NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental BLA
Application Number(s)	761037 S-015 (pre-filled syringe) b) (4)
Priority or Standard	Standard
Submit Date(s)	August 10, 2023
Received Date(s)	August 10, 2023
PDUFA Goal Date	June 10, 2024
Division/Office	DRTM
Review Completion Date	See electronic stamp date
Established/Proper Name	Sarulimab
(Proposed) Trade Name	Kevzara
Pharmacologic Class	IL—6 receptor inhibitor
Applicant	Sanofi
Dosage form	Subcutaneous injection
Applicant proposed Dosing Regimen	S-015: Pre-filled syringe • 200 mg given subcutaneously once every 2 weeks for pJIA patients who weigh 63 kg or greater using the 200 mg/1.14 mL pre-filled syringe b) (4)
Applicant Proposed Indication(s)/Population(s)	S-015: Patients who weigh 63 kg or greater with active polyarticular juvenile idiopathic arthritis (pJIA) b) (4)
Recommendation on Regulatory Action	Approval S-015 b) (4)
Recommended Indication(s)/Population(s)	S-015: Pre-filled syringe • Pediatric patients who weigh 63 kg or greater with active polyarticular juvenile idiopathic arthritis (pJIA)
Recommended Dosing Regimen	S-015: Pre-filled syringe • 200 mg given subcutaneously once every 2 weeks for pJIA patients who weigh 63 kg or greater using the 200 mg/1.14 mL pre-filled syringe

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Javonna Stevens, PharmD, BCPS
Nonclinical Reviewer	Eleni Salicru
Nonclinical Team Leader	Tim Robison, PhD
Office of Clinical Pharmacology Reviewer(s)	Selim Fakhruddin, PhD
Office of Clinical Pharmacology Team Leader(s)	Jianmeng Chen, MD, PhD
Clinical Reviewer	Keith M Hull MD, PhD
Clinical Team Leader	Nadia Habal, MD
Statistical Reviewer	Hongling Zhou, PhD
Statistical Team Leader	Karen Higgins, ScD
Cross-Disciplinary Team Leader	Nadia Habal, MD
Signatory	Ozlem Belen, MD, MPH

Additional Reviewers of Application

OPQ Product quality Team Leader/Application team lead	Chana Fuchs, PhD
OPQ Product quality reviewer	Zachary Kraus, PhD
OPQ Microbiology and Facilities reviewer	Liqun Zhao
OPQ Microbiology Team Leader	Maxwell Van Tassell, PhD
OPQ Facilities Team Leader	Zhong Li, PhD
OSE/DMEPA	Sarah Vee/Idalia Rychlik

OPQ=Office of Pharmaceutical Quality
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Selim Fakhruddin, PhD	DIIP/OCP/OTS/CDER	Section: 5, 14.3	**Select one:** _X__ Authored ___ Approved
	Signature: Selim Fakhruddin -S Digitally signed by Selim Fakhruddin -S Date: 2024.06.07 15:25:19 -04'00'			
Clinical Pharmacology Team Leader	Jianmeng Chen, MD, PhD	DIIP/OCP/OTS/CDER	Section: 5, 14.3.1	**Select one:** ___ Authored _X__ Approved
	Signature: Jianmeng Chen -S Digitally signed by Jianmeng Chen -S Date: 2024.06.07 15:33:55 -04'00'			
Pharmacometrics Reviewer	Selim Fakhruddin, PhD	DIIP/OCP/OTS/CDER	Section: 14.3.2	**Select one:** _X__ Authored ___ Approved
	Signature: Selim Fakhruddin -S Digitally signed by Selim Fakhruddin -S Date: 2024.06.07 15:26:28 -04'00'			
Pharmacometrics Team Leader	Youwei Bi, PhD	DPM/OCP/OTS/CDER	Section: 14.3.2	**Select one:** ___ Authored _X__ Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2024.06.07 15:37:45 -04'00'			
Clinical Reviewer	Keith Hull, MD, PhD	OND/OII/DRTM	Sections: 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 14	**Select one:** _X_ Authored ___ Approved
	Signature: Keith M. Hull -S Digitally signed by Keith M. Hull -S Date: 2024.06.10 10:26:02 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Nadia Habal, MD	OND/OII/DTM	Sections: 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 14	**Select one:** ___ Authored _X__ Approved
	Signature: Nadia Habal -S Digitally signed by Nadia Habal -S Date: 2024.06.10 10:47:11 -04'00'			
Deputy Division Director (Clinical)	Ozlem Belen, MD, MPH	OND/OII/DRTM	Sections: All	**Select one:** ___ Authored _X_ Approved
	Signature: Ozlem A. Belen -S Digitally signed by Ozlem A. Belen -S Date: 2024.06.10 10:51:50 -04'00'			

1 Executive Summary

1.1. Product Introduction

Sarilumab (KEVZARA) is a recombinant human IgG1 monoclonal antibody (mAb) targeting the interleukin-6 receptor (IL-6R) alpha subunit that binds specifically to both soluble and membrane-bound IL-6R (sIL-6Rα and mIL-6Rα) and inhibits IL-6-mediated signaling.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Clinical Pharmacology review team has determined that the proposed weight-based dosing strategy provides comparable sarilumab exposure in pediatric patients 2 to less than 18 years of age with active pJIA as 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 descriptive efficacy endpoints in Study DRI13925.

(b) (4)

The current studies demonstrated that children weighing ≥63 kg are to be treated using the adult dose of 200 mg, which is currently available in two formulations, prefilled syringe (PFS) and prefilled pen. Sarilumab solutions in the marketed PFS and in the vial have the same composition. Therefore, the PFS containing 200 mg/1.14 mL solution could be approved for pediatric patients who weigh 63 kg or greater with active pJIA based on data from the pediatric study (DRI13925) conducted with the vial. The ability of pediatric patients to self-inject with the pre-filled pen has not been tested.

In summary, the KEVZARA prefilled syringe for the use in patients with pJIA weighing ≥63 kg will be approved (S-015) (b) (4) the required PREA PMR 3218-3 will be not be considered fulfilled since no formulation of KEVAZARA will be available for children 2 years of age and older who weigh less than 63 kg.

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 and encompasses the RF+ polyarthritis and RF- polyarthritis subtypes of the International League of Associations for Rheumatology (ILAR) classification for Juvenile Idiopathic Arthritis (JIA). Polyarticular JIA is the form of JIA most similar to adult RA, with articular manifestations being predominant. Without appropriate treatment, pJIA can lead to significant life-long disability that starts in childhood. Although there are 7 recently FDA-approved therapies for pJIA and polyarticular-course JIA (pcJIA or JIA with active polyarthritis) in the United States (abatacept, adalimumab, etanercept, golimumab, tocilizumab, tofacitinib, and upadacitinib), there still remains an unmet need for additional therapeutic options in this population since not all patients respond to the approved treatments.

The clinical development program for sarilumab in children 2 to 17 years of age with pJIA consisted of a single study (Study DRI13925) that assessed the PK, PD, efficacy, and safety of sarilumab. The study was designed to determine the appropriate dose regimen while avoiding a placebo arm considering that the disease course and the treatment response are sufficiently similar to the adult RA patients thereby permitting an extrapolation of efficacy from adults to children. Given that the underlying pathogenesis of the clinical course of pJIA is similar to that of adult RA, the pediatric dose regimens assessed in Study DRI13925 were selected via PK modeling and simulation to be equivalent to the adult RA approved dose regimens evaluated in clinical studies, which were shown to have a favorable risk benefit for adult RA. Given the overall design and analysis of study DRI13925, the data used to determine approval for this submission is solely based on the extrapolation of PK data, while the clinical safety and efficacy provide supportive data for the use of sarilumab for the treatment of children with pJIA.

The review of the safety data base did not identify any new safety concerns and demonstrated an acceptable safety profile in patients with pJIA. The current risk profile of sarilumab did not change based review on the pJIA safety data and in comparison to the safety data in adults with RA.

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 form of JIA, is a	• PJIA is a serious, disabling form of juvenile inflammatory arthritis with significant impact on quality of life for patients and families.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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. • The prevalence of JIA in developed countries has been reported to be between 16 and 150/100,000 children, and pJIA accounts for approximately 13-35% children with JIA. • PJIA is the form of JIA most similar to adult rheumatoid arthritis (RA) in clinical manifestations as well as response to therapy.	
Current Treatment Options	• Recommendations for treatment are based on Expert Consensus Treatment Guidelines, and treatment is determined based on active disease manifestations. • Approved treatments include some NSAIDs, corticosteroids (oral, parenteral, and intra-articular), conventional DMARDs such as sulfasalazine and methotrexate, tofacitinib, and biologic DMARDs such as tumor necrosis factor (TNF) inhibitors, tocilizumab, upadacitinib, and abatacept.	• There are several approved therapies for pJIA. However, there remains a population of patients with uncontrolled disease despite currently available treatments.
Benefit	• The approval of sarilumab for the treatment of children with pJIA is based on the PK comparability data between children with pJIA and adults with RA. • The efficacy results reviewed for study DRI13925 serve as supportive data to the comparability PK data given that the study was conducted open-labeled, uncontrolled, and was not statistically rigorous.	• The efficacy of sarilumab in pediatric patients age 2 years and older with active pJIA is based on PK-exposure matching and extrapolation from the established efficacy of sarilumab in adults with RA in pivotal trials. This approach is justified based on similarities of disease manifestation and disease progression in adults with RA and pediatric patients with pJIA. The descriptive efficacy data of sarilumab administered subcutaneously every two weeks at the dose of 3 mg/kg and 4 mg/kg in patients weighing ≥30 kg and ≥10 kg to <30 kg,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		respectively, provides strong descriptive evidence to support the use of sarilumab in subjects with pJIA aged two years and older.
Risk and Risk Management	• No deaths were reported during Study DRI13925. • The review of the safety data base did not identify any new safety concerns and demonstrated an acceptable safety profile in patients with pJIA.	• The current risk profile of sarilumab did not change based review on the pJIA safety data and in comparison to the safety data in adults with RA.

1.4. Patient Experience Data

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

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	X	Clinical outcome assessment (COA) data, such as		Section 7
		X	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	
		☐	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

Juvenile idiopathic arthritis (JIA) as defined by the International League of Associations for Rheumatology (ILAR) classification is an arthritis of unknown etiology that begins prior to 16 years of age and persists for at least six weeks with other conditions excluded (1). Juvenile idiopathic arthritis affects primarily females (3:1 female/male ratio) (2, 3) and is the most common rheumatic disease of childhood with a global prevalence estimated to range from 4 to 400/100,000 persons with an incidence of 2 to 23/100,000 persons-year (2, 3, 4, 5). The disease consists of seven subtypes categorized by age of onset, range, and disease characteristics in the first six months after onset (5).

The following subtypes of JIA are collectively referred to as polyarticular-course JIA (pJIA) since they present with similar clinical features affecting five or more joints and potentially developing to permanent joint damage):

- Oligoarticular JIA (oJIA) subtype is the most common subtype of juvenile arthritis, representing approximately 50% of all patients with JIA in the US and Western Europe. It is defined as an aseptic inflammatory synovitis that affects generally up to four large joints and is not associated with constitutional findings such as fever, weight loss, fatigue, or systemic signs of inflammation. Disease onset ranges from one to five years of age and peaks at two to three years of age. Oligoarticular JIA carries a risk for developing chronic anterior uveitis, especially when patients have a positive antinuclear antibody (ANA) titer present.

- Polyarticular JIA (pJIA) is defined as an arthritis affecting five or more joints during the first six months of the disease. Both large and small joints can be involved, and often are found in a symmetric bilateral distribution. Low grade fever can accompany the arthritis. Presence of Rheumatoid Factor (RF) differentiates two forms of pJIA:

    - Rheumatoid Factor-positive (RF+) pJIA is diagnosed in only 3% to 5% of children and adolescents with JIA. Features of RF+ pJIA include a mean onset at 12 to 14 years-old and a marked female gender predominance (13:1 female/male ratio).

    - Rheumatoid Factor-negative (RF-) pJIA represents 11% to 28% of all children with JIA. It presents at a younger age, typically 6 to 12 years of age, in contrast to patients with RF-positive pJIA. Radiologic changes in RF-negative disease occur later than in RF-positive disease and may not be as destructive to the joints and less persistent.

In their submission, the Applicant chose to use the term polyarticular-course JIA (pcJIA), which describes any form of juvenile arthritis that affects five or more joints[1]. Traditionally, the Agency has used the term pJIA instead of pcJIA to describe any form of JIA that affects at least five or more joints except when referring to systemic JIA, which is its own unique disease entity. Similar to previous applications for the treatment of pJIA, the current study (DRI13925) specifically enrolled children with RF+, RF-, and extended oJIA who had five or more actively swollen/tender joints. In this context, pJIA and pcJIA refer to the same clinical entity and the term pJIA will be used in this review and the approved product labeling for reasons of consistency with other products currently marketed.

Analysis of Current Treatment Options

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Abatacept	pJIA	2005/2008	Children ≥ 2 years: IV formulation <75 kg 10 mg/kg at wks 0, 2, and 4, then q4w ≥75 kg 750 mg at wks 0, 2, and 4, then q 4w Children ≥2 years: SC formulation 10 kg to <25 kg: 50 mg qw 25 kg to <50 kg: 87.5 mg qw ≥50 kg: 125 mg qw	RW study with fewer flares (IV); OL PK-extrapolation (SC)	Similar to safety profile in adults
Adalimumab	pJIA	2002/2008	Children ≥2years: 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 vs PBO	Infections, hypersensitivity, and ↑CPK
Etanercept	pJIA	1998/1999	Children ≥2 years: <63 kg: 0.8 mg/kg SC qw ≥63 kg: 50 mg SC qw	RW study with fewer flares vs PBO	Similar to safety profile in adults
Golimumab	pJIA	2009/2020	Children ≥2 years: IV formulation 80mg/m^2 at wks 0, 2, and 4, then q8w	OL, single-arm PK, safety, and exploratory efficacy	Similar to safety profile in adults

[1] Jones NT, Keller CL, Abadie RB et al. Cureus. 2023;15(11)

				study; PK extrapolation	
Tocilizumab	pJIA	2010/2013	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	Similar to safety profile in adults
Tofacitinib	Polyarticular Course JIA*	2012/2020	Children ≥2 years: 10 to <20 kg: 3.2 mg (3.2 mL oral solution) BID; 20 to <40 kg: 4 mg (4 mL oral solution) BID ≥40 kg: 5 mg (one 5 mg tablet or 5 mL oral solution) BID	RW study with fewer flares vs PBO	Similar to safety profile in adults
Upadacitinib	pJIA	2019/2024	Children >2 years: 10 to <20 kg: 3 mg (3 mL oral solution) twice daily 20 to <30 kg: 4 mg (4 mL oral solution) twice daily ≥ 30 kg: 6 mg (6 mL oral solution) twice daily or 15 mg (one 15 mg tablet) once daily	OL, single-arm PK, safety, and exploratory efficacy study; PK extrapolation	Similar to safety profile in adults

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

In 2017, KEVZARA received initial approval to treat adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease modifying antirheumatic drugs (DMARDs) from Health Canada (February 9, 2017), FDA (May 22, 2017) and the European Commission (EC) (June 23, 2017).

On February 28, 2023, the FDA approved sarilumab for the treatment of adult patients with polymyalgia rheumatica (PMR) who have had an inadequate response to corticosteroid taper or who cannot tolerate corticosteroid taper.

3.2. Summary of Presubmission/Submission Regulatory Activity

The current submission is intended to support the extension of sarilumab for the treatment of pJIA in patients aged two years of age and older. The development program in pJIA initially included two separate dose-finding and efficacy/safety studies, which were streamlined into a single two-phase study designed to allow dose-selection, extrapolation of efficacy from the RA adult population to the pJIA pediatric population based on PK data, and evaluation of the safety and efficacy of the selected dose regimen of sarilumab in children with pJIA. The proposed approach is consistent with the FDA Draft Guidance on "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products" and the European updated guideline on "Clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis".

The study design was agreed upon with FDA and with European Medicines Agency (EMA, Pediatric Committee) in the context of the pediatric investigational plan (PIP).

The current BLA is also submitted to fulfill the requirement of pediatric assessment under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). With the original approval of this BLA on May 22, 2017, two post-marketing requirements (PMR; 3218-1 and 3218-2) were issued for the Applicant to conduct two pediatric studies in children ages ≥2 to 17 years with pJIA. On November 22, 2019, in response to the Applicant's request to modify the required pediatric studies, the Agency issued a single PMR (3218-3) to conduct a single pediatric study (DRI13925), the data and reports of which were submitted to support the current submission.

In addition, the Applicant conducted population pharmacokinetics (PopPK), dose/exposure-response and dose/exposure-safety analyses based on the data from study DRI13925 to support proposed dosing regimen.

The original supplement was later split into two efficacy supplements on May 31, 2024.

- Supplement 015: Patients who weigh 63 kg or greater with active polyarticular juvenile idiopathic arthritis (pJIA)
- b) (4)

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

4.1. Office of Scientific Investigations (OSI)

A biopharmaceutical inspection was requested for the bioanalytical site of Study DRI13925. However, the Office of Study Integrity and Surveillance (OSIS) remarked that an inspection for the above-mentioned bioanalytical site was not needed. The rationale for this decision is that OSIS conducted a Remote Regulatory Assessment (RRA) for the site in [redacted]. The RRA was conducted under BLA [redacted] OSIS concluded that data from the reviewed studies were reliable. Refer to the OSIS inspection report by Dr. Folaremi Adeyemo in the DARRTS dated [redacted]

4.2. Product Quality

For 761037 S-015 (pre-filled syringe), no product quality review is required as the pre-filled syringe is the currently marketed product.

[redacted]

4.3. Devices and Companion Diagnostic Issues

The current studies demonstrated that children weighing ≥63 kg are to be treated using the adult dose of 200 mg, which is currently available in two formulations, prefilled syringe and prefilled pen. However, only the prefilled syringe will be approved for use in pJIA patients ≥63 kg.

For full discussion, refer to DMEPA use-related risk analysis review. As per this review, the Applicant does not need to submit human factor (HF) validation study results for the PFS to support addition of the proposed pJIA indication for this supplement.

5 Clinical Pharmacology

5.1. Executive Summary

The Applicant (Sanofi US Services Inc.) submitted this BLA supplement (sBLA) seeking the approval of Kevzara (sarilumab) for the treatment patients aged 2 years and older with polyarticular juvenile idiopathic arthritis (pJIA). The proposed dosage regimen i [redacted] 200 mg for patient with BW ≥63 kg. Sarilumab can be used as monotherapy or in combination with conventional disease modifying anti-rheumatic drugs (DMARDs).

This sBLA is submitted to fulfill the requirement of pediatric assessment under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). With the original approval of this BLA on 5/22/2017, two post-marketing requirements (PMRs) such as 3218-1 and 3218-2 were issued for the Applicant to conduct two pediatric studies in children aged ≥2 to 17 years with polyarticular juvenile idiopathic arthritis. In response to the Applicant's request to modify the required pediatric studies, the Agency released initially issued 2 PMRs on 11/22/2019 and instead issued a single PMR (3218-3) to conduct a single pediatric study (DRI13925), the data and reports of which were submitted to support the current submission.

In addition, the Applicant conducted population pharmacokinetics (PopPK), dose/exposure-response and dose/exposure-safety analyses based on the data from study DRI13925 to support proposed dosing regimen.

[redacted] Sarilumab solutions in the marketed PFS and in the vial have the same composition. Therefore, the PFS containing 200 mg/1.14 mL solution could be approved for pediatric patients who weigh 63 kg or greater with active pJIA based on data from the pediatric study (DRI13925) conducted with the vial.

Key Clinical Pharmacology Findings for the Current Review:

- Body weight-based dosing regimens of 4 mg/kg SC Q2W and 3 mg/kg SC Q2W in pediatric patients weighing ≥10 kg to <30 kg and ≥30 kg (capped at 200 mg for ≥63 kg) with pJIA provided comparable steady state exposures as that of adult patients with RA at the approved dosage regimens (150 mg/200 mg SC Q2W). Though the exposures for [redacted] pediatric dose are 24 – 43% lower in patients with body weight ≥30 kg compared to that of adult receiving 200 mg Q2W, the sarimumab concentrations remain higher than that of 150 mg Q2W approved for adults with RA to manage certain laboratory abnormalities including neutropenia and thrombocytopenia.The comparable

exposure supports the efficacy extrapolation from adults with RA to pediatric subjects with pJIA.

- Sarilumab exhibits nonlinear PK with target-mediated drug disposition in patients aged 2 – 17 years with pJIA. In population PK analysis, body weight has been identified as a significant covariate on sarilumab clearance in pediatric patients, supporting the proposed weight-based dosing regimen of sarilumab in pediatric patients. Population PK analysis suggested that exposure parameters (e.g., AUCτ,ss, Ctrough,ss) were comparable across age/weight groups (≥2 years and ≥10 kg, **Figure 3**, **Figure 4**) [redacted] No dose adjustments are needed based on patient covariates other than body weight.

- Descriptive dose-response analysis for Juvenile Idiopathic Arthritis American College of Rheumatology 30/50/70 (JIA ACR 30/50/70) endpoints demonstrated a dose-dependent increase in ACR 50/70 and flat response for ACR 30 across all doses. While [redacted] (dose 2) has comparable exposure to that of adult with RA, the exposure (AUCτ,ss, Ctrough,ss) is slightly lower for pediatric patients with a body weight ≥30 kg. Nevertheless, dose 2 showed greater efficacy compared to dose 1, and a higher dose of dose 3 showed similar efficacy as dose 2 at Week 12 for the observed exposure ranges, hence this dose-response analysis for efficacy provided supportive evidence of efficacy for dose 2.

- Descriptive analysis of dose-safety for absolute neutrophil count (ANC) indicated dose-dependent decrease in ANC levels and increase the proportion of patients with ANC <1.0 Giga/L, with increasing Ctrough from dose 1 to dose 3 at Week 12 in pediatric. PK-PD model analysis also showed a trend toward greater percentage change of ANC from baseline with increasing Ctrough across doses 1, 2, and 3. For dose 2, PK-PD analysis suggested a steep decline in ANC levels at Ctrough up to 20 mg/L, beyond which E-R relationship was shallow in participants with pJIA. The E-R relationship for ANC levels is similar in pediatric participants with pJIA at Dose 2 and adult participants with RA.

- The treatment-emergent ADA incidence rate was 4.3% (3/70) based on pooled data from group A and B of the selected dose 2. The sarilumab concentrations in ADA-positive patients are generally within the exposure range observed in ADA-negative patients. Because of the low occurrence of ADA in participants with pJIA, the effect of these antibodies on the safety, and/or effectiveness of sarilumab is unknown.

- Solutions in the marketed PFS and in the vial have the same composition. Therefore, the PFS containing 200 mg/1.14 mL solution could be approved based on data from pediatric study conducted with the vial.

5.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the S15 b) (4) of BLA761037, and found b) (4) acceptable for approval from a clinical pharmacology standpoint.

5.2. Summary of Clinical Pharmacology Assessment

5.2.1. Pharmacology and Clinical Pharmacokinetics

Table 1: Summary of Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• Sarilumab exhibits nonlinear PK with target mediated drug disposition in pediatric patients with pJIA, which is consistent with that of adult patients with RA. • The observed mean (SD) Ctrough at steady state (Week 48) was 11.6 (10.4) mg/L and 14.2 (8.23) mg/L in group A (BW: ≥30 kg) and B (BW: ≥10 kg to <30 kg) for the selected dose of 3 and 4 mg/kg, respectively, in pJIA patients. In adults with RA, the mean (SD) Ctrough at steady state (Week 24) was 18.8 (16.3) mg/L and 7.63 (9.73) mg/L following 200 mg Q2W and 150 mg Q2W regimens, respectively, as observed in a study (EFC11072, part B). The data indicates high variability for Ctrough in both pJIA patients (%CV: 58-89%) and adults (88-128%) following SC administration of sarilumab at the above-mentioned dosing regimens. • Based on the PopPK analysis, the median time to steady state was 28 weeks and 12 weeks for dose 2 group A and group B, respectively, with an accumulation of approximately 2- to 4-fold based on for Ctrough, Cmax, and AUC0-τ. • At steady state, sarilumab exposure (Cmax, AUC0-14 days, and Ctrough was generally comparable in participants with pJIA at Dose 2 and in participants with RA at 150 mg/200 mg Q2W. Though group A (BW: ≥30 kg) of the selected dose 2 (3 mg/kg) had slightly lower concentration than that in group B (4 mg/kg), it is still higher than that resulting from 150 mg Q2W in adults.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Per PopPK analysis, only body weight is the most significant covariate. Hence, body weight-based dosing was selected for pediatric study (DRI13925) in patients with pJIA with a weight cutoff value of 30 kg. A dosing regimen of 3 mg/kg Q2W for ≥30 kg (capped at 200 mg Q2W if BW ≥63 kg) and a 4 mg/kg Q2W for ≥10 kg to <30 kg resulted in sarilumab exposures that match

	with those of approved adult dosing regimens of 200 mg/150 mg Q2W. • No other covariates were found to have significant effects on sarilumab PK therefore no dose adjustment is needed based on other covariates. For more information, refer to **pharmacometrics review in Appendix 14.3.2.**
Same formulation for PFS and vial	Solutions in the marketed PFS and in the vial have the same composition. No dedicated PK bridging study is needed between the PFS and vial presentation.

5.2.2. General Dosing and Therapeutic Individualization

General Dosing

Unlike in adults with RA, dose reduction of Kevzara has not been studied in the pJIA population. Instead of dose reduction in pJIA patients, it is recommended to discontinue Kevzara if ALT or AST >5 ULN, platelet count ≤ 50,000 cells/mm^3, neutrophil count <500 cells/mm^3 associated with infection. Hold KEVZARA dosing for ALT or AST >3 to ≤5 ULN, platelet count >50,000 to ≤ 100,000 cells/mm^3, and neutrophil count ≥500 to <1000 cells/mm^3, and until the clinical condition has been evaluated. The laboratory abnormalities for safety monitoring were similar between pediatric and adult patients. This recommendation is consistent with the Study DRI13925 protocol. For details about safety assessment, see section 7.

Therapeutic Individualization

Other than the recommended (b) (4) dosing, no other therapeutic individualization is necessary for sarilumab SC injection. Based on submitted clinical pharmacology information along with

PopPK and E-R analyses, no intrinsic patient factors other than body weight have been identified that would warrant for adjustment of the proposed dosing regimen.

Outstanding Issues

There are no outstanding issues that would preclude the approval of this BLA supplement from a clinical pharmacology perspective. See section 4 for product quality assessment.

5.3. Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

Sarilumab is a human IgG1 monoclonal antibody that binds to both soluble and membrane-bound IL-6 receptors, thereby inhibits IL-6-mediated signaling through these receptors.

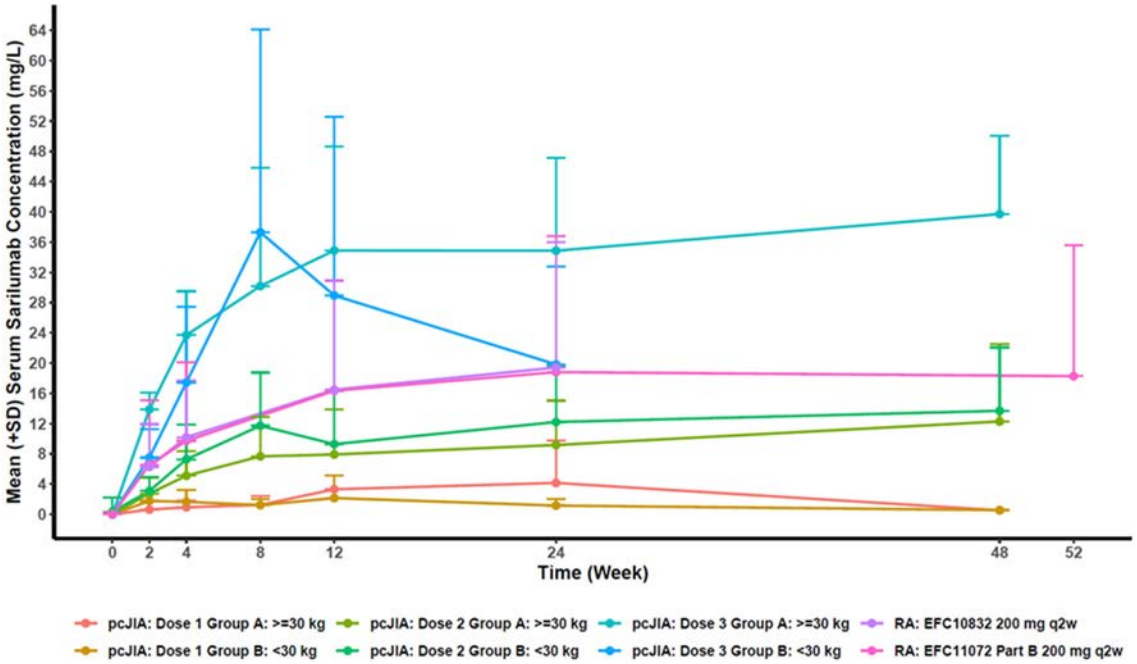
To support this BLA supplement, data from a phase 2b open label study (DRI13925) that evaluated PK/PD, efficacy, safety, and immunogenicity in pediatric patients aged 2 to 17 years old with pJIA were submitted (see **section 7** for detailed study design). Briefly, the study has 3 portions of which portion 1 includes a dose-finding core treatment phase up to 12 weeks followed by an extension phase. In dose-finding portion, 3 dose regimens were evaluated in each body weight category of pJIA patients: group A (≥30 kg) and group B (≥10 kg to <30 kg). After completing 12-week treatment, a dose and dosing regimen was selected with the aid of PopPK and E-R analyses and the selected dose was used in extension phase of this portion. In portion 2 and 3, the selected dose was directly used from the outset.

Pharmacokinetics of sarilumab in pJIA patients was characterized using population PK approach and compared with that of adults with RA. Cross-study comparison of PK (based on Ctrough) was performed between pediatric and adult patients across.

Pharmacokinetics of sarilumab in patients with pJIA and RA

The observed PK of sarilumab was described based on predose concentrations (Ctrough) from the pediatric study (DRI13925) and an adult RA study (EFC11072 Part B). The selected dose 2 of pJIA patients (3 mg/kg Q2W in group A and 4 mg/kg in group B) provided comparable mean Ctrough at steady state (Ctrough,ss) with that of adult following 200 mg Q2W (**Figure 1**). However, observed mean Ctrough,ss for group A of pediatric patients weighing ≥30 kg is approximately 38% lower than that of adult patients with 200 mg Q2W dosing regimen, but higher when compared with that of 150 mg Q2W approved for adult with RA for management of laboratory abnormalities (**Table 2**).

Figure 1. Sarilumab trough concentrations between pJIA patients and adults with RA. The PK resulting from Dose 2 of pediatric patients closely matches with that of adults following 200 mg Q2W



Abbreviations: SC = subcutaneous; SD = standard deviation; pJIA = polyarticular-course juvenile idiopathic arthritis; RA = rheumatoid arthritis.
Note: Participants enrolled in Dose 2 from the 2nd and 3rd portions of the study are combined with participants enrolled in Dose 2 from the dose-finding portion of the study. Summaries on the non-selected doses only include the data collected prior to the first dose adjustment to the selected dose.
Source: Reviewer's plot based on poh1134-pkpd-final.csv (study DRI13925), adpc.xpt (studies EFC11072-part B and study EFC10832).

Table 2. Mean (SD) sarilumab pharmacokinetic parameters in serum at the steady state, following repeated SC administrations of sarilumab to participants with pJIA and RA.

Population (Study ID)	Dose	N	Cmax (mg/L)	AUC0-14 days[a] (day.mg/mL)	Ctrough (mg/L)		
			Predicted[b]	Predicted[b]	Predicted[b]	N	Observed[c]
pJIA (DRI13925) Group A (≥30 kg)	2 mg/kg q2w	5	11.1 (4.82)	90.7 (30.8)	1.36 (0.87)	5	0.343[d]
	3 mg/kg q2w	39	27.1 (11.6)	276 (121)	9.57 (5.84)	37	11.6 (10.4)
	2 mg/kg qw	5	37.6 (8.52)	470 (122)	28.0 (9.06)	4	39.7 (10.3)
PJIA (DRI13925) Group B (≥10 kg to <30 kg)	2.5 mg/kg q2w	5	14.0 (2.97)	110 (40.9)	1.39 (1.44)	5	0.355 (0.231)
	4 mg/kg q2w	24	40.4 (7.77)	395 (101)	14.4 (9.81)	24	14.2 (8.23)
	2.5 mg/kg qw	5	28.9 (5.32)	352 (64.8)[e]	21.6 (5.16)[e]	4	NA[f]
RA (EFC11072 Part B)	150 mg q2w	366	20.4 (9.23)	207 (119)	6.57 (7.53)	274	7.63 (9.73)
	200 mg q2w	426	35.9 (15.5)	400 (213)	16.9 (14.5)	266	18.8 (16.3)

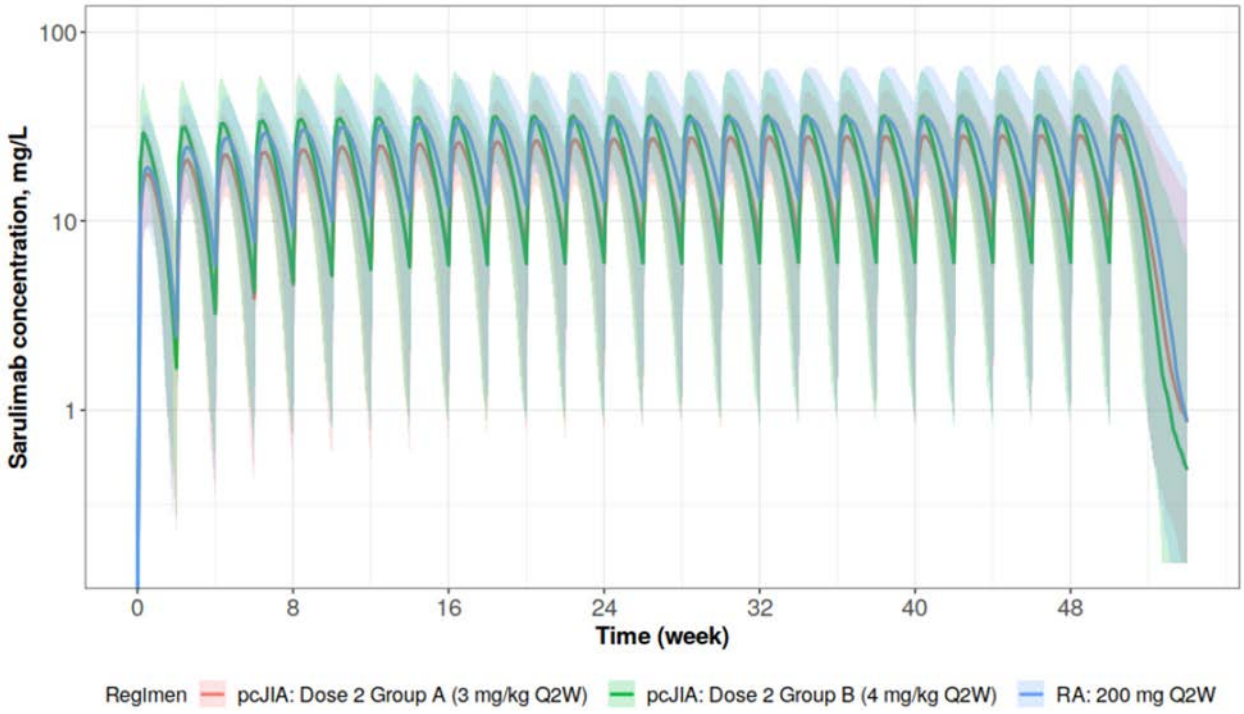
[a] AUC0-14 days = AUC[Week 22 – Week 24 for RA] for 200 mg q2w or 150 mg q2w and AUC[Week 30 – Week 32 for pJIA] for all 3 dose cohorts.
[b] Predicted: summary statistics of post-hoc estimates of exposure parameters in Study POH1134 (pJIA) at steady state (Week 30) and Study POH0428 (RA) at steady state (Week 24).

[c] Observed Ctrough at Week 48 for pJIA and at Week 24 for RA.
[d] N = 2; SD calculation not applicable.
[e] Two participants with 1 or 2 missing doses (at week 28 or week 28 and 29) were included in the summary at steady state for Cohort 3 Group B. After exclusion these 2 participants, the Mean (SD) of Cmax , AUC0-τ, and Ctrough are 29.8 (7.19) mg/L, 360 (89.2) mg·day/L, and 20.9 (7.19) mg/L in other 3 participants.
[f] No observed data available at Week 48.
Note: The reviewer's analysis provided similar results. The highlighted are selected and recommended doses for pediatric patients with pJIA. The number of subjects for observed Ctrough is a little smaller than the reported due to BLQs at Week 48. However, the number is appropriate for model-predicted Ctrough.

Source: m2.7.2-seq0168 – summary of clinical pharmacology studies, table 3.

Further, PK comparison between patients with pJIA and RA was evaluated using PopPK analysis, which suggests that model-predicted Ctrough,ss is consistent with observed data. Model-predicted mean Cmax and $AUC_{0\text{-}14days}$ at steady state for pediatric dose 2 are generally comparable between pJIA and RA, with a slightly lower exposure (25 – 31%) in group A of pJIA patients compared to that of adult 200 mg Q2W regimen. PK simulation indicates that the exposures (mean with 95% prediction interval) of dose 2 in pJIA patients are highly overlapped with those in adult patients with RA at 200 mg Q2W (**Figure 2**).

Figure 2. Mean and 95% prediction interval of sarilumab concentration-time profiles at dose 2 in patients with pJIA and at 200 mg Q2W in patients with RA predicted by PopPK models (Studies POH1134 and POH0428)



Source: m2.7.2-seq0168 – summary of clinical pharmacology studies, page 43.

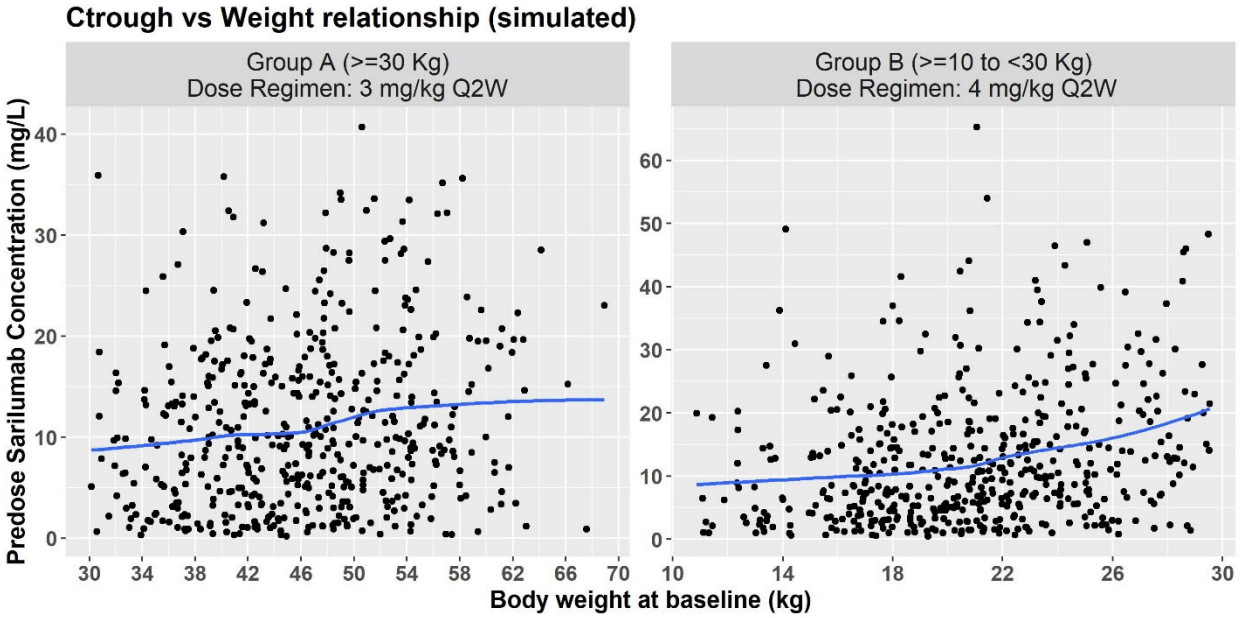
Note that sarilumab exposures decreased with a decrease in body weight within each pediatric group A and B despite administration of body weight-based (mg/kg) doses. For example, at dose 2 (3 mg/kg) in group A, AUCτ,ss and Ctrough,ss decreased by 12.1% and 26.9%, respectively, when BW decreased from 46.5 kg (median) to 30.8 kg, and increased by 7.5% and

19.1%, respectively, when BW increased from 46.5 kg to 64.2 kg. Similar trend was found for Cmax,ss.

On the other hand, at dose 2 (4 mg/kg) in group B, AUCτ,ss and Ctrough,ss decreased by 13.8% and 33.7%, respectively, when BW decreased from 18.4 kg (median) to 12.4 kg, and increased by 20.7% and 50.4%, respectively, when BW increased from 18.4 kg to 28.7 kg. Similar trend was found for Cmax,ss. The change in exposure with respect to BW change for a group remains within observed PK variabilities (58 – 89%) of pJIA patients. The trend of increase in PK exposure with increasing BW was supported by PopPK simulation as illustrated in **Figure 3**.

Additionally, PK simulation was performed to describe the trends in exposure at steady state with body weight and age for each of pediatric groups (group A and B). The model predicted concentrations tended to increase with increased BW for its range corresponding to each group (**Figure 3**). The average change in exposure from the median to 5th percentile or 95th percentile BW of each group is similar to that reported by the Applicant as mentioned above. However, there was no trend in concentration-age relationship for pediatric group A and B (**Figure 4**).

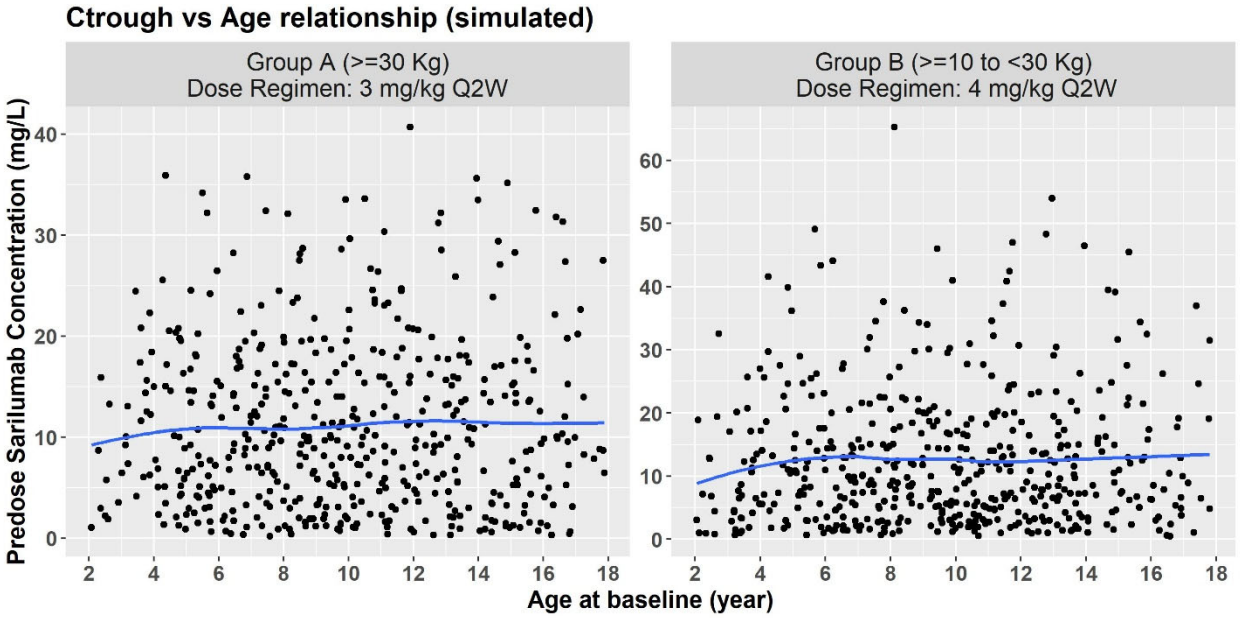
Figure 3. Simulated relationship between body weight vs steady state Ctrough at Week 32



Source: Reviewer's analysis.

Note: 500 patients were simulated for each group based on the final PopPK model. BW was sampled based on its distribution found in literature (mean [SD]: 45.7 [8.4] for group A, mean [SD]: 20.7 [4.65] for group B. Baseline age and albumin were simulated based on distribution observed in pJIA study DRI13925. Dose was capped at 200 mg if estimated dose exceeded 200 mg for body weight >66 kg. Black dot: simulated individual prediction; Blue line: A trend line (loess smooth) describing the relationship between Ctrough,ss and BW.

Figure 4. Simulated relationship between age vs steady state Ctrough at Week 32



Source: Reviewer's analysis. Note: 500 patients were simulated for each group based on the final PopPK model.

The Applicant proposes that patients in group B who are already receiving 4 mg/kg should continue the same dose regimen despite the BW exceeds 30 kg until 39.5 kg. Pharmacokinetic simulation suggests that continuing the same dose of lower BW (27.5 to <30 kg) to higher BW (30 – 39.5 kg) decreases exposures by 18-24% depending on simulated PK parameters. However, the decreased exposures is not expected to be clinically meaningful as these are still within the exposure ranges of 200 mg Q2W administered in adults with RA. (**See section 14.3.2 – Pharmacometrics review for details**).

Overall, observed and model-predicted data conclude that sarilumab PK profiles in pediatric patients with pJIA at dose 2 were generally similar to those in adult participants with RA at 200 mg Q2W. Sarilumab exposure (e.g., AUCτ,ss, Ctrough,ss) were comparable across age/weight groups (≥2 years and ≥10 kg, Figure 3, Figure 4) following the [redacted] dosing regimen.

5.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

In this supplemental BLAs, the evidence of effectiveness of sarilumab is extrapolated from that of adults with RA based on matching PK exposures. The data from the open-label study (DRI13925) in pediatric patients with pJIA provided supportive evidence that the efficacy at Week 12 for the selected dose 2 in pJIA patients (N=73) is numerically higher than that in adults following 200 mg Q2W regimen (N = 331) based on JIA ACR30, 50, and 70 response rates. Refer to **section 7** for more information on efficacy between patients with pJIA and RA.

A log linear E-R relationship based on logistic regression analysis between Ctrough and JIA ACR30/50/70 response rates provided a consistent E-R relationship with a trend toward greater

response with increasing Ctrough. Collectively, the maximum response is predicted for dose 2, which is comparable or higher than that predicted for adult with RA at 200 mg Q2W. Other PK/PD analyses for biomarkers (e.g., IL-6, sIL-R, C-reactive protein) also provided similar E-R relationship in pediatric participants with pJIA and in the RA adult patients. Overall, the clinical pharmacology information submitted with the current sBLA supports extrapolation of evidence of effectiveness of sarilumab to pediatric patients with pJIA from adults with RA.

In line with adult dosing recommendation, pediatric dosing is also recommended to be held or discontinued at certain laboratory conditions as described in 'general dosing' section.

Exposure-response (E-R) analyses

E-R analyses for efficacy

Exposure-response relationship for efficacy were investigated using descriptive analyses and/or empirical E-R modeling and compared with those in patients with RA (Study EFC11072 Part A and Part B). To allow a fair comparison between pediatric and adult efficacy, the adult ACR20/50/70 response (used in adult RA study) was translated to JIA ACR30/50/70 response by excluding one ACR component (e.g., pain VAS).

Descriptive analyses of exposure-efficacy based on JIA ACR30/50/70 response using non-responder imputation approach showed that dose 2 resulted in higher response rates than those observed in adults at 200 mg/150 mg Q2W regimens at Week 12. There was a similar trend of dose related increases of JIA ACR 30/50/70 response from Dose 1 to Dose 2 and no further increase of JIA ACR30/50/70 response from Dose 2 to Dose 3 in pediatric participants with pJIA. Similarly, response was increased from adult 150 mg Q2W to 200 mg Q2W, with no further increase at higher dosing regimen of 150 mg QW. These descriptive analyses indicate a consistent dose-response relationship of JIA ACR30/50/70 response between pediatric patients with pJIA and in adult patients with RA (**Table 3**).

Table 3. JIA ACR30/50/70 based on the non-responder imputation approach by dose groups at Week 12 in participants with pJIA at Dose 1, Dose 2, and Dose 3 (Study DRI13925) and in adult participants with RA (Study EFC11072 Part A and Part B)

	Pediatrics (pJIA)			Adults (RA)		
	Dose 1	Dose 2	Dose 3	150 mg Q2W	200 mg Q2W	150 mg QW
	N=13	N=73	N=15	N=341	N=331	N=50
Range of C_{trough} (min, max, mg/L)[a]	(0.16, 5.6)	(0.16, 24.9)	(2.41,68.4)	(0.00, 40.6)	(0.00, 67.8)	(10.2, 59.8)
Mean Ctrough (mg/L)[a]	0.91	7.98	25.7	5.28	16.5	36.3
JIA ACR30 Response Rate (%)	76.9	93.2	73.3	78.1	85.7	80.0
JIA ACR50 Response Rate (%)	69.2	89.0	73.3	62.7	73.8	70.0
JIA ACR70 Response Rate (%)	38.5	75.3	73.3	38.9	44.7	42.0

[a] If the observed Ctrough was missing at Week 12, Ctrough was imputed with a last observation carried forward approach.
Note: Ctrough = trough concentration; JIA ACR30 = Juvenile Idiopathic Arthritis American College of Rheumatology 30% improvement score; JIA ACR50 = Juvenile Idiopathic Arthritis American College of Rheumatology 50% improvement score; JIA ACR70 = Juvenile Idiopathic Arthritis American College of Rheumatology 70% improvement score; pJIA = polyarticular-course juvenile idiopathic arthritis; RA = rheumatoid arthritis.
Source: m2.7.2-seq0168 – summary of clinical pharmacology studies, Table 10.

Within dose 2 of pJIA study, Ctrough tertile analyses showed a flat E-R relationship at Week 12 (100% response rates across all tertiles except at low tertile for ACR50 response) for patients who remained on treatment. The ACR70 response rate is much higher at medium tertile than low tertile but similar between medium and high tertile. Similar E-R relationship was also observed at Week 48 implying sustained efficacy of sarilumab in pediatric subjects with pJIA (**Table 4**).

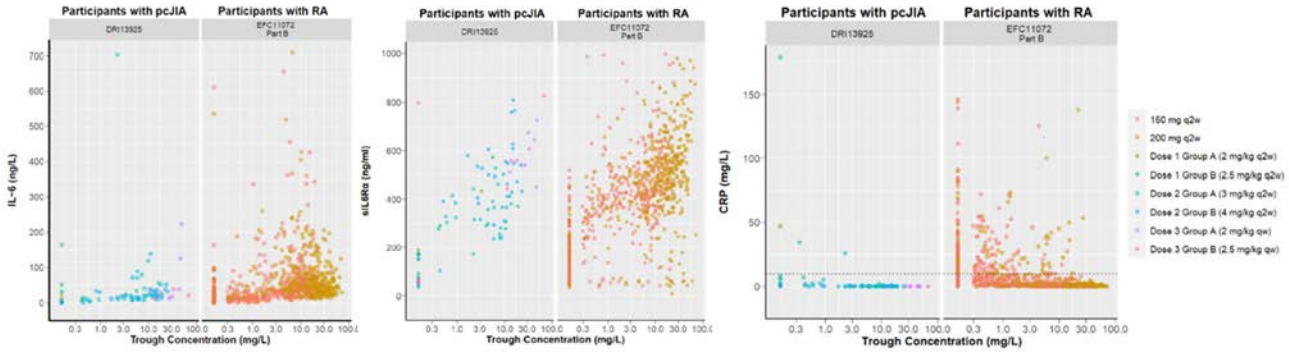
Table 4**.** JIA ACR30/50/70 (as observed, completer approach) by Ctrough tertiles at Weeks 12 and 48 in participants with pJIA at Dose 2 (Study DRI13925)

	Week 12			Week 48		
	Low (1st tertile)	Medium (2nd tertile)	High (3rd tertile)	Low (1st tertile)	Medium (2nd tertile)	High (3rd tertile)
	N=23	N=22	N=23	N=20	N=20	N=20
Range of C_{trough} (min, max, mg/L)[a]	0.16, 4.20	4.52, 10.7	10.9, 24.9	0.16, 5.70	8.04, 15.5	15.6, 52.3
Mean Ctrough (mg/L)[a]	1.49	7.63	15.6	3.22	11.3	22.8
JIA ACR30 Response Rate (%)	100	100	100	100	100	100
JIA ACR50 Response Rate (%)	87.0	100	100	100	100	100
JIA ACR70 Response Rate (%)	56.5	95.5	91.3	85.0	95.0	100

[a] If the observed Ctrough was missing at Week 12, Ctrough was imputed with a last observation carried forward approach. **Source**: The Applicant's PK/PD study report (cts0123) – Tables 9-10, m5.3.3.5-seq-0168.

Additionally, PK/PD analyses for biomarkers of IL-6, sIL-6 receptor alpha subunit, and C-reactive proteins suggested similar trend of change with increased Ctrough between pediatric patients with pJIA and adults with RA. IL-6 and sIL-6R increased and CRP decreased with increased Ctrough levels (**Figure 5**). This further supports the extrapolation of efficacy from adults to pediatric patients.

Figure 5. Relationship between trough concentration of sarilumab and biomarkers such as IL-6, sIL-6R (total), and CRP after 12 weeks of sarilumab SC treatment in patients with pJIA and RA

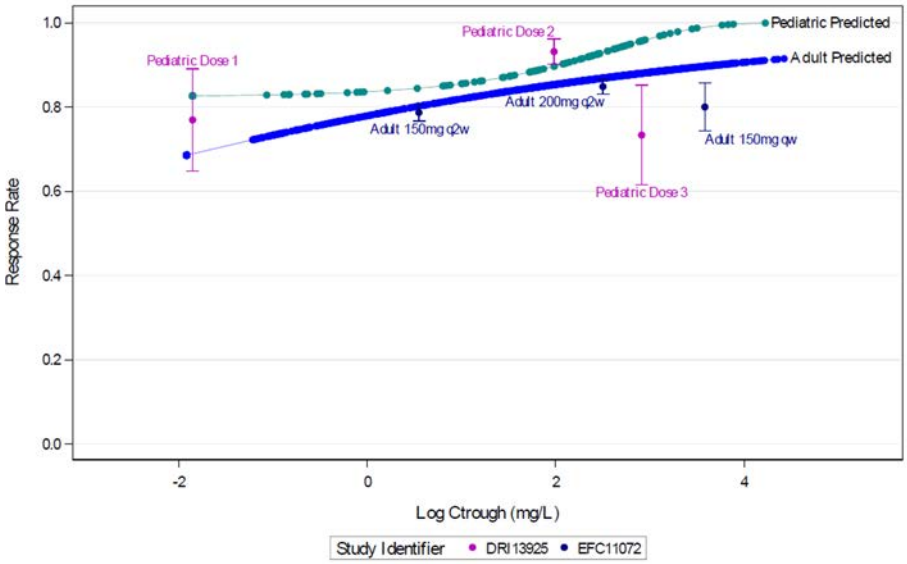


IL-6 = interleukin-6; sIL6R: soluble interleukin-6 receptor; CRP = C-reactive protein; pJIA = polyarticular-course juvenile idiopathic arthritis; q2w = every 2 weeks; qw = once a week; RA = rheumatoid arthritis; SC = subcutaneous. Note: Dashline represent the limit of normal range (10 mg/L) of CRP. **Source**: m2.7.2-seq0168 – summary of clinical pharmacology studies, Figures 13-15.

Empirical E-R modeling analyses for efficacy

The model-based analyses in pJIA participants using non-responder imputation approach demonstrated a linear or log linear E-R relationship between the JIA ACR30 response and the sarilumab Ctrough at Week 12 for dose 1, 2, and 3. Efficacy increased with increasing Ctrough (median within each dose group) from Dose 1 to Dose 2 while the increase was minor from Dose 2 to Dose 3, (e.g., the effect appeared to have reached a plateau with Dose 2) (**Figure 6**). Similarly, E-R relationship for JIA ACR50/70 demonstrated a consistent trend of increasing effect with increased median Ctrough of each dose group reaching plateau at dose 2. The maximum effect seen with dose 2 along with its matching sarilumab exposures with those of approved adult dose supports the selection of dose 2.

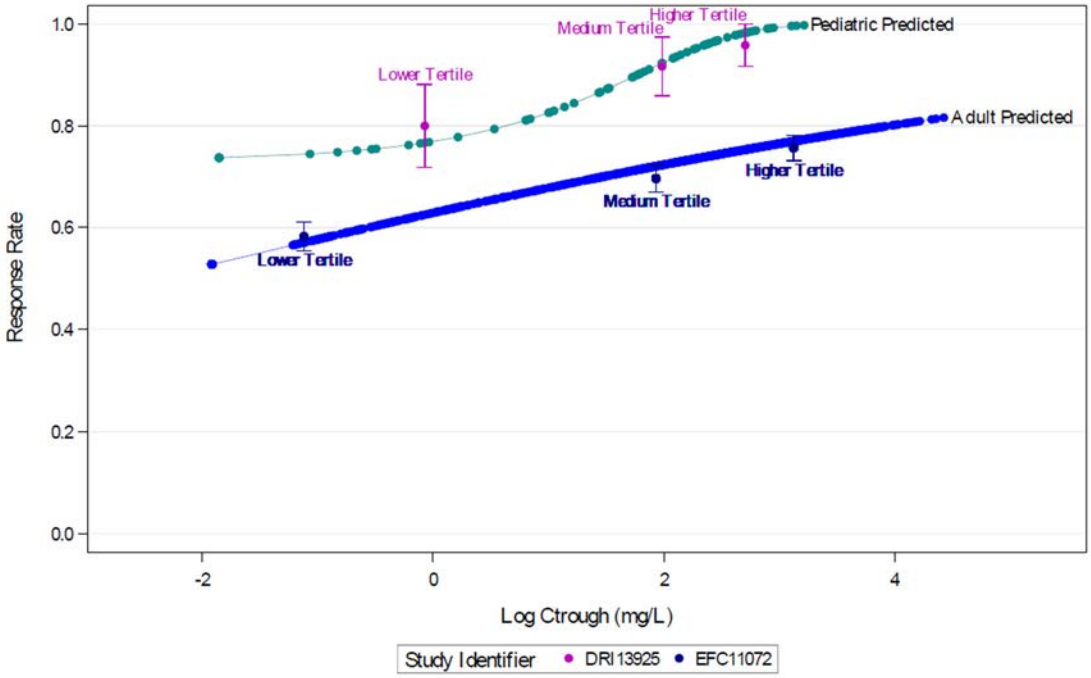
Figure 6. Relationship of JIA ACR30 based on non-responder imputation approach versus sarilumab Ctrough at Week 12 in pediatric participants with pJIA at Dose 1, Dose 2, and Dose 3 and in adult participants with RA by dose groups



Source: m2.7.2-seq0168 – summary of clinical pharmacology studies, Figure 18.

For dose 2, E-R relationship was established between JIA ACR30/50/70 and median Ctrough for each tertile at Week 12 based on the non-responder imputation approach. The analysis suggests an increasing trend in the treatment effect from lower to higher tertile Ctrough (at median of each tertile) for all endpoints, except ACR30 showing similar response across all exposure tertiles. The treatment effect plateaued at a mean trough concentration of ~8 mg/L (within medium tertile) for ACR50/70 (**Figure 7**) . Overall, the results are consistent with that of prior E-R analyses for all doses where the treatment effect approached a plateau at dose 2. The E-R in pediatric patients with pJIA showed similar trend as seen in adults with RA, albeit efficacy is numerically higher in pediatric patients than adults for the corresponding tertile exposure. See pharmacometrics review in **section 14.3.2** for details.

Figure 7. Relationship of JIA ACR50 based on the non-responder imputation approach versus sarilumab Ctrough at Week 12 in pediatric participants with pJIA at Dose 2 and in adult participants with RA by Ctrough tertiles



Source: m2.7.2-seq0168 – summary of clinical pharmacology studies, Figure 22.

E-R analyses for safety

Exposure-safety relationship was evaluated using descriptive analyses and/or empirical E-R modeling for safety endpoint of absolute neutrophil count (ANC) in patients with pJIA and RA. Descriptive data shows that ANC level is decreased dose-dependently in pJIA patients. The increase in proportion of patients with ANC <1.0 Giga/L was also dose-dependent at Week 12, which is similar to that of Week 24 suggesting that the risk of ANC <1.0 Giga/L did not increase over time (**Table 5**).

For dose 2 of pediatric patients, Ctrough tertile analyses at Weeks 12 demonstrated a trend of decrease in ANC level with increased Ctrough. Conversely, the proportion of patients with ANC <1.0 Giga/L was similar in the medium, and high exposure tertiles, with a trend of increase with increasing concentration of sarilumab from the low tertile to medium tertile and reached a plateau at Ctrough in the medium tertile. The risk of decreased ANC levels or increased proportion of patients with <1.0 Giga/L is similar between Week 12 and 48 (**Table 5**).
In adults with RA based on pooled data (studies EFC11072 Part A, EFC11072 Part B, and EFC10832), there was no clear trend for the proportion of participants with ANC <1.0 Giga/L to increase with increasing trough concentration at 200 mg Q2W, except a greater proportion of participants (%) with ANC <1.0 Giga/L is seen in Q4 than those in Q1 to Q3 (**Table 5**).

Table 5. ANC and proportion of participants with ANC<1.0 Giga/L across doses and Ctrough tertiles of dose 2 in pJIA patients and Ctrough,ss quartiles of 200 mg Q2W in adults with RA

	Week 12			Week 24		
	Dose 1	**Dose 2**	**Dose 3**	**Dose 1**	**Dose 2**	**Dose 3**
	N=13	**N=73**	**N=15**	**N=10**	**N=67**	**N=11**
Range of C_{trough} (min, max, mg/L)[a]	0.16, 5.6	0.16, 24.9	2.41,68.4	0.16, 12.5	0.16, 23.3	11.4, 68.4
Mean Ctrough (mg/L)[a]	0.91	7.98	25.7	2.06	9.67	33.90
Mean ANC (Giga/L)	3.98	2.74	2.24	4.30	2.71	2.49
Mean ANC change from baseline (%)	17.52	-35.87	-48.23	17.67	-33.98	-46.22
ANC<1.0 Giga/L, n (%)	2 (15.38%)	16 (21.92%)	6 (40.00%)	1 (10.00%)	12 (17.91%)	3 (27.27%)
Dose 2: Ctrough tertile-based analyses for ANC endpoints at Weeks 12 and 48 in pJIA patients						
	Week 12			Week 24		
	T1	**T2**	**T3**	**T1**	**T2**	**T3**
	N=25	**N=24**	**N=24**	**N=21**	**N=20**	**N=21**
Range of C_{trough} (min, max, mg/L)[a]	0.16,4.20	4.52,10.7	10.9,24.9	0.16, 5.70	8.04, 15.3	15.6, 52.3
Mean Ctrough (mg/L)[a]	1.43	7.40	15.4	3.20	11.0	22.4
Mean ANC (Giga/L)	2.99	3.02	2.22	3.49	2.35	2.46
Mean ANC change from baseline (%)	-27.19	-36.55	-44.24	-16.53	-43.47	-38.86
ANC<1.0 Giga/L, n (%)	2 (8.00%)	7 (29.17%)	7 (29.17%)	1 (4.76%)	6 (30.0%)	4 (19.05%)
Sarilumab 200 mg Q2W + DMARD in adults with RA: $C_{trough,ss}$ quartile-based analyses for ANC endpoints						
	Placebo	**Q1**	**Q2**	**Q3**	**Q4**	**Combined**
	N=661	**N=141**	**N=140**	**N=140**	**N=140**	**N=561**
Range of C_{trough} (min, max, mg/L)[b]	-	0.15, 4.88	4.93, 13.2	13.3, 26.6	26.7, 93.4	0.147, 93.4
Mean (SD) Ctrough (mg/L)[b]	-	1.35 (1.46)	8.78 (2.59)	19.1 (3.71)	39.5 (12.0)	17.2 (15.7)
Mean (SD) ANC (Giga/L)	5.94 (2.47)	5.31 (2.49)	3.90 (2.13)	3.29 (1.57)	2.93 (1.42)	3.84 (2.14)
Mean (SD) ANC change from baseline (Giga/L)[c]	-0.18 (2.17)	-1.19 (2.35)	-2.53 (2.44)	-2.70 (2.00)	-2.81 (2.42)	-2.32 (2.39)
ANC<1.0 Giga/L, n (%)[d]	1 (0.2%)	10 (7.1%)	7 (5.0%)	12 (8.6%)	16 (11.4%)	45 (8.0%)

T1, 2, 3: Tertile-1, 2, 3 (low, medium, and high tertile); Q1, 2, 3, 4: Quartile-1, 2, 3, 4; ANC = absolute neutrophil count; pJIA = polyarticular juvenile idiopathic arthritis; Ctrough = trough concentration observed immediately before dose administration; Ctrough,ss: trough concentration at steady state; DMARD = disease-modifying antirheumatic drug; q2w = every 2 weeks; RA = rheumatoid arthritis; SD = standard deviation.

[a] If the observed Ctrough was missing, Ctrough was imputed with the last observation carried forward approach

[b] Based on Ctrough value at Week 24; for participants with missing Ctrough at Week 24, the closest non-missing value measured at Week 12, 36, or 48 is used

[c] ANC change from baseline at Week 24.

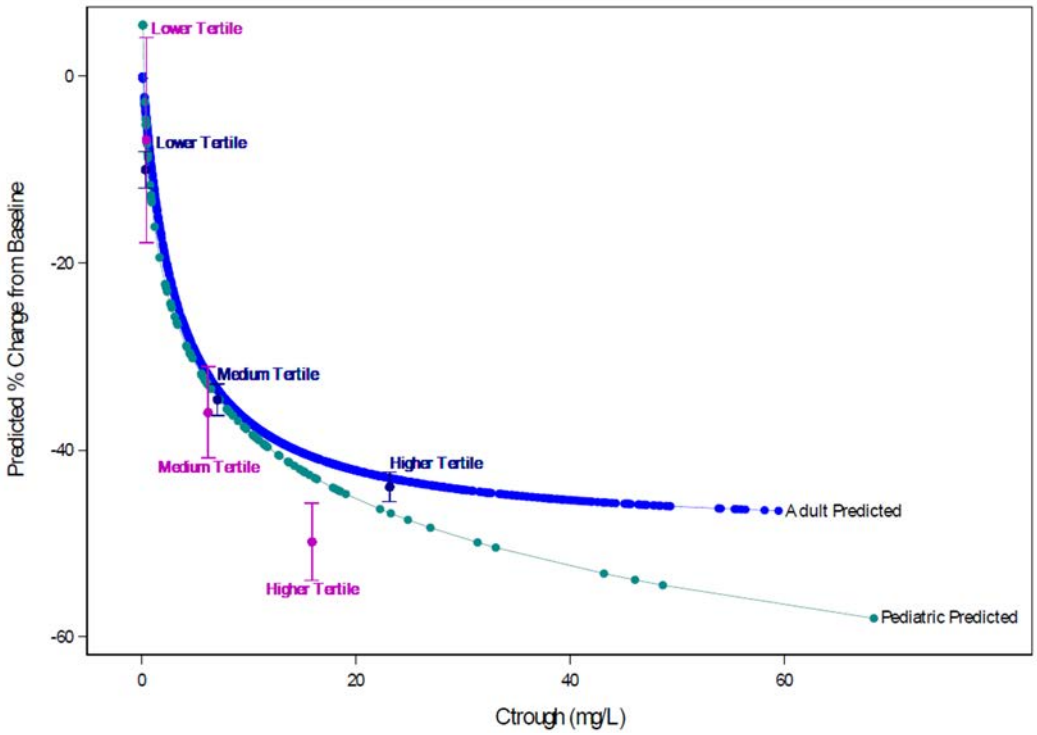
[d] During the treatment-emergent adverse event (TEAE) period.

Empirical E-R modeling analyses for safety

A logistic-regression analysis was conducted to establish linear E-R relationship between ANC and sarilumab Ctrough at Week 12 in pediatric participants with pJIA across Dose 1, 2, and 3.

The PK/PD model-predicted treatment effect for the mean percentage change from baseline of ANC at the median Ctrough was consistent with the observed effect. A trend of greater percentage change from baseline of ANC is seen with increase in median Ctrough (from low to high tertile) reaching a plateau at >20 mg/mL. Although E-R analysis did not indicate reaching a plateau in pJIA participants, the results should be interpreted with caution due to the limited number of participants in Dose 3 (N=11) (**Figure 8**). Similar to pediatric patients, adults also showed similar trend of change in ANC from baseline with increased Ctrough which is consistent with the observed effect.
The trend of change in ANC levels is consistent with the analyses for all doses after 101 patients completed 1 year treatment (clinical data cut off dated 13 Jan 2023).

Figure 8. Relationship of ANC percent change from baseline versus sarilumab Ctrough at Week 12 in pediatric participants with pJIA at Dose1, Dose 2 and Dose 3 and adult participants with RA by dose groups



Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Other than body weight-based dosing, a dose adjustment or management strategy for subpopulations based on intrinsic factors is not necessary.
Though albumin was identified as statistically significant covariate, it was not considered to have clinically meaningful impact on sarilumab PK, hence an alternative dosing regimen is not necessary.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant did not conduct any new drug interaction studies. The current approved label of sarilumab indicates that sarilumab may cause clinically meaningful effects on CYP substrates with narrow therapeutic index. The label recommends monitoring of therapeutic effect (e.g., warfarin) or drug concentration of CYP3A4 substrates upon initiation or discontinuation of sarilumab and adjusting the individual dose of the medicinal product as needed. It is also recommended to exercise caution when co-administering sarilumab with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of sarilumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

What was the immunogenicity incidence and its impact on the PK of sarilumab?

The ADA incidence in pediatric patients with pJIA was low. Overall, across Dose 1, Dose 2 and Dose 3, 4 participants (4.1%) had treatment-emergent ADA positive responses during the TEAE period (one patient had an ADA positive response during the 12-week dose-finding portion. Of the 4 patients, 3 patients (3.1%) had persistent ADA, 2 patients (2.1%) had NAb positive responses.
For the selected Dose 2, 3 patients (4.3%) had treatment-emergent ADA positive responses during the TEAE period. Two (2) patients (2.9%) had persistent ADA and 1 patient (1.4%) had NAb positive responses. The patient with NAb did not have persistent ADA.

Impact of ADA on sarilumab exposure
Patients with treatment-emergent positive ADA and positive NAb responses had lower sarilumab exposure than patients who were ADA negative at each corresponding dose. However, the individual sarilumab concentrations in ADA-positive patients were generally within the exposure range observed in ADA-negative participants.

Impact of ADA on efficacy and safety
There was no clear evidence of lack or loss of efficacy in patients who developed ADA response. In patients with pJIA randomized to Dose 2, all 3 patients who had treatment-emergent ADA positive responses were JIA ACR30 responders at Week 12. None of the patients who had treatment-emergent ADA positive responses experienced any anaphylaxis, serious and/or clinically significant hypersensitivity reactions, or injection site reactions.
Because of the low occurrence of ADA in patients with pJIA, the effect of these antibodies on the safety, and/or effectiveness of sarilumab is unknown.

Are the bioanalytical methods adequately validated to measure PK in serum samples?

A validated sandwich enzyme-linked immunoassay (ELISA) was used to determine the concentration of functional sarilumab in the serum samples. The assay has a lower limit of quantification (LLOQ) of 0.313 µg/mL for sarilumab in human serum.

The validated functional sarilumab assay (REGN88-AV-13131-VA-01V1) was described in detail in the original marketing application (RA Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods). An amendment to this original validation was made by including an extra time point (15 months) to the long-term stability (LTS) testing. The amended validation report (REGN88-AV-13131-VA-01V2) was submitted with the current supplement. This amended report includes results from the LTS testing that evaluated the stability of sarilumab in human serum after long-term storage at both -20^{0}C and -80^{0}C. The original validation method was reviewed and reported in the clinical pharmacology review (dated August 29, 2016) as part of the original BLA submission for RA. The amended validation of LTS has been reviewed and reported in **OCP appendix, section 14.3.1**.

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Study	Subjects Enrolled (n)	Dosing	Study Design	Endpoints
DRI13925	Portion 1: 42 Portions 1, 2, 3: 102	Portion 1: • Dose 1: -Group A (≥30 kg and ≤60 kg): 2 mg/kg Q2w -Group B (<30kg and ≥30 kg): 2.5 mg/kg Q2w • Dose 2: -Group A (≥30 kg and ≤60 kg): 3 mg/kg Q2w -Group B (<30kg and ≥30 kg): 4 mg/kg Q2w • Dose 3: -Group A (≥30 kg and ≤60 kg): 2 mg/kg Qw -Group B (<30kg and ≥30 kg): 2.5 mg/kg Qw Portion 2: -Group A (≥30 kg and ≤60 kg): 3 mg/kg Q2w -Group B (<30kg and ≥30 kg): 4 mg/kg Q2w	MC, OL, 2-phase study: a 12-week core treatment phase comprised of a dose-finding portion within two weight groups followed by a 144-week extension phase.	Primary Endpoint: PK exposure Secondary Endpoints: -safety -efficacy -PD

Q2w: every two weeks; Qw: every week; MC=multicenter; OL=open-label; PK=pharmacokinetics; PD=pharmacodynamics

6.2. Review Strategy

The clinical development program for sarilumab in children 2 to 17 years of age with pJIA consisted of a single study (Study DRI13925) that assessed the PK, PD, efficacy, and safety of sarilumab. The study was designed to determine the appropriate dose regimen while avoiding a placebo arm considering that the disease course and the treatment response are sufficiently similar to the adult RA patients thereby permitting an extrapolation strategy of data from adults to children. Given that the underlying pathogenesis of the clinical course of pJIA is similar to that of adult RA, the pediatric dose regimens assessed in Study DRI13925 were selected via PK modeling and simulation to be equivalent to the adult RA approved dose regimens evaluated in clinical studies, which were shown to have a favorable risk benefit for adult RA. Given the overall design and analysis of study DRI13925, the data used to determine approval for this submission is solely based on the extrapolation of PK data, while the clinical safety and efficacy provide supportive data for the use of sarilumab for the treatment of children with pJIA.

7 Review of Efficacy

7.1. Review of Relevant Individual Trials Used to Support Efficacy

7.1.1. Study DRI13925

Study DRI13925 consists of three portions: one dose-finding portion and two expansion portions (Figure 9).

Study DRI13925 was designed as a three-portion study with two phases. Each Portion included a 12-week core phase and an extension phase (up to 144 weeks for Portions 1 and 2, and up to 84 weeks for Portion 3). The total on-treatment period is therefore 3 years for Portions 1 and 2, and two years for Portion 3. Portion 1 was the dose-finding portion in which three ascending dose regimens were tested in two body weight groups. As the main goal of the two subsequent portions was to provide sufficient data for PK and PD parameters and for PK-PD relationship assessments in Portion 2 as well as for description of safety in Portion 3. Participants enrolled in Portions 2 and 3 received the Dose 2 regimen selected after analysis of the 12-week data obtained from Portion 1.

Figure 9. Schematic of Study DRI13925

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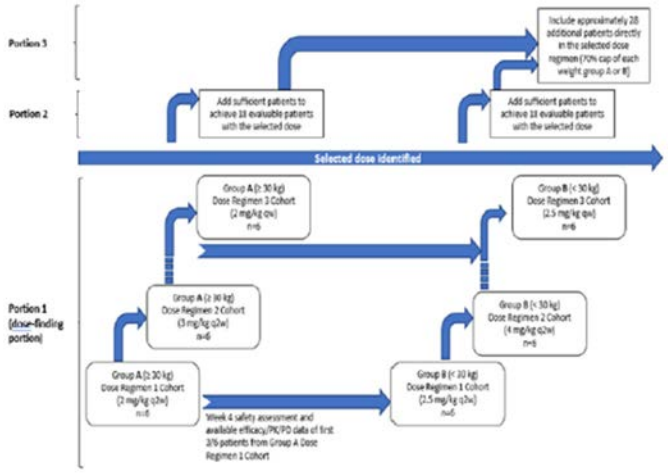


Abbreviations: PD = pharmacodynamics, PK = pharmacokinetic, qw = once every week, q2w = once every other week.

Note: in Portion 1, core treatment phase, enrollment in Group B (<30 kg and ≥10 kg) initiated after the review of safety and available data from the first 3 out of the 6 participants planned in the first tested dose regimen in Group A (≥30 kg and ≤80 kg) who had completed at least 4 weeks of study treatment.

Source: Applicant's Summary of Clinical Efficacy, page 19, Figure 2)

Each portion had a 12-week core phase followed by an extension phase (Figure 10).

Figure 10. Flow Diagram of Study DRI13925

Abbreviations: EOS = end-of-study (V28), EOT = end of treatment, F/u = follow-up, PK = pharmacokinetic, V = visit, Wk = week

Notes: All participants must complete an end-of-treatment (EOT) visit (V27, Week 156 for dose-finding and second portions/Week 96 for third portion) at the completion of treatment (last IMP injection at Week 154/Week 94 for Dose 1 and 2 Cohorts and at Week 155 for Dose 3 Cohort) or at the time of early permanent treatment discontinuation (regardless of treatment phase).

For a participant who discontinues study treatment prematurely during the 12-week core treatment phase, interleukin-6 (IL-6) and soluble interleukin-6 receptor (sIL-6R) will be measured at the EOT visit. For participants in the dose-finding and second portions who discontinue study treatment prematurely during 12-week core treatment phase, an additional PK visit, 2 weeks after the EOT visit, is required for blood sampling (V88).

All participants must complete a post-treatment follow-up visit (V28) 6 weeks after the EOT visit. However, participants discontinuing treatment prematurely during the core treatment phase should continue to return for the study visits as protocol scheduled without treatment administration through Week 12 (as per Food and Drug Administration [FDA] guidelines for missing data).

Source: Applicant's Summary of Clinical Efficacy, page 20, Figure 3)

The extension phase assessed subjects who had enrolled in Portion 1 and Portion 2 for up to 144 weeks and for up to 84 weeks for subjects enrolled in Portion 3. For Portions 1 and 2, only subjects who demonstrated a clinical response, as determined by achieving at least a JIA ACR30 response at Week 12, were permitted to continue in the extension phase. All subjects enrolled in Portion 3 were allowed to continue in the extension phase irrespective of their JIA ACR response level.

Portion 1 was designed as a sequential, ascending dose-finding study aimed at determining the appropriate dose and regimen for adequate treatment of subjects with pJIA in which three dose regimens (Table 6) were assessed in two weight groups (Group A, subjects weighing ≥30 kg to ≤60 kg; Group B, subjects weighing ≥10 kg to <30 kg) with a planned number of six subjects by dose and weight group. The three dose regimens tested, referred in this review as Dose 1, 2, and 3, were defined as follows:

- Doses 1 and 2 targeted PK exposures similar to the approved dose regimens in adults with RA (i.e., 150 mg Q2w and 200 mg Q2w).
- Dose 3 targeted PK exposures similar to the highest dose regimen that demonstrated efficacy together with an acceptable safety profile in the adult RA studies (i.e., 150 mg Qw).

Table 6. Study DRI13925, Dose by Body Weight and Dose Regimen-Portion 1

Study DRI13925, Dose by Body Weight and Dose Regimen-Portion 1

Body Weight	Dose Regimen 1 Subjects (n)	Dose Regimen 2 Subjects (n)	Dose Regimen 3 Subjects (n)
Group A: ≥30 kg to ≤60 kg	2 mg/kg Q2W n=7	3 mg/kg Q2W n=7	2 mg/kg QW n=6
Group B: ≥10 kg to <30 kg	2.5 mg/kg Q2W n=6	4 mg/kg Q2W n=7	2.5 mg/kg QW n=9

Source: Applicant's Summary of Clinical Efficacy, page 20, Table 1. Abbreviations: Q2W=once every two weeks; QW=once every week

A total of 42 subjects were enrolled in Portion 1. The 12-week data allowed selection of the dose regimen for subjects to be enrolled in the subsequent portions of the study. Subjects enrolled in Portion 1 continued on the same dose regimen of sarilumab they were assigned to receive in the 12-week core phase of the study until the selected dose regimen was determined. Once the dose was selected, subjects who were not already on this dose regimen had their dose regimen adjusted to the selected dose regimen.

Portions 2 and 3 of the study were designed to further assess the selected dose from Portion 1 (i.e., Dose 2) for a total of at least 100 subjects enrolled and treated. The enrollment in Portion 2 was completed with 31 subjects and Portion 3 was completed with a total of 29 subjects for a total number of 102 subjects.

The subject population selected for the study DRI13925 was a RF- or RF+ pJIA subtype or extended oJIA subtype as defined by ILAR 2001 JIA Classification Criteria. Enrolled subjects had at least five active joints at screening, per ACR definition for "active arthritis", an inadequate response to current treatment and considered as a candidate for treatment with a biologic DMARD (bDMARD). Exclusion criteria were the same for the three portions except the removal of the upper limit of 60 kg for the subjects' weight in Portions 2 and 3.

The primary endpoint of the study involved comparison of PK parameters between subjects with pJIA and adult RA. The reader is referred to Section 6 of this document for a detailed analysis of the data.

Major secondary endpoints included safety assessment and efficacy endpoints evaluating the JIA ACR 30/50/70/90/100 response rate at Week 12; change from baseline in individual ACR components and Juvenile Arthritis Disease Activity Score (JADAS)-27 change from baseline at Weeks 24, 48, and every 24 weeks thereafter until completion of study.

MAJOR INCLUSON CRITERIA

- Male and female subjects aged ≥2 and ≤17 years.
- Diagnosis of RF- or RF+ pJIA subtype or oJIA subtype according to the ILAR 2001 JIA Classification Criteria with at least five active joints per ACR definition for "active arthritis".

- Subject with an inadequate response to current treatment and considered as a candidate for a bDMARD.

MAJOR EXCLUSION CRITERIA

- Diagnosis of JIA subtypes except RF+ or RF- pJIA or extended oJIA.
- Body weight <10 kg or >60 kg for subjects enrolled in the three ascending dose cohorts, then BW <10 kg for subjects subsequently enrolled at the selected dose regimen.
- Active TB or a history of incompletely treated TB, history of invasive opportunistic infections, positive test for HIV, Hepatitis B (HBs-Ag or HBc-Ab) or Hepatitis C.
- Laboratory abnormalities: hemoglobin <7.0 g/dL, white blood cells <3000/mm3, neutrophils <2000/mm3, platelet count <150 000 cells/mm3, AST or ALT 1.5 x ULN, total bilirubin >ULN unless documented Gilbert's disease, cholesterol >350 mg/dL or 9.1 mmol/L (or hypertriglyceridemia >500 mg/dL, 5.6 mmol/L), estimated glomerular filtration rate <30 mL/min/1.73m^2 (using the modified Schwartz formula).
- Stable doses of NSAIDS were permitted provided a stable dose for more than two weeks prior to the Baseline visit.
- Nonbiologic DMARDs were permitted provided stable doses for more than six weeks prior to the Baseline visit.
- Oral glucocorticoids were permitted provided stable doses for more than two weeks prior to Baseline visit and did not exceed the equivalent prednisone dose of 0.5 mg/kg/day.
- Use of parenteral or intra-articular glucocorticoid injection within four weeks prior to Baseline visit.
- Prior treatment with anti-IL-6 or IL-6R antagonist therapies.
- Treatment with any biologic treatment for pJIA within five half-lives prior to the first dose of sarilumab.
- Treatment with a JAK inhibitor or with growth hormone within four weeks prior to the first dose of sarilumab.

Study Objectives

The primary objective of the current study was to describe the PK profile of sarilumab in subjects aged 2 to 17 years with pJIA. The secondary objectives included assessment of the PD profile, efficacy, and long-term safety of sarilumab in subjects with pJIA.

Statistical Analysis Plan

No pooled analyses were done as the current application included the results of a single open-labeled study. The primary analysis of Study DRI13925 was sarilumab PK analysis and is described in Section 6.

Data for participants who achieved a JIA ACR30/50/70/90/100 response for each dose cohort, overall, and by weight group were summarized by visit using counts, proportions, and 95% CIs. All observed data, while the participant remained on treatment, were included without missing data imputation.

For the summaries on the JIA ACR responses at Week 12, three different approaches were used for the handling of treatment discontinuations and missing data: non-responder imputation, last observation carried forward; and as observed including post discontinuation. Overall score and change from baseline in JADAS-27 were summarized by visit for each dose cohort and weight group.

The Sponsor analyzed several additional efficacy parameters taking into account the more recent efficacy assessments and definitions of inactive disease or low disease activity of pcJIA disease prior to the database lock of the interim analysis performed 1 year after last subject was enrolled. These analyses included the following:

- Overall score and change from baseline in JADAS-10, clinical JADAS-10, and clinical JADAS-27 summarized by visit (including number, mean, SE, SD, median, minimum, and maximum) for each dose cohort and weight group.
- Proportion of participants with no active joints, JADAS-10 inactive disease (JADAS-10 ≤2.7), cJADAS-10 inactive disease (cJADAS-10 ≤2.5) and no glucocorticoids use, JADAS-10 minimal disease activity (JADAS-10 ≤6) and cJADAS-10 minimal disease activity (cJADAS-10 ≤5), and clinical remission summarized for each dose cohort and weight group.

To assess the consistency in treatment effects across subgroup levels, subgroups analyses for JIA ACR70 response rate and proportion of participants with inactive disease (cJADAS-10 ≤2.5) were also assessed.

The first interim analysis of 12 weeks of data from the sequential, ascending dose cohort, dose finding portion (Portion 1) of the study, was completed on August 8, 2018. In this first interim analysis, a total of 42 participants with pJIA with an inadequate response to current treatment and considered as candidates for a bDMARD were enrolled in one of three sarilumab ascending dose cohorts. A total of 34 out of 42 participants completed the 12-week core treatment phase. Based on these interim analysis results, the Dose 2 (3 mg/kg q2w for Group A [≥30 kg and ≤60 kg] and 4 mg/kg q2w for Group B [≥10 kg and <30 kg]) was selected. All new participants subsequently enrolled in the study after the dose selection, were assigned to receive Dose 2. The participants initially enrolled in Dose 1 and Dose 3 subsequently had their dose regimen adjusted to the Dose 2 during the extension phase.

The summary of clinical efficacy provides efficacy data for the interim analysis that was performed one year from the time the last participant was enrolled in the study. All participants enrolled in the three sequential portions of the study were included in this interim analysis.

Protocol Amendments

- January 14, 2016: Amendment to Russian sites only.
- March 8, 2016: Amendment to Russian sites only.

- July 15, 2016: Amendment to French sites only.
- July 20, 2016: Amendment to German sites only.
- January 3, 2017: Amendment to German sites only.
- April 21, 2017: Amendment to Russian sites only.
- June 27, 2017: Protocol Amendment to all sites:
    - Modification of study design to implement the amended Pediatric Investigation Plan approved by the European Medicines Agency (EMA).
    - Updated the exclusion criteria to better define study population.
    - Incorporated several local protocol amendments that had already been approved, which addressed local health authorities (HAs) and/or Independent Review boards (IRBs) requests related to initial protocol. All but one of those local amendments remained applicable on a local basis.
- April 6, 2018: Amended Clinical Trial Protocol 1 all sites:
    - Modify the study design to implement the amended Paediatric Investigations Plan (PIP) approved by the EMA.
    - Updated the exclusion criteria section to better define the study population.
    - Incorporated several local protocol amendments that had already been approved, which addressed local health authorities (HAs) and/or Independent Review boards (IRBs) requests related to initial protocol. All but one of those local amendments remained applicable on a local basis.
- December 13, 2018: Amended Clinical Trial Protocol 2 all sites:
    - Updated stopping rules for Grade 4 neutropenia.
    - Updated Exclusion criterion 6 to add “dose stable for <2 weeks”.
    - Updated the term “parenteral” to “systemic parenteral (IV)”.
    - New section added to state that all assessments are standard assessments for evaluation of the drug in that population.
    - Cross-reference provided to Appendix G.
    - Grade 4 neutropenia without signs of infection removed from that list.

  - Protocol appendix updated to allow for sarilumab to be resumed in the event of Grade 4 neutropenia without infection.
  - Protocol appendix updated as per current standard of care for a patient enrolled in a clinical trial.

- September 12, 2019: Amended Clinical Trial Protocol 3 all sites:
  - The main purpose of this amendment is to enroll additional patients to receive the selected dose of sarilumab (3 mg/kg in patients ≥30 kg and 4 mg/kg in patients ≥10 to <30 kg) as per a health authority recommendation.
  - To address this recommendation, approximately 28 additional patients will be enrolled in the study in order to achieve a total of approximately 100 treated patients in the study.
  - The study will also streamline the study procedures for these additional patients, such as reduction in the number of blood draws for the pharmacokinetic (PK) assessment between Baseline and Week 2; safety monitoring during on-site visit every 3 months after Week 12; PK, anti-drug antibody, and efficacy assessments every 6 months after Week 12.
  - An interim analysis will be conducted once all patients have completed 1 year of treatment.
  - Other specifications applicable to the approximately 28 additional patients are detailed in the summary of changes.
  - To harmonize the term throughout the protocol, Dose Regimen refers to the dose administered to the patient and Dose Regimen Cohort refers to the patient group receiving the specified Dose Regimen.
- July 8, 2020: Amended to Italian sites only.

7.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

Financial Disclosure

The Applicant submitted the required financial disclosure forms for the 128 investigators involved with study DRI13925. Only one investigator disclosed a financial interest in the outcome of the study.

- b) (6) was a sub-investigator participating in DRI13925 who had received a total of $28,345 as honoraria for medical advisory board, customer interactions, general consulting and speaker program during the period that the study was conducted.

The Applicant certifies that the remaining 127 investigators had not entered into any financial arrangement with the Clinical Investigators whereby the value of compensation to the Clinical Investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that each Clinical Investigator was required to disclose whether they had a proprietary interest in the product or a significant equity in the Sponsor as defined in 21 CFR 54.2(b) and no single investigator disclosed any such interests. None of the investigators were full-time or part-time employee of the Applicant.

The overall contribution of subjects enrolled by b) (6) did not make a significant contribution to the outcome of the current study.

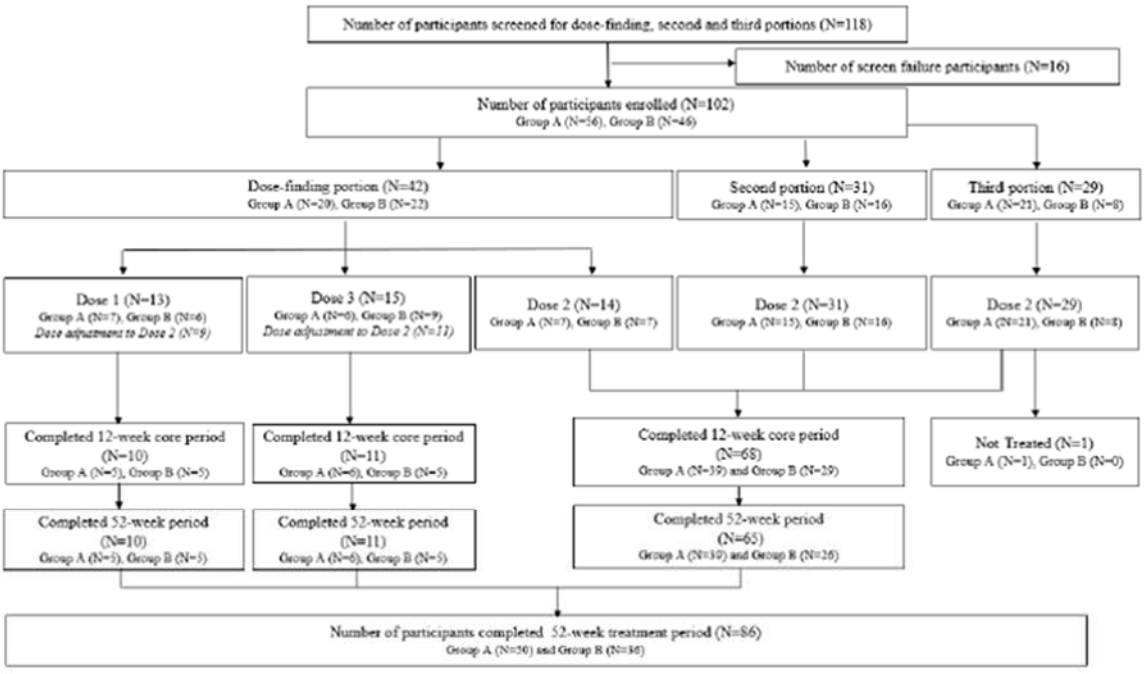
Patient Disposition

As shown in Figure 11, a total of 118 subjects were screened and 102 subjects were enrolled: 42 subjects in Portion 1, 31 subjects in Portion 2, and 29 subjects in Portion 3. Enrolled subjects were randomized at 29 sites located in 15 countries as follows: North America (n=3); Europe (n=55); Latin America (n=19); and rest of the world (n=25).

Of the 102 enrolled subjects, 101 were treated and 86 subjects completed at least 52 weeks of treatment. Among the 73 subjects who received Dose 2 from baseline, 68 (92% of subjects in Dose 2 group) completed the 12-week core treatment phase and 65 (88%) subjects completed the 52-week duration period. A total of eight subjects did not complete the first year of treatment with no notable difference among the weight groups (three and five subjects in Group A and B, respectively). Among those eight subjects, five subjects discontinued before Week 12 (Group A [n=3] and Group B [n=2]). The reasons for discontinuing were due to an AE (n=5), poor compliance (n=20 and one subject listed as “other”.

There were 20 subjects enrolled in Portion 1 who had their dose adjusted to Dose 2 during the extension phase: nine subjects with Dose 1 (Groups A [n=4]; Group B [n=5]) and 11 subjects with Dose 3 (Groups A [n=6]; Group B [n=5]).

Figure 11. Subject Disposition in DRI13925-Portions 1, 2, and 3



Group A [≥30 kg]; Group B [≥10 kg and <30 kg]; Source: Table 28 and DRI13925 1y3p, Appendix 16.2.1 [16.2.1.1.4]

Source: Applicant's Summary of Clinical Efficacy, page 39, Figure 7.

Baseline Demographic Characteristics

The demographic characteristics had similar distribution across the three doses within Group A and B. Overall, the majority of subjects were female (76%), White (87%) and from Europe (54%). The mean weight and age were 47 kg and 13 years in Group A and 20 kg and 5 years in Group B, respectively. The demographic characteristics were similar in subjects who have received Dose 2 since baseline with 58 (80%) female subjects, 67 (92%) White, and 37 (51%) from Europe, with a mean weight and age of 47 kg and 13 years in Group A and 20 kg and five years in Group B, respectively (data not shown).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Overall, the distribution of subjects with RF+ pJIA, RF- pJIA, and extended oJIA subtypes was 19%, 66%, and 15%, respectively without notable imbalance across the dose cohorts. The proportion of subjects with RF- pJIA was slightly lower in Group B (n=35 [76%]) compared to Group A (n=32 [58%]). There were approximately twice as many subjects with RF+ pJIA and twice as many subjects with extended-oJIA in Group A (n=13 [24%] and n=10 [18%], respectively) compared with Group B (n=6 [13%] and n=5 [11%], respectively), reflecting the age distribution of the disease. There were no notable differences across the dose cohorts for other disease characteristics.

In subjects who have received Dose 2 from baseline, the mean disease duration was 2.5 years (Group A, 3.1 years, and Group B, 1.7 years) again reflecting a longer disease duration proportional to the age of the subjects. The distribution of the disease subtypes per body weight group was similar to the overall population: 66%, 18% and 16% for RF- pJIA, RF+ pJIA, and extended oJIA, respectively. The median number of active joints for Group A was 17 (range: 5 to 46) and 11 (range: 5 to 40) for Group B.

In general, subjects entered the study with a high degree of inflammatory disease with baseline mean hs-CRP of 15 ± 37 mg/L. Group A subjects averaged a hs-CRP of 10 ± 21 mg/L and Group B subjects averaged a hs-CRP of 20 ± 51 mg/L. All subjects, as well as those subjects who have received Dose 2 since baseline, had a mean CHAQ-DI at baseline of 1.2 ± 1. Most subjects demonstrated a CHAQ-DI corresponding to a moderate to severe disability (52% and 26%, respectively).

Prior Concomitant Medications
Overall, 23% of subjects entered the study taking at least one bDMARD prior to enrollment in the study and approximately 85% of subjects were receiving a conventional synthetic DMARD (mainly methotrexate). A total of 20 (20%) of subjects were receiving systemic corticosteroids with a mean prednisolone equivalent dose of 0.2 mg/kg/day and 46% of subjects were treated with NSAIDs. Among the subjects who received Dose 2 since baseline, the proportion of those who received a prior bDMARD, conventional synthetic DMARD, or NSAIDs was similar to the overall population. The distribution of conventional DMARDs was higher in Group A (91%) than in Group B (77%). There was a slightly lower proportion of subjects who were receiving systemic glucocorticoids (14%) compared to the overall population with a greater number of subjects taking corticosteroids in Group A then Group B (19% vs. 7%, respectively).

Efficacy Results

Portion 1
All the three sarilumab dose regimens evaluated were demonstrated to be effective in improving the signs and symptoms of disease activity as defined by subjects achieving a JIA ACR30 response rate using the "as observed while on-treatment" approach of 100% at Week 12 in both body weight groups. However, using non-responder analyses demonstrated lower response rates for the three different cohorts in both body weight groups as shown in Table 7 with subjects in

Cohort 2 (Dose 2, i.e., 3 mg/kg Q2w or 4 mg/kg Q2w) achieving the highest JIA ACR30 response rates of 71% and 100%, respectively.

Table 7. Summary of JIA ACR Response Rates at Week 12-Efficacy Population-Portion 1

	As observed while on-treatment					Non-responder imputation approach[a]				
	JIA- ACR30	JIA- ACR50	JIA- ACR70	JIA- ACR90	JIA- ACR100	JIA- ACR30	JIA- ACR50	JIA- ACR70	JIA- ACR90	JIA- ACR100
Cohort 1 Group A	5/5 (100%)	4/5 (80.0%)	3/5 (60.0%)	3/5 (60.0%)	0/5	5/7 (71.4%)	4/7 (57.1%)	3/7 (42.9%)	3/7 (42.9%)	0/7
Cohort 1 Group B	5/5 (100%)	5/5 (100%)	2/5 (40.0%)	1/5 (20.0%)	0/5	5/6 (83.3%)	5/6 (83.3%)	2/6 (33.3%)	1/6 (16.7%)	0/6
Cohort 1 Total	**10/10 (100%)**	**9/10 (90.0%)**	**5/10 (50.0%)**	**4/10 (40.0%)**	**0/10**	**10/13 (76.9%)**	**9/13 (69.2%)**	**5/13 (38.5%)**	**4/13 (30.8%)**	**0/13**
Cohort 2 Group A	6/6 (100%)	5/6 (83.3%)	3/6 (50.0%)	2/6 (33.3%)	0/6	6/7 (85.7%)	5/7 (71.4%)	3/7 (42.9%)	2/7 (28.6%)	0/7
Cohort 2 Group B	7/7 (100%)	7/7 (100%)	5/7 (71.4%)	2/7 (28.6%)	2/7 (28.6%)	7/7 (100%)	7/7 (100%)	5/7 (71.4%)	2/7 (28.6%)	2/7 (28.6%)
Cohort 2 Total	**13/13 (100%)**	**12/13 (92.3%)**	**8/13 (61.5%)**	**4/13 (30.8%)**	**2/13 (15.4%)**	**13/14 (92.9%)**	**12/14 (85.7%)**	**8/14 (57.1%)**	**4/14 (28.6%)**	**2/14 (14.3%)**
Cohort 3 Group A	6/6 (100%)	6/6 (100%)	6/6 (100%)	4/6 (66.7%)	2/6 (33.3%)	6/6 (100%)	6/6 (100%)	6/6 (100%)	4/6 (66.7%)	2/6 (33.3%)
Cohort 3 Group B	5/5 (100%)	5/5 (100%)	5/5 (100%)	3/5 (60.0%)	2/5 (40.0%)	5/9 (55.6%)	5/9 (55.6%)	5/9 (55.6%)	3/9 (33.3%)	2/9 (22.2%)
Cohort 3 Total	**11/11 (100%)**	**11/11 (100%)**	**11/11 (100%)**	**7/11 (63.6%)**	**4/11 (36.4%)**	**11/15 (73.3%)**	**11/15 (73.3%)**	**11/15 (73.3%)**	**7/15 (46.7%)**	**4/15 (26.7%)**

a Discontinued patients are automatically considered as non responders at the visits after their discontinuation.

Source: Applicant's Summary of Clinical Efficacy, page 35, Table 11.

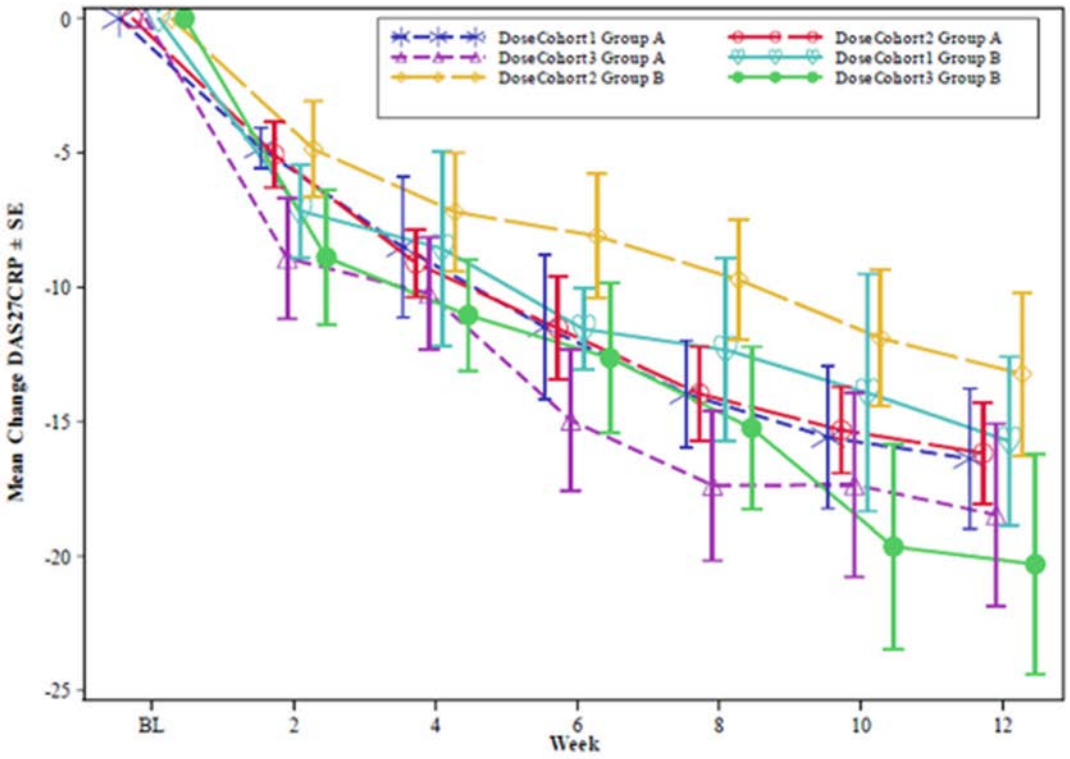
A dose-dependent effect was seen both on magnitude of response and on time to response when evaluated using other endpoints. At Week 12, as observed while on-treatment, the JIA ACR70 response rates were 50%, 62%, and 100% in Dose 1, 2, and 3, respectively. The JIA ACR30 response rates plateaued to 100% achievement within the first two months of sarilumab treatment for Dose 2 and 3. In Dose 1, the JIA ACR30 response rate fluctuated up to Week 12.

As calculated by a nonresponder imputation approach, 77%, 93%, and 73% of patients achieved JIA ACR30 in Doses 1, 2, and 3, respectively (Table X2). As calculated by LOCF approach, 85%, 100%, and 87% of patients achieved JIA ACR30 in Doses 1, 2, and 3, respectively.

Improvements were seen at Week 12 in all JIA ACR components, and 13 subjects completed Week 12 with no active arthritis with four subjects from receiving Doses 1 and 2, and five subjects receiving Dose 3 (data not shown). Overall, the CHAQ-DI scores and mean hs-CRP decreased for patients in all doses for both body weight groups throughout the 12-week core treatment phase.

The decrease in disease activity was seen in all dose and body weight groups as early as Week 2 with a mean change in JADAS-27 from baseline at Week 12 of -17, -15, and -20 in Dose 1, 2, and 3, respectively (Table 8).

Table 8. Change From Baseline in JADAS-27 (hs-CRP) Through Week 12-Efficacy Population-Portion 1.



# subjects							
Dose Cohort 1 Group A	7	7	6	6	6	6	5
Dose Cohort 2 Group A	7	7	7	7	6	5	6
Dose Cohort 3 Group A	6	6	6	6	6	6	6
Dose Cohort 1 Group B	6	6	6	6	6	6	6
Dose Cohort 2 Group B	7	7	7	7	7	6	6
Dose Cohort 3 Group B	9	9	9	9	8	6	6

Source: Applicant's Summary of Clinical Efficacy, page 36, Figure 5

Based on these data Dose 2 was selected for enrolling subsequent subjects in Portions 2 and 3 based on the demonstration of a more rapid and generally more pronounced improvement in signs and symptoms of pJIA in Dose 2 and Dose 3 compared to Dose 1, together with the comparative PK, PD and safety data. Dose 3 (weekly regimen) was considered not appropriate based on safety results which showed more events of neutropenia compared to the other two doses.

As per protocol, subjects enrolled in the subsequent Portions 2 and 3 of the study were treated with the selected Dose 2, i.e., 4 mg/kg Q2w in subjects weighing ≥10 kg to <30 kg and 3 mg/kg Q2w in subjects weighing 30 kg or more (capped at 200 mg Q2w).

Portions 1, 2, and 3

JIA ACR Response

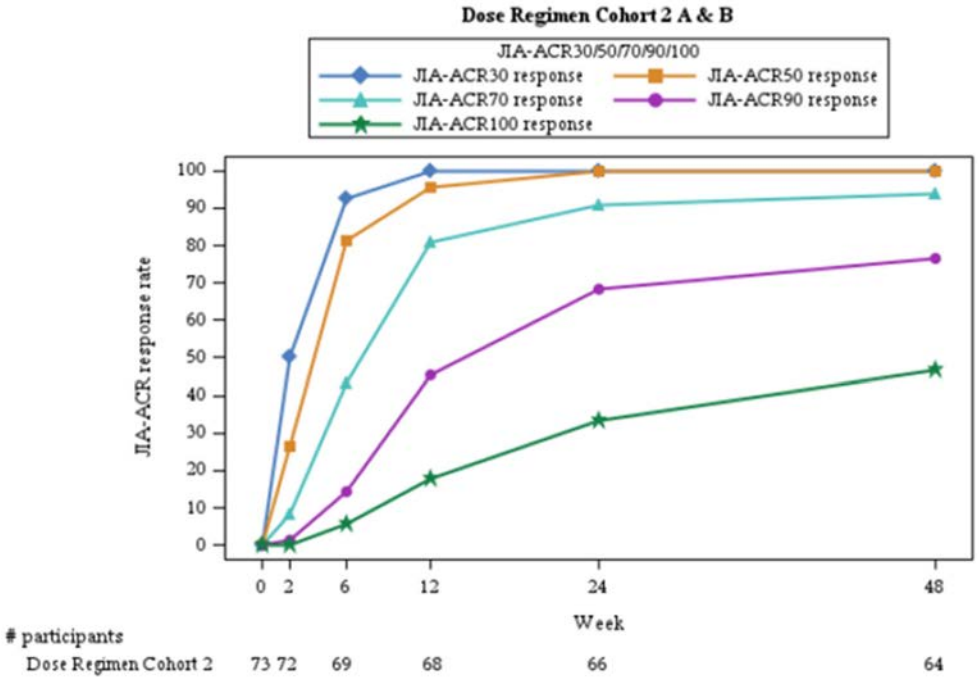
Using the as observed while on-treatment approach, Dose 2 showed a rapid effect in improving the signs and symptoms of pJIA as assessed by subjects achieving a JIA ACR30 response as early as Week 2 and plateauing at 100% from Week 12 onwards. Analyses using non-responder imputation and LOCF showed similar results at Week 12 and the JIA ACR responses continued (Table 9).

Table 9.Summary of JIA ACR Response at Week 12-Efficacy Population	**Dose 2 (N=73)**		
	Statistical Analyses		
JIA ACR Response	**As Observed**	**LOCF**	**Non-Responder Imputation**
JIA ACR30 (%)	100%	99%	93%
JIA ACR50 (%)	96%	95%	89%
JIA ACR70 (%)	81%	78%	75%
JIA ACR90 (%)	46%	43%	43%

Source: Applicant's Summary of Clinical Efficacy, page 50, Table 15. LOCF=last observation carried forward

As shown in Figure 12, the JIA ACR responses continued to improve throughout the review period up to Week 48 analyzed by observed while on treatment approach. The JIA ACR70 response rate was achieved in 81% at Week 12 and 95% at Week 48. Similarly, the JIA ACR90 and 100 response rates were achieved in 46% and 18% of subjects, respectively at Week 12 and in 77% and 47% of subjects, respectively, at Week 48, using the as observed while on-treatment analysis.

Figure 12. JIA ACR Response Rates for Subjects on Dose 2 Through Week 48- Periods 1, 2, and 3.



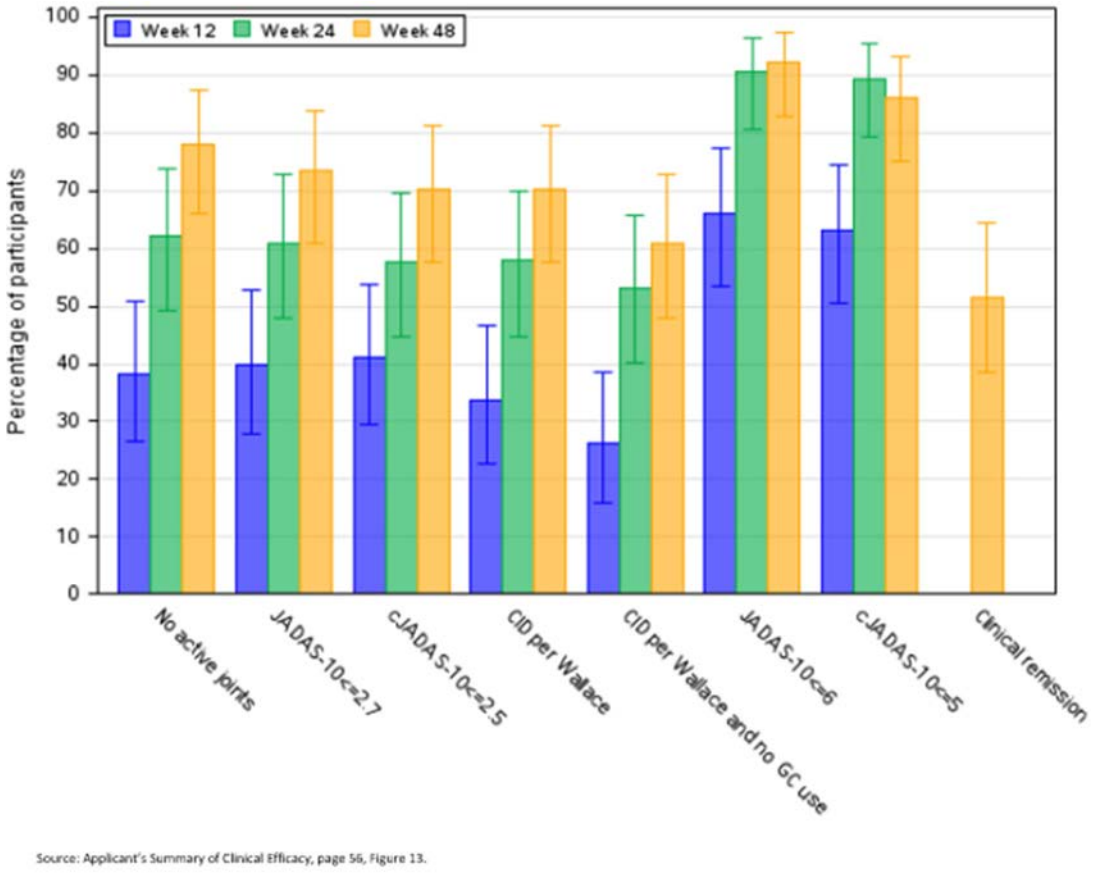
Source: Applicant's Summary of Clinical Efficacy, page 51, Figure 9. Note: subjects enrolled in the selected dose cohort from Portion 2 and 3 are combined with subjects from Portion 1 of the study.

Consistent with the JIA ACR responses, improvements were seen in all JIA ACR components throughout the treatment period with Dose 2. Similar results were observed in both body weight groups (data not shown). The CHAQ-DI decreased rapidly with a change from baseline of -0.8 at Week 12 and -1 at Week 48; no patients experienced worsening of their quality of life (defined by a change from baseline in CHAQ-DI ≥0.75) through Week 48 and the proportion of patients who experienced an improvement of disability (defined by a change from baseline in CHAQ-DI ≤0.13) reached 93% at Week 48. No difference based on body weight groups was observed. At Week 48, a total of 61% of subjects had clinically inactive disease without glucocorticoids use and 52% had low disease activity as defined as inactive disease for six consecutive months.

JADAS (hs-CRP)

Consistent with the JIA ACR response, a decrease in disease activity based on the change from baseline in JADAS-27 was observed as early as Week 2, which was the first efficacy assessment timepoint following the first injection. Mean changes from baseline of -18 at Week 12, -20 at Week 24, and -21 at Week 48 corresponding to a mean percent change from baseline of -78%, -89%, and -91%, respectively (Figure 13).

Figure 13.Histogram of Proportion of Subjects with Disease Activity Reduction Criteria at Week 12, 24, and 48 for Subjects Receiving Dose 2.



Source: Applicant's Summary of Clinical Efficacy, page 56, Figure 13.

At Week 12, a greater proportion of subjects in Group B (90%) compared to Group A (75%) reached a clinically significant improvement as assessed by achieving a JIA ACR70 response. This trend continued through Week 48 with 100% of Group B and 90% of Group A subjects achieving a JIA ACR70 response. Similarly, a great proportion of Group B subjects reported no active joints at Week 12 and Week 48, 48% and 92%, respectively, compared to Group A subjects, 31% and 68%, respectively. A plausible explanation for the differences between the groups may reflect the disease characteristics of Group A subjects representing more difficult to treat and a longer duration of disease compared to Group B subjects. Compared to Group B, Group A has approximately double the mean disease duration (3.1 versus 1.7 years), a greater proportion of subjects with RF+ pJIA, a lower proportion of subjects with extended oJIA, a greater proportion of subjects with concomitant use of glucocorticosteroids and conventional synthetic DMARD use, and a higher proportion of subjects who failed at least one prior bDMARD.

Subjects enrolled in Dose 1 or Dose 3 during Portion 1 who had their dose adjusted to

Dose 2

Prior to dose adjustment, subjects who were initially randomized to Dose 1 (n=13) required a longer time to achieve a clinically meaningful effect (JIA ACR70) compared with subjects treated with Dose 2 (n=73) at Week 12. At Week 24, the proportion of subjects achieving JIA ACR70 was higher but still less than subjects who were randomized to Dose 2, 80% vs. 91%, respectively.

Conversely, all subjects initially randomized to Dose 3 (n=15) attained a more rapid and sustained JIA ACR70 at Week 12 and Week 24 compared to either Dose 1 or Dose 2. Despite the apparent higher degree of efficacy, weekly dosing of Dose 3 resulted in a higher frequency of AEs including neutropenia and was therefore determined to be inappropriate from a risk-benefit perspective. There were no apparent changes in efficacy parameters for the 20 subjects who had their dose of sarilumab adjustment. However, given the low number of subjects, the results after dose adjustment need to be considered with caution.

Clinical Response After Dose Adjustment

All subjects randomized to Dose 1 and Dose 3 achieved a JIA ACR30/50/70 six weeks after being changed to Dose 2. No discernable changes in JIA ACR response rates were observed in subjects who switched from Dose 1 or Dose 3 to the selected Dose 2. These data suggest the efficacy of Dose 2 in comparison to the other dosing regimens. Furthermore, the change from baseline in JIA ACR components in subjects who were randomized to Dose 1 or 3 before dose adjustment remained stable up to 24 weeks after dose adjustment.

Similarly, the change from baseline up to Week 24 in JADAS-27 remained stable in all subjects who were randomized to receive Dose 1 or Dose 3 before dose adjustment. Additionally, the proportions of subjects with minimal or inactive disease activity characterized by JADAS-10 as well as the proportions of subjects with no active joints remained stable after dose adjustment in subjects initially enrolled in Dose 1 or Dose 3 and who switched to Dose 2.

Immunogenicity and Efficacy

There was an overall incidence of positive anti-drug antibodies (ADA) of approximately 4% and persistent ADA positivity reported at approximately 3% of subjects. Neutralizing antibodies were reported in three (3%) subjects. Analysis of the effect of positive ADA status did not demonstrate a lack or loss of efficacy in these subjects. Three positive ADA-subjects who were randomized to Dose 2 from baseline and had experienced an AE were JIA ACR30 responders at Week 12.

Dose Selection for Study DRI13925

Initial sarilumab dose regimens studied in DRI13925 study were selected based on efficacy and safety data of sarilumab in adult patients with RA and were further supported by PK simulations based on a population PK model derived from adult studies in RA patients. The dose regimens evaluated in the pediatric program were anticipated to achieve similar exposures in pJIA as observed with dose regimens that demonstrated efficacy and an acceptable safety profile in the adult RA program.

Dosing Data from Portion 1

Sarilumab exposure was similar between the two body weight groups for each of the three dose regimens. For each dose regimen, sarilumab was also generally similar to the corresponding adult dose regimen in RA patients. The PD biomarker effects and the JIA ACR response were lower in Dose 1 compared to the two other doses. The safety profile was as expected in this pediatric population based on the knowledge of the sarilumab adult program, with neutropenia and infections being the most frequently reported adverse events (Section 8).

Improvement in the signs and symptoms of pJIA was more rapid and generally more pronounced in Dose 2 and Dose 3 compared to Dose 1; however, the weekly dosing of Dose 3 led to more frequent Grade 3/4 neutropenias compared to the two other doses. Based on the results of the 12-week data from Portion 1 of the study, Dose 2 was chosen for the remaining subjects enrolling in Portions 2 and 3. This recommended dose regimen is the dose regimen that provided similar sarilumab exposure as the recommended dose regimen of 200 mg Q2w in adults with RA and is based on Week 12 efficacy and safety data seen in subjects enrolled in Portion 1.

Analysis of the one-year data supported that sarilumab exhibited nonlinear PK consistent with target-mediated drug disposition in subjects with pJIA. Following repeated subcutaneous administration, sarilumab concentrations increased in a greater than dose proportional manner and accumulated approximately five-fold over 48 weeks at Dose 2. After switching to Dose 2 in subjects who previously were on Dose 1 and Dose 3, observed sarilumab concentrations initially increased (Dose 1) or decreased (Dose 3), then reached the comparable level in subjects on Dose 2 after 12 weeks from the time of switching. For each dose cohort, the doses tested in Groups A and B achieved similar exposure.

The efficacy results presented here from the 73 subjects who have received Dose 2 since baseline in the three portions of the study demonstrated clinically meaningful improvements across all efficacy endpoints. Treatment effects were noted as early as Week 2 and continued to improve throughout the first year of the study. Furthermore, results of the PK-PD analyses (Section 6) are consistent with the evaluation of efficacy. The effect at Dose 2 was greater than Dose 1 for JIA ACR30/50/70 and there was a minimal difference between Dose 2 and Dose 3 except in the JIA ACR70 assessment. The PK-PD analyses also demonstrated a higher proportion of subjects achieving a JIA ACR response at Dose 2 compared to Dose 1, while the differences between Dose 3 and Dose 2 were similar in subjects with pJIA.

Efficacy Summary

The approval of sarilumab for the treatment of children with pJIA in the current submission is based on the PK comparability data between children with pJIA and adults with RA. The efficacy results reviewed here only serves as supportive data to the comparability PK data given that the study was conducted open-labeled, uncontrolled, and was not statistically rigorous. That said, the descriptive efficacy data of sarilumab administered subcutaneously every two weeks at the dose of 3 mg/kg and 4 mg/kg in patients weighing ≥30 kg and ≥10 kg to <30 kg, respectively, provides strong descriptive evidence to support the use of sarilumab in subjects with pJIA aged two years and older.

The study was designed with three portions. Portion 1 was a 12-week dose-finding study in which three doses were assessed in two body weight groups: Group A, subjects weighing 30 kg to <60 kg and Group B, ≥10 kg to <30 kg. Doses 1, 2 and 3 were defined to target PK exposures similar to the adult doses of 150 mg Q2w, 200 mg Q2w, and 150 mg Qw, respectively. Based on the aggregate PK, PD, efficacy and safety data from the 12-week period of Portion 1, Dose 2 was selected as the dose to be carried forward in a larger number of subjects in the subsequent Portions 2 and 3 in the two body weight groups.

At the time of the one-year interim analysis of Study DRI13925 performed one year after the last subject was enrolled, a total of 101 subjects with pJIA who were candidates for a bDMARD enrolled and treated with sarilumab in one of the three portions of the study (Portion 1, n=42; Portion 2 (n=28); Portion 3 n=31). Among the 73 subjects on Dose 2 since baseline, 65 (88%) completed the 52-week duration period, with no notable difference among the weight groups. The majority of subjects were female (80%) with a mean weight and age of 47 kg and 13 years of age in Group A and 20 kg and 5 years of age in Group B, respectively. The majority of subjects had RF- pJIA (66%) while 18% of subjects had RF+ pJIA. Baseline mean duration of JIA since diagnosis was 2.5 years, median number of active joints was 14.0, and baseline median JADAS-27 was 22, reflecting a long disease history proportionally to the age of the subject and a pediatric population with highly active disease. Also reflecting the difficulties in controlling the disease, there was a total of 14 (19%) subjects having failed at least one bDMARD prior to the study and a large proportion (85%) of subjects who entered the study were receiving a conventional synthetic DMARD. Additionally, 14% of subjects were receiving a systemic glucocorticoid.

Compared to Group B, Group A subjects had a longer disease duration (3.1 years compared to 1.7 years, respectively), a higher proportion of RF+ pJIA (24% compared to 10%) and of concomitant use of conventional synthetic DMARDs (91% compared to 77%). The median duration of study treatment was 675 days and the cumulative exposure to treatment was 155 PY.

In the 73 subjects assigned to dose regimen 2 from baseline, improvements in signs and symptoms as assessed by JIA ACR responses were seen as early as Week 2 reaching a JIA ACR70 response in 81% of subjects at Week 12 using the as observed while on treatment approach. Using the LOCF and non-responder approaches demonstrated that 78% and 75% of subjects achieved a JIA ACR70 at Week 12 with continued improvement up to Week 48 in both weight groups.

Achievement of JIA ACR70 was more rapid and pronounced in Group B compared to Group A at Week 12 and Week 48, 90% vs. 74% and 100% vs. 90%, respectively. Improvements were seen in all JIA ACR components. The proportion of subjects who experienced an improvement CHAQ-DI score reached 93% at Week 48 and none of the subjects worsened from baseline in CHAQ-DI up to Week 48. The efficacy results were consistent across all demographic and disease characteristics subgroups.

(b) (4)

7.2. Review of Safety

7.2.1. Safety Review Approach

Safety data in this review are presented based on two following methods of analysis:

- Data for the three dose regimens of sarilumab in 101 subjects for the 12−week core-treatment period, the 24−week treatment period and the 52−week treatment period. Data for the 12−week treatment period provide an overview of the safety profile of sarilumab at the first exposure to the three different doses of sarilumab. An overview of the safety profile of sarilumab over longer exposure periods to the three doses is provided with 24-week and 52-week treatment data. For this analysis, summary for the selected Dose 2 includes data from the 73 subjects who were treated with Dose 2 only (Dose 2 from baseline). Summaries for Dose 1 and Dose 3 include only data collected prior to the first dose adjustment to Dose 2, i.e., 12 weeks.
- Data with focus on the selected Dose 2 data with the analysis extended to the entire treatment period (up to the cut-off date of January 13, 2023. A total of 93 subjects who received at least one dose of Dose 2 during the entire treatment period. This combines the 73 subjects treated with Dose 2 from baseline and 20 subjects initially treated with one of the non-selected Doses, i.e., Dose 1 or Dose 3 and who had their dose adjusted to Dose 2. For these 20 subjects, the second analysis includes data collected after dose switching.

Both analyses include safety parameters for treatment-emergent adverse events (TEAEs), common TEAEs (≥5% in the combined Any Dose group), serious adverse events (SAEs), TEAEs leading to discontinuation, and adverse events of special interest (AESI).

To account for the differences in the exposure time across the three dose cohorts, exposure−adjusted analyses of the safety events are reported for the 52-week treatment period and the entire treatment period. Any differences between the two body weight groups are described. Specific analyses on selected safety events are discussed with a focus on severe neutropenia and infections, the two most frequent TEAEs based on the known safety profile of sarilumab in adult RA patients and the anticipated safety profile of IL-6 signaling inhibition.

Summaries of safety data are provided by time periods 0-12 weeks, 0-24 weeks, 0-52 weeks, and entire treatment period for the three dose cohorts. For the summaries of the 0-52 weeks treatment period and the entire treatment period, data on the non-selected doses (Dose 1 and Dose 3) only included those data collected prior to the dose-adjustment to the selected Dose 2. 'Any Dose' group include all the data collected for all the 101 treated subjects regardless of the dose adjustment. As a result, the data on Dose 1, Dose 2, and Dose 3 do not necessarily equal to the sum of the Any Dose group. Data is also summarized for the 73 subjects treated with Dose 2 from baseline and separately for the 20 subjects initially enrolled in Dose 1 and Dose 3 and who switched to the selected Dose 2.

7.2.2. Review of the Safety Database

Overall Exposure

12-week Treatment Period

The 12-week core-treatment period was completed by 89 of 101 (88%) subjects treated with sarilumab Any Dose, and 12 subjects (12%) discontinued treatment prior to Week 12. Among the 89 subjects treated, 10 subjects received Dose 1 (10 of 13 [77%]), 68 subjects received Dose 2 from baseline (68 of 73 subjects [93%]), and 11 subjects received Dose 3 (11 of 15 subjects [73%]).

24-week Treatment Period

The 24-week treatment period (6 months of treatment) was completed by 87 of 101 (86%) subjects and 14 subjects (14%) discontinued treatment. The 87 subjects included the same 10 subjects and 11 subjects who completed the 12−week core-treatment period in Dose 1 and Dose 3, respectively, and a total of 66 of 73 (90%) subjects in Dose 2 from baseline.

52-week Treatment Period

The 52-week treatment period was completed by 86 of 101 (84%) subjects with 15 subjects (15%) discontinuing prior to Week 52. The 86 subjects who completed the 52-week treatment period included 65 subjects (65 of 73 [89%] subjects) treated with Dose 2 from baseline, 10 subjects in Dose 1, and 11 subjects in Dose 3.

Entire Treatment Period

A total of 63 of 101 (62%) subjects completed the entire study treatment period (i.e., the total three years of the study in which data was collected. Among these subjects, 45 subjects (62%) were treated with Dose 2 from and 18 subjects switched from non-selected dose to the selected Dose 2. Fourteen (14%) subjects are still receiving treatment as of the data cut-off date.

Overall, the majority of discontinuations occurred during the first 12 weeks of exposure to sarilumab.

Among the 101 total subjects treated with sarilumab:

- 42 subjects were enrolled in Portion 1
    - 13 subjects were treated with Dose 1
    - 14 subjects were treated with Dose 2
    - 15 subjects were treated with Dose 3

The subjects who had Dose 1 or Dose 3 as ongoing treatment at the time of Dose 2 selection had their dose adjusted to the selected Dose 2. In total 20 subjects had their dose adjusted: Dose 1 had 9 of 13 subjects and Dose 3 had 11 of 15 subjects adjusted to Dose 2. Thirty-one subjects were enrolled to be treated with Dose 2 during the Portion 2 of the study and an additional 28 subjects were enrolled to be treated with Dose 2 during the Portion 3 of the study. A total of 73 subjects received Dose 2 from baseline and 93 subjects received at least a single dose of Dose 2. The cumulative exposure for all 101 treated subjects who received Any Dose of sarilumab during the entire treatment period was 214 patient years (PY). The cumulative exposure for Dose 2 from baseline was 155 PY versus 19 PY for Dose 1 and 11 PY for Dose 3. The median duration of study treatment for all 101 treated subjects who received Any Dose was 1078 days.

Dose 1
The median duration of study treatment for the 13 subjects receiving Dose 1 was 595 days. Three subjects discontinued treatment prior to Week 12 and the ten remaining subjects were treated with Dose 1 between 72 and 144 weeks. The switch to the selected Dose 2 occurred at the earliest at Week 84 and the longest duration of Dose 1 treatment was 840 days (120 weeks) for 2 subjects.

Dose 2
A total of 73 subjects were treated with Dose 2 from baseline with a median duration of treatment of 675 days. The 20 subjects who switched to Dose 2 from Dose 1 or Dose 3 had a median duration of treatment with Dose 2 of 505 days. Fifty-three subjects received Dose 2 for 672 days, which included 48 subjects in Dose from baseline and five subjects who had their dose adjusted. Thirty subjects who received Dose 2 from baseline were treated for 1092 days.

Dose 3
The median duration of study treatment for the 15 subjects receiving Dose 3 was 273 days. Four subjects discontinued treatment prior to Week 2 and subjects were treated between 24 and 96 weeks.

Summary of Extent of Exposure
The cumulative exposure for the 101 treated subjects who received Any Dose of sarilumab was 214 PY, and 155 PY for Dose 2 from baseline. The cumulative exposure for Dose 1 was 19 PY and 11 PY for subjects treated with Dose 3. Seventy-three subjects treated with Dose 2 from baseline had a median duration of treatment for 675 days and the 20 subjects who switched to Dose 2 from Dose 1 or Dose 3 had a median duration of treatment with Dose 2 of 505 days. Duration of treatment was different across the three dose cohorts. the median duration was 595 days for Dose 1, 273 days for Dose 3.

Adequacy of the safety database:

Overall, the data integrity and submission quality of the current application was adequate. The submission was complete, well-organized, easily navigable in electronic format and the data consistent between case report tabulations, case report forms and narrative summaries for individual subjects. Review of the study sites using the site selection tool did not identify any potential problems with safety reporting.

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

Integrated safety analyses and summaries for the pooled subject populations were based on the safety analysis sets for each dosing cohort as previously described and included all subjects who received at least one dose of study treatment. Subjects were analyzed by treatment received.

Descriptive summaries encompassed demographics, disposition, exposure to study medications, TEAEs, deaths, vital signs, and safety laboratory values. Exposure to study drug was assessed as number of days on treatment. All treatment-emergent adverse events from the study used in the integrated safety analysis were summarized using MedDRA (version 25.1). The integrated summaries defined any TEAE as any adverse event with onset on or after the first dose of study drug.

Integrated summaries of the incidence of TEAEs were prepared by System Organ Class (SOC) and Preferred Term (PT) using raw cumulative incidence rates and weighted incidence rates in proportion to the sample size of each study. In addition, exposure-adjusted incidence rates (EAIR) were calculated for certain groups of TEAEs as the number of subjects experiencing their first event divided by the total time at risk for all subjects in the treatment group and displayed as the number of events per 100 years of exposure. The difference (voclosporin minus placebo) between the EAIR and 95%.

Routine Clinical Tests

Routine clinical testing, including prespecified assessments of safety occurred at regular prespecified intervals coinciding with the timing of clinical assessments. Scheduled visits included physical exam, vital signs, ECG, laboratory assessments, urinalysis, adverse event assessment, concomitant medications, patient reported outcome measures, and study drug/concomitant medication dispensing.

Laboratory assessments included hematology, chemistry, hepatic function, lipid profile, and urinalysis performed at a central laboratory using standard validated methods.

In general, the prespecified routine safety assessment methods and time points used in the study were adequate and reasonable.

7.2.4. Safety Results

All Dose Cohorts During the 12-week, 24-week and 52-week Treatment Periods

12-week and 24-week Treatment Periods

In the combined Any Dose group, a total of 75 of 101 (74%) subjects during the 12-week treatment period and 81 of 101 (80%) subjects during the 24-week treatment period experienced at least one TEAE (Table 10 and Table 11).

Table 10. Overview of Adverse Event Profile During the 12-week Treatment Period-Safety Population

	Dose Regimen Cohort			
Weight Group n (%)	**Dose 1 (N=13)**	**Dose 2 (N=73)**	**Dose 3 (N=15)**	**Any Dose (N=101)**
All				
Number	13	73	15	101
TEAE	11 (85%)	51 (70%)	13 (87%)	75 (75%)
SAE	0	1 (1%)	0	1 (1%)
Deaths	0	0	0	0
TEAE leading to treatment discontinuation	2 (15%)	3 (4%)	3 (20%)	8 (8%)
≥30 kg				
Number	7	42	6	55
TEAE	7 (100%)	25 (60%)	4 (67%)	36 (66%)
SAE	0	0	0	0
Deaths	0	0	0	0
TEAE leading to treatment discontinuation	2 (29%)	1 (2%)	0	2 (6%)
<30 kg				
Number	6	31	9	46
TEAE	4 (67%)	26 (84%)	9 (100%)	39 (85%)
SAE	0	1 (3%)	0	1 (1%)
Deaths	0	0	0	0
TEAE leading to treatment discontinuation	0	2 (7%)	3 (33%)	5 (11%)

Source: Applicant's Summary of Clinical Safety, page 41, Table 5. TEAE=treatment emergent adverse event; SAE=serious adverse events.
Note: subjects enrolled in the selected dose regimen cohort from Portions 2 and 3 are combined with subjects enrolled in Dose 2 regimen cohort from the dose-finding portion of the study.

Table 11. Overview of Adverse Event Profile During the 24-week Treatment Period-Safety Population.

	Dose Regimen Cohort			
Weight Group n (%)	**Dose 1 (N=13)**	**Dose 2 (N=73)**	**Dose 3 (N=15)**	**Any Dose (N=101)**
All				
Number	13	73	15	101
TEAE	12 (92%)	56 (77%)	13 (87%)	81 (80%)
SAE	0	2 (3%)	0	2 (2%)
Deaths	0	0	0	0
TEAE leading to treatment discontinuation	2 (15%)	4 (6%)	3 (20%)	9 (9%)
≥30 kg				
Number	7	42	6	55
TEAE	7 (100%)	28 (67%)	4 (67%)	39 (71%)
SAE	0	1 (2%)	0	1 (1%)
Deaths	0	0	0	0
TEAE leading to treatment discontinuation	2 (29%)	1 (2%)	0	3 (6%)
<30 kg				
Number	6	31	9	46
TEAE	5 (83%)	28 (90%)	9 (100%)	42 (91%)
SAE	0	1 (3%)	0	1 (1%)
Deaths	0	0	0	0
TEAE leading to treatment discontinuation	0	3 (10%)	3 (33%)	6 (13%)

Source: Applicant's Summary of Clinical Safety, page 42, Table 6. TEAE=treatment emergent adverse event; SAE=serious adverse events.
Note: subjects enrolled in the selected dose regimen cohort from Portions 2 and 3 are combined with subjects enrolled in Dose 2 regimen cohort from the dose-finding portion of the study.

Among the three treatment doses, Dose 2 had the lowest percentage of subjects with TEAEs during the 12-week treatment period (70%) compared with Dose 1 (85%) and Dose 3 (87%). A similar trend was observed for the 24-week treatment period (77%, 92%, and 87%, respectively). For the 12-week and the 24-week treatment periods, a difference between the two body weight groups was observed in Dose 2 and Dose 3 with the Group B subjects reporting higher percentages of TEAEs compared to Group A subjects.

One subject in the Dose 2 Group B reported three SAEs (bone tuberculosis, pancreatic pseudocyst, pancreatitis acute) and one additional subject in the Dose 2 Group A reported an SAE of ligament rupture during the 24-week treatment period. Serious adverse events are discussed in more detail below.

TEAEs leading to treatment discontinuation were reported in 8 of 101 (8%) subjects during the 12-week treatment period and only one additional subject discontinued due to TEAEs in the 24-week treatment period. Dose 2 subjects discontinued treatment due to TEAE less frequently than subjects in the other two dosing regimens. TEAEs leading to treatment discontinuation are discussed in more detail below.

52-week Treatment Period

A majority (91/101 [90%]) of Any Dose subjects experienced at least on TEAE during the 52-week treatment period (data not shown). The exposure-adjusted event rate during the 52-week

treatment period was lower in Dose 2 (611/100 PY) compared to Dose 3 (855/100 PY). As observed for the 12-week and the 24-week treatment periods, Group B subjects enrolled to receive Dose 2 and Dose 3 reported higher percentages of TEAEs compared to Group A subjects. Subjects in Dose 1 all experienced a TEAE in the two body weight groups.

Serious adverse events were reported in six of 101 (6%) subjects with two subjects in Dose 1 and four subjects in Dose 2. No subjects in Dose 3 reported a SAE. The exposure-adjusted events rate for SAEs in Dose 2 (10/100 PY) was lower compared to Dose 1 subjects (19/100 PY). Serious adverse events are discussed in more detail below.

The percentage of subjects with TEAEs leading to treatment discontinuation in the 52-week treatment period was minimally larger compared to the 12-week and the 24-week treatment period with two additional subjects and one additional subject, respectively. Dose 2 subjects had a lower exposure-adjusted events rates for TEAE leading to treatment discontinuation (7/100 PY) compared to Dose 3 (30/100 PY) and Dose 1 (19/100 PY). Overall exposure-adjusted events rates for TEAE leading to treatment discontinuation in Group B subjects (18/100 PY) was higher compared to Group A subjects (6/100 PY). The exposure−adjusted events rates for TEAE leading to treatment discontinuation in Group B subjects on Dose 3 (71/100 PY) was higher compared to Group B subjects on Dose 2 (14/100 PY). TEAEs leading to treatment discontinuation are discussed in more detail below.

Dose 2 TEAEs for the Entire Study Period

An overview of TEAEs that occurred during the entire treatment period in the 93 subjects who received at least one dose of the selected Dose 2 (data not shown). No notable difference in terms of incidence, type, severity, and seriousness of TEAEs was observed in the 93 subjects compared to the 73 subjects who received Dose 2 from baseline.

A total of 89 of 93 (96%) subjects experienced at least one TEAE. The exposure-adjusted event rates for any TEAE were similar in subjects on Dose 2 from baseline (397/100 PY) and those who switched from Dose 1 to Dose 2 (356/100 PY) and from Dose 2 to Dose 3 (313/100 PY).

Serious adverse events were reported by six (7%) subjects and were all treated with Dose 2 from baseline. No subjects who switched to Dose 2 from one of the two other dosing regimens reported an SAE. No SAE was reported after Week 52.

The exposure-adjusted events rates of TEAE leading to treatment discontinuation calculated for the entire treatment period was 4/100 PY for the 73 subjects on Dose 2 from baseline and was 4/100 PY for the 93 subjects who received at least one dose of Dose 2. For the subjects in Dose 2 from baseline, the exposure-adjusted events rate for the entire treatment period (4/100 PY) was lower than that at 52-weeks of treatment (7/100 PY) and this reflects the finding that only two additional subjects discontinued treatment due to TEAE after Week 52.

Common TEAEs

Common TEAEs were defined as TEAEs with incidence ≥5.0% at Preferred Term (PT) level in the combined Any Dose Group (all 101 treated subjects evaluated).

The most frequently reported System Organ Class (SOC) during the 12-week, 24-week, and the 52-week treatment periods were Infections and Infestations and Blood and Lymphatic System Disorders. For the exposure periods longer than 12 weeks (24-week, 52-week, and entire treatment period), Gastrointestinal Disorders and General Disorders and Administration Site Conditions were also among the most frequently reported SOCs.

The most frequent Preferred Terms in all the three doses were neutropenia and nasopharyngitis across all the evaluated treatment periods with higher incidences observed in the longer treatment periods. The exposure-adjusted event rates for both neutropenia and nasopharyngitis for the 52-week treatment period were lower for Dose 2 compared to Dose 3. Both neutropenia and nasopharyngitis were reported with higher incidence in Group B subjects compared to Group A subjects. Upper respiratory infection was the third most frequently reported Preferred Term in the three doses, and it was less frequently reported in Dose 2 subjects compared to subjects in the two other dosing regimens.

All Dose Cohorts - 12-week, 24-week and 52-week Treatment Periods

12-week and 24-week Treatment Periods

During the 12-week and 24-week treatment periods, the most common SOCs were the same for both periods: Infections and Infestations (51% and 63%, respectively) and Blood and Lymphatic System Disorders (25% and 31%, respectively). For both SOCs, Dose 2 subjects reported lower percentages of TEAEs compared to Dose 3.

At the Preferred Term level, the most frequent TEAEs reported in ≥5.0% of subjects in Any Dose group in both the 12-week and 24-week treatment groups were:

- Neutropenia: 22% in the 12-week period and 27% in the 24-week period.
- Nasopharyngitis: 16% in the 12-week period and 25% in the 24-week period.
- Upper respiratory tract infections: 9% in the 12-week period and 13% in the 24-week period.

For the two treatment periods, Dose 2 subjects reported lower percentage of neutropenia compared to Dose 3 subjects. In Dose 2, Group B subjects had higher percentages of both neutropenia and nasopharyngitis compared to Group A.

For the 12-week and 24-week treatment periods, the third most frequently reported Preferred Term was upper respiratory tract infection and was reported with lower incidence in subjects treated with Dose 2 4% and 8%, respectively) compared to either Dose 1 (31 % and 31%, respectively) or Dose 3 (13% and 20%, respectively). Upper respiratory tract infection was reported more frequent in Group A compared to Group B, in all dose groups.

TEAEs in the SOC Gastrointestinal Disorders occurred with a similar percentage in Group A (22%) and Group B (22%) during the 12-week treatment period and in higher percentages of subjects in Group B (33%) compared to Group A (26%) during the 24−week treatment period. However, the most frequent Preferred Terms were different depending on the specific body weight group, e.g., diarrhea was the most frequent TEAES in Group B while Group A reported nausea, abdominal pain, and vomiting.

52-week Treatment Period

The most common TEAEs reported in the three doses during the 52-week treatment period were consistent with those described for the 12-week and 24-week treatment periods with increased incidences. The most frequently represented SOCs in the combined Any Dose group were Infections and Infestations (75%), Blood and Lymphatic System Disorders (35%), and Gastrointestinal Disorders (32%). General Disorders and Administration Site Conditions were reported in 21% of subjects.

During the 52-week treatment period, additional Preferred Terms, that could be categorized as "upper respiratory tract infections" (i.e., rhinitis, bronchitis, and viral upper tract respiratory infection) were observed to be more frequent in Group B compared to Group A subjects. This finding is expected as they represent common conditions in the younger pediatric population. For the two most frequent Preferred terms, neutropenia and nasopharyngitis, Dose 2 subjects reported lower percentages compared to Dose 3. In Dose 2, Group B subjects had higher percentages of both Preferred Terms compared to Group A.

The third most frequent Preferred Term, upper respiratory tract infection was reported with lower incidence in Dose 2 compared to the other dosing regimens. The exposure-adjusted event rates were 16/100 PY in Dose 2 versus 62/100 PY in Dose 1 and 49/100 PY in Dose 3. Upper respiratory infection was reported more frequently in Group A subjects compared to Group B subjects across all three doses.

Dose 2-Entire Study

Analysis of the most frequent TEAEs during the entire treatment period for the 93 subjects who received at least a single dose of Dose 2 was similar to those described for the 52-week treatment period for the 73 subjects treated with Dose 2 from baseline.

In the 93 subjects treated with at least one dose of Dose 2 during the entire treatment period, the most frequently reported SOCs were Infections and Infestations (81%), Blood and Lymphatic System Disorders (37%), Gastrointestinal Disorders (33%), and General Disorders and Administration Site Conditions (23%).

At the Preferred Term level, the most frequently reported TEAEs were nasopharyngitis (37%; 29% in Group A and 46% in Group B). The exposure-adjusted event rate for the 93 subjects who received at least one dose of Dose 2 was 36/100 PY.

A higher frequency of the following SOCs was reported in Group B subjects compared to Group A subjects: Infections and Infestations (75% in Group A and 88% in Group B), Blood and Lymphatic System Disorders (27% in Group A and 49% in Group B), Gastrointestinal Disorders (25% in Group A and 44% in Group B), and General Disorders and Administration Site Conditions (17% in Group A and 29% in Group B).

At the Preferred Term level, nasopharyngitis and neutropenia were reported more frequently in Group B subjects compared to Group A subjects. Other frequently occurring TEAEs at the Preferred Term level with differences between body weight groups include upper respiratory tract infection (17% in Group A and 10 % in Group B), pharyngitis (12% in Group A and 7% in Group B), rhinitis (8% in Group A and 15% in Group B and), gastroenteritis (8% in Group A and 20% in Group B), vomiting (4% in Group A and 17% in Group B). Conditions such as nasopharyngitis, upper/lower respiratory tract infections, and gastrointestinal infections are common in the general pediatric population.

Severity of the TEAEs

All the reported TEAEs for the three dose group were mild or moderate in severity with the exception of the SAEs which are described above.

Deaths

No deaths were reported during Study DRI13925.

Serious Adverse Events

During the 52-week treatment period, a total of nine SAEs were reported in six subjects, four subjects receiving Dose 2 and two subjects receiving Dose 1. Each SAE term was only reported once. The exposure-adjusted events rate for SAEs in Dose 2 (10/100 PYs) was lower compared to subject treated with Dose 1 (19/100 PY).

Four subjects treated with Dose 2 reported seven SAEs. All four subjects received Dose 2 from baseline.

- Subject (b) (6) was enrolled in Group B and reported three SAEs, bone tuberculosis, pancreatic pseudocyst, and pancreatitis acute. The bone tuberculosis event occurred on Day 3. Treatment discontinuation occurred after 14 days of treatment with only a single sarilumab dose administered. One month later, the subject was diagnosed with acute pancreatitis followed one month later with a pancreatitis pseudocyst.

- Subject (b) (6) was enrolled in Group A and reported a ligament rupture and meniscus injury.

- Subject (b) (6) was enrolled in Group B and reported an inguinal hernia.

- Subject (b) (6) was enrolled in Group B and reported a case of tonsillar hypertrophy.

Two subjects receiving Dose 1 reported two SAEs.

- Subject (b) (6) was enrolled in Group B and reported a case of infectious mononucleosis.

- Subject (b) (6) was enrolled in Group A and reported a single case of syncope.

Two additional subjects reported a SAE following the 52-week treatment period.

- Subject (b) (6) was enrolled in Group A and reported a case acute sinusitis.

- Subject (b) (6) was enrolled in Group A and reported an event of worsening juvenile idiopathic arthritis.

The majority of the reported SAEs are consistent with childhood disorders including tonsillar hypertrophy, infectious mononucleosis, and worsening JIA. Given the mechanism of action of sarilumab, it is unlikely that ligament rupture with meniscal tear and inguinal hernia are directly related to therapy; however, the case of acute sinusitis may be related to sarilumab-related immunosuppression. The etiologies of the two remaining SAEs are unknown.

Dropouts and/or Discontinuations Due to Adverse Effects

Overall, treatment discontinuation due to TEAEs mostly occurred due to neutropenia, which was observed for all three dose cohorts and during all treatment periods.

12-week Core- and 24-week Treatment Period

A total of eight of 101 (8%) treated subjects, experienced a TEAEs leading to treatment discontinuation during the 12-week core-treatment period and one additional subject discontinued due to TEAE during the 24-week treatment period.

52-week Treatment Period

One additional subject discontinued treatment due to TEAE during remainder of the study for a total 10 of 101 (10%) subjects in the combined Any Dose group through the 52-week treatment period. These data suggest that treatment discontinuation due to TEAEs predominantly occurred during the first 12-weeks of exposure to sarilumab.

The exposure-adjusted event rate for TEAEs leading to treatment discontinuation was lower in Dose 2 (7/100 PY) compared to Dose 1 (19/100 PY) and Dose 3 30/100 PY). Of the 10 subjects who discontinued treatment due to TEAEs, seven subjects were in Group B (Dose 2, n=4; Dose 3, n=3) and three subjects were in Group A (Dose 1, n=2; Dose 2, n=1).

Eight of the 10 subjects who discontinued study treatment was due to neutropenia. Exposure-adjusted rate of neutropenia leading to treatment discontinuation was lower in Dose 2 (56/100

PY) compared to Dose 3 (30/100 PY) and Dose 1 (10/100 PY). The TEAEs leading to treatment discontinuation are as follows:

- Neutropenia (n=8):
  - Dose 1 (n=1). Subject was enrolled in Group A and discontinued after 14 days of drug exposure.
  - Dose 2 (n=4). One subject was enrolled in Group A and discontinued after 14 days of drug exposure and three subjects in Group B were discontinued after 14 days, 16 weeks and 50 weeks of drug exposure.
  - Dose 3 (n=3). All three subjects were enrolled in Group B to receive the Dose 3 regimen. All subjects discontinued after seven days of drug exposure.
- Bone tuberculosis (n=1)
  - Subject was enrolled in Group B to receive Dose 2. As discussed above, the event was serious and occurred at Day 3. Treatment discontinuation occurred after 14 days of treatment.
- ALT increased (n=1)
  - Subject was randomized to Dose 1 and enrolled in Group A. The subject discontinued treatment after 42 days of treatment and did not show any signs or symptoms of clinically evident hepatic injury and bilirubin was within normal ranges during the entire study period. Transaminasemia is a known adverse reaction of anti-IL-6 treatment.

Four additional subjects discontinued treatment due to TEAEs following the 52-week treatment period. One subject discontinued treatment due to neutropenia (Dose 2, Group B) after 72 weeks of treatment; two subjects reported ALT elevation (Dose 2, Group B and Dose 1, Group A), and one subject with cystitis who discontinued treatment after 86 weeks.

Therefore, the total number of subjects who experienced TEAEs leading to treatment discontinuation throughout the entire study was 14 subjects. The exposure-adjusted event rates for TEAEs leading to treatment discontinuation during the entire treatment period were 4/100 PY in Dose 2 versus 25/100 PY in Dose 3 and 15/100 PY in Dose 1.

Significant Adverse Events

Hypersensitivity

During the 52-week treatment period, hypersensitivity was reported by 12 of 101 (12%) subjects in the combined Any Dose group. Dose 1 reported two of 13 (15%) subjects; Dose 2 reported six of 73 (8%) subjects; and Dose 3 reported four of 15 (27%) subjects with hypersensitivity. The most frequently reported Preferred Term was rhinitis allergic in five of 101 (5%) subjects in the combined Any Dose group.

Nineteen (20%) of the 93 subjects in the Dose 2 cohort reported hypersensitivity. Thirteen were treated with Dose 2 from baseline and six subjects had their dose adjusted from either Dose 1 or

Dose 3. The most frequently reported hypersensitivity events were rash (n=4), dermatitis allergic (n=3), rhinitis allergic (n=3).

COVID-19

During the 52-week treatment period, COVID-19 was reported by 2 of 101 (2%) subjects in the combined Any Dose group. Both subjects were from the Dose 2 from baseline cohort with one subject from each body weight group. A total of nine of 93 (10%) subjects from the Dose 2 from baseline group reported COVID-19.

Elevations in Lipids

During the 52-week treatment period, blood triglycerides elevated was reported by 3 of 101 (3%) subjects in the combined Any Dose group. The subjects were all in the Dose 2 cohorts from baseline. Events in all the subjects were reported as mild in intensity. Increases above upper limit of normal (ULN) were minimal and study treatment was not adjusted.

Local Tolerability

During the course of the study, subjects were observed for a minimum of 30 minutes after each sarilumab dose administration either on site or at home and any local reactions were noted in the diary regardless of being clinically significant. Investigators evaluated each local reaction and reported them as AEs according to protocol instructions for AE reporting.

During the 52-week treatment period, 15 of 101 (145%) subjects in the combined Any Dose group had reported injection site reactions. Subjects in Dose 1 reported one (13) subject, Dose 2 reported 12 of 73 (16%) subjects, and Dose 3 reported two (13%) subjects. The most frequently reported Preferred Term was injection site erythema that occurred in nine of the 15 subjects. All the events were reported as mild or moderate in severity. There were no notable observed differences between the two body weight groups in the incidence or type of reported Preferred Term in any of the treatment periods. All the injection site reactions were of mild intensity and were transient in nature with the majority resolving within 24 hours.

In the Dose 2 cohort, during the entire treatment period, 13 of 93 (14%) subjects treated with at least one dose of the selected Dose 2 regimen experience injection site reactions. All 13 subjects were treated with Dose 2 from baseline. No subjects reported injection site reactions following adjustment to Dose 2 from either Dose 1 or Dose 3. The most frequently reported Preferred Term was injection site erythema and all reported events were reported as mild or moderate in severity. There were no notable observed differences between the two body weight groups.

Adverse Reactions and Treatment Emergent Adverse Events

Adverse drug reactions are defined as undesirable effects that are reasonably associated with the use of a drug and may occur as part of the pharmacological action of the drug or may be unpredictable in their occurrence. This does not include all events observed during the use of a drug however, only those events for which there is a reasonable possibility of a causal relationship between the study drug and its occurrence.

Sarilumab is approved for treatment of patients with RA and polymyalgia rheumatica (PMR). It is reasonable to assume that ADRs associated with sarilumab in patients with RA are also expected to be applicable to patients with pJIA. Per the current KEVZARA labelling, serious ADRs that have occurred in the adult RA and PMR population include infections, laboratory abnormalities (most notably neutropenia), gastrointestinal perforation, and hypersensitivity reactions. Common ADRs include neutropenia, ALT increased, injection site erythema, injection site pruritus, upper respiratory tract infection, urinary tract infection, hypertriglyceridemia, and leukopenia.

All TEAEs from the current study in the 73 subjects treated with the Dose 2 from baseline were evaluated to confirm whether the ADRs seen in the RA subjects also occurred in the pJIA subjects treated with sarilumab and identify any additional ADRs. Additional assessment was performed for the 20 subjects who had their dose adjusted from Dose 1 or Dose 3 to Dose 2. In this review, ADRs were determined by a sequential process, initially by applying a threshold as the objective criteria, followed by clinical assessment to determine if a reasonable relationship could be established. A TEAE that did not meet the threshold could also be identified for additional review based on clinical relevance and medical judgement. Clinical assessment for ADRs focused on the following considerations: a plausible mechanism of action; presence of confounders and/or alternative explanation; a plausible dose/exposure relationship; and consistency of evidence across studies and subject groups.

Potential events for ADR consideration were identified from TEAEs based on the criteria that TEAEs occurred in ≥4% of the 73 subjects treated with Dose 2 of sarilumab from baseline, which equates to a minimum of three subjects. All events analyzed that could potentially be an ADR were nonserious since SAEs occurred as single events, SAEs would not meet the ADR criteria.
The event terms of neutropenia, injection site reactions, ALT increased, upper respiratory tract infection, and nasopharyngitis are already identified as ADRs for the RA indication; however, other AEs are reviewed here for completeness and identification of potential differences between the RA and pJIA populations. The following analysis reviews all TEAEs that occurred ≥4% of children enrolled in the current study but not all events met criteria to be classified as an ADR.

Nasopharyngitis

Nasopharyngitis is currently a listed ADR as one of the most commonly reported infections in the adult RA population. - For the ADR selection purposes, this term includes two Preferred Terms “nasopharyngitis” and “pharyngitis”. These two Preferred Terms are subsequently discussed as the clinical term nasopharyngitis. In the current study, nasopharyngitis was reported in 34 of 73 (47%) of subjects, of which 18 (53%) subjects were in Group B and 16 (47%) were in Group A. The majority of events (70%) were reported as mild in severity with the remaining subjects were reported as moderate. All observed events were reported as nonserious, and all recovered within a median duration of seven days. An additional eight subjects had nasopharyngitis after dose adjustment for a total of 42 of 93 (45%) subjects. No notable difference was observed in severity, seriousness, latency, or outcome between subjects treated with Dose 2 from baseline and subjects who had their dose adjusted to Dose 2.

Neutropenia

The IL-6 inhibitor-induced reduction of neutrophils is believed to be primarily due to margination into rapidly mobilizable noncirculating pools and not from myelotoxicity. Though IL-6 inhibitors have been shown to reduce circulating neutrophils, neutrophil functional capacity remained with intact respiratory burst and phagocytic activity[2]. This supports the current observation that infections have not been correlated with neutropenia. As a consequence of this pharmacodynamic effect, neutropenia is observed with sarilumab and is currently listed as an ADR.

For ADR selection purposes, the term neutropenia two Preferred Terms "neutropenia" and "neutrophil count decreased". In the current study, neutropenia was reported in 30 of 73 (41%) subjects treated with Dose 2 from baseline. Overall, the exposure-response relationship of absolute neutrophil count (ANC) in patients with RA showed a consistent trend of a greater ANC reduction with an increase in sarilumab serum concentration. In this study, the mean ANC level and ANC change from baseline increased with increasing sarilumab C_{trough} with the effect approaching a plateau over concentration ranges of the medium to high tertile of sarilumab following the 3 mg/kg and 4 mg/kg Q2w dosing regimen in subjects with pJIA. As in previous sarilumab studies, neutropenia in the pJIA study was not associated with an increased risk of infection.

An additional four subjects reported neutropenia after dose adjustment from Dose 1 and Dose 3 for a total of 34 of 93 (37%). In addition, neutropenia mostly occurred during the first weeks of exposure to sarilumab. No notable difference was observed in severity, seriousness, latency, and outcome between subjects treated with Dose 2 from baseline and subjects who had dose adjustment to Dose 2.

<u>Upper Respiratory Tract Infection</u>

Upper respiratory tract infection is currently a listed ADR in the adult RA population. For the ADR selection purposes, this term includes two Preferred Terms "upper respiratory tract infection" and "viral upper respiratory tract infection". In the current study, upper respiratory tract infection was reported in 12 of 73 (16%) subjects. All events were reported as mild in severity, nonserious, and all subjects recovered within a median duration of eight days.

- Upper respiratory tract infections are one of the most common infections in this study population. An additional five subjects reported upper respiratory tract infection after dose adjustment for a total of 17 of 93 (18%) subjects. No notable difference was observed in severity, seriousness, latency, and outcome between subjects treated with Dose 2 from baseline and subjects who their dose adjusted to Dose 2.

<u>Injection Site Reactions</u>

Injection site pruritus is currently a listed ADR with the majority of cases reported to be mild in severity. As sarilumab is administered subcutaneously, an injection site reaction would not be

[2] Lok LSC, Farahi N, Juss JK et al. Rheumatology. 2017;56(4):541-9

unexpected with the administration of an exogenous protein. For the ADR selection purposes, this term includes all Preferred Terms under the High-Level Term "Injection site reactions", which includes Injection site erythema, Injection site pruritus, Injection site swelling, Injection site bruising, Injection site inflammation, Injection site reaction, Injection site urticaria, and Injection site warmth.

In the current study, all injection site reaction Preferred Terms were reported in 13 of 73 (18%) subjects in the Dose 2 from baseline population the majority (84%) of which were mild in severity. The most commonly reported injection site reactions were injection site erythema and injection site pruritus. All events occurred in the subjects treated with Dose 2 from baseline; no events occurred after dose adjustment.

ALT Increased

ALT increased is currently listed as a potentially serious ADR for sarilumab. IL-6R blockade in the RA program had been associated with an increase in liver transaminases. This association was more prevalent in studies in which sarilumab was used concomitantly with methotrexate.
In the current study, TEAEs of ALT increased were reported in seven of 73 (10%) subjects receiving Dose 2 from baseline. All events were reported as mild in severity and all subjects were treated with concomitant methotrexate at the time of event.

Review of laboratory abnormalities identified one patient with any potentially clinically significant abnormalities for transaminases (defined as >5x and ≤10x ULN). For bilirubin, there were four such cases with three subjects reporting a bilirubin >1.3 ULN, and one subject with bilirubin >2 ULN. There were no subjects who reported an ALT increase > 3 and bilirubin >2 ULN. No cases meeting Hy's law were identified. No significant transaminase elevations were seen in sarilumab-treated subjects with and transaminase elevations did not lead to clinically evident hepatic injury.

An additional two subjects had ALT increased after dose adjustment for a total of nine of 93 (10%) of subjects. No notable difference was observed in severity, seriousness, latency, and outcome between subjects treated with Dose 2 from baseline and subjects who had their dose adjusted to Dose 2

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Gastroenteritis

In the current study, gastroenteritis was reported in 12 of 73 (16%) subjects in the Dose 2 from baseline population. All events were reported in subjects who were treated with Dose 2 from baseline. No events occurred in any subject after dose adjustment. All observed events were reported as nonserious and all recovered within a median duration of two days. The majority of events were mild, while a minority of events reported as moderate in severity. Gastroenteritis events occurred in eight of 12 (67%) subjects in weight Group B and in four of 12 (33%) subjects in weight Group A.

As gastroenteritis is generally a nonspecific finding with no specific mechanism to establish a relationship, the currently available data do not support the inclusion of gastroenteritis as an ADR.

Abdominal Pain

For ADR selection purposes, the Abdominal pain term includes the two Preferred Terms "abdominal pain" and "abdominal pain upper". In the current study, abdominal pain was reported in 10 of 73 (14%) subjects in the Dose 2 from baseline population. Half of all abdominal pain events were mild in severity and the other half were reported as moderate in severity. All events occurred in the subjects treated with Dose 2 from baseline and no events occurred in any subject after dose adjustment. Abdominal pain events occurred in three subjects in Group B and seven subjects enrolled in Group A. The median time to onset from first sarilumab injection to first episode of event was 101 days. In nine of the subjects, the event was only reported once. All observed events were reported as nonserious, and all subjects recovered within a median duration of six days. No clear association with sarilumab was identified and events were usually an isolated AE.

Otitis Media

For ADR selection purposes, this term includes the two Preferred Terms of "otitis media" and "otitis media acute". In the current study, otitis media was reported in nine of 73 (12%) subjects in the Dose 2 from baseline population. The majority of events were reported as mild in severity, while rest were moderate in severity. Otitis media events occurred in six subjects enrolled in Group B and three subject in Group A. The median age of patients with otitis media was four years old. All observed events were reported as nonserious, and all recovered within a median of seven days.

An additional subject reported a case of otitis media after dose adjustment. No notable differences were observed in severity, seriousness, latency and outcome between subjects treated with Dose 2 from baseline and the subject who had their dose adjusted to Dose 2. Event of otitis media was usually an isolated adverse event.

Bronchitis

In the current study, bronchitis was reported in seven of 73 (10%) subjects in the Dose 2 from baseline population. The majority of events were mild while rest were reported as moderate in severity. All events occurred in the subjects treated with Dose 2 from baseline and no events occurred in any subject who had their dose adjusted. Bronchitis occurred in three subjects in Group B and four subjects in Group A. The median age of subjects was 10 years old. All observed events were reported as nonserious, and all recovered within a median duration of nine days. In one case, bronchitis occurred in the setting of rhinitis allergic, and an additional case was reported in conjunction of upper respiratory tract infection and rhinitis.

Rhinitis

In the current study, rhinitis was reported in seven of 73 (10%) subjects from the Dose 2 from baseline population that included three subjects in Group B and four subjects in Group A. The

median age of patients with rhinitis was 11 years old. The majority of events were mild and the remainder were reported as moderate in severity. All observed cases were reported as nonserious with subjects recovering within a median of seven days.

Diarrhea

In the current study, diarrhea was reported in seven of 73 (10%) subjects in the Dose 2 from baseline population and were reported as mild to moderate in severity. Diarrhea occurred in four subjects in Group B and three subjects in Group A. All observed events of diarrhea were nonserious, and all recovered with median duration of three days. One additional subject had diarrhea after dose adjustment. No notable difference was observed regarding severity, seriousness, latency, and outcome between subjects treated with Dose 2 from baseline and the subject who had their dose adjusted to Dose 2.

Mouth Ulceration

For ADR selection purposes, this term includes two Preferred terms “mouth ulceration” and “aphthous ulcer”. In the current study, mouth ulceration was reported in six of 73 (8%) subjects with all events reported as mild in severity. Mouth ulceration events occurred in three subjects in Group B and three subjects in Group A. All events were reported as nonserious and all recovered within a median of 18 days.

An additional subject reported a mouth ulceration event after dose adjustment. No notable difference was observed in severity, seriousness, latency, and outcome between subjects treated with Dose 2 from baseline and the subject who had dose adjustment to Dose 2.

Eosinophil Count Increased

In the current study, eosinophil count increased was reported in six of 73 (8%) subjects in the Dose 2 from baseline population. All events occurred in the subjects treated with Dose 2 from baseline and all were reported as mild in severity. No events occurred in any subject after dose adjustment. All cases of eosinophil count increased occurred in subjects in Group B. All observed events were reported as nonserious, and the majority recovered within a median duration of 84 days. However, one subject did not recover during the study period but no clinical manifestation of the eosinophilia was reported for this subject.

Review of the mean change from baseline eosinophil count at each visit during the entire treatment period demonstrated a trend in a slight decrease of eosinophils was observed. Despite the slight mean decrease from baseline, absolute values remain within reference range for majority of subjects.

Fall

In the current study, fall was reported in six of 73 (8%) subjects in the Dose 2 from baseline population. All events occurred in the subjects treated with Dose 2 from baseline with no events reported for any subject after dose adjustment. Fall occurred in three subjects from Group A and Group B. The median age of subjects with the Preferred Term Fall was 6 years old. The majority of events were mild, while rest were moderate in severity.

There was no reported event preceding a fall that would indicate that fall was a consequence of another adverse event. Fall was not a consequence of syncope in these subjects and no medical intervention was required.

Paronychia

In the current study, paronychia was reported in five of 73 (7%) subjects in the Dose 2 from baseline population with all events occurring in the subjects treated with Dose 2 from baseline. Paronychia occurred in one subject from Group B and four subjects in Group A. The majority of events were mild, while rest were reported as moderate in severity. All observed events were reported as nonserious and all recovered within a median of 78 days.

Headache

In the current study, headache was reported in five of 73 (7%) subjects in the Dose 2 from baseline population with the majority of events reported as mild in severity and the remainder as moderate in severity. Headache occurred in three subjects in Group B and two subjects in Group A. The median age of patients reporting headache was 10 years old.

One additional subject reported headache after dose adjustment. No notable difference was observed in severity, seriousness, latency, and outcome between subjects treated with Dose 2 from baseline and the subject who had their dose adjusted to Dose 2.

Cough

In the current study, cough was reported in five of 73 (7%) subjects in the Dose 2 from baseline population. The majority of events were mild and the remainder were reported as moderate in severity. All events occurred in the subjects treated with Dose 2 from baseline and all events occurred in subjects in Group B. All cases were reported as nonserious and all subjects recovered within a median duration of 14 days.

Nausea

In the current study, nausea was reported in five of 73 (7%) subjects and all events occurred in the subjects treated with Dose 2 from baseline with no events occurring in any subject after dose adjustment. Nausea occurred in two subjects in Group B three subjects in Group A. The median age of subjects with nausea was 12 years old.

Vomiting

In the current study, vomiting was reported in five of 73 (7%) subjects in the Dose 2 from baseline population The majority of events were mild while rest were moderate in severity. Vomiting occurred in two subjects in Group B, three subjects in Group A. An additional four subjects reported vomiting after their dose adjustment. No notable difference was observed in severity, seriousness, latency, and outcome between subjects treated with Dose 2 from baseline and subjects who had dose adjustment to Dose 2.

Conjunctivitis

In the current study, conjunctivitis was reported in four of 73 (6%) subjects in the Dose 2 from baseline population. The majority of events were mild while the rest were moderate in severity.

All events occurred in the subjects treated with Dose 2 from baseline and no events of conjunctivitis were reported in any subject after dose adjustment. All conjunctivitis events occurred in subjects in weight Group B. All observed events were reported as nonserious, and all recovered within a median duration of 8 days.

Epistaxis

In the current study, epistaxis was reported in four of 73 (6%) subjects. All events occurred in the subjects treated with Dose 2 from baseline and were reported as mild in severity. Epistaxis occurred in two subjects each in Group B and Group A. All events were reported as nonserious and all recovered within a median duration of 4 days.

Monocyte Count Decreased

In the current study, monocyte count decreased was reported in four of 73 (6%) and all events occurred subjects in subjects treated with Dose 2 from baseline. All events were mild in severity. Two subjects from each body weight group reported monocyte count decrease. All observed events were reported as nonserious, and all subjects recovered within a median duration of 58 days. No associated infectious AEs were reported during monocyte count decreased period in these four subjects.

Monocytes are one of the cell lines composing the clinical laboratory value of leukocytes/white blood cells. Leukopenia has been observed with sarilumab in adult RA population and is currently listed as an ADR. The review of the safety data from this study supports that monocyte count decreased as a cell type of leukocytes remains as an ADR, however without any new Warnings or Precautions.

Ear Pain

In the current study, ear pain was reported in four of 73 (6%) subjects with all events occurring in the subjects treated with Dose 2 from baseline. Two subjects from each body weight group reported ear pain. All events were reported as nonserious and all subjects recovered within a median duration of two days. In three subjects, no associated infectious AEs were reported between the start and stop dates of the ear pain events. One subject had concurrent oropharyngeal pain. No action was taken with sarilumab treatment due to events and all events resolved.

Tonsillitis

In the current study, tonsillitis was reported in three of 73 (4%) subjects in the Dose 2 from baseline population. Two events were reported as mild and one event was reported as moderate in severity. Tonsillitis occurred one subject in Group B two subjects in Group A. All events were reported as nonserious and all subjects recovered within a median duration of six days.

An additional three subjects were reported to experience tonsillitis after dose adjustment for a total of six of 93 (7%) subjects. No notable difference was observed in severity, seriousness, latency, and outcome between subjects treated with Dose 2 from baseline and the subjects who had dose adjustment to Dose 2.

Blood Triglycerides Increased

In the current study, blood triglycerides increased was reported in three of 73 (4%) subjects all in subjects in the Dose 2 from baseline population. All events were mild in severity. Blood triglycerides increased occurred in one subject in Group B two subjects in Group A. All events were reported as nonserious. Two of the events resolved but one event of blood triglycerides increased was ongoing at the time of database lock. No action was taken with sarilumab for any of these events.

Hypertriglyceridemia has been observed with sarilumab in adult RA population and is currently listed as an ADR. A review of safety data from this study supports that blood triglycerides increased remains as an ADR, however without any new Warnings or Precautions.

In summary, following review of the safety data from the current study, no new ADRs were identified. The ADRs identified for sarilumab in the RA indication which are also applicable for patients with pJIA include neutropenia, nasopharyngitis, upper respiratory tract infection, injection site reactions, and ALT increased. In addition to these ADRs, monocyte count decreased (leukopenia) and lipid abnormalities (hypertriglyceridemia) were identified as ADRs in patients with pJIA similar to adult patients with RA.

Adverse Events Not Meeting Criteria for Adverse Drug Reactions

Analysis of other AEs, which have not been established as ADRs, are described in this section. Some events were reported as either underlying disease, e.g., Preferred Term Juvenile idiopathic arthritis, or signs and symptoms of underlying disease, e.g., Preferred Terms such as arthralgia and pain in extremity. Some events were reported as unspecified terms without further clarification precluding further assessment, e.g., unspecified gastrointestinal infection and arthropod bite. Other events were reported in the context of other AEs, e.g., contusion after the event of the Preferred Term Fall

.

Six subjects had acute sinusitis/sinusitis, with all subjects having reported only one episode of sinusitis during treatment with the median time to onset of 410 days. All sinusitis events resolved with the median duration of 12 days. It was unknown whether any of the sinusitis events met established clinical criteria for a diagnosis of sinusitis or if these subjects presented with the common conditions in general pediatric population, e.g., rhinitis.

Intertrigo occurred between toes in two subjects and vulvar intertrigo was reported in one subject. Intertrigo is a condition typically induced or aggravated by heat, moisture, friction and lack of air circulation. No infection events were associated with intertrigo in any of these subjects. Varicella was reported in three subjects. Varicella is a highly contagious, common, and mild disease in childhood and the virus spreads easily through close contact.

Rash was reported in three subjects and were considered nonserious. The median time to onset for events of rash was 163 days from first dose of sarilumab. No action was taken regarding sarilumab dosing for any of the rash events, and all recovered within median duration of 3 days.

A comparative analysis was performed to assess the current ADRs of diverticulitis and thrombocytopenia which are in the KEVZARA label in adults with RA and none of these events occurred in the current pJIA study.

In the subjects treated with the Dose 2 in the entire treatment period, one subject had nonserious, mild urinary tract infection that occurred on study Day 112 and resolved five days after receiving cefuroxime without any action taken with sarilumab. The same subject also had cystitis prior to first administration of sarilumab.

Additionally, two subjects treated with Dose 2 throughout the entire treatment period had six episodes of oral herpes with median time to onset of 2 years. All events of oral herpes were nonserious and resolved with median duration of five days.
None of the events of diverticulitis, thrombocytopenia, urinary tract infection or oral herpes were assessed as ADRs for the pediatric population based on the following criteria: not occurring in the pJIA study, lack of consistency in pattern of presenting symptoms, and lack of consistency of time to onset.

Laboratory Findings

HEMATOLOGY
There were no clinically meaningful hematology changes as defined by white blood cell count, lymphocytes, monocytes, basophils, eosinophils, hemoglobin concentration, or hematocrit during the 52-week study period.

Absolute Neutrophil Count
During the current study, ANC was monitored at regular prespecified intervals. Monitoring included assessment prior to the second injection (at Day 12 ±1 day for subjects with Dose 1 and Dose 2, and between Day 5 and Day 8 for subjects who received Dose 3), every 2 weeks during the 12-week treatment phase of Portion 1 and every 4-12 weeks during the extension phase. Additionally, Investigators had to perform testing when a decrease in ANC to $<1.0 \times 10^3/\mu L$ was observed and could decide to perform more frequent hematology monitoring between two on-site visits by utilizing a local laboratory. All ANC results obtained by central and local laboratories were collected and analyzed for this study.

The analysis of ANC decrease is presented for the all 101 subjects treated with sarilumab for the 12-week treatment period and the 52-week treatment period. The incidence of ANC to $<1.0 \times 10^3/\mu L$ is analyzed during the entire treatment period by three-month intervals for the three doses and the selected Dose 2.

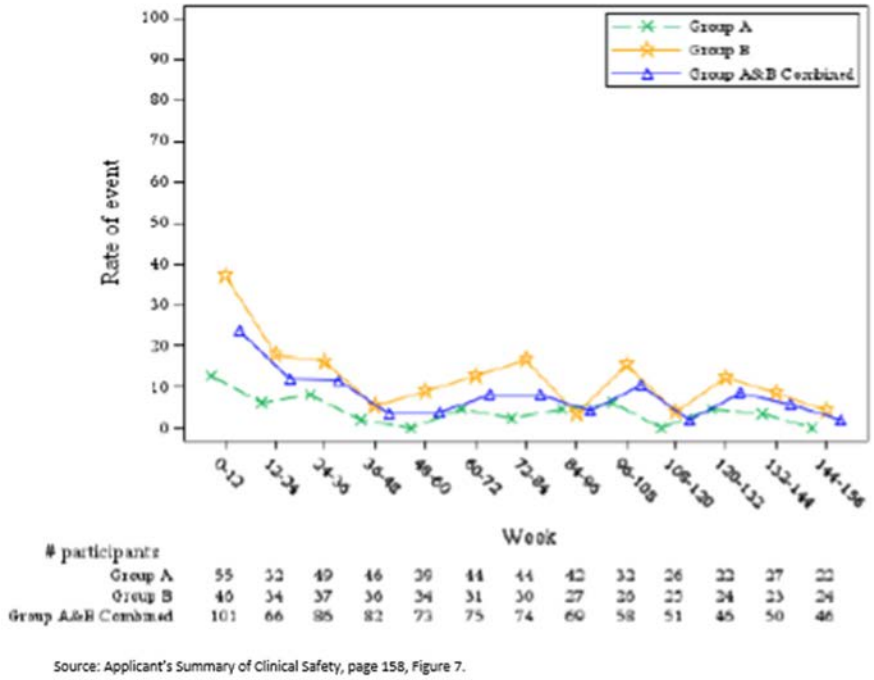
All Dose Cohorts for 12-Week, 24-Week, and 52-Week Treatment Period
The percentages of subjects in the combined Any Dose group who reported at least one episode of decrease in ANC were as follows:

- 49 of 101 (49%) subjects in the 12-week treatment period

- 53 of 101 (53%) subjects in the 24-week treatment period
- 59 of 101 (58%) subjects in the 52-week treatment period

These findings show that most of the ANC decrease events started during the 12-week treatment period and remained low throughout the remainder of treatment (Figure 14).

Figure 14. Proportion of Subjects with At Least One incidence of ANC <1 x 103/µL by Three-Month Period During Study DRI13925- All Dose Group.



Source: Applicant's Summary of Clinical Safety, page 158, Figure 7.

The majority of ANC decreases were Grade 2 (≥1− 1.5 x 10^3/µL) or Grade 3 (≥0.5−1 x 10^3/µL) in severity:

- 19 of 101 (19%) subjects had Grade 2 neutropenia and 14 of 101 (14%) subjects had Grade 3 neutropenia during the 12-week treatment period.
- 20 of 101 (20%) subjects had Grade 2 and 17 of 101 (17%) subjects had Grade 3 neutropenia in the 24-week-treatment period.
- 22 of 101 (22%) subjects had Grade 2 and 21 of 101 (21%) subjects had Grade 3 neutropenia in the 52-week-treatment period.

There was no notable difference across the three dose cohorts with the exception of Grade 4 neutropenia which occurred in the Dose 3 cohort at a higher frequency compared to the Dose 2 across the three treatment periods. Most Grade 3 or 4 neutropenia (4 of 6 events) reported in subjects receiving Dose 3 were observed at the first pre-specified blood sampling after the first administration of sarilumab (Day 5), which corresponds to the nadir period for ANC. For that reason, the weekly dosing was considered inappropriate for the pJIA patients.

Differences between the two body weight groups were observed with Group B subjects experiencing higher percentages of more severe (Grade 3 and Grade 4) neutropenia compared to Group A subjects for all treatment periods:

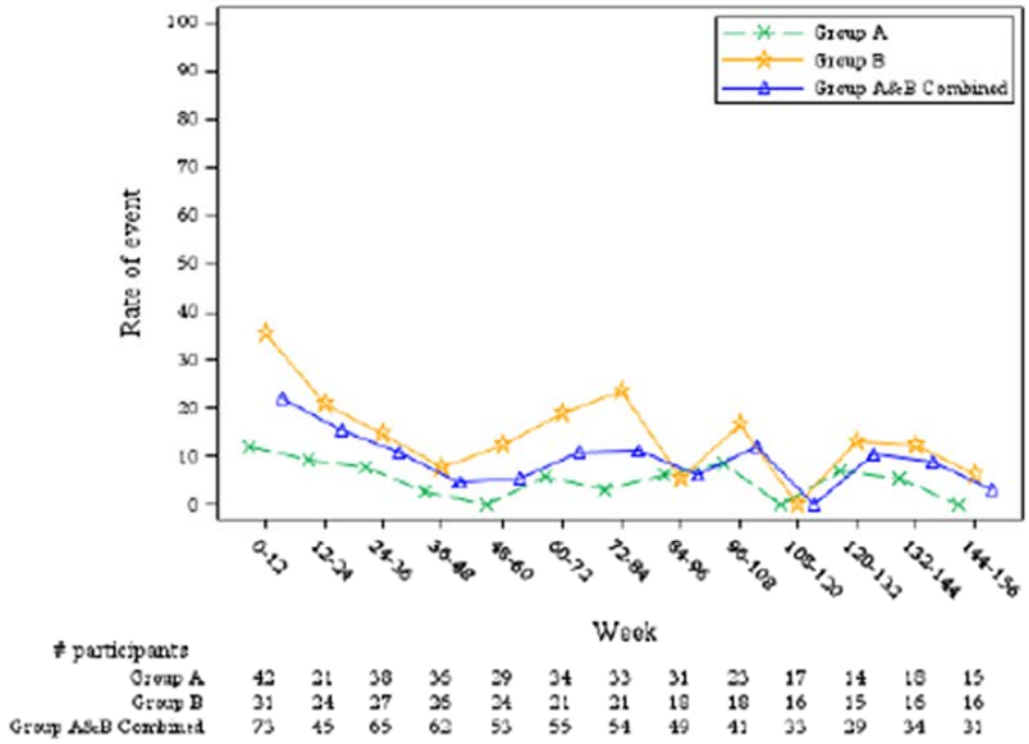
- 9 of 46 (20%) subjects in Group B versus 5 of 55 (9%) subjects in Group A had Grade 3 neutropenia, and 8 of 46 (17%) subjects in Group B versus 2 of 55 (4%) in Group A had Grade 4, in the 12-week treatment period.
- 10 of 46 (22%) subjects in Group B versus 7 of 55 (13%) subjects in Group A had Grade 3 neutropenia and 9 of 46 (20%) subjects in Group B versus 2 of 55 (4%) subjects in Group A who had Grade 4 in the 24-week-treatment period.
- 12 of 46 (26%) subjects in Group B versus 9 of 55 (16%) subjects in Group A had Grade 3 neutropenia and 9 of 46 (20%) subjects in Group B versus 2 of 55 (4%) subjects in Group A had Grade 4 in the 52-week-treatment period.

In total, 11 of 20 (55%) subjects had at least one decrease in ANC. As observed for the 101 treated subjects, most subjects had Grade 1 or Grade 2 ANC decrease. Grade 3 was reported by three subjects and no Grade 4 events were reported. All three of the subjects who reported Grade 3 ANC decrease were in Group B.

The incidence of ANC count <1.0 x 10^3/µL during the entire TEAE period was analyzed for the three dose cohorts by three-month periods. In the 101 subjects treated with any dose of sarilumab, the highest percentage of subjects with ANC decrease was reported in the first 12 weeks (24% in the combined Any dose group). From 12 weeks to 36 weeks, the percentage of ANC decrease over time declined by half and after Week 36, it showed a plateau with minor individual fluctuations that occurred mostly in the Group B subjects (Figure XX).

A graphical representation of proportions of subjects with at least one ANC<1.0 x 10^3/µL by three−month period during the TEAE period for the selected Dose 2 is provided in Figure 15.

Figure 15. Proportion of Subjects with At Least One incidence of ANC <1 x 10^3/µL by Three-Month Period During Study DRI13925-Dose 2 Group.



Source: Applicant's Summary of Clinical Safety, page 160, Figure 8.

The analysis of the entire TEAE period for the 101 subjects treated with Any dose of sarilumab and the 73 subjects treated with the selected Dose 2 from baseline demonstrated that after Week 36, a steady plateau in the incidence of at least one ANC<1.0 x 10^3/µL was reached for both Group A and B. Minor individual fluctuations in ANC values <1.0 x 10^3/µL occurred between Week 60 to Week 84 and between Week 96 and Week 108 for Group B subject receiving Dose 2. These findings indicate that the ANC levels are mostly susceptible to the pharmacologic effect of sarilumab in the initiation phase of sarilumab treatment.

<u>pJIA Population Exposure-Response</u>

The exposure-response relationship was evaluated between absolute neutrophil count (ANC) and sarilumab C_{trough} in subjects with pJIA at Week 12 for all doses and at Week 12 and Week 48 for Dose 2. The data is presented by tertile of sarilumab trough concentration (C_{trough}).

At Week 12, dose-dependent changes in ANC were observed. The mean ANC level decreased and ANC percent change from baseline and the proportion of subjects with ANC <1 x 10^3/µL increased with increasing sarilumab C_{trough} from Dose 1 to Dose 3.

For Dose 2 at Week 12, the mean ANC level decreased and the ANC percent change from baseline increased with increasing sarilumab C_{trough} from the low tertile to the high tertile. The proportion

of subjects with ANC <1 x 10^3/µL was similar in the medium and high exposure tertiles with a trend of increase with increasing concentration of sarilumab from the low tertile to medium tertile and reached a plateau at the trough concentration in the medium tertile. At Week 48, a higher mean ANC level and a smaller mean ANC change from baseline in the lower exposure tertiles compared to the medium and high tertiles. The mean ANC level and ANC change from baseline increased with increasing sarilumab C_{trough} from the low tertile to the medium tertile. The effect approached a plateau over a concentration range of the medium to high tertiles. The proportion of subjects with ANC <1 x 10^3/µL showed a trend of increase with increasing concentration of sarilumab from the low tertile to medium tertile and reached a plateau at the trough concentration in the medium tertiles.

Compared to Week 12, a similar mean ANC level and a smaller mean ANC changes from baseline were observed in each tertile at Week 48, suggesting the magnitude of ANC reduction did not increase over time. Similarly, the risk of ANC <1.0 x 10^3/µL did not increase over time.
Decrease in ANC is an expected pharmacodynamic effect of sarilumab treatment, and this was observed when comparing the mean change from baseline in ANC values; however the effect reached a plateau which was also observed in adult RA patients. The exposure-response relationship of ANC percent change from baseline is similar in pediatric subjects with pJIA at Dose 2 and adult subjects with RA.

CLINICAL CHEMISTRY
There were no clinically meaningful changes in chemistry values (cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and protein) or electrolytes parameters values across the visits during the entire study period.

Liver Function
No subjects had abnormal liver function test results that were considered as SAEs. One of 101 (1%) subjects was reported with ALT values of >3 x ULN and ≤5 x ULN, and 2 of 101 (3%) subjects reported with ALT values of >5 x ULN and ≤10 x ULN during the study. Both subjects with ALT value between >5 x ULN and ≤10 x ULN were permanently discontinued from the study drug.

- Subject 616-0072-05001 was randomized to Dose 1, Group A had an AE of ALT increase (217 U/L during the 12-week treatment period.
- Subject 152-0016-05002 was randomized to Dose 3, Group B had an AE of ALT increase (258 U/L on Day 428 of the study.

None of these events were associated with an increase in bilirubin level.

Vital Signs

During the entire treatment period, several subjects had recorded sporadic potential clinically significant abnormalities in vital sign parameters, i.e., systolic blood pressure, diastolic blood pressure, weight, and temperature, reported at least once across dose groups. In all 101 treated subjects in the combined Any Dose group with normal or missing value at baseline:

- 6 (8%) subjects reported a decrease in SBP.
- 19 (25%) subjects reported an increase in SBP.
- 8 (11%) subjects reported a decrease in DPB.
- 26 (37%) subjects reported an increase in DBP.

No trend in time to onset was observed and no subjects had abnormal vital signs parameters that were reported as SAEs or TEAEs leading to study treatment discontinuation during the treatment period.

Electrocardiograms (ECGs)

Electrocardiogram data was not collected during the study.

QT

Prolongation of QT interval was not assessed during the study.

Immunogenicity

During the entire study, a total of 97 of 101 treated subjects had ADA assay results available during the entire study. Of the 97 subjects with available ADA assay results 93 of 97 (96%) were ADA-negative and four of 97 (4%) subjects were ADA-positive. Of the subjects who were ADA-positive, three were receiving Dose 2 and one subject was receiving Dose 1. Additionally, three of the subjects were from Group A and one was from Group B. No observable difference was noted across the three dose cohorts.

One subject in Dose 1 received three successive doses of sarilumab and discontinued due to an AE of ALT increased (>5 UNL and ≤10 ULN) at Week 4 prior to ADA positivity was detected. This subject reported neutralizing ADA.

No subjects with ADA-positive responses experienced hypersensitivity events during the study. Due to the low number of ADA-positive subjects, no conclusion on a potential association between ADA development and safety can be reached.

7.2.5. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest

<u>All Dose Cohorts</u>
During the 52-week treatment period, 16 of 101 (16%) in the Any Dose group had reported an AESI. The majority of these AESI occurred during the 12-week treatment period with 13 of 101 (13%) subjects in the combined Any Dose group. Two additional subjects had reported AESI during the 24-week treatment period and one additional subject had an AESI reported during the 52-week treatment period.

The exposure-adjusted event rate for AESIs were lower in Dose 2 (18/100 PY) compared to either Dose 1 (19/100 PY) or Dose 3 (49/100 PY). Most of the 16 subjects with AESI were enrolled in Group B of the Dose 2 (12 of 16 subjects) and Dose 3 (5 of 5 subjects) cohorts. The most frequently reported AESI was Grade 4 neutropenia or any neutropenia leading to treatment discontinuation, which occurred in 13 of 16 subjects.

AESI of Clinically Significant Infections

During the 52-week treatment period two subjects, who were both treated with Dose 2 from baseline, experienced infections that were reported as meeting the definition of AESI "clinically significant infections:

- Subject b) (6) was enrolled in Group B and developed bone tuberculosis (See Section 8.2.4, SAEs). The event was reported as serious and considered to be related to treatment with sarilumab. The subject was permanently discontinued from after 14 days of exposure.
- Subject b) (6) was enrolled in Group B and developed an opportunistic infection reported as Herpes zoster. The event occurred after approximately 54 weeks of exposure, the infections was not classified as serious and may have been related to sarilumab therapy.

AESI of ALT Increase

One subject reported an ALT increase that led treatment discontinuation during the 52 week-treatment period. The event was reported as meeting the definition of AESI "ALT increase leading to permanent treatment discontinuation". The subject was in randomized to Dose 1, Group A. Two additional subjects reported ALT increases that led to treatment discontinuation during the study after Week 52. Both subjects were treated with Dose 2.

AESI of Grade 4 Neutropenia

During the 52-week treatment period, 13 (13%) events of neutropenia were reported as meeting the definition of AESI of "Grade 4 neutropenia or any neutropenia leading to permanent discontinuation". Of the 13 subjects, one subject was treated with Dose 1, seven subjects were treated with Dose 2, and five subjects received Dose 3. These events were reported as an AESI as per study protocol definition. Events of any grade neutropenia reported as TEAE are described in Section 8.2.4 Laboratory Findings.

AESI in Subjects Treated with Dose 2

A total of 14 of 93 (15%) subjects treated with at least a single dose of Dose 2 reported at least one AESI. Among these 14 subjects, three subjects were in Group A and 11 subjects were in Group B. All the subjects were treated with Dose 2 from baseline, except for one subject who switched from Dose 3. Of the 14 subjects receiving Dose 2 with a documented AESI two subjects reported infections, two subjects reported ALT elevation, and ten subjects reported neutropenia.

7.2.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There is no marketing experience with KEVZARA in the pJIA population as sarilumab is not currently approve for the treatment of pJIA.

7.2.7. Integrated Assessment of Safety

The safety data was derived from study DRI13925, which consisted of 101 subjects with pJIA treated with sarilumab and contain all safety information up until the time of the database lock (January 13, 2023). The study was conducted in an open-labeled manner and was analyzed using descriptive statistics. Therefore, the review primarily focused on the available safety data from the portions of the study in subjects pJIA with the aim of identifying new safety signals and special focus on adverse events of special interest related specifically to the known safety profile of sarilumab in adult patients with RA. On the whole, these studies provided a sufficient amount of drug exposure for evaluation of the safety of sarilumab in children with pJIA.

My review of the data demonstrated a safety profile consistent with the adult RA population and did not identify new safety signals. Overall, the safety profile of sarilumab in children with pJIA appears to provide an acceptable degree of risk given the severity of the underlying disease and the demonstrated efficacy of sarilumab.

7.3. Statistical Issues

The primary analysis of study DRI13925 was sarilumab PK analysis and is described in Section 6. All efficacy and safety endpoints were secondary endpoints and primarily used descriptive statistical methods. No statistical issues were identified.

7.4. Conclusions and Recommendations

While the primary data for approval of the current application is derived from PK comparability data between the proposed dosing in children with pJIA and that of adult patients with RA, the supportive efficacy data provided in this submission demonstrated that sarilumab, [redacted] demonstrated a clinical benefit as evidenced by improvement in signs and symptoms, disease activity, and physical function in a pJIA population with highly active disease of long duration. Clinical effects were observed in more than two-thirds of subjects by Week 12 with continued improvement through Week 48.

The review of the safety data base did not identify any new safety concerns and demonstrated an acceptable safety profile in patients with pJIA. The current risk profile of sarilumab did not change based review on the pJIA safety data and in comparison to the safety data in adults with RA.

The data submitted in the current application supports approval of sarilumab at the proposed dosing for the treatment of children two years of age and older with active pJIA.

b) (6)

The current studies demonstrated that children weighing greater than or equal to 63 kg are to be treated using the adult dose of 200 mg. Therefore, the KEVZARA prefilled syringe will be approved for pJIA in patients who weigh greater than or equal to 63 kgs, b) (6) the required PREA PMR 3218-3 will not be fullifilled given that there is no available dosage form for pJIA patients 2-17 years of age who weigh less than 63 kgs.

8 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not conducted for the current application.

9 Pediatrics

The Division met with the pediatric review committee (PeRC) on May 14, 2024, who agreed with the approval of KEVZARA prefilled syringe formulation for the treatment of children diagnosed with pJIA weighing greater than or equal to 63 kg.

(b) (6) no presentation of KEVAZARA being available for children 2 years of age and older who weigh less than 63 kg, the PeRC agreed that PMR 3218-3 is considered unfulfilled.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

Major Labeling Changes S-015

Indications and Usage:
Added Indication: For patients who weigh 63 kg or greater with active polyarticular juvenile idiopathic arthritis (pJIA)

(To allow flexibility for adult patients with pJIA diagnosed during childhood)

Dosage and Administration:

- Added: The recommended dosage of KEVZARA for patients who weigh 63 kg and greater is 200 mg once every two weeks given as a subcutaneous injection (maximum dose 200 mg). Dosage in this patient population can be achieved by administering the 200 mg/1.14 mL pre-filled syringe. The prefilled pen is not approved for this patient population.

  In patients with pJIA, KEVZARA can be used alone or in combination with conventional DMARDs.

- Dosage Modification for Patients with Polyarticular-Course Juvenile Idiopathic Arthritis

  Dose reduction of KEVZARA has not been studied in the pJIA population. Discontinue KEVZARA if ALT > 5 ULN, platelet count ≤ 50,000 cells/mm^3, neutrophil count < 500 cells/mm^3 associated with infection. Hold KEVZARA dosing for ALT > 3 to ≤ 5 ULN, platelet count > 50,000 to ≤ 100,000 cells/mm^3, and neutrophil count ≥ 500 to < 1000 cells/mm^3, and until the clinical condition has been evaluated. The decision to discontinue KEVZARA should be based upon the medical assessment of the individual patient. If appropriate, the dose of concomitant methotrexate and/or other medications should be modified or discontinued.

- KEVZARA is not approved in pediatric patients weighing less than 63 kg because of the lack of an appropriate dosage form.

- The ability of pediatric patients to self-inject with the pre-filled pen has not been tested.

Pediatric Use:
Added: KEVZARA is approved for active polyarticular juvenile idiopathic arthritis (pJIA) in pediatric patients who weigh 63 kg or greater. Use of KEVZARA in this patient population is supported by evidence from adequate and well-controlled studies of KEVZARA in adults with RA, pharmacokinetic data from adult patients with RA, and a pharmacokinetic, pharmacodynamic,

dose-finding, and safety study in pediatric patients with pJIA 2 years of age and older. KEVZARA is not approved in pediatric patients weighing less than 63 kg because of the lack of an appropriate dosage form.

The safety and effectiveness of KEVZARA have not been established in pediatric patients with pJIA below the age of 2 years.

11 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable

12 Postmarketing Requirements and Commitment

With the original approval of BLA 761037 on May 22, 2017, two post-marketing requirements (PMR; 3218-1 and 3218-2) were issued for the Applicant to conduct two pediatric studies in children ages ≥2 to 17 years with pJIA. On November 22, 2019, in response to the Applicant's request to modify the required pediatric studies, the Agency issued a single PMR (3218-3) to conduct a single pediatric study (DRI13925), the data and reports of which were submitted to support the current submission. [redacted] this PMR will not be fulfilled until an appropriate pediatric formulation is approved for ages ≥2 to 17 years with pJIA.

13 Division Director (Clinical) Comments

I agree with the review team's assessment of the data submitted, the benefit-risk assessment, and the conclusions regarding the data supporting the recommended regulatory actions.

The regulatory action for S-015 is approval with labeling changes agreed upon with the Applicant. (b) (6)

PREA PMR 3812-3 will be not be considered fulfilled.

14 Appendices

14.1. References

See references in the document

14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): DRI13925

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 128		
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): 1		
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: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		

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)

14.3. OCP Appendices (Technical documents supporting OCP recommendations)

14.3.1. Bioanalytical Method Validation and In-Study Report

Functional sarilumab serum concentrations were assayed using a validated enzyme-linked immunosorbent assay (REGN88-AV-13131-VA-01V1). The analytical range of the assay was 0.313 to 20.0 µg/mL. The original validation method was reviewed before as part of the original BLA. In this amendment of validation method, long-term stability testing was performed by including an extra time point (15 months). The method validation summary results including long-term stability results are reported in **Table 12**. All validation parameters including LTS provided the accuracy (percent of analyte recovery) and precision (% coefficient of variation [%CV]) that are within acceptance criteria, supporting the adequacy (robustness, selectivity, reproducibility) of the bioanalytical method.

Table 12. Summary of validation parameters including newly added long-term stability as a part of validation amendment

Validation Parameters and Acceptance Criteria	Results
Assay Range Neat Human serum (ULOQ - LLOQ) 2% Human serum (Assay MRD = 1:50)	 20 – 0.313 µg/mL 400 – 6.25 ng/mL
Inter-assay-Accuracy %AR 80-120% (ULOQ and LLOQ 75-125%)	94 - 107%
Inter-assay-Precision CV% ≤ 20% (ULOQ and LLOQ ≤ 25%)	4 - 8%
Inter-assay-Linearity %AR 80-120% (Standard 1 and 7: 75-125%) CV% Dose ≤ 20% (Standard 1 and 7: ≤ 25%)	97 - 105% 1 - 2%
Intra-assay-Accuracy %AR 80-120%	94 - 105%
Intra-assay-Precision	2 - 3%

CV% ≤ 20%	
Intra-assay-Linearity %AR 80-120% (Standard 1 and 7: 75- 125%) CV% Dose ≤ 20% (Standard 1 and 7: ≤ 25%)	96 - 105% 1 - 3%
Matrix Interference 80% individual samples BLQ	15 of 15 samples BLQ
Selectivity at LLOQ %AR 75-125% of LLOQ for 80 % of LLOQ-spiked individual samples CV% Dose ≤ 25%	15 of 15 samples 85 - 106% of LLOQ 0 - 4%
Dilution Recovery %dAR 80-120% CV% ≤ 20%	97 - 107% 1 - 2%
Analyte Stability (4°C Overnight, 4 hours Room Temperature, 8X Freeze/Thaw) %AR 80-120% CV% ≤ 20%	92 - 111% 0 - 4%
Long-term Analyte Stability (-20°C Freezer) %AR 80–120%	At least 24 months 87 – 119%
Long-term Analyte Stability (-80°C Freezer) %AR 80–120%	At least 24 months 89 – 119%
Robustness (Standards; Quality Controls) %AR 80-120% (ULOQ and LLOQ 75-125%) CV% ≤ 20% (ULOQ and LLOQ ≤ 25%)	95 – 105%; 92 - 106% 0 – 3%; 0 - 5%
Ruggedness (Standards; Quality Controls) %AR 80-120% (ULOQ and LLOQ 75-125%) CV% ≤ 20% (ULOQ and LLOQ ≤ 25%)	98 – 104%; 99 - 110% 0 – 2%; 1 - 7%
Specificity %AR 80 - 120% ;CV% Conc ≤ 20% (Free REGN88 QCs) Free IL-6Rα QC = BLQ	98-111%, 0-5% BLQ

%AR = percent analyte recovery; CV% = percent coefficient of variation; ULOQ = upper limit of quantitation; LLOQ: lower limit of quantitation; BLQ = below the limit of quantitation; %dAR = percent dilution analyte recovery.

The bioanalytical method described in **Table 12** was used to measure sarilumab concentrations in serum samples from study DRI13925. The in-study method performance for this study is described in **Table 13** below and is acceptable.

Table 13. Method performance summary – determination of functional sarilumab in human serum

Parameters	Results (Study DRI13925)
Standard curve performance	Precision (%CV): 1% to 2% Accuracy (%AR): 96% to 109%

QC performance QC levels: 18, 80, and 300 ng/mL	Precision (%CV): 6% to 8% Accuracy (%AR): 96% to 97%
Method reproducibility	Incurred sample re-analysis was performed on 941 study samples, of which 91 (96.8%) samples had %difference within ±30% (an acceptance criteria).
Source Documents	m5.3.5.2-BLA 761037 – DRI13925-BA-01V3

14.3.2. APPLICANT'S POPULATION PHARMACOKINETIC ANALYSES

To support this pediatric supplement, population pharmacokinetics (PopPK) modeling and simulations followed by PK-PD analyses were performed to aid in dose exploration, dose selection, and justification of the selected dose in pediatric patients with polyarticular juvenile idiopathic arthritis (pJIA) aged 2 – 17 years old. Initially, the PopPK model developed in adult with RA was used to simulate PK exposures in pJIA patients to identify a range of doses to be explored in the study DRI13925. Then, an interim PopPK and PK-PD analyses were performed based on the data up to 12 weeks derived from the core dose-finding portion of DRI13925 in pJIA patients to aid in dose selection. This follows the final PopPK and PK-PD analyses for the data up to at least 52 weeks of study DRI13925 to provide the totality of evidence in support of the dosing regimen proposed for the treatment of patients aged 2 to 17 years old with pJIA. The key points of PopPK and PK-PD analyses are summarized below:

- PopPK simulation based on adult PK model using allometric scaling approach supported weight-based dosing regimen in pediatric patients with a weight cutoff at 30 kg. This resulted in different dose exploration in two different weight groups: a) >30 kg (2, 3 mg/kg Q2W, and 2 mg/kg QW) and b) ≥10 kg to <30 kg (2.5, 4 mg/kg Q2W, and 2.5 mg QW).
- PopPK modeling and simulation based on the PK data up to week 12 of the pediatric study suggested that dose 2 (3 mg/kg Q2W in group A and 4 mg/kg Q2W in group B) provided comparable exposures (Cmax,ss, AUCτ,ss, and Ctrough,ss) with those of adults with RA at the approved dosing regimen of 200 mg Q2W. Both descriptive and logistic regression analyses of dose/exposure-response relationship supported dose 2 at which the efficacy is maximum. There is a trend of increased efficacy with increase in median exposure (Ctrough,ss) within each dose plateauing at dose 2. Hence, both PopPK and PK-PD analyses supported the selection of dose 2, which was further explored beyond Week 12 of the study DRI13925.
- (b) (4) Model-predicted exposures for 3 mg/kg and 4 mg/kg in group A and B, respectively, are comparable with those of adults with RA at the approved dosing regimen. Though the exposures for the selected pediatric dose are 24 – 43% lower in group A compared to that of adult receiving 200 mg Q2W, it remains higher than that of 150 mg Q2W approved and recommended for adults with RA to manage certain laboratory abnormalities including neutropenia and thrombocytopenia.

- The PK-PD analyses indicated that there is a trend of increased efficacy with increase in dose which reaches at plateau at dose 2. Overall, exposure-response (E-R) analyses for efficacy endpoints for dose 2 also showed similar trend that an increase in exposure from low tertile to medium tertile increases efficacy beyond which the E-R curve remains flat. The E-R relationship in pJIA patients is comparable to that of adults with RA, albeit the efficacy is numerically higher in pediatric patients.
- Further, dose/exposure-response analyses for safety endpoints (e.g., ANC percentage change from baseline, proportion of patients with ANC <1.0 Giga/L) supported dose 2. There is a higher ANC reduction and a higher proportion of pediatric patients with ANC <1.0 Giga/L with an increase in sarilumab trough concentrations from dose 1 to dose 3. The proportion of pediatric patients with ANC <1.0 Giga/L was similar in the medium, and high exposure tertiles, with a trend of increasing rate with increasing concentration of sarilumab from the low tertile to medium tertile at dose 2 in patients with pJIA. The E-R relationship of ANC was consistent in patients with pJIA at Dose 2 and in adults with RA.

Table 14. Summary of PopPK analyses

General Information	
Objectives of PopPK analysis	• To develop a PopPK model to characterize sarilumab PK in pediatric participants aged 2 to 17 years with polyarticular juvenile idiopathic arthritis (pJIA), based on a previously developed PopPK base model for adult rheumatoid arthritis (RA) patients • To assess the influence of intrinsic and extrinsic factors on sarilumab PK in pediatric participants aged 2 to 17 years with pJIA • To generate individual sarilumab post-hoc PK exposures in pediatric participants aged 2 to 17 years with pJIA in study DRI13925.
Study and population included	The PopPK analysis dataset contained data from a single phase 2 conducted in pediatric patients aged ≥2 years to 17 years old with pJIA (See section 7 for detailed study design of this study).
Dose(s) included	Three (3) dose regimens were tested in portion 1 of the study for each of 2 groups with a body weight (BW) of ≥30 kg (group A) and ≥10 kg to <30 kg (group B) up to 12 weeks (dose-finding phase) **Group A**: 2 mg/kg Q2W, 3 mg/kg Q2W, and 2 mg/kg QW **Group B**: 2.5 mg/kg Q2W, 4 mg/kg Q2W, and 2.5 mg/kg QW. A dose regimen was selected at the end of 12-week treatment and the patients who were on selected dose regimen continued the same regimen during extension phase. Conversely, those who were on non-selected dose regimens had their regimens adjusted to selected dose regimen and continued treatment in extension phase. Portion 2 and 3 directly enrolled patients to the selected dose regimen. PK data up to a cut-off date of November 18, 2022, from all 3 portions were included in the PopPK analysis.
PopPK analysis dataset	The source dataset contained a total of 1266 functional sarilumab observations, from which 285 PK observations were excluded due to either BLQs (N=277) or outliers (N=8). Outliers include a pre-dose sample above BLQ at time 0 and 7 samples with absolute value of conditional weighted residuals (CWRES) ≥5.

No. of patients, PK samples, and BLQ	Pediatric Patients with pJIA: 101 Number of PK samples Included: 981 Total BLQs: None (All BLQs [N = 277] were excluded from the PopPK dataset) See **Figure 16** for PK sample distribution.	
Population Characteristics	See **Table 15**	
Final Model	**Summary**	**Acceptability [FDA's Comments]**
Software and version	• Nonlinear mixed effects modeling (NONMEM) (Version 7.5.1) • R statistical software (version 4.2.0) was used for data tabulation/ visualization/ simulation activities.	**Acceptable**
Model Structure	The PopPK model, previously developed in adult RA patients (see PopPK report POH0428), was used as a starting point for the model development in pJIA patients. The model is a two-compartment model with parallel linear and nonlinear elimination (Michaelis-Menten) and first order absorption. The model was parameterized in terms of Ka, CL, Vc, Q, Vm, and Km. Sensitivity analyses was conducted to evaluate the impact of different combination of IIV for key PK parameters, the impact of omega block and the impact of different methods (estimating or fixing) for incorporating exponents of weight effect on PK parameters. The final models using baseline weight and time-varying weight were compared to evaluate the impact of time-varying weight in model performance.	**Acceptable**
Base Model Parameters	Due to the wide range of weight in the pJIA patients aged 2 to 17 years, the impact of body weight on PK parameters was included in the base model development, in order to adequately characterize the PK of sarilumab in pediatric patients. Body weight was included as a covariate on CL, Vc, Vp, Q, and Vm parameters base model consistent with the previous modeling in RA. See **Table 16** for final parameter estimates. All parameters were estimated with good precision (%RSE <35%). The magnitude of estimated IIV was moderate for CL/F, Vc/F, and Vm with CV% of 39.0%, 51.8%, and 29.1%, respectively. The 95% CI of parameter estimates obtained from bootstrap analysis also supports the precision of final parameter estimates.	**Acceptable**
Final Model Parameters	See **Table 16** for parameter estimates. Besides the BW included as a covariate in base model, other covariates that were statistically significant in PopPK model of adults with RA, were also evaluated in this model. These include albumin, creatinine clearance normalized by body surface area (CLCRN), c-reactive protein (CRP), anti-drug antibody (ADA), and gender. The impact of age on sarilumab PK was also evaluated in the	**Acceptable**

	covariate analysis in pJIA patients, even though age was not a statistically significant covariate in adult RA patients. Drug product, one of the statistically significant covariates identified in adult RA patients, was not evaluated in the covariate analysis, as it was not relevant for pediatric participants with pJIA. Selected covariates were assessed using stepwise forward selection and backward elimination approach. Covariates contributing to at least a 6.63 unit change in objective function value (OFV) (α = 0.01, one degree of freedom) was considered statistically significant during forward selection. In backward elimination step, each covariate was removed from the parameter equation separately. A covariate was considered significant if it contributed to at least a 10.83 change in the OFV (α = 0.001, one degree of freedom) when removed from the model. The backward elimination process was repeated for each covariate and only statistically significant ($p < 0.001$) covariates were kept in the final PopPK model.	
GOF, VPC plots	The goodness-of-fit plots and VPC (visual predictive check) plots of the final population PK model are shown in **Figure 17** and **Figure 18,** respectively.	**Acceptable**
Effect of Covariates	Only body weight and albumin were identified as statistically significant covariates on sarilumab PK in pediatric participants with pJIA. However, albumin was not considered to have clinically meaningful impact on sarilumab PK due to similar level of inter-individual variability of PK in pJIA patients. Body weight was the primary source of sarilumab PK variability in pediatric patients with pJIA. Hence, body weight-based various dose regimens were evaluated as supported by initial PK simulation based on adult PK model (SIM0284) using allometric scale; and a dose regimen was selected following interim PopPK analyses at the end of dose finding phase (12-week) of clinical study DRI13925 (PopPK Study POH0516). Based on matched exposures with those of adults, 3 mg/kg Q2W and 4 mg/kg Q2W were selected for pJIA patients with a BW of ≥30 kg (group A) and ≥10 kg to <30 kg (group B), respectively. All other tested covariates, including gender, baseline age, baseline CLCRN, and baseline CRP, were not found to have statistically significant effect on sarilumab PK in pediatric participants with pJIA. Note that there was insufficient data (<10%: 6 out of 101 patients with positive ADA at any time and 1 out of 101	**Acceptable**

	patients with non-Caucasian race) to evaluate the impact of ADA and RACE on sarilumab PK as part of the covariate analysis.	

Ka: absorption rate constant; CL: Linear clearance from central compartment; Vc: Central volume of distribution; Vm: Maximum elimination rate; Q: Inter-compartment clearance.

Table 15. Summary of Demographics and Baseline Characteristics for Pediatric Participants Included in the Population Pharmacokinetic Analyses

Covariate Candidates (At Baseline)	**Continuous Characteristics**		
	Group A	**Group B**	**Total**
	Median (Minimum-Maximum)		Mean±SD; Median (Min – Max)
N	**55**	**46**	**101**
Body weight (kg) (kg)	46.5 (30 – 71.8)	18.4 (11.5 – 29.5	34.4±15.9; 32.5 (11.5 – 71.8)
Age (year)	13 (6 – 18)	5 (2 – 14)	9.4±4.7; 9 (2 – 18)
CLCRN (mL/min/1.73 m^2	118.7 (62.3 – 217.9)	177.2 (50.9 – 282.8)	150.4±48.8; 152 (50.9 – 283)
Albumin (g/L)	45.0 (30.8 – 51)	44.5 (36 – 51)	44±3.7; 45 (30.8 – 51)
CRP (mg/L)	1.79 (0.1 – 94.5)	1.71 (0.1 – 267)	12.2±32; 1.72 (0.1 – 267)
Categorical Characteristics			
N (%)			
Sex			
Female	43 (78%)	34 (74%)	77 (76%)
Male	12 (22%)	12 (26%)	24 (24%)
Race			
Caucasian	49 (89%)	39 (85%)	88 (87)
Asian	1(2%)	0 (0%)	1 (1%)
Missing	5 (9%)	7 (15%)	12 (12%)

Source: Reviewer's analysis based on data from PopPK dataset, poh1134-pkpd-final.csv

Table 16. Pharmacokinetic and Covariate Parameters in Final Population PK Model

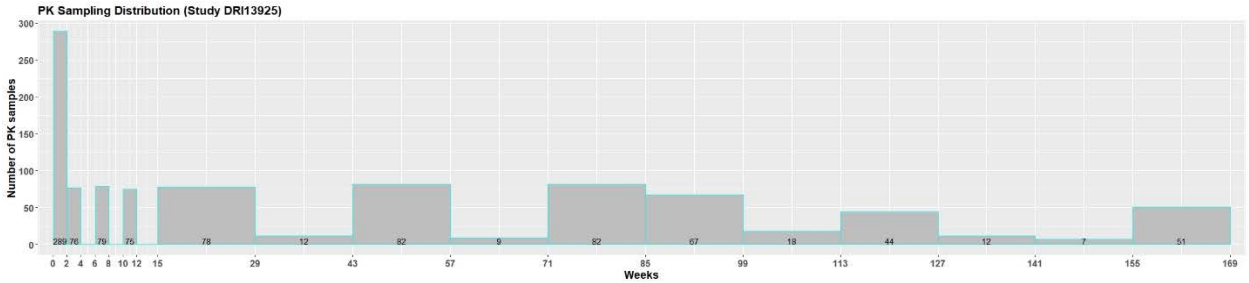
Model Parameter (Unit)	**Population Estimate (%RSE)**	**IIV %CV (%RSE) [Shrinkage]**	**95% CI from Bootstrap Analysis**	
			Population Estimate	IIV
CL/F (L/day)	0.190 (8.94)	39.0 (30.9) [25.1%]	[0.156, 0.224]	[24.1, 49.6]
V_c/F (L)	1.23 (14.7)	51.8 (35.1) [22.0%]	[0.156, 0.224	[28.2, 67.6]
V_p/F (L)	4.58 (17.9)	-	[2.94, 6.21]	-
Q/F (L/day)	0.103 (15.0)	-	[0.072, 0.134]	-
Vm (mg/day)	3.84 (10.6)	29.1 (34.5) [34.5%]	[3.03, 4.66]	[16.2, 37.8]
Km (mg/L)	0.921 (22.2)	-	[0.511, 1.33	-
Ka (1/day)	0.169 (10.8)	-	[0.133, 0.206]	-
Covariates effects (Power Coefficient)				
BW on Vm[a]	0.880 (11.5)	-	[0.680, 1.08]	-
BW on CL/F[b]	0.621 (20.4)	-	[0.368, 0.874]	-
BW on Vc/F[c]	1.33 (14.2)	-	[0.949, 1.70]	-
BW on Vp/F[d]	2.12 (19.2)	-	[1.31, 2.94]	-
BW on Q/F[e]	1.07 (31.1)	-	[0.404, 1.73]	-
Albumin on Vm[f]	-1.46 (29.8)	-	[-2.32, -0.589]	-
Residual Variability (RV)				
Additive (mg/L)	0.480 (4.74)	-	[0.434, 0.525	-

IIV: Inter-individual variability; CI: confidence interval; CL/F: apparent linear clearance; CV: coefficient of variation; Ka : absorption rate constant ; Km: Michaelis constant; Q/F: apparent inter-compartment distribution clearance; Vc/F: volume of central compartment; Vp/F: volume of peripheral compartment; Vm: maximum target-mediated rate of elimination; RSE: percentage of relative standard error (100% * SE / estimate).

a	Vm = population Vm*(WT/32.5)$^{0.880}$, where WT is body weight and 32.5 is median body weight from the study DRI13925.
b	CL/F = population CL*(WT/32.5)$^{0.621}$, where WT is body weight and 32.5 is median body weight from the study DRI13925.
c	VC/F = population Vc*(WT/32.5)$^{1.33}$, where WT is body weight and 32.5 is median body weight from the study DRI13925.
d	Q/F = population Q*(WT/32.5)$^{1.07}$, where WT is body weight and 32.5 is median body weight from the study DRI13925.
e	Vp/F = population Vp*(WT/32.5)$^{2.12}$, where WT is body weight and 32.5 is median body weight from the study DRI13925.
f	Vm = population Vm*(ALB/45)$^{-1.46}$, where ALB is albumin and 45 is median albumin from the study DRI13925.

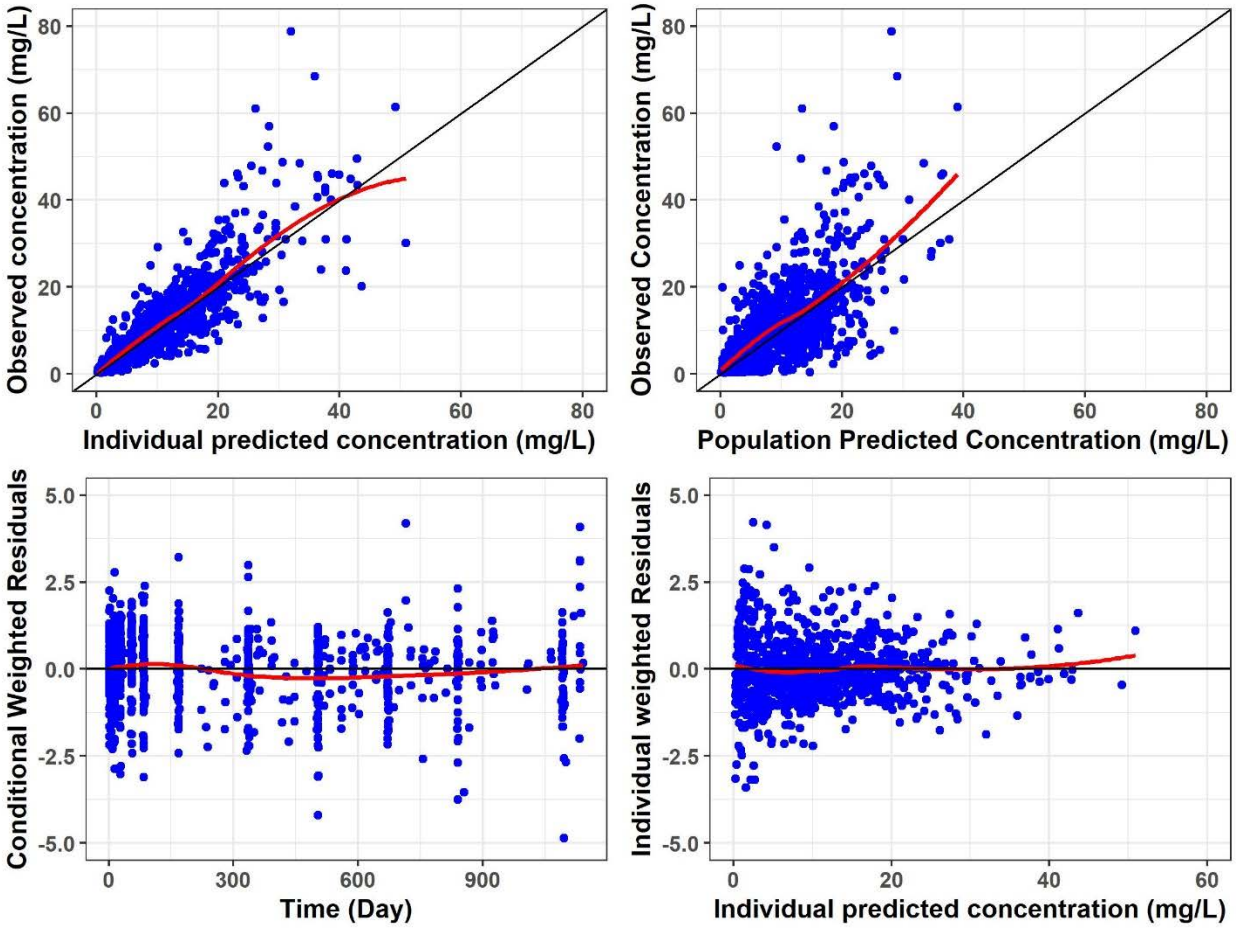
Source: Adapted from population pharmacokinetic analysis report (poh1134, table 9) available at m5.3.3.5-seq0168:. Reviewer's independent analysis provides the similar base model parameters.

Figure 16. PK sampling distribution of PopPK dataset



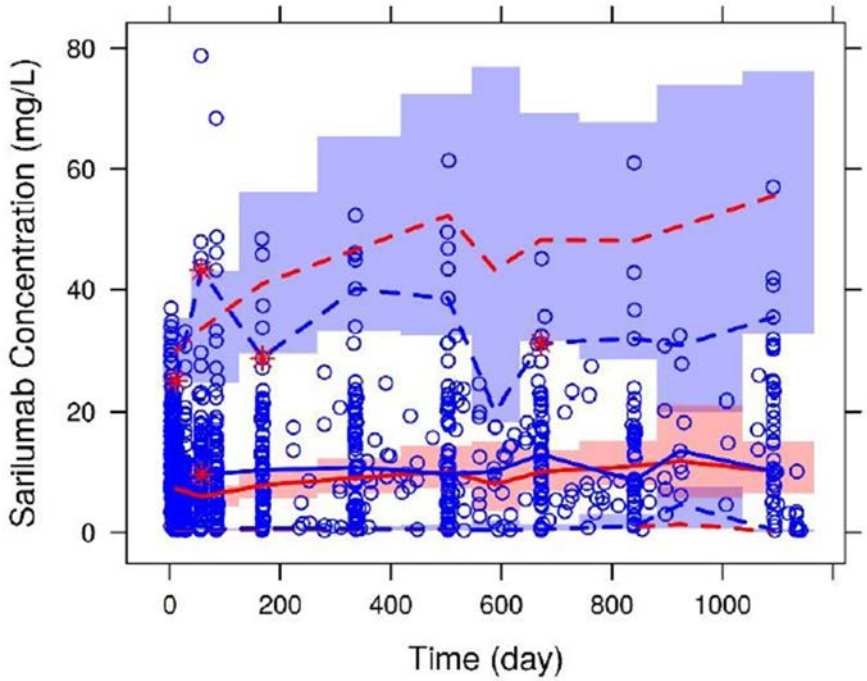
Source: Reviewer's plot generated based on PopPK data.

Figure 17. Goodness-of-fit plots from final Pop PK model in pediatric participants with pJIA



Source: Based on the reviewer's model output from final model run.

Figure 18. Visual predictive checks for final PopPK model in pediatric participants with pJIA



Note: Blue dots: observations; blue solid and dashed lines: the median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; red solid and dashed lines: the median and bounds (5th and 95th percentiles) of predicted concentrations at each time bin; pink and light blue areas: confidence intervals of median and percentiles of predicted concentrations at each time bin.
Source: Applicant's PopPK report (poh1134), Figure 12.

Applicant's Summary of Pharmacokinetics Analyses

Stage 1: Simulation to determine dose/dosing regimens for exploration

The Applicant conducted simulation (SIM0284) based on the PopPK model (2-compartment model) developed in adult patients with RA using allometric scaling method to extrapolate the exposures to pediatric patients with pJIA (polyarticular juvenile idiopathic arthritis). The range of dose regimens for exploration in pJIA were guided by matching PK exposures derived from adults with RA at different dosing regimens.

The simulated exposures in adult patients with RA and pediatric patients with pJIA are presented in **Table 17** and **Table 18**, respectively.

Table 17. Mean (CV%) [median; 5th, 95th percentile] of individual sarilumab exposure at steady-state in adult patients (simulated and observed) with RA

	Simulated				Observed[c]	
Dose (mg)	N	$AUC_{0\text{-}14\ day}$ (day.mg/L)	C_{max} (mg/L)	C_{trough} (mg/L)	N	C_{trough} (mg/L)
150 mg q2w	1000	172 (107) [148; 43.3, 380]	17.9 (8.64) [16.5; 6.47, 34.0]	4.93 (5.93) [2.46; 0.260, 17.4]	341	5.28 (6.72)[a] [1.81; 0.147, 40.6]
200 mg q2w	1000	328 (178) [295; 99.8, 668]	31.2 (13.8) [29.1; 12.6, 56.9]	12.0 (11.0) [9.16; 0.480, 33.6]	331	16.5 (13.9)[a] [13.3; 0.147, 67.8]
150 mg qw	1000	690 (324) [644; 247, 1290]	52.9 (23.7) [49.5; 20.6, 96.9]	42.5 (22.0) [39.6; 12.2, 83.1]	38	38.3 (20.3)[b] [36.9; 0.00, 83.5]

[a]: EFC11072 Part B; [b]: EFC11072 Part A; [c]: observed reported as mean (SD) [median; min, max]

Source: PopPK report – SIM0284, m5.3.3.5-seq0168-BLA761037.

Table 18 . Mean (CV%) [median; 5th, 95th percentile] of individual sarilumab exposure at steady-state in simulated pediatric patients with pJIA

Cohort	Weight kg	Dose mg/kg	$AUC_{0\text{-}14\ days}$ day*mg/L	C_{max} mg/L	C_{trough} mg/L
1	≥ 10 to < 30	2.5 mg/kg q2w	181 (81.3) [168; 74.3, 335]	22.1 (8.11) [21.2; 10.7, 37.0]	2.99 (3.98) [1.23; 0.210,11.4]
	≥ 30 to < 60	2 mg/kg q2w	134 (64.4) [124; 47.9, 254]	15.6 (6.10) [14.9; 6.98, 26.7]	2.58 (3.19) [1.22; 0.220, 9.31]
2	≥ 10 to < 30	4 mg/kg q2w	488 (196) [457; 223, 854]	49.7 (16.4) [47.6; 26.6, 79.9]	15.1 (12.1) [12.5; 0.770, 38.5]
	≥ 30 to < 60	3 mg/kg q2w	337 (138) [317; 149, 591]	33.3 (11.3) [32.1; 17.4, 53.7]	10.9 (8.69) [9.11; 0.610, 27.7]
3	≥ 10 to < 30	2.5 mg/kg qw	710 (282) [672; 319, 1230]	56.1 (20.7) [53.3; 27.3, 93.9]	41.1 (19.2) [38.6; 14.2, 76.5]
	≥ 30 to < 60	2 mg/kg qw	577 (223) [548; 267, 986]	44.9 (16.3) [42.7; 22.1, 74.6]	34.4 (15.2) [32.7; 14.2, 76.5]

Source: PopPK report – SIM0284, m5.3.3.5-seq0168-BLA761037.

The mean Cmax, Ctrough, and $AUC_{0\text{-}14\ days}$ values using allometric scaling exponent of 0.75 on CLO/F are slightly lower than the mean values for the body weight 30-60 kg as seen in the **Table 18**. The impacts on the low body weight group (10-30 kg) were greater than high body weight group (30-60 kg). Overall, the simulated results suggested the following summaries (see **Table 17** and **Table 18**):

- Pediatric doses of 2.5 mg/kg SC Q2W for pediatric patients ≥ 10 to < 30 kg and 2 mg/kg SC Q2W for pediatric patients ≥ 30 to < 60 kg are expected to provide similar exposure to that arising from a 150 mg SC Q2W sarilumab dose in adult patients with RA.
- Similarly, pediatric doses of 4 mg/kg SC Q2W for pediatric patients ≥ 10 to < 30 kg and 3 mg/kg SC Q2W for pediatric patients ≥ 30 to < 60 kg are expected to provide similar

exposure to that arising from a 200 mg SC Q2W sarilumab dose in adult patients with RA.

Therefore, the dosing regimens of 4 and 3 mg/kg Q2W for the BW groups of ≥10 kg to <30 kg and ≥30 kg, respectively, were evaluated in the phase 2 study (DRI13925) of pediatric patients with pJIA.

Stage 2: Interim PopPK analyses for the dose selection

The study DRI13925 had a core dose-finding portion up to Week 12 during which all dosing regimens suggested by PopPK simulations in stage 1 were explored. At the end of Week 12, an interim PopPK analysis (POH0516) was performed to select a dosing regimen that provides similar PK exposures with those of adult patients with RA at the approved regimen of 200 mg Q2W. Note that the PK model used in the interim analyses is the same as the model described in stage 3 except that creatinine clearance was significant covariate in the interim PK model while albumin was significant in the latter PK model (described in **Table 14**).

Simulations were conducted using the final PopPK model to evaluate PK exposure after first SC administration and repeated SC administration. The final PopPK model was used to generate post-hoc estimates of individual PK parameters and PK exposure for each pJIA patient. A dosing regimen for each body weight category was selected based on comparable PK exposures with those of adults. The post-hoc estimates of exposures presented in **Table 19** support the selection of dose 2 (3 mg/kg Q2W for a BW of ≥30 kg and 4 mg/kg Q2W for a BW of ≥ 10 kg to <30 kg) based on matched PK exposures at Week 10-12 with those from 200 mg Q2W at steady state in adults with RA.

Table 19. Mean (CV%) [median] of individual sarilumab exposure following repeated SC administration at Week 10-12

Dose Cohort	Weight Group	Dose mg/kg	N	C_{max} (mg/L)	$AUC_{0-\tau}$ day*mg/L)	C_{trough} (mg/L)
1	Group A ≥ 30 kg	2 mg/kg q2w	5	13.2 (13.6) [12.6]	114 (17.5) [116]	1.99 (85.6) [1.40]
	Group B < 30 kg	2.5 mg/kg q2w	5	14.1 (26.5) [13.7]	118 (36.6) [101]	1.83 (101) [1.27]
2	Group A ≥ 30 kg	3 mg/kg q2w	6	26.4 (26.2) [24.4]	269 (33.6) [250]	8.46 (68.2) [8.25]
	Group B < 30 kg	4 mg/kg q2w	7	30.1 (19.7) [31.1]	310 (26.1) [331]	11.9 (41.2) [13.1]
3	Group A ≥ 30 kg	2 mg/kg qw	6	38.8 (22.7) [39.3]	250 (24.4) [254]	30.4 (28.2) [31.4]
	Group B < 30 kg	2.5 mg/kg qw	5	31.4 (22.4) [29.9]	203 (25.0) [197]	25.1 (29.2) [27.3]

Abbreviations: $AUC_{0-\tau}$: area under the serum concentration versus time curve during a dose interval (τ) of 2 weeks (q2w regimen) or one week (qw regimen); Cmax: maximum serum concentration; Ctrough: serum concentration observed before drug administration during repeated dosing.
Source: PopPK report – POH0516, m5.3.3.5-seq0168-BLA761037.

Stage 3: PopPK analyses of pediatric data (up to at least 52 Weeks) from Study DRI13925

The final PopPK model was a 2-compartment model with parallel linear and nonlinear elimination with first order absorption and impact of BW on Vm, CL/F, Vc/F, Vp/f, Q/F and impact of albumin on Vm. The model adequately described the PK of pediatric patients with pJIA as supported by GOF and VPC plots. The reviewer's independent analyses provided similar parameter estimates, precision, and predictive performance as reported by the Applicant (see **Table 14** and hyperlinked model results and plots). Only BW and albumin were identified as significant covariates affecting PK exposures in pJIA patients. Though albumin was a statistically significant covariate, it was not considered to have clinically meaningful impact as the exposure variability due to albumin lies within general PK variability in pediatric patients.

PK results based on PopPK model analyses in stage 3:

The Applicant conducted post-hoc analyses and simulation using the final PopPK model described in **Table 14**, which provided the following PK results:

- Post-hoc estimates of PK exposures at steady state in pJIA patients indicate that the PK of dose 2 closely matches with those in adults with RA. However, sarilumab mean exposure at steady state in Group A (≥30 kg) was approximately 24 – 43% lower than that of adults following 200 mg Q2W, depending on PK parameters (see section 5.3 – clinical pharmacology review, **Table 2**).
- At the selected dose 2, post-hoc estimates of exposure parameters following first dose and at steady state (Week 30 – 32) demonstrated that the accumulation ratios (based on the estimated mean values of the PK exposures) were 4.06 to 4.13, 1.68 to 1.71, and 1.93 to 2.01-fold at steady state for Ctrough, Cmax, and AUC0-τ, respectively (**Table 20**).

Table 20. Mean (SD) [CV%] sarilumab PK exposures following first and repeated SC administration at steady state in pediatric participants with pJIA – on the selected Dose 2

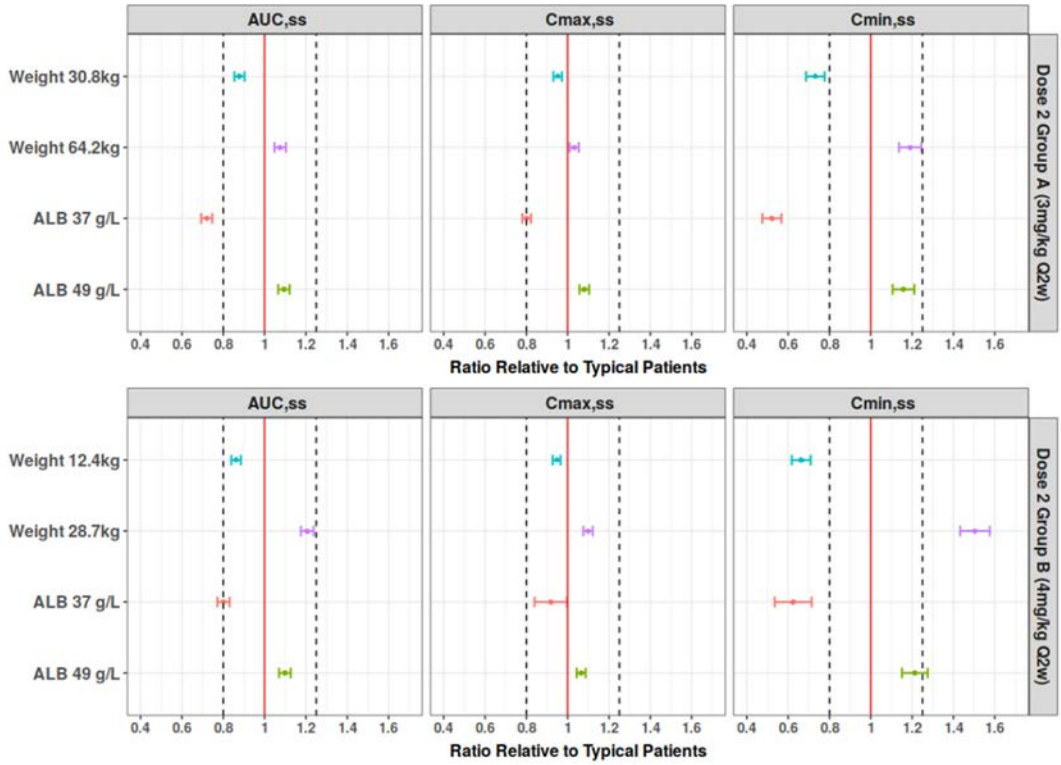
Weight Group	Dose	After first SC dose				Following repeated SC dose at SS			
		N	C_{max} (mg/L)	$AUC_{0-\tau}$ (day.mg/mL)	C_{trough} (mg/L)	N	$C_{max,ss}$[a] (mg/L)	$AUC_{0-\tau,ss}$[a] (day.mg/mL)	$C_{trough,ss}$[a] (mg/L)
Group A ≥30 kg	3 mg/kg q2w	42	15.9 (5.45) [34.4]	138 (43.7) [31.7]	2.38 (1.80) [75.6]	39	27.1 (11.6) [42.9]	276 (121) [44.0]	9.57 (5.84) [61.0]
Group B <30 kg	4 mg/kg q2w	31	24.0 (3.93) [16.4]	205 (42.6) [20.8]	3.62 (2.33) [64.2]	24	40.4 (7.77) [19.3]	395 (101) [25.6]	14.4 (9.81) [67.9]

Abbreviations: AUC0-τ: area under the serum concentration versus time curve during a dose interval (τ) of 2 weeks (q2w regimen); Cmax: maximum serum concentration observed; Ctrough: concentrations observed before treatment administration during repeated dosing; CV: coefficient of variation; pJIA: polyarticular-course juvenile idiopathic arthritis; q2w: once every other week; SC: subcutaneous.

[a]Cmax, ss were calculated over week 30 to week 32 for q2w regimens; AUC0-τ, ss= AUC [Week 32 – Week 30] for q2w regimens; Ctrough, ss was calculated at week 32 for all regimens.
Source: PopPK report – POH1134, m5.3.3.5-seq0168-BLA761037.

- At the selected Dose 2 (3 mg/kg Q2W for Group A of ≥30 kg and 4 mg/kg Q2W for Group B of <30 kg), the impact of body weight on sarilumab exposure was 7.50%- 50.4%, over the range of the 5th to 95th percentiles of body weights relative to typical patients. The impact of albumin on sarilumab exposure was 9.40%-47.9%, over the range of the 5th to 95th percentiles of albumin relative to typical patients. Both impact of body weight and albumin was within the inter-individual variability (29.1%-51.8%) in pediatric participants with pJIA (**Figure 19**).

Figure 19. Weight and albumin effect on sarilumab steady state exposure in pediatric participants with pJIA



Abbreviations: AUC,ss: AUCτ,ss, area under the concentration-time curve at steady state; Cmax,ss: maximum concentration at steady state; Ctrough,ss: minimum concentration at steady state; Q2W: every 2 weeks

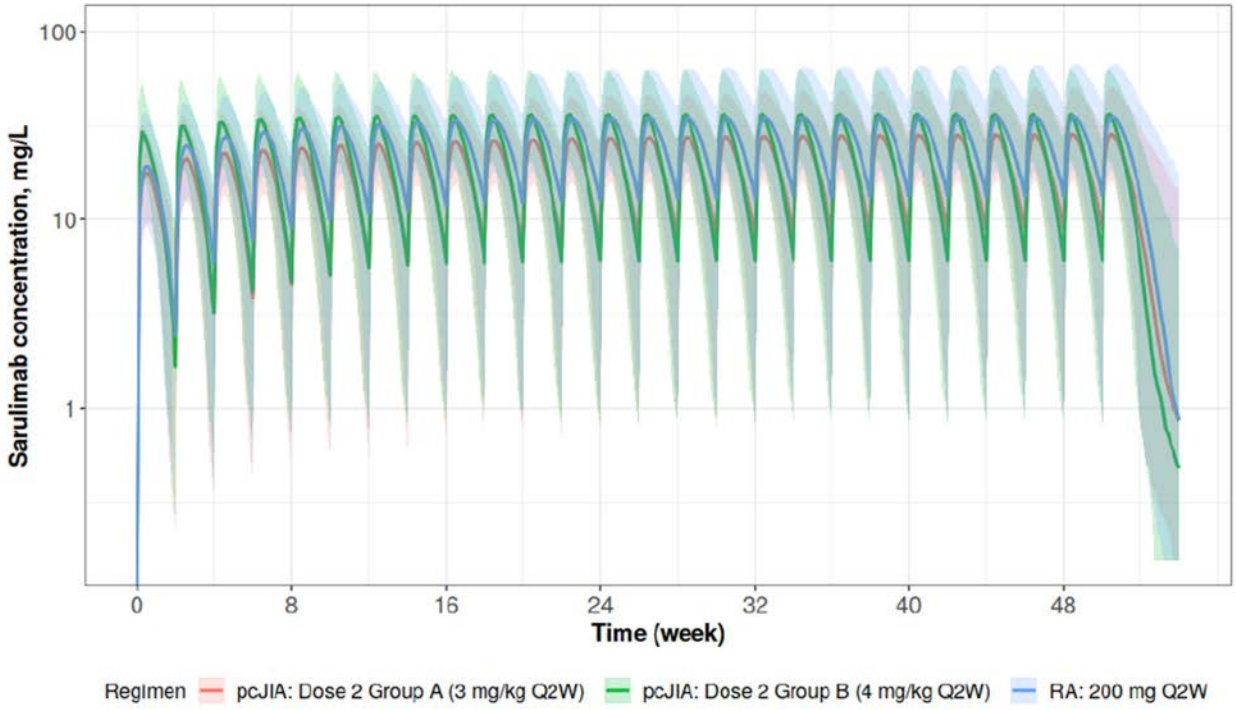
Notes: Typical pJIA patients are typical patients with median values of the covariate in pJIA population as follows: weight of 46.5 kg for Dose 2 group A patients and 18.4 kg for Dose 2 group B patients, albumin of 45 g/L for both group A and B patients. The covariate values for simulation (n=1000) represented 5% and 95% percentile of the baseline weight distribution of population PK population. Sarilumab mean steady-state exposures (ie, AUCτ,ss, Cmax,ss and Ctrough,ss) for the simulated typical patients were represented by the red solid vertical line. The black dashed vertical lines represented 80 and 125% of the typical mean steady-state exposures for simulated patients. The solid square and error bars represented the mean and 90% confidence interval (calculated based on standard errors) for the fold change of sarilumab steady-state exposures in simulated patients relative to typical patients.

Source: PopPK report – POH1134, m5.3.3.5-seq0168-BLA761037.

- Baseline age, gender, baseline CLCRN, baseline albumin, and baseline CRP had no apparent effect on sarilumab PK based on the available data. There was insufficient data (<10% patients with positive ADA or non-Caucasian race) to evaluate the impact of ADA and RACE on sarilumab PK in post-hoc assessment.

- The simulation results showed that sarilumab exposure with Dose 2 in pediatric participants with pJIA is similar compared to 200 mg Q2W dose regimen in adult RA participants (**Figure 20**).

Figure 20. Comparison of typical concentration-time profiles of sarilumab at 3 mg/kg Q2W and 4 mg/kg Q2W in pediatric patients with pJIA compared with RA adult participants at 200 mg Q2W



Abbreviations: pJIA: Polyarticular juvenile idiopathic arthritis; q2w: every two weeks; RA: rheumatoid arthritis Note: The simulation was conducted using PopPK model for a typical pJIA patient with weight of 46.5 kg and albumin of 45.0 g/L in Group A and weight of 18.4 kg and albumin of 44.5 g/L in Group B. The PK profile in a typical adult patient with RA was simulated in study POH0428 with weight of 71 kg and relative albumin of 0.78. **Source**: PopPK report – POH1134, m5.3.3.5-seq0168-BLA761037.

Reviewer's PopPK analysis:

The reviewer's independent analysis of the final PopPK model provided similar parameter estimates with similar precision as reported by the Applicant. The adequacy and predictability of the Applicant's PopPK model is supported by the reviewer's independent analysis. The summary results of the final PopPK model were provided in **Table 14**. The reviewer's estimates of post-hoc exposures at Week 30-32 interval were aligned with those of the Applicant except Ctrough,ss for group B, which is slightly lower than the Applicant's estimate (**Table 21**).

Table 21. Reviewer's post-hoc estimate of exposures following repeated SC administration at steady state in pediatric participants with pJIA – on the selected Dose 2

Weight Group	Dose	Model-predicted exposures Following repeated SC dose at SS

		N	$C_{max,ss}$[a] (mg/L)	$AUC_{0-\tau,ss}$[a] (day.mg/mL)	$C_{trough,ss}$[a] (mg/L)
Group A ≥30 kg	3 mg/kg q2w	40	27.1 (12.5) [46.0]	274 (129) [47.0]	9.17 (5.87) [64.0]
Group B <30 kg	4 mg/kg q2w	27	37.9 (13.88) [36.6]	365 (160) [43.8]	11.5 (7.27) [63.26]

[a] Estimates are presented as mean (SD) [%CV). AUC0-τ, ss= AUC [Week 30 – Week 32] for q2w regimens; Cmax, ss were calculated over week 30 to week 32 for q2w regimens; Ctrough, ss was calculated at week 32 for all regimens.
Source: Reviewer's analyses based on the final model.

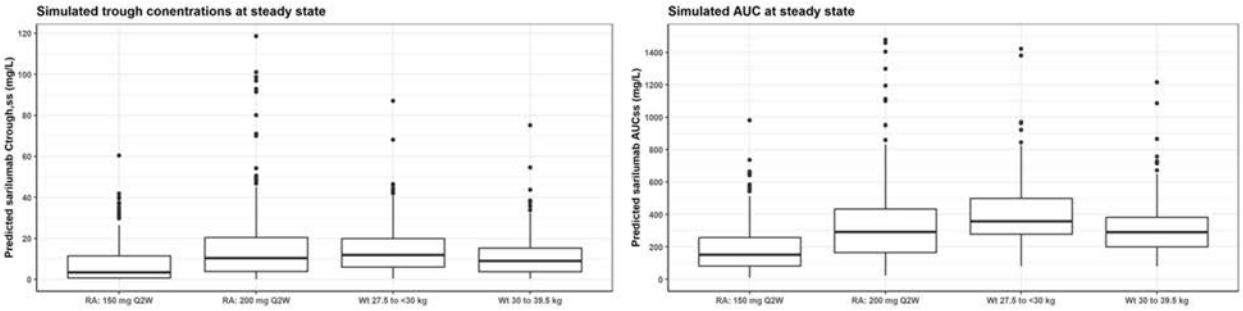
Body weight was identified as a significant covariate. The pediatric patients with a wide range of BW (11.5 – 71.8 kg) were included in the PopPK analysis. Simulation was performed to evaluate the trend of exposures with increase in body weight within each group (≥10 kg to <30 kg and ≥30 kg). Simulation indicates that at the selected dose 2, the exposures were increased with increase in BW from a median body weight within a group, while exposures decreased with a decrease in BW. However, the change in exposures within each group remains within the observed PK variabilities (58 – 89%) of pJIA patients. Hence, the selection of 4 mg/kg Q2W and 3 mg/kg Q2W corresponding to a BW of ≥10 kg to <30 kg and ≥30 kg (capped at 200 mg Q2W for BW≥63 kg) is reasonable. Refer to clinical pharmacology review **section 5.3** for further details.

Simulation was also performed to evaluate the change in exposures if a patient in group B (≥10 kg to <30 kg) continues taking 4 mg/kg despite the BW exceeding the upper limit of 30 kg. The comparison was made between the upper weight range of group B (27.5 kg to <30kg) and a higher body weight range (30 – 39.5 kg) for the same dose allocated for 27.5 – 30 kg. For simulation setup, body weight was increased from 27.5 kg to <30 kg to 30 – 39.5 kg at Week 32 by random sampling based on the observed BW distribution for each of these weight ranges.

Interestingly, simulation shows a slight decrease in exposures with increase in BW though BW-based dosing implied increasing trend of exposure with higher BW. It is to note that the parameter-BW relationship of CL and Vm indicates decreasing exposure with increase in BW. However, for BW-based dosing, the clearance does not increase in proportion to increased dosing as the exponent is <1 that describes CL/Vm~BW relationship, hence showing lower clearance with higher BW. For example, patients weighing 20 kg and 25 kg will receive 80 mg and 100 mg dose, respectively, indicating a 25% increase in dose for a 25% increase in BW. But for 20 kg BW, clearance will increase only ~15% for a 25% dose increment as estimated using the equation of CL-BW relationship mentioned in the **Table 16**. This supports the increasing trend of exposure with increased BW.

However, for increase in BW from 27.5 kg - <30 kg to 30 kg - 39.5 kg, exposures ($C_{trough,ss}$ and $AUC_{\tau,ss}$) were 18- 24% lower in higher BW group as the dose was not adjusted for higher body weight. Despite this change, the exposures are comparable with those of adult regimen of 200 mg Q2W (**Figure 21**).

Figure 21. Comparison of simulated exposures (AUC,ss and Ctrough during Weeks 30-32) between pediatric and adult patients when dosing at the same rate of 4 mg/kg

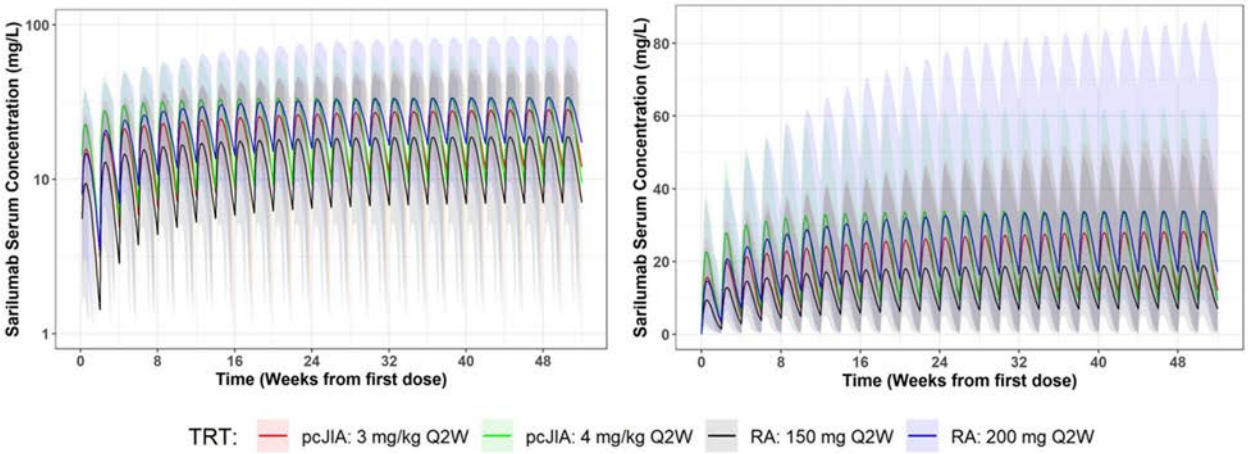


Note: 250 virtual pJIA patients were generated with body weights sampled from the observed distribution (for 27.5 - <30 kg: mean: 28.38 kg, SD: 0.61 and 30 – 39.5 kg: mean: 35.96 kg and SD: 2.56). Exposures were predicted at Weeks 30 – 32 and 62 – 64 weeks for 27.5 - <30 kg and for 30 – 39.5 kg categories, respectively. Similarly, 250 virtual adult patients with RA were generated with relevant covariates sampled from phase 3 adult trials. For adult, exposures were also predicted for Weeks 30 – 32. **Source:** Reviewer's analysis based on the final model of pJIA patients.

The Applicant's typical concentration-time profile indicates that the mean Ctrough at steady state is apparently lower for 4 mg/kg Q2W than that of 3 mg/kg Q2W (**Figure 20**). In contrary, post-hoc estimates of mean Ctrough at steady state for 4 mg/kg Q2W was greater than that of 3 mg/kg Q2W (**Table 20**).

Hence, additional simulations were performed to compare the PK profiles of pJIA patients for the selected dose regimens with those of adults following 150 mg/200 mg Q2W regimens. Though, the mean exposures appear to be slightly lower compared to that of 200 mg Q2W, these are bracketed between 150 mg Q2W (lowest regimen approved for adults to manage certain laboratory abnormalities) and 200 mg Q2W approved adult regimens for the treatment of RA (**Figure 22**). The reviewer's simulation results appear to be consistent with those reported by the Applicant for both groups. Though predicted Ctrough,ss was higher for 4 mg/kg regimen compared to that of 3 mg/kg based on post-hoc analyses, simulated typical PK profiles suggests opposite trends (**Figure 22**). This may be due to use of a typical BW for each groups (46.5 kg for group A and 18.4 kg for group B) in contrast to variable BW considered for post-hoc estimates. In both post-hoc and simulation analysis, reviewer's findings are generally consistent with those of the Applicant.

Figure 22. Comparison of sarilumab PK profiles in pJIA with those in adults for different dosing regimens



Notes: left panel is in semi-log scale; right panel is in linear scale. The simulation was conducted using PopPK model for a typical pJIA patient with weight of 46.5 kg and albumin of 45.0 g/L in Group A and weight of 18.4 kg and albumin of 44.5 g/L in Group B. The PK profile in a typical adult patient with RA was simulated in study POH0428 with weight of 71 kg and relative albumin of 0.78.

Exposure-Response Analyses

The Applicant conducted exposure-response (E-R) analyses for sarilumab collected in pediatric patients aged 2 to 17 years with pJIA using descriptive analyses and/or empirical E-R modeling and compared with those in patients with RA. The descriptive approach and data for E-R analyses has been described in section 5.3 of clinical pharmacology review. Here the E-R modeling approach and results are described.

The objectives of E-R analyses are

- To evaluate the E-R relationship in pediatric patients with pJIA and
- To assess the E-R relationship similarity between pediatric patients with pJIA and adult patients with RA.

Data used in E-R modeling

- For adults, the E-R analyses on efficacy were performed using the data from study EFC11072 Part A and Part B Cohort 2. All the data from EFC11072 (Part A and Part B Cohort 1 and 2) and EFC10832 were used for the E-R analyses on safety (see **Table 22**)

Table 22. Studies included in the E-R analyses for adult RA

Study	Phase/ Population	Design	Treatments	N	Duration	Included in E-R analysis
EFC11072 Part A	2/MTX-IR	R, DB, PC, add-on MTX	100 mg q2w 150 mg q2w 100 mg qw 200 mg q2w 150 mg qw Placebo	51 51 50 52 50 52 N=306	12 weeks	Efficacy and Safety
EFC11072 Part B Cohort 1	3/MTX-IR	R, DB, PC, add-on MTX, rescue[a] at 16 weeks	100 mg q2w 150 mg q2w 100 mg qw 200 mg q2w 150 mg qw Placebo	28 30 29 28 27 30 N=172	52 weeks[b]	Safety
EFC11072 Part B Cohort 2	3/MTX-IR	R, DB, PC, add-on MTX, rescue[a] at 16 weeks	150 mg q2w 200 mg q2w Placebo	400 399 398 N=1197	52 weeks	Efficacy and Safety
EFC10832	3/TNF-IR[c]	R, DB, PC, add-on DMARDs[d], rescue[a] at 12 weeks	150 mg q2w 200 mg q2w Placebo	181 184 181 N=546	24 weeks	Safety

Abbreviations: IR=inadequate response; DB=double-blind; DMARD=disease-modifying antirheumatic drug; MTX=methotrexate; R=randomized; PC=placebo controlled; qw=once weekly; q2w=every other week; TNF=tumor necrosis factor

a Patients with an inadequate response were rescued with open-label highest sarilumab dose.

b After dose selection, blinding of the patients in Cohort 1 who were receiving the selected doses (or placebo) was maintained. Patients in the "non-selected" sarilumab dose in Cohort 1 were discontinued from Study EFC11072 and could enter the long-term safety Study LTS11210

c Patients with a history of IR or intolerant of TNF antagonists were also allowed to enroll.

d Concomitant DMARDs: MTX, leflunomide, hydroxychloroquine, or sulfasalazine

Source: The Applicant's PK/PD study report (cts0123), m5.3.3.5-seq-0168

- For pJIA patients, a total of 101 pediatric patients with pJIA were included, who have at least completed the 52-week study intervention period or discontinued from the study before Week 52 with a data cut-off dated January 13, 2023.

Methodology of E-R analyses

E-R analyses were conducted using observed trough concentration of functional sarilumab. In addition, potential impacts of baseline covariates on the E-R relationship were explored. The efficacy endpoints considered for E-R analyses include JIA-ACR (Juvenile Idiopathic Arthritis-American College of Rheumatology) responses. Specifically, JIA-ACR30/50/70 responses at Week 12 for adults with RA and pediatric patients with pJIA were used. For E-R analyses of safety, the percent change from baseline in Absolute Neutrophil Counts (ANC) at Week 12 were compared between adults with RA and pediatric patients with pJIA.

Handling of missing data

For the E-R analyses using observed Ctrough, missing data at Week 12 were imputed using last observation (measured during the 12-week core treatment period) carried forward (LOCF) approach in the pJIA study. In analyses at Week 24 and/or Week 48, any missing PK exposure at Week 24 was imputed with the observed value at Week 12. Any missing PK exposure at Week 48 was imputed with the observed value at Week 24.

In regards to the efficacy endpoints, missing data were handled using the below 3 approaches:

- **Non-responder imputation approach**: Patients with missing data at Week 12 will be automatically considered as non-responders. This non-responder imputation approach was used in the adult RA application both for the primary analysis of efficacy and in the E-R analysis. As a result, this imputation approach is therefore implemented in the pJIA study to be consistent with the approach used in adult RA;
- **LOCF approach**: The missing data at Week 12 were imputed using the last value measured during the 12-week core treatment period. This imputation approach is to ensure alignment with the imputed PK concentrations;
- **Completers approach**: Only patients who completed the 12-week core treatment period and with data available at Week 12 were included in the analysis. This approach is to eliminate any potential bias introduced by the missing data imputations.

In regards to the safety endpoints including ANC measurements and number of Grade 3 or 4 neutropenia, missing data at Week 12 were imputed using the LOCF approach. No missing data were imputed for other safety endpoints.

JIA ACR30/50/70 responders and non-responders at Week 12 in pediatric patients with pJIA were modeled using a logistic regression. For patients who discontinued treatment prior to Week 12, their JIA ACR30/50/70 status were considered as non-responders at Week 12 and their last observed trough serum concentration values were carried over to Week 12. Due to the fact that baseline body weight was a critical patient enrollment criterion, it was considered as main effect in base PK-PD model. For each endpoint, the following 3 base models were tested to select the best fitted base model by AICc.

- Logit(Responder) = $b0$ + $b1$ × Sarilumab Exposure + $b2$ × Baseline Weight +
- Logit(Responder) = $b0$ + $b1$ × ln(Sarilumab Exposure) + $b2$ × Baseline Weight

  Note: Natural-log was used.
- Logit(Responder) = $b0$ + Emax × Sarilumab Exposure/(EC50 + Sarilumab Exposure) + $b2$ × Baseline Weight +

Where Logit() is the natural log function of the odds and Responder odds is Probability(Responder)/(1 − Probability(Responder)).

Based on the best-fitted base model, effects of additional covariates, as a main effect and/or an interaction with sarilumab concentration, were tested and included in the PK-PD model.

The same base models with respect to safety endpoints (e.g., %change from baseline in neutrophil counts) were evaluated. The best-fit model was selected and effects of additional covariates, as a main effect and/or an interaction with sarilumab concentration were tested.

The effects of baseline covariates were explored in the PK-PD model. The covariates that were tested in the adult E-R model were considered as the potential covariates for the pediatric E-R model.
Univariate analysis was implemented to select the potential significant covariates. Next forward selection with significant level 0.05 was used to choose the covariates that were significant in univariate analysis. The potential covariates are listed below.

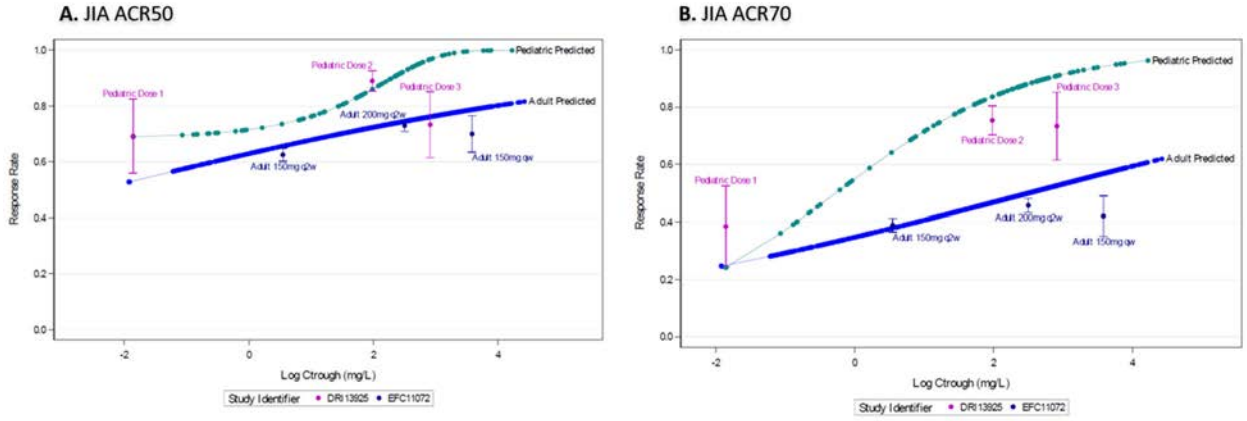
For efficacy or safety endpoint, its baseline-by-concentration (or baseline-by-ln(concentration) for log-linear model) interaction was also tested in the base PK-PD model and considered for inclusion if the interaction P value was highly signification (P value ~ 0.01 or less).

Applicant's summary of PK-PD analyses
Both descriptive and logistic regression analyses were conducted to describe the dose/exposure-response relationship at Week 12 in pediatric and adult patients. Since the number of components and response criteria are very different between ACR responses for adult RA and JIA-ACR response for pJIA, to better compare the E-R relationships on efficacy between adult RA and pJIA, the 'JIA-ACR' responses are defined in adult RA using the definition of JIA-ACR responses. This led to conversion of adult ACR responses to JIA ACR 30/50/70 response that were used for PK-PD analyses.

- Descriptive dose/exposure-response analyses were conducted in pediatric participants with pJIA and adults with RA for JIA ACR30/50/70 at Week 12. The analyses indicated that response rates in pJIA patients increased from dose 1 to dose 2 and no further increase of response rates from Dose 2 to Dose 3 based on non-responder imputation approach, justifying the selection of dose 2. Similar trends were observed in analysis conducted with LOCF approach at Week 12. The response rates at dose 2 were numerically higher compared to that of 200 mg Q2W in adult with RA (see section 5.3.2 for details).
- The logistic regression analyses were performed to establish a linear relationship between the JIA ACR30/50/70 and Ctrough at Week 12 in pediatric and adult patients. Across all efficacy endpoints, there is a trend of increased model-predicted response rates with increase in exposures based on non-responder imputation approach, which agrees with the observed response rates except for dose 3. However, the model-predicted response rates showed a departure from the observed for JIA ACR70 though the trend of E-R is similar to that for JIA ACR30/50 (**Figure 23** and see section 5.3.2 - **Figure 6**). In pJIA patients, the model-predicted response rates plateaued at the median Ctrough of dose 2, supporting its selection for the treatment of pediatric patients with pJIA. It is noted that the results between interim PK-PD analyses (in 42 pJIA patients for dose range finding portion) and final PK-PD analyses for all doses after 101 pediatric patients completed 1-year treatment are consistent that further justifies dose 2 selection. In line with the descriptive dose-response relationship, the empirical modeling also suggests that response rates were higher in pJIA patients compared to those in adults at the approved dosing regimen of 200 mg Q2W. However, the trend of

E-R relationship is similar and comparable between pediatric and adult patients (**Figure 23**).

Figure 23. E-R Relationship based on the non-responder imputation approach in pediatric participants with pJIA at Dose 1, Dose 2 and Dose 3 and in adult participants with RA by dose groups



Log Ctrough: concentration observed before drug administration during repeated dosing presented in the natural log values. Error bar for observed value is 95% CI of response rate. **Source**: The Applicant's PK/PD study report (cts0123), m5.3.3.5-seq-0168.

- For dose 2 in pJIA patients, E-R relationship suggested an increasing trend of response rate with the Ctrough tertiles reaching a plateau at second tertile except for JIA ACR30 based on non-responder imputation approach. The response rates are similar across all tertiles for JIA ACR30. Overall, the E-R trend for dose 2 is consistent with that of adult with RA as response increased with increasing Ctrough tertiles.
- Exposure-response analyses for safety were conducted on safety endpoints such as ANC percentage change from baseline at Week 12 using both descriptive and logistic regression approaches. The exposure-safety relationship indicates that the increase in dose or Ctrough is associated with greater percentage of ANC decrease from baseline with maximum decrease occurring at around 20 mg/L, beyond which the curve is mostly flat (**Figure 8**). See section 5.3.2, clinical pharmacology section for more data and discussion on exposure-safety analyses.

Reviewer's Comments

Based on the cumulative experience with drug development in pJIA, 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)", the Agency has reevaluated its approach to pediatric assessment for pJIA and pediatric PsA. Specifically, the Agency has taken into consideration the high degree of similarity between adults with RA and PsA and pediatric patients with JIA and PsA, respectively, 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 and PsA could be extrapolated to pediatric patients with RA and PsA, respectively, based on matching of the PK exposures between the two populations. This extrapolation of efficacy is based on appropriate scientific justification and robust data to support the expectation of similarity in exposure-response between the two populations which could be product-specific.

The reviewer found the exposure response assessments are in general acceptable and in support of the proposed dose in pediatric patients with pJIA. There is a trend of greater model-predicted response at Week 12 with increasing Ctrough that plateaued at the median Ctrough of proposed dose for JIA ACR 30/50/70 supporting the dose selection. PK-PD model analysis also showed a trend toward greater percentage change of ANC from baseline with increasing Ctrough across evalauted doses 1, 2, and 3. For [redacted] dose 2, PK-PD analysis suggested a steep decline in ANC levels at Ctrough up to 20 mg/L, beyond which E-R relationship was shallow in participants with pJIA. The exposure-safety relationship is similar in pediatric participants with pJIA [redacted] and adult participants with RA.

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