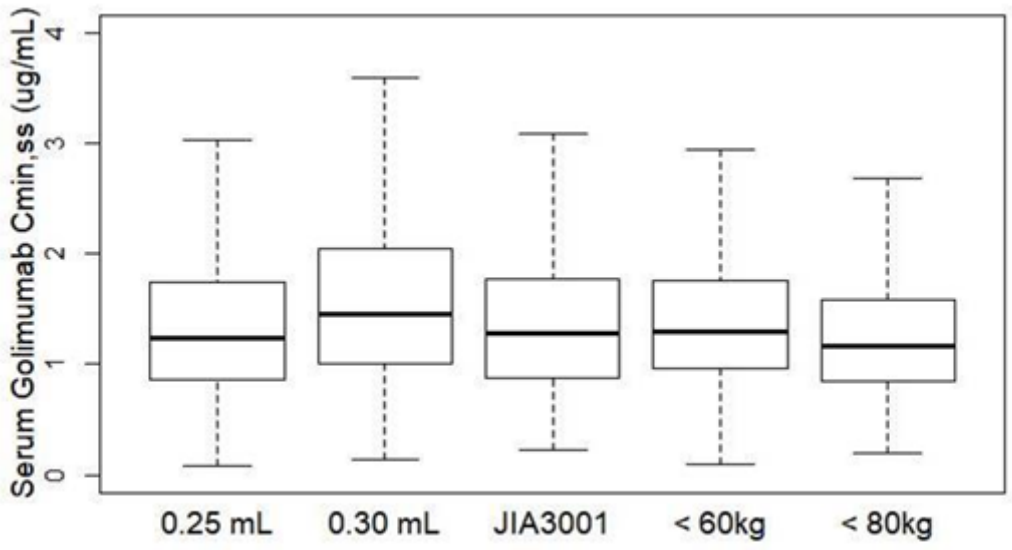


Figure 5 Simulated serum golimumab concentrations through Week 48

2.4.3. Pharmacodynamics

Mechanism of action

Golimumab is a human monoclonal IgG antibody that binds to human tumor necrosis factor alpha (TNFα), thereby neutralizing the biological activity of TNFα. Simponi is an immunomodulator whose mechanism of action is inhibition of TNFα.

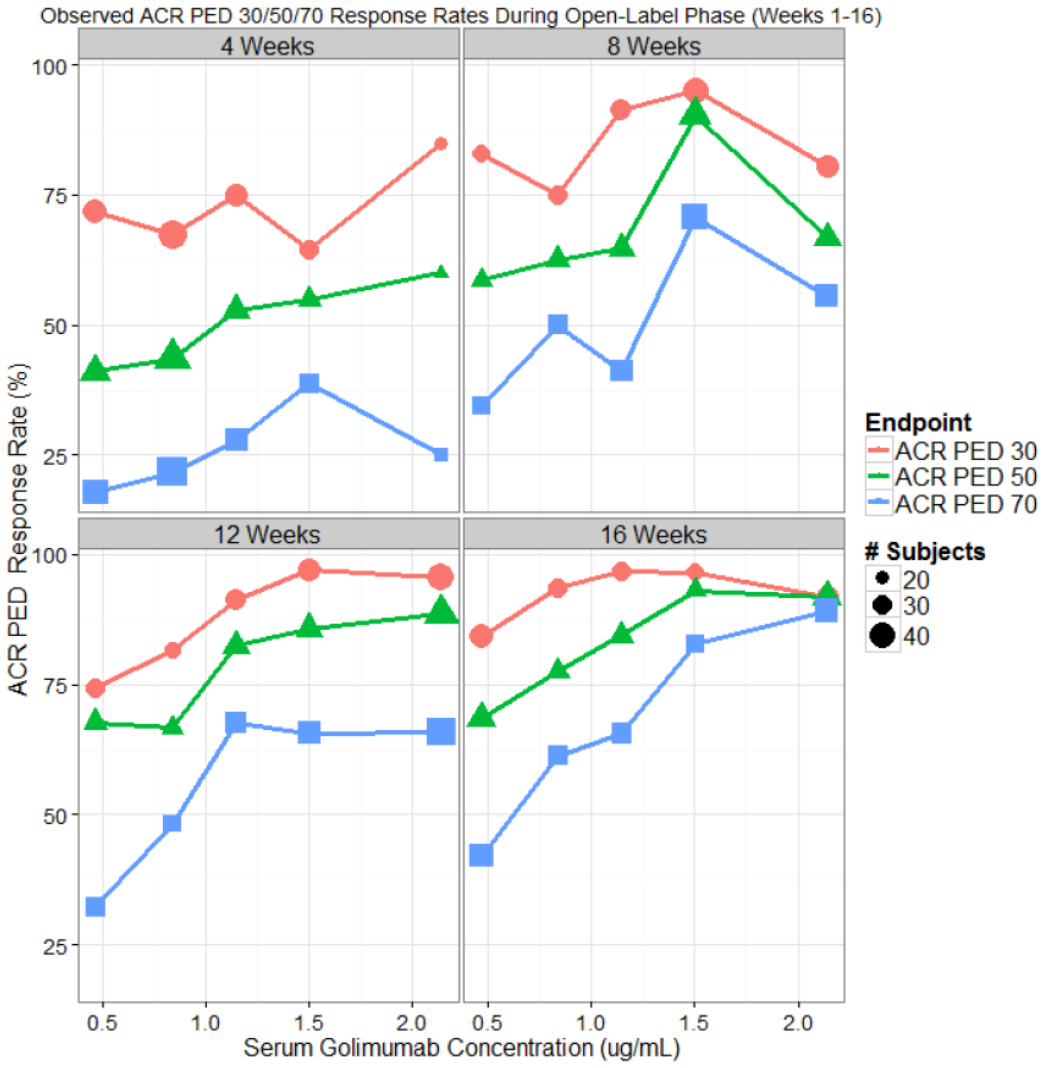
Primary and Secondary pharmacology

No new exposure-response (ER) data was submitted as part of this application. The exposure-response relationships for American College of Rheumatology (ACR) Ped responses and Juvenile Arthritis Disease Activity Score (JADAS)-71 responses, based on the open-label and randomized withdrawal phases of CNTO148JIA3001, were provided in Variation EMEA/H/C/000992/II/63. A summary of the ER analyses are presented below.

The ER relationship of ACR Ped 30, ACR Ped 50 and ACR Ped 70 response at each study visit were explored graphically by performing local logistic regressions as well as plots of observed and predicted ACR Ped response rates by quintile of serum golimumab concentration values. The observed response rate values were then superimposed on the local logistic regression plots. Finally, a univariate logistic regression of ACR Ped response on concentration was performed for each study week, and the associated p-value was determined.

Generally, the ER relationships in ACR Ped 30, ACR Ped 50 and ACR Ped 70 showed positive slopes especially in the later time points of the study (eg, Week 12 or Week 16). Statistical significance from the local logistic regression (at $\alpha = 0.05$) was shown at Week 12 for ACR Ped 30; Weeks 4, 12, and 16 for ACR Ped 50; and Weeks 8, 12, and 16 for ACR Ped 70. Of note, the ACR Ped 30 at Week 16 did not show statistical significance ($p=0.077$), which is likely due to maximum response rates being achieved regardless of the golimumab exposures. As higher bar clinical responses, ACR Ped 50 and ACR Ped 70 were more sensitive to show positive ER slopes.

The observed ACR Ped response rates during the open-label phase are superimposed for all 3 endpoints in the figure below. During this open-label phase of the study, all subjects received golimumab, of which 92% achieved ACR Ped 30 response at Week 16. Furthermore, a high ACR Ped 30 response rate of 84.2% was maintained even in the lowest 20% of the exposure range. All the paediatric ACR response rates show increasing tendency with respect to golimumab concentrations and they also increased as time passes.

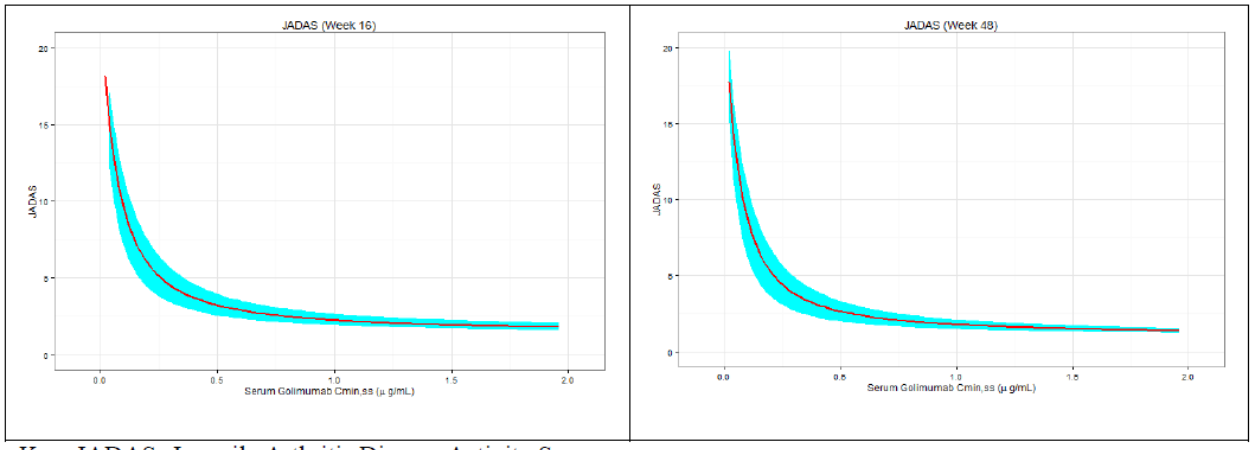


Key: ACR PED=American College of Rheumatology Pediatric.

Figure 6 Observed ACR Ped 30, ACR Ped 50, and ACR Ped 70 Response Rates During the Open-Label Trial Phase. Response Rates Were Computed for Each Concentration Quintile. The Symbol Size Reflects the Number of Subjects.

An analysis of JADAS-71 response in pJIA receiving 30 mg/m2 SC golimumab q4w was performed using an indirect-response population PK-pharmacodynamics (PD) model. JADAS-71 as a continuous measure of disease activity has the utility of being able to capture both disease activity response (by change in absolute score) and disease activity state (by using actual scores) in a single measure. The Figure below displays JADAS-71 score by steady-state trough serum concentrations (Cmin,ss) at Week 16 and Week 48 for a typical individual based on the exposure-response modelling for JADAS (figure below).

There was a clear ER relationship for the suppression of JADAS-71. The inter-quartile range (0.52-1.78 µg/mL with a median of 1.05 µg/mL) of $C_{min,ss}$ resulting from golimumab 30 mg/m^2 q4w fell within the range of approximately maximal JADAS response.



Key: JADAS=Juvenile Arthritis Disease Activity Score.

Figure 7 Exposure-JADAS response in a typical individual for JADAS score at Week 16 and Week 48 with 90% uncertainty bands.

2.4.4. Discussion on clinical pharmacology

No new PK data or analyses have been submitted. A full assessment of golimumab PK in the pJIA patient population was made in Variation EMEA/H/C/000992/II/63 and the population PK analysis was found to adequately describe the PK data and the golimumab plasma exposure was similar between adults and the paediatric population.

The MAH has provided PK simulations to comparing dosing presentation of 1 mg or 5 mg increments, respectively. It is agreed that there are marginal differences in exposure ranges between the two increment levels across all age groups.

The MAH also presented a PK-simulations to justify the proposed acceptance criteria. This shows small differences in drug exposure with overlapping overall PK-concentrations. The variability was shown to be similar to adults <60kg and <80 kg. The MAH´s conclusion that the clinical safety for these delivered volumes is not expected to be different from what was observed in the adult RA studies at the 50 mg dose level is endorsed.

In general, the ACR PED response rates versus golimumab concentration display increasing response with increasing exposure. The exposure-JADAS analysis indicate that close to maximum effect has been reached at a Cmin,ss of 1.0 µg/mL. In the RSI #3 of variation EMEA/H/C/000992/II/63 the percentage of subjects achieving an average concentration above EC80 (1.7 ug/mL) was 90.9% and 76.0% for body weights <40 kg and ≥ 40 kg, respectively, indicating adequate dosing for children <40 kg.

2.4.5. Conclusions on clinical pharmacology

The golimumab PK and ER relationships in the pJIA patient population have been adequately described. The proposed dosing regimen of 30 mg/m^2 q4w for patients <40 kg is considered acceptable to the CHMP.

2.5. Clinical efficacy

No new studies were submitted to support the current application, since efficacy and safety in children with pJIA aged 2-17 has already been submitted and assessed in variation EMEA/H/C/000992/II/63. The most important aspects of the data submitted in that procedure are discussed below.

The golimumab subcutaneous (SC) clinical development program for pJIA included 1 Phase 3 study (study CNTO148JIA3001; GO-KIDS; EudraCT No: 2009-015019-42) titled "A Multicenter, Double Blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab, a Human Anti TNFα Antibody, in Pediatric Subjects with Active Polyarticular Course Juvenile Idiopathic Arthritis (pJIA) Despite Methotrexate Therapy"

The primary objective of this study was to 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. The secondary objectives were to evaluate golimumab in pediatric subjects with pJIA with respect to safety, physical function, health-related quality of life, disease activity status over time, pharmacokinetics (PK), immunogenicity, and pharmacodynamics.

2.5.1. Dose response study(ies)

2.5.2. Main study(ies)

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

The study population was comprised of subjects with pJIA receiving MTX, ages 2 to less than 18 years, with at least a 6-month history of arthritis, and active arthritis in ≥5 joints. Subjects had to have one of the following JIA subtypes: polyarticular course JIA (RF positive or RF negative), extended oligoarticular, systemic JIA with no current systemic symptoms but with polyarthritis, or JPsA. Active disease at the time of screening and before first injection was defined by the presence of polyarticular disease involving ≥5 joints with active arthritis as defined by ACR criteria (ie, presence of swelling, or if no swelling is present, limitation of motion accompanied by pain, tenderness, or both).

Subjects with exposure to only 1 prior anti-TNFα agent before entering screening for this study were permitted to enroll in the study but were limited to no more than 20% of the total number of subjects. These subjects were allowed to enter the study after the first interim analysis of 30 subjects at Week 8 was completed.

Objectives

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

The major secondary endpoints were:

- Proportion of ACR Ped 30 responders at Week 16 with ACR Ped 30 response at Week 48
- Proportion of ACR Ped 30 responders at Week 16 who had inactive disease at Week 48
- Proportion of ACR Ped 30 responders at Week 16 who were in clinical remission at Week 48

Outcomes / endpoints

Study CNTO148JIA3001 was a randomized-withdrawal, double-blind, placebo-controlled, parallel-group, multicentre study of SC golimumab in paediatric subjects with active polyarticular course JIA despite current treatment with MTX.

Treatments

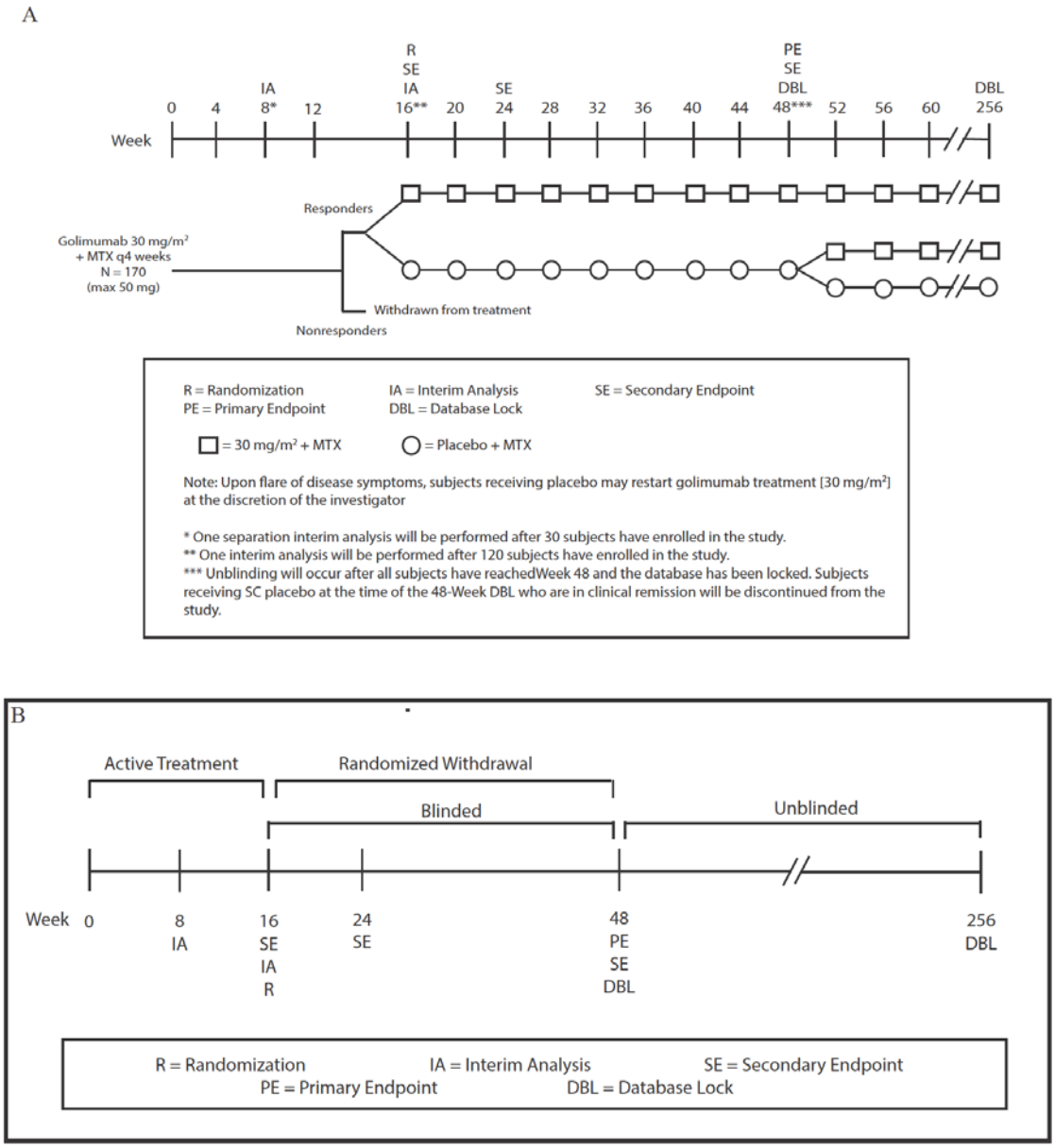


Figure 8 Study Schema for Study CNTO148JIA300

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 randomization (1:1) of ACR Ped 30 responders at Week 16 to receive placebo + MTX or golimumab 30 mg/m2 (maximum 50 mg) + MTX. The main portion of the study was through the Week 48 visit. An LTE with golimumab treatment through Week 248 and final visit at Week 256 was planned, but the study was prematurely discontinued as the primary and secondary endpoints were not met at Week 48.

Sample size

The total number of subjects enrolled in the study was 173. The number of subjects of 12 years or younger was 95 and the number of subjects randomized at Week 16 who were 12 years or younger was 82.

Statistical methods

All efficacy analyses were based on an intent-to-treat (ITT) principle. 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.

Results

Baseline data

The figures below provide histograms of subjects 12 years and younger at the time of enrolment and those randomized at Week 16.

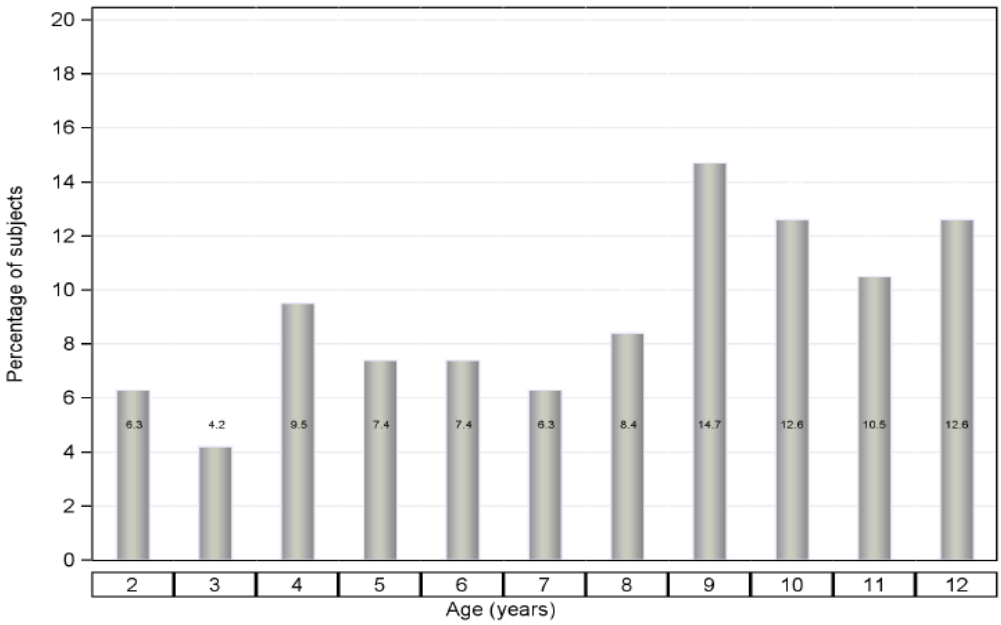


Figure 9 Histogram of Subjects Between the Age of 2 and 12 (Inclusive); Enrolled Subjects

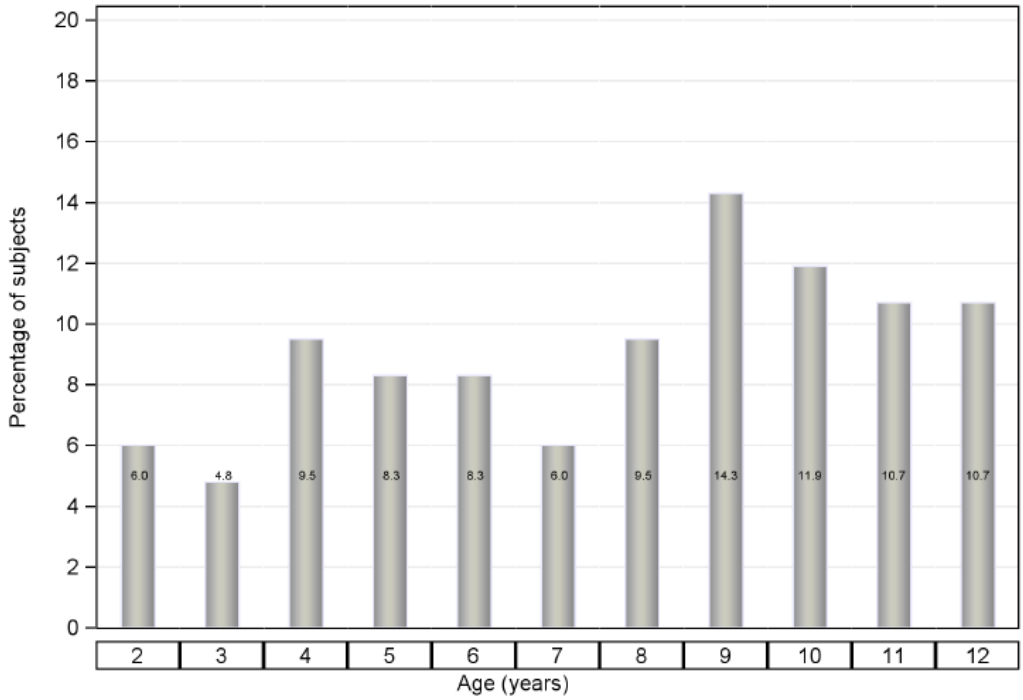


Figure 10 Histogram of Subjects Between the Age of 2 and 12 (Inclusive); Randomized Subjects at Week 16

The demographic characteristics of subjects at baseline were generally well balanced between treatment groups. Approximately 75.7% of randomized subjects were female and 87.9% were Caucasian. The median age was 12.0 years (range: 2 to 17 years) and the median weight was approximately 43.0 kg (range: 11.2 to 109.8 kg). Median BSA was 1.4 m^2 (range: 0.5 to 2.3 m^2). The majority of subjects were prepubescent (Tanner stage I).

Baseline clinical disease characteristics were generally well balanced across treatment groups including enrolled subjects who did not enter randomized-withdrawal and the subjects randomized to placebo + MTX or golimumab 30 mg/m2 + MTX. The enrolled subjects who did not respond at Week 16 had a higher median number of joints with a limited range of motion (11.0) and a higher Childhood Health Assessment Questionnaire (CHAQ; 1.38) than those subjects who were ACR 30 responders at Week 16 (8.0 and 0.88, respectively). For all enrolled subjects, median number of joints with arthritis was 12, median Physician Global Assessment was 5.4, median Parent Overall Assessment of well-being was 4.5, and median Parent Assessment of pain was 4.7.

Additionally, all treatment groups had median ESR levels in the normal range, ESR (median 16 mm/h; normal <20 mm/h) and CRP (median 0.17 mg/dL; normal <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.

Baseline Child Health Questionnaire (CHQ) subscale scores indicated that enrolled subjects with pJIA 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 perceptions, bodily pain/discomfort, parent impact-emotional and parent impact-time scales.

Baseline characteristics are therefore indicative of the protocol-defined population of subjects with moderately to severely active pJIA and the proposed pJIA indication.

Median baseline CRP and ESR levels were low compared with populations in pJIA studies with other biologics.

Outcomes and estimation

Efficacy through Week 16

Proportions of ACR Ped 30, 50, 70, and 90 responders Through Week 16

The proportions of randomized subjects with ACR Ped 30, 50, 70, and 90 responses increased over time through Week 16. As early as Week 4, subjects demonstrated ACR Ped 30, 50, 70, and 90 responses. At Week 16, 151 (87.3%) of all enrolled subjects (n=173) were ACR Ped 30 responders, and 137 (79.2%), 114 (65.9%), and 63 (36.4%) of all enrolled subjects were ACR Ped 50, ACR Ped 70, and ACR Ped 90 responders, respectively.

Inactive Disease at Week 16

The proportions of subjects with inactive disease increased over time. By Week 16, the proportion of subjects with inactive disease was 34.1% in all enrolled subjects. Inactive disease is defined as having the presence of all of the following:

- No joints with active arthritis,
- No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA,
- No active uveitis; normal ESR (<20 mm/hour) or CRP (<1.0 mg/dL),
- Physician global assessment of disease activity indicating no active disease (≤ 5 mm on the VAS),
- Duration of morning stiffness <15 minutes.

Physical Function: CHAQ Scores at Week 16

At Week 16, median improvement in CHAQ score was 0.38 in all enrolled subjects.

Health-related Quality of Life: CHQ Scores at Week 12

Positive mean changes, indicating improvements, from baseline were observed at Week 12 in all subscales of the CHQ. The greatest improvements were seen in the subscales of global health, physical function, bodily pain, change in health, parent impact-emotional, and parent impact time scales.

Primary Endpoint

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 was 59.0% (46/78) subjects in the golimumab group compared with 52.6% (40/76) in the placebo group. This endpoint was not statistically significant (p=0.414).

Thirty-three subjects who were randomized to the placebo group at Week 16 received golimumab through Week 48 because of a flare.

Subgroup Analysis by CRP for Primary Endpoint

Supportive pre-specified subgroup analyses were performed on the primary endpoint. Subjects were analyzed based on baseline CRP <1.0 mg/dL and ≥ 1.0 mg/dL. Subjects with baseline CRP ≥ 1.0 mg/dL

demonstrated significant differences in non-flare rates between the treatment groups based on a logistic regression, with odds ratio of 9.8 and a respective 95% confidence interval.

In a post-hoc analysis, the proportion of subjects who did not flare from Week 16 through Week 48 by CRP levels at baseline is presented in the table below. The proportion of subjects who did not flare among subjects who continued with golimumab 30 mg/m2 administration after Week 16 remained relatively similar regardless of the baseline CRP levels, between 55.6% (20/36) to 65.0% (13/20). However, for subjects who were withdrawn to placebo at Week 16 and had a higher baseline CRP level cutoff, the proportion of subjects who did not flare was dramatically lower compared with subjects who had a lower baseline CRP level. For subjects who were randomized to placebo at Week 16 and had baseline CRP levels ≥ 0.02 mg/dL, the proportion of subjects who did not flare was 51.4% (37/72). This percentage steadily decreased for subjects with progressively higher levels of baseline CRP cutoffs. For subjects who had baseline CRP levels ≥ 1.0 mg/dL, the proportion of subjects who did not flare was 13.3% (2/15) among subjects who were randomized to placebo at Week 16.

Table 2 Number of Subjects Who Did Not Flare From Week 16 Through Week 48 by CRP Levels at Baseline; Randomized 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

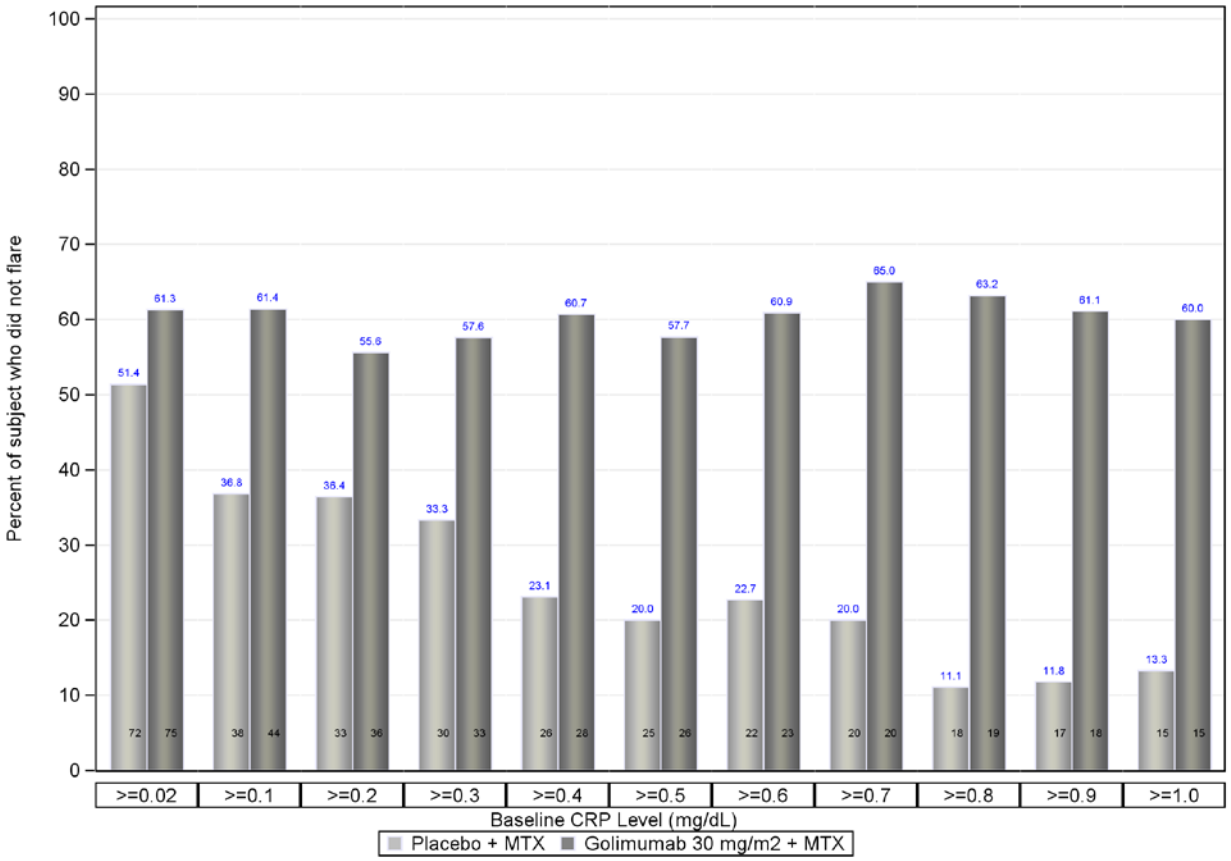


Figure 11 Number of Subjects Who Did Not Flare From Week 16 Through Week 48 by CRP Levels at Baseline; Randomized Subjects

Major Secondary Endpoints

Number of Subjects who Were ACR Ped 30 Responders at Week 16 who were ACR Ped 30 Responders at Week 48

The proportion of randomized subjects who achieved an ACR Ped 30 response at Week 16 with ACR Ped 30 response at Week 48 was 52.6% (41/78) subjects in the golimumab group compared with the placebo group 55.3% (41/76; p = 0.751).

Proportion of Subjects who were Responders at Week 16 and had Inactive Disease at Week 48

The proportion of randomized subjects who achieved an ACR Ped 30 response at Week 16 and had inactive disease at Week 48 was 39.7% (31/78) subjects in the golimumab group compared with the placebo group 27.6% (21/76; p = 0.119).

Proportion of Subjects who were Responders at Week 16 and were in Clinical Remission While on Medication for JIA at Week 48

The proportion of randomized 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% (10/78) subjects in the golimumab group compared with the placebo group 11.8% (9/76, p=0.848).

2.5.3. Discussion on clinical efficacy

In this application, the MAH propose to introduce a new presentation for paediatric use, 45 mg/0.45 ml in pre-filled pen, and to broadening the pJIA indication from children with a body weight of at least

40kg to children 2 years of age or older. The clinical data supporting this change is derived from study CNTO148JIA3001, together with the reasonable extrapolation of efficacy, PK and safety from the adult to the paediatric population. This data was previously assessed confirming the positive benefit-risk balance for golimumab in pJIA in children in procedure variation EMEA/H/C/000992/II/63. However, as that time a presentation that can be dosed per body area was not yet available and therefore, the use of the product in pJIA was limited to the population that can use the the available formulation i.e. children with a body weight of at least 40 kg.

Design and conduct of clinical studies

The CNTO148JIA3001 study (GO-KIDS) consisted of a 16-week open label portion with golimumab 30 mg/m2 SC 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 in subjects aged 2-17 years. 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. Baseline median levels of inflammation were normal.

Efficacy data and additional analyses

After 12 weeks of open label golimumab treatment, the proportions of subjects achieving ACR Ped 30, 50, 70, and 90 responses at Week 16 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%). Median percent improvements in number of active joints were 92%.This indicates a good effect of golimumab on active pJIA.

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

In contrast, the proportion of subjects not experiencing a flare through Week 48 did not differ significantly between the placebo and the treated group. The primary and major secondary endpoints were thus not met and therefore the study failed to formally establish the efficacy of golimumab treatment in JIA. None of the secondary endpoints (proportions of subjects with ACR Ped 30 response, rates of inactive disease or rates of clinical remission while on medication) were met.

Prespecified 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 evaluating flare rates based upon Week 0 CRP levels ranging from 0.1 to 1.0 mg/dL, showed that in a subgroup with CRP levels above 0.3mg/dL at baseline, a statistically significant difference between placebo and continued treatment arms was seen.

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 were 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 indicated 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 were considered sufficient evidence of benefit in the framework of extrapolation.

The totality of the data from study CNTO148JIA3001 supported that golimumab in combination with MTX was efficacious in the treatment of pJIA in children aged 2-17 years. 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 the primary endpoint was met, further supported this conclusion.

2.5.4. Conclusions on the clinical efficacy

No new efficacy data was submitted as part of this application. As assessed by the CHMP as part of the variation EMEA/H/C/000992/II/63, the efficacy of golimumab in pJIA in children from 2 years onwards is considered acceptable.

2.6. 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 beyond Week 16 presented in this Clinical Overview 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. The average golimumab exposure was 22 administrations of golimumab.

Adverse events

Through Week 16, the proportion of subjects experiencing at least 1 AE was 68.2% in all enrolled subjects.

From Week 0 through the end of the study, the proportion of subjects experiencing at least 1 AE was similar among the treatment groups:

- All randomized subjects: 94.2%
- Golimumab 30 mg/m2 + MTX: 92.3%
- Combined placebo + MTX: 96.1%

The system-organ classes (SOCs) with the highest proportion (≥ 20% of all randomized subjects) of subjects with at least 1 AE through the end of the study were:

- Infections and infestations: 80.5%
- Gastrointestinal disorders: 44.8%
- Musculoskeletal and connective tissue disorders: 38.3%
- General disorders and administration site conditions: 33.1%

- Skin and subcutaneous tissue disorders: 32.5%
- Injury poisoning, and procedural complications: 24.0%
- Respiratory, thoracic, and mediastinal disorders: 24.0%
- Nervous System Disorders: 20.8%

Serious adverse event / deaths / other significant events

Through Week 16, 4.6% of all enrolled subjects in the pJIA study experienced at least 1 serious adverse event (SAE).

Through the end of the study, 22.7% of all randomized subjects experienced at least 1 SAE. The most common SAEs were JIA and Arthritis.

- 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 end of the study 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.
- Constipation: 2 (1.3%) in the all randomized subjects group, 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.

Laboratory findings

The most frequently reported markedly abnormal hematologic value was an elevation of eosinophils in 114 (65.9%) subjects with 55 (70.5%) subjects in the group randomized to golimumab + MTX, 52 (68.4%) in the combined placebo group, and 7 (36.8%) subjects in the group that did not enter the randomized withdrawal period. Eighty-four (48.6%) subjects had >1 abnormal value.

Safety in special populations

Across the weight and age subgroups, the overall proportions of subjects with 1 or more AEs through the final DBL were similar in the all randomized subjects groups. There was a trend for AEs related to elevations in transaminases to occur more commonly in younger (<12 years) and in lighter (<40 kg) children. This finding did not translate into more SAEs nor more discontinuations due to AEs related to elevations in transaminases. In general, SAEs, infections, and serious infections occurred more commonly in younger (<12 years) and in lighter (<40 kg) children driven primarily by a higher frequency of infections, as expected in younger children. Discontinuations due to an AE occurred more commonly in older (≥ 12 years) children.

Immunological events

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. it was found that subjects positive for antibodies to golimumab had significantly decreased steady-state trough levels when the titer level was >1:100; however, the effect of antibodies to golimumab on efficacy was less sensitive requiring titers >1:1000 in order to show apparent efficacy reduction.

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).

Discontinuation due to AES

The majority who left before randomization (14 out of 19) did this because of lack of efficacy.

In the randomized group, 2 out of 10 subjects left the study due to lack of efficacy, one in each treatment group.

Two golimumab-treated and 3 placebo-treated subjects in the randomized group left due to AEs. Two withdrew consent and 1 was lost to follow-up. No particular pattern is seen in the type of AEs leading to discontinuation. In both groups, the discontinuations were evenly distributed over the age range.

Discontinuations due to an AE occurred more commonly in older (≥ 12 years) children. After Week 48 through the final DBL, 7 (4.5%) of all randomized subjects discontinued study agent due to an AE.

2.6.1. 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.

The most frequently reported markedly abnormal hematologic value was an elevation of eosinophils in 114 (65.9%) subjects with 55 (70.5%) subjects in the group randomized to golimumab + MTX, 52 (68.4%) in the combined placebo group, and 7 (36.8%) subjects in the group that did not enter the randomized withdrawal period. Eighty-four (48.6%) subjects had >1 abnormal value. This finding was further addressed by the MAH, who pointed out that the classification “markedly abnormal” was used for all abnormal eosinophil values. The threshold limits were $0.2x10^9$/L for females and $0.3x10^9$/L for males. Those who continued on golimumab treatment did not reach higher eosinophil values than those who did not.

Overall, 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. There was no concerning pattern by age and there was no apparent correlation with AEs.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of golimumab is well characterised through a number of clinical trials in the adult population. Comparing the safety data from the pediatric study CNTO148JIA3001 to the existing safety database in adult studies did not reveals any major safety concerns in CNTO148JIA3001 that were considered new and related to golimumab. The frequency, type, and severity of the adverse reactions seen in children in study CNTO148JIA3001 were comparable to those observed in adults.

No new safety data was submitted as part of this application. As assessed by the CHMP as part of the variation EMEA/H/C/000992/II/63, the safety of golimumab in pJIA in children from 2 years onwards is considered acceptable.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Serious infections including opportunistic infections and TB Demyelinating disorders Hypertension Lymphoma (excluding HSTCL) Hepatitis B virus reactivation Congestive heart failure Autoimmune processes Haematologic reactions Serious systemic hypersensitivity (including anaphylactic reaction) Skin cancer Leukaemia
Important potential risks	Malignancy Serious hepatotoxicity Exposure during pregnancy Serum sickness Maladministration/administration error Serious depression including suicidality Colon cancer/dysplasia (in UC) HSTCL Medication error (wrong dose related to different

Summary of safety concerns	
	strengths)
Missing information	Use in paediatric patients with ulcerative colitis Use in patients with hepatic impairment Use in patients with renal impairment Use in patients with a past history of latent or active TB Use in patients with concurrent malignancy or a history of malignancy Use in patients with active infections including HIV, hepatitis B, hepatitis C Use in patients with recent prior use of other biologics excluding anti-TNFα agents Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF Use in patients with history of demyelinating disease Use in patients with a history of lupus or lupus-like syndrome Use in patients after recent vaccination with live bacterial or viral vaccine Long-term safety in adult patients Long-term safety in paediatric patients

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable.				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
P04480: Long-term observation of treatment with biologics in rheumatoid arthritis Ongoing	To evaluate the long-term safety of biologics	• Serious infections including opportunistic infections and TB • Demyelinating disorders • Lymphoma (excluding HSTCL) • Congestive heart failure • Haematologic reactions • Serious systemic hypersensitivity (including anaphylactic reaction) • Skin cancer • Malignancy • Serum sickness • Long-term safety in adult patients	Final report	December 2022

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
CNTO148ART4002: Golimumab safety and surveillance programme using the Optum Research Database Ongoing	To estimate the incidence rate of serious infections, TB and non-TB mycobacterial infections, malignancies, and other selected outcomes of interest in a cohort of patients with RA, PsA, or AS initiating golimumab and in treated comparator cohorts of similar patients initiating other anti-TNF biologics, non-anti-TNF biologics, or non-biological treatments. Incidence rates will also be estimated in SIMPONI-exposed individuals without claims evidence of a diagnosis of RA, PsA, or AS.	• Serious infections including opportunistic infections and TB • Demyelinating disorders • Hypertension (new onset hypertension only) • Lymphoma (excluding HSTCL) • Hepatitis B virus reactivation • Congestive heart failure • Autoimmune processes • Haematologic reactions • Serious systemic hypersensitivity (including anaphylactic reaction) • Leukaemia • Malignancy • Serious hepatotoxicity • Exposure during pregnancy • Serum sickness • Serious depression including suicidality • Use in patients with hepatic impairment • Use in patients with renal impairment • Use in patients with a past history of latent or active TB • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with active infections including HIV, hepatitis B, hepatitis C • Use in patients with recent prior use of other biologics excluding anti-TNFα agents • Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF • Use in patients with a history of demyelinating disease • Use in patients with a history of lupus or lupus like syndrome • Long-term safety in adult patients	Final report	September 2018

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
CNTO148ART4001: Exposure to golimumab during pregnancy: A review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers Ongoing	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 To collect and analyse information pertaining to health status, during the first year following delivery, of infants born to women following prenatal exposure to golimumab, infants born to women with diseases of interest but treated with other biologics, infants born	• Exposure during pregnancy	Final report	December 2022

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	to women with diseases of interest but treated with non-biologic systemic therapy, and infants born to general population controls.			

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
MK-8259-013: An Observational Longitudinal Post-Authorisation Safety Study (PASS) of Simponi in Treatment of Ulcerative Colitis using Nordic National Health Registries Ongoing	To describe the risk of the following endpoints in patients exposed to golimumab and alternative therapies: • Incident CRC and incident HGD as a composite endpoint • Colectomy for intractable disease • Incident CRC • Incident HSTCL Among patients with UC who discontinue golimumab after achieving remission, describe the duration of remission and potential determinants.	• Colon cancer/dysplasia (in UC) • HSTCL • Long-term safety in adult patients (in UC)	Final report	October 2022

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
CNTO148UCO1001: A Phase 1b open-label study to assess the safety and pharmacokinetics of subcutaneously administered golimumab, a human anti-TNFαantibody, in paediatric subjects with moderately to severely active ulcerative colitis Ongoing	To evaluate the PK and safety of golimumab in paediatric subjects aged 2 through 17 years with moderately to severely active UC. To evaluate the efficacy of golimumab induction (ie, short-term therapy) in these paediatric subjects	• Use in paediatric patients with UC • Long-term safety in paediatric patients	Final report	2024
MK-8259-050: An observational post-approval safety study of golimumab in treatment of polyarticular Juvenile Idiopathic Arthritis (pJIA)– using the German Biologics JIA Registry (BiKeR) Ongoing	To investigate long-term safety of golimumab in pJIA subjects	• Serious infections including opportunistic infections and TB • Malignancies • Autoimmune processes • Exposure during pregnancy Secondary objectives will include crude incidence rates of: • Demyelinating disorders • Congestive heart failure • Hypertension • Serious hepatotoxicity • Haematologic reactions • Serious systemic hypersensitivity (including anaphylactic reaction) • Serum sickness • Hepatitis B virus reactivation • Serious depression including suicidality • Maladministration/administration error • Medication error (wrong dose related to different strengths)	Final report	June 2027

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
MK-8259-042: A Post-Authorization Safety Study of Golimumab in UC Using the Spanish ENEIDA Registry Ongoing	To describe the clinical and demographic profile of first-time users of golimumab in the treatment of UC compared with the corresponding profile of first time users of comparator therapies (other anti-TNF agents or thiopurines). For patients with UC initiating golimumab or other anti-TNF agents, describe the risk of incident colectomy for intractable disease For patients with UC initiating golimumab, other anti-TNF agent, or a thiopurine, describe the risk of the composite endpoint of incident CRC or HGD (hereafter 'advanced colonic neoplasia' [ACN]).	• Colon cancer/dysplasia (in UC) • HSTCL • Long-term safety in adult patients (in UC)	Final report	March 2023

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious infections including opportunistic infections and TB	Routine risk minimisation measures: *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *SIMPONI Educational Programme* *Patient Alert Card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *P04480* *CNTO148ART4002* *MK-8259-050*
Demyelinating disorders	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *P04480* *CNTO148ART4002* *MK-8259-050*
Hypertension	Routine risk minimisation measures: *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002 (new onset hypertension only)* *MK-8259-050*
Lymphoma (excluding HSTCL)	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *P04480*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	measures: *None*	*CNTO148ART4002* *MK-8259-050*
Hepatitis B virus reactivation	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *SIMPONI Educational Programme* *Patient Alert Card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002* *MK-8259-050*
Congestive heart failure	Routine risk minimisation measures: *SmPC section 4.3 (Contraindications)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *SIMPONI Educational Programme* *Patient Alert Card*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *P04480* *CNTO148ART4002* *MK-8259-050*
Autoimmune processes	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002* *MK-8259-050*
Haematologic reactions	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *P04480* *CNTO148ART4002*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	measures: *None*	*MK-8259-050*
Serious systemic hypersensitivity (including anaphylactic reaction)	Routine risk minimisation measures: *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *SIMPONI Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *P04480* *CNTO148ART4002* *MK-8259-050*
Skin cancer	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *SIMPONI Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *P04480* *MK-8259-050*
Leukaemia	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *CNTO148ART4002* *MK-8259-050*
Malignancy	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *P04480* *CNTO148ART4002*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	None	*MK-8259-050*
Serious hepatotoxicity	Routine risk minimisation measures: *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002* *MK-8259-050*
Exposure during pregnancy	Routine risk minimisation measures: *SmPC section 4.6 (Fertility, Pregnancy, and Lactation)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002* *CNTO148ART4001* *MK-8259-050*
Serum sickness	Serum sickness is a type of hypersensitivity. Routine risk minimisation measures for serious systemic hypersensitivity reactions (including anaphylactic reaction): *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *SIMPONI Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *P04480* *CNTO148ART4002* *MK-8259-050*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Maladministration/ administration error	Routine risk minimisation measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 6.6 (Special Precautions for Disposal and Other Handling)* Additional risk minimisation measures: *SIMPONI Educational Programme*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *MK-8259-050*
Serious depression including suicidality	Routine risk minimisation measures: *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002* *MK-8259-050*
Colon cancer/dysplasia (in UC)	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *MK-8259-013* *MK-8259-042*
HSTCL	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: *MK-8259-013* *MK-8259-042* *MK-8259-050*
Medication error (wrong dose related to	Routine risk minimisation measures: *SmPC section 4.2 (Posology and*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
different strengths)	*Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use)* *Packaging design* Additional risk minimisation measures: *None*	*None* Additional pharmacovigilance activities: *MK-8259-050*
Use in paediatric patients with ulcerative colitis	Routine risk minimisation measures: *SmPC section 4.2 (Posology and Method of Administration)* *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148UCO1001*
Use in patients with hepatic impairment	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002*
Use in patients with renal impairment	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with a past history of latent or active TB	Routine risk minimisation measures: *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002*
Use in patients with concurrent malignancy or a history of malignancy	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002*
Use in patients with active infections including HIV, hepatitis B, hepatitis C	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002*
Use in patients with recent prior use of other biologics excluding anti-TNFα agents	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF	Routine risk minimisation measures: *SmPC section 4.3 (Contraindications)* *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002*
Use in patients with history of demyelinating disease	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002*
Use in patients with a history of lupus or lupus-like syndrome	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148ART4002*
Use in patients after recent vaccination with live bacterial or viral vaccine	Routine risk minimisation measures: *SmPC section 4.4 (Special Warnings and Precautions for Use)* *SmPC section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction)* *SmPC section 4.6 (Fertility, Pregnancy, and Lactation)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term safety in adult patients	Routine risk minimisation measures: *None* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *P04480* *CNTO148ART4002* *MK-8259-013 (in UC)* *MK-8259-042 (in UC)*
Long-term safety in paediatric patients	Routine risk minimisation measures: *None* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *CNTO148UCO1001* *MK-8259-050*

Conclusion

The CHMP and PRAC considered that the risk management plan version 18.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

The following indication was approved for the new formulation:

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Simponi in combination with methotrexate (MTX) is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

In addition, the indication for the 50 mg solution for injection in pre filled pen and pre filled syringe was revised as follows:

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Simponi in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older ~~with a body weight of at least 40 kg~~, who have responded inadequately to previous therapy with MTX.

Consequently the sections 4.1, 4.2, and 5.1 of the SmPC are amended.

In addition, the marketing authorisation holder took the opportunity to:

- update the Product Information in line with the latest QRD template (version 10):

Minor changes were made in sections 2, 4.1, 4.2, 4.4, 4.5, 4.7, 4.8, 5.1, 6.1, 6.6 of the SmPC, Annexes IIIA and IIIB for the 50 mg solution for injection in pre filled pen and pre filled syringe formulations and the 100 mg solution for injection in pre filled pen and pre filled syringe formulations.

- implement the recommendations stated in the revised Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' with regards to the excipient Sorbitol (E420);

Section 4.4 of the SmPC was updated as follows:

"Excipients
Simponi contains sorbitol (E420). In patients with rare hereditary problems of fructose intolerance, the additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account (see section 2)."

- add a statement in Section 4.4 of the SmPC to record the name and the batch number of the administered product, in line with Good Pharmacovigilance Practice (GVP) Module PII: Biological medicinal products.

Section 4.4 of the SmPC was updated as follows:

"Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded."

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The current application concerns a new presentation for Simponi 45mg/0.45mL solution and indication in Polyarticular juvenile idiopathic arthritis (pJIA) “Simponi in combination with methotrexate (MTX) is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.” This new formulation would allow extending the paediatric population being treated as dosing in children weighing less than 40kg, who can now be dosed by body surface area (BSA). Therefore the indication is modified accordingly with introduction of an age group instead of a body weight based indication.

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.

3.1.2. Available therapies and unmet medical need

NSAIDs are the usual first-line treatment. They provide symptomatic relief, but are not considered to be disease-modifying. Methotrexate (MTX) is considered to have an acceptable level of toxicity relative to its efficacy; most children demonstrate at least some response to MTX therapy, although remission is rare. Other types of traditional medications commonly used to treat rheumatoid arthritis (RA) in adults are less preferable for use in paediatric subjects. Five biologic agents are approved for the treatment of pJIA whereof 2 approved TNF-inhibitors, dosed once weekly and q2w respectively.

3.1.3. Main clinical studies

The data from study CNTO148JIA3001 were assessed previously as part of variation EMEA/H/C/000992/II/63, and no new clinical study data were submitted as part of this application.

Study CNTO148JIA3001 was a randomized-withdrawal, double-blind, placebo controlled, parallel-group, multicentre study of SC golimumab in paediatric subjects with active polyarticular course JIA despite current treatment with MTX. Subjects had to have one of the following JIA subtypes: polyarticular course JIA (RF positive or RF negative), extended oligoarticular, systemic JIA with no current systemic symptoms but with polyarthritis, or JPsA, with at least a 6-month history of arthritis, and active arthritis in ≥ 5 joints.

The study enrolled 173 subjects; 95 were 12 years or younger. Of the subjects younger than 12 years, 82 were randomized at week 16.

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 randomization (1:1) of ACR Ped 30 responders at Week 16 to receive placebo + MTX or golimumab 30 mg/m2 (maximum 50 mg) + MTX.

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

The major secondary endpoints were:

- Proportion of ACR Ped 30 responders at Week 16 with ACR Ped 30 response at Week 48.
- Proportion of ACR Ped 30 responders at Week 16 who had inactive disease at Week 48.
- Proportion of ACR Ped 30 responders at Week 16 who were in clinical remission at Week 48.

3.2. Favourable 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.

The proposed dosing regimen of 30 mg/m2 q4w for patients <40 kg is considered acceptable to the CHMP.

3.3. Uncertainties and limitations about favourable 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.

The MAH has provided PK simulations to comparing dosing presentation of 1 mg or 5 mg increments, respectively. It is agreed that there are marginal differences in exposure ranges between the two increment levels across all age groups.

The acceptance criteria for the delivered volume is in compliance with ISO 11608-1. The variability was shown to be similar to adults <60kg and <80 kg. The clinical safety for these delivered volumes is not expected to be different from what was observed in the adult RA studies at the 50 mg dose level.

3.4. 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, diarrhoea, 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.

3.5. Uncertainties and limitations about unfavourable effects

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 is included in the Risk Management Plan of Simponi.

3.6. Effects Table

Table 3 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 Primary and major secondary endpoints of the trial failed at week 48, possibly due to significant suppression of inflammatory burden achieved at week 16 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 Serious	%	79.2 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

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Simponi is dosed every fourth week, which would be of benefit in the targeted population.

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.

3.7.2. Balance of benefits and risks

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 confirmed the positive benefit-risk balance for golimumab in pJIA in children in procedure variation EMEA/H/C/000992/II/63. However, as a presentation that can be dosed per body area was not yet available, use of the product in pJIA was limited to the population that can use the by that time available formulation i.e. children with a body weight of at least 40 kg. In the current application the MAH proposes to introduce a new presentation for paediatric use, 45 mg/0.45 ml in pre-filled pen, and to broaden the use of Simponi in pJIA patients weighing less than 40 kg.

The development, manufacture and control of the DP in the new pen VarioJect intended for paediatric use and SC administration in the dose range 0.1-0.45 ml, is found acceptable. The acceptance criteria for the control of delivered volume are found acceptably justified. The criteria are in compliance with the ISO standard.

Furthermore, to justify the dose accuracy from a clinical safety point, the MAH has upon request from the CHMP provided PK-simulations indicating that steady-state golimumab exposures are expected to be similar when rounding the nearest 1mg or 5 mg in all age groups and that that the clinical safety for these delivered volumes is not expected to be different from what was observed in the adult RA studies at the 50 mg dose level.

3.8. Conclusions

The overall B/R of Simponi (extension application for 45 mg/0.45 ml solution for injection for paediatric use and type II variation for modification of the therapeutic indication polyarticular juvenile idiopathic arthritis) and extend it to paediatric patients weighting less than 40 kg is considered to be positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Simponi 45 mg/0.45 mL solution for injection in pre-filled pen is favourable in the following indication:

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Simponi in combination with methotrexate (MTX) is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

The CHMP therefore recommends the extension of the marketing authorisation for Simponi subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The educational programme consists of a Patient Reminder Card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professional(s) treating the patient about on-going treatment with the product.

The Patient Reminder Card shall contain the following key messages:

- A reminder to patients to show the Patient Reminder Card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using Simponi.
- A statement that the brand name and batch number should be recorded.
- Provision to record the type, date, and result of TB screenings.
- That treatment with Simponi may increase the risks of serious infection, opportunistic infections, tuberculosis, hepatitis B reactivation, and congestive heart failure; and when to seek attention from a HCP.
- Contact details of the prescriber.

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.

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None

C.I.6.a - Extension of indication to include paediatric patients from the age of 2 years and older for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) with Simponi 50 mg solution for injection in pre-filled pen and pre-filled syringe. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. The labelling and package leaflet are also updated accordingly.
C.I.11.z - To update the RMP to version 18.0 to delete the following safety concerns: vasculitis, psoriasis (new onset or worsening of pre-existing), and sarcoidosis/sarcoid like reaction as the result of the CHMP in the outcome of variation Type II/068.
C.I.11.z - To update the RMP to version 18.0 to change the due date of the category 3 study MK-8259-050 as the result of the CHMP outcome of MEA033.
In addition, the marketing authorisation holder took the opportunity to:
- update the Product Information in line with the latest QRD template (version 10);
- implement the recommendations as stated in the revised Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' with regards to the excipient Sorbitol (E420);
- add a statement in section 4.4 of the SmPC to record the name and the batch number of the administered product, in line with Good Pharmacovigilance Practice (GVP) Module PII: Biological medicinal products.

Appendices

n/a