NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sBLA
Application Number(s)	125433
Priority or Standard	Simponi Aria
Submit Date(s)	August 29, 2019
Received Date(s)	August 29, 2019
PDUFA Goal Date	September 29, 2020 (3-month extension)
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM)/Office of Immunology and Inflammation (OII)
Review Completion Date	See electronic stamp date
Established/Proper Name	Golimumab
(Proposed) Trade Name	Simponi Aria
Pharmacologic Class	TNFα inhibitor
Applicant	Janssen Biotech, Inc.
Dosage form	Intravenous injection (IV)
Applicant proposed Dosing Regimen	80 mg/m^2 given as an intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter
Applicant Proposed Indication(s)/Population(s)	Pediatric patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (pJIA)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older
Recommended Dosing Regimen	80 mg/m^2 intravenous infusion over 30 minutes at weeks 0 and 4, and every 8 weeks thereafter

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Christine Ford, MS, RPh
Nonclinical Reviewer	Timothy Robison, PhD
Nonclinical Team Leader	Timothy Robison, PhD
Office of Clinical Pharmacology Reviewer(s)	Renu Singh, PhD Tao Liu, PhD
Office of Clinical Pharmacology Team Leader(s)	Jianmeng Chen, MD, PhD Jingyu (Jerry) Yu, PhD
Clinical Reviewer	Jane Filie, MD Jin Chen, MD, PhD
Clinical Team Leader	Rachel Glaser, MD
Statistical Reviewer	Cesar Torres, PhD
Statistical Team Leader	Rebecca Rothwell, PhD
Cross-Disciplinary Team Leader	Rachel Glaser, MD
Division Director/Signatory (DRTM)	Nikolay Nikolov, MD

Additional Reviewers of Application

OPQ/Office of Biotechnology Products	Scott Lute, MSc Cyrus Agarabi, PhD William Hallet, PhD
Microbiology	NA
DMPP **OPDP**	Kelly Jackson, PharmD Sharon Williams, MSN, BSN, RN LaShawn Griffiths, MSHS-PH, BSN, RN Adewale Adeleye, PharmD, MBA
OSIS	Xiaohan Cai, PhD Young M. Choi, PhD Seongeun Cho, PhD

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
NA: Not applicable

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer/Team Leader	Timothy W. Robison	OND/OII/DPT-II	Section: 5	Select one: _X__ Authored _X__ Approved
	Signature: Timothy W. Robison -S Digitally signed by Timothy W. Robison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300110610, cn=Timothy W. Robison -S Date: 2020.09.29 13:27:33 -04'00'			
Clinical Pharmacology Reviewer	Renu Singh	OTS/OCP/DIIP	Section: 6	Select one: _X__ Authored ___ Approved
	Signature: Renu Singh -S Digitally signed by Renu Singh -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Renu Singh -S, 0.9.2342.19200300.100.1.1=2001813906 Date: 2020.09.29 13:24:48 -04'00'			
Clinical Pharmacology Team Leader	Jianmeng Chen	OTS/OCP/DIIP	Section: 6	Select one: ___ Authored _X__ Approved
	Signature: Jianmeng Chen -S Digitally signed by Jianmeng Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianmeng Chen -S, 0.9.2342.19200300.100.1.1=2000743816 Date: 2020.09.29 13:39:42 -04'00'			
Pharmacometrics Reviewer	Tao Liu	OTS/OCP/DIIP	Section: 6, 15.3	Select one: _X_ Authored ___ Approved
	Signature: Tao Liu -S Digitally signed by Tao Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tao Liu -S, 0 9.2342.19200300.100.1.1=2001206753 Date: 2020.09.29 13:43:02 -04'00'			
Pharmacometrics Team Leader	Jingyu (Jerry) Yu	OTS/OCP/DPM	Section: 6, 15.3	Select one: ___ Authored _X_ Approved
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jingyu Yu -S, 0.9.2342.19200300.100.1.1=2000794699 Date: 2020.09.29 14:10:10 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Jane Filie	OII/DRTM	Sections: 8	**Select one:** _X__ Authored ___ Approved
	Signature: Jane Filie -S Digitally signed by Jane Filie -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jane Filie -S, 0.9.2342.19200300.100.1.1=1300218646 Date: 2020.09.29 13:34:32 -04'00'			
Clinical Team Leader	Rachel Glaser	OII/DRTM	Sections: All	**Select one:** _X__ Authored 1-5, 7, 9-13, 15.1, 15.2 __X_ Approved All
	Signature: Rachel Glaser -S Digitally signed by Rachel Glaser -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rachel Glaser -S, 0.9.2342.19200300.100.1.1=0013432915 Date: 2020.09.29 13:18:55 -04'00'			
Division Director (Clinical)/Signatory	Nikolay Nikolov	OII/DRTM	Sections: All	**Select one:** ___ Authored _X__ Approved
	Signature: Nikolay P. Nikolov -S Digitally signed by Nikolay P. Nikolov -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S Date: 2020.09.29 14:13:02 -04'00'			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
JIA	juvenile idiopathic arthritis
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MOA	mechanism of action
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PRCSG	The Pediatric Rheumatology Collaborative Study Group
PRINTO	Pediatric Rheumatology INternational Trials Organisation
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TNF	tumor necrosis factor

1 Executive Summary

1.1. Product Introduction

Golimumab is a human IgG1κ monoclonal antibody specific for human tumor necrosis factor alpha (TNFα) that exhibits multiple glycoforms with molecular masses of approximately 150 to 151 kilodaltons. SIMPONI ARIA (golimumab IV) is a preservative-free sterile solution of golimumab for intravenous (IV) infusion. The subcutaneous formulation of golimumab (Simponi) was originally approved on April 24, 2009, for the treatment of adults with active rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Simponi was subsequently approved for moderate to severe ulcerative colitis on May 15, 2013. Simponi Aria was first approved in the United States (US) on July 18, 2013, for the treatment of adult patients with moderately to severely active rheumatoid arthritis. Subsequently, Simponi Aria was approved for PsA and AS on October 20, 2017. IV golimumab is available as a solution in a single-dose vial.

Janssen submitted supplement 30 to Biological Licensing Application (BLA) 125433 for IV golimumab for the treatment of active polyarticular juvenile idiopathic arthritis, in patients aged 2 years or older. The proposed dose is 80 mg/m^2 given as an IV infusion at weeks 0 and 4, then every 8 weeks thereafter. No changes to the currently marketed presentation are proposed in this supplemental BLA (sBLA).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is Approval for IV golimumab for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients ages 2 years of age and older. This recommendation is based on the extrapolation of efficacy of IV golimumab established in adults with rheumatoid arthritis, based on a PK-matching approach, and supportive exploratory efficacy assessments observed in juvenile idiopathic arthritis (JIA) with active polyarthritis from Study CNTO148JIA3003.

Juvenile Idiopathic Arthritis (JIA) is the term used to refer to multiple subtypes of inflammatory arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age. PJIA is one form of JIA, and is defined by the presence of ≥ 5 inflammatory joints with onset prior to age 16 years and a minimum duration of 6 weeks. The clinical manifestations are discussed further in Section 2.1. Other subtypes of JIA may also have polyarticular joint involvement, but are defined based on other clinical characteristics, such as psoriatic skin disease in juvenile psoriatic arthritis. Study CNTO148JIA3003 and Study CNTO148JIA3001 enrolled patients with JIA with polyarticular involvement of multiple subtypes, not specifically limited to ILAR classification criteria for pJIA. Therefore, in this review, the study populations will be referred to as JIA with active polyarthritis.

Based on the cumulative experience with drug development in JIA, as discussed at the FDA/M-CERSI (University of Maryland Center of Excellence in Regulatory Science and Innovation) public workshop on October 02, 2019, titled "Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA)" [1], the Agency has considered the high degree of similarity between adults with RA and pediatric patients with pJIA to support a scientific rationale for a pediatric extrapolation of efficacy, meaning that efficacy established in adequate and well-controlled studies in adults with RA could be extrapolated to pediatric patients with pJIA based on matching of the PK exposures between the two populations. This extrapolation of efficacy is based on appropriate scientific justification and data provided by the Applicant to support the expectation of similarity in exposure-response between the two populations. Safety, and immunogenicity, if relevant, in pediatric patients cannot be extrapolated from the studies in adults, however, and would need to be supported by a reasonable safety database in pediatric patients with pJIA or, with appropriate justification, another relevant pediatric patient population.

Study CNTO148JIA3003 was a 52-week, open-label, single-arm PK, safety and exploratory efficacy study conducted in JIA patients with active polyarthritis, ages of 2 to <18 years, with an inadequate response to or inability to tolerate methotrexate. The clinical pharmacology review team has determined that the steady state Ctrough concentrations observed in JIA patients with active polyarthritis treated with IV golimumab in Study CNTO148JIA3003 were within the range of exposures seen in RA patients treated with IV golimumab in Study CNTO148ART3001, a pivotal adequate and well-designed phase 3 study, submitted to support the approval of IV golimumab in patients with moderately to severely active RA. The steady state AUC was 50-64% higher in JIA with active polyarthritis as compared to RA. The proposed dosing strategy (80 mg/m^2) provides comparable steady state trough concentrations across age groups in pediatric patients (2-17 yrs old) to that with the currently approved dosing regimen in adult RA patients, supporting the extrapolation of efficacy from adult RA patients. In addition, supportive numerical trends of improvement from baseline were observed for the exploratory efficacy endpoints in the open-label uncontrolled Study CNTO148JIA3003 in JIA patients with active polyarthritis.

[1] Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA). FDA White Oak Campus, Silver Spring, Maryland, Oct 2, 2019

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Polyarticular Juvenile Idiopathic Arthritis (pJIA) is a childhood-onset inflammatory arthritis affecting ≥ 5 joints during the first 6 months of disease. PJIA is the subtype of Juvenile Idiopathic Arthritis (JIA) most similar to adult RA, with articular manifestations being predominant. Extraarticular manifestations, such as uveitis, can also be present. Without appropriate treatment, pJIA can lead to significant life-long disability that starts in childhood. Although multiple therapies are approved for pJIA in the United States, there still remains an unmet need for additional therapeutic options in this population.

Simponi Aria is an intravenous (IV) formulation of golimumab, a humanized monoclonal antibody against human TNFα. The product was first approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) on July 18, 2013 with a deferred pediatric PMR study (PMR-1) under PREA (Pediatric Research Equity Act) to evaluate the safety, efficacy, PK/PD and immunogenicity of IV golimumab in pediatric patients between the ages of 2 to 17 years and 11 months with active juvenile idiopathic arthritis (JIA) despite standard therapy with methotrexate. The Applicant conducted Study CNTO148JIA3003, the subject of this submission, to address the PMR.

Study CNTO148JIA3003 was a 52-week, open-label, single-arm PK, safety and exploratory efficacy study conducted in 127 JIA patients with active polyarthritis ages 2 to <18 years, with an inadequate response to or inability to tolerate methotrexate, who received golimumab IV 80mg/m^2 at Weeks 0 and 4, and every 8 weeks thereafter. The efficacy of IV golimumab in pJIA is based on exposure and extrapolation of established efficacy of IV golimumab in RA. The similarities between the clinical presentation, disease progression and responsiveness to therapies, including TNFα-inhibitors, of pJIA and RA support the extrapolation of efficacy based on PK-matching. The clinical pharmacology review team has determined that the exposures observed in JIA patients with active polyarthritis treated with IV golimumab in Study CNTO148JIA3003 were within the range of exposures seen in RA patients treated with IV golimumab in Study CNTO148ART3001, a pivotal adequate and well-designed phase 3 study, submitted to support the approval of IV golimumab in moderately to severely active RA. The proposed dosing strategy (80 mg/m^2) provides comparable steady state trough concentrations across age groups in pediatric patients (2-17 years old) to that with the currently approved dosing regimen in adult RA patients. In addition, supportive numerical trends of improvement from baseline were observed for the exploratory efficacy endpoints in the open-label uncontrolled Study CNTO148JIA3003 in JIA with active polyarthritis.

The safety assessment of IV golimumab for the proposed pJIA indication is primarily based on the safety data from 127 patients in Study CNTO148JIA3003, with additional supportive safety data from Study CNTO148JIA3001, which evaluated SC golimumab in 173 JIA patients with active polyarthritis. The overall safety profile was generally consistent with the safety observed with treatment with SC golimumab in JIA patients with active polyarthritis and with IV golimumab in adult RA patients, and the known safety profile of other TNF-inhibitors in pJIA/JIA with active polyarthritis. No new safety signals were identified.

The Applicant has provided adequate data to inform the benefit-risk assessment of IV golimumab for the treatment of active pJIA in patients 2 to < 18 years of age. Overall, the efficacy and safety evidence provided in this submission supports a favorable benefit-risk profile of IV golimumab for the treatment of pJIA patients at ages of 2 to < 18 years old at the proposed dosing of IV golimumab 80 mg/m^2 Weeks 0 and 4, and every 8 weeks thereafter. The safety of IV golimumab in JIA with active polyarthritis was consistent with the known safety of IV golimumab and offers an acceptable risk for the therapeutic benefits. Approval of IV golimumab will provide an additional treatment option in the US and the first intravenous TNF inhibitor treatment for pJIA in the US. Therefore, we recommend approval of IV golimumab for active pJIA in pediatric patients 2 years of age and older. In addition, Study CNTO138JIA3003 was designed and conducted consistent with the post-marketing requirement; we recommend the PMR be considered fulfilled based on the results of Study CNTO138JIA3003.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Juvenile Idiopathic Arthritis (JIA) refers to multiple subtypes of inflammatory arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age • Polyarticular juvenile idiopathic arthritis (pJIA), one subtype of juvenile idiopathic arthritis, is a serious inflammatory arthritis in children, defined by the presence of ≥ 5 inflammatory joints with onset prior to age 16 years and a minimum duration of 6 weeks • Extraarticular manifestations, such as uveitis, may be present • The prevalence of JIA in developed countries has been reported to be between 16 and 150/100,000 children	PJIA is a serious disabling form of juvenile inflammatory arthritis with significant impact on quality of life for patients and families.
Current Treatment Options	• Current treatment approach is based on consensus treatment pathways • Approved treatments include some NSAIDs, corticosteroids (oral, parenteral and intra-articular), conventional DMARDs such as sulfasalazine and methotrexate, and biologic DMARDs such as tumor necrosis factor (TNF) inhibitors, tocilizumab, and abatacept	There are several approved therapies for pJIA, however there remains a population of patients with uncontrolled disease despite currently available treatments.
Benefit	• In Study CNTO148JIA3003, 127 JIA patients with active polyarthritis ages 2 to <18 years received golimumab IV 80mg/m^2 at Weeks 0 and 4, and every 8 weeks thereafter • The exposures observed in JIA patients with active polyarthritis treated with IV golimumab in Study CNTO148JIA3003 were within the range of exposures seen in adult RA patients in Study CNTO148ART3001, a phase 3 pivotal study submitted to support the approval of IV golimumab for moderately to severely active RA • Numerical trends of improvement from baseline were observed for exploratory efficacy endpoints in Study CNTO148JIA3003, providing additional supportive evidence of efficacy	Efficacy of IV golimumab in patients with pJIA 2 to < 18 years of age is based on PK-exposure matching and extrapolation of established efficacy of IV golimumab in adults with RA in Study CNTO148ART3001. In addition, exploratory efficacy assessments in CNTO148JIA3003 were consistent with improvement with treatment with IV golimumab in patients with JIA with active polyarthritis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Risk and Risk Management	• The safety database is sufficient to provide a risk assessment for IV golimumab in the pJIA population and is further supported by the safety of SC golimumab in 173 pJIA patients (reviewed under BLA 125289/s133)
	• In CNTO148JIA3003, there were no deaths reported through Week 52. One death due to septic shock was reported after Week 52
	• SAEs and AEs leading to discontinuation were singular by preferred term, except for 3 AEs of JIA (worsening of) leading to discontinuation of 3 patients
	• SAEs and AEs were most frequently reported within the Infections and Infestations system organ class, consistent with the known safety profile of IV golimumab
	• Adverse Events of Special Interest and Other AEs of Interest reported through Week 52 included:
	  ○ 7 (5.5%) patients with serious infections, including 1 patient with opportunistic infection (herpes zoster disseminated)
	  ○ 3 (2.4%) patients with infusion reactions.
	  ○ 1 (0.8%) patient with malignancy
	  ○ 1 (0.8%) patient with autoimmune disorder
	• The overall safety profile of IV golimumab in the pJIA population was generally consistent with the safety observed with treatment with SC golimumab and other TNF inhibitors in pJIA/JIA with active polyarthritis patients and with IV golimumab in adult RA patients.
	• There were no new safety signals
		The overall safety profile of IV golimumab in the pJIA population was generally consistent with the safety observed with treatment with SC golimumab and other TNF inhibitors in pJIA/JIA with active polyarthritis patients and with IV golimumab in adult RA patients. There were no new safety signals.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	8.1.2
		X	Observer reported outcome (ObsRO)	8.1.2
		X	Clinician reported outcome (ClinRO)	8.1.2
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

The classification system historically used to characterize arthritis in children and adolescents used the nomenclature of Juvenile Rheumatoid Arthritis (JRA), as defined by the American College of Rheumatology (ACR). This classification system distinguished categories of disease into pauciarticular, polyarticular, and systemic disease.[2] The more detailed classification system proposed by the International League of Associations for Rheumatology (ILAR) in 1997 and revised in 2001, is the currently accepted classification system.[3] In this system, Juvenile Idiopathic Arthritis (JIA) is the term used to encompass all the included subtypes: systemic-onset JIA, persistent or extended oligoarthritis, rheumatoid factor (RF)-positive polyarthritis, RF-negative polyarthritis, psoriatic JIA, enthesitis-related arthritis, and undifferentiated JIA. Broadly, JIA is defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age, where other diagnoses have been excluded.

Polyarticular Juvenile Idiopathic Arthritis (pJIA) is a childhood-onset inflammatory arthritis affecting ≥ 5 joints during the first 6 months of disease. Differences in classification criteria complicates epidemiologic studies. The prevalence of JIA in developed countries has been reported to be between 16 and 150/100,000 children.[4] In a recent systematic literature review, prevalence rates of pJIA in Europe varied from 1.6 to 54.2/100,000 children.[5] PJIA occurs more frequently in females than males. There is a bimodal distribution in the age of onset with a peak between ages 2 and 5 years, and a second peak between 10 and 14 years. In children under 10 years of age, the disease often begins with an oligoarthritis course, affecting one or two joints, and then progresses to involve five or more joints. Older children may have a more rapid onset. The laboratory findings are notable for the presence of antinuclear antibodies typically in younger children, whereas a rheumatoid factor is more often present in older children, particularly females. PJIA is the JIA subtype most similar to adult RA, with articular manifestations being predominant. Extraarticular manifestations, such as uveitis, can also be present. Without appropriate treatment, pJIA can lead to significant life-long disability starting in childhood.

---

[2] Brewer EJ, Bass J, Baum J, et al. Current proposed revision of JRA criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1997;20(Suppl)195-9.

[3] Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390–392.

[4] Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369(9563):767–78.

[5] Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: A systematic review. Joint Bone Spine 2014; 81(2):112-117.

2.2. Analysis of Current Treatment Options

The classes of therapies for treatment of JIA include non-steroidal anti-inflammatory drugs (NSAIDs), systemic and intra-articular glucocorticoids, and conventional/non-biologic and biologic disease modifying anti-rheumatic drugs (DMARDs). A summary of approved and off-label DMARDs for JIA/JRA are presented in Table 1. In addition, there are nonsteroidal anti-inflammatory drugs (NSAIDs), such as celecoxib, naproxen, meloxicam, and naproxen/esomeprazole, as well as glucocorticoids, that are approved for the treatment of JIA and JRA.

Table 1. US-licensed Biologic and Non-biologic DMARDs for pJIA and JRA

Product Name	Relevant Indication	Year of First Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments					
Sulfasalazine	JRA	1950	Children ≥ 6 years: Initial therapy: 40-60 mg/kg/day, divided into 3 to 6 doses Maintenance: 30 mg/kg/day in 4 divided doses	Approval based on submission of 19 published studies	• Leukopenia • Elevated liver enzymes • Gastrointestinal symptoms • Hypersensitivity reactions
Methotrexate	JRA	1953	Starting dose 10 mg/m^2 once weekly; Experience with doses up to 30 mg/m^2/wk	Improvement in PhGA or patient composite over PBO	Similar to safety profile in adults with RA
Etanercept	pJIA	1998	Children ≥ 2 years: < 63 kg: 0.8 mg/kg SC qw ≥ 63 kg: 50 mg SC qw	RW study with fewer flares compared to PBO	Similar to safety profile in adults
Adalimumab	pJIA	2002	Children ≥ 2 years: 10 to < 15 kg: 10 mg SC q2w 15 to < 30 kg: 20 mg SC q2w ≥ 30 kg: 40 mg SC q2w	RW study with fewer flares compared to PBO	• Infections • Hypersensitivity • Elevated CPK

Abatacept	pJIA	2005	IV formulation: Children ≥ 6 years: <75 kg: 10 mg/kg ≥75 kg: adult dosage Following initial IV dose, administer at 2 and 4 weeks, then q4w SC formulation: Children ≥ 2 years: 10-25 kg: 50 mg QW 25 - <50 kg: 87.5 mg QW ≥ 50 kg: 125 mg QW	IV: RW study with fewer flares compared to PBO SC: PK extrapolation	• Infections • Hypersensitivity
Tocilizumab	pJIA	2010	Children ≥ 2 years: IV formulation ≥ 2 years of age: < 30 kg: 10mg/kg q2w ≥ 30 kg: 8 mg/kg q2w SC formulation < 30kg: 162 mg q3w ≥ 30kg: 162 mg q2w	IV: RW study with fewer flares compared to PBO SC: PK extrapolation	• Infection • Infusion reactions • Neutropenia, thrombocytopenia • Elevated liver enzymes
Other Treatments					
Anakinra	*	2001			
Infliximab	*	1998		Failed R, DB, efficacy study	• Infection • Infusion reactions • Immunogenicity
Leflunomide	*	1998		Failed DB, active-controlled study	• Abdominal pain, nausea, vomiting • Elevated liver enzymes

Abbreviations: CPK=creatine phosphokinase; DB=double blind; IV=intravenous; JRA=Juvenile Rheumatoid Arthritis; PBO=placebo; PC=placebo-controlled; PhGA=Physician Global Assessment; PK=pharmacokinetic; Q2W=every other week; QW=every week; Q4W=every four weeks; R=randomized; RW=randomized withdrawal; SC=subcutaneous

*Not approved for JRA/pJIA

In 2013, the American College of Rheumatology published an update to the 2011 ACR Recommendations for the Treatment of JIA[6] that included consensus treatment pathways for patients with JIA with and without active systemic features. For patients without active systemic features and with lower levels of synovitis (active joint count >0 and ≤4), the recommended initial therapy is with intra-articular glucocorticoid injections or NSAID monotherapy. For patients with higher degrees of synovitis (active joint count > 4), the recommended initial therapy is NSAID

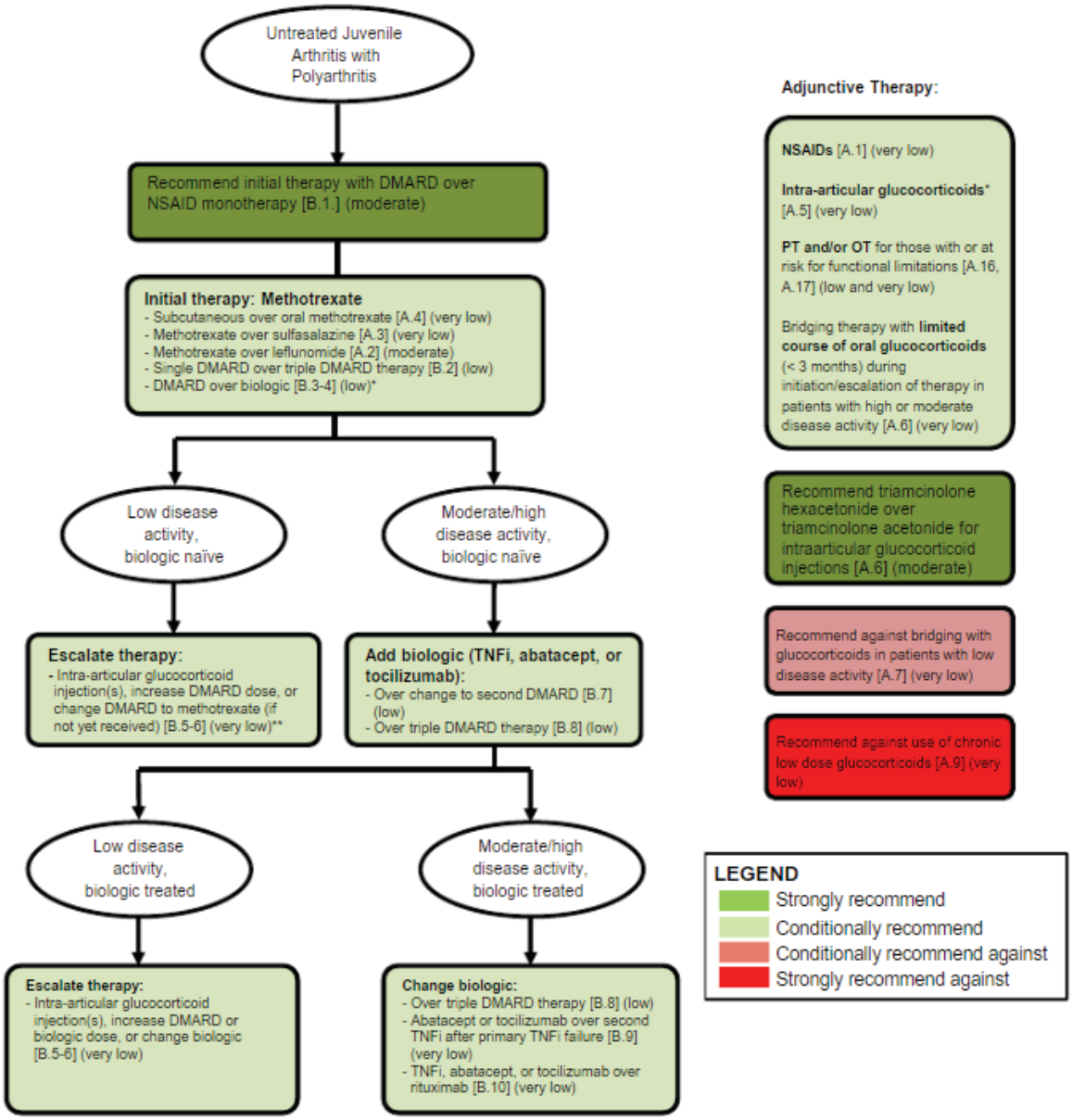
[6] Ringold S, Weiss PF, Beukelman T, et al. 2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications. Arthritis & Rheumatism 2013, 65: 2499–2512.

monotherapy or MTX or leflunomide. For patients with continued disease activity, recommended treatments include MTX, leflunomide, anakinra, abatacept, TNF-inhibitor, or tocilizumab. Steps as laid out in the treatment pathways may be additive or sequential, except biologic therapies which are sequential.

More recent treatment guidelines for children with JIA and polyarthritis, defined as ≥ 5 joints ever involved, may include patients from different ILAR JIA categories and exclude children with systemic arthritis, sacroiliitis, or extraarticular manifestations.[7] The primary recommendations for the initial and subsequent treatment of JIA and active polyarthritis are presented in Figure 1. Initial therapy with a DMARD is strongly recommended over NSAID monotherapy in all patients. For patients with risk factors for disease severity and potentially a more refractory disease course, initial therapy with a DMARD is conditionally recommended over a biologic, although initial biologic therapy may be considered in certain circumstances. For patients with moderate/high disease activity on DMARD monotherapy, adding a biologic to the original DMARD is conditionally recommended over changing to second DMARD or changing to triple DMARD therapy. If a patient has moderate/high disease activity while on TNFα-inhibitor (+/- DMARD), switching to a non-TNFi biologic is conditionally recommended over switching to a second TNFi.

[7] Ringold S et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care & Res, 2019, 71: 717-734, 2019

Figure 1. ACR recommendations for the initial and subsequent treatment of JIA and active polyarthritis



Source: Ringold S et al, Arthritis Care & Res, 2019

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BLA 125433 for IV golimumab was initially approved for treatment of moderately to severely active rheumatoid arthritis in adults in combination with methotrexate on July 18, 2013. It was subsequently approved for treatment of adults with active ankylosing spondylitis (AS) and psoriatic arthritis (PsA) on October 20, 2017.

The following postmarketing study was required at the time of original approval:

PMR-1 (2394-1): To conduct a trial that will evaluate the safety, efficacy, PK/PD and immunogenicity of IV golimumab in pediatric patients between the ages 2 to 17 years and 11 months with active juvenile idiopathic arthritis (JIA) despite standard therapy with methotrexate.

The original final report submission date was December 2018. On May 30, 2018, a deferral extension until September 2019 was granted.

Simponi Aria has been marketed in the US for the approved indications since it was launched in January 18, 2014.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Agency had several regulatory interactions with the Applicant regarding the development of IV golimumab for the treatment of pJIA. Key discussion points are summarized below:

Dec 21, 2012: The Applicant submitted a JIA clinical development plan for IV golimumab with a 52-week, randomized-withdrawal, placebo-controlled design to evaluate the efficacy, safety, PK, pharmacodynamics (PD) and immunogenicity of IV golimumab in 158 patients ages 2 years and older with active pJIA despite standard therapy with MTX. As discussed in the CDTL review dated June 28, 2013, the Division found the Applicant's proposed randomized-withdrawal design to be reasonable for obtaining clinical efficacy and safety data to confirm the proposed pediatric dosing regimen.

Mar 11, 2014: The Applicant submitted a revised JIA with active polyarthritis study protocol CNTO148JIA3003 to an open-label PK and safety study to support PK-based extrapolation between patients with pJIA and adult RA. The Applicant's justification for the open-label design was based on the results from Study CNTO148JIA3001, a randomized withdrawal study with SC golimumab in JIA with active polyarthritis, which posed operational/ethical constraints for an IV

golimumab study in pJIA patients with the same design as for SC golimumab. The Applicant believed that PK-based extrapolation would be a more appropriate approach to address the PREA PMR for IV golimumab. The Agency concurred with the revised proposal.

April 2, 2015: Orphan-drug designation for golimumab was granted for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) in pediatric patients (0 - 16 years of age).

May 4, 2017: In response to the Applicant's amendment to Protocol CNTO148JIA3003, the Agency recommended that the Sponsor provide the PK information stratified by age groups (2 to <6 years, 6 to <12 years, and 12 to <18 years). The Agency also advised the PK should be measured using a validated assay. The Applicant agreed to address this accordingly in the study.

May 30, 2018: Deferral Extension Request for PMR-1 granted

April 4, 2019: A pre-sBLA meeting (Type B) was held to discuss the completed study CNTO148JIA3003 and the planned submission to support the proposed pJIA indication based on PK-based extrapolation of efficacy. The Agency expressed concerns with the similarity of exposure-response (E-R) with golimumab between adults with RA and pediatric patients with pJIA due to the lack of efficacy observed with SC golimumab in JIA with active polyarthritis. The Agency recommended an efficacy study of IV golimumab in JIA with active polyarthritis or to consider amending CNTO148JIA3003 to include a randomized withdrawal portion to obtain controlled efficacy data. However, the Agency agreed the safety data from Study CNTO148JIA3003 could serve as the basis to fulfill the PREA PMR with labeling update in Section 8.4. A determination regarding fulfillment of the PREA PMR would be a review issue.

Aug 20, 2019: The Applicant submitted Supplement 30 with the Study CNTO148JIA3003 report and proposed labeling update in Section 8.4, intended to fulfill the PREA PMR for IV golimumab.

Oct 17, 2019: The Agency initiated a teleconference with the Applicant to further consider potential PK-based extrapolation of efficacy to support a pJIA indication for IV golimumab based on the discussions from the "FDA/UMD CERSI pJIA Drug Development Workshop" held on October 2, 2019. The Applicant was advised that an Information Request (IR) would be sent regarding further analysis of exposure-response in adult RA at multiple doses compared to the response in JIA patients with polyarthritis from Study CNTO148JIA3003.

Dec 6, 2019: The Applicant notified the Agency of their intent to seek an indication for pJIA and committed to providing the analysis requested in the Agency's IR dated Nov

8, 2019.

Mar 30, 2020: Additional exposure-response analyses submitted as major amendment to Supplement 30, resulting in extension of the review timeline.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspection was not requested as it was not deemed necessary for this submission. However, an OSIS inspection was requested for the analytical site for Study CNTO148JIA3003 given the importance of the PK data for this submission. As an onsite inspection was not possible due to disruption of inspectional activities by the COVID-19 global pandemic, a Remote Record Review was conducted at Janssen Research & Development, LLC, Spring House, PA. The OSIS reviewer concluded that the PK data and ADA screening assay data from Study CNTO148JIA3003 are reliable. The Applicant has provided immunogenicity data for Study CNTO148JIA3003 based on the previously validated and used cut-point for the drug-tolerant ADA assay that are reflected in the label for other indications. This information was used in the benefit risk assessment for the pJIA population and will be described in the label.

Of note, the Applicant has also assessed immunogenicity in this study using a new cut-point for ADA analyses. The reliability of ADA confirmatory data with the new cut-point and NAb data is pending additional data evaluation and validation experiments to be conducted by Janssen. Janssen has committed to providing this data to validate the new acceptance criterion used for the ADA assay. However, the cut-point validation data for the new cut-point is not required to inform the benefit risk or for regulatory action for this supplement and is outside the scope of this submission.

See review by Xiaohan Cai, PhD, for additional details of the OSIS Remote Record Review.

4.2. Product Quality

No new Chemistry, Manufacturing and Controls (CMC) of Simponi Aria is provided or required for this sBLA submission.

4.3. Clinical Microbiology

No clinical microbiology data is provided or required for this sBLA submission.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

Pediatric patients (2 years old to <18 years old), with of active polyarticular juvenile idiopathic arthritis (pJIA), will receive a dose of 80 mg/m^2 given as an IV infusion at weeks 0 and 4 and then every 8 weeks thereafter. A juvenile toxicology study with golimumab was not conducted, as nonclinical support for treatment of pediatric patients was based upon a 25-week IV toxicology study in Cynomolgus monkeys and a pre- and postnatal development study with Cynomolgus monkeys.

In a 25-Week IV toxicology study, Cynomolgus monkeys were administered 0, 25, or 50 mg/kg per week of the test article with an interim sacrifice at Week 13 (13^{th} dose on Day 85, sacrificed on Day 91), a terminal sacrifice at week 25 (25th dose on Day 169, sacrificed on Day 175), and a sacrifice after the 12-week recovery period. There were no treatment-related effects on mortality, clinical observations, physical examination, ophthalmic examination, body weights, feed consumption, ECG, blood pressure or heart rate, lymphocyte subsets, hematology parameters, coagulation, clinical chemistry parameters, urinalysis parameters, organ weights, and macroscopic and microscopic pathology. The intravenous test article administration was associated with dose-responsive decreases of IgG and IgM antibody responses to a KLH challenge. IgG antibody production was more affected than IgM antibody production. There was a dose-related increase in test article exposure (Cmax and AUC). A terminal half-life of 18 days was reported at this NOAEL dose. No sex-related differences in drug exposures were noted. ADA was detected in one (female) out of 32 animals dosed with the test article. A NOAEL of 50 mg/kg was identified from this study. C_{max} and $AUC_{0\text{-}7d}$ (from Day 168-175 day) values at the NOAEL (steady state Day 113, Dose 17) were 2627 µg/mL and 11635 µg*day/mL, respectively.

In a pre- and post-natal developmental (PPND) study in which pregnant cynomolgus monkeys were treated with golimumab at subcutaneous doses up to 50 mg/kg twice weekly from gestation day 50 to postpartum day 33. Maternal subcutaneous doses up to 50 mg/kg twice weekly were not associated with any evidence of developmental defects in infants. There was no evidence of maternal toxicity. Golimumab was present in fetal serum at the end of the second trimester and neonatal serum from the time of birth and for up to 6 months postpartum.

Exposure ($AUC_{0\text{-}7d}$ = 11635 µg*day/mL) at the NOAEL in the 6-month monkeys provides large safety margins for the mean steady-state exposure in pediatric patients (AUCss = 390 µg*day/mL). Golimumab was present in neonatal serum from the time of birth and for up to 6 months postpartum.

Based on the above information, this application is recommended for approval from Pharmacology/Toxicology perspective.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant, Janssen Biotech, Inc., has submitted a BLA 125433 (S-30) for intravenous (IV) injection of golimumab for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA). The proposed dosing regimen for IV golimumab in patients with pJIA is 80 mg/m^2 administered at week 0, 4 and then every 8 weeks. See Section 3 for details of regulatory interactions with the Applicant.

Adult RA and pJIA share sufficiently similar disease course and generally respond similarly to interventions with TNF inhibitors and other classes of products, which supports extrapolation of efficacy between the two populations where the mechanism of action and pharmacokinetics of a product are sufficiently characterized. Respectively, the proposed basis of approval for this sBLA is extrapolation of efficacy from adult RA patients to pJIA patients based on PK exposure matching and assessment of safety and immunogenicity from one open label phase 3 study CNTO148JIA3003 in JIA patients with active polyarthritis. For further details, refer to Section 2 and Section 8. The following are the major clinical pharmacology findings from the current review:

- Golimumab steady state Ctrough was generally comparable between pediatric patients with JIA with active polyarthritis and adult patients with RA. The steady state AUC was 50-64% higher in JIA with active polyarthritis as compared to RA. The proposed dose of 80 mg/m^2 provides similar/slightly higher exposure in JIA patients with active polyarthritis compared to the currently approved dosing regimen in RA patients (2 mg/kg) as shown in Table 2 below. Therefore, the PK analysis supports the proposed golimumab dose for treatment of pJIA and extrapolation of efficacy from adult RA patients.
- Comparable steady state trough concentrations across age groups were achieved following the proposed BSA–based dosing regimen in JIA patients with active polyarthritis 2 to < 18 years old (Figure 2).
- Response comparison for clinical endpoints (e.g., ACR Response Criteria and subcomponents of ACR Response) was conducted graphically between JIA with active polyarthritis and RA populations. Due to difference in study design, i.e. open label study in JIA with active polyarthritis versus double-blind placebo-controlled study in RA, definitive conclusions based on a direct ACR/subcomponents response comparison alone is limited. Nonetheless, as expected, the ACR and subcomponent responses in JIA with active polyarthritis was generally similar/better than adult RA response.
- The steady state AUC was 50-64% higher in JIA with active polyarthritis as compared to RA when cross study comparison was conducted. Refer to section 8 for safety findings from the open label phase 3 study CNTO148JIA3003 in the JIA with active polyarthritis population.

- The ADA incidence in study CNTO148JIA3003 was 31% using the currently labeled assay and cut-point which is comparable to the immunogenicity incidence in the currently approved indications for IV golimumab. The Applicant also presented the ADA incidence using a new cut-point. While this change was outside of the scope of this application, the changes to the ADA confirmatory cut-point increased the incidence rate from 31% (old cut-point) to 39.2% (new cut-point) for JIA patients with active polyarthritis but had no impact on the overall incidence rate of neutralizing antibodies to golimumab, with a 20% overall rate in patients with JIA with active polyarthritis (See OBP review for assay assessment). Median trough golimumab concentrations tended to be lower in patients who were positive for antibodies to golimumab than in patients who were negative for antibodies to golimumab. The immune response effect on golimumab clearance in patients with JIA with active polyarthritis was comparable to adults with RA. Anti-golimumab antibodies had no clear impact on the safety or efficacy of IV golimumab (See Section 8).

6.2. Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM), have reviewed the clinical pharmacology data submitted under BLA 125433/S-30. This sBLA is recommended for approval from a clinical pharmacology perspective for the treatment of patients with pJIA.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The exposure comparison between JIA with active polyarthritis and RA population are based on observed values for Ctrough and population PK analyses for AUC (Table 2). Golimumab steady state Ctrough was generally comparable for pediatric patients with JIA with active polyarthritis as compared to adult patients with RA across all age groups. The JIA with active polyarthritis patients have higher steady state AUC compared to adult RA patients across all age groups.

Table 2. Descriptive statistics of exposure metrics of golimumab IV

Parameter	Study	Week	Age Group	N	Mean	Std.Dev.	Median	IQR
Trough (ug/mL)	JIA3003	28	2 to <6 yrs	7	0.37	0.28	0.31	0.28
		28	6 to <12 yrs	29	0.53	0.44	0.41	0.56
		28	12 < 18 yrs	50	0.51	0.44	0.48	0.64
		28	Combined	86	0.50	0.43	0.40	0.61
Trough (ug/mL)	JIA3003	52	2 to <6 yrs	6	0.40	0.35	0.33	0.34
		52	6 to <12 yrs	30	0.65	0.61	0.62	0.97
		52	12 < 18 yrs	59	0.46	0.40	0.42	0.58
		52	Combined	95	0.52	0.47	0.45	0.63
Trough (ug/mL)	ART3001	20	All	342	0.31	0.44	0.21	0.34
		52	All	319	0.41	0.52	0.30	0.47
AUCss (ug*day/mL)	JIA3003	28	2 to <6 yrs	9	413	95	390	73
		28	6 to <12 yrs	41	436	136	424	212
		28	12 < 18 yrs	77	390	121	387	188
		28	Combined	127	390	143	399	273
AUCss (ug*day/mL)	JIA3003	52	2 to <6 yrs	9	423	89	407	73
		52	6 to <12 yrs	41	452	136	446	205
		52	12 < 18 yrs	77	410	121	402	194
		52	Combined	127	425	125	421	200
AUCss (ug*day/mL)	ART3001		All	463	259	75	248	99

Source: BLA 125433, Module 5.3.3.5, Population PK Report for pJIA and Adult RA, page 33

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The golimumab IV dosage regimen is 80 mg/m^2 given as an IV infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter.

Therapeutic Individualization

The proposed BSA based dosing is appropriate for patients with pJIA. No other dose adjustments are required for all other covariates, such as anti-drug-antibody formation, gender, or age.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Golimumab is a human IgG1κ monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human tumor necrosis factor alpha (TNFα) with molecular masses of approximately 150 to 151 kilodaltons.
The PK characteristics of golimumab in adults are summarized below:

- Golimumab exhibited approximately dose proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous dose.
- Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, a mean Cmax of 44.4 ± 11.3 mcg/mL was observed in patients with RA.
- Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, the mean volume of distribution was estimated to be 115 ± 19 mL/kg in healthy subjects, and 151 ± 61 mL/kg in patients with RA.
- Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, the systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg in healthy subjects and 7.6 ± 2.0 mL/day/kg in patients with RA. The mean terminal half-life was estimated to be 12 ± 3 days in healthy subjects and the mean terminal half-life in RA patients was 14 ± 4 days.
- Population PK analysis indicated that concomitant use of MTX, NSAIDs, oral corticosteroids, or sulfasalazine (SSZ) did not significantly influence the clearance of golimumab following IV administration.
- When 2 mg/kg SIMPONI ARIA was administered intravenously to patients with RA at weeks 0, 4 and every 8 weeks thereafter, serum concentrations reached steady state by Week 12. With concomitant use of MTX, treatment with 2 mg/kg golimumab every 8 weeks resulted in a mean steady state trough serum concentration of approximately 0.4 ± 0.4 mcg/mL in patients with active RA. The mean steady-state trough serum concentration in patients with PsA was 0.7 ± 0.6 mcg/mL. The mean steady-state trough serum concentration in patients with AS was 0.8 ± 0.6 mcg/mL.
- Patients with RA, PsA and AS who developed antibodies to golimumab generally had lower trough steady state serum concentrations of golimumab.
- Following intravenous administration, patients with higher body weight tended to have slightly higher serum golimumab concentrations than patients with lower body weights when golimumab was administered on a mg/kg (body weight) basis. However, based on population PK analysis, there were no clinically relevant differences in golimumab exposure following intravenous administration of 2 mg/kg SIMPONI ARIA in patients across a range of different body weights.

6.3.2. Clinical Pharmacology Questions

What are the clinical studies submitted under this supplement BLA?

The IV golimumab clinical development program for pJIA included one phase 3 study (CNTO148JIA3003; GO-VIVA) titled "A Multicenter, Open-Label Trial of Intravenous Golimumab, a Human Anti-TNFα Antibody, in Pediatric Subjects With Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy". All subjects who enrolled in CNTO148JIA3003 received open-label administrations of IV golimumab (80 mg/m^2), at Weeks 0, 4, and every 8 hours (q8w) through Week 28 and then q8w thereafter.

Was the marketed drug product used in Study?

Golimumab was supplied as a sterile liquid for IV infusion at a volume of 4 mL (50 mg, 12.5 mg/mL) in single-use vials. This formulation is the commercially available presentation.

What are the findings from OSIS inspection?

OSIS inspection was requested for the analytical site for study CNTO148JIA3003. The OSIS reviewer concluded that the PK data and ADA screening assay data from Study CNTO148JIA3003 are reliable. Refer to Section 4.1 for details.

What were the immunogenicity findings?

Subjects were evaluated for antibody status to golimumab using a validated, highly sensitive drug-tolerant enzyme immunoassay (EIA) method. In January 2019, the EIA anti-drug antibody (ADA) assay screening and confirmatory (specificity) cut-points were updated based on the newly finalized FDA guidance on immunogenicity assay development ("Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection"). The incidence and titers of antibodies to golimumab were summarized using both the original and new ADA screening and confirmatory (specificity) assay cut-points. Additional patients were identified as antibody positive based on the new ADA assay cut-points. The changes to the ADA confirmatory cut-point increased the incidence rate from 31% to 39.2% for JIA patients with polyarthritis but had no impact on the overall incidence rate of neutralizing antibodies to golimumab, with a 20% overall rate in patients with JIA with active polyarthritis. Refer to OBP review by Dr Scott Lute for further details. However, the change in the ADA specificity cut-point presents the data that are difficult to compare to the currently labeled ADA rates across programs and is therefore, outside of the scope of this supplement.

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, since RA and pJIA share sufficiently similar disease course, it is reasonable to assume that pediatric patients with pJIA would have similar response to IV golimumab as patients with RA. In addition, the responses to golimumab in JIA patients with active polyarthritis in Study CNTO148JIA3003 is generally consistent with the treatment effect in adult RA studies (See Section 15.3) when exposure was matched between the two populations. Thus, the efficacy of golimumab in pJIA could be extrapolated from the efficacy in RA based on similar or higher golimumab exposure. Adequate pharmacokinetic (i.e. exposure) matching (similar/higher) is

considered pivotal information to support the efficacy extrapolation and approval. The similar to better response in JIA patients with active polyarthritis in the open label study CNTO148JIA3003 provide additional supportive evidence of efficacy.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of 80 mg/m^2 q8w is appropriate. The trough concentration (C_{trough}) in pediatric patients with JIA with active polyarthritis after 80 mg /m^2 q8w administration was comparable to the C_{trough} in adult patients with RA. The corresponding area under the concentration time profile at steady state (AUCss) was 50 -64% higher in pediatric patients with JIA with active polyarthritis. The PK analysis supports the proposed golimumab dose for treatment of pJIA and extrapolation of efficacy from adult RA patients.

Also, comparable steady state trough concentrations across age groups were achieved following the proposed BSA–based dosing regimen in JIA patients with active polyarthritis 2 to < 18 years old (Figure 2). Therefore, the proposed 80 mg/m^2 q8w dosing regimen was appropriate for pJIA patients (2-<18 yrs).

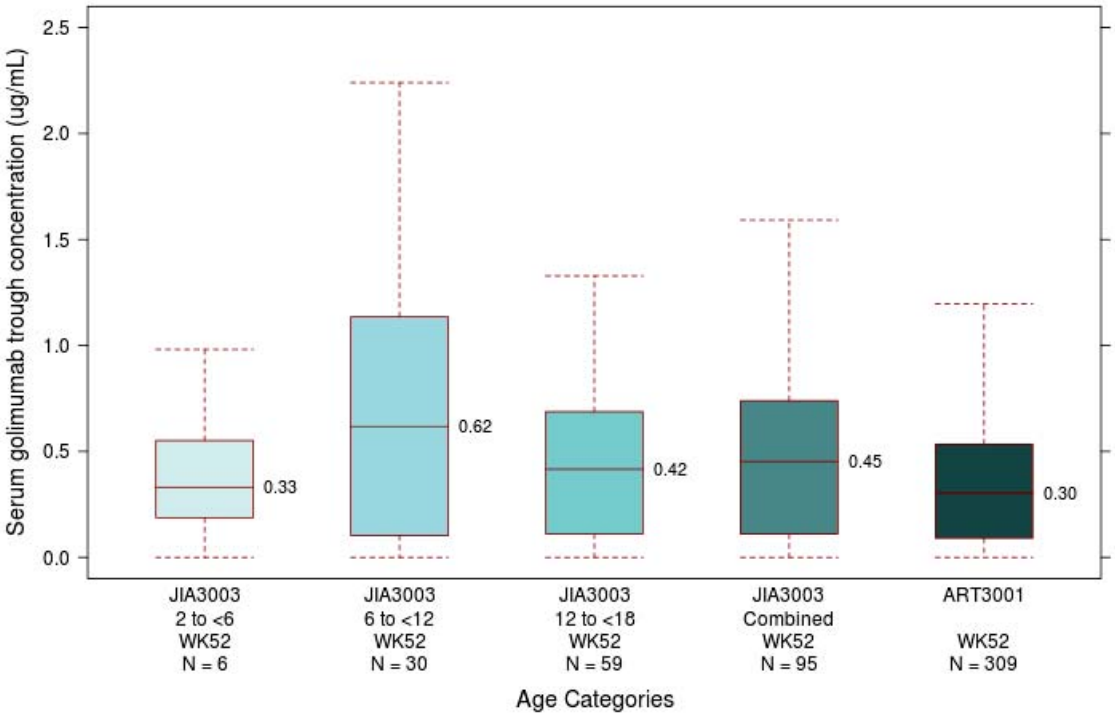
Is the population PK model adequate to determine individual exposures in pediatric patients with pJIA?

Yes, a two-compartment linear PK model with first-order elimination was used to describe the observed PK data in JIA (Study CNTO148JIA3003). The structural PK model, estimated PK parameters, and the covariate effects on PK parameters were similar to the previous experience in adults. See section 15.3.1 for details.

Is the exposure in patients with pJIA similar to that in adult RA?

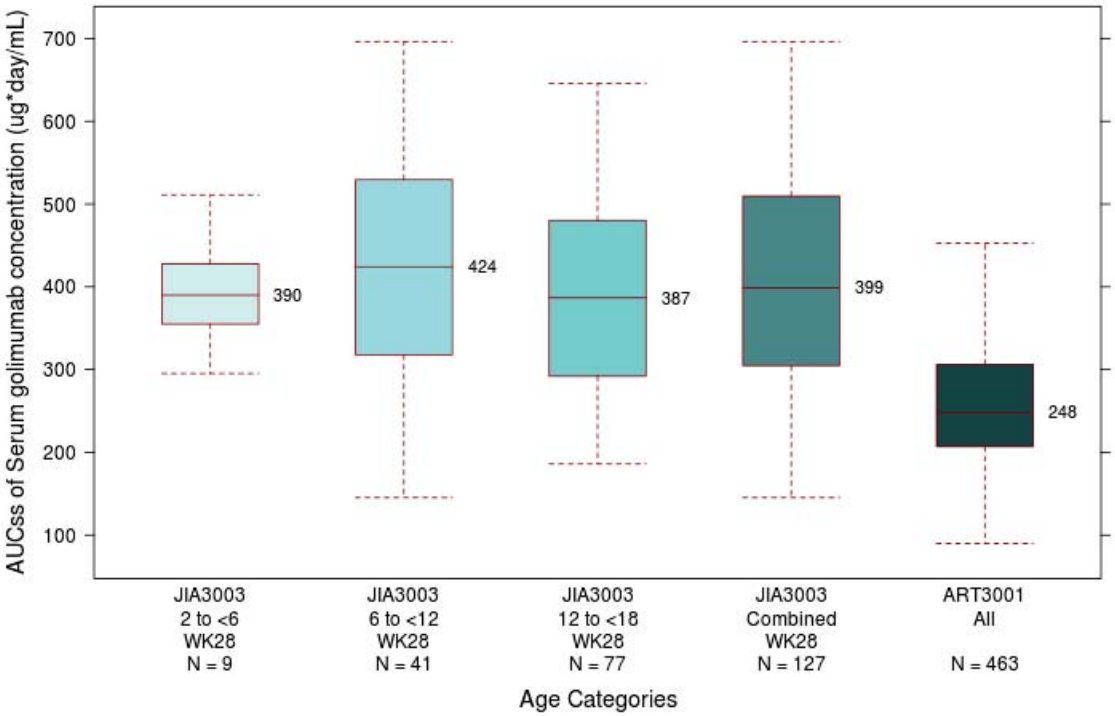
The steady state trough concentration and AUC were compared across different age groups in JIA with active polyarthritis with all the patients in RA. The comparisons are depicted in Figure 2 and Figure 3. Pediatric patients with JIA with active polyarthritis showed a comparable trough concentration compared to adults with RA. However, the AUCss (or Caverage) was about 60% higher in JIA with active polyarthritis compared to RA. Overall, the similar/higher exposure in pJIA compared to RA supports the extrapolation of efficacy from adult RA patients.

Figure 2. Serum Golimumab Trough Concentration at Week 52 by JIA with Active Polyarthritis Age Groups (CNTO148JIA3003) and at Week 52 for Adult RA (CNTO148ART3001)



Source: Figure 11 in the Applicant's PopPK report

Figure 3. Steady-state AUC Over an 8-hour Dosing Interval at Week 28 by JIA with Active Polyarthritis Age Groups (CNTO148JIA3003) and Adult RA (CNTO148ART3001)



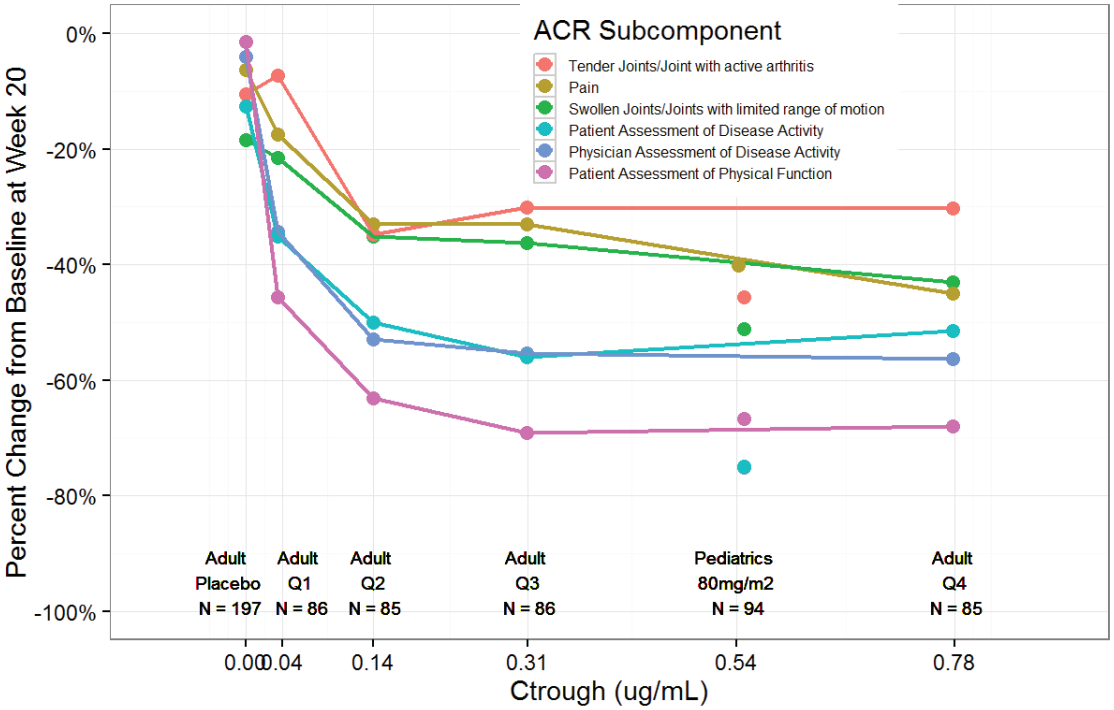
Source: Figure 9 in the Applicant's PopPK report

Does the comparison between adults and pediatrics support that, pJIA patients would have similar response compared to RA patients with comparable exposure?

Yes. Efficacy data were collected from Study CNTO148ART3001 and Study CNTO148JIA3003. Study CNTO148ART3001 was a double blind, placebo-controlled study in adult patients with RA, and Study CNTO148JIA3003 was an open label study without placebo control in pediatric patients with JIA with active polyarthritis. Each subcomponent in ACR Response criteria for RA and JIA with active polyarthritis was compared at the corresponding exposure (C_{trough}) level (Figure 4.). Generally, with comparable exposure (C_{trough}) of golimumab, the response in JIA with active polyarthritis was similar or better compared to the response in RA for each of the subcomponents of ACR. The better response observed in JIA with active polyarthritis might be partly due to the study design (double-blind placebo-controlled study in RA vs. open label study in JIA with active polyarthritis). Overall, this comparison of exposure-response for efficacy suggested that with comparable exposure, pJIA patients would have similar response compared to RA. In addition, for patients with RA, golimumab tended to reach its maximum effect on efficacy when trough concentration was above 0.14 ug/mL (Figure 4.). In pediatric patients

with JIA with active polyarthritis, the proposed dosing regimen of 80 mg/m^2 resulted in a median trough concentration of 0.33-0.62 ug/mL across the age groups (Figure 2).

Figure 4. Exposure (C_{trough})-Response (ACR Subcomponent) Comparison in JIA with Active Polyarthritis and RA



Source: Figure 13 in 15.3.2 Exposure Response Relationship of Golimumab in JIA

Is the bioanalytical method properly validated to measure golimumab concentration in serum samples?

Golimumab in PK samples (human serum) from Study CNTO148JIA3003 and CNTO148ART3001 were analyzed with a validated electrochemiluminescent-based assay (ECLIA) on the Meso Scale Discovery (MSD®) platform utilizing a Hamilton Star liquid handling system. Briefly, Streptavidin-coated 96-well MSD® plates served as the binding or support surface for the assay. The plates were first blocked with assay buffer. The capture biotinylated antibody CNTO 1716 (C1415A), the ruthenium labeled detection antibody CNTO 8673 (C1414A), and the samples, standards and controls were added together to the appropriate wells of the streptavidin-coated 96-well MSD® plate. The plates were covered and incubated at room temperature for 2 hours on a plate shaker. Following the incubation, the plates were washed and MSD® Read Buffer T was added to each well. Plates were then read on the MSD® S600 reader. Golimumab concentrations were determined by interpolation from a standard curve. The lower limit of quantification (LLOQ) was determined to be 0.039 µg/mL.

The assay validation and performance data for serum golimumab concentration were submitted previously (validations report CP2008V-043). Long term stability at -70ºC has been assessed to support bioanalysis and is obtainable from the following Validation Report addenda CP2008V-043-A6, A8, and A10. These reports were reviewed during previous BLA submissions (see OCP review dated 06/07/2013, Reference ID: 3325465 for further details).

For Study CNTO148JIA3003 samples, all the assay acceptance criteria were met. Incurred Sample Reproducibility (ISR) and Parallelism assessments were conducted using study samples in accordance with TV-SOP-12788 and demonstrated acceptable results within SOP defined limits. The %bias for QC samples was 5.03% to 11.37% and CV% was 4.53 to 5.78%.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

One phase 3 trial, Study CNTO148JIA3003, was submitted in this supplement to support golimumab IV for the proposed pJIA indication. Two previously submitted phase 3 trials, Study CNTO148JIA3001, a study of SC golimumab in JIA patients with active polyarthritis, and Study CNTO148ART3001, a study of IV golimumab in adult RA patients, were cross-referenced. A population-PK analysis report was submitted to support PK-based efficacy extrapolation. Study CNTO148JIA3003 is summarized in Table 3.

Table 3. Relevant Studies to BLA 125433/s30

Study ID	Trial Design	Study Population	Treatment	Primary Endpoints	No. of Centers and Countries
CNTO148JIA3003	OL, single-arm, study 52 weeks (ongoing up to 252 weeks)	130 patients with JIA with active polyarthritis despite MTX ages 2 to < 18 years enrolled, 127 received ≥ 1 dose of IV golimumab	IV GOL 80 mg/m^2 at Week 0 and 4, then q8w thereafter	• PK exposure at Week 28 • Bayesian AUCss over one 8-week dosing interval	37 centers in 9 countries
CNTO148JIA3001	R, W, DB, PC, PG 12 wk OL 32 wk DB, RW 208 wk LTE	173 patients with JIA with active polyarthritis despite MTX ages 2 to < 18 years enrolled, 154 patients randomized in DB portion	OL (Wk 0-12): • IV GOL 30mg/m^2 q4w + MTX DB (Wk 16-48): • IV GOL 30mg/m^2 q4w + MTX • PBO	ACRp30 responders at Wk 16 without flare Wks 16-48	33 centers in 12 countries
CNTO148ART3001	R (2:1), DB, PC, PG, study 52 weeks	592 Adults age ≥ 18 years with active RA despite MTX	• IV GOL 2 mg/kg at Wks 0, 4, then q8w + MTX • PBO + MTX through Wk 16, then IV GOL	AC20 response at Wk 14	103 centers in 13 countries

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

7.2. Review Strategy

The Applicant conducted Study CNTO148JIA3003, an open-label, single-arm, multicenter, PK immunogenicity, safety, and efficacy study of IV golimumab in patients, ages 2 to < 18 years, with JIA with active polyarthritis despite treatment with MTX. All patients received 80 mg/m^2 golimumab as an IV infusion at Weeks 0, 4, and every 8 weeks thereafter. The primary objective was to assess the PK following IV golimumab in patients with JIA with active polyarthritis manifested by ≥ 5 joints with active arthritis despite MTX therapy for ≥ 2 months. The secondary objectives were to evaluate IV golimumab in patients with JIA with active polyarthritis with respect to PK, efficacy (relief of signs and symptoms, physical function, and quality of life), safety, and immunogenicity.

The proposed basis for approval of this sBLA is the extrapolation of efficacy from RA patients to pJIA patients based on PK exposure matching. As discussed in Section 0, review of the pharmacokinetic data demonstrated a similar range of exposures observed in Study CNTO148JIA3003 as observed with the IV route of administration in Study CNTO148ART3001, the randomized, double-blind, placebo-controlled study that served as the pivotal study to support the use of IV golimumab in RA patients. In addition, Study CNTO148JIA3003 provides exploratory efficacy data for IV golimumab in JIA patients with active polyarthritis to support the efficacy of IV golimumab in pJIA.

The safety assessment of IV golimumab for the proposed pJIA indication is primarily based on the safety data from 127 patients in Study CNTO148JIA3003. Safety analyses are based on all patients who received at least one dose of study drug administration. Additional supportive safety data for golimumab in pJIA are provided from Study CNTO148JIA3001, a randomized withdrawal study of SC golimumab in 173 JIA patients with active polyarthritis. Quantitative comparisons of the observed safety in JIA patients with active polyarthritis treated with IV and SC golimumab are limited by differences in study designs and cross-study comparison.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Protocol CNTO148JIA3003 (GO-VIVA)

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

Trial Design

Overall Design
Study CNTO148JIA3003 is a phase 3, open-label, single-arm, multicenter study in JIA patients with active polyarthritis, 2 to <18 years of age, despite current treatment with MTX. Patients could have received no more than 2 therapeutic agents targeted at reducing TNFα at study entry. The study design is presented in Figure 5.

In this supplement, the Applicant has provided data through December 19, 2018, the date of last observation for the Week 52 analysis. The long-term extension is ongoing.

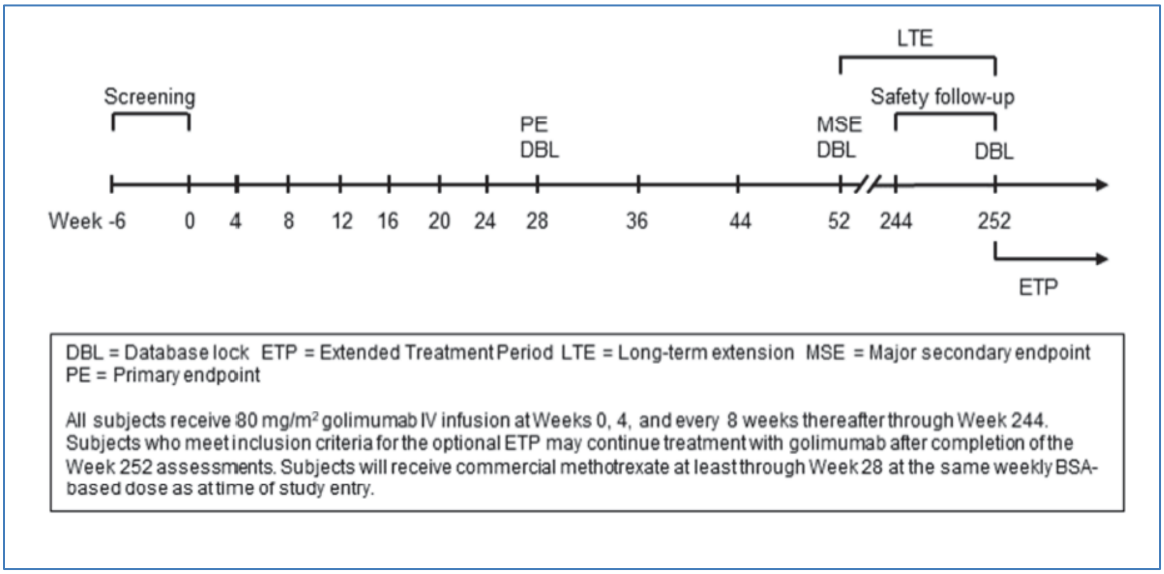
Objectives:
- Primary objective: To assess the PK of IV golimumab in patients, ages 2 to less than 18 years, with JIA with active polyarthritis manifested by ≥ 5 joints despite MTX therapy for ≥ 2 months.
- Secondary objectives: To evaluate IV golimumab in JIA patients with active polyarthritis with respect to PK, efficacy, safety and immunogenicity.

Treatment
Patients were treated for 52 weeks for the primary endpoint assessment, followed by a long-term extension for a total study duration up to 252 weeks:
- Golimumab IV dosing regimen: 80 mg/m^2 [Body Surface Area (BSA)] diluted in a single-use infusion bag containing 100 ml of 0.9% sodium chloride for IV infusion over 30 minutes at Weeks 0, 4 and q8w thereafter. The dosage was chosen based on exposure-response data from the phase 3 trial in adult RA with IV golimumab (refer to the Clinical Pharmacology review for detail). During the long-term extension (Weeks 52 to 252), all patients continued to receive 80 mg/m^2 q8w.
- Methotrexate (MTX): Commercial oral MTX products were used:
  - Stable dose during the first 28 weeks: 10-30 mg/m^2 for patients with BSA <1.67 m^2 and ≥15 mg/week for patients with BSA ≥1.67 m^2
  - Flexible dose after Week 28
- Folic or Folinic Acid: Commercial products were used.

- Age <12 years: At the discretion of the physician
- Age ≥12 years: ≥5 mg weekly or folinic acid at half the MTX dose

- Permitted concomitant medications:
  Stable doses before Week 28, unless change required due to safety concern:
  - Oral corticosteroids: ≤10 mg/day prednisone or prednisone equivalent or 0.20 mg/kg/day (whichever was lower). Intra-articular injections of corticosteroid, if clinically required, was limited to 2 over any 24-week period. Intramuscular administration of corticosteroids for the treatment of JIA with active polyarthritis was not allowed.
  - NSAIDs
  - Other DMARDs

Figure 5. Schematic overview of Study CNTO148JIA3003



Source: Applicant's Figure 1, Study CNTO148JIA3003 Clinical Study Report (CSR)

Study Population

JIA patients 2 to <18 years of age, were enrolled from 37 study sites in 9 countries, who met the following selection criteria. Key eligibility criteria are presented below. For full details, see protocol CNTO148JIA3003, Amendment INT-3 (February 28, 2017).

Key inclusion criteria:

1) Male or female aged 2 to <18 years with a body weight >15 kg at the time of screening and at Week 0 (baseline).
2) Had a diagnosis of JIA per JIA ILAR diagnostic criteria with onset of disease before 16th birthday.
3) Had active JIA for ≥3 months of one of the following JIA subtypes:
   a. RF-positive or negative pJIA

   b. Systemic JIA with no systemic symptoms, but with polyarthritis
   c. Extended oligoarticular JIA
   d. Polyarticular juvenile PsA
   e. Enthesitis-related arthritis
4) Had ≥5 joints with active arthritis at screening and at Week 0 as defined by ACR criteria (i.e., a joint with either swelling, or in the absence of swelling, limited range of motion associated with pain on motion or tenderness).
5) Had a screening CRP of ≥0.1 mg/dL (exception of approximately 30% of the study population).
6) Had active JIA despite current use of oral, IM, or SC MTX for ≥2 months before screening. The dose of MTX must have been stable for ≥4 weeks.
7) If using, corticosteroids or NSAIDs was on stable doses.
8) Had no active TB or history of latent or active TB prior to screening. Patients with a history of latent TB who were receiving treatment for latent TB, or who initiated treatment for latent TB prior to first administration of study agent, or who had documentation of appropriate treatment for latent TB within 3 years prior to first administration of study agent were eligible for enrollment.

Key exclusion criteria:

1) Had an inflammatory disease other than JIA.
2) Had BSA >3.0 m2.
3) Had received:
   a. IL-1ra (anakinra) within 1 week prior to first study drug administration.
   b. Janus kinase (JAK) inhibitor (including but not limited to tofacitinib) within 2 weeks prior to first study agent administration.
   c. DMARDs (except MTX) and/or immunosuppressive therapy, intra-articular, IM, or IV corticosteroids (including IM corticotropin), or etanercept within 4 weeks prior to first study agent administration.
   d. Leflunomide within 4 weeks (irrespective of undergoing a drug elimination procedure) or from 4 to 12 weeks before first study agent administration without undergoing a drug elimination procedure.
   e. Adalimumab or certolizumab pegol within 6 weeks prior to first study agent administration.
   f. Abatacept, infliximab, or tocilizumab within 8 weeks prior to first study agent administration.
   g. Any therapeutic agent targeted at reducing IL-12 or IL-23 (including but not limited to ustekinumab and ABT-874) or alefacept within 3 months prior to first study agent administration.
   h. Canakinumab within 4 months prior to first study agent administration.
   i. Natalizumab, efalizumab, or therapeutic agents that deplete B or T cells (e.g., rituximab, alemtuzumab, or visilizumab) during the 12 months before first study agent administration or had evidence at screening of persistent depletion of the

targeted lymphocyte after receiving any of these agents.

j. Cytotoxic agents, including cyclophosphamide, nitrogen mustard, chlorambucil, or other alkylating agents.
k. IV or SC golimumab.

4) Had received more than 2 therapeutic agents targeted at reducing TNFα (including, but not limited to, infliximab, etanercept, adalimumab, or certolizumab pegol) or the reason for discontinuation of an anti-TNFα agent was a severe or serious AE consistent with the class of anti-TNFα agents.
5) Had side effects related to MTX or conditions that would preclude treatment with MTX.
6) Had a serious infection (including but not limited to hepatitis, pneumonia, or pyelonephritis) or had been hospitalized or received IV antibiotics for an infection during the 2 months before first study agent administration.
7) Had a chronic or recurrent infectious disease.
8) Had active uveitis within 3 months prior to screening.
9) Had known malignancy or a history of malignancy.
10) Had history of severe progressive or uncontrolled liver or renal insufficiency; or significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, psychiatric, or metabolic disturbances.

Efficacy Evaluation

During the 52-week study period, efficacy was assessed every 4 weeks based on the following:

- Standard PRINTO/PRCSG joint evaluations (68 joints for swelling and 75 joints for tenderness)
- Physician Global Assessment of Disease Activity
- Duration of Morning Stiffness
- Childhood Health Assessment Questionnaire (CHAQ)
- Parent/Subject Assessment of Overall Well-being
- Parent/Subject Assessment of Pain
- C-reactive protein (CRP)

Efficacy Criteria:

- ACR30, ACR50, ACR70 and ACR90 response criteria: a 30%, 50%, 70% and 90% improvement from baseline in at least 3 of the following 6 components, with worsening of 30% or more in no more than 1 of the following components:
    1) Physician Global Assessment of Disease Activity on 100-mm VAS (0=Not active and 100=Extremely active)
    2) Parent/Subject Assessment of Overall Well-being on 100-mm VAS (0=Very well and 100=Very poor)
    3) Number of active joints (swelling, limited motion with pain or tenderness) (0-73)
    4) Number of joints with limited range of motion (0-69)

5) Physical function by CHAQ (0-3)
6) CRP (unit=mg/dL)

- Inactive Disease: by the presence of **all** of the following:
  1) No joints with active arthritis
  2) No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA
  3) No active uveitis
  4) Normal CRP (≤0.287 mg/dL for subjects without underlying inflammatory disease)
  5) Physician Global Assessment of Disease Activity indicating no active disease (≤5 mm)
  6) Duration of morning stiffness <15 minutes
- Clinical Remission While on Medication for JIA: Inactive disease at each visit for ≥6 months while on medication
- Juvenile Arthritis Disease Activity Score (JADAS): A composite disease activity score including physician global rating, parent/child rating, number of active joints and CRP.

Safety Evaluation:

- Drug class-related evaluations:
  - Infusion reaction, infection, allergic reactions
  - Tuberculosis (TB) evaluation for signs and symptoms at all visits and at telephone follow-up (q8-12w), QuantiFERON-TB Gold test at screening and week 52 visits, and chest X-ray at screening visit
- Disease-specific evaluation:
  - Uveitis by the investigator and slit-lamp by ophthalmologist at screening, Weeks 20, 44 and final visit
  - Serum ANA and anti-dsDNA antibodies at screening and week 24 and 52 or at early termination/final visit
  - Rheumatoid factor (RF) at screening visit
- Routine safety monitoring:
  - Clinical laboratory tests (hematology, chemistry, and pregnancy testing) at screening and weeks 0, 4, 12, 20, 28, 36, 44 and 52 or at early termination/final visit
  - Vital sign, body weight/height and review of system (for new symptomatology) at all visits
  - Physical examinations (including height and body weight) at screening and weeks 8, 20 and 36
  - Adverse events (AEs) at all visits and during the entire study

PK of Serum Golimumab:

- Trough PK samples (prior to IV infusion) at Weeks 8, 20, 28, and 52 or at early termination

- Pop-PK samples: immediately before and 1 hour after the end of IV infusion for Weeks 0, 4 and 12; and at any time between Weeks 0-8 other than Weeks 0, 4 and 8.

Immunogenicity Assessments

Blood samples were collected prior to IV infusion of golimumab at the same time as the PK sampling to analyze serum antibodies to golimumab, the anti-drug antibody (ADA), followed by further analysis of golimumab neutralizing antibodies (NAb).

Study Endpoints:

- Primary endpoint: PK exposure at Week 28 (the trough concentrations at Week 28) and the Bayesian area under the concentration-time curve (AUC) at steady state (AUCss) over 1 dosing interval of 8 weeks (from population PK modeling and simulation).

- Major secondary endpoints*:* PK exposure at Week 52 (the trough concentrations at Week 52) and the Bayesian AUCss at Week 52 (from population PK modeling and simulation).

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

Statistical Analysis Plan

No formal hypothesis testing was planned for this study. Tabular data summaries, graphical data displays, and subject listings were used to summarize the data.

Sample size:

- Approximately 120 patients were chosen assuming that if 20 patients dropped out or did not provide PK samples, with approximately 100 patients remained at Week 52.
- The sample size estimate was not based on statistical consideration but to provide a sufficient population PK model and 1 year of safety data.

Analysis population:

- Full analysis set (FAS) or safety population: All enrolled patients who received at least 1 infusion were analyzed for efficacy and safety.
- PK analysis set: Treated patients who had sufficient PK samples for analysis.
- Immunogenicity analysis set: Patients who received ≥1 dose of golimumab and had ≥1 valid sample obtained after their first dose of golimumab.

Planned statistical analyses:

- Primary endpoint at Week 28:
  - PK exposure (trough concentration of golimumab) at Week 28
  - Bayesian AUC_{ss} over 1 dosing interval of 8 weeks (from population PK modeling and simulation)
- Major secondary endpoints at week 52:
  - PK exposure (trough concentrations) at Week 52
  - Bayesian AUC_{ss} at Week 52 (from population PK modeling and simulation)
- Immunogenicity analysis:
  - Incidence and titers of ADA and the NAb status were summarized.
  - The effect of ADA on PK, efficacy (JIA ACR response), and safety (infusion reactions) was evaluated.
- Efficacy analysis:
  - Descriptive summary statistics in the FAS for all efficacy endpoints across visits
  - Relationship analyses between efficacy measures and systemic exposure to golimumab
- Safety analysis:
  - Descriptive summary of all safety parameters. AEs were coded in accordance with MedDRA version 21.1.
  - Descriptive summary of safety relative to golimumab exposure across visits.

Protocol Amendments

There were five protocol amendments to the original protocol (dated Mar 10, 2014), including three global protocol amendments (1-3) and two country-specific (Russian) amendments (4-5):

- Amendment-1 (global) on August 12, 2014: To add safety information from golimumab studies in adults and pediatric patients to the protocol and to address recommendations from the Pediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG).

- Amendment-2 (global) on July 11, 2016:
  1) To revise the criteria to determine subject eligibility to enhance enrollment in the study (e.g., active pJIA despite current MTX use changed from ≥3 to ≥2 months

before screening; failure or inadequate response to MTX changed from at least a 3-month course to at least a 2-month course; washout periods for biologic agents prior to the first dose of study agent decreased; previous treatment with up to 2 therapeutic agents targeted at reducing TNFα allowed).
2) To provide clarification and additional details regarding the efficacy and safety evaluations to be used during the study.
3) To clarify the timing of changes that can be made to background medications
4) To remove the ultrasound substudy.
5) Inclusion of anticipated events due to progression of the disease in the overall safety analyses for the study.

- Amendment-3 (global) on February 28, 2017:
  1) To change the inclusion criterion regarding CRP.
  2) To provide clarification on the MTX dose to be used during the study.
  3) To modify the requirements and intervals for slit-lamp evaluations.
  4) To remove the term "emancipated" to describe a juvenile.
  5) To remove unnecessary wording regarding blinding.
  6) To indicate that a local laboratory may be used for the QuantiFERON®-TB Gold test.

- Amendment-4 (regional-Russia only) on March 8, 2017: To change the age at enrollment in the Russian Federation to at least 12 years to comply with requirements of the Ministry of Health of the Russian Federation (Ethics Board) and to remove text related to ineligible age groups.

- Amendment-5 (regional-Russia only) on April 5, 2017: To update the minimum age requirement of eligible subjects in the Russian Federation to 6 years of age from 12 years of age. This amendment accompanied an appeal request to the Russian Ministry of Health to seek approval to expand the minimum age to 6 years of age; this appeal was accepted.

Overall, the study design of Study CNTO480JIA3003, including protocol amendments is reasonable to address the pre-specified primary objectives, to characterize the PK profile of golimumab IV in JIA patients with active polyarthritis, and secondary objectives (safety, immunogenicity and efficacy).

8.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) and applicable regulatory requirements.

Financial Disclosure

Financial disclosures were reported by one principal investigator and one sub-investigator in Study CNTO148JIA3003. A total of 5 patients were enrolled at the two study sites. As the primary endpoint of Study CNTO148JIA3003 was PK, the study was conducted in an open-label manner, and the number of patients enrolled at the study sites were small, the disclosable interests are unlikely to influence the outcomes of the study. See 15.2 Financial Disclosure for additional details.

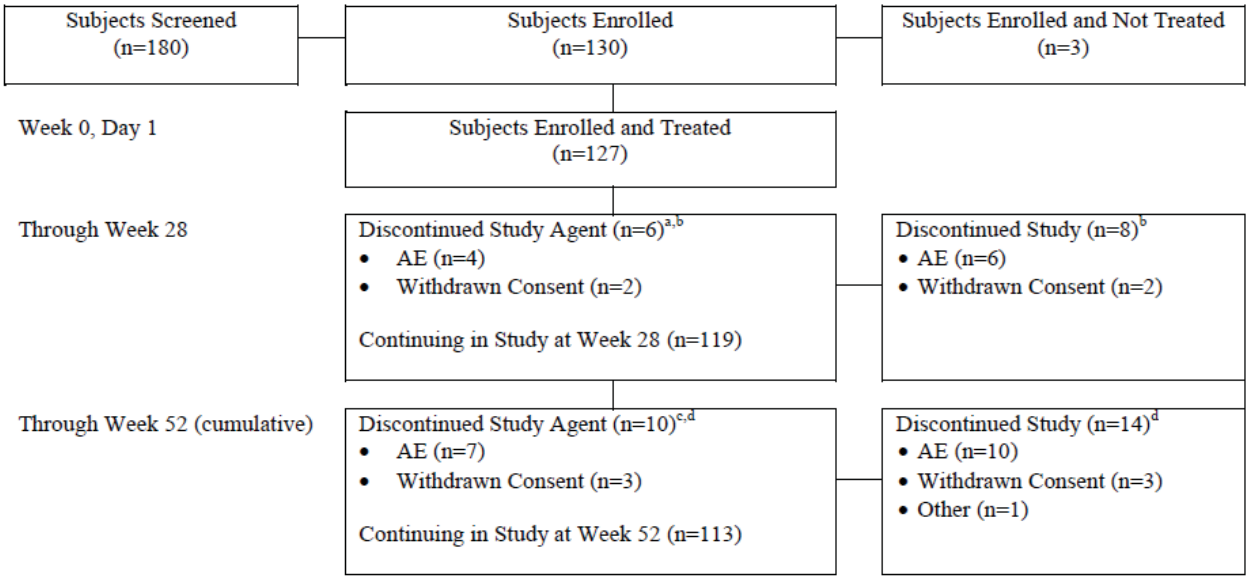
Data Quality and Integrity

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

Patient Disposition

Of the 180 patients screened, 130 were enrolled, and 127 were treated with IV golimumab at 33 study sites in 9 countries, including 52% from Latin America, 24% from North America, and 24% from other regions (Africa, Russia, and Israel).

Figure 6. Patient Disposition Through Week 52



Abbreviations: AE=adverse event; eCRF=electronic case report form; n=number (of subjects).

[a] Discontinued study agent prior to the Week 20 infusion.

[b] Two subjects received the Week 20 infusion but discontinued study agent due to an AE before the Week 28 infusion; therefore, these 2 subjects were included as discontinuing study participation through Week 28, but not as discontinuing study agent.

[c] Discontinued study agent prior to the Week 44 infusion.

[d] Two subjects received the Week 44 infusion but discontinued study agent before the Week 52 infusion (1 due to an AE and 1 due to Other reason). Another 2 subjects discontinued study agent prior to the Week 44 infusion, but did not have the Study Agent Treatment Disposition-Week 52 eCRF completed as both subjects terminated study participation prior to the Week 28 infusion. Therefore, these 4 subjects were included as discontinuing study participation through Week 52, but not as discontinuing study agent.

Source: Applicant's Figure 2 in Study CNTO148JIA3003 CSR

As presented in Figure 6, a total of 119 and 113 patients continued in the study at Weeks 28 and 52, respectively. Overall, discontinuation at Week 52 was 11% (n=14) from the study and 8% (n=10) from the study drug. The main reasons for discontinuation from study drug and study discontinuation were AEs. At Week 52, reasons for discontinuing study agent included AE (5.5%) and Withdrawal of consent (2.4%), while reasons for discontinuing study participation were (AE (7.9%), Withdrawal by patient (2.4%), and Other (0.8%).

Discrepancies between the number of patients discontinuing study agent and number discontinuing study participation were due to rules followed for treatment completion. Patients were considered to have completed treatment for the time period (i.e., through Week 28 or through Week 52) if they completed the infusion prior to the end of the treatment period (i.e., Week 20 or Week 44 infusion, respectively). Two patients received the Week 20 infusion but discontinued study agent due to AE before the Week 28 infusion; these patients were included as discontinuing study participation through Week 28, but not as discontinuing study agent. In

addition, 2 patients received the Week 44 infusion, but discontinued study agent before the Week 52 infusion (1 due to AE, 1 due to Other reason). These patients were included as discontinuing study participation through Week 52 but not as discontinuing study agent.

Protocol Violations/Deviations

Approximately 46% (n=59) patients had ≥1 major protocol deviation, mostly related to exclusion criteria (such as informed consent/assent) or procedure deviations. No deviations were related to wrong study drug or incorrect dosage of golimumab. The protocol deviations were not likely to have affected the integrity of the study nor introduced bias into the results.

Table of Demographic Characteristics

The demographic characteristics of the full analysis population (n=127) are summarized in Table 4. Overall, the demographic profile of the patients enrolled appears consistent with that expected for the enrolled population of JIA patients with active polyarthritis with regard to gender (73% female), race (67% White) and age (mean 11.6 years, range 2 to 17 years). The proportion of patients 2 to <6 years of age (7%) was smaller than the proportion of patients 12 to <18 years of age (61%). The mean body weight was 45.57 kg (range 15.1 to 142.7 kg) and the mean body surface area (BSA) was 1.3412 m^2 (range 0.608 to 2.763 m^2). Approximately half of the patients (49.6%) were Hispanic/Latino, which is consistent with 52.0% of study sites being in Latin America. The distribution of gender, race and age is consistent with that of pJIA which was the predominant JIA subtype enrolled.

Table 4. Demographic Characteristics at Baseline, FAS Population

Demographic Parameters	Golimumab IV N=127 n (%)
Sex	
Male	34 (26.8%)
Female	93 (73.2%)
Age (years)	
Mean ±SD	11.6 ±3.9
Median	13.0
Range (min, max)	2, 17
2 to <6	9 (7.1%)
6 to <12	41 (32.3%)
12 to <18	77 (60.6%)
Race	
White	85 (66.9%)
Black or African American	5 (3.9%)
Asian	1 (0.8%)
American Indian or Alaska Native	4 (3.1%)
Native Hawaiian or Other Pacific Islander	0
Multiple	4 (3.1%)
Other†	28 (22.0%)
Ethnicity	
Hispanic or Latino	63 (49.6%)
Not Hispanic or Latino	62 (48.8%)
Not reported	2 (1.6%)
Weight (kg)	
Mean ±SD	45.57 ±21.122
Median	42.4 (15.0, 142.7)
<40 kg	57 (44.9%)
≥40 kg	70 (55.1%)
Height (cm)	
Mean ±SD	146.18 ±20.88
Median (range)	152.5 (88.0, 192.6)
Body Mass Index (kg/m^2)	
Mean ±SD	20.23 ±5.28
Median (range)	19.1 (12.0, 38.5)
Body surface area (m^2)	
Mean ±SD	1.34 ±0.39
Median (range)	1.34 (0.61, 2.76)
Region	
North America	30 (23.6%)
Latin America	66 (52.0%)
Europe (Russian)	14 (11.0%)
Africa (South)	15 (11.8%)
West Asia (Israel)	2 (1.6%)

Source: Adapted from Applicant's Table 4 in Study CNTO148JIA30031 CSR
† Race and/or ethnicity data were not collected in countries because of local regulations.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline characteristics were consistent with the intended population of patients with JIA with active polyarthritis with moderate to severe disease activity based on active joint count, joints with limited range of motion, physician's global assessment of disease activity, the parent/subject's assessment of overall well-being, and serum CRP level (Table 5). All of the patients enrolled had 5 or more active joints regardless of the JIA subtype. The majority of patients had polyarticular rheumatoid factor positive JIA (34.6%) or polyarticular rheumatoid factor negative JIA (42.5%), while juvenile psoriatic arthritis (3.9%) and systemic JIA without systemic symptoms (3.1%) were the least frequent ILAR JIA subtypes. The mean duration of disease was 32.5 months.

Table 5. Baseline Disease Characteristics, FAS Population

Characteristics	Golimumab IV N=127 *Mean ± SD (range) or n(%)*
Duration of JIA disease (months)	32.5 ±36.9 (1.4 - 176.6)
Physician's global assessment of disease activity (VAS 0-10 cm)	5.7 ±1.8
Parent/subject assessment of overall well-being (VAS 0-10 cm)	5.0 ±2.4 (0 - 10.0)
Number of active joints	17.0 ±10.5 (5 - 60)
Number of joints with limited range of motion	12.9 ±11.9 (0 – 58)
Morning stiffness >15 minutes	93 (73.2%)
Childhood Health Assessment Questionnaire (CHAQ)	1.2 ±0.8
C-reactive protein (CRP) (mg/dL)	1.4 ±3.1 (0.01 – 19.1)
Uveitis	0
ILAR classification	
Polyarticular rheumatoid factor-negative	54 (42.5%)
Polyarticular rheumatoid factor-positive	44 (34.6%)
Oligoarticular extended	8 (6.3%)
Juvenile psoriatic arthritis	5 (3.9%)
Enthesitis-related arthritis	12 (9.4%)
Systemic without systemic symptoms but with polyarticular course	4 (3.1%)

Source: Adapted from Applicant's Tables 5, 6 in Study CNTO148JIA3003 CSR

Prior to the study, 119 patients (93.7%) received NSAIDs, 72 patients (56.7%) received systemic corticosteroids, 25 patients (19.7%) received a TNF-inhibitor, 3 patients (2.4%) received biologics other than TNF-inhibitor, and 3 patients (2.4%) used immunosuppressives [cyclosporine (2), azathioprine (1)] for JIA. Twenty-three patients (18.1%) received DMARDs other than MTX prior to first study agent administration; the most common DMARD was sulfasalazine (16 patients, 12.6%).

All patients received concomitant medications through Week 52. As specified in the protocol, all patients received MTX for JIA. The mean dose of MTX at screening was 17.42 mg/week.

Additionally, 72.4% of patients took NSAIDs at baseline and 37.0% took oral corticosteroids (mean prednisone-equivalent dose of 6.61 mg/day). Through Week 52, the most frequently used concomitant medications were vitamin B12 and folic acid (93.7%) and non-steroidal anti-inflammatory and anti-rheumatic product (82.7%). The latter category includes NSAIDs, hydroxychloroquine, and sulfasalazine.

Additionally, through Week 52, patients received:

- Systemic corticosteroids: 47% (n=60)
- Antibiotics: 33.8% (n=43)
- Other analgesics and antipyretics: 32% (n=40)
- Antihistamines for systemic use: 31% (n=39)
- Drugs for peptic ulcer and gastro-esophageal reflux disease: 24% (n=31)
- TB drugs (isoniazid and pyrazinamide): 13% (n=16)
- Antiemetics and antinauseants: 12% (n=15)
- Hormonal contraceptives: 7.9% (n=10)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

As the study was an open-label study in which all patients enrolled received the active treatment. No rescue medication was pre-specified or used during the study and only relevant concomitant medications were permitted as listed above.

A total of 127 patients received golimumab IV treatment and overall, complied satisfactorily with the study protocol for the main study objectives (PK and safety evaluations). Through Week 28, 105 patients (83%) were treatment compliant. Of the 22 patients not compliant through Week 28 (17%), 21 patients received study agent outside the protocol-specified time window and 2 patients missed 1 or more doses. Patients may have had more than 1 reason for noncompliance. Through Week 52, 89 patients (70.1%) were treatment compliant. Of the 38 patients (29.9%) who were not compliant through Week 52, 36 patients received study agent outside the protocol-specified time window and 4 patients missed 1 or more doses.

Through Week 52, 127 patients received at least one administration of IV golimumab with a mean cumulative dose of 732.238 mg/m^2. One hundred twenty-seven patients also received at least one dose of MTX through Week 52, with a mean cumulative dose of 811.344 mg. The mean weekly dose of MTX ranged from 16.7 mg to 17.4 mg.

Primary Endpoint

The primary efficacy endpoint was PK exposure at Week 28 (trough concentrations at Week 28) and the Bayesian AUCss over 1 dosing interval of 8 weeks (from population PK modeling and simulation). Refer to Section 6 Clinical Pharmacology for discussion of the PK results.

Major secondary endpoints

Major secondary endpoints of the study were PK exposure at Week 52 (trough concentrations at Week 52) and the Bayesian AUCss at Week 52 (from population PK modeling and simulation). Refer to Section 6 Clinical Pharmacology for discussion of the PK results.

Other relevant endpoints – efficacy results

No primary or secondary efficacy endpoints were defined for this study due to the nature of the single-arm, open-label design. Exploratory efficacy data was assessed as other endpoints.

JIA ACR Response
JIA ACR responses were noted as early as 4 weeks and the JIA ACR responder rate increased through Week 28. At Week 28, the JIA ACR responses were as follows: JIA ACR 30 83.5%, JIA ACR 50 79.5%, JIA ACR 70 70.1%, and JIA ACR 90 46.5%. After Week 28 through Week 52, the majority of the patients had a JIA ACR 30 75.6%, JIA ACR 50 74.0%, or JIA ACR 70 65.4%, and 48.8% of patients had a JIA ACR 90 response. Response rates were generally similar across ILAR JIA subtypes, except for patients with systemic JIA with no systemic symptoms, in which response rates were generally lower. Conclusions about response based on JIA subtype are limited by the small number of patients with some disease subtypes. Similarly, responses were generally similar based on demographic subgroups of age, gender, race, weight, BSA, geographic region).

According to the Applicant, there were 11 patients who were JIA ACR 30 responders at Week 44 but non-responders at Week 52. This included 3 patients who discontinued after Week 44 but prior to Week 52 and, therefore, were imputed as non-responders at Week 52, 4 patients who had a worsening in the parent/subject assessment of overall wellbeing component score, and 4 patients who had a worsening of other component scores. One patient who was a non-responder at Week 44 became a JIA ACR 30 responder at Week 52.

Except for CRP, the mean percent improvement from baseline in JIA ACR component scores improved with the composite scores as described above for physician's global assessment of disease activity, number of active joints, number of joints with limited range of motion, and physical function by CHAQ. The mean percent improvement in patient/subject of overall well-being was maintained through Week 44, but not at Week 52 and the mean percent improvement in CRP was highly variable after Week 28.

Inactive Disease
The proportion of patients with inactive disease through Week 28 was 37 patients, (29.1%), and through Week 52 was 43 patients (33.9%).

Clinical remission while on Medication
Clinical remission while on medication was defined as inactive disease at each visit for ≥ 6 months. At Week 24, there were no patients in clinical remission, consistent with the requirement for 6 months of inactive disease in the definition of clinical remission. At Week 28, there were 2 patients (1.6%) in clinical remission. The proportion of patients who achieved clinical remission while on medication at Week 52 was 16 patients (12.6%)

Childhood Health Assessment Questionnaire (CHAQ)
A meaningful improvement in CHAQ (decrease of at least 0.188) was observed as early as Week 4. By Week 28, 82 patients (70.1%) had a meaningful improvement in CHAQ score. The proportion of patients with meaningful improvement in CHAQ decreased to 72 patients (64.3%) at Week 44, and at Week 52, meaningful improvement was reported in 80 patients (72.1%).

Juvenile Arthritis Disease Activity Score
Mean decreases (improvements) in JADAS scores were observed for JADAS10, JADAS27, and JADAS71. At Week 28, the mean decreases from baseline were -14.51 for JADAS 10, -17.02 for JADAS 27, and -21.28 for JADAS71. At Week 52, mean decreases from baseline were -15.51, -17.72, and -22.18, respectively.

Overall, open-label efficacy assessments showed consistent improvement with treatment of JIA patients with active polyarthritis with IV golimumab. Responses were generally similar by demographic subgroup and disease subtype.

Dose/Dose Response

Not applicable, a single dose level was assessed in Study CNTO148JIA3003.

Persistence of Effect

Not applicable. The study was not designed to evaluate persistence of effect.

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (COA) Endpoints

The following Patient Reported Outcome (PRO) measures were used as a part of exploratory efficacy assessments in this single-arm uncontrolled study. The results appear generally consistent with the JIA ACR response across 52 weeks.

- Physician Global Assessment of Disease Activity
- Childhood Health Assessment Questionnaire (CHAQ)
- Parent/Subject Assessment of Overall Well-being
- Parent/Subject Assessment of Pain

Integrated Review of Effectiveness

Not applicable as only a single clinical study was conducted.

8.1.3. Assessment of Efficacy Across Trials

Not applicable as only a single clinical study was conducted.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation of IV golimumab for pJIA relies on data from one clinical study, Study CNTO148JIA3003, an open-label PK, immunogenicity, safety, and efficacy study in 127 patients ages 2 to < 18 years, with JIA with active polyarthritis, who received IV golimumab 80 mg/m^2 for 52 weeks. Study CNTO148JIA3001, a randomized withdrawal study of the treatment of JIA patients with active polyarthritis with SC golimumab, provides additional supportive safety data for golimumab in 173 patients ages 2 to < 18 years with JIA with active polyarthritis despite MTX therapy. The safety of IV golimumab in JIA with active polyarthritis as observed in Study CNTO148JIA3003 was also compared to the established safety profile of IV golimumab in adult RA patients. Direct comparisons of safety of treatment with IV golimumab and SC golimumab in JIA with active polyarthritis, and the safety of IV golimumab in JIA with active polyarthritis as compared to other indications are limited by differences in study designs, differences in frequencies of some types of events between the JIA and RA populations, and the limitations of cross-study comparisons.

8.2.2. Review of the Safety Database

Overall Exposure

Through Week 52, 127 patients received at least one administration of IV golimumab with a mean cumulative dose of 732.238 mg/m^2. A total of 113 patients completed 52 weeks of treatment with IV golimumab IV (7 scheduled doses for the 52 weeks). The mean number of doses in the Safety Population (n=127) was 6.6 (Table 6).

One hundred twenty-seven patients also received at least one dose of MTX through Week 52, with a mean cumulative dose of 811.344 mg. The mean weekly dose of MTX ranged from 16.7 mg to 17.4 mg.

Table 6. Extent of Exposure of Safety Population in Study CNTO148JIA3003

Exposure	IV Golimumab N=127
Patients received scheduled dose IV golimumab, *n (%)*	
Week 0	127 (100%)
Week 4	125 (98.4%)
Week 12	122 (96.1%)
Week 20	121 (95.3%)
Week 28	117 (92.1%)
Week 36	117 (92.1%)
Week 44	113 (89.0%)
Total number of IV golimumab doses	
Mean ±SD	6.6 ±1.2
Median (min, max)	7 (1, 7)
Cumulative doses of IV golimumab (mg/m^2)	
Mean ±SD	732.2 ±248.8
Median (min. max)	766.3 (95, 1584)
Doses of MTX	
Average number of MTX doses	47.8
Weekly mean dose , mg	16.7-17.4
Cumulative mean ±SD, mg	811.3 ±305.8
Median (min. max)	780 (15, 1990)

Source: Adapted from Applicant's Tables 9, 10, 16, TSIEXP02a, TSIEXP05a and TSIEXP06a in Study CNTO148JIA3003 CSR

Adequacy of the Safety Database

The safety database for this application primarily relies on Study CNTO148JIA3003 and includes data from 127 JIA patients with active polyarthritis ages 2 to < 18 years who received treatment with IV golimumab for up to 52 weeks. The demographic and disease characteristics of the patients in Study CNTO148JIA3003 are described in Section 8.1.2. In general, the patients in Study CNTO148JIA3003 appear to adequately represent the US population of patients with JIA with active polyarthritis in which biologic therapy would be appropriate. Additional supportive evidence of safety is provided by Study CNTO148JIA3001 which evaluated SC golimumab in 173 patients with active JIA with active polyarthritis. Overall, the safety data provided from Study CNTO148JIA3003, and the supportive safety data from Study CNTO148JIA3001, are adequate to inform the safety assessment of IV golimumab in patients with pJIA, in the context of the established safety profile in adult RA and the overall safety profile of TNF inhibitors in pJIA.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No important concerns regarding data integrity and the quality of overall submission were identified to impact the safety review.

Categorization of Adverse Events

The Applicant utilized standard definitions of AEs and SAEs. An assessment of severity grade was made using mild, moderate, and severe categories. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1. Events of special interest were defined as newly identified malignancy or case of active TB occurring after the first administration of study agent.

Routine Clinical Tests

Clinical laboratory tests measured during the study included routine hematology, blood chemistry, and CRP through 52 weeks and serum/urine pregnancy testing for females of childbearing potential. Hepatitis B and Hepatitis C serologies and rheumatoid factor were assessed at screening. QuantiFERON-TB Gold testing was conducted at Screening and Week 52 and a TB questionnaire was administered at each study visit. ANA and dsDNA antibodies were assessed at screening, Week 24, and Week 52. In addition, uveitis evaluations were performed at least every 6 months by the investigator; slit-lamp evaluations were performed by an ophthalmologist/optometrist at intervals based on disease-related factors as specified in the protocol. Refer to the Schedule of Assessments in 15.4 Clinical Appendices.

Laboratory results were graded according to National Cancer Institute (NCI)- Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. NCI-CTCAE grades were used in the summary of laboratory data (Grades 1–4).

8.2.4. Safety Results

Overall Adverse Event Profile

A summary of AEs at Weeks 28 and 52 is presented in Table 7 and described below.

Table 7. Summary of TEAEs through Week 52 in CNTO148JIA3003

	Golimumab IV Exposure	
	Week 28 N=127 n (%)	Week 52 N=127 n (%)
Patients with ≥1 AEs	98 (77.2%)	108 (85.0%)
Patients with ≥1 SAEs	6 (4.7%)	9 (7.1%)
Patients with ≥1 AEs leading to discontinuation	9 (7.1%)	11 (8.7%)
Patients who died during study	0	0
Patients with ≥1 severe AEs	3 (2.4%)	5 (3.9%)
Patients with ≥1 reasonably related AEs	28 (22.0%)	37 (29.1%)
Patients with ≥1 reasonably related SAEs	4 (3.1%)	7 (5.5%)
Patients with ≥1 infections	70 (55.1%)	83 (65.4%)
Patients with ≥1 serious infections	4 (3.1%)	7 (5.5%)
Patients with ≥1 opportunistic infections	1 (0.8%)	1 (0.8%)
Patients with active TB	0	0
Patients with ≥1 infusion reactions	2 (1.6%)	3 (2.4%)
Patients with ≥1 malignancies	1 (0.8%)	1 (0.8%)

Source: Applicant's Tables 18 and 19 in Study CNTO148JIA3003 CSR

Deaths

No deaths were reported through 52 weeks in Study CNTO148JIA3003. However, one death due to septic shock was reported after Week 52. A 5-year-old White female (Subject (b) (6) with a history of pJIA for approximately 5 months prior to enrolling into the study. At Week 76 of golimumab therapy, the patient experienced constipation which improved partially following a phosphate enema treatment. The following day she was admitted to the hospital due to sudden onset of epigastric pain, distal cyanosis and normal laboratory tests except for thrombocytopenia (49x $10^3/\mu L$). She developed hypothermia, tachycardia, and decreased peripheral perfusion, and died from shock 2 days later. The cause of death was "refractory septic shock" and "sepsis with no microorganism isolation" of unknown origin", which was considered by the investigator as probably related to golimumab, attributed to possible "bacterial translocation in the gut". The clinical presentation of this patient is consistent with septic shock in children. Of note, approximately 3 weeks prior to hospitalization this patient suffered a non-displaced fracture of nasal bones with no orbital fracture as the result of a fall and 10 days later she was diagnosed by computerized tomography with bilateral maxillary and ethmoid sinusitis and bilateral periorbital cellulitis which improved the next day with oral antibiotics. Four days after the start of treatment with antibiotics, the patient presented with abdominal pain and constipation leading to the hospitalization. The association of sepsis with

the sinusitis and periorbital cellulitis versus an abdominal source cannot be ruled out. The current labeling for IV golimumab includes a boxed warning for risks of serious infections leading to hospitalization or death.

Serious Adverse Events

Overall, 9 patients (7.1%) of patients experienced an SAE through Week 52, including 6 patients who reported SAEs during the first 28 weeks. As summarized in Table 8 by system organ class (SOC) and preferred terms (PT), the most frequent SAEs are related to infections (n=7); pneumonia streptococcal and pleural effusion were reported in the same patient. Serious infections were singular by PT.

The two SAEs not related to infections include an SAE of suicidal ideation and an SAE of mycosis fungoides. The SAE of suicidal ideation was reported by a 13-year-old female with a history of depression, 4 suicide attempts, and 3 prior hospitalizations for suicidal ideation. Her history of depression with suicidality is a likely contributing factor to the SAE.

Mycosis fungoides was reported in a 13-year-old male with a history of eczema who experienced progression of existing hypopigmented skin lesions at Week 12, after 3 doses of golimumab treatment. The patient had hypopigmented skin lesions on the neck and torso since 7 years of age, unresponsive to anti-fungal treatment. A skin biopsy showed CD8+ atypical lymphoid infiltrate, consistent with hypopigmented mycosis fungoides. The investigator considered the event as possibly related to golimumab and the patient discontinued from the study. This case was an isolated event and occurred after a short duration of treatment (3 months), however TNF-inhibitors may increase the risk of lymphoma and other malignancies, in children and adolescents. The labeling for IV golimumab includes a boxed warning regarding the risks of lymphoma and other malignancies in children and adolescents treated with TNF-blockers.

Overall, the SAE profile of IV golimumab in JIA patients with active polyarthritis is generally consistent with the safety observed with SC golimumab in JIA patients with active polyarthritis and IV golimumab in adult RA patients, noting the limitations of cross-study comparisons due to differences in study designs and conduct.

Table 8. Serious Adverse Events through Week 52 in Study CNTO148JIA3003

System Organ Class/Preferred Term	IV Golimumab N=127 n (%)
Patients with ≥1 SAEs	9 (7.1%)
Infections and infestations	7 (5.5%)
Cellulitis	1 (0.8%)
Herpes zoster disseminated	1 (0.8%)
Infective exacerbation of bronchiectasis	1 (0.8%)
Pneumonia	1 (0.8%)
Pneumonia streptococcal	1 (0.8%)
Sepsis	1 (0.8%)
Varicella	1 (0.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8%)
Mycosis fungoides	1 (0.8%)
Psychiatric disorders	1 (0.8%)
Suicidal ideation	1 (0.8%)
Respiratory, thoracic and mediastinal disorders	1 (0.8%)
Pleural effusion	1 (0.8%)

Source: Applicant's Table 22 in Study CNTO148JIA3003 CSR

Dropouts and/or Discontinuations Due to Adverse Effects

A total of 8.7% (n=11) of patients discontinued golimumab due to ≥1 AEs through Week 52, and the majority of the discontinuations occurred during the first 28 weeks (n=9). The AEs resulting in discontinuation of study drug were mainly due to serious infections and musculoskeletal and connective tissue disorders. The most frequently reported AE leading to discontinuation by PT was JIA (3 patients, 2.4%). Other AEs leading to discontinuation reported by 1 patient each included arthritis, systemic lupus erythematosus, mycosis fungoides, suicidal ideation, pleural effusion, empyema, herpes zoster disseminated, infective exacerbation of bronchiectasis, pneumonia streptococcal, and sepsis.

Significant Adverse Events

The protocol-specified AEs of Special Interest included malignancy and active TB. AESI were then further defined by the Applicant for all golimumab studies as follows:

- Infections (including serious infections or opportunistic infections), active TB
- Infusion reactions (serious or severe regardless of seriousness)
- Newly identified malignancies (including skin cancers)
- Anaphylactic, serum sickness, or serum sickness-like reactions related to study agent
- Other AE of interest: new autoimmune disorders, heart failure, selected hematologic laboratory abnormalities, selected neurologic events (including demyelinating events),

interstitial lung disease, and pregnancies with negative outcome

The table below summarizes the AESI in Study CNTO148JIA3003 through Week 52:

Table 9. Adverse Events of Special Interest through Week 52 in Study CNTO148JIA3003

System Organ Class/Preferred Term	Golimumab IV N=127 n (%)
Patients with ≥1:	
Infections and infestations	83 (65.4%)
Serious Infections	7 (5.5%)†
Upper respiratory tract infection	27 (21.3%)
Nasopharyngitis	23 (18.1%)
Gastroenteritis	5 (3.9%)
Tonsillitis	5 (3.9%)
Opportunistic Infections	1 (0.8%)
Herpes zoster disseminated	1 (0.8%)
Active TB	0
Infusion Reactions	3 (2.4%)
Cough	1 (0.8%)
Dyspnea	1 (0.8%)
Fatigue	1 (0.8%)
Laryngeal edema	1 (0.8%)
Anaphylactic Reactions, Hypersensitivity, or Serum Sickness	0
Hepatobiliary event	0

Source: Applicant's Tables 24, LSFOPIN01a and TSFAE13a in Study CNTO148JIA3003 report
† See the details of the serious infection events in Table 8.

Infections

Through Week 52, 65.4% of patients experienced at least 1 AE identified as an infection by the investigator. The majority of the infections were non-serious. Serious infections are discussed under Serious Adverse Events above. The most frequently reported infections were upper respiratory tract infection (21.3%), nasopharyngitis (18.1%), gastroenteritis (3.9%), and tonsillitis (3.9%). Other infections were reported by ≤ 4 patients. The proportions of patients with infections were similar between the age subgroups of ≥ 2 to < 8 years (66.7%) and ≥ 8 to < 18 years (65.0%). While more serious infections were reported in the age subgroup of ≥ 2 to < 8 years (3 cases, 11%) versus ≥ 8 to < 18 years of age (4 cases, 4%) through Week 52, the numbers were small draw definitive conclusions.

One patient (0.8%) reported an opportunistic infection of disseminated herpes zoster. This was considered an SAE and an AE leading to discontinuation and is discussed above. None of the patients developed active TB during treatment with IV golimumab.

Infusion reactions

Infusion reactions were defined as an AE that occurs during or within 1 hour following the infusion of study agent. Through Week 52, there were 4 infusion reactions in 3 patients (2.4%): cough and dyspnea (1 event each in same patient), fatigue (2 events in 1 patient), and laryngeal edema (1 event in 1 patient). In addition, 1 patient reported a mild dry cough and subjective dyspnea 30 minutes after the end of the Week 28 infusion that resolved without treatment. None of the infusion reactions were considered to be severe or serious, and none led to discontinuation of the study agent through Week 52.

There was no impact of antibodies to golimumab on infusion reactions. Two (2.3%) of the 86 ADA-negative and 1 (2.6%) of 39 ADA-positive patients had an infusion reaction through Week 52.

Malignancies

Through Week 52, one patient had a malignancy of mycosis fungoides as discussed in Serious Adverse Events above.

Anaphylactic Reactions or Serum Sickness Reactions

None of the patients experienced an anaphylactic reaction or serum sickness through Week 52.

Hepatobiliary Events

Clinically important hepatobiliary events were defined as an ALT value ≥3×ULN and either total bilirubin ≥2×ULN or occurrence of an SAE in the hepatobiliary disorders SOC. Criteria for hepatotoxicity were defined as persistent ALT or AST >5xULN; ALT or AST >3xULN with total bilirubin >2xULN, jaundice, or liver injury. In addition, any ALT or AST value >5xULN was considered to be clinically relevant.

None of the patients had a postbaseline clinically important hepatobiliary event through Week 52, and none had a post-baseline ALT or AST value >5xULN through Week 52. Four patients had one ALT or AST elevation ≥3×ULN through Week 52, but none of them had a total bilirubin >2×ULN, jaundice or a liver biopsy. ALT and AST values ≥3×ULN either returned to the normal range or were minimally elevated (1-2×ULN) at other time points.

Other Adverse Events of Interest

One patient was diagnosed with a new autoimmune disorder (systemic lupus erythematosus (SLE)). The patient had positive ANA and dsDNA antibodies at baseline without lupus manifestations. On Study Day 192, the patient had an AE of SLE with malar rash, vasculitis lesions, and non-remitting arthritis. The event was nonserious, moderate in intensity and not related to study agent. The event resulted in discontinuation of study agent.

There were no demyelinating events, heart failure, interstitial lung disease, selected

hematologic laboratory abnormalities, interstitial lung disease, or pregnancies with negative outcome reported through Week 52.

Treatment Emergent Adverse Events and Adverse Reactions

Through Week 52, 108 patients (85%) treated with IV golimumab experienced ≥1 AE as listed in Table 10 regardless of causality.

The most frequently reported AEs by SOC were:

- Infections and infestations: 66.9% (n=85)
- Gastrointestinal disorders: 23.6% (n=30)
- Musculoskeletal and connective tissue disorders: 18.9% (n=24)
- Injury, poisoning and procedural complications: 18.1% (n=23)
- Nervous system disorders: 15.7% (n=20)

The most frequently reported AEs by PT were:

- Upper respiratory tract infection: 21.3% (n=27)
- Nasopharyngitis: 18.1% (n=23)
- Headache: 11.0% (n=14)
- Juvenile idiopathic arthritis: 11.0% (n=14)
- Nausea: 8.7% (n=11)
- Vomiting: 7.9% (n=10)

The majority of AEs were mild to moderate in severity. Through Week 52, 5 patients (3.9%) treated with golimumab had at least 1 AE considered to be severe by the investigator. Severe AEs were:

- Herpes zoster disseminated (n=1)
- Pneumonia streptococcal and pleural effusion (n=1)
- Varicella (n=1)
- ALT elevation (n=1)
- Migraine (n=1)

Overall, the common AEs experienced by the JIA patients with active polyarthritis in this study is generally consistent with the types and frequencies of AEs in the SC golimumab study in JIA patients with active polyarthritis, and the known safety profile of TNF-inhibitors.

Table 10. Treatment-Emergent Adverse Events Reported by ≥2% through Week 52 in Study CNTO148JIA3003

System Organ Class/Preferred Term	Golimumab IV N=127 n (%)
Patients with ≥ 1 TEAEs	108 (85.0%)
Infections and infestations	85 (66.9%)
Upper respiratory tract infection	27 (21.3%)
Nasopharyngitis	23 (18.1%)
Gastroenteritis	6 (4.7%)
Tonsillitis	5 (3.9%)
Gastroenteritis viral	4 (3.1%)
Pharyngitis	4 (3.1%)
Rhinitis	4 (3.1%)
Sinusitis	4 (3.1%)
Varicella	4 (3.1%)
Viral infection	4 (3.1%)
Viral upper respiratory tract infection	4 (3.1%)
Bronchitis	3 (2.4%)
Ear infection	3 (2.4%)
Impetigo	3 (2.4%)
Molluscum contagiosum	3 (2.4%)
Oral herpes	3 (2.4%)
Respiratory tract infection viral	3 (2.4%)
Tinea versicolor	3 (2.4%)
Musculoskeletal and connective tissue disorders	24 (18.9%)
Juvenile idiopathic arthritis	14 (11%)
Arthritis	4 (3.1%)
Gastrointestinal disorders	30 (23.6%)
Nausea	11 (8.7%)
Vomiting	10 (7.9%)
Abdominal pain	8 (6.3%)
Diarrhea	5 (3.9%)
Abdominal pain upper	4 (3.1%)
Injury, poisoning and procedural complications	23 (18.1%)
Contusion	4 (3.1%)
Arthropod bite	3 (2.4%)
Skin laceration	3 (2.4%)
Nervous system disorders	20 (15.7%)
Headache	14 (11.0%)
Migraine	5 (3.9%)
Respiratory, thoracic and mediastinal disorders	16 (12.6%)
Epistaxis	6 (4.7%)

System Organ Class/Preferred Term	Golimumab IV N=127 n (%)
Cough	5 (3.9%)
Oropharyngeal pain	4 (3.1%)
Skin and subcutaneous tissue disorders	16 (12.6%)
Alopecia	3 (2.4%)
Prurigo	3 (2.4%)
Rash	3 (2.4%)
Investigations	13 (10.2%)
Alanine aminotransferase increased	7 (5.5%)
Aspartate aminotransferase increased	5 (3.9%)
General disorders and administration site	7 (5.5%)
Pyrexia	4 (3.1%)
Blood and lymphatic system disorders	5 (3.9%)
Anemia	3 (2.4%)
Eye disorders	4 (3.1%)
Conjunctivitis allergic	3 (2.4%)

Source: Applicant's Table 20 in Study CNTO148JIA3003 CSR

Laboratory Findings

In Study CNTO148JIA3003, clinical laboratory testing included hematology and blood chemistry. The laboratory values were categorized by CTCAE grading system.

Hematology

Post-baseline changes in hematology parameters through Week 52 by maximum CTCAE grade were as follows (based on Applicant's CSR Table TSFLAB04a):

- Grade 4 (n=0)
- Grade 3 (3.1%, n= 4): transient decrease in neutrophils (n=1), hemoglobin (n=1) and lymphocytes (n=2)
- Grade 2 (13.4%, n=17): decrease in leukocytes (n=1), neutrophils (n=8), Hb (n=7), and lymphocytes (n=1)
- Grade 1 (81%, n=103): decrease in leukocytes (n=30), neutrophils (n=5), Hb (n=45) and lymphocytes (n=7)

Patients with markedly abnormal postbaseline hematology values through Week 52 were as follows (based on Applicant's CSR Table TSFLAB02a):

- Neutropenia: 7.1% (n=9) had ≥1 markedly abnormal low absolute neutrophil value (i.e., percent decrease ≥33 and value $<1.5\times10^9$/L)
- Eosinophilia: 1.6% (n=2) had ≥1 markedly abnormal elevated eosinophil value (i.e., percent increase ≥100 and value $>1.3\times10^9$/L),
- Low hematocrit: 1.6% (n=2) had at least 1 markedly abnormal hematocrit values (i.e.,

<0.27)
- Low hemoglobin: 0.8% (n=1) had 1 markedly abnormal hemoglobin value (i.e., decrease >20.0 g/L and value <100.0 g/L)
- Lymphopenia: 11.1% (n=14) had at least 1 markedly abnormal lymphocyte value (i.e., percent decrease ≥33 and value $<1.5\times10^9$/L)
- Leukocytosis: 0.8% (n=1) had 1 markedly abnormal elevated leukocyte value (i.e., $>20\times10^9$/L)

Blood chemistry

Post-baseline changes in blood chemistry values through Week 52, as summarized below, were mostly due to ALT and/or AST elevation, without changes in total bilirubin.

Post-baseline blood chemistry changes through Week 52 by maximum CTCAE Grade were as follows (based on Applicant's CSR Table TSFLAB03):
- Grade 4 (0.8%, n=1): hyperkalemia (7.3 mmol/L) reported at Week 36 but Grade 0 at all other visits through Week 52
- Grade 3 (0.8%, n=5): hyperkalemia (6.2 mmol/L) reported at Week 28, but Grade 0 at all other visits through Week 52; n=3 (2.4%) ALT elevation
- Grade 2 (4%, n=5) ALT elevation (n=3), alkaline phosphatase (n=1) and AST elevation (n=1)
- Grade 1: n=29 (23.0%) ALT elevation, n=24 (19.0%) alkaline phosphatase, n=14 (11.1%) AST elevation and n=15 (11.9%) urate elevation (hyperuricemia)

Markedly abnormal chemistry tests through Week 52 were as follows (based on Applicant's CSR Table TSFLAB01a):
- Potassium: 3.2% (n=4) had 1 markedly abnormal potassium value (increase ≥0.8 mmol/L and value >5.5 mmol/L).
- Calcium: 0.8% (n=1) had 1 markedly abnormal calcium value (decrease ≥0.37 and value <1.87 mmol/L)
- AST: 0.8% (n=1) had 1 markedly abnormal AST value (percent increase ≥100 and value >150 U/L)
- ALT: 0.8% (n=1) had 1 markedly abnormal ALT value (percent increase ≥100 and value >150 U/L)

Overall the observed laboratory changes are consistent with the safety profile of golimumab and other TNF inhibitors. The IV golimumab prescribing information includes a warning and precaution for hematologic cytopenias, which states there have been reports of pancytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anemia, and thrombocytopenia. Caution should be exercises when using TNF-blockers, including Simponi Aria, in patients who have or have had significant cytopenias. In addition, liver enzyme elevations were observed in the studies in RA and PsA and are described in Section 6 Clinical Trials Experience of the prescribing information.

Vital Signs

Vital signs were assessed at all visits and no clinically relevant changes in vital sign parameters were observed through Week 52. TEAEs related to vital sign parameters included pyrexia (4 patients, 3.1%), blood pressure increased (1 patient, 0.8%), and chills (1 patient, 0.8%). No AEs related to vital signs were considered to be severe, serious, or led to discontinuation of study drug.

Electrocardiograms (ECGs)

ECGs were not assessed in Study CNTO148JIA3003.

Immunogenicity

The immunogenicity analysis was based on the PK analysis set (n=127). Through Week 52, the incidence of positive antibodies to golimumab (ADA) in 125 treated patients who had appropriate samples was 31.2% (n=39) based on the original ADA assay cut-point and 39.2% (n=49) based on the new ADA assay cut-point. The majority of the ADA observed were of low titer < 1:1000. The additional 10 patients identified based on the new cut-point were identified as positive at the lowest titer of 1:6. Of the 39 ADA-positive patients based on the original cut-points, 24 patients (61.5%) were positive for NAbs, while of the 49 ADA positive based on the new assay cut-points, 25 patients (51%) were positive for NAbs.

Median trough golimumab concentrations were generally lower in patients who were ADA-positive compared with patients who were ADA-negative with either the old or the new assay cut point. Refer to the Clinical Pharmacology section for additional discussion of the impact of ADA on golimumab concentration.

A lower proportion of patients who were ADA positive achieved a JIA ACR response (JIA ACR 30: 74.4%, JIA ACR 50: 69.2%, JIA ACR 70: 53.8%, and JIA ACR 90: 41.0%) through Week 52 as compared to patients who were ADA negative (JIA ACR 30: 77.9%, JIA ACR 50: 77.9%, JIA ACR 70: 72.1%, and JIA ACR 90: 53.5%). Similar findings were observed using the new assay cut-point to determine ADA status. Response rates were similar by antibody titer group, however, conclusions are limited by the small number of patients in each titer group.

While the numbers of patients with immunogenicity-related AEs was small, there was no increase in infusion reactions among patients with ADA. Of the 3 patients with infusion reactions through Week 52, 2 were ADA-negative (2.3%, 2 of 86 ADA-negative patients) and 1 was ADA-positive (2.6%, 1 of 39 ADA-positive patients). None of the patients experienced anaphylaxis, serum sickness or hypersensitivity through 52 weeks of IV golimumab treatment.

8.2.5. Analysis of Submission-Specific Safety Issues

Refer to Section 8.2.4 Safety Results/Specific Adverse Events.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

While the number of adverse events of interest were small, no meaningful differences were observed across the age groups studied.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Lymphoma and other malignancies have been reported in children and adolescent patients treated with TNF-inhibitors as described in a boxed warning and the Warnings and Precautions in the approved USPI for IV golimumab. One patient with JIA with active polyarthritis in Study CNTO148JIA3003 developed mycosis fungoides, a type of cutaneous T-cell lymphoma as described in Section 8.2.4 Safety Results/Serious Adverse Events.

Human Reproduction and Pregnancy

There were no reports of pregnancy through Week 52 in Study CNTO148JIA3003. No new information on human reproduction and pregnancy were submitted nor required for this supplement.

Pediatrics and Assessment of Effects on Growth

Study CNTO148JIA3003 was conducted in a pediatric population of patients with JIA with active polyarthritis. Assessment of effects of treatment with IV golimumab on growth was not included in this study.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No new information regarding overdose, drug abuse potential, withdrawal and rebound was submitted in this supplement.

120-Day Safety Update

On January 30, 2020, the Applicant submitted the 120-day safety update. The update included safety information from 127 treated JIA patients with active polyarthritis in the ongoing Study CNTO148JIA3003 through August 12, 2019. As of August 12, 2019, the last patient enrolled in the study had completed the Week 84 visit. The average duration of follow-up was 107.9 weeks (approximately 2 years) with an average number of IV golimumab administrations of 14.5. Overall, the safety presented in the 120-day safety update is similar to what was reported during the first 52 weeks (Table 11).

Table 11. Summary of TEAEs through August 12, 2019

	IV Golimumab N=127 n (%)
Average duration of follow-up (weeks)	107.9
Average number of doses	14.5
Patients with:	
≥1 TEAEs	113 (89.0)
Death	1 (0.8)
≥1 SAEs	15 (11.8)
≥1 AEs leading to discontinuation	15 (11.8)
≥1 Infections	99 (78.0)
≥1 Serious infections	12 (9.4)
≥1 Opportunistic infections	1 (0.8)
≥1 Infusion reactions	6 (4.7)
≥1 Malignancies	1 (0.8)

Source: Adapted from Applicant's 120-day safety update Table 2

There was one reported death due to septic shock after Week 52 that is described in Section 8.2.4 above. Fifteen patients (11.8%) reported SAEs. SAEs were most commonly reported in the Infections and Infestations (9.4%) and Cardiac Disorders (2.4%) SOCs. Serious infections of cellulitis, pneumonia, and varicella were reported in 2 patients each; other serious infections were singular by preferred term. Cardiac SAEs were reported in 3 patients, including single events of cyanosis, myocarditis, and supraventricular tachycardia (SVT). The SAE of cyanosis occurred in the clinical course of events reported in the sepsis-related death, and is discussed above. Myocarditis was reported in a 12-year-old boy during hospitalization for pneumonia; he was discharged after 8 days of hospital management and events were both reported as resolved on that day. Both myocarditis and pneumonia were considered SAEs and AEs leading to discontinuation. SVT was reported in a 16-year-old adolescent who experienced palpitations with dizziness, without syncope or shortness of breath on Day 416 of IV golimumab treatment. The SVT was confirmed by ECG and the patient responded to treatment with adenosine. The patient had two similar shorter episodes of palpations without report of the timing related to golimumab. Relatedness to Study Agent was assessed as Doubtful by the investigator. The

observed cardiac SAEs were singular by preferred term and do not suggest a new safety signal.

Fifteen patients (11.8%) reported AEs leading to discontinuation. The SOCs with more than 1 AE leading to discontinuation were Infections and Infestations (5 patients, 3.9%), Musculoskeletal and Connective Tissues Disorders (5 patients, 3.9%), and Cardiac Disorders (2 patients, 1.6%). Worsening of JIA (3 patients, 2.4%) was the only AE leading to discontinuation reported by more than one patient.

AESI reported in the safety update were consistent with those observed during the 52-week period. Twelve patients (9.4%) had serious infections as discussed above. One patient (0.8%) reported an opportunistic infection (herpes zoster disseminated) that was assessed as serious and also an AE leading to discontinuation; this event was included in the 52-week database lock. One patient had a malignancy (mycosis fungoides); this event was also included in the 52-week database lock and is discussed above. A total of 7 infusion reactions were reported in 6 patients; none of the infusion events were considered severe or serious. There were no events of active TB, demyelination events, clinically important hepatobiliary events, or anaphylactic reaction or serum sickness reactions.

In summary, no new safety signals are identified in the additional safety information through August 12, 2019, provided in the 120-day safety update.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There are no post-marketing data for golimumab IV or SC in pJIA patients submitted with this supplement.

Expectations on Safety in the Postmarket Setting

The observed safety profile for IV golimumab in JIA with active polyarthritis in Study CNTO148JIA3003 is generally similar to the observed safety profile of IV golimumab in the approved adult indications, and the known safety profile of other TNF-inhibitors in pJIA/JIA with active polyarthritis. Therefore, the safety profile of IV golimumab in the post market setting would be expected to be consistent with the known risks associated with TNF-inhibitors in pJIA and other indications. As a treatment administered by IV infusion, the expected risks of infusion reactions are expected to be higher, while the risks of injection site reactions are lower, as compared to SC treatments. There are no new safety issues that cause concern when considering how the drug may be used in the postmarket setting.

8.2.11. Integrated Assessment of Safety

A single study was conducted to evaluate the PK, safety, and efficacy of IV golimumab in JIA patients. No integration of safety is presented. Additional supportive safety data for golimumab in pJIA are provided from Study CNTO148JIA3001, a randomized withdrawal study of SC golimumab in 173 JIA patients with active polyarthritis. In that study, there were no deaths, SAEs were reported by 23% of patients randomized to SC golimumab, while AEs leading to discontinuation were reported by 8% of patients randomized to SC golimumab. The most frequently reported SAEs were JIA and arthritis; JIA was also the most frequently reported AE leading to discontinuation. Infections and serious infections were reported by 79.5% and 5.1%, respectively, of patients in the SC golimumab treatment group. Comparison of the observed safety in JIA patients with active polyarthritis treated with IV and SC golimumab is limited by differences in study designs and cross-study comparison, however no new safety signals were identified. See BLA 125289s133 Clinical Review (DARRTs Reference ID: 4100247) for full details of safety in Study CNTO148JIA3001.

The Applicant has provided information on the safety of IV golimumab through Week 16 as compared to other approved biologics for pJIA (data not shown). While the proportions of patients with AEs, SAEs, serious infections, and AEs leading to discontinuation are generally similar, differences in study designs and limitations of cross study comparisons limit definitive conclusions that can be drawn. In addition, the safety observed in Study CNTO148JIA3003 is generally consistent with the known safety of IV golimumab in RA.

8.3. Statistical Issues

Study CNTO148JIA3003 was a 52-week, open-label, single-arm PK, immunogenicity, safety and exploratory efficacy study conducted in 127 JIA patients with active polyarthritis, ages of 2 to <18 years, with an inadequate response to or inability to tolerate methotrexate. The primary objective of Study CNTO148JIA3003 was to assess the PK following IV golimumab in patients with JIA with active polyarthritis. Efficacy was assessed as a supportive endpoint.

The substantial evidence of efficacy to support the proposed pJIA indication relies on the extrapolation of efficacy of IV golimumab established in adults with rheumatoid arthritis, based on a PK-matching approach. The exploratory efficacy assessments observed in JIA with active polyarthritis from Study CNTO148JIA3003 provide additional supportive efficacy data. No statistical issues were identified from review of the open-label efficacy data provided by Study CNTO148JIA3003 that impact the overall conclusions on safety and efficacy.

8.4. Conclusions and Recommendations

The Applicant submitted Study CNTO148JIA3003 to support the sBLA for IV golimumab for the treatment of active pJIA in patients ages 2 years and older and to fulfill the PMR (PMR-1) required at the time of approval for the RA indication, to evaluate the safety, efficacy, PK, and immunogenicity of IV golimumab in pediatric patients between the ages of 2 to 17 years and 11 months with active juvenile idiopathic arthritis (JIA) despite standard therapy with methotrexate. The study was designed and conducted as an open-label, single-arm, multicenter, PK, immunogenicity, safety, and efficacy study of IV golimumab in patients, ages 2 to < 18 years, with JIA with active polyarthritis despite treatment with MTX. The primary objective was to assess the PK following IV golimumab in patients with JIA with active polyarthritis despite MTX therapy for ≥ 2 months. Efficacy was assessed as a supportive endpoint.

The efficacy of IV golimumab in pJIA is based on matching systemic exposure and extrapolation of established efficacy of IV golimumab in RA. As discussed in Section 0, the clinical pharmacology review team has determined that the exposures observed in JIA patients with active polyarthritis treated with IV golimumab in Study CNTO148JIA3003 were within the range of exposures seen in RA patients treated with IV golimumab in Study CNTO148ART3001, a pivotal phase 3 study, submitted to support the approval of IV golimumab in moderately to severely active RA. In addition, supportive trends of improvement from baseline were observed for the exploratory efficacy endpoints in the open-label uncontrolled Study CNTO148JIA3003 in JIA with active polyarthritis, providing additional support for the efficacy of IV golimumab in pJIA.

The safety assessment of IV golimumab for the proposed pJIA indication is primarily based on the safety data from 127 JIA patients with active polyarthritis in Study CNTO148JIA3003, treated with IV golimumab at the proposed dosing regimen of 80 mg/m^2 at Weeks 0 and 4, and every 8 weeks thereafter. There was a single death reported after the Week 52 database lock due to septic shock. Infections were the most frequently reported AEs and SAEs, consistent with the known safety profile of IV golimumab. The safety data is further supported by the safety data from Study CNTO148JIA3001, which evaluated SC golimumab in 173 JIA patients with active polyarthritis. The overall safety profile was similar to that previously known in JIA patients with active polyarthritis treated with SC golimumab and other TNF inhibitors, and in adult RA patients treated with IV golimumab. No new safety signals were identified.

The Applicant provided adequate data to inform the benefit-risk assessment of IV golimumab for the treatment of active pJIA in patients 2 to < 18 years of age. Overall, the efficacy and safety evidence provided in this submission supports a favorable benefit/risk profile of IV golimumab for the treatment of pJIA patients ages 2 to < 18 years at the proposed dosing of IV golimumab 80 mg/m^2 at Weeks 0 and 4, and every 8 weeks thereafter. The safety of IV golimumab in pJIA was consistent with the known safety of IV golimumab and offers an

acceptable risk for the therapeutic benefits. Approval of IV golimumab will provide an additional treatment option in the US and the first intravenous TNF inhibitor treatment available for treatment of pJIA in the US. Therefore, we recommend approval of IV golimumab for active pJIA in pediatric patients 2 years of age and older. In addition, Study CNTO138JIA3003 was designed and conducted consistent with the post-marketing requirement; we recommend the PMR be considered fulfilled based on the results of Study CNTO138JIA3003.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not held for this supplemental BLA. No issues were identified warranting advisory committee input.

10 Pediatrics

BLA 125433/s30 was submitted to fulfill the PREA post-marketing requirement (PMR)-1 as required at the time of approval for the indication of RA. The study has adequately addressed all PMR requirements, including assessments of PK, safety, immunogenicity and efficacy in pediatric patients between the ages 2 to 17 years and 11 months with active JIA despite standard therapy with methotrexate. The review team recommends that the PMR to conduct a trial that will evaluate the safety, efficacy, PK/PD and immunogenicity of IV golimumab in pediatric patients between the ages 2 to 17 years and 11 months with active JIA despite standard therapy with methotrexate be considered fulfilled. The submission was reviewed at the FDA Pediatric Review Committee (PeRC) on July 29, 2020. PeRC agreed with the Division's assessment and recommendation that the study fulfills the intent of the PMR.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
Table 12 presents a high-level summary of the labeling proposal and subsequent interactions between the Applicant and the Agency. Labeling for S-030, as well as for S-031 to support the treatment of pediatric patients with PsA, were reviewed concurrently. Refer to the Multidisciplinary review for BLA 125433/s31 for details of the information to support the efficacy and safety of IV golimumab in pediatric patients with PsA. Details of the labeling revisions for both supplements are included below.

Table 12. Summary of Significant Labeling Changes (High Level Edits)

Section	Labeling Changes and Discussions
Section 1 Indications and Usage	• Indication for "Treatment of active pJIA in patients 2 years of age and older" was added • Revision to existing indication for PsA, as follows "Treatment of active PsA in patients 2 years of age and older (b) (4) (supported by data reviewed under supplement S-031)
Section 2 Dosage and Administration	• Inclusion of dosing instructions for pediatric patients • A statement advising prescribers to follow the dilution and administration instructions for Simponi Aria was added to Sections 2.1 and 2.2. • In Section 2.1 of currently approved labeling, the following statement was removed "For patients with PsA or AS, Simponi Aria may be given with or without methotrexate or other DMARDs" • In Sections 2.1 and 2.2, the statement advising concomitant corticosteroids, NSAIDs, and/or analgesics may be continued, was removed as the statement informs the use of other products, and is not necessary for the safe and effective use of Simponi Aria • Removed statement (b) (4) • The Applicant proposed (b) (4)
Section 5.2 Malignancies	Revised to indicate that malignancies had been reported in patients who received golimumab
Section 5.10 Vaccinations/Therapeutic Infectious Agents	• Inclusion of statement that live vaccines in infants exposed to Simponi Aria *in utero* is not recommended for 6 months following mother's last infusion. This information is also retained in Section 8.1 • Addition of guidance to update immunizations prior to initiation of treatment and advise patients to discuss

	immunizations with the physician
Section 6.1 Clinical Trials Experience	Description of Trial pJIA added with statement that adverse reactions observed were consistent with the established safety profile of golimumab in adult patients with RA
Section 6.2 Immunogenicity	• Revisions to description of immunogenicity to include observed ADA incidence in Trial pJIA • Inclusion of pJIA patients in the statement that RA, PsA, AS, and pJIA patients with antibodies to golimumab generally had lower trough steady-state serum concentrations of golimumab
Section 7.1 Drug Interactions, Methotrexate	• Statement that (b) (4) was removed • Deletion of existing statement that Simponi Aria may be used with or without MTX for the treatment of AS
Section 8.4 Pediatric Use	• Revisions to statements describing pediatric populations in which safety and efficacy information is available • Addition of description of data supporting use of SIMPONI ARIA in indicated pediatric populations: o Data from adequate and well-controlled studies in adults with RA and PsA o PK data from adults with RA and PsA and pediatric patients with pJIA o Safety data from study in JIA with active polyarthritis, ages 2 to < 18 years • Statement regarding comparable PK between adults with RA and PsA and pediatric patients with pJIA, and expectation of comparable PK exposure between adult PsA and pediatric patients with PsA • Inclusion of reference to Simponi Aria in TNF-inhibitor class language regarding reported malignancies • Updates to statement of populations in which safety and effectiveness have not been established in pediatric patients
Section 12.3 Pharmacokinetics, Pediatrics	• Description of observed PK in pJIA study • Statement that observed steady state Ctrough in JIA with active polyarthritis were within the range observed for adult RA and PsA • The following statement r (b) (4) was removed (b) (4) : (b) (4)

	(b) (4) [redacted] • Statement that "there were no clinically relevant differences in golimumab exposure following intravenous administration of 80 mg/m^2 SIMPONI ARIA in pediatric patients across a range of age and different body weight." was added • Statement that the immune response effect on golimumab clearance in patients with active pJIA was comparable to adults with RA was added
Section 14, Clinical Studies	Addition of NCT numbers
Section 14.2, Clinical Studies, PsA	• Addition of subheading 'Treatment of Pediatric Patients' • Statement describing efficacy in pediatric patients with PsA based on PK exposure and extrapolation of established efficacy in adult PsA patients
Section 14.4, Clinical Studies, PJIA	• The Agency proposed revisions to clarify that efficacy is based on PK exposure and extrapolation of efficacy from established efficacy of SIMPONI ARIA in RA patients. • The study description was revised to specify the JIA patient subtypes enrolled and to streamline the concomitant medication description • The PK information was removed as it is redundant to Section 12.3 • As efficacy endpoints were supportive endpoints in Study CNTO148JIA3003, discussion of (b) (4) [redacted] was replaced with description that the efficacy endpoints were generally consistent with the responses in patients with RA.
Section 17, Patient Counseling Information	• Revised to include vaccine information in updated Section 5.10 • Revised to recommend periodic skin examination for all patients, particularly those with risk factors for skin cancer

Other Prescription Drug Labeling
Revisions to patient labeling were made to align with the revised prescribing information, including the addition of the pJIA indication, expansion of the PsA indication to pediatric patients, and updates to the statement describing the pediatric populations for which safety and effectiveness is not known. The statement regarding continuing other medicines while receiving Simponi Aria, such as NSAIDs, prescription steroids, and pain relief medicines, was removed for consistency with the revisions to Section 2 of the PI.

Labeling consultants, including DMEPA, OPDP, and DMPP, have reviewed the submitted labeling and their recommendations which pertain primarily to internal consistency, improving readability and clarity of the labeling, have been considered and conveyed to the Applicant. All labeling changes were agreed upon with the Applicant.

12 Risk Evaluation and Mitigation Strategies (REMS)

No new risk management plans are submitted as part of this supplement. As no new safety signals have been identified, a Risk Evaluation and Management Strategy (REMS) is not recommended for this product.

13 Postmarketing Requirements and Commitment

There are no potential or new safety or efficacy issues determined from this review that warrant further assessment with a postmarketing requirement or postmarketing commitment.

14 Division Director (Clinical) Comments

I agree with the team's assessment of the data submitted, the benefit-risk assessment, and the conclusions regarding the data supporting recommended regulatory action. The team's recommendations are supported by the data submitted by the Applicant and are consistent with a discussion at the FDA/M-CERSI (University of Maryland Center of Excellence in Regulatory Science and Innovation) public workshop on October 02, 2019, titled "Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA)." [8] Based on the cumulative experience with drug development in JIA space, as discussed at the workshop, the Agency has considered the high degree of similarity between adults with RA and pediatric patients with pJIA to support a scientific rationale for a pediatric extrapolation of efficacy, meaning that efficacy established in adequate and well-controlled studies in adults with RA could be extrapolated to pediatric patients with pJIA based on matching of the PK exposures between the two populations. The extrapolation of efficacy is based on appropriate scientific justification and data provided by the Applicant to support the expectation of similarity in exposure-response between the two populations. Safety, and immunogenicity, were supported by a reasonable safety database in 127 JIA pediatric patients with active polyarthritis, the safety data in JIA patients with active polyarthritis treated with SC golimumab, and the safety in adult RA patients treated with IV golimumab.

The regulatory action is Approval with labeling changes agreed upon with the Applicant.

The data provided in this submission fulfill the PREA PMR 2394-1 under BLA 125433. No new postmarketing studies are required, based on this submission.

Of note, in parallel with this review, the Agency also reviewed a supplemental BLA application (S-031) for expanding the IV golimumab PsA indication to include pediatric patients 2 years of age and older (Refer to the Multidisciplinary review for BLA 125433/S-031).

[8] Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA). FDA White Oak Campus, Silver Spring, Maryland, Oct 2, 2019

15 Appendices

15.1. References

Brewer EJ, Bass J, Baum J, et al. Current proposed revision of JRA criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1997;20(Suppl)195-9.

Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390–392.

Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369(9563):767–78.

Ringold S, Weiss PF, Beukelman T, et al. 2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications. Arthritis & Rheumatism 2013, 65: 2499–2512.

Ringold S, Angeles-Han S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care & Res, 2019, 71: 717-734, 2019.

Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: A systematic review. Joint Bone Spine 2014; 81(2):112-117.

15.2. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators. The Applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. (b) (6) is a principal investigator in Study CNTO148JIA3003 and reported stock ownership within a limited partnership. (b) (6) patients were enrolled at this site. (b) (6) is a subinvestigator in Study CNTO148JIA3003 who reported significant payment for consultancy and advisory board. (b) (6) patients were enrolled at this site. As the primary endpoint of Study CNTO148JIA3003 was PK, the study was conducted in an open-label manner, and the number of patients enrolled at the study sites were small, the disclosable interests are unlikely to influence the outcomes of the study.

Covered Clinical Study (Name and/or Number): Study CNTO148JIA3003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 43		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Population Pharmacokinetics of Golimumab in Pediatrics with JIA with active polyarthritis

Sponsor's Analysis:

The Applicant submitted a population pharmacokinetics (PopPK) analysis report titled "Population Pharmacokinetic Report for Golimumab in Pediatric Subjects with Polyarticular Juvenile Idiopathic Arthritis from Study CNTO148JIA3003 and Adult Subjects with Rheumatoid Arthritis from Study CNTO148ART3001", hereafter referred to as the Applicant's PopPK report.

CNTO148JIA3003 was a Phase 3, open-label, single-arm, multicenter study to evaluate the PK, safety, and efficacy of IV golimumab in patients with active polyarticular Juvenile Idiopathic Arthritis (pJIA) despite current treatment with MTX and/or corticosteroids and/or non-steroidal anti-inflammatory agents and/or prior use of anti-TNFα agents. One hundred and twenty-seven subjects (n=127) received 80 mg/m^2 golimumab as an IV infusion (over 30 ±10 minutes) at Weeks 0, 4, and every 8 weeks (q8w; ± 3 days) through Week 28 and q8w (± 1 week) thereafter (maximum single dose 240 mg [maximum BSA 3.0 m^2 x 80 mg/m^2]), along with commercial MTX at a dose of 10-30 mg/m^2/week. For subjects greater than 1.67 m^2, a minimum fixed dose of 15 mg/week is required.

CNTO148ART3001 was a Phase 3, multicenter, randomized, double-blind, placebo controlled, 2-arm study of golimumab 2 mg/kg IV infusions at Weeks 0, 4, and every 8 weeks thereafter in adult subjects with active RA. Five hundred and ninety-two subjects (n=592) were randomly assigned to 1 of 2 treatment groups (2 mg/kg golimumab or placebo) in a 2:1 ratio during Week 0 to Week 24. Subjects initially randomized to golimumab treatment received 2 mg/kg IV at Weeks 0, 4, and q8w thereafter, with a placebo infusion at Week 16 and Week 24 to maintain the blind. Subjects initially randomized to placebo received placebo (normal saline) infusions at Weeks 0, 4, 12, and 16 followed by golimumab treatment at week 24, 28, and q8w thereafter. All subjects maintained their stable dose of MTX (between 15 to 25 mg/week) throughout the study.

The demographics and baseline characteristics in Study CNTO148JIA3003 and CNTO148ART3001 are listed in Table 13. Notably, C-Reactive Protein (CRP) in pediatric patients with JIA with active polyarthritis was significantly lower than adult patients with RA.

Table 13. Comparison of Demographic and Baseline Characteristics in Study CNTO148JIA3003 and Study CNTO148ART3001

	CNTO148JIA3003				CNTO148ART3001
	2 to <6 yrs (n=9)	6 to <12 yrs (n=41)	12 to <18 yrs (n=77)	Combined (n=127)	(n=463)
Age (years)					
Median	5.00	8.00	14.0	13.0	52.0
Mean (SD)	4.11 (1.17)	8.17 (1.75)	14.3 (1.65)	11.6 (3.85)	51.6 (12.3)
IQ	3.00 - 5.00	7.00 - 10.0	13.0 - 16.0	8.00 - 15.0	45.0 - 60.0
Range	2.00 - 5.00	6.00 - 11.0	12.0 - 17.0	2.00 - 17.0	18.0 - 83.0
Albumin (g/L)					
Median	4.50	4.40	4.30	4.30	3.70
Mean (SD)	4.34 (0.292)	4.38 (0.377)	4.31 (0.423)	4.33 (0.399)	3.70 (0.352)
IQ	4.30 - 4.50	4.20 - 4.60	4.10 - 4.60	4.10 - 4.60	3.50 - 3.90
Range	3.70 - 4.60	3.30 - 5.10	2.50 - 5.20	2.50 - 5.20	2.30 - 4.70
Baseline Body Weight (kg)					
Median	16.8	29.2	52.6	42.4	70.0
Mean (SD)	18.0 (3.90)	30.9 (10.5)	56.6 (18.7)	45.6 (21.1)	71.8 (16.6)
IQ	15.1 - 18.7	23.5 - 37.3	43.6 - 65.6	29.3 - 56.8	60.0 - 81.2
Range	15.1 - 25.8	18.1 - 66.4	24.3 - 143	15.1 – 143	39.0 – 125
Baseline C-reactive protein (mg/dL)					
Median	0.323	0.448	0.589	0.471	2.58
Mean (SD)	0.531 (0.605)	1.55 (3.45)	1.49 (3.12)	1.44 (3.12)	3.30 (2.47)
IQ	0.166 - 0.593	0.0790 - 1.34	0.0640 - 1.13	0.0750 - 1.13	1.70 - 3.99
Range	0.133 - 2.06	0.0100 - 18.7	0.0100 - 19.1	0.0100 - 19.1	1.00 - 16.4
Baseline Swollen Joints Counts					
Median	13.0	13.0	12.0	13.0	12.0
Mean (SD)	17.6 (12.9)	17.2 (12.4)	13.8 (8.09)	15.2 (10.1)	14.8 (8.05)
IQ	6.00 - 22.0	8.00 - 23.0	7.00 - 19.0	8.00 - 21.0	9.00 - 19.0
Range	6.00 - 46.0	4.00 - 58.0	0.00 - 37.0	0.00 - 58.0	4.00 - 56.0

	CNTO148JIA3003				CNTO148ART3001
	2 to <6 yrs (n=9)	6 to <12 yrs (n=41)	12 to <18 yrs (n=77)	Combined (n=127)	(n=463)
White Blood Cell Count (x10^9/L)					
Median	8.57	7.63	7.28	7.42	8.47
Mean (SD)	8.91 (1.73)	8.06 (4.52)	7.77 (3.00)	7.95 (3.49)	8.79 (2.63)
IQ	8.00 - 9.98	5.35 - 9.09	5.75 - 8.79	5.73 - 9.24	6.94 - 10.3
Range	6.57 - 12.2	3.51 - 32.3	3.83 - 20.9	3.51 - 32.3	3.48 - 22.5
Diabetes					
No	9 (100.0%)	41 (100.0%)	77 (100.0%)	127 (100.0%)	439 (94.8%)
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	23 (5.0%)
Immunogenicity					
Positive	3 (33.3%)	12 (29.3%)	24 (31.2%)	39 (30.7%)	83 (17.9%)
Negative	6 (66.7%)	28 (68.3%)	53 (68.8%)	87 (68.5%)	365 (78.8%)
Unavailable/Missing	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.8%)	15 (3.2%)
Sex					
Male	3 (33.3%)	11 (26.8%)	20 (26.0%)	34 (26.8%)	80 (17.3%)
Female	6 (66.7%)	30 (73.2%)	57 (74.0%)	93 (73.2%)	383 (82.7%)
Race					
White	3 (33.3%)	30 (73.2%)	52 (67.5%)	85 (66.9%)	380 (82.1%)
Black	0 (0.0%)	0 (0.0%)	5 (6.5%)	5 (3.9%)	1 (0.2%)
Asian	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.8%)	32 (6.9%)
American Indian	1 (11.1%)	1 (2.4%)	2 (2.6%)	4 (3.1%)	50 (10.8%)
Multiple	1 (11.1%)	3 (7.3%)	0 (0.0%)	4 (3.1%)	0 (0.0%)
Other	4 (44.4%)	7 (17.1%)	17 (22.1%)	28 (22.0%)	0 (0.0%)
Smoking					
No	9 (100.0%)	41 (100.0%)	77 (100.0%)	127 (100.0%)	347 (74.9%)
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	115 (24.8%)

Source: Table 3 in the Applicant's PopPK Report

Based on previous modeling of PK in adult RA subjects, a two-compartment linear PK model with first-order elimination and intravenous administration was used to describe the observed concentration profiles in CNTO148JIA3003. The final parameter estimates and the covariate model are given in Table 14, and the covariate effect is also depicted in Figure 7.

Table 14. Parameter Estimates of Final Population Pharmacokinetic Model of Study CNTO148JIA3003 with Data through Week 52

Parameter	Estimate (%RSE)	95% Conf. Int	Magnitude of Change [a]
TVV1 (L)	2.64 (2.43)	(2.51, 2.77)	--
θ_5: Body Weight /70 (kg)	0.760 (4.25)	(0.696, 0.823)	--
TVCL (L/day)	0.390 (5.54)	(0.347, 0.432)	--
θ_6: Body Weight /70 (kg)	0.709 (6.18)	(0.623, 0.795)	--
θ_{11}: White	-0.122 (29.8)	(-0.193, -0.0508)	(0.82, 0.94)
θ_{13}: C-Reactive Protein/0.471 (mg/dL)	0.0527 (17.7)	(0.0344, 0.0709)	(1.11, 1.20)
θ_{14}: Positive Immune Response	0.229 (22.3)	(0.129, 0.329)	(1.14, 1.31)
θ_{15}: Albumin/4.3 (g/dL)	-1.18 (13.5)	(-1.49, -0.865)	(0.85, 0.90)
TVQ (L/day)	0.0764 (25.3)	(0.0386, 0.114)	--
TVV2 (L)	1.01 (14.6)	(0.721, 1.30)	--
θ_8: Body Weight/70 (kg)	0.519 (14.7)	(0.370, 0.668)	--
Ω: Inter-subject variability (%)			
V1	10.3 (21.7)		
Correlation (CL, V1)	62.2 (17.2)		
CL	21.3 (6.98)		
V2	27.3 (15.7)		
σ: intra-subject variability (%)	24.9 (6.24)		

$$V1\ (L) = TVV1 \times \left(\frac{BWT}{70}\right)^{\theta 5}$$

$$CL\ \left(\frac{L}{day}\right) = TVCL \times \left(\frac{BWT}{70}\right)^{\theta 6} \times (1 + \theta_{11}\ White) \times \left(\frac{CRP}{0..471}\right)^{\theta 13} \times (1 + \theta_{14}\ Immune) \times \left(\frac{ALB}{4.3}\right)^{\theta 15}$$

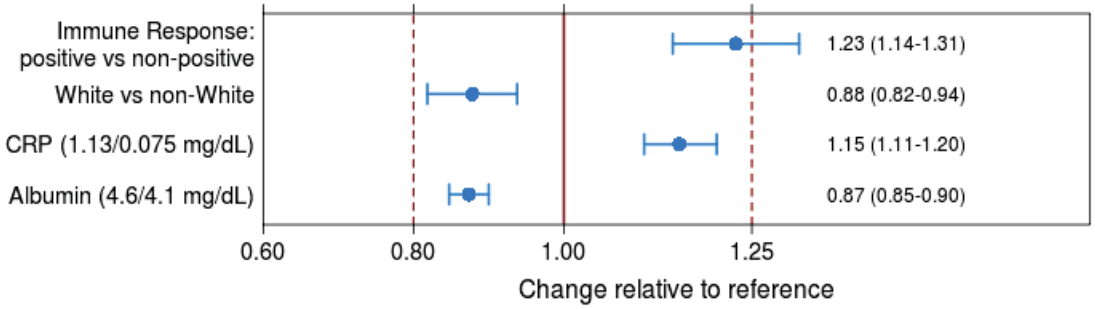
$$V2\ (L) = TVV2 \times \left(\frac{BWT}{70}\right)^{\theta 8}$$

[a] The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, ie, % change from the median value when the covariate factor varied from 25th percentile to 75th percentile of the population. For discrete covariates with two categories, changes were expressed as difference between categories.

Abbreviations: CL, clearance; TVQ, typical value of inter-compartmental clearance; TVCL, typical value of clearance; TVV1, typical value of central volume of distribution; TVV2, typical value of peripheral volume of distribution; V1, central volume of distribution; V2, peripheral volume of distribution.

Source: Table 8 in the Applicant's PopPK Report

Figure 7. Forest Plot for Covariate Effects on Clearance for Study CNTO148JIA3003 Through Week 52



90% Confidence Intervals for the Ratios of Clearance Between Subjects with the 75th and 25th Percentiles of the Continuous Covariate Values, or Between Subjects in Each Category for the Discrete Covariate for Study CNTO148JIA3003 using data up to Week 52
Source: Figure 3 in the Applicant's PopPK report

Similarly, the PK profile of golimumab in study CNTO148ART3001 was also characterized by a two-compartment linear PK model with first-order elimination and intravenous administration. The final parameter estimates and the covariate model are given in Table 15, and the covariate effects on clearance is depicted in Figure 8.

Table 15. Parameter Estimates of Final Population Pharmacokinetic Model of Study CNTO148ART3001

Parameter	Estimate (%RSE.)	95% Confidence Interval	Magnitude of Change [a]
TVV1 (L)	3.51 (0.880)	(3.45, 3.57)	--
θ_5: Body Weight/70 kg	0.557 (7.51)	(0.475, 0.640)	--
TVCL (L/day)	0.562 (2.58)	(0.533, 0.590)	--
θ_6: Body Weight (Kg) on CL	0.503 (11.3)	(0.391, 0.615)	--
θ_{10}: Male	0.135 (23.3)	(0.0735, 0.197)	(1.08, 1.19)
θ_{11}: White	-0.0924 (25.2)	(-0.138, -0.0468)	(0/87, 0.95)
θ_{14}: Positive Immune Response	0.195 (15.8)	(0.134, 0.256)	(1.14, 1.25)
θ_{15}: Albumin (g/dL)	-0.920 (11.5)	(-1.13, -0.712)	(0.89, 0.92)
θ_{18}: White Blood Cell Count(10^9/L)	0.110 (28.6)	(0.0485, 0.172)	(1.02, 1.07)
TVQ (L/day)	0.157 (4.02)	(0.144, 0.169)	--
TVV2 (L)	1.90 (2.59)	(1.81, 2.00)	--
Ω: Inter-subject variability (%)			
V1	12.8 (8.83)		
Correlation (CL, V1)	63.9 (8.79)		
CL	23.4 (4.41)		
V2	30.8 (5.74)		
σ: intra-subject variability (%)	27.2 (2.66)		

$$V1\ (L) = TVV1 \times \left(\frac{BWT}{70}\right)^{\theta 5}$$

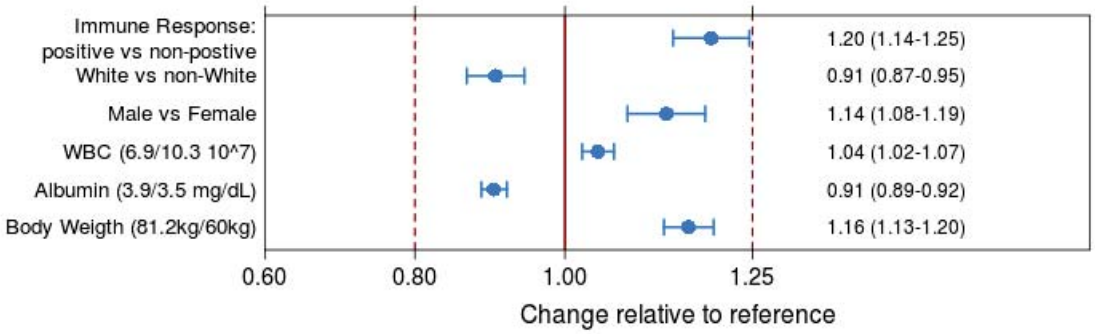
$$CL\ (L/day) = TVCL \times \left(\frac{BWT}{70}\right)^{\theta 6} \times (1 + \theta_{10}\ Male) \times (1 + \theta_{11}\ White) \times (1 + \theta_{14}\ Immune) \times \left(\frac{ALB}{3.8}\right)^{\theta 15} \times \left(\frac{WBC}{8.2}\right)^{\theta 18}$$

[a] The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, ie, % change from the median value when the covariate factor varied from 25th percentile to 75th percentile of the population. For discrete covariates with two categories, changes were expressed as difference between categories.

Abbreviations: CL, clearance; TVQ, typical value of inter-compartmental clearance; TVCL, typical value of clearance; TVV1, typical value of central volume of distribution; TVV2, typical value of peripheral volume of distribution; V1, central volume of distribution; V2, peripheral volume of distribution.

Source: Table 10 in the Applicant's PopPK Report

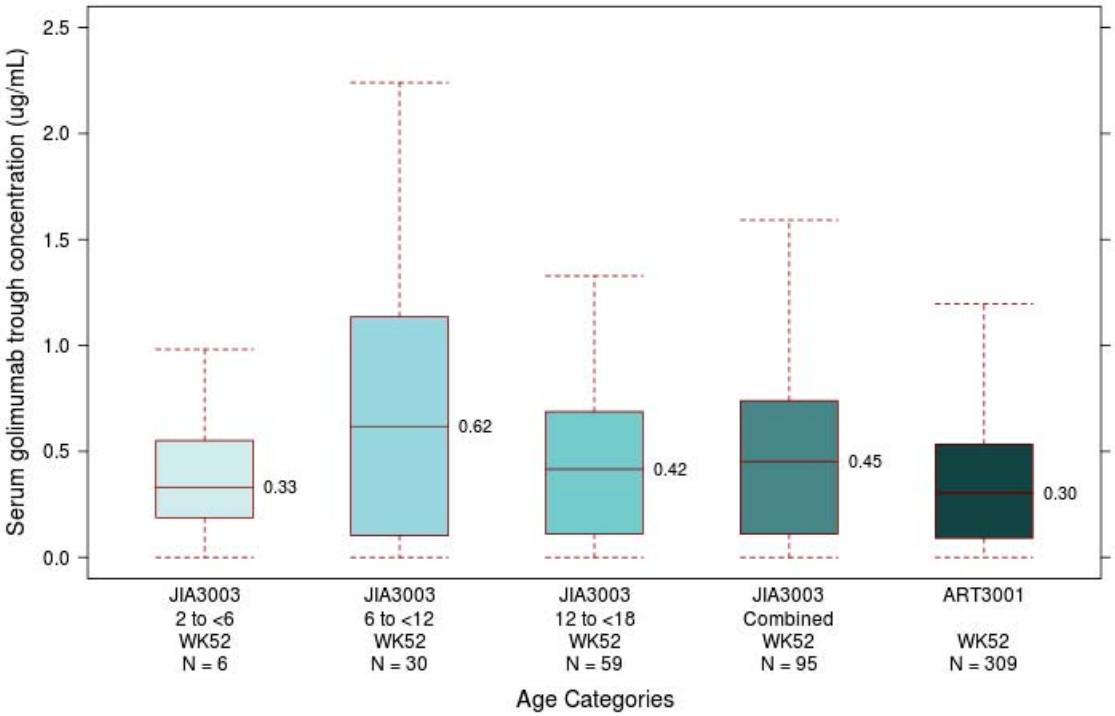
Figure 8. Forest Plot for Covariate Effects on Clearance for Study CNTO148ART3001 Through Week 52



90% Confidence Intervals for the Ratios of Clearance Between Subjects with the 75th and 25th Percentiles of the Continuous Covariate Values, or Between Subjects in Each Category for the Discrete Covariate for Study CNTO148ART3001
Source: Figure 4 in the Applicant's PopPK report

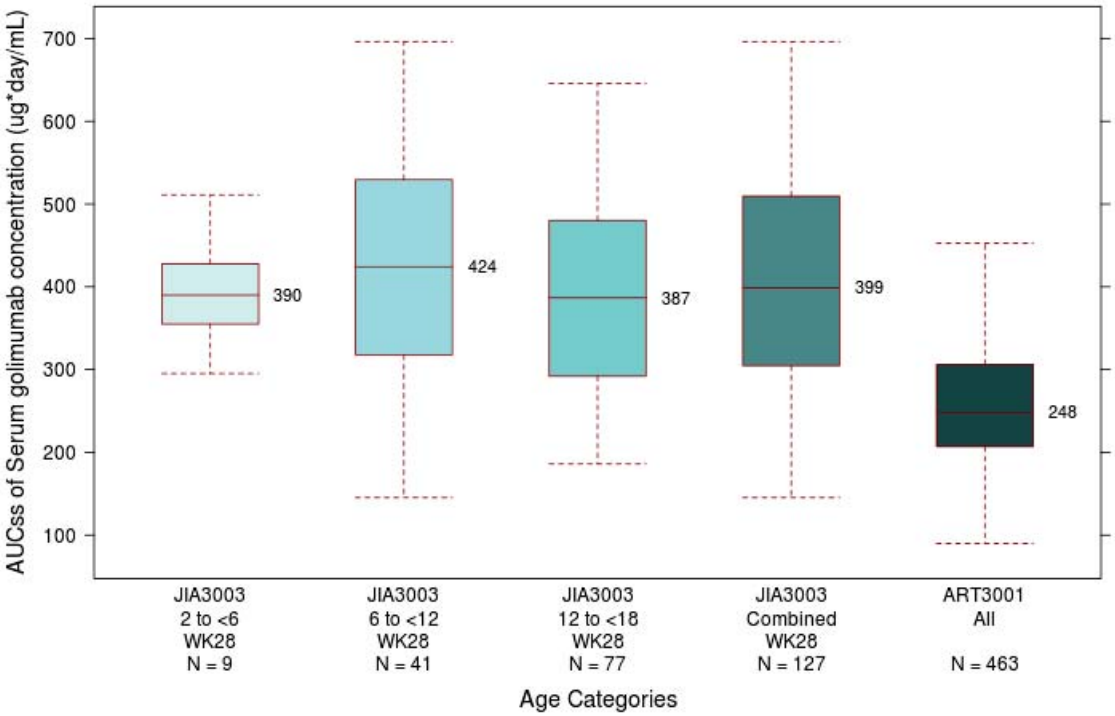
The estimated PK parameters and covariate effect were similar between JIA with active polyarthritis and RA. These results suggested similar pharmacokinetic characteristics between patients with JIA with active polyarthritis and RA. The steady state trough concentration and AUC were compared across different age groups in JIA with active polyarthritis with all the patients in RA. The comparisons are depicted in Figure 9 and Figure 10. Pediatric patients with JIA with active polyarthritis showed a similar trough concentration compared to adults with RA. However, the AUCss was about 60% higher in JIA with active polyarthritis compared to RA.

Figure 9. Serum Golimumab Trough Concentration at Week 52 by JIA with active polyarthritis Age Groups (CNTO148JIA3003) and at Week 52 for Adult RA (CNTO148ART3001)



Source: Figure 11 in the Applicant's PopPK report

Figure 10. Steady-state AUC Over an 8-hour Dosing Interval at Week 28 by JIA with active polyarthritis Age Groups (CNTO148JIA3003) and Adult RA (CNTO148ART3001)



Source: Figure 9 in the Applicant's PopPK report

Reviewer's Comments:
The two PopPK models in JIA with active polyarthritis and RA were reproducible and reasonable.
The similar covariate effects and PK parameters estimates demonstrated similar PK characteristics in JIA with active polyarthritis and RA. At the proposed dosing regimen of 80 mg/m^2, C_{trough} was similar between pJIA and RA while AUC/$C_{average}$ was higher in JIA with active polyarthritis.

15.3.2. Exposure Response Relationship of Golimumab in JIA with active polyarthritis

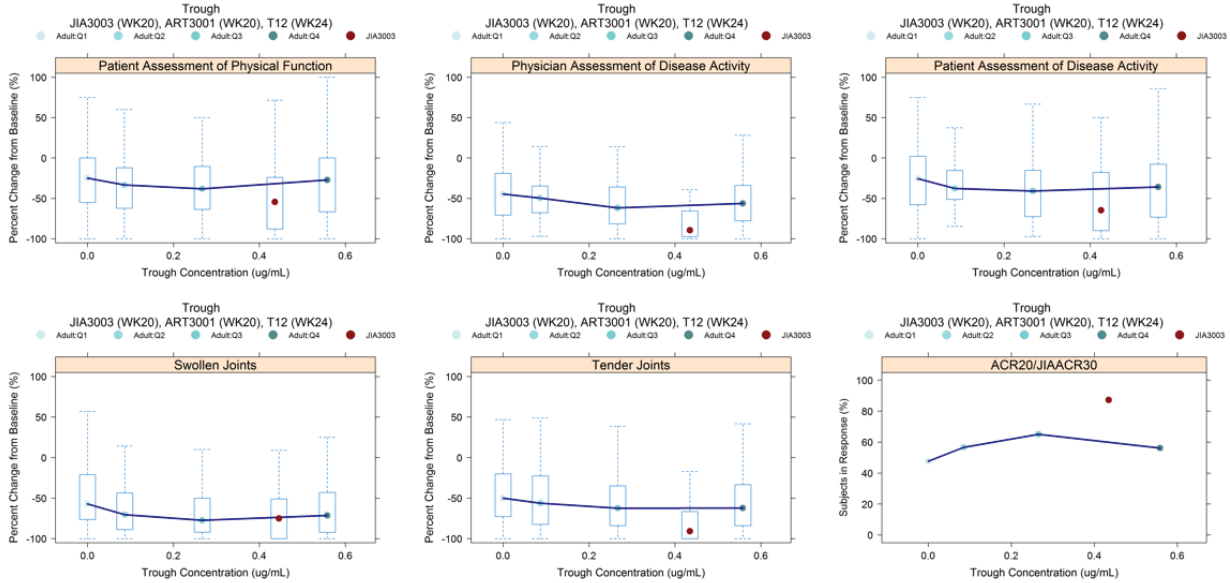
In response to the Agency's information request dated on 11/8/2019 and 12/23/2019, the Applicant submitted additional analysis on March 30th, 2020 titled "FDA request for clinical pharmacology information to support a pJIA indication for Simponi Aria (golimumab) - BLA 125433/S-030", hereafter referred to as the Applicant's ER analysis.

Based on the PopPK model, the Applicant conducted an ER analysis for each subcomponent in ACR Response Criteria for RA and ACR Pediatric Response Criteria as well as the overall response rate of ACR20 and JIA ACR30 (Figure 11 and Figure 12).

In addition to CNTO148ART3001, Study C0524T12 was also included in the ER analysis. Study C0524T12 was a safety and efficacy study testing 4 different dosing regimens (i.e., 2 mg/kg and 4 mg/kg golimumab dosed every 12 weeks with and without MTX) in RA subjects with an inadequate response to MTX, corticosteroids, NSAIDs, and/or anti-TNFα agents.

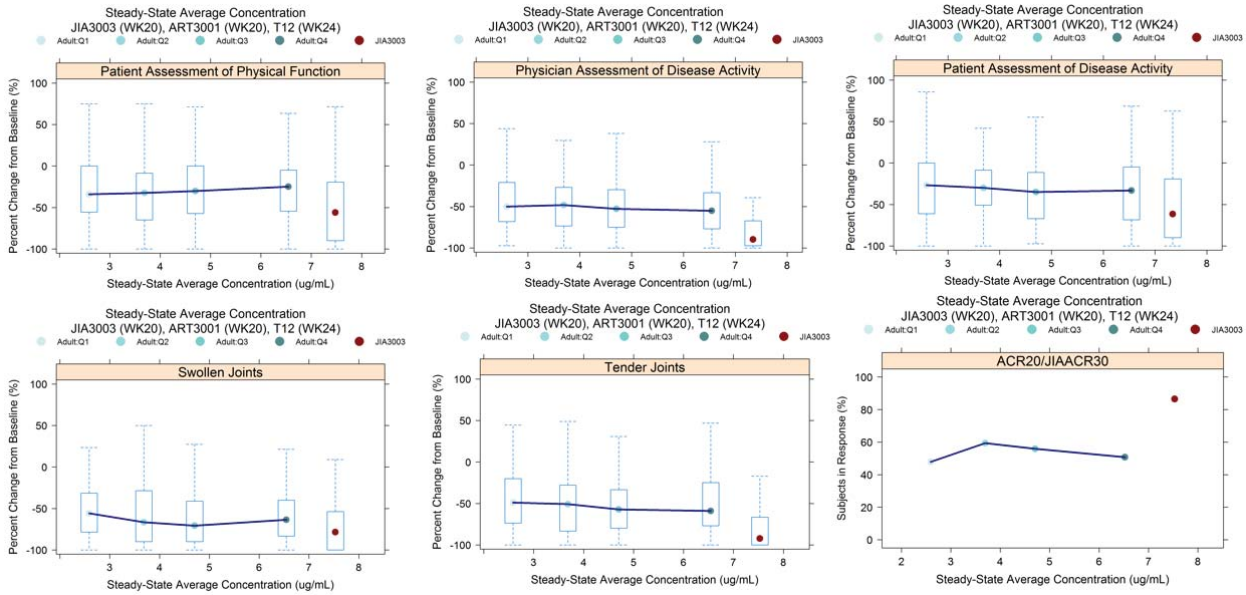
The ER analysis for each subcomponent in ACR Response Criteria / ACR Pediatric Response Criteria are depicted in Figure 11 and Figure 12 below.

Figure 11. Percent change from baseline in each subcomponent in ACR Response Criteria and subjects achieving ACR20 or JIA ACR30 response versus C_{trough} (medians) from CNTO148JIA3003 (Week 20), CNTO148ART3001 (Week 20) and C0524T12 (Week 24)



Source: The Applicant's ER analysis

Figure 12. Percent change from baseline in each subcomponent in ACR and subjects achieving ACR20 or JIA ACR30 response versus $C_{average}$ (medians) from CNTO148JIA3003 (Week 20), CNTO148ART3001 (Week 20) and C0524T12 (Week 24)



Source: The Applicant's ER analysis

Reviewer's Comments:

To be noted, Study CNTO148ART3001 was a double blinded, placebo-controlled study, and Study CNTO148JIA3003 was an open label study without placebo control. The comparison between the RA and JIA with active polyarthritis for the magnitude of efficacy is not feasible.

In the Applicant's ER analysis, the placebo arm in Study CNTO148ART3001 and C0524T12 were not included in this ER analysis. For trough concentration below the lower limit of quantification (LLOQ), 0 ug/mL was imputed by the Applicant. Therefore, the trough concentration at 0 ug/mL in Figure 11 did not represent placebo response but patients on active treatment (golimumab) with a trough concentration below LLOQ.

The dosing frequency in Study C0524T12 (q12w) were different from Study CNTO148ART3001 (q8w). Therefore, the comparison of efficacy across different exposure levels tends to be confounded by different dosing regimens.

Reviewer's Analysis:

The definition of ACR20 for RA and JIA ACR30 for JIA with active polyarthritis are described below:

ACR Response Criteria: the definition of ACR20

The ACR Response Criteria measures improvement in tender or swollen joint counts in improvement in at least three of the following parameters:

1) patient assessment
2) physician assessment
3) pain scale
4) disability/functional questionnaire
5) acute phase reactant (ESR or CRP)

ACR20 has a positive outcome if 20% improvement in tender or swollen joint counts were achieved as well as a 20% improvement in at least three of the other five criteria.

ACR Pediatric Response Criteria: the definition of JIA ACR30
JIA ACR30 is defined as an improvement of 30% or more in at least three of the six core criteria and a worsening of 30% or more in no more than one of the criteria.

1) the number of joints with active arthritis
2) the number of joints with limitation of passive motion
3) physician's global assessment of disease activity
4) patient's or the parent's global assessment of overall well-being
5) physical function (measured by the Disability Index of the Childhood Health Assessment Questionnaire), and
6) a laboratory assessment of inflammation (C-reactive protein concentrations were used in this study)

To be noted, pain scale was not included in the ACR Pediatric Response Criteria. However, as part of the assessment in pJIA, pain scale was also reported as a VAS score separately.

A head-to-head comparison between the baseline characteristics in each subcomponent in ACR Response Criteria/ACR Pediatric Response Criteria is given in Table 16. Notably the pediatric patients had fewer tender joints/joints with active arthritis and lower CRP levels at baseline as compared to adult RA patients.

Table 16. Comparison of ACR Response Criteria subcomponents between JIA with active polyarthritis and RA at baseline

	CNTO148JIA3003 (N = 127)	**CNTO148ART3001** (N = 592)
Tender Joints/Joint with active arthritis	**14.0 (9.0; 22.0)**	**23.0 (15.0, 35.0)**

Swollen Joints/Joints with limited range of motion	10.0 (4.0; 18.0)	12.0 (9.0, 19.0)
Patient Assessment of Disease Activity Parent/subject assessment of overall well-being	5.40 (3.30; 6.90)	6.70 (5.10, 7.90)
Physician Assessment of Disease Activity	5.50 (4.50; 6.80)	6.30 (5.20, 7.40)
HAQ CHAQ	1.250 (0.750; 1.875)	1.625 (1.125, 2.000)
CRP (mg/dL)	**0.471 (0.072; 1.130)**	**1.935 (0.943, 3.285)**

[#]Median (interquartile range)
Source: Table 5 in Clinical Study Report CNTO148JIA3003

In comparison to the Applicant's ER analysis, the following modifications were made in the reviewer's ER analysis:

1) Study C0524T12 was removed from the ER analysis due to the differences in dosing interval and study length
2) The placebo arm in Study CNTO148ART3001 was included in the ER analysis to provide a clear ER relationship
3) BLQ C_{trough} samples were imputed with LLOQ/2 instead of zero
4) Pain score was included in the ER analysis

The modified ER analysis are depicted in Figure 13 to Figure 16 below. The efficacy responses including each subcomponent in ACR Response and the overall responder rate had a stronger correlation with trough concentration in comparison to average concentration or AUC. In patients with RA, IV golimumab tended to reach its maximum effect on efficacy when trough concentration was above 0.14 ug/mL. In pediatric patients with JIA with active polyarthritis, 80 mg/m^2 resulted in a 4-fold higher trough concentration of 0.54 ug/mL, suggesting the proposed dosing regimen in pJIA provides a sufficient systemic exposure.

Figure 13. Exposure (C_{trough}) Response (ACR Subcomponent) Comparison in JIA with active polyarthritis and RA

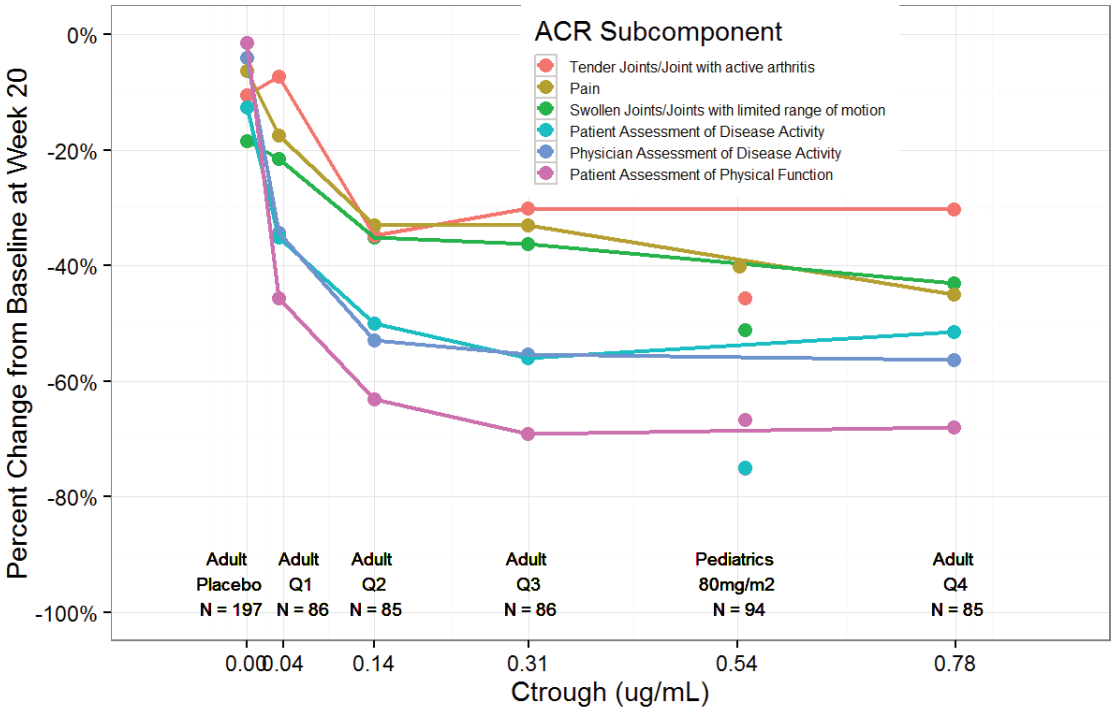


Figure 14. Exposure (C_{trough}) Response (JIA ACR30/ACR20) Comparison in JIA with active polyarthritis and RA

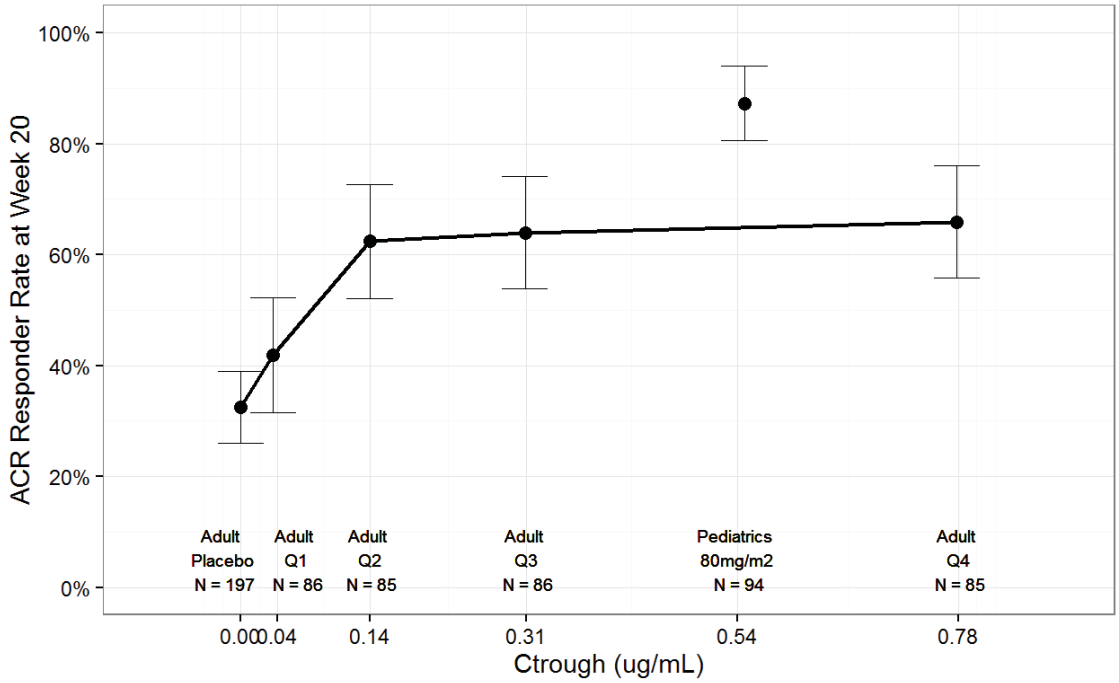


Figure 15. Exposure ($C_{average}$) Response (ACR Subcomponent) Comparison in JIA with active polyarthritis and RA

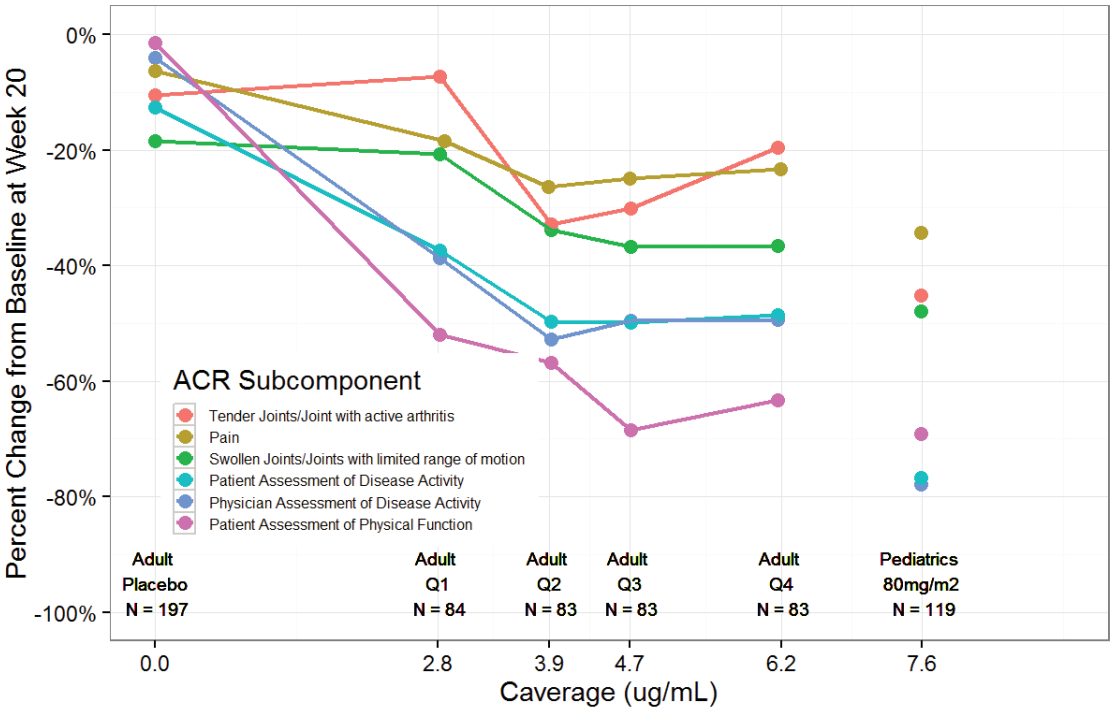
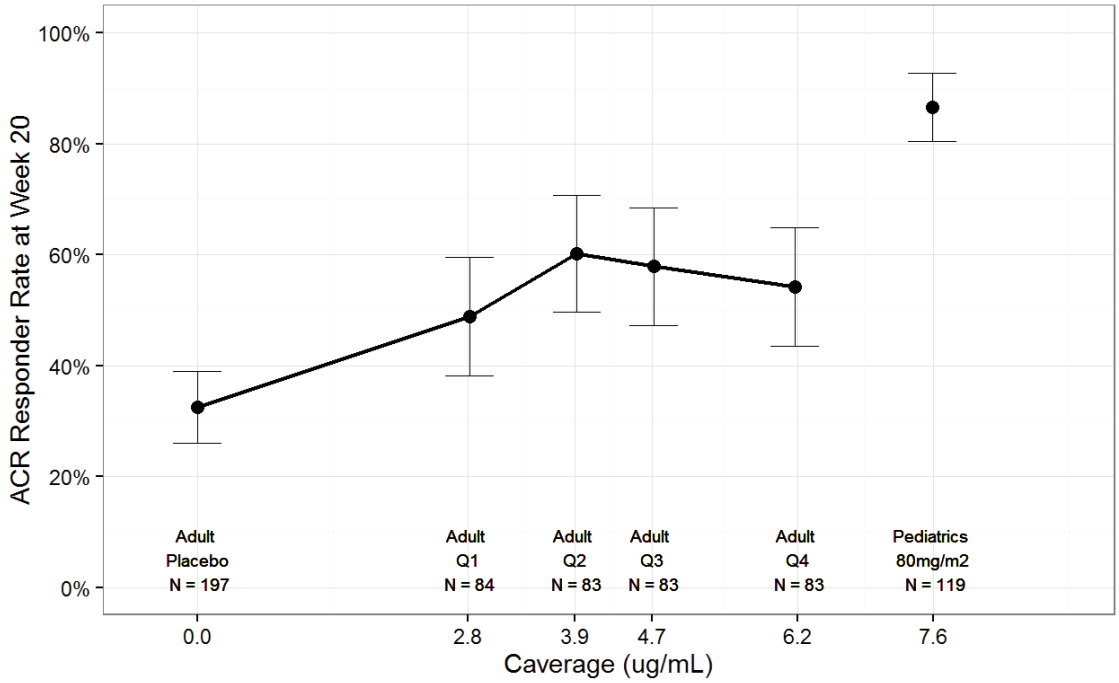


Figure 16. Exposure ($C_{average}$) Response (JIA ACR30/ACR20) Comparison in JIA with active polyarthritis and RA



In addition to the exposure response comparison in each subcomponent of ACR response criteria between JIA with active polyarthritis and RA, the response to IV golimumab in CRP were also compared (see Figure 17 and Figure 18 below). Although the absolute decreases in CRP were different between JIA with active polyarthritis and RA, the percent change from baseline (%CFB) in CRP were similar. This is expected because of the significant lower CRP at baseline in JIA with active polyarthritis (see Table 13). Therefore, the responses in CRP to IV golimumab were considered similar between JIA with active polyarthritis and RA.

Figure 17. Change from Baseline in C-Reactive Protein by Age and Treatment Group

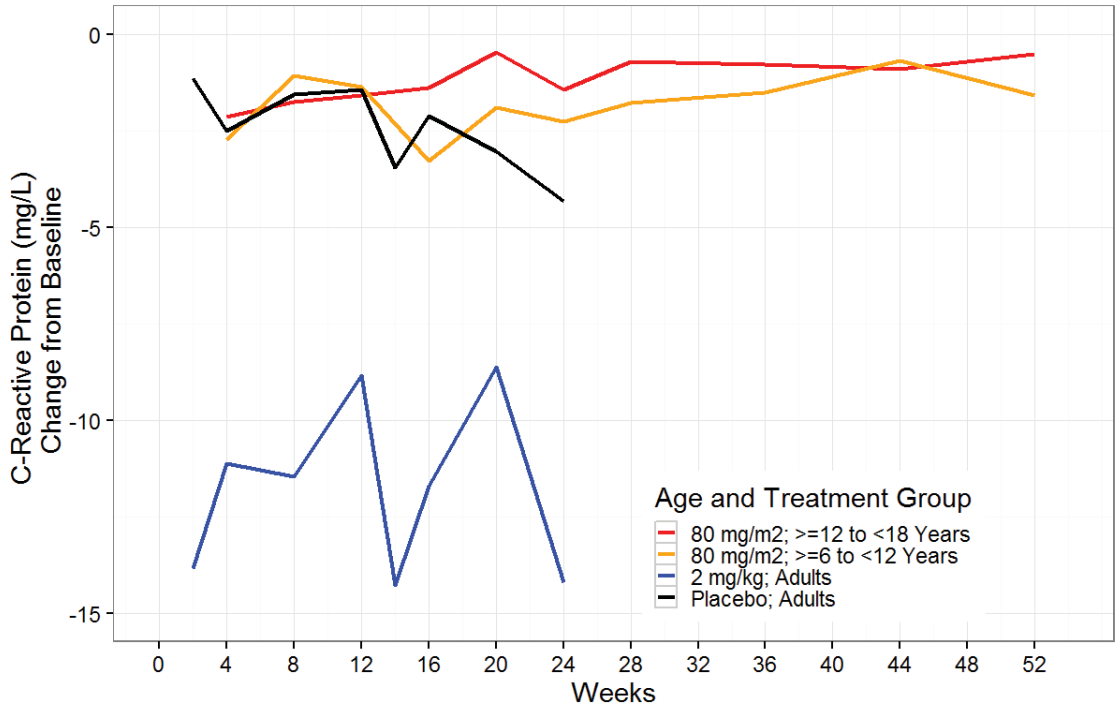
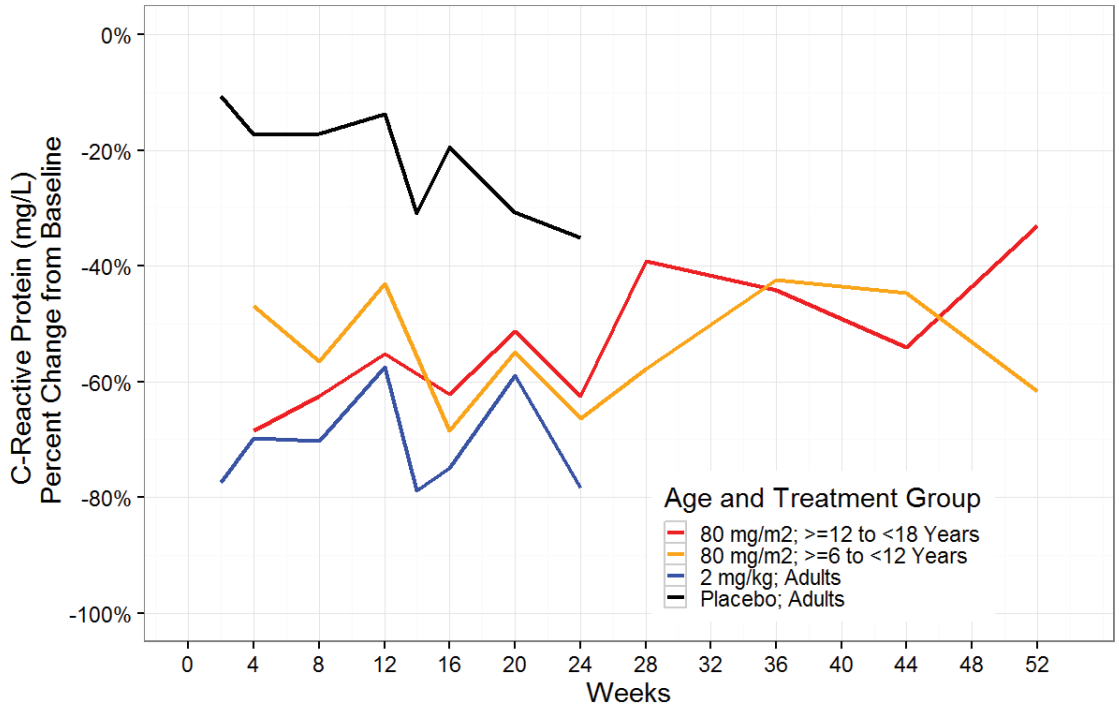


Figure 18. Percent Change from Baseline in C-Reactive Protein by Age and Treatment Group



15.4. Clinical Appendices

15.4.1. Schedule of Assessments - Screening Through W52

Table 1: Screening Through Week 52

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

Table 1: Screening Through Week 52

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

Table 1: Screening Through Week 52

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 1: Screening Through Week 52

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

n. The same serum samples may be used for the measurement of golimumab concentration and detection of antibodies to golimumab. For visits with study agent administration, all blood samples for assessing golimumab concentration and antibodies to golimumab MUST be collected BEFORE the administration of the study agent.

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

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

Source: Excerpted from Clinical Protocol CNTO148JIA3003, April 5 2017, p. 63-66

15.4.2. Schedule of Assessments – W60 Through W156 (Long-Term Extension)

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

	Week 60[a]	Week 68[a]	Week 76[a]	Week 84[a]	Week 92[a]	Week 100[a]	Week 108[a]	Week 116[a]	Week 124[a]	Week 132[a]	Week 140[a]	Week 148[a]	Week 156[a]	Final Safety Follow-up Visit[b]
Procedures and Evaluations														
Administrative														
Concomitant medications collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Agent														
IV administration of study agent	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety														
Review of systems	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[c]	X			X			X			X			X	
Body weight measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X
Routine laboratory analyses			X			X			X			X		X
ANA/Anti-dsDNA antibodies			X			X			X			X		X
QuantiFERON®-TB Gold test[e]						X[f]						X[f]		
TB evaluation (questionnaire)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray[g]	X													
Uveitis evaluations[h]		X			X			X			X			X
Pregnancy test (urine)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Infusion reaction evaluation[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy														
Joint assessments		X		X		X		X		X		X		X
JIA assessments[k,l]		X		X		X		X		X		X		X
CRP		X		X		X		X		X		X		X

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

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

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

b. All subjects who discontinue study agent administration before Week 156 but do not withdraw consent must return to the study site for a final safety visit approximately 8 weeks after the last infusion (Section 10.2).

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

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

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

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

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

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

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

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

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

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

m. The same serum samples may be used for the measurement of golimumab concentration and detection of antibodies to golimumab. For visits with study agent administration, all blood samples for assessing golimumab concentration and antibodies to golimumab **MUST** be collected **BEFORE** the administration of the study agent.

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

Source: Excerpted from Clinical Protocol CNTO148JIA3003, April 5 2017, p. 67-68

15.4.3. Schedule of Assessments– W164 Through W252 (Cont. of LT Extension)

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

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

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

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

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

b. All subjects who discontinue study agent administration before Week 244 but do not withdraw consent must return to the study site for a final safety visit approximately 8 weeks after the last infusion (Section 10.2).

c. Includes skin exam and Tanner staging.

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

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

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

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

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

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

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

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

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

m. The same serum samples may be used for the measurement of golimumab concentration and detection of antibodies to golimumab. For visits with study agent administration, all blood samples for assessing golimumab concentration and antibodies to golimumab **MUST** be collected **BEFORE** the administration of the study agent.

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

Source: Excerpted from Clinical Protocol CNTO148JIA3003, April 5 2017, p. 69-70

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RACHEL GLASER
09/29/2020 02:31:54 PM

NIKOLAY P NIKOLOV
09/29/2020 02:37:16 PM