14 November 2024
EMA/572171/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kevzara

International non-proprietary name: Sarilumab

Procedure No. EMEA/H/C/004254/X/0043/G

Note

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

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List of abbreviations

ACR:	American College of Rheumatology
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse events of special interest
ANC:	absolute neutrophil count
AUC_{0-T}:	area under the concentration versus time curve calculated using the trapezoidal method over the dosing interval
bDMARD:	biologic DMARD
BW:	body weight
CHAQ-DI:	childhood health assessment questionnaire-disease index
CL0/F:	apparent linear clearance
C_{max}:	maximum concentration
csDMARD:	conventional synthetic disease-modifying antirheumatic drug
Ctrough:	trough concentration
DMARD:	disease modifying antirheumatic drug
EOS:	end-of-study
E-R:	exposure-response
ESR:	erythrocyte sedimentation rate
GCP:	Good Clinical Practice
hs-CRP:	high-sensitivity C-reactive protein
IL-6R:	interleukin-6 receptor
IMP:	investigational medicinal product
JADAS:	juvenile arthritis activity score
JIA:	juvenile idiopathic arthritis
mAb:	monoclonal antibody
MTX:	methotrexate
Nab:	neutralizing antibody
oJIA:	oligoarticular JIA
pcJIA:	polyarticular-course juvenile idiopathic arthritis
PD:	pharmacodynamic
PK:	pharmacokinetics
PMR:	polymyalgia rheumatica
Pop PK:	population pharmacokinetic
PT:	preferred term
PY:	participant-years
q2w:	every 2 weeks
qw:	every other week
RA:	rheumatoid arthritis
RF:	rheumatoid factor
RF-:	rhumatoid factor negative
RF+:	rhumatoid factor positive
SAE:	serious adverse event
SAP:	statistical analysis plan
SOC:	system organ class
TEAE:	treatment non emergent adverse event
TNF-α:	tumor necrosis factor alpha
URTI:	upper respiratory tract infections
Vm:	maximum target mediated rate of elimination

1. Background information on the procedure

1.1. Submission of the dossier

Sanofi Winthrop Industrie submitted on 24 November 2023 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to add a new strength of 175 mg/ml solution for injection in vial, grouped with an Extension of indication to include treatment of active polyarticular-course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older for KEVZARA, based on results from study DRI13925; this is a multinational, multi-center, open-label, 2 phase, 3 portions study to describe the PK profile as well as safety and efficacy of sarilumab. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

1.3. Information on Paediatric requirements

At the time of submission of the application, the PIP P/0067/2013 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	24 November 2023
The procedure started on	28 December 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	25 March 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 March 2024
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	04 April 2024
The CHMP and PRAC Rapporteur's updated Assessment Report was circulated to all CHMP and PRAC members on	17 April 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 April 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	19 July 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 August 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 September 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	12 September 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	19 September 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	15 October 2024
The CHMP Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 October 2024
The CHMP Rapporteur circulated the updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	07 November 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kevzara on	14 November 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood.

The following subtypes of JIA are collectively referred to as polyarticular-course juvenile idiopathic arthritis pcJIA since they present similar clinical features (affecting 5 or more joints and ultimately evolving to permanent joint damage):

- Oligoarticular JIA (oJIA) 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 4 joints (typically large joints, such as knees, ankles, wrists) and is not associated with constitutional findings such as fever, weight loss, fatigue or systemic signs of inflammation. Disease onset ranges from 1 to 5 years and peaks at 2 to 3 years. If greater than 4 joints become affected after the first 6 months of disease, it is designated as extended oligoarthritis (e-oJIA) in contrast to persistent oJIA that features only up to 4 joints throughout the course of the disease. Oligoarticular JIA carries a risk for developing chronic anterior uveitis, especially when antinuclear antibody is present and disease onset is in early childhood.
- Polyarticular JIA (pJIA) that is defined as an arthritis affecting 5 or more joints during the first 6 months of disease. Both large (e.g., hips and knees) and small (e.g., joints of the hand) joints can be involved, and often in symmetric bilateral distribution. Low grade fever can accompany the arthritis. Presence of Rheumatoid Factor (RF) differentiates 2 forms of pJIA:

    - Rheumatoid Factor-positive (RF+) pJIA is diagnosed in only 3% to 5% 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: it represents 11% to 28% of all children and adolescents with JIA. It presents at a younger age (in late childhood, 6 to 12 years) with respect to the RF+ pJIA. Radiologic changes in RF-negative disease occur later than in RF-positive disease and it may not be as destructive and persistent.

2.1.2. Epidemiology

JIA is the most common rheumatic disease of childhood with a global prevalence estimated to range from 3.8 to 400/100,000 persons with an incidence of 1.6 to 23/100,000 persons-year. JIA affects primarily females (3:1 female/male ratio) and comprises 7 subtypes categorised by age of onset, range and disease characteristics in the first 6 months after onset.

2.1.3. Aetiology and pathogenesis

Juvenile idiopathic arthritis (JIA) as defined by International League of Associations for Rheumatology (ILAR) classification is an arthritis of unknown aetiology that begins before 16 years of age and persists for at least 6 weeks with other known conditions excluded.

2.1.4. Clinical presentation, diagnosis

Clinical features of oJIA and pJIA subtypes in patients from the USA and Europe are presented in the table below.

Feature	Oligoarticular JIA			Polyarticular JIA	
	Overall	Persistent	Extended	**RF−**	RF+
				pcJIA subtypes	
Age at onset	Peak at age 2–4 years	—	—	Biphasic pattern: early peak at age 1–4 years, later peak at age 6–12 years	Late childhood or adolescence
Female:male ratio	3:1	—	—	3.2:1	5.7:1
Number of joints affected	1–4 joints in the first 6 months	1–4 joints throughout the disease course	5 or more joints after first 6 months	5 or more joints	5 or more joints
Pattern of arthritis	Affects large joints asymmetrically in the first 6 months (commonly knees and ankles)	Pattern maintained throughout the disease	After 6 months small joints also affected Presence of ankle and/or wrist involvement within the first 6 months is more common in this subcategory Erosive disease	Polyarthritis in large and small joints Tends to be symmetric, and to affect fewer joints than polyarticular RF+ JIA	Symmetric polyarthritis in large and small joints, similar to adult rheumatoid arthritis
Frequency	30–60% of all JIA	50% of all oJIA[a]	50% of all oJIA[a]	10–30% of all JIA	5–10% of all JIA
Uveitis[b]	17–26%[c]	14–26%[c]	17–36%[c], [d]	4–25%[c]	0–2%
Systemic symptoms (eg, fever, weight loss, anemia)	Absent	—	—	Rare	Present
Anti-nuclear antibody	75–85%	70–80%	80–95%	50–80%	~ 55%
Rheumatoid factor	Absent	—	—	Absent	Present[e]
Anti-CCP antibody[f]	0–6%	0–9%	0–6%	50–80%	~ 55%

Feature	Oligoarticular JIA			Polyarticular JIA	
	Overall	Persistent	Extended	**RF−**	RF+
				pcJIA subtypes	

a 4–6 years after disease onset.

b Risk factors for uveitis include ANA+, young age at diagnosis, female sex and oJIA subtype.

c Higher percentage reported in Finland.

d Uveitis generally develops before extension of arthritis.

e RF detected in two or more tests at least 3 months apart during the first 6 months of the disease.

f Using a synthetic CCP variant. Low et al found CCP+ for in 60% of patients with oJIA and 93% of those with polyarticular RF− JIA.

Abbreviations: + = positive; − = negative; ANA = antinuclear antibody, CCP = cyclic citrullinated peptide; CTLA-4-Ig = cytotoxic T-lymphocyte-associated protein 4 immunoglobulin

2.1.5. Management

The treatment of pcJIA combines anti-inflammatory and immunomodulatory medications with physical and occupational therapy, an occasional need for surgery, nutritional support and psychosocial and educational partnership with patients and parents. In the past 2 decades, there have been major improvements in the treatment paradigm of the different subtypes of JIA, including pcJIA. Clinical remission or, if not possible, reaching a minimal or low disease activity are the main objectives of treatments, consisting of early adoption of treatments, distinct treatment approaches for this heterogeneous group of childhood arthritis, as well as patient centered approach with treat-to-target strategy.

As a first line treatment, patients with pcJIA who have no systemic manifestations can be treated with either non-steroidal anti-inflammatory drugs (NSAIDs) or intra-articular injections of glucocorticoids (GCs). If patients do not respond to the first line of treatment, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX) that are immunosuppressive and immunomodulatory, targeting intracellular or extracellular elements of an inflammation pathway, can be administered. Since the demonstration of its efficacy for treatment of JIA in 1992, MTX has become the systemic drug of choice for the disease.

According to international guidelines and recommendations, addition of biologic disease modifying antirheumatic drugs (bDMARDs) are suggested if moderate or high disease activity persists after 3 months of treatment with MTX. The 2019 ACR guidelines recommend changing or adding biologic DMARDs to MTX if no or minimal response is observed after 6-8 weeks with MTX.

Biologic DMARDs approved for pcJIA are TNF-α antagonists, selective T-cell costimulator modulator, humanized mAb against IL- 6R and janus kinase (JAK) inhibitor.

2.2. About the product

Sarilumab is a recombinant human immunoglobulin 1 monoclonal antibody (mAb) of the immunoglobulin isotype 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 signalling.

Sarilumab is currently authorised in combination with methotrexate for the treatment of moderately to severely active rheumatoid arthritis (RA) adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs).

Initially the claimed indication was:

Kevzara is indicated for the treatment of active polyarticular-course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older.

2.3. Type of Application and aspects on development

The application is supported by results from study DRI13925, a multinational, multi-center, open-label, 2 phase, 3 portions trial to describe the PK profile as well as safety and efficacy of sarilumab. Study DRI13925 was initially designed as a dose-finding study to determine the appropriate dose regimen in pcJIA participants, and the design was subsequently modified based on health authority recommendations in order to minimize the number of paediatric participants to be enrolled and to avoid a placebo arm. The disease course and the treatment response are considered to be sufficiently similar to those observed in adult RA participants to enable an extrapolation of data from adults to children.

The study design was agreed upon European Medicines Agency (EMA, Paediatric Committee [PDCO]) in the context of the paediatric investigational plan (PIP).

2.4. Quality aspects

2.4.1. Introduction

This is an extension application to add a new strength of 175 mg/ml solution for injection in a vial, to the already approved 150 mg and 200 mg strengths available in prefilled syringe (PFS) and prefilled pen (PFP) presentations. The extension application is grouped with an extension of indication to include treatment of active polyarticular-course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older.

The finished product (FP) is presented as solution for injection containing 175 mg/mL of sarilumab as active substance (AS) in 2R (2 mL) vials.

Other ingredients are: histidine, arginine, polysorbate 20, sucrose and water for injections.

The composition for the new Kevzara presentation (vial) is the same as the approved PFS and PFP presentations.

The product is available in vials (type I glass) closed with copolymer of ethylene and tetrafluoroethylene (ETFE)-coated bromobutyl stoppers and crimped with an aluminium seal with a flip-off cap. This is a single use vial for subcutaneous administration.

2.4.2. Active Substance

There is no change to the active substance section. The approved sarilumab formulated drug substance (FDS) for the 200 mg PFS and PFP is also used for the manufacture of the new proposed presentation sarilumab solution for injection 175mg/mL in 2R vials. Therefore, the approved AS sections are applicable also to the sarilumab solution for injection 175mg/mL.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The nominal relative composition of the components is the same for the proposed Kevzara 175 mg/mL solution for injection in vial and the approved 200 mg PFS and PFP presentations as the same AS and excipient concentrations are used (175 mg/mL sarilumab, L-histidine/L-histidine monohydrochloride monohydrate, L-arginine, sucrose, polysorbate 20, pH 6.0). An overfilling is introduced for the vial presentation. Each vial is filled with at least 1.54 mL (equivalent to 270 mg) of finished product in order to ensure that 1.14 mL (equivalent to 200 mg) can be withdrawn.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the FP formulation.

The primary packaging is a type I glass vial closed with ETFE-coated bromobutyl stoppers and crimped with an aluminium seal with a flip-off cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Developmental studies were conducted to demonstrate that choice of the manufacturing process and container closure system is acceptable. Comparability of the technical/justification vial batches to different batches of pre-filled syringes was demonstrated.

2.4.3.2. Manufacture of the product and process controls

Manufacturing, labelling, packaging and release / stability testing are performed at the same manufacturing site which is already involved and approved for the testing of FDS, Bulk-PFS, PFS and for the manufacturing, testing, labelling, release and secondary packaging of PFP Sarilumab solution for injection. The GMP documentation has been adequately updated.

The manufacturing process for production of the vials is standard and consists of the following steps: thawing, pooling and mixing of sarilumab FDS, prefiltration of the bulk solution, sterilizing filtration, aseptic filling of bulk finished product solution into vials, stoppering and crimping, visual inspection, container closure integrity testing, labelling and packaging. For each manufacturing step the critical process parameters and in-process controls were adequately defined, validated and ensure the control of the manufacturing process. The rationale of the critical status for CPPs and CIPCs setting were provided in the manufacturing process development section.

The manufacturing process of sarilumab finished product, 175 mg/mL in vials has been successfully validated and it has been demonstrated that the manufacturing process is capable of producing the FP of intended quality in a reproducible manner. During validation runs, all results of the in-process controls and additional in-process tests met the predefined acceptance criteria. All process steps operated within the predefined ranges and conformed to the microbiological control. Analytical results of the release testing of the validation batches are provided in the dossier. The results of all validation batches comply with the acceptance criteria defined for the final FP. The impact of transport on product quality, integrity and performance was assessed and considered acceptable.

2.4.3.3. Product specification, analytical procedures, batch analysis

The proposed release specification for sarilumab, solution for injection, 175 mg/mL (270 mg) in vials is comparable to the release specification of sarilumab in bulk pre-filled syringes (200 mg) as the same concentration of the active ingredient (175 mg/mL) and the identical formulation are used. Nevertheless, the test items for the functionality of the syringe are not relevant for the vial presentation. Instead, the

test item“extractable volume”was introduced for the vial presentation. The proposed release specification for sarilumab, solution for injection in vials is acceptable.

Release tests performed on sarilumab solution for injection in vials are Identity by immunoassay, potency, total protein content, identification and analysis of charge variant, purity, appearance, clarity, color, pH, particulate matter, extractable volume, sterility, and bacterial endotoxins. The documentation of analytical procedures used for sarilumab solution for injection, 175 mg/mL in vials is acceptable.

A 2 mL, colorless clear glass vial, Type I and a Type I bromobutyl rubber closure coated with an ethylene tetrafluoroethylene (ETFE) polymer type film on the product contact side is used for this new presentation. The closures are crimped to the vials with an aluminum seal with plastic flip-off cover. Compliance to the current Pharmacopoeia is confirmed.

2.4.3.4. Stability of the product

A shelf life of 24 months when stored protected from light at 5 ± 3 °C is proposed for the vial presentation. This is supported by real time stability data. The test parameters and test intervals long-term, accelerated, and stress stability studies are satisfactory. The results after up to 24 months of storage at +5 ± 3°C complied with the acceptance criteria and confirm the stability of the FP at long term.

Based on available stability data, the shelf-life of 24 months when stored at 5 ± 3 °C protected from light, as stated in the SmPC, is acceptable.

2.4.3.5. Post approval change management protocol(s)

N/A

2.4.3.6. Adventitious agents

There is no change to approved adventitious agent’s safety evaluation, which remains applicable.

2.4.3.7. GMO

N/A

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

This extension application includes the addition of a new strength and presentation of Kevzara, sarilumab solution for injection 175mg/mL, in 2R vials. The new container closure system is a 2 ml vial (type I glass) containing 270 mg sarilumab in 1.54 ml solution, which is closed with ETFE-coated bromobutyl stoppers and crimped with an aluminium seal with a flip-off cap. This new presentation is required for the treatment of active polyarticular-course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older as the dose should be calculated based on the patient’s body weight (kg) at each administration.

Manufacturing, labelling, packaging and release / stability testing are performed by Sanofi. The GMP documentation has been adequately updated.

The same AS and FDS as for the approved 200 mg PFS and PFP presentations is used to manufacture Kevzara, sarilumab solution for injection 175mg/mL in 2R vials. Therefore, the composition for the proposed presentation is the same as the approved 200 mg PFS and PFP presentations. The

manufacturing operations of the FP thawing, pooling and mixing, prefiltration and sterilization by filtration are also the same. The manufacturing process has been successfully validated.

The proposed release specification is comparable to the release specification of sarilumab 200 mg in bulk pre-filled syringes except for functionality of the syringe. The parameter extractable volume was introduced for the vial presentation.

A shelf life of 24 months when stored protected from light at 5 ± 3 °C is proposed for the vial presentation and supported by real time stability data.

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

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical data have been submitted in this application, which is considered acceptable.

Non-clinical safety was assessed in a comprehensive program submitted as part of the original marketing application for treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients.

An amendment related to an assay used in the previously submitted juvenile mouse toxicity study report using the surrogate murine monoclonal antibody, REGN844, (JUV0030) was made and the amended report "*REGN844: 9-Week Subcutaneous Toxicity Study in the Juvenile Mouse Followed by a 13-Week Recovery Period"* was provided in this application.

2.5.2. Pharmacokinetics

2.5.3. Toxicology

2.5.3.1. Reproductive and developmental toxicity

REPORT AMENDMENT: A 9-WEEK SUBCUTANEOUS TOXICOLOGY STUDY IN JUVENILE MICE WITH A 13-WEEK RECOVERY PERIOD

The report was amended due to the fact that the detection assay for IgG was not specific to endogenous mouse IgG2a, and would also detect REGN844 (a murine IgG2a). Therefore, the increased

IgG noted in the original report is now considered a combination of endogenous IgG and REGN844. The increases noted in the IgM and IgG concentrations were reversible at the end of the recovery period. None of the increases in IgG or IgM was considered biologically relevant effects related to REGN844 administration.

In summary, REGN844 treatment was well tolerated in juvenile mice at doses up to 200 mg/kg/week. The study does not raise concern for the use of sarilumab in young children.

2.5.4. Ecotoxicity/environmental risk assessment

A claim of exclusion from environmental risk assessment testing is made according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline) because sarilumab is a monoclonal antibody consisting of linked naturally occurring amino acids unlikely to present environmental risk. Per the ERA Guideline, "In the case of products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment."

2.5.5. Discussion on non-clinical aspects

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

An amendment related to an assay used in the previously submitted juvenile mouse toxicity study report using the surrogate murine monoclonal antibody, REGN844, (JUV0030) was made and the amended report "*REGN844: 9-Week Subcutaneous Toxicity Study in the Juvenile Mouse Followed by a 13-Week Recovery Period"* was provided in this application.

Overall the amendment of the report does not alter the overall conclusion or validity of the study and the nonclinical assessment of the original marketing application for treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients is still valid.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, sarilumab is not expected to pose a risk to the environment.

2.5.6. Conclusion on the non-clinical aspects

Non-clinical safety was assessed in a comprehensive program submitted as part of the original marketing application for treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients. From the non-clinical point of view, the extension of indication application is considered acceptable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The MAH has provided a statement to the effect that clinical trials conducted outside the community

were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of study	- Study identifier - Location of study report - Coordinating Investigator (and center) - Number of centers	- Objective(s) of study - Study design and type of control	Test product(s): - Formulation - Dosage regimen - Route of administration	Reference therapy: - Formulation - Dosage regimen - Route of administration	Number of study participants - Total[a, b, c] - Gender[b] (M/F) - Race[b] (C/B/O) - Age[b] mean ± SD (range) - Treatment group[b]	Healthy study participants or diagnosis of study participants	Duration of treatment	Study status Type of report
Study reports of uncontrolled clinical studies								
PK, PD, efficacy and safety	[DRI13925 12-week core treatment phase] [DRI13925 1-year 3 portions] Sec. 5.3.5.2 Pr De Benedetti F. (Ospedale Pediatrico Bambino Gesu, Roma, Italy) 15 active centers	To describe the PK profile of sarilumab in patients aged 2 to 17 years with pcJIA in order to identify the dose and regimen for adequate treatment of this population. To describe the long-term safety of sarilumab in patients with pcJIA and to describe the PD profile and the efficacy of sarilumab in patients with pcJIA. Multinational, multicenter, open-label, 2-phase study: a 12-week core	**Sarilumab:** **Portion 1:** **Dose 1:** - Group A (≥30 kg and ≤60 kg): 2 mg/kg q2w - Group B (<30 kg and ≥10 kg): 2.5 mg/kg q2w **Dose 2:** - Group A (≥30 kg and ≤60 kg): 3 mg/kg q2w - Group B (<30 kg and ≥10 kg): 4 mg/kg q2w **Dose 3:** - Group A (≥30 kg and ≤60 kg): 2 mg/kg qw - Group B (<30 kg and ≥10 kg): 2.5 mg/kg qw **Portion 2 and 3:** **Dose 2:**	NA	**12-week core treatment phase (portion 1):** - 42/42/34 - 15/27 - 33/0/9 - 8.9 ± 4.8 (2-17) - Dose 1: 13 - Dose 2: 14 - Dose 3: 15 **-1-year (portions 1, 2 and 3):** - 102/101/86 - 24/77 - 88/0/13 - 8.9 ± 4.8 (2-17) - Dose 1: 13	Study participants with pcJIA	156 weeks for portion 1 and 2, 96 weeks for portion 3	On-going Interim
		treatment phase comprised of a dose-finding portion within 2 weight groups followed by an extension phase of up to 144 weeks.	- Group A (≥30 kg): 3 mg/kg q2w (capped at 200 mg q2w for participants with BW ≥63 kg) - Group B (≥10 kg and <30 kg): 4 mg/kg q2w		- Dose 2: 73 - Dose 3: 15			

a Randomized,
b Treated,
c Completed the 12-week treatment period for 12-week core treatment phase or the 52-week treatment period for the 1-year 3 portions analysis.
B: black, BW: body weight, C: Caucasian, F: female, M: male, O: other, pcJIA: polyarticular-course juvenile idiopathic arthritis, PD: pharmacodynamic, PK: pharmacokinetic, qw: every week, q2w: every 2 weeks, SD standard deviation.

2.6.2. Clinical pharmacology

The PK of sarilumab has been characterized in healthy subjects and adult participants with RA; the results were provided in the original RA marketing application. For this application, semi-intensive (first dose only) and/or sparse sampling and PK-population analyses were used to assess the PK in participants aged 2 to 17 years with pcJIA in the Study DRI13925.

The PK, PD, immunogenicity, and E-R relationships of sarilumab were assessed in participants aged 2 to 17 years with pcJIA in the Phase 2b Study DRI13925 (1 year from the time the last patient was enrolled in the study). The data from Study DRI13925 were used for the Pop PK analysis and the PK-PD analyses (for the key efficacy and safety endpoints) in the pcJIA population, and compared with those in adults with RA. The primary endpoint was sarilumab PK exposure from baseline to Week 12. The secondary endpoints included descriptive safety, pharmacodynamics, and efficacy endpoints.

A total of 101 participants were enrolled and treated in the study.

The proposed posology in patients with pcJIA above 2 years of age is 4 mg/kg subcutaneously once every 2 weeks in patients weighing 10 to less than 30 kg or 3 mg/kg subcutaneously once every 2

weeks in patients weighing greater than or equal to 30 kg capped at 200 mg q2w for patients weighing ≥63 kg. Doses were selected to provide sarilumab exposure similar to the recommended 200 mg q2w dose regimen in adults with rheumatoid arthritis as detailed in the corresponding paediatric investigational plan (PIP).

A previously established Pop PK model for patients with RA (Study POH0428) served as the basis for Pop PK simulations (after extrapolation to paediatric patients with allometric exponents driven by body weight) supporting the selection of three doses in the dose finding portion of Study DRI13925 for patients with pcJIA. Pop PK model development in participants with pcJIA was based on the previously established Pop PK model and stepwise adapted: two population PK studies have been performed using nonlinear mixed effect modelling: POH0516, explorative interims pop PK on dose-finding portion data from DRI13925 (N=42), and POH1134 on the full data set from DRI13925 (101 treated subjects, semi-intensive first-dose only sampling and/or sparse sampling, data cut-off:13 Jan 2023) from all participants with pcJIA who completed the 52-week study intervention period (or discontinued from the study before Week 52).

The latter model (POH1134) was used to characterize PK in paediatric subjects with pcJIA, to assess the influence of intrinsic and extrinsic factors on sarilumab PK in paediatric participants aged 2 to 17 years and to estimate individual sarilumab post-hoc PK exposures in patients with pcJIA. Given additional PK data were added at the time of initiation of study POH1134 (N=101) compared with POH516 (N=42), only data from Study DRI13925 in participants with pcJIA were used for this analysis, without pooling PK data in participants with RA.

Table 1: Sarilumab pharmacokinetic and pharmacodynamic assessments in clinical studies and analyses in participants with pcJIA

Study type	Study code/ Portion	Dose or dose range Treatment duration	Number of study participants enrolled	PK sampling
PK and PD assessments in efficacy/safety studies in participants aged 2 to 17 years with pcJIA				
Repeated SC dose (12-week core phase followed by an extension phase)	DRI13925	3 portion study (dose-finding, 2nd and 3rd portions, as detailed below) consisting of a 12-week core phase followed by an extension phase Participants: Group A: ≥30 kg and ≤60 kg for Portion 1 and ≥30 kg for Portions 2 and 3 Group B: ≥10 kg and <30 kg	102 Total (101 treated) 56 Group A (55 treated) 46 Group B	Semi-intensive (first dose only) and/or sparse sampling [a]
	Dose-finding portion [b]	Sequential, ascending dose finding portion with 3 investigated doses for the selection of dose in each body weight group Dose 1 Group A: 2 mg/kg q2w Group B: 2.5 mg/kg q2w Dose 2 Group A: 3 mg/kg q2w Group B: 4 mg/kg q2w Dose 3 Group A: 2 mg/kg qw Group B: 2.5 mg/kg qw	42 total 20 Group A 22 Group B	Semi-intensive (first dose only) and sparse sampling [a]
	Portion 2	• Group A: 3 mg/kg q2w (capped at 200 mg q2w) • Group B : 4 mg/kg q2w	31 total 15 Group A 16 Group B	Semi-intensive (first dose only) and sparse sampling [a]
	Portion 3	• Group A: 3 mg/kg q2w (capped at 200 mg q2w) • Group B: 4 mg/kg q2w	29 total (28 treated) 21 Group A (20 treated) 8 Group B	Sparse sampling [a]

Study type	Study code/ Portion	Dose or dose range Treatment duration	Number of study participants enrolled	PK sampling
Pop PK analysis in participants aged 2 to 17 years with pcJIA				
Pop PK (explorative)	POH0516	Dose-finding portion data from DRI13925	42 Total 20 Group A 22 Group B	Semi-intensive (first dose only) and/or sparse sampling [a]
Pop PK	POH1134	Data from DRI13925	102 Total (101 treated) 56 Group A 46 Group B	Semi-intensive (first dose only) and/or sparse sampling [a]
PK/PD analysis in participants aged 2 to 17 years with pcJIA				
PK/PD for key efficacy and safety parameters (explorative) [c]	POH0596	Dose-finding portion data from DRI13925	42 total 20 Group A 22 Group B	Semi-intensive (first dose only) and sparse sampling [a]
PK/PD for key efficacy and safety parameters	CTS0123	Data from DRI13925	102 Total 56 Group A 46 Group B	Semi-intensive (first dose only) and/or sparse sampling [a]

Abbreviations: pcJIA = polyarticular-course juvenile idiopathic arthritis; PK = pharmacokinetic; Pop PK = population pharmacokinetic; q2w = every 2 weeks; SC = subcutaneous

a During the 12-week core treatment phase in the dose-finding and second portions, samples in Group A participants (≥30 kg) were collected prior to IMP administration (Day 1), during treatment after first IMP administration (Day 3, 5, 8, and 12), and during the treatment prior to further IMP administrations (Week 2, 4, 8, and 12) while samples in Group B participants (≥10 kg and <30 kg) were collected prior to IMP administration (Day 1), during treatment after first IMP administration (Day 3 or 5 and Day 8 or 12, depending on assigned sampling schedule), and during the treatment prior to further IMP administrations (Week 2, 4, 8, and 12). Additional samples had been collected every 24 weeks since Week 24 during the extension phase. For participants enrolled in the third portion, the PK sampling were not applicable at Day 3, 5, 8, and 12 during the core treatment phase.

b Interim analysis data cut-off dated 08 Aug 2018.

c Including the comparisons of PK/PD relationships based on pooled data of Studies EFC11072 Part A and Part B and/or EFC10832 in adults with RA.

Table 2: Parameter estimates for final Pop PK model in paediatric participants with pcJIA

Parameter	Estimate (% RSE)	[95%CI]
CL/F (L/day)	0.190 (8.94)	[0.156, 0.224]
V_c/F (L)	1.23 (14.7)	[0.868, 1.59]
V_p/F (L)	4.58 (17.9)	[2.94, 6.21]
Q/F (L/day)	0.103 (15.0)	[0.0720, 0.134]
V_m (mg/day)	3.84 (10.6)	[3.03, 4.66]
K_m (mg/L)	0.921 (22.2)	[0.511, 1.33]
K_a (1/day)	0.169 (10.8)	[0.133, 0.206]
Power coefficient of weight on V_m	0.880 (11.5)	[0.680, 1.08]
Power coefficient of weight on CL/F	0.621 (20.4)	[0.368, 0.874]
Power coefficient of weight on V_c/F	1.33 (14.2)	[0.949, 1.70]
Power coefficient of weight on V_p/F	2.12 (19.2)	[1.31, 2.94]
Power coefficient of weight on Q/F	1.07 (31.1)	[0.404, 1.73]
Power coefficient of albumin on V_m	-1.46 (29.8)	[-2.32, -0.589]
Inter-individual variability (IIV)		
	CV% (RSE%) [shrinkage%]	**[95%CI]**
IIV on CL/F	39.0 (30.9) [25.1%]	[24.1, 49.6]
IIV on V_m	29.1 (34.5) [34.5%]	[16.2, 37.8]
IIV on V_c/F	51.8 (35.1) [22.0%]	[28.2, 67.6]
Residual variability (RV)		
	Estimate (% RSE)	**[95%CI]**
Additive term (mg/L)	0.480 (4.74)	[0.434, 0.525]

Abbreviations: CI: confidence interval; CL/F: apparent linear clearance; CV: coefficient of variation; K_a: absorption rate constant ; K_m: Michaelis constant; Q/F: apparent inter-compartment distribution clearance; V_c/F:volume of central compartment; V_p/F: volume of peripheral compartment; V_m: maximum target-mediated rate of elimination; RSE: percentage of relative standard error (100% * SE / estimate)

2.6.2.1. Pharmacokinetics

Absorption

The maximum concentration of sarilumab was achieved at a median tmax approx. of 2 to 4 days after the first dose in paediatric participants with pcJIA after SC administration. After a single dose administration for the selected dose regimen of the total cohort 2, a maximum mean functional sarilumab concentration of 18,017.58 ng/mL was observed after approx. 3 days (n=33). For participants with ≥30 kg (n=22) in the selected cohort 2, a mean maximum concentration of 14,158.18 ng/mL was observed at day 3, whereas a mean Cmax of 25,736.36 ng/mL at day 3 (n=11) was observed for participants with<30 kg. The predicted mean Cmax of the selected dose of cohort 2 after the first SC administration (15.9 mg/L in group A [3mg/kg, q2w, ≥ 30 kg] and 24.0 mg/L in group B [4mg/kg, q2w, < 30 kg], respectively) was more or less similar compared to the observed mean serum concentration. However, the number of samples in the first two weeks is low (range: n=21-41).

No PK data following IV administration of sarilumab were available for pop PK modelling or AUC comparison. Thus, no direct estimate for F could be derived.

Distribution

Volume of distribution at steady state (Vss/F) was smaller for participants with pcJIA than that for RA participants. Vc/F was estimated to 1.23 (14.7) L and Vp/F to 4.58 (17.8) L.

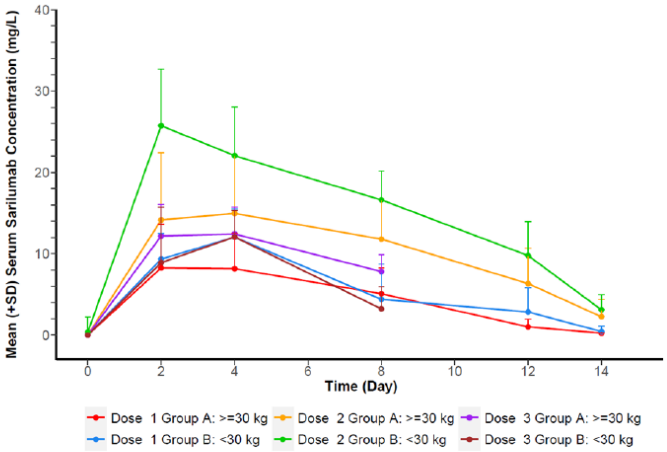
Elimination

Sarilumab in paediatric participants with pcJIA showed no clear linear clearance. Similar to the observation in adults with Rheumatoid arthritis, the elimination occurred biphasic by parallel linear and non-linear pathways and was concentration-dependent. For the first 5 to 7 days after a single dose of sarilumab, the elimination was quite slow for almost all tested dose regimens in paediatric participants with pcJIA, followed by a faster elimination phase (half-life: 2 to 3 days). Based on pop PK, the apparent linear clearance (CL0/F) was estimated to 0.190 (8.94) L/day for pcJIA patients. Based on the Pop PK analysis, after the last steady state dose, simulations of typical paediatric patient sarilumab concentrations were measurable up to a median time of 7 weeks and 8 weeks for Dose 2 Group A and Dose 2 Group B, respectively.

Dose proportionality and time dependencies

Sarilumab exhibited nonlinear PK, consistent with target-mediated drug disposition in participants with pcJIA.

Figure 1: Mean (+SD) sarilumab concentrations in serum after first SC administration in participants with pcJIA

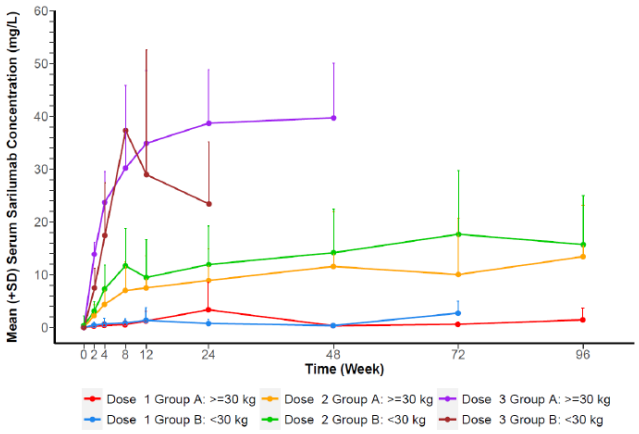


Abbreviations: SC = subcutaneous; SD = standard deviation.
Source: 5.3.5.2 DRI13925 1y3p [Figure 34]

An accumulation of 1.9- to 2.2-fold for participants with Dose 2 (q2w regimens) over 12 weeks has been observed. After the first dose and following repeated SC administration, sarilumab exposure (observed Ctrough) increased in a greater than dose proportional manner and accumulated 4.6- to 5.1-fold over 48 weeks at Dose 2. At the selected Dose 2, the observed mean Ctrough of sarilumab increased over time and reached 11.6 mg/L for Group A and 14.2 mg/L for Group B at Week 48.

For each dose cohort, doses tested in the 2 body weight groups achieved similar exposures.

Figure 2: Mean (+SD) sarilumab trough concentrations in serum following repeated SC administration in participants with pcJIA



Abbreviations: SC = subcutaneous; SD = standard deviation.
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: 5.3.5.2 DRI13925 1y3p [Table 49]

Table 3: Summary of observed sarilumab Ctrough concentrations (mg/L) in serum in participants with pcJIA (Study DRI13925)

Body Weight	Dose	Mean ± SD (N)										
		Week 0	Week 2	Week 4	Week 8	Week 12	Week 24	Week 48	Week 72	Week 96	Week 120	Week 156
Group A (≥30 kg)	2 mg/kg q2w SC	0.00 ± 0.00 (6)	0.224 [a] ± 0.178 (7)	0.415 ± 0.551 (6)	0.518 ± 0.759 (6)	1.21 ± 1.82 (3)	3.35 ± 5.17 (5)	0.343 (2) [b]	0.588 ± 0.436 (5)	1.45 ± 2.17 (4)	NA	NA
	3 mg/kg q2W SC	0.00 ± 0.00 (41)	2.24 ± 2.13 (40)	4.28 ± 3.50 (39)	6.46 ± 4.93 (36)	7.45 ± 6.24 (35)	8.75 ± 6.11 (35)	11.0 ± 10.0 (36)	10.0 ± 10.8 (28)	11.5 ± 9.32 (28)	14.9 ± 13.7 (17)	16.4 ± 12.8 (12)
	2 mg/kg qw SC	0.00 ± 0.00 (6)	13.9 ± 2.24 (6)	23.7 ± 5.81 (5)	30.2 ± 15.7 (6)	34.9 ± 13.7 (6)	38.7 ± 10.1 (4)	39.7 ± 10.3 (5)	NA	NA	NA	NA
Group B (≥10 kg and <30 kg)	2.5 mg/kg q2w SC	0.00 ± 0.00 (6)	0.425 ± 0.659 (6)	0.655 ± 1.06 (6)	0.936 ± 0.890 (5)	1.35 ± 2.38 (5)	0.758 ± 0.825 (5)	0.355 ± 0.231 (4)	2.72 ± 2.23 (4)	NA	NA	NA
	4mg/kg q2W SC	0.348 ± 1.88 (29)	3.10 ± 1.84 (29)	6.83 ± 4.05 (26)	11.9 ± 7.32 (23)	9.47 ± 7.14 (24)	11.9 ± 7.34 (24)	14.1 ± 8.03 (22)	16.0 ± 11.8 (18)	16.3 ± 11.5 (21)	14.9 ± 12.3 (16)	18.8 ± 15.0 (13)
	2.5 mg/kg qw SC	0.00 ± 0.00 (9)	7.50 ± 3.76 (6)	17.4 ± 10.0 (6)	37.3 ± 26.8 (5)	28.9 ± 23.6 (5)	23.4 ± 11.8 (4)	NA	NA	NA	NA	NA

Ctrough = concentration observed before drug administration during repeated dosing; N = number of participants; q2W = every 2 weeks; SC = subcutaneous
NA = Not applicable

a Mean Ctrough values is below LLOQ (0.3125 mg/L)

b N = 2; SD calculation not applicable

Model-based conclusions on dose proportionality and time dependencies:

Table 4: Mean (SD) sarilumab pharmacokinetic parameters in serum, following first SC administration of sarilumab to participants with pcJIA and RA

Population (Study identifier)	Dose	N	C_{max} (mg/L)	$AUC_{0\text{-}14\ days}$ [a] (day•mg/L)	C_{trough} (mg/L)		
			Predicted [b]	Predicted [b]	Predicted [b]	N	Observed
pcJIA (DRI13925) Group A (≥ 30 kg)	2 mg/kg q2w	7	7.61 (2.69)	54.2 (15.9)	0.481 (0.379)	7	0.224 (0.178) [c]
	3 mg/kg q2w	42	15.9 (5.45)	138 (43.7)	2.38 (1.80)	40	2.24 (2.13)
	2 mg/kg qw	6	11.3 (1.84)	62.0 (11.6)	6.98 (2.22)	6	13.9 (2.24)
pcJIA (DRI13925) Group B (≥10 kg and <30 kg)	2.5 mg/kg q2w	6	10.3 (1.65)	69.2 (20.2)	0.419 (0.240)	6	0.425 (0.659)
	4 mg/kg q2w	31	24.0 (3.93)	205 (42.6)	3.62 (2.33)	29	3.10 (1.84)
	2.5 mg/kg qw	9	10.4 (2.84)	55.3 (17.1)	5.64 (2.46)	6	7.50 (3.76)
RA (EFC11072 Part B + EFC10832)	150 mg q2w	547	10.7 (4.68)	87.4 (42.8))	2.44 (3.29)	318	1.98 (3.12) [d] 1.70 (2.73) [e]
	200 mg q2w	609	17.5 (6.47)	159 (62.5)	5.54 (5.71)	296	5.40 (6.41) [d] 5.15 (5.21) [e]

Abbreviations: C_{max} = maximum concentration; C_{trough} = trough concentration; NA = not applicable.

a $AUC_{0\text{-}14\ days}$ = AUC[Week 22 – Week 24 for RA] for 200 mg q2w or 150 mg q2w and AUC[Week 30 – Week 32 for pcJIA] for all 3 dose cohorts

b Mean (standard deviation) for post hoc individual pharmacokinetic parameters for participants with pcJIA (Study DRI13925) and RA (Study EFC11072 Part B, EFC10832, and EFC14092 were estimated from population pharmacokinetic study POH1134 and POH0428, respectively).

c Mean C_{trough} value is below LLOQ (0.3125 mg/L)

d From Study EFC11072 Part B

e From Study EFC10832

Sources: Predicted values: 5.3.3.5 Study POH1134 Pop PK analysis report and Study POH0428 Pop PK analysis report; Observed C_{trough} data: CSR-DRI13925-16.2.5.4.1-EN, CSR-EFC11072-16.2.5.4.1-EN and CSR-EFC10832.16.2.5.4.1-EN

Table 5: Mean (SD) sarilumab pharmacokinetic parameters in serum at the steady state, following repeated SC administrations of sarilumab to participants with pcJIA and RA

Population (Study identifier)	Dose	N	C_{max} (mg/L)	$AUC_{0\text{-}14\ days}$ [a] (day•mg/L)	C_{trough} (mg/L)		
			Predicted [b]	Predicted [b]	Predicted [b]	N	Observed [c]
pcJIA (DRI13925) Group A (≥ 30 kg)	2 mg/kg q2w	5	11.1 (4.82)	90.7 (30.8)	1.36 (0.872)	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)
pcJIA (DRI13925) Group B (≥10 kg and <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)

Abbreviations: C_{max} = maximum concentration; C_{trough} = trough concentration; NA = not applicable.

a $AUC_{0\text{-}14\ days}$ = AUC[Week 22 – Week 24 for RA] for 200 mg q2w or 150 mg q2w and AUC[Week 30 – Week 32 for pcJIA] for all 3 dose cohorts.

b Predicted: summary statistics of post-hoc estimates of exposure parameters in Study POH1134 (pcJIA) at steady state (Week 30) and Study POH0428 (RA) at steady state (Week 24).

c Observed C_{trough} at Week 48 for pcJIA 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 C_{max} , $AUC_{0\text{-}\tau}$ and C_{trough} 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

Sources: 5.3.3.5 Study POH1134 Pop PK analysis report; Study POH0428 Pop PK analysis report; Observed C_{trough} data: CSR-DRI13925-16.2.5.4.1-En, CSR-EFC11072-16.2.5.4.1-EN and CSR-EFC10832.16.2.5.4.1-EN

Overall, a greater than dose-proportional effect was observed and also suggested by model-based analysis.

Based on the Pop PK analysis, the median time to steady state was 26 weeks and 22 weeks for Dose 2 Group A and Dose 2 Group B, respectively, with the accumulation ratios of 4.02, 1.70, and 2.00-fold in Group A, and 3.98, 1.68, and 1.93-fold in Group B at steady state based on post-hoc estimated PK parameters for Ctrough, Cmax and AUC0-τ, respectively. The model-predicted trough concentration at Week 12 was approximately 71% of that at Week 28, suggesting the slow increase of trough concentration after Week 12 for Dose 2 Group A.

Special populations

Baseline age, gender, baseline CLCRN, baseline albumin and baseline CRP were tested based on available data. The current final pop PK model identified weight and albumin as statistically significant covariates on the description of sarilumab PK in paediatric pcJIA subjects.

Age in the study population (N=101 subjects, paediatric study DRI13925) ranged from 2 to 18 years, with median age of 9 years of age. The participants with pcJIA in the PK analysis data set were 26 (25.7%) participants of 2 to <6 years of age; 37 (36.6%) participants with 6 to <12 years of age and 38 (37.6%) participants with 12 to <18 years of age.

The justification for the three ascending doses tested in each weight group of the Portion 1 was based on PK modelling in order to target PK exposure similar to:

• 150 mg q2w in adults, which is the lowest effective dose in adult patients with RA (Dose 1)

• 200 mg q2w, which is the recommended dose in adult patients with RA (Dose 2)

• 150 mg qw, which yielded the highest exposures in chronic dosing studies in adult patients with RA (Dose 3)

The enrolment has been completed (N=42). Based on the interim analysis of the 12-week core phase data Dose 2 (Group A: 3 mg/kg q2w and capped at 200 mg q2w for participants with a body weight of ≥63 kg, Group B: 4 mg/kg q2w) was selected.

Thus, the extrapolation concept of exposure bridging was implemented to support the indication in paediatric patients with pcJIA, targeting the exposure range following 200 mg Q2W in adult subjects with related indication of RA.

The Pop PK analysis using the current final model (POH1134) did not identify impact of age on sarilumab PK in participants with pcJIA after accounting for weight.

2.6.2.2. Pharmacodynamics

Mechanism of action

Sarilumab is a recombinant human immunoglobulin 1 monoclonal antibody (mAb) of the immunoglobulin isotype 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 signalling.

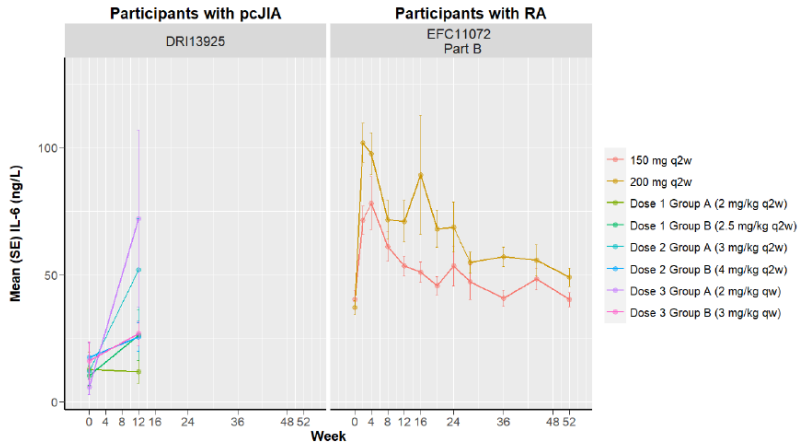
Elevated levels of IL-6 are found in the synovial fluid of patients with rheumatoid arthritis (RA) and polyarticular-course juvenile idiopathic arthritis (pcJIA) and play an important role in both the pathologic inflammation and joint destruction which are hallmarks of RA and pcJIA. IL-6 is involved in diverse physiological processes such as migration and activation of T-cells, B-cells, monocytes, and osteoclasts leading to systemic inflammation, synovial inflammation, and bone erosion in patients with RA and pcJIA. The activity of sarilumab in reducing inflammation is associated with laboratory changes such as decrease in Absolute Neutrophils Count (ANC) and elevation in lipids.

Primary and Secondary pharmacology

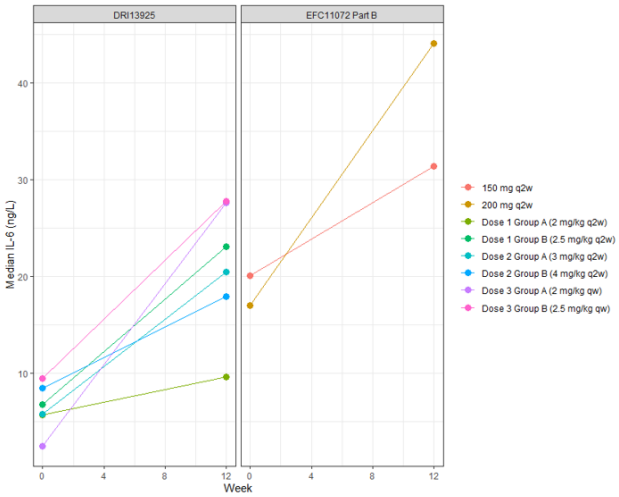
The PD biomarker over time profiles were compared in participants with pcJIA and RA. The data for hs-CRP, ESR, IL-6, and sIL-6Rα over time were summarized using descriptive statistics.

Interleukin-6

Figure 3: Mean (SE) and median concentrations of IL-6 following repeated SC administration in participants with pcJIA (left panels) and RA (right panels)



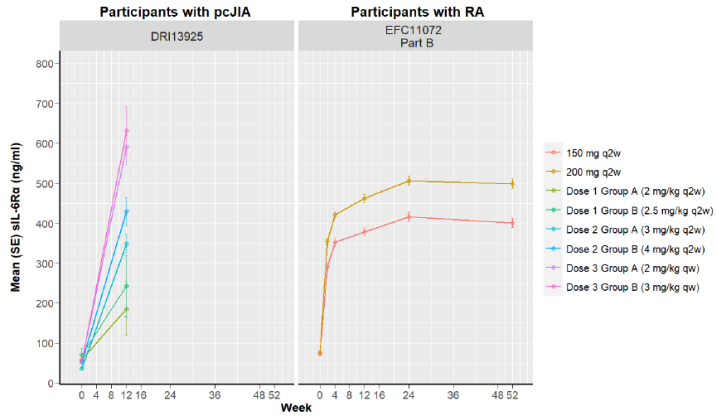
Abbreviations: pcJIA = polyarticular-course juvenile idiopathic arthritis; Q2w = every 2 weeks; RA = rheumatoid arthritis; sIL-6R = soluble interleukin-6 receptor.



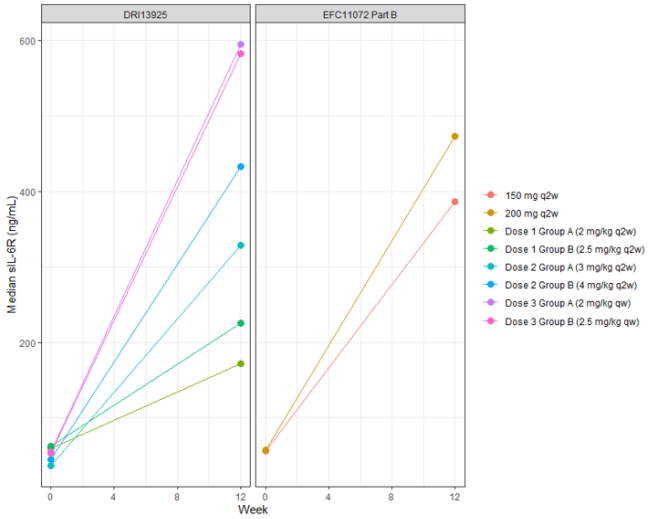
Abbreviations: pcJIA = polyarticular-course juvenile idiopathic arthritis; Q2W = every 2 weeks; RA = rheumatoid arthritis; sIL-6R = soluble interleukin-6 receptor.

Soluble interleukin-6 receptor

Figure 4: Mean (SE) and median concentrations of sIL-6Ra following repeated SC administration in participants with pcJIA (left panels) and RA (right panels)



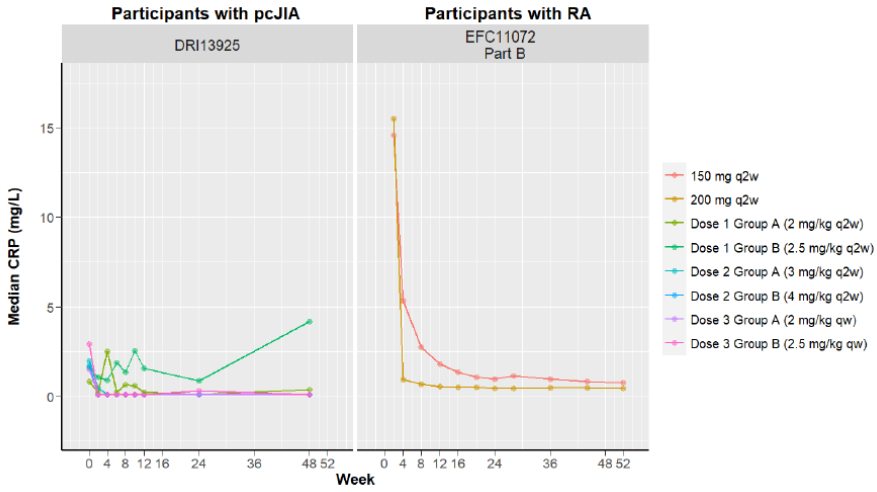
Abbreviations: pcJIA = polyarticular-course juvenile idiopathic arthritis; Q2w = every 2 weeks; RA = rheumatoid arthritis; sIL-6R = soluble interleukin-6 receptor.



Abbreviations: pcJIA = polyarticular-course juvenile idiopathic arthritis; Q2W = every 2 weeks; RA = rheumatoid arthritis; sIL-6R = soluble interleukin-6 receptor.

C-reactive protein

Figure 5: Median concentrations of CRP following repeated SC administration in participants with pcJIA and RA



Abbreviations: CRP = C-reactive protein; pcJIA = polyarticular-course juvenile idiopathic arthritis; q2w = every 2 weeks; RA = rheumatoid arthritis.

Erythrocyte sedimentation rate (ESR)

ESR was not measured in the adult participants with RA (Study EFC11072 Part B).

Therefore, a comparison of ESR between paediatric participants with pcJIA and adult participants with RA was not performed.

Immunogenicity

In Study DRI13925, across Dose 1, Dose 2 and Dose 3 (pooled data), the majority (93 [95.9%]) of the participants were ADA negative during the TEAE period. In total, 4 (4.1%) participants have had ADA positive measurement during TEAE period. Of these 4 participants, 3 (3.1%) participants had persistent ADA (defined as 2 consecutive ADA positive results spacing >16 weeks or ADA positive at the last measurement by default) and 2 (2.1%) participants had NAb positive responses. No participant reported treatment-boosted ADA.

Participants with treatment-emergent positive ADA and positive NAb responses had lower sarilumab exposure than participants who were ADA negative at each corresponding dose.

The individual sarilumab concentrations in ADA-positive participants were generally within the exposure range observed in ADA-negative participants.

Table 6: Summary of ADA assay response post-baseline in participants with pcJIA – ADA population (Study DRI13925)

Anti-sarilumab antibody	2 mg/kg q2w (N=7)	3 mg/kg q2w (N=42)	2 mg/kg qw (N=6)	2.5 mg/kg q2w (N=6)	4 mg/kg q2w (N=31)	2.5 mg/kg qw (N=9)	Pool 3 mg/kg and 4 mg/kg q2w (N=70)	Any Dose (N=97)
	Group A ≥30 kg and ≤60 kg			Group B ≥10 kg and <30 kg			Groups A and B	
Treatment-emergent ADA positive participants	1 (16.7%)	2 (5.0%)	0	0	1 (3.3%)	0	3 (4.3%)	4 (4.1%)
Number of transient treatment-emergent ADA positive participants	0	1 (2.5%)	0	0	0	0	1 (1.4%)	1 (1.0%)
Number of persistent treatment-emergent ADA positive participants	1 (16.7%)	1 (2.5%)	0	0	1 (3.3%)	0	2 (2.9%)	3 (3.1%)
Peak post-baseline titer								
Number	1	2	0	0	1	0	3	4
Median	960	30			120		30.0	75.0
Q1; Q3	960; 960	30.0 ; 30.0			120; 120		30.0; 120	30.0; 540
Minimum; Maximum	960; 960	30.0; 30.0			120; 120		30.0; 120	30.0; 960
Treatment-boosted ADA positive participants	0	0	0	0	0	0	0	0
Number of participants with neutralizing antibody	1(16.7%)	1 (2.5%)	0	0	0	0	1 (1.4%)	2 (2.1%)

Abbreviations: ADA = anti-drug antibody; pcJIA = polyarticular-course juvenile idiopathic arthritis; q2w = every 2 weeks; qw = every week.
Sources: 5.3.5.2 Study DRI13925 [Table 5]

Relationship between plasma concentration and effect and safety

Exposure-efficacy response analyses were investigated using descriptive statistics and/or empirical E-R modelling and compared in paediatric subjects with pcJIA (Study CTS0123, all three data portions) with those in participants with RA (Study EFC11072 Part A and Part B) as provided in POH0596. Efficacy endpoints included JIA ACR 30/50/70/90/100 response rates. The safety endpoints included laboratory abnormalities of interest, absolute neutrophil count (ANC) as a continuous endpoint, and the binary endpoints ANC <1.0 Giga/L. The PK-PD relationships were compared in participants with pcJIA and RA. In adults with RA, Study EFC11072 Part A and/or Part B for efficacy endpoints or Studies EFC11072 Part A and Part B and EFC10832 for safety endpoint were included in E-R relationship comparisons.

Results from POH0596: Overall, trends of an increase in response rate with increase in Ctrough were also observed in JIA ACR50 and JIA ACR70, similar to that in JIA ACR30. Meanwhile, both JIA ACR50 and JIA ACR70 response rates were higher, along with a higher Ctrough, for Dose 3 compared to Dose 1 and Dose 2. The E-R model for efficacy indicated that with increasing exposure, there is a similar (JIAACR30) or higher (JIA-ACR50 and JIA-ACR70) response in paediatric participants with pcJIA compared to adult participants with RA. E-R analyses indicated that higher Ctrough was associated with a lower ANC value. The E-R relationship between the ANC percent change from baseline at Week 12 and Ctrough at Week 12 was described by a log-linear model. In adults, it was indicated that the decrease in ANC approached a plateau at Ctrough higher than 20 mg/L. This trend is not observed in the paediatric data, possibly due to the limited number of paediatric patient (N=42).

Results from CTS0123: In paediatric participants with pcJIA, a linear or log-linear logistic regression model was selected to describe the E-R relationships between the efficacy endpoints, JIA ACR30/50 or JIA ACR70, and sarilumab Ctrough at Week 12. This model indicated a trend of increasing efficacy as sarilumab concentration increased in Study DRI13925. The E-R model-predicted effect at the mean Ctrough following sarilumab Dose 1, Dose 2 and Dose 3 is overall consistent. For ANC, the E-R model predicted effect at the median Ctrough following sarilumab Dose 1, Dose 2 and Dose 3 was provided. Overall predicted effects (Dose 2 and 3) are consistent with observed effect for the E-R data set, but deviated for Dose 1. Overall, results from CTS0123 are in line with those from POH0596.

2.6.3. Discussion on clinical pharmacology

The MAH is seeking approval for the following indication: treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older.

The PK, PD, immunogenicity, and E-R relationships of sarilumab were assessed in participants aged 2 to 17 years with pJIA in Phase 2b Study DRI13925 (1 year from the time the last patient was enrolled in the study). The data from Study DRI13925 were used for the Pop PK analysis and the PK-PD analyses (for the key efficacy and safety endpoints) in the pJIA population, and compared with those in adults with RA.

The proposed posology in patients with pJIA above 2 years of age is 4 mg/kg subcutaneously once every 2 weeks in patients weighing 10 to less than 30 kg or 3 mg/kg subcutaneously once every 2 weeks in patients weighing greater than or equal to 30 kg (capped at 200 mg q2w for patients weighing ≥63 kg). Doses were selected to provide sarilumab exposure similar to the recommended 200 mg q2w dose regimen in adults with rheumatoid arthritis. This is agreed.

Pharmacokinetics

Bioanalytical methods

The bioanalytical methods used for the determination of the sarilumab concentration, the total sIL-6Ra, the anti-sarilumab-antibodies and neutralizing anti-sarilumab antibodies, have already been investigated, validated and reported in the original marketing application and are considered to be acceptable. The bioanalytical results provided in the original marketing application demonstrated that the assays performed accurate and precise and are suitable for their intended use.

ADME

The maximum serum concentration of functional sarilumab achieved at a median tmax of 2 to 4 days, with no apparent dose effect.

For 3 mg/kg sarilumab (patients with a body weight ≥30 kg) given every 2 weeks, the estimated mean (±SD) steady-state AUC, Cmin, and Cmax of sarilumab were 294 ± 148 mg.day/L, 9.84 ± 6.35 mg/L, and 29.2 ± 15.0 mg/L, respectively by population PK analysis.

For 4 mg/kg sarilumab (patients with a body weight 10 to <30 kg) given every 2 weeks, the estimated mean (± SD) steady-state AUC, Cmin, and Cmax of sarilumab were 375 ± 102 mg.day/L, 14.5 ± 8.56 mg/L, and 37.3 ± 8.10 mg/L, respectively by population PK analysis.

The elimination of sarilumab in paediatric participants with pJIA is biphasic including an initial slower elimination phase (half-life: 5 to 7 days) and a faster terminal elimination phase (half-life: 2 to 3 days). The clearance of sarilumab is concentration-dependent.

These information have been reflected in section 5.2 of the SmPC.

Population PK

Two population PK studies have been performed. POH0516, explorative pop PK on dose-finding portion data from DRI13925, pooled with adult RA data, and POH1134 on the full data set from DRI13925 (101 treated subjects, semi-intensive first-dose only sampling and/or sparse sampling). In principle, given the similarity between RA and pJIA indication, the stepwise approach and building on the RA population PK model for adults is endorsed. It is not expected, that the overall structure of the PK model is significantly different, but the focus is on the inclusion of weight as pop PK modelling was applied to describe PK in paediatrics patients. As detailed in the Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (EMA/CHMP/239770/2014 Rev. 2),

a modelling and simulation approach could be taken using data from adults and other diseases along with adequate validation of the model and analysis of its applicability to all age groups and JIA subtypes must be performed.

Considering the wide range of weight (11.5 – 71.8 kg) in paediatric participants aged 2 to 17 years with pJIA, the impact of weight on PK parameters was included in the base model development (POH1134). Estimated allometric coefficients ranged from 0.621 and 1.07 for CL/F and Q/F, and from 1.33 to 2.12 for Vc/F and Vp/F, respectively. Vm was estimated to be scaled by weight with exponent of 0.880. Scaling was per 32.5 kg (median value of weight from population in study DRI13925) and exponents were characterized with wide 95% CIs including the exponent of albumin on Vm. Besides weight, albumin was selected as covariate during the final pop PK selection.

Visual predictive check plots indicated overall a trend of underprediction of median sarilumab concentration while overpredicting the overall exposure range, especially the 95th percentile of concentrations. Stratified by Group, the underprediction of median concentration was more prominent in Group B (<30 kg), while mismatch with p95 was more prominent in Group A (>30 kg) beyond day 500.

Based on the data provided, there were concerns regarding the targeted comparability between the proposed posology in patients with pcJIA and the recommended 200 mg q2w dose regimen in adults with rheumatoid arthritis. To justify the compliance with the extrapolation concept as detailed in the corresponding PIP, the MAH was asked to provide further analyses. The MAH conducted a sensitivity analysis assuming time-varying allometric scaling over scaling by baseline weight (fix and estimated allometry) to find the most adequate PopPK model. Different models varying in the way of allometric scaling methodology and incorporation of IIV have been tested by the MAH vs as the fixed scaling approach did not lead to significant improvements, allometric exponents were estimated which was supported by the CHMP.

To better assess the model predictivity, upon CHMP request, the MAH provided VPC plots separated for all doses by early time span (0-12 weeks) and later time span for both groups A and B, stratified by different weight categories (<18.4 kg and 18.4 kg<30kg for Group B; and 30kg < 46.5 kg and 46.5 kg < 63 kg and > 63kg for Group A). Stratification by more narrow body weight categories indicate, that the under-predictive trend is most prominent for Group B (18.4 kg- <30 kg) and Group A (46.5 kg - <63 kg). The derived parameter estimates resulting from both the former and updated pop PK model were provided for each of the dosing regimen (3 mg/kg Q2W and 4 mg/kg Q2W) proposed for pJIA patients. Predicted Ctrough after single dose and at steady state are overall predicted to the same level. Thus, although the predictiveness did not improve significantly, model-derived PK estimates seem to sensitively react to structural changes (e.g. description of time to steady state).

Additional simulations were provided comparing post-hoc estimates of C_{trough} at weeks 12, 24 and 48 which overall were consistent with observed data for these time points. Even though, the underlying data do not permit a NCA and the variabilities seen in the simulations, the Pop PK model derived parameters can be considered reasonable.

In addition, the MAH was asked to compare predictive performance until week 12 from these analyses with that based on the PK model developed in POH0516. The model derived parameters for adults with RA, paediatric patients with pJIA in groups A and B stemming from Pop PK simulations were, where available, compared with observed data from the first SC administration of sarilumab. These predicted parameters were generally in line with available observed parameters.

Intra- and interindividual variability

Due to limited data in Dose 1 and Dose 3, the assessment for the sources of PK variability focused on PK data at Dose 2 in Study DRI13925. The magnitude of estimated IIV was estimated by population PK

to be moderate for CL/F, Vc/F, and Vm with CV% of 39.2%, 52.5% and 31.4%, respectively, and considered moderate to high. Of note, allometric scaling factors were estimated individually on all three parameters (5 in total), indicating overparameterization.

Comparison of sarilumab PK in paediatric participants with pcJIA and in adult participants with RA

In study DRI13925, the primary endpoint was to assess the PK exposure of sarilumab from baseline to week 12 to identify the dose and regimen for adequate treatment of paediatric participants with pcJIA. The doses tested were selected based on Pop-PK modelling to provide sarilumab exposure similar to the dose regimens tested in adults with rheumatoid arthritis (concept of exposure bridging). The proposed posology is based on the dose cohort 2 of study DRI13925 that was selected to provide sarilumab exposure similar to the recommended 200 mg q2w dose regimen tested in adults with rheumatoid arthritis. The assessment of the observed PK data and thus the assumptions on the PK similarity as defined in the extrapolation concept and plan was limited due to the sparse PK sampling in the clinical studies. Although the observed Ctrough was slightly higher in Group B of cohort 2 compared to group A of cohort 2, in general, the observed Ctrough in participants with pJIA who received dose cohort 2 was below the observed (and predicted) Ctrough in RA adults following 200 mg q2w. This was not fully regarded in compliance with the agreed PIP. However, Ctrough (Cohort 2) was at least within the range of the Ctrough in adult participants with RA who received 150 mg q2w or 200 mg q2w.

The predicted Cmax in participants with pJIA for the group B of cohort 2 after the single and repeated SC administration was higher (single: 24 mg/L, repeated: 40.4 mg/L) than the predicted Cmax of the recommended 200 mg q2w in adult participants with RA (single: 17.5 mg/L, repeated: 35.9 mg/L). Nevertheless, standard deviations were overlapping and based on the data available, there is no indication of an increased safety risk. The median Ctrough of dose cohort 2 was overall observed within the range of the Ctrough in adult participants with RA who received 150 mg q2w or 200 mg q2w and based on the PK data available of all tested dosing regimens for paediatric patients with pcJIA in this study, the recommended dose regimen of 3 mg/kg Q2W (capped at 200 mg Q2W) dose for participants with body weight ≥30 kg and 4 mg/kg Q2W for participants with body weight ≥10 kg and <30 kg, respectively, most closely matched the dose regimen of adults with RA. Moreover, effectiveness and a tolerable safety profile of sarilumab was observed for the recommended dose regimen of 3 mg/kg Q2W and 4 mg/kg Q2W for pcJIA participants. Nevertheless, it needs to be considered that the study was not powered for efficacy, the data available are limited and the primary endpoint of this study was to evaluate the PK of sarilumab in paediatric participants with pcJIA at week 12.

In addition, to further investigate the comparability to exposure in adult RA patients that includes the alternative regimen (150 mg Q2W, dose recommended in case of neutropaenia, thromocytopaenia and liver enzyme elevations), the MAH was asked to provide a detailed comparison of observed and predicted PK parameters including Cmax, AUC, Ctrough after single dose, and multiple dose at Week 12, 24, 32 and 48 in paediatrics with the PK parameters in the adult RA population. Although, Ctrough for paediatric patients when compared with adult patients receiving was low, it was higher than the values for adults receiving 150mg q2w. For C_{max} and AUC_{0-T} the resulting values were comparable to the adults with RA receiving 200mg q2w. When considering multiple dosing, the estimated values for Ctrough, Cmax and AUC at Dose 2 for paediatric patients with pJIA in group B were similar to the values for adults receiving 200 mg q2w. For paediatric patients with pJIA in group A these values were consistently lower than for adults dosed with 200 mg q2w, but still closer to that than to adults receiving 150 mg q2w. As an alternative scenario, simulated PK parameters at 4 mg/kg at steady state for paediatric patients with pJIA in groups A/B and adult patients with RA at 150mg and 200mg q2w at steady state were provided. The simulations show that at 4mg/kg a higher number of participants would reach the median and 5th percentile of exposure in adults with RA at 200 mg q2w, but also that

exposure in paediatric individuals in group A would likely exceed exposure in adults with RA at 200 mg q2w. Therefore, even though exposure for paediatric patients with pJIA in group A under the Dose 2 regimen was slightly lower than the targeted levels of adults with RA given 200 mg q2w, Dose 2 can be considered to be comparable for adults with RA and paediatric patients with pJIA.

Therapeutic window

The target therapeutic window for the pcJIA paediatric population had not been specifically addressed. Given that the recommended posology for subjects from 2-17 years of age is selected to that expected exposure is not exceeding but matching the range expected in adult RA patients following 200 mg Q2W, the latter range might be set to the target therapeutic window. While the median trend of supported the proposed posology, it was indicated that exposure might be below the target range for a percentage of paediatric patients. To further confirm the adequacy pf the proposed posology, the MAH provided additional simulated percentages of paediatric subjects that would exceed the relevant target ranges.

For this purpose an updated final paediatric Pop PK model, was utilized and the MAH showed exposure metrics (Cmax, AUC, Ctrough (median, min/max and percentiles)) for updated weight groups (bins of 10 kg from 10 to 100 kg) and also included reference exposure ranges. The new analysis suggested that sarilumab steady state exposures (Cmax, AUC0-14 days and Ctrough) highly overlapped between two populations. In the view of the additional analysis it can be agreed that the model reasonably well describes the observed data in pJIA and the comparability of exposure ranges can be supported.

Special populations

Given the amount of data, it was agreed to focus covariate analysis on those already observed in the assessment of the related RA indication in addition to age. The Pop PK analysis using the current final model (POH1134) did not identify impact of age on sarilumab PK in participants with pcJIA after accounting for weight. This was considered plausible due to the correlation of weight and age. Consistent with the Pop PK model for adult participants with RA, body weight exerted a notable effect explaining between-subject variability of sarilumab concentration in paediatric participants with pcJIA, justifing a dosing per weight bands. The cut-off set to 30 kg was considered acceptable by the CHMP.

Based on the current PK model it was agreed that within the same dosing group (3 mg/kg q2w or 4 mg/kg q2w), sarilumab exposure in participants with pcJIA was generally similar between age subgroups in Study DRI13925, although differences between Group A and B following Dose 2 could be detected not affecting efficacy and safety.

Pharmacodynamic

The mechanism of action of sarilumab has been sufficiently characterised. IL6 receptor is a known target with respect to the indication rheumatoid arthritis and polyarticular course juvenile idiopathic arthritis (pJIA).

According to the mode of action, the PD effects of sarilumab were assessed through measurement of the following biomarkers: hs-CRP, IL-6, total sIL-6R, and ESR and compared to the PD biomarker profile in adult participants with RA.

For the selected Dose 2 in paediatric participants with pJIA, the mean sIL-6Rα concentration showed an increased and the mean ESR concentration and the mean hs-CRP concentration showed a decrease from baseline until Week 12. Numerical difference in the mean hs-CRP and mean ESR concentration observed between Cohort 2A and Cohort 2B might result due to outliers as well as due to the small N and high variability of individual, as overall no difference was observed in the median hs-CRP and median ESR concentration during the entire treatment period between both weight groups.

Descriptive statistics for IL-6 and total sIL-6Rα concentrations were performed only from baseline to Week 12. Therefore, no additional data until week 48 or longer was available for IL-6 and total sIL-6Rα. Overall, due to the binding of sarilumab to IL-6Rα, a normalization of levels of acute phase proteins and inflammatory markers (CRP and ESR) was apparently observed. Therefore, the selected dose cohort 2 might be supported. However, based on the very limited data available, the results should be interpreted with caution overall. Comparing the PD biomarker over time profiles for hs-CRP, IL-6, and sIL-6Rα in participants with pJIA and participants with RA, repeated sarilumab SC administration in both, participants with pJIA and adult participants with RA, results in a rapid decrease of the hs-CRP from baseline, in a stable suppression of hs-CRP level over time and in an IL-6 concentration increased up to Week 12 relative to baseline. Therefore, a similar effect on the PD markers was observed between participants with pJIA (cohort 2) and adult participants with RA. However, since the concentration levels of the PD markers differ between participants with pJIA and adult participants with RA, especially at baseline, and the IL-6 and sIL-6R concentrations in participants with pJIA do not fully achieve the concentration level of the 200 mg q2w dosage regimen of adult participants with RA, a potential impact of these differences on the treatment and safety of paediatric patients over time is currently unclear. Therefore, the MAH will continue to monitor safety in post marketing setting via routine signal detection activities and will provide update to agency in PSUR if any new safety signal is observed. Overall, based on the limited data available a similar effect on the PD marker was observed between participants with pJIA and adult participants with RA and efficacy and safety of the treatment was demonstrated for the pJIA population (Cohort 2) in this study.

Immunogenicity

During the entire TEAE period, the majority of the participants for whom ADA assay results were available (97 out of all 101 treated participants) were ADA negative (93/97 [95.9%]). In total 4 (4.1%) of the participants were ADA positive and thus the immunogenicity of Sarilumab in participants with pJIA appears to be low.

One of these 4 ADA positive participants was included in the cohort 1 group A, and the remaining three (4.3%) were included in the cohort 2 (2 in group A and one in group B). The Sarilumab concentrations for all of these 4 ADA positive participants were low during the 12-week core-treatment period and during the 52-week treatment period, except for the one participant who was included in the cohort 2 group B that showed an increasing sarilumab concentration between week 12 and week 48. However, in total 3 (3.1%) of the 4 participants had persistent ADA and 2 (2.1%) participants had NAb positive responses.

In addition, no participants with treatment-emergent ADA positive responses experienced any anaphylaxis, serious and/or clinically significant hypersensitivity reactions, or injection site reactions neither during the 12-week core-treatment period nor during the 52-week treatment period.

Overall, the number of ADA positive patients was in general quite low, and the serum concentration of ADA positive participants was in the range of the serum concentration of ADA negative participants. Thus, based on the limited data available, no conclusion on a potential impact of ADAs on safety and efficacy can be made. Therefore, the impact of ADAs on the safety and/or efficacy of sarilumab is unknown. This is reflected in section 4.8 of the SmPC and is considered acceptable by the CHMP.

Relationship between plasma concentration and effect, and safety

Two studies have been conducted to analyse dose- and exposure response with respect to efficacy and safety in the paediatric population and for comparison with adults RA patients.
From POH0596: Overall, trends of an increase in response rate with increase in Ctrough were also observed in JIA ACR50 and JIA ACR70, similar to that in JIA ACR30. Meanwhile, both JIA ACR50 and JIA ACR70 response rates were higher, along with a higher Ctrough, for Dose 3 compared to Dose 1

and Dose 2. The E-R model for efficacy demonstrated that with increasing exposure, there is a similar (JIAACR30) or higher (JIA-ACR50 and JIA-ACR70) response in paediatric participants with pJIA compared to adult participants with RA.
E-R analyses indicated that higher Ctrough was associated with a lower ANC value. The E-R relationship between the ANC percent change from baseline at Week 12 and Ctrough at Week 12 was described by a log-linear model. In adult E-R relationship model, the decrease in ANC approached a plateau at Ctrough higher than 20 mg/L. However, the paediatric E-R relationship model did not seem to reach a plateau in the observed Ctrough range, possibly due to the limited number of paediatric patient (N=42).

From CTS0123: In paediatric participants with pJIA, a linear or log-linear logistic regression model was selected to describe the E-R relationships between the efficacy endpoints, JIA ACR30/50 or JIA ACR70, and sarilumab Ctrough at Week 12. This model indicated a trend of increasing efficacy as sarilumab concentration increased in Study DRI13925. The E-R model-predicted effect at the mean Ctrough following sarilumab Dose 1, Dose 2 and Dose 3 is overall consistent with the observed effect for the E-R data set, but indicates some deviation in mean observed and predicted response in particular for dose 3 and ACR70 (all doses), while 95%CI are overlapping.
The lowest exposure tertile is indicated to achieve lower response rates, especially for JIA ACR70 (56.5%). However, the reached response rate is observed to be above the adult pendants following 150 mg and 200 mg Q2W in adults This, together with analyses conducted in POH0596 supports the proposed dose 2 for the paediatric population.
For ANC, the E-R model predicted effect at the median Ctrough following sarilumab Dose 1, Dose 2 and Dose 3 was provided. Overall predicted effects (Dose 2 and 3) are consistent with observed effect for the E-R data set, but deviated for Dose 1. Overall, results from CTS0123 are in line with those from POH0596.

Overall, it can be concluded that although the exposure range in adults (200 mg Q2W) is not fully met following Dose 2 in paediatric subjects, there is no concern indicating lack of efficacy. This may be due to the slightly different E-R relationship for both subpopulations, respectively.

2.6.4. Conclusions on clinical pharmacology

The PK, PD, immunogenicity, and E-R relationships of sarilumab were assessed in participants aged 2 to 17 years with pJIA in Phase 2b Study DRI13925. The data from this study were used for the Pop PK analysis and the E-R analyses (for the key efficacy and safety endpoints) in the pJIA population, and compared with those in adults with RA. Overall, comparison of PK and E-R with the adult participants with RA indicate some differences, however, a similar effect on the PD markers has been observed between adults with RA and paediatric participants with pJIA (cohort 2) based on the data available, and thus supports the principle assumption for the extrapolation concept with respect to a similar PD profile for both populations. In addition, it is concluded that the mismatch in exposure is not expected to exceed the safe exposure range observed so far in adults. This lower exposure following Dose 2 in paediatric patients is not expected to be linked to a significant drop or loss in efficacy, as greater responsiveness in paediatric patients is indicated at similar sarilumab levels. Overall, even though there are some remaining uncertainties to ultimately confirm the validity of the extrapolation (concept) the data package on clinical pharmacology is supporting a positive benefit-risk relationship of Kevzara in pJIA patients.

In conclusion, the clinical pharmacology data are sufficient to support the following posology (section 4.2 of the SmPC) for sarilumab: 4 mg/kg subcutaneously once every 2 weeks in patients weighing 10 to less than 30 kg or 3 mg/kg subcutaneously once every 2 weeks in patients weighing greater than or equal to 30 kg.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

No dedicated dose response studies were performed. Dosage, treatment regimen, route of administration were determined based on adult phase 3 studies in rheumatoid arthritis and further supported by a population PK model subcutaneous use. Study DRI13925 was an open-label study with 3 subsequent portions: one dose-finding portion, and two expansion portions. The Portion 1 of the study is detailed below.

Portion 1 of the study was designed as a sequential, ascending, dose-finding part of the study that aimed at determining the appropriate dose and regimen for adequate treatment of participants with pcJIA. In this portion, 3 subsequent dose regimens were investigated in 2 body weight (BW) groups (Group A, participants weighing ≥30 kg to ≤60 kg and Group B, participants weighing ≥10 kg to <30 kg) with a planned number of 6 participants by dose and BW group. The results would support the choice of the dose for the enrolment of subsequent participants in Portions 2 and 3.

The 3 dose regimens tested were selected as follows:

- Doses 1 and 2 targeting PK exposures similar to the approved dose regimens in RA (150 mg q2W and 200 mg q2w, respectively);
- Dose 3 targeting PK exposures similar to the highest dose regimen that demonstrated efficacy together with an acceptable safety profile in RA studies (150 mg qw).

Table 7: Portion 1 of DRI13925 study – Planned dose by body weight and dose regimen

Body weight	Dose Regimen 1	Dose Regimen 2	Dose Regimen 3
Group A ≥30 kg and ≤60 kg	2 mg/kg q2w (6 participants planned/ 7 participants enrolled)	3 mg/kg q2w (6 participants planned/ 7 participants enrolled)	2 mg/kg qw (6 participants planned/ 6 participants enrolled)
Group B <30 kg and ≥10 kg	2.5 mg/kg q2w (6 participants planned/ 6 participants enrolled)	4 mg/kg q2w (6 participants planned/ 7 participants enrolled)	2.5 mg/kg qw (6 participants planned/ 9 participants enrolled)

Abbreviations: qw = once every week, q2w = once every other week.

In both phases (12−week core phase and extension phase), the dose administered at each injection was capped at 0.85 mL/148.75 mg for Dose 1 and Dose 3, and 1.1 mL/192.5 mg (capped at 200 mg) for Dose 2, respectively.

A total of 42 patients were enrolled in Portion 1 to be treated with one of the 3 dose regimens. An interim analysis (completed on 08 August 2018) was performed on 34 out of the 42 participants who had completed the 12-week core-treatment period. Selection of Dose 2 was based on efficacy and safety data included in this interim analysis. Improvement in signs and symptoms of pcJIA was more rapid and generally more pronounced in Dose 2 and Dose 3 compared to Dose 1.

Safety

The type of observed AEs was consistent with the safety profile of sarilumab in adult RA patients, with neutropenia and upper respiratory tract infection being the most frequently reported TEAEs. Based on the association in adult RA patients of sarilumab treatment with transient decreases in circulating ANC,

frequent hematology monitoring was adopted for the DRI13925 study. Haematology monitoring per DRI13925 protocol included assessments prior to the second injection (at Day 12 ±1 day for Dose 1 and Dose 2, and between Day 5 and Day 8 for Dose 3) and every 2 weeks. Among the 42 treated participants (safety population), 12 participants (28.5%) experienced Grade 3 or 4 neutropenia (decrease in absolute neutrophil count) during the 12-week core-treatment period, with a higher incidence of neutropenia in Dose 3 (6/12 participants) compared to the 2 other doses (3/12 participants in each dose cohort) and in Group B (8/12 participants) compared to Group A (4/12 participants). However, none of the Grade 3 or 4 neutropenia events were associated with infections or severe infections and all resolved within a few days. Based on the higher incidence of neutropenia in Dose 3 and considering the stopping rules of the DRI13925 protocol (in the initial protocol, sarilumab was to be discontinued in case of severe neutropenia [for details refer to Section 2.1.2.2]), Dose 2 was selected for Portion 2 and Portion 3 of the DRI13925 study as it showed the best benefit/risk balance. A comprehensive analysis of the safety profile of Dose 2 compared to Dose 1 and Dose 3 can be found in the following sections of this document and in the 12-week core treatment phase CSR.

2.6.5.2. Main study

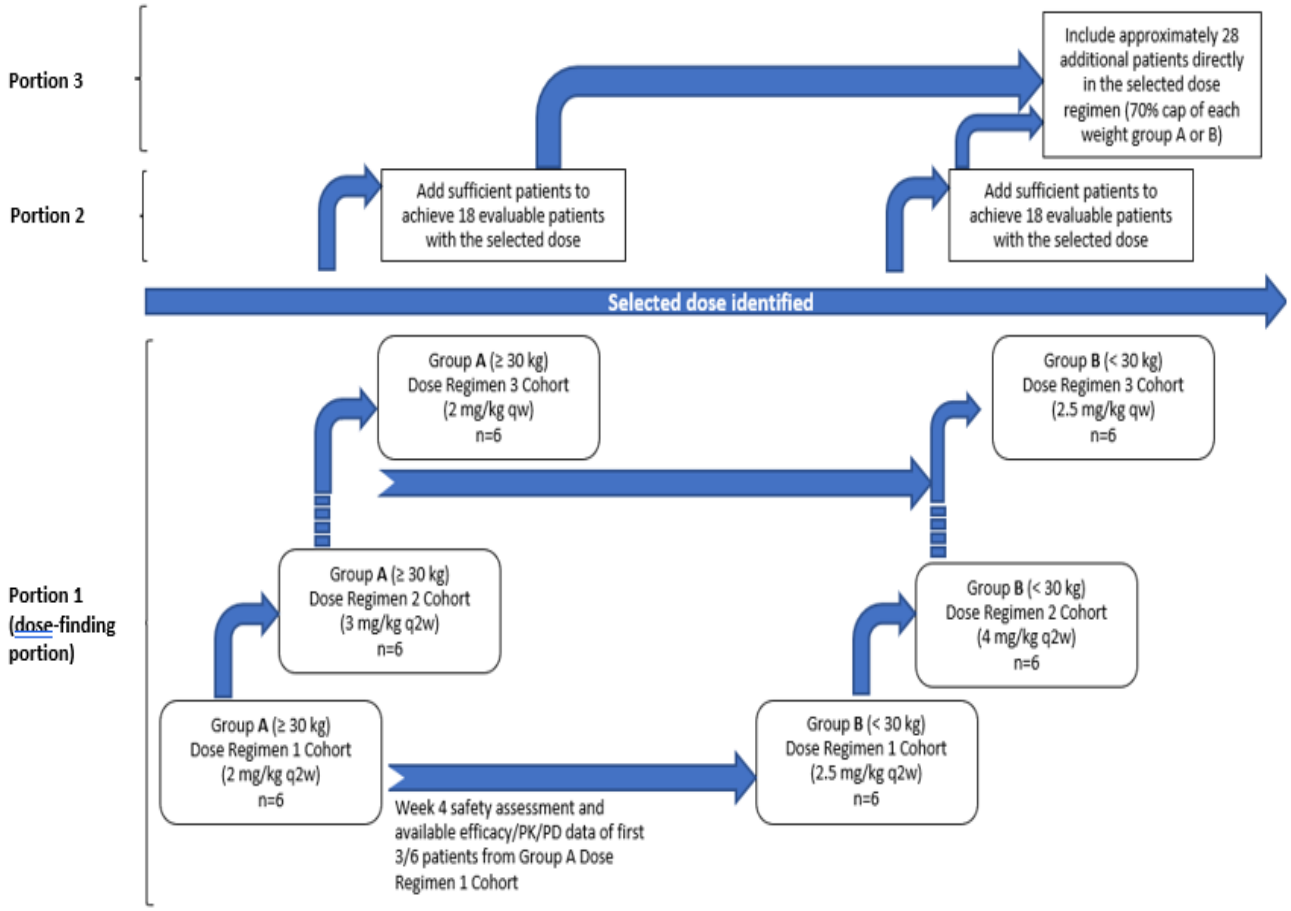
Open-label, Sequential, Ascending, Repeated Dose-finding Study of Sarilumab, Administered with Subcutaneous (SC) Injection, in Children and Adolescents, Aged 2 to 17 Years, with Polyarticular-course Juvenile Idiopathic Arthritis (pcJIA) Followed by an Extension Phase

Methods

Study Design

Study DRI13925 consisted of 3 subsequent portions: one dose-finding portion, and two expansion portions. Each portion had a 12-week core phase and an extension phase.

The extension phase was up to 144 weeks for participants enrolled in Portion 1 and Portion 2, and up to 84 weeks for the participants enrolled in Portion 3. For Portions 1 and 2, only participants who responded (i.e., those who have reached a JIA ACR30 response) at Week 12 were permitted to continue in the extension phase while all participants enrolled in Portion 3 were allowed to continue in the extension phase irrespective of their JIA ACR response level.



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 ≤60 kg) who had completed at least 4 weeks of study treatment.

- Study Participants

The patient population selected for Study DRI13925 was a RF- or RF+ pJIA subtype or extended oJIA subtype as defined by ILAR 2001 JIA Classification Criteria. The enrolled population had at least 5 active joints at screening, per ACR definition for "active arthritis", an inadequate response to current treatment and considered as a candidate for a bDMARD treatment. Exclusion criteria were the same for the 3 portions except the removal of the upper limit of 60 kg for the participants' weight in portions 2 and 3.

Inclusion criteria	• Male and female participants 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 5 active joints per ACR definition for "active arthritis" • Patient with an inadequate response to current treatment and considered as a candidate for a bDMARD
Exclusion criteria	• Diagnosis of JIA subtypes except RF+ or RF- pJIA or extended oJIA • BW <10 kg or >60 kg for participants enrolled in the 3 ascending dose cohorts, then BW <10 kg for participants subsequently enrolled at the selected dose regimen • Active TB or a history of incompletely treated TB, history of invasive opportunistic infections, and other infections TB as defined in the protocol, positive test for HIV, Hepatitis B (HBs-Ag or HBc-Ab) or C. • Laboratory abnormalities: hemoglobin <7.0 g/dL, white blood cells <3000/mm^3, neutrophils <2000/mm^3, platelet count <150 000 cells/mm^3, 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) • If NSAIDs (including COX-2 inhibitors) taken, dose stable for less than 2 weeks prior to the Baseline visit and/or dosing prescribed outside of approved label • If nonbiologic DMARD taken, dose stable for less than 6 weeks prior to the Baseline visit or at a dose exceeding the recommended dose as per local labeling • If oral glucocorticoid taken, dose stable for <2 weeks or dose exceeding equivalent prednisone dose 0.5 mg/kg/day (or 30 mg/day) within 2 weeks prior to Baseline • Use of parenteral or intra-articular glucocorticoid injection within 4 weeks prior to Baseline. • Prior treatment with anti-IL-6 or IL-6R antagonist therapies • Treatment with any biologic treatment for pcJIA within 5 half-lives prior to the first dose of sarilumab (Etanercept: within 4 weeks, Infliximab: within 8 weeks, Adalimumab: within 15 weeks, Anakinra: within 2 days, Canakinumab: within 19 weeks, Abatacept: within 10 weeks, Rituximab or other cell-depleting agent: within 16 weeks or until total lymphocyte count and CD 19+ lymphocyte count are normalized, whichever is longer, Intravenous Ig: within 15 weeks) • Treatment with JAK inhibitor or with growth hormone within 4 weeks prior to the first dose of sarilumab

Abbreviations: ACR = American college of rheumatology, bDMARD = biologic DMARD, DMARD = disease modifying antirheumatic drug, BW = body weight, COX2 = cyclo-oxygenase-2, IL-6 = interleukin-6, IL-6R = interleukin-6 receptor, JAK = Janus kinase, NSAIDs = non-steroidal anti-inflammatory drugs, pJIA = polyarticular juvenile idiopathic arthritis, pcJIA = polyarticular-course juvenile idiopathic arthritis, RF- = rheumatoid factor negative, RF+ = rheumatoid factor positive, TB = tuberculosis.

- Treatments

Study portion	N	Study duration	Treatment
1	42 Dose 1: 13 Dose 2: 14 Dose 3: 15	Core phase: 12 weeks Extension phase: 144 weeks	Core phase: 1) Group A: ≥30 kg and ≤60 kg - Dose 1: 2 mg/kg q2w - Dose 2: 3 mg/kg q2w - Dose 3: 2 mg/kg qw 2) Group B: <30 kg and ≥10 kg - Dose 1: 2.5 mg/kg q2w - Dose 2: 4 mg/kg q2w - Dose 3: 2.5 mg/kg qw Extension phase (for patients having a JIA ACR 30 response at Week 12): patients to continue with their baseline until dose selection, after which patients who received Doses 1 and 3 had their dose adjusted to Dose 2
2	31 Dose 2: 31	Core phase: 12 weeks Extension phase: 144 weeks	1) Group A: ≥30 kg: - Dose 2: 3 mg/kg q2w 2) Group B: <30 kg and ≥10 kg: - Dose 2: 4 mg/kg q2w
3	29 Dose 2: 28	Core phase: 12 weeks Extension phase: 84 weeks	3) Group A: ≥30 kg: - Dose 2: 3 mg/kg q2w 4) Group B: <30 kg and ≥10 kg: - Dose 2: 4 mg/kg q2w

Background therapy for all portions: Drugs permitted at dosage prescribed within approved label:
- NSAIDs at dose stable ≥ 2 weeks prior to Baseline
- csDMARD at dose stable ≥ 6 weeks prior to Baseline

Oral glucocorticoid at dose stable ≥ 2 weeks prior to Baseline and did not exceed equivalent prednisone dose 0.5 mg/kg/day (or 30 mg/day)

Drugs not allowed included any prior treatment with anti-IL-6 or IL-6R antagonist therapies, as well as any bDMARD within 5 half-lives prior to baseline

- Objectives and Outcomes/endpoints

The evaluation of the clinical efficacy were secondary / exploratory objectives

Summary of efficacy endpoints per protocol

Phase	Objectives	Endpoints[a]	Timepoints
12-week core phase	Describe the efficacy of sarilumab in participants with pcJIA	• Juvenile Idiopathic Arthritis ACR 30/50/70/90/100 response rate • Change from baseline in individual JIA ACR components • Juvenile Arthritis Disease Activity Score (JADAS)-27 change from baseline	Week 12
Extension phase		• Juvenile Idiopathic Arthritis ACR 30/50/70/90/100 response rate • Change from baseline in individual JIA ACR components • Juvenile Arthritis Disease Activity Score (JADAS)-27 change from baseline	Week 24, Week 48 and every 24 weeks up to the end of the study

JIA ACR: juvenile idiopathic arthritis American College of Rheumatology, JADAS: juvenile arthritis disease activity score, pcJIA: polyarticular-course juvenile idiopathic arthritis.

a Prespecified per amended protocol 03 and SAP dated 12 Sep 2019

Additional efficacy parameters

Objectives	Parameters[a]	Timepoints
To describe the efficacy of sarilumab in participants with pcJIA	Change from baseline in Clinical JADAS-27 (cJADAS-27; ie, JADAS-27 without CRP component) Change from baseline in JADAS-10 Change from baseline in Clinical JADAS-10 (ie, JADAS-10 without CRP component) Proportion of participants with - no active joints - JADAS-10 inactive disease: JADAS-10 ≤2.7 - Clinical JADAS-10 inactive disease: cJADAS-10 ≤2.5 - Clinical inactive disease (CID) per 2004 Wallace criteria - CID and no systemic glucocorticoid use (Wallace) - JADAS-10 minimal disease activity: JADAS-10 ≤6 - Clinical JADAS-10 minimal disease activity: JADAS-10 ≤5 - Clinical remission defined as inactive disease per Wallace criteria for 6 consecutive months prior to the assessment visits	Weeks 6, 12, 24, 48, and every 24 weeks up to EOS

Abbreviations: cJADAS = clinical juvenile arthritis disease activity score, CID = clinical inactive disease, CRP = C-reactive protein, JADAS = juvenile arthritis disease activity score, pcJIA = polyarticular-course juvenile idiopathic arthritis.

a Additional efficacy parameters added before the database lock of the interim analysis taking into account the more recent efficacy assessments for pcJIA disease. Details are in 5.3.5.2, Study DRI13925 1y3p, Appendix 16.1.9 [Supporting statistical documentation]

- Sample size

No formal sample size calculation was conducted. In portion 1, 36 patients (6 per weight/dose group) were planned to be included, expecting the coefficient of variation for PK parameters to be similar in a paediatric population to that reported in adult rheumatoid arthritis patients. In portion 2, 24 additional patients (12 per weight group) were planned to be assigned to the selected doses, allowing to estimate the sarilumab PK parameters so that the 95% confidence interval (CI) is within 60% to 140% of the geometric mean. In portion 3, 28 additional patients were planned to be directly enrolled to the selected dose regimen in the third portion to achieve a total of approximately 100 treated patients for the entire study as per health authority recommendation.

- Randomisation and Blinding (masking)

Not applicable.

- Statistical methods

All efficacy analyses were descriptive.

DOSE ESCALATION

No explicit definitive rules to guide the choice of the dose to be further investigated in portions 2 and 3 of the trial were prespecified in the protocol. The dose escalation decision was planned to be taken by the Dose Escalation Committee (DEC), subject to DMC recommendation. A review of the aggregate PK, PD, efficacy and safety data was planned to be performed on the preceding dose cohort before proceeding to the next dose cohort.

DOSE EXTENSION/EFFICACY - Analysis of JIA ACR30 response

Patients achieving JIA ACR30 (without fever in the case of sJIA) response for each dose regimen cohort, overall and by weight group, were summarized by visit using counts, proportions and 95% CIs. The primary approach was based on all observed data while the patient remained on treatment. No missing data were planned to be imputed, but the following sensitivity analyses were planned:

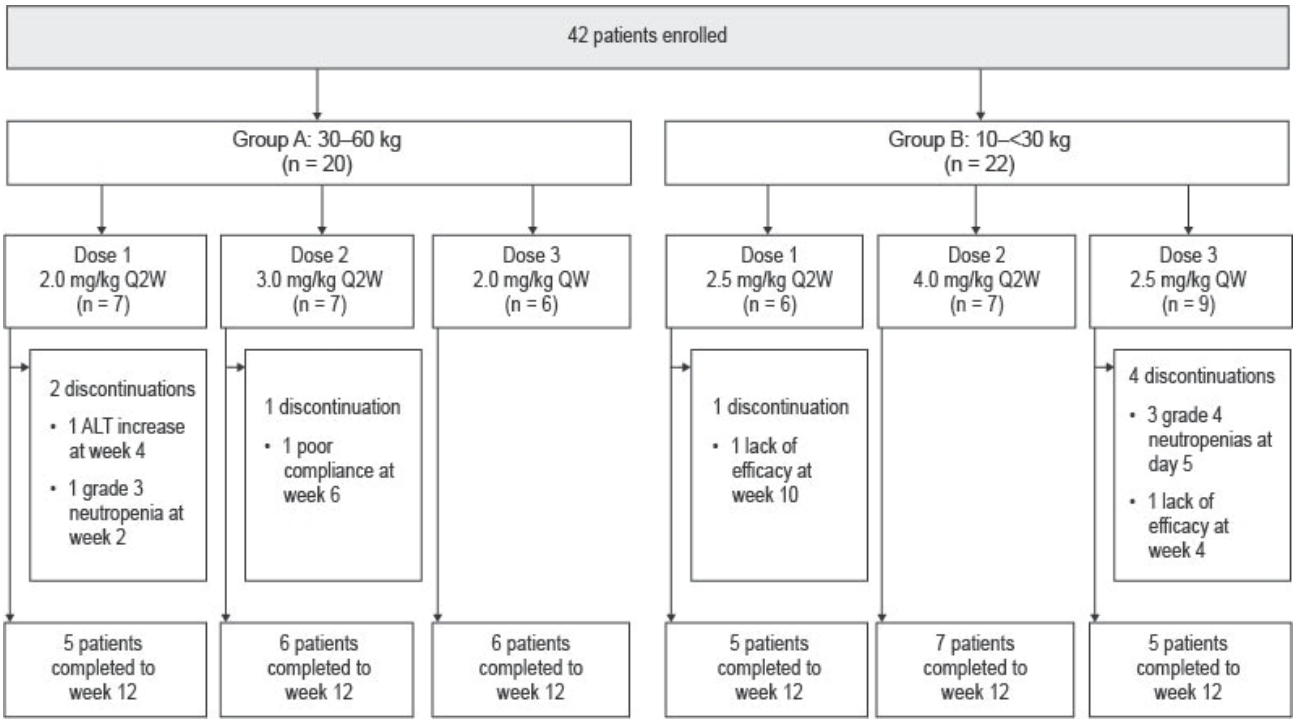
- Non-responder imputation approach: Data collected after treatment discontinuation will be set to missing. No imputation of missing post-baseline values will be performed. Responder status will be determined using available data and patients will automatically become non-responders for all time points beyond the time point they discontinued study treatment or for which there is insufficient data.
- LOCF approach: Missing data will be imputed using the last observation carried forward (LOCF) procedure from the point of treatment discontinuation for all 6 ACR components (and temperature for sJIA) for all visits post that point. Responder status will be determined using the imputed data.
- As observed including post discontinuation follow-up: All observed data up to week 12, including those collected after treatment discontinuation, will be included in the analysis. No missing data will be imputed.

Further endpoints were analysed descriptively using a while-on-treatment strategy.

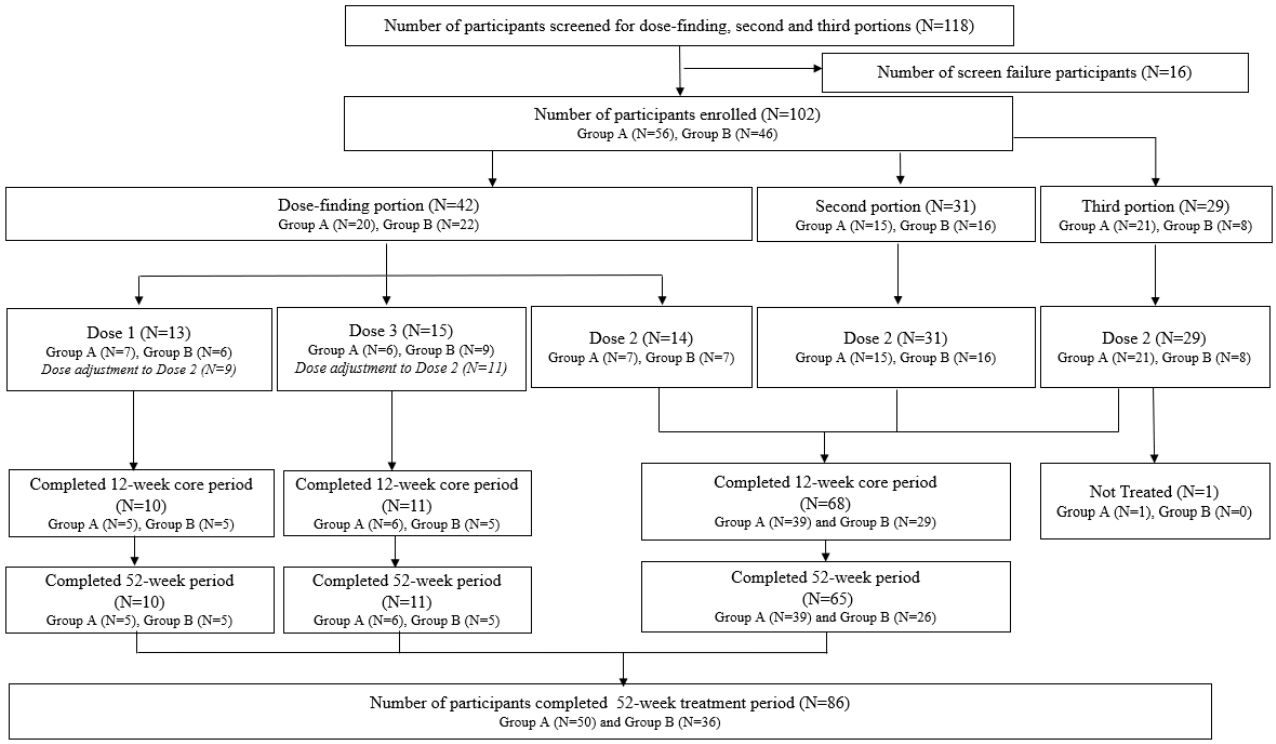
Results

- Participant flow

Participant disposition in DRI13925 (Portion 1)



Participant disposition in DRI13925 (Portions 1, 2 and 3)



- Recruitment

Study DRI13925 consisted of 3 subsequent portions: one dose-finding portion, and two expansion portions. Each portion had a 12-week core phase and an extension phase.

The extension phase was up to 144 weeks for participants enrolled in Portion 1 and Portion 2, and up to 84 weeks for the participants enrolled in Portion 3. For Portions 1 and 2, only participants who responded (i.e., those who have reached a JIA ACR30 response) at Week 12 were permitted to continue in the extension phase while all participants enrolled in Portion 3 were allowed to continue in the extension phase irrespective of their JIA ACR response level.

- Conduct of the study

There were 6 amendments of the protocol, 5 of them were local amendments. The most salient amendment 6.

Table 8: Summary of protocol amendments and global amendments

No. (country)[a]	Date	Purpose of amendments
Protocol Amendment 1	08-Mar-2016	• To comply with Health Authority guidelines for age of inclusion in pediatric population.
Protocol Amendment 2 (France)	15-Jul-2016	• To include within the exclusion criteria a requirement for post-pubertal male patients to use effective methods of contraception, including abstinence, per ANSM request, so that contraception requirements applied for both male and female participants child-bearing potential.
Protocol Amendment 3 (Germany)	20-Jul-2016	• To include within the exclusion criteria clarification on language regarding hypersensitivity reaction to any biologic drug. • To update exclusion criteria relating to contraception to add Germany as an applicable country for list of acceptable forms of effective contraception.
Protocol Amendment 4 (Germany)	03-Jan-2017	• To include mandatory performing Hepatitis B, C, and HIV serology testing at Screening Visit. • To extend monitoring duration for any signs and symptoms of a hypersensitivity reaction after the first sarilumab administration for a minimum of 1 hour instead of 30 minutes. • To include explicit statement of pain prevention including mandatory pain prevention for patients aged 6 to 11 years. • To include effective contraception at least 2 months before first sarilumab injection for female adolescent patients of child-bearing potential.
Protocol Amendment 5	21-Apr-2017	• To reestablish the partial approval of age extension for inclusion in the study as 6 to 17 years old instead of 12 to 17 years (initially included in the first local amendment).
Amended Protocol 1 /Protocol Amendment 6	06-Apr-2018 /27-Jun-2018	• To modify the study design to implement the amended Pediatric Investigations Plan approved by the European Medicines Agency. • To split the 12-week core treatment phase of the study into 2 portions: a dose-finding portion corresponding to the 12-week core treatment phase of the initial protocol where 3 ascending dose regimens will be tested in 36 patients; and a second portion where additional patients will receive the dose regimen selected from data of the first portion of the study in order to provide sufficient precision for PK parameters and PK-PD relationship assessments at that selected dose regimen.

No. (country)[a]	Date	Purpose of amendments
		• To prolong the extension phase of the study from 92 weeks to 144 weeks for a total study duration of 166 weeks (per patient). • To increase the number of enrolled patients from 36 to 60 evaluable patients by 24 additional patients enrolled in the second portion of the study. • To revise the secondary efficacy endpoints. • To update the exclusion criteria section to better define the study population. • To incorporate several local protocol amendments that have already been approved, which address local health authorities and/or IRB requests related to the initial protocol.
Amended Protocol 2/Protocol Amendment 7	13-Dec-2018	• To update the stopping rules for Grade 4 neutropenia: The stopping rules for Grade 4 neutropenia was updated during the study after analysis of the 12-week core phase of the Portion 1 in order to provide the best chance for participants to benefit from treatment while continuously monitoring for safety events. Prior to the amendment, sarilumab had to be discontinued in case of Grade 4 neutropenia (ANC <0.5 Giga/L) whether or not associated with signs of infection. Per the amendment, any Grade 4 neutropenia without infection led to temporary hold of treatment and the decision to resume sarilumab could be considered by the Investigator when ANC returned to >1.0 Giga/L and based upon medical benefit-to-risk assessment. The rule stayed unchanged for any Grade 3 and 4 neutropenia associated with signs of infection (discontinuation) and Grade 3 neutropenia without infection (ANC ≥0.5 Giga/L and <1.0 Giga/L) (temporary hold).
Amended Protocol 3/Protocol Amendment 8	12-Sep-2019	• To increase the planned total number of enrolled participants (28 additional participants) to achieve a total of approximately 100 treated participants (based on health authority [FDA] recommendations).
Amended Protocol 4 /Protocol Amendment 9 (Italy)	08-Jul-2020	• To include the rationale for the dose selected by the Dose Escalation Committee on 31 October 2018 (based upon the request of Italian Health Authority).

Abbreviations: ANC = absolute neutrophil count, ANSM = Agence Nationale de Securite du Medicament, HIV = human immunodeficiency virus; IRB = Independent Review Board; PK = pharmacokinetic; PD: pharmacodynamic.
a Country of amendment, if applicable.

- Baseline data

Demographics and participant characteristics at baseline - All treated population

The demographic and disease characteristics at baseline were comparable across the 3 doses within each BW group. Participants were mostly female (64.3%). A total of 78.6% of participants were Caucasian. The mean weight and age were 45.0 kg and 13.0 years in Group A and 19.7 kg and 5.2 years in Group B, respectively.

Similar to the overall population in the study, participants who received Dose 2 from baseline were mostly female (58 [79.5%]), White (67 [91.8%]), and from EU countries and the UK (37 [50.7%]). There were 3 participants from North America (2 and 1 from the US and Canada, respectively). The mean weight and age were 46.7 kg and 12.6 [6 to 17] years in Group A and 20.1 kg and 5.4 [2 to 14] years in Group B, respectively.

Disease characteristics at baseline - All treated population

Overall, the distribution of participants with RF- pJIA, RF+ pJIA, and extended-oJIA subtypes was 66.3%, 18.8%, and 14.9%, respectively without notable imbalance across the doses. In the entire population, the proportion of participants with RF- pJIA was slightly lower in Group A (58.2%) when compared to group B (76.1%), while there were approximately twice as many participants with RF+ pJIA or with extended-oJIA in Group A compared with Group B, reflecting the age distribution of the disease. Overall, the mean duration of JIA since diagnosis was 2.6 years (3.4 years and 1.7 years in Groups A and B, respectively), reflecting the long disease history. The overall baseline median JADAS-10 CRP and JADAS-27 CRP were 20.5 and 21.9, respectively, reflecting a patient population with high disease activity (JADAS-27 CRP and JADAS-10 thresholds for high disease activity are >8.5 and >17, respectively). For the other disease characteristics, there were no notable differences across the doses.

Almost one third of participants had been treated with bDMARDs prior to baseline and, at baseline, about three fourths and one third of participants were receiving a csDMARD and a systemic glucocorticoid, respectively.

- Numbers analysed

	Dose Regimen Cohort		
Weight Group	**1 (N=13)**	**2 (N=74)**	**3 (N=15)**
All			
Number	13	74	15
Safety population	13 (100%)	73 (98.6%)	15 (100%)
Efficacy population	13 (100%)	73 (98.6%)	15 (100%)
PK population	13 (100%)	73 (98.6%)	15 (100%)
PD population	13 (100%)	73 (98.6%)	15 (100%)
Immunogenicity population	13 (100%)	73 (98.6%)	15 (100%)
COVID-19 impacted population	0	0	0
≥ 30 kg (Group A)			
Number	7	43	6
Safety population	7 (100%)	42 (97.7%)	6 (100%)
Efficacy population	7 (100%)	42 (97.7%)	6 (100%)
PK population	7 (100%)	42 (97.7%)	6 (100%)
PD population	7 (100%)	42 (97.7%)	6 (100%)
Immunogenicity population	7 (100%)	42 (97.7%)	6 (100%)
COVID-19 impacted population	0	0	0
< 30 kg (Group B)			
Number	6	31	9
Safety population	6 (100%)	31 (100%)	9 (100%)
Efficacy population	6 (100%)	31 (100%)	9 (100%)
PK population	6 (100%)	31 (100%)	9 (100%)
PD population	6 (100%)	31 (100%)	9 (100%)
Immunogenicity population	6 (100%)	31 (100%)	9 (100%)
COVID-19 impacted population	0	0	0

PD = Pharmacodynamic, PK = Pharmacokinetic.
Note: participants are tabulated according to treatment actually received (as treated) for all the populations.
PGM=PRODOPS/SAR153191/DRI13925/CSR_1YEAR/REPORT/PGM/dis_populations_r_t.sas
OUT=REPORT/OUTPUT/dis_populations_r_t_i.rtf (30MAR2023 - 8:56)

- Outcomes and estimation

Portion 1 – 12 weeks data

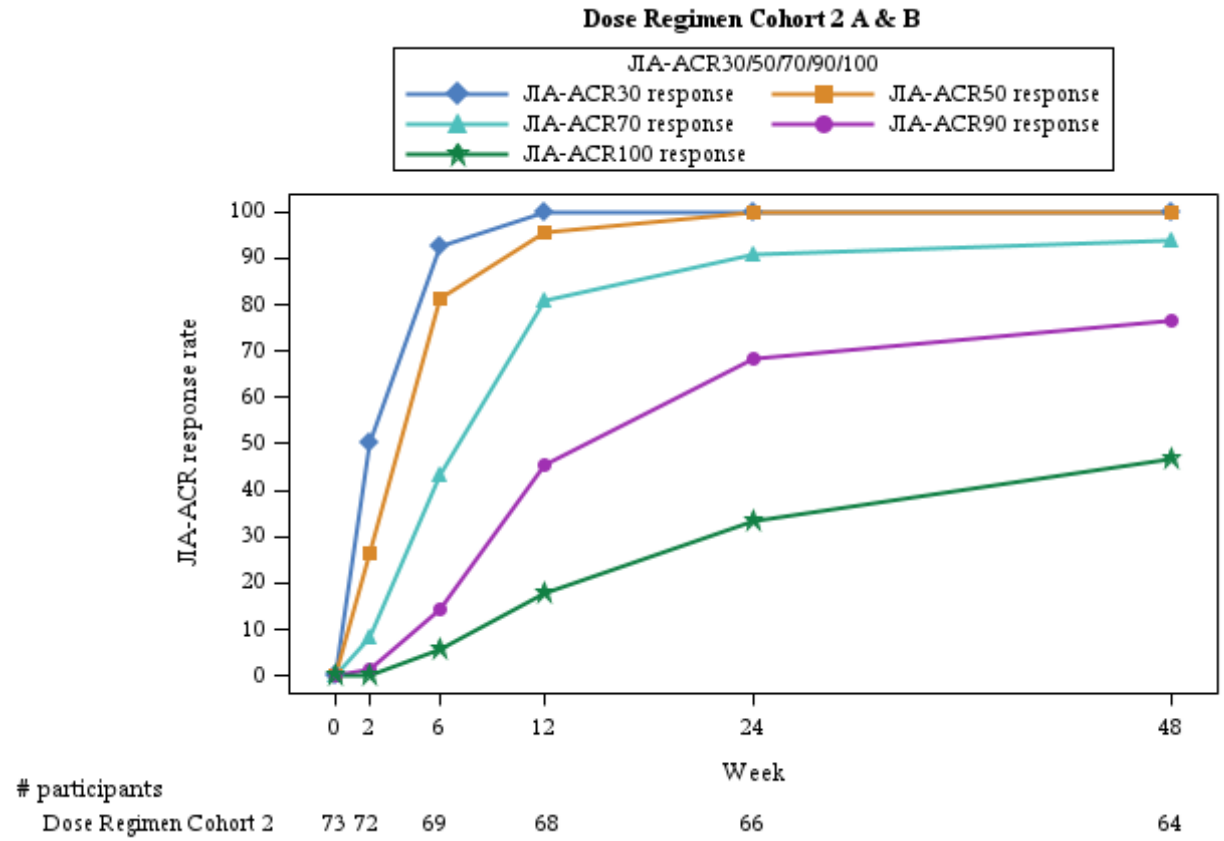
The 3 sarilumab dose regimens evaluated were demonstrated to be effective in improving the signs and symptoms of disease activity, with a JIA ACR30 response rate with the "as observed while on-treatment" approach of 100% at Week 12 in all 3 doses in both BW groups.

- At Week 12, as observed while on-treatment, the JIA ACR70 response rates were 50.0%, 61.5%, and 100% in Dose 1, 2, and 3, respectively.
- As observed while on-treatment, the JIA ACR30 response rates plateaued to 100% achievement within the first 2 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 non-responder imputation approach, 76.9%, 92.9%, and 73.3% of patients achieved JIA ACR30 in Doses 1, 2, and 3, respectively. As calculated by LOCF approach, 84.6%, 1 and 86.7% 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 participants completed Week 12 with no active arthritis (4 each with Doses 1 and 2, and 5 with Dose 3). Overall, the CHAQ-DI scores and mean hs-CRP decreased for patients in all doses for both BW groups throughout the 12-week core treatment phase. The largest mean decrease at Week 12 was observed for participants in Group B, Dose 2 (mean change of 1.0 for CHAD-DI and -15.2 mg/L for hs-CRP).
- The decrease in disease activity was seen in all dose and BW groups as early as Week 2 with a mean change in JADAS-27 from baseline at Week 12 of -17.2, -14.7, and -19.7 in Dose 1, 2, and 3, respectively.

Based on these data that demonstrated a more rapid and generally more pronounced improvement in signs and symptoms of pcJIA in Dose 2 and Dose 3 compared to Dose 1, together with the aggregate PK, PD and safety data, Dose 2 was selected for enrolling subsequent participants in Portions 2 and 3. Dose 3 (weekly regimen) was considered not appropriate based on safety results, which showed more events of neutropenia compared to the other two doses (every other week regimen). Thereafter, the participants enrolled in the subsequent Portions 2 and 3 of DRI13925 study were treated with the selected Dose 2, namely: "4 mg/kg q2w in participants weighing ≥10 kg to <30 kg" and “3 mg/kg q2w in participants weighing 30 kg or more (capped at 200 mg q2w)”.

Portions 1, 2 and 3: One-year data analysis

Figure 6: JIA ACR30/50/70/90/100 (hs-CRP) response (as observed while on treatment) during the first year of treatment period - Participants on the selected dose (Dose 2)

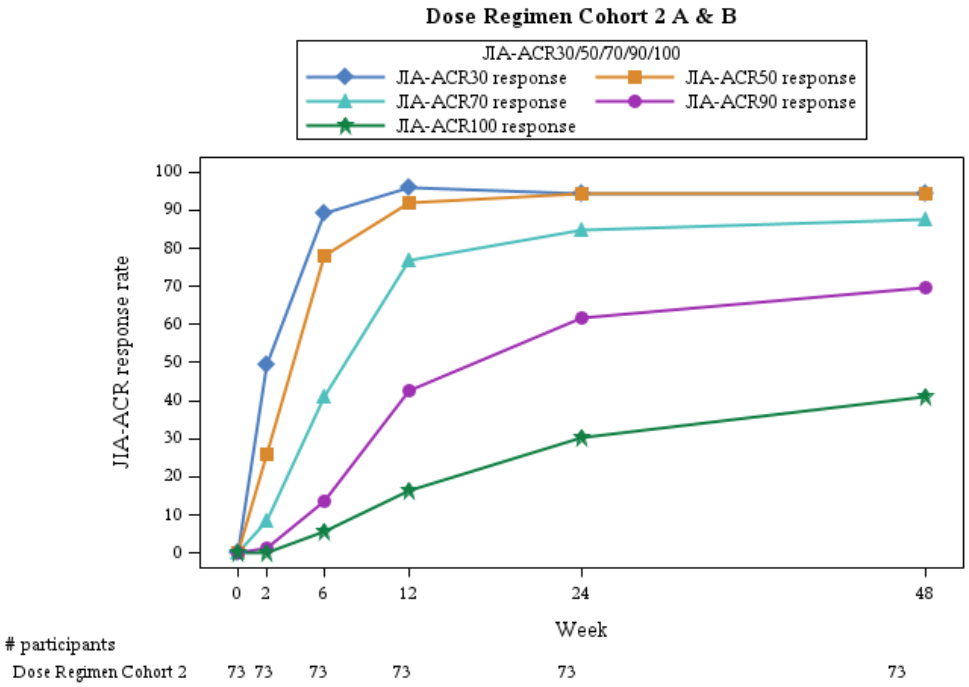


Note: participants enrolled in the selected dose cohort from the 2nd and 3rd portions of the study are combined with participants enrolled in Dose Regimen Cohort 2 from the dose-finding portion of the study.

All participants had JIA ACR30 response at Week 12 and improvement continued up to Week 48 as seen with the JIA ACR70 response rate that was achieved by 80.9% of participants at Week 12 and 93.8% at Week 48.

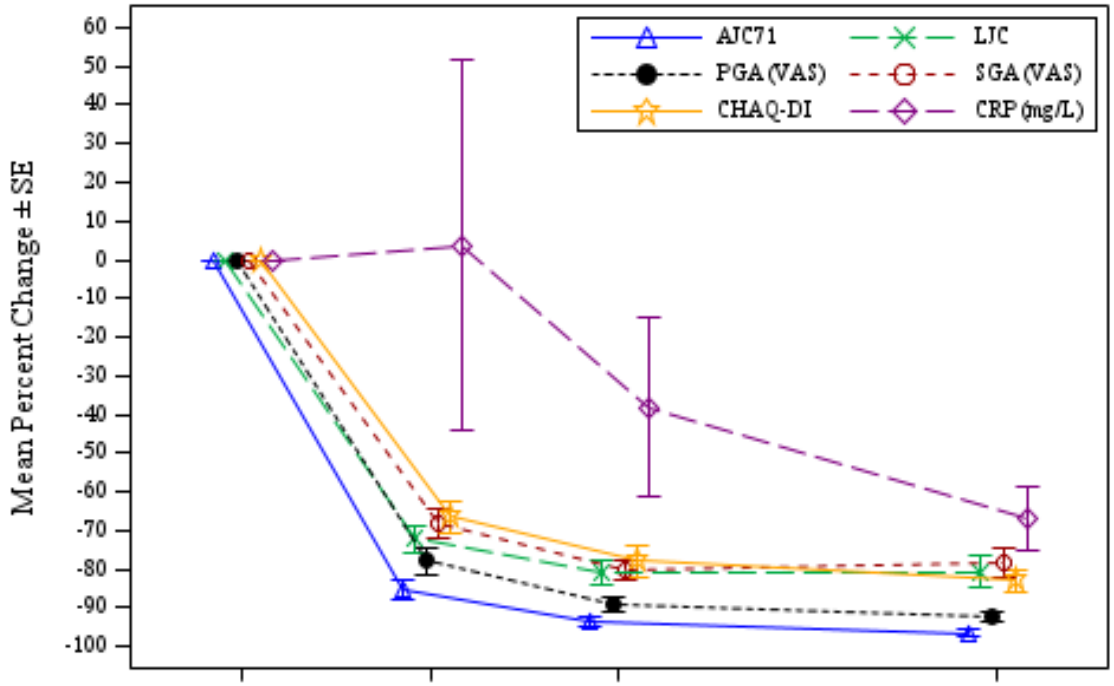
Upon CHMP request the MAH performed the responder analyses on JIA ACR 30/50/70/90/100 at Week 12, Week 24, and Week 48 based on ITT approach.

Figure 7 - JIA ACR30/50/70/90/100 (hs-CRP) response rates during the first year of treatment period - Participants on the selected Dose 2– ITT approach



The proportion of patients with JIA ACR 70 response rate were 76.7% and 87.7% at Week 12 and Week 48, respectively. The proportion of patients with JIA ACR 90 response rate were 42.5% and 69.9% at Week 12 and Week 48, respectively.

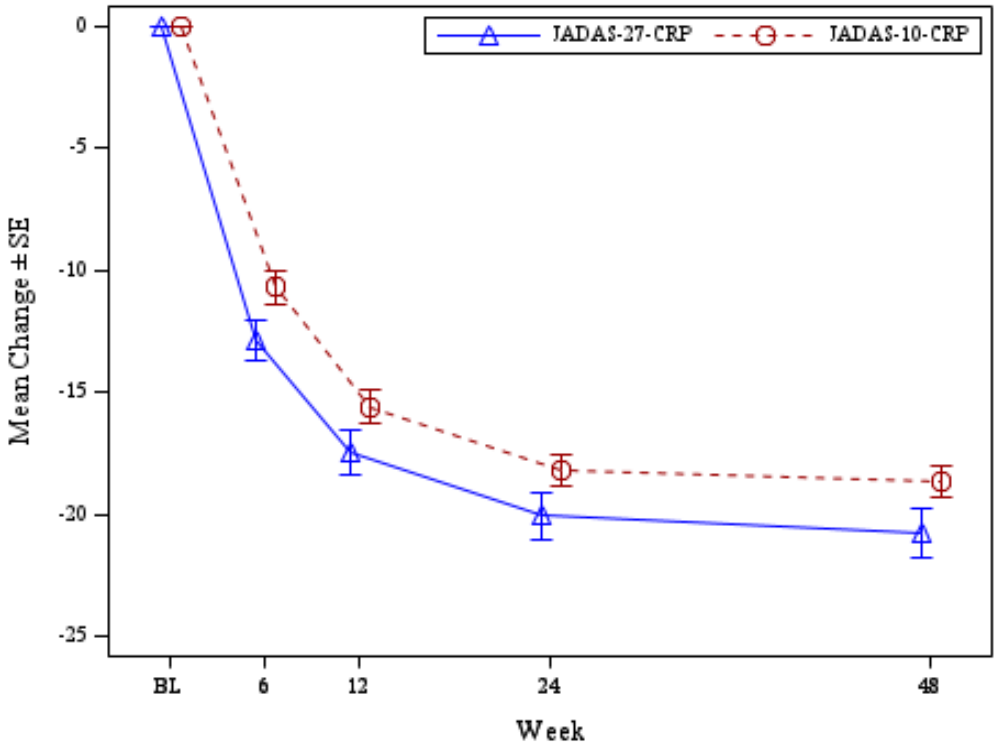
Figure 8: JIA ACR components during the first year of treatment period - Percent change from baseline - participants on the selected dose (Dose 2)



# participants				
AJC71	73	68	66	64
LJC	71	66	64	62
PGA (VAS)	73	68	66	64
SGA (VAS)	73	68	66	65
CHAQ-DI	70	65	63	62
CRP (mg/L)	73	66	66	65

Improvement for all JIA ACR components were seen. In particular, the proportion of participants with normal hs-CRP and undetectable hs-CRP increased from 93.9% and 63.6%, respectively, at Week 12 to 98.5% and 81.5%, respectively, at Week 48.

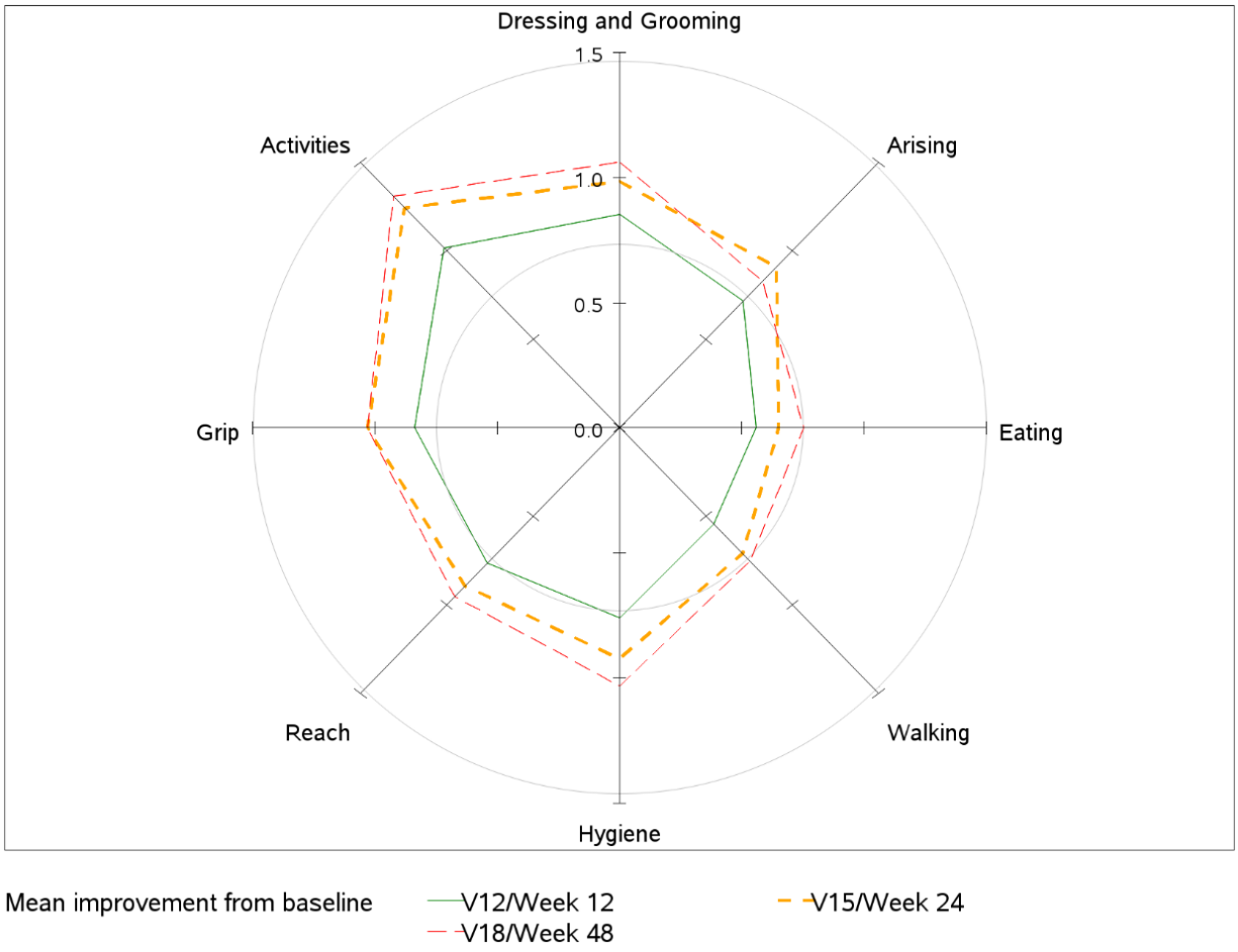
Figure 9: Change from baseline in JADAS-27 (CRP) and JADAS-10 (CRP) during the first year of treatment period - participants on the selected dose (Dose 2)



# participants					
JADAS-27-CRP	73	65	65	64	64
JADAS-10-CRP	73	65	65	64	64

A decrease in disease activity based on the change from baseline in JADAS-27 was observed as early as Week 12.

Figure 10: Post-hoc analysis: Evolution of mean improvement from baseline in CHAQ-DI domains during the first year of treatment period on the selected dose (Dose 2)

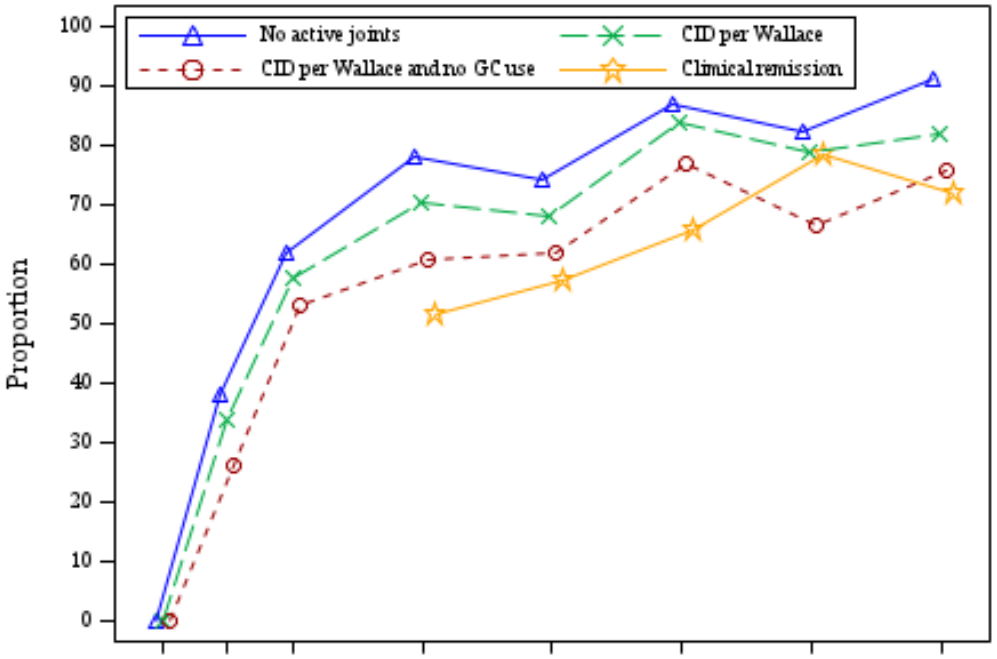


The functional ability of patients with JIA assessed in 8 domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) by the CHAQ-DI questionnaire also showed a rapid improvement in all domains with a change from baseline of -0.76 and -0.96 at Week 12 and 48, respectively corresponding to a mean percent change from baseline of -77.6% and -90.7%. A post-hoc analysis confirmed that no participants had a worsening of their functional ability (using the minimum clinical worsening threshold of 0.75) at Weeks 12, 24 or 48, and the proportion of patients who experienced an improvement of disability (using the minimal clinical important improvement threshold of 0.13) reached 92.3% at Week 48.

Additional efficacy parameters

All additional parameters (proportion of participants with no active joints, minimal disease activity or inactive disease (JADAS-10), minimal clinical disease activity or clinically inactive disease (cJADAS-10), clinically inactive disease (CID) per Wallace criteria and CID per Wallace criteria without glucocorticoids use) showed a large improvement in disease activity from baseline to Week 48.

Figure 11: Proportions of participants with no active joints, CID per Wallace, CID per Wallace and no GC use, and clinical remission during the entire treatment period - Participants on the selected dose (Dose 2)



# participants								
No active joints	73	68	66	64	54	46	34	34
CID per Wallace	73	65	64	64	50	43	33	33
CID per Wallace and no GC use	73	65	64	64	50	43	33	33
Clinical remission				62	49	35	28	32

Note: participants enrolled in the selected dose cohort from the 2nd and 3rd portions of the study are combined with participants enrolled in Dose Regimen Cohort 2 from the dose-finding portion of the study.
Clinical remission is defined as achieving inactive disease per Wallace criteria for at least 6 consecutive months prior to the assessment visit.
CID=clinical inactive disease

The long-term efficacy with Dose 2 (46 and 33 participants had JIA-ACR measurements available at Week 96 [2-year] and Week 156 [3-year], respectively) showed continuous improvements of sarilumab for all these efficacy endpoints and additional clinical parameters. Disease activity continued to improve beyond Week 48 with more than 70% of participant in clinical remission at the last time-points (22/28 participants [78.6%] at Week 120 and 23/32 participants [71.9%] at Week 144)

Participants enrolled in Doses 1 or 3 who had their dose adjusted to Dose 2

A total of 20 participants initially enrolled to receive Doses 1 or 3 had their dose adjusted to Dose 2:

- 9 participants initially enrolled in Dose 1 (4 participants at Week 84, 1 at Week 96, 2 at Week 108, and 2 at Week 120).
- 11 participants initially enrolled in Dose 3 had dose adjustment to Dose 2 (3 participants at Week 32, 1 at Week 40, 2 at Week 48, 1 at Week 60, and 4 at Week 72).

In participants on Dose 1 and Dose 3 before dose adjustment, the JIA ACR30, 50 and 70 were 100% 6 weeks after dose adjustment for participants who switched from Dose 1 and were 100% from the time

of dose adjustment for those who switched from Dose 3. No discernable changes in JIA ACR response rates were observed in participants who switched from Dose 1 (the lowest dose) or Dose 3 (the highest dose) to the selected Dose 2

The change from baseline in JIA ACR components in participants who were on Dose 1 or 3 before dose adjustment remained stable up to 24 weeks after dose adjustment

All participants who switched to the selected Dose 2 (N=20) had normal hs-CRP (hs-CRP <10 mg/L) 12 and 24 weeks after dose adjustment. Of these, 55.6% of participants who switched from Dose 1 to Dose 2 (N=9) had undetectable hs-CRP (hs-CRP <0.2 mg/L) 24 weeks after dose adjustment. The hs-CRP was undetectable in 80.0% of participants who switched from Dose 3 to Dose 2 (N=11), 24 weeks after dose.

For participants who were on Dose 1 or Dose 3 before dose adjustment, the change from baseline up to Week 24 in JADAS (JADAS-27, JADAS-10, clinical JADAS-10 and clinical JADAS-27) remained stable with a score change ranging approximately from -17 to -21.

The proportions of participants with minimal or inactive disease activity characterized by JADAS- 10 or clinical JADAS-10 and the proportions of participants with no active joints remained stable after dose adjustment in participants initially enrolled in Dose 1 or Dose 3 and who switched to Dose 2.

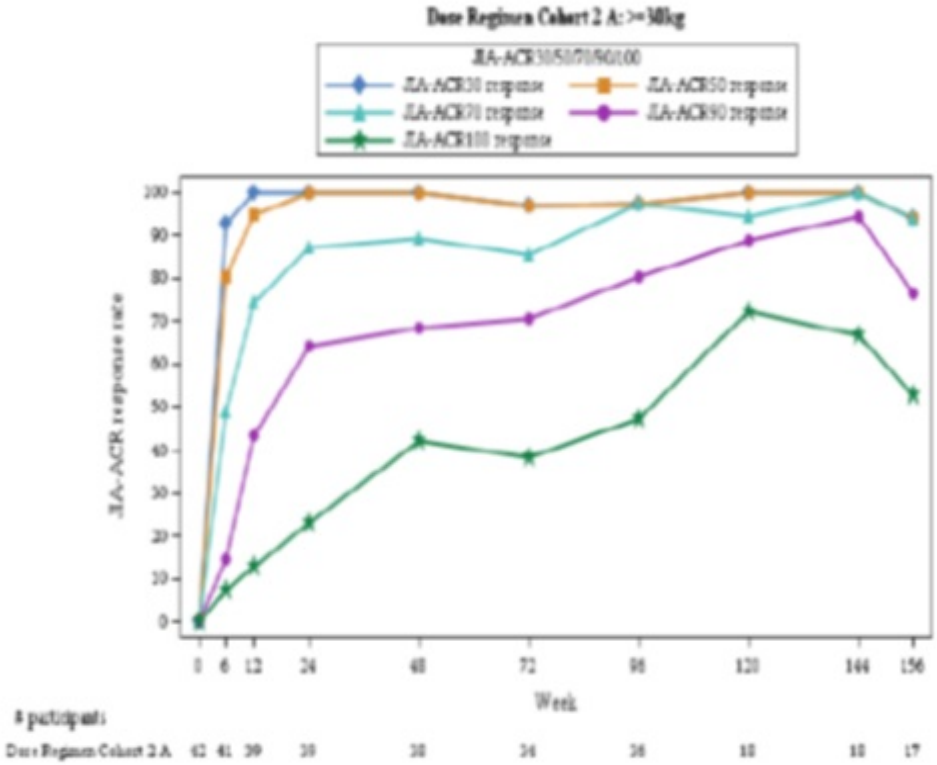
Final study report.

Two interim study reports have been submitted with the initial submission of the present extension application to support the extrapolation approach from adults with RA to paediatric patients with pJIA based on PK data, as well as the efficacy and safety of sarilumab in pJIA up to one year. During the procedure, the final study report was submitted, providing long-term data of up to 3 years.

2- and 3-year efficacy results

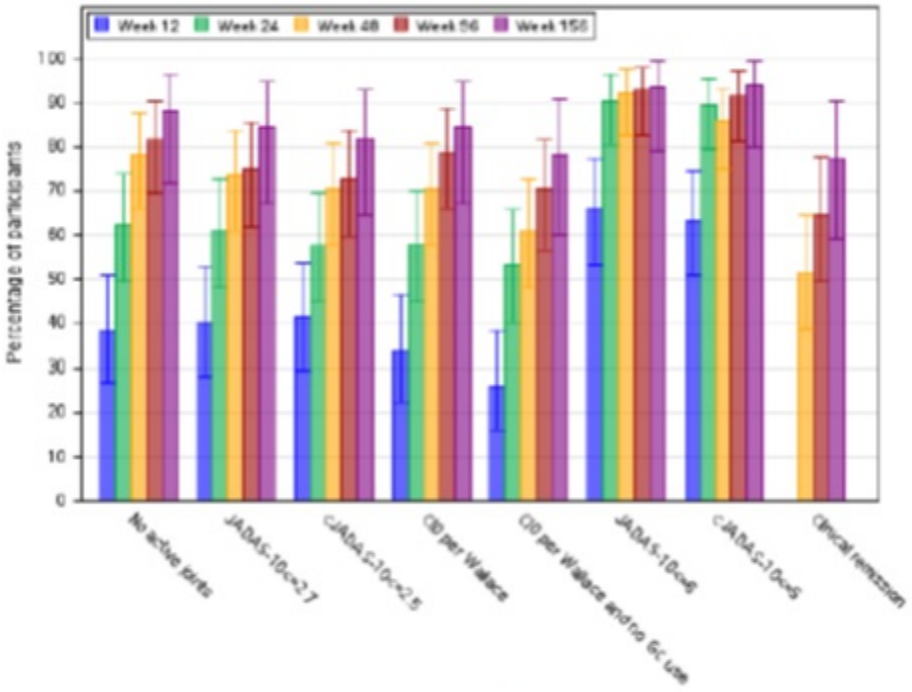
The long-term efficacy results with Dose 2 (60 and 33 participants had JIA-ACR measurements available at Week 96 [2-year] and Week 156 [3-year], respectively) showed continuous improvements of sarilumab for all efficacy endpoints and additional clinical parameters with JIA ACR70 response using the “as observed while on-treatment approach” (98.3% of participants at Week 96 and 97.0% at Week 156), JIA ACR90 response (76.6% at Week 48, 86.7% at Week 96 and 87.9% at Week 156) (Figure 12), with increasing proportion of participants with no more active joints (78.1% at Week 48, 81.7% at Week 96 and 87.9% at Week 156), with clinically inactive disease (per Wallace criteria) (78.9% at Week 96 and 84.4% at Week 156), or with clinical inactive disease (per Wallace criteria) and no systemic glucocorticoid use (70.2% at Week 96 and 78.1% at Week 156) or in clinical remission (64.6% at Week 96 and 77.4% at Week 156) (Figure 13).

Figure 12: JIA ACR30/50/70/90/100 (hs-CRP) response (as observed while on treatment) during the entire treatment period – Participants on the selected dose (Dose 2) from baseline



Note: participants enrolled in the selected dose cohort from the 2nd and 3rd portions of the study are combined with participants enrolled in Dose Regimen Cohort 2 from the dose-finding portion of the study.
PGM=PRODOPS/SAR153191/DRI13925/CSR_FINAL/REPORT/PGM/eff_resp_acr_byvis_d2_i_g.sas
OUT=REPORT/OUTPUT/eff_resp_acr_byvis_d2a_i_g_i.rtf (07FEB2024 - 9:26)

Figure 13: Histogram of proportion (%) of participants with specified disease activity by visit – Participants on the selected dose (Dose 2) from baseline



CID=clinical inactive disease; no GC use=no systemic glucocorticoid use.
PGM=PRODOPS/SAR153191/DRI13925/CSR_FINAL/REPORT/PGM/eff_disact_d2_i_g.sas
OUT=REPORT/OUTPUT/eff_disact_d2_i_g_i.rtf (07FEB2024 - 9:24)

Improvements in efficacy parameters were seen in both BW groups with a greater proportion of participants in Group B (< 30 kg) compared to Group A (≥30) achieving at Week 156 a clinically significant improvement assessed by JIA ACR70 response (94.1% in Group A versus 100% in Group B) and JIA ACR90 response (76.5% in Group A versus 100% in Group B), with no more active joints (76.5% in Group A versus 100% in Group B), with clinically inactive disease (per Wallace criteria) (68.8% in Group A versus 100% in Group B), or with clinical inactive disease (per Wallace criteria) and no systemic glucocorticoid use (62.5% in Group A versus 93.8% in Group B) or in clinical remission (62.5% in Group A versus 93.3% in Group B).

The CHAQ-DI decreased rapidly in participants on Dose 2 and the mean change from baseline at Week 12, 48, 96 and 156 was -0.76, -0.96, -1.01 and -1.13, respectively. A post-hoc analysis showed a proportion of participants who experienced an improvement in their functional ability, as assessed by CHAQ-DI, of 90.0% at Week 96, and 94.1% at Week 144.

The efficacy results were consistent across demographic or disease characteristics subgroups except for the participants' weight as above-described, which can be explained by the disease characteristics of Group A participants representing a more difficult to treat population compared to Group B.

- Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9: Summary of Efficacy for trial DRI13925

Title: An open-label, sequential, ascending, repeated dose-finding study of sarilumab, administered with subcutaneous (SC) injection, in children and adolescents, aged 2 to 17 years, with polyarticular-course juvenile idiopathic arthritis (pcJIA) followed by an extension phase		
Study identifier	Study number: DRI13925 IND Number(s): 100632 EudraCT number: 2015-003999-79 NCT: NCT02776735	
Design	This study was a Phase 2b multi-national, multi-center, open-label, 2-phase, 3-portion study in children and adolescents aged 2 to 17 years with pcJIA who had inadequate response to current therapy and were considered as candidates for a biologic disease modifying antirheumatic drug (bDMARD). The study was split in 3 subsequent portions (Portions 1 (dose-finding portion), 2, and 3). Each portion includes an initial 12-week core treatment phase followed by an extension phase of 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 2 years for Portion 3. Portion 1 was the dose-finding portion in which 3 ascending dose regimens were tested in 2 bodyweight groups (Group A, patients ≥30 kg and ≤60 kg and Group B, patients <30 kg and ≥10 kg). Patient enrolment was staggered by bodyweight group and dose regimen, starting with Group A and Dose Regimen 1 Cohort. In the extension phase, once the dose regimen was selected, patients who were not already on this dose regimen have had their dose regimen adjusted to the selected dose regimen. Portions 2 and 3 enrolled additional patients to the selected dose regimen to achieve a total of approximately 100 treated patients for the entire study. These patients have undergone the same on-site visits during the 12-week core treatment phase as patients recruited in the dose finding portion	
	Duration of main phase:	12 weeks core treatment phase
	Duration of Run-in phase:	up to 4-week screening period
	Duration of Extension phase:	Up to 144-weeks for Portions 1 and 2, up to 84-weeks for Portion 3
Hypothesis	The primary objective is PK estimation and there is no formal hypothesis testing. Efficacy is assessed descriptively (secondary endpoint).	

Treatments groups	Portion 1	N=42 randomized and treated: • Dose 1: Dose targeting PK exposures similar to the approved dose regimen of 150 mg q2w in adults with Rheumatoid Arthritis (RA) - Group A (≥30 kg and ≤60 kg): 2 mg/kg q2w (N=7) - Group B (<30 kg and ≥10 kg): 2.5 mg/kg q2w (N=6) • Dose 2: Dose targeting PK exposures similar to the approved dose regimen of 200 mg q2w in adults with RA - Group A: 3 mg/kg q2w (N=7) - Group B: 4 mg/kg q2w (N=7) • Dose 3: Dose targeting PK exposures similar to the highest dose that demonstrated efficacy together with an acceptable safety profile in RA studies (150 mg qw) - Group A: 2 mg/kg qw (N=6) - Group B: 2.5 mg/kg qw (N=9)	
	Portion 2	N=31 randomized and treated - Group A: 3 mg/kg q2w (N=15) - Group B: 4 mg/kg q2w (N=16)	
	Portion 3	N=29 randomized, N=28 treated - Group A: 3 mg/kg q2w (N=21, N=20 treated) - Group B: 4 mg/kg q2w (N=8)	
Endpoints and definitions	Primary endpoint	PK exposure	Sarilumab PK exposure (maximum serum concentration observed [C_{max}] and area under the serum concentration versus time curve using the trapezoidal method during a dose interval [AUC_{0-t}]), following the first dose, concentration observed before treatment administration during repeated dosing (Ctrough) from baseline to Week 12.

	Secondary	Efficacy: JIA ACR 30/50/70/90/100 response rate	The JIA ACR (Juvenile idiopathic arthritis American college of rheumatology) core set includes 6 variables: • Physician global assessment of disease activity measured on a 10-cm VAS where 0 = no activity and 10 = maximum activity • Patient/parent assessment of overall well-being, measured on a 10-cm VAS where 0 = very well and 10 = very poor • Functional ability determined by Childhood Health Assessment Questionnaire (CHAQ) • Number of joints with active arthritis (0-71 joints) • Number of joints with limitation of motion (0-67 joints) • High sensitivity C-reactive protein response The JIA ACR 30/50/70/90/100 response is defined as a patient with 3 of 6 core set variables improved by at least 30%/50%/70%/90%/100% from baseline with no more than 1 of the remaining variables worsened by more than 30%.
	Secondary	Efficacy: Juvenile Arthritis Disease Activity Score - 27 change from baseline	The JADAS (Juvenile arthritis disease activity Score) includes 4 measures: • Physician global assessment of disease activity • Parent/patient global assessment of well-being • Count of joints with active disease (The JADAS-27 includes the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles.) • Erythrocyte sedimentation rate (ESR) normalized to a 0-10 scale according to the following formula: [ESR (mm/hour)-20]/10. The JADAS is calculated as the simple linear sum of the scores of its 4 components.

Database lock: 09-February-2023 (1-year Interim analysis)					
Results and Analysis					
Analysis description	Primary Analysis				
Analysis population and time point description	• The PK population consisted of all included participants who received at least 1 dose of sarilumab and had at least one post-dose drug concentration. • The efficacy population consisted of all included participants who received at least 1 dose of sarilumab. Participants were analyzed according to the treatment that they actually received.				
Descriptive statistics and estimate variability	PK analysis: Effect estimate (primary endpoint)	Sarilumab exhibited nonlinear PK with target mediated drug disposition, and systemic exposure to sarilumab was similar between the 2 weight groups in each Dose Cohort. At steady state, sarilumab exposure ($C_{max,}$ $AUC_{0\text{-}14\ days}$ and C_{trough}) was comparable in participants with pcJIA at Dose 2 and in participants with RA at 200 mg q2w.			
	Efficacy analysis at Week 12: Portion 1 (secondary endpoint)	JIA ACR response rates (as observed while on-treatment)	Dose 1	Dose 2	Dose 3
		JIA-ACR30	10/10 (100%)	13/13 (100%)	11/11 (100%)
		JIA-ACR50	9/10 (90.0%)	12/13 (92.3%)	11/11 (100%)
		JIA-ACR70	5/10 (50.0%)	8/13 (61.5%)	11/11 (100%)
		JIA-ACR90	4/10 (40.0%)	4/13 (30.8%)	7/11 (63.6%)
		JIA-ACR100	0/10	2/13 (15.4%)	4/11 (36.4%)
		Mean change from baseline in JADAS-27 CRP	-17.2	-14.7	-19.7
	Efficacy analysis at Week 12: Portions 1-3, selected dose (dose 2) (secondary endpoint)	JIA ACR response rates (as observed while on-treatment)	Selected Dose Regimen (Dose 2) (3 mg/kg q2w, ≥30 kg and ≤60 kg; 4 mg/kg q2w; <30 kg and ≥10 kg)		
			≥30kg	<30kg	All
		Number of participants	N=42	N=31	N=73
		JIA-ACR30, 95% CI	39/39 (100%) (91.0%, 100.0%)	29/29 (100%) (88.1%, 100.0%)	68/68 (100%) (94.7%, 100.0%)
		JIA-ACR50, 95% CI	37/39 (94.9%) (82.7%, 99.4%)	28/29 (96.6%) (82.2%, 99.9%)	65/68 (95.6%) (87.6%, 99.1%)
		JIA-ACR70, 95% CI	29/39 (74.4%) (57.9%, 87.0%)	26/29 (89.7%) (72.6%, 97.8%)	55/68 (80.9%) (69.5%, 89.4%)
		JIA-ACR90, 95% CI	17/39 (43.6%) (27.8%, 60.4%)	14/29 (48.3%) (29.4%, 67.5%)	31/68 (45.6%) (33.5%, 58.1%)
		JIA-ACR100, 95% CI	5/39 (12.8%) (4.3%, 27.4%)	7/29 (24.1%) (10.3%, 43.5%)	12/68 (17.6%) (9.5%, 28.8%)
		Mean change from baseline in JADAS-27 CRP (SE), 95% CI	-18.23 (1.256) (-20.77, -15.68)	-16.31 (1.421) (-19.24, -13.38)	-17.46 (0.944) (-19.35, -15.57)

	Efficacy analysis at Week 48 (secondary endpoint)	JIA ACR response rates (as observed while on-treatment)	Selected Dose Regimen (Dose 2) (3 mg/kg q2w, ≥30 kg and ≤60 kg; 4 mg/kg q2w ; <30 kg and ≥10 kg)		
			≥30kg	<30kg	All
		Number of participants	N=42	N=31	N=73
		JIA-ACR30, 95% CI	38/38 (100%) (90.7%, 100.0%)	26/26 (100%) (86.8%, 100.0%)	64/64 (100%) (94.4%, 100.0%)
		JIA-ACR50, 95% CI	38/38 (100%) (90.7%, 100.0%)	26/26 (100%) (86.8%, 100.0%)	64/64 (100%) (94.4%, 100.0%)
		JIA-ACR70, 95% CI	34/38 (89.5%) (75.2%, 97.1%)	26/26 (100%) (86.8%, 100.0%)	60/64 (93.8%) (84.8%, 98.3%)
		JIA-ACR90, 95% CI	26/38 (68.4%) (51.3%, 82.5%)	23/26 (88.5%) (69.8%, 97.6%)	49/64 (76.6%) (64.3%, 86.2%)
		JIA-ACR100, 95% CI	16/38 (42.1%) (26.3%, 59.2%)	14/26 (53.8%) (33.4%, 73.4%)	30/64 (46.9%) (34.3%, 59.8%)
		Mean change from baseline in JADAS-27 CRP (SE), 95% CI	-21.65 (1.231) (-24.14, -19.15)	-19.44 (1.577) (-22.69, -16.19)	-20.75 (0.974) (-22.70, -18.81)
Effect estimate per comparison		No comparator was used in the study.			

2.6.5.3. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

Comparison between results of Portion 1 (12-week data) and results of Portions 1, 2, 3 (at week 12)

Two efficacy analysis were included in the study: one analysis based on 12-week core phase of the dose-finding portion (Portion 1) in which 14 participants were treated with Dose 2 and one analysis performed 1 year after the last participant of the last portion (Portion 3) was enrolled that included a total of 101 participants enrolled and treated with sarilumab, including 73 participants treated with the selected Dose 2 since baseline.

Overall baseline demographic and disease characteristics in participants with Dose 2 were generally similar in Portion 1 and in all 3 portions. With Dose 2, the proportion of participants with RF+ pJIA was slightly higher in Portion 1 (21.4%) compared to the 3 portions (17.8%).

- A longer duration of disease was observed in Portion 1 than in the overall study (mean [SD]: 3.4 [4.9] years versus 2.5 [3.3] years).
- The proportion of patients having already failed a prior biologic DMARD was higher in Portion 1 (21.4% with Dose 2) compared to those who received Dose 2 in the 3 portions (13.7%).

The efficacy results observed in the first portion of the study with Dose 2 at Week 12 (N=14) have been confirmed by the efficacy results observed in all portions with Dose 2 (N=73):

- As observed while on-treatment, the JIA ACR30 response rates plateaued to 100% achievement within the first 2 months of sarilumab treatment in both Portion 1 and the 3 portions.
- A total of 61.5% and 80.9% of participants in Portion 1 and in 3 portions, respectively, had a JIA ACR70 response using the as observed while on-treatment approach.
- Improvements were seen at Week 12 in all JIA ACR components.
- A total of 30.8% and 38.2% of participants in Portion 1 and the 3 portions, respectively, completed Week 12 with no active arthritis.
- The decrease in JADAS-27 was seen as early as Week 2 and onwards with a mean change from baseline of -14.7 at Week 12 (in Portion 1) and -17.5 at Week 12 in the 3 portions.

Descriptive comparison between adults and paediatric patients

Study EFC11072 Part B, which was one of the pivotal studies provided in the initial application for adults RA, was used to compare JIA ACR and ACR response rates between paediatric participants with pcJIA and adult participants with RA.

EFC11072 Part B was a randomised, multicentre, multinational, double-blind, parallel-group, placebo-controlled, 52-week study to assess the efficacy and safety of sarilumab, administered with concomitant MTX, in patients with moderately to severely active RA who had an inadequate response to MTX. There were 3 co-primary efficacy endpoints: ACR20 response rate at Week 24, change from baseline in HAQ-DI at Week 16, and change from baseline in van der Heijde mTSS at Week 52. The percentage of patients achieving a Major Clinical Response was the key secondary endpoint.

Table 10: JIA ACR30/50/70 in participants with pcJIA at Dose 2 (Study DRI13925) and ACR20/50/70 in adult participants with RA at 200 mg q2w (Study EFC11072) at Week 12 in the efficacy population

Endpoint	Pediatrics (pcJIA) Dose 2 N=73			Adults (RA) EFC11072 PART B 200 mg q2w N=399
Statistical approaches	As observed	LOCF	Non-responder imputation	Non-responder imputation
JIA ACR30 (pcJIA)/ACR20 (RA) Response Rate (%)	100%	98.6%	93.2%	64.9%
JIA ACR50 (pcJIA)/ACR50 (RA) Response Rate (%)	95.6%	94.5%	89.0%	36.3%
JIA ACR70 (pcJIA)/ACR70 (RA) Response Rate (%)	80.9%	78.1%	75.3%	17.5%

Source: DRI13925 1y3p Appendix 16.2.6.1.1.1 EFC11072 Part B Appendix 16.2.6.1.1.3, 16.2.6.1.7.4, 16.2.6.1.8.4.

Abbreviations : ACR = American College of Rheumatology, JIA ACR = juvenile idiopathic arthritis American College of Rheumatology, LOCF = last observion carried forward, pcJIA = polyarticular-course juvenile idiopathic arthritis, q2W = every 2 weeks

A greater proportion of responders with the selected Dose 2 in patients with pcJIA than with sarilumab 200 mg q2w dose used in adult patients with RA was observed.

The results of the descriptive analysis of JIA ACR30/50/70 for Dose 2 in pcJIA and in adult participants with RA with sarilumab 200 mg q2w (Study EFC11072 Part B) in the PK/PD analyses are presented below.

Table 11: JIA ACR30/50/70 at Week 12 (non-responder imputation approach) in participants with pcJIA at Dose 2 (Study DRI13925) and in adult participants with RA at 200 mg q2w (Study EFC11072 Part B) in PK population

	Pediatrics (pcJIA)	Adults (RA) EFC11072 PART B
	Dose 2	200 mg q2w
	N=73	N=331
Range of C_{trough} (min, max, mg/L)[a]	(0.16, 24.9)	(0.00, 67.8)
Mean C_{trough} (mg/L)[a]	7.98	16.5
JIA ACR30 Response Rate (%)	93.2	85.7
JIA ACR50 Response Rate (%)	89.0	73.8
JIA ACR70 Response Rate (%)	75.3	44.7

a If the observed Ctrough was missing at Week 12, Ctrough was imputed with a last observation carried forward approach from Week 0 to Week 12

Extract from 2.7.2 [Table 10]

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH submitted one pivotal study: study DRI13925, a multinational, multicentre, open-label, 2-phase, study in children and adolescents aged 2 to 17 years with pJIA who had inadequate response to or who were intolerant to current therapy or who were considered as candidates for a bDMARD.

The study was initially designed as a dose-finding study to determine the appropriate dose regimen in pJIA participants. The MAH explained that the design was subsequently modified based on health authority recommendations in order to minimize the number of paediatric participants to be enrolled and to avoid a placebo arm. This approach was based on the assumption that the disease course and the treatment response are sufficiently similar to those observed in adult RA participants to enable an extrapolation of data from adults to children. Although the study is compliant with the PIP (Compliance report EMEA-C1-001045-PIP01-10-M03), the design and conduct of the study allow only for exploratory analysis of the efficacy in the target population.

Since no dedicated dose finding was performed. The selected dose is based on the PK, efficacy and safety results observed in the dose finding part. Three dose regimens were investigated in the 2 BW groups and a dose of 3 mg/kg q2w was selected for participants with bodyweight > 30 kg and < 60 kg and 4 mg/kg q2w bodyweight < 30 kg and > 10 kg. Upon CHMP request, the MAH explained that the choice of the dose was based on similarity with adult patients with RA, efficacy, acceptable safety findings and pharmacodynamics data. Based on these findings (improvement in signs and symptoms more rapid and more pronounced as well as greater PD effect in Dose Cohorts 2 and 3 compared to Dose Cohort 1, Grade 3/4 neutropenia mostly occurring in Dose Cohort 3), Dose 2 was the selected

dose. No explicit definitive criteria were planned for the selection of the doses; the choices appeared to be ad-hoc, however overall this was considered reasonable by the CHMP.

The patient population selected for Study DRI13925 was a RF- or RF+ pJIA subtype or extended oJIA subtype as defined by ILAR 2001 JIA Classification Criteria from > 2 to < 17 years of age. The study population is acceptable.

Several changes in the conduct of the study were implemented, including changes to inclusion/exclusion criteria, endpoints, dose cohorts and sample size. While the changes are overall reasonable and acceptable, some of the changes were late and substantial. Flexibility in the design and conduct underlines the exploratory nature of the study.

Portion 3 of the trial was added in amendment 6 to comply with the PDCO recommendation of long-term data collection and to allow for the investigation of slightly more heterogeneous populations, but its scope and trial intervention are the same as portion 2.

Portions 2 and 3 of the trial were not randomised, controlled, or masked, hence these portions of the trial can be regarded as a single arm trial, and the reasonings presented in the “Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation” (EMA/CHMP/564424/2021) can be applied to this case.

The choice of the uncontrolled design is understood, given the paediatric population and the original scope of the trial (dose-finding), but problematic from an efficacy assessment perspective. As stated in the aforementioned Reflection paper, one of the key criteria to conclude evidence of a treatment in an SAT setting is that the success of the trial (“cure”) – which is also linked to the primary endpoint definition – would not be achievable without treatment, which does not seem to be the case in this indication.

The justification for the open-label design of portion 1 was not convincing. It is understood that originally the trial was only planned to generate hypotheses to be tested in a separate Phase 3 trial, and that only later the trial was amended to include the long-term portion 3 to generate efficacy data. However, from a methodological perspective, a double-blind portion 1 of the trial would have been both ethical (12 weeks, treatment not disease-modifying) and beneficial in term of data generation, especially considering that no objective rules for the dose decision were prespecified.

The primary objective was to describe the PK profile (see section 2.6.2 Clinical pharmacology).

The key secondary objective was to describe the efficacy of sarilumab in participants with pJIA.

The prespecified efficacy endpoints were descriptive secondary endpoints, the key endpoints i.e. juvenile Idiopathic Arthritis ACR 30/50/70/90/100 response rate, change from baseline in individual JIA ACR components and juvenile Arthritis Disease Activity Score (JADAS)-27 change from baseline were planned to be determined at Week 12 (core phase) and Week 24, Week 48 and every 24 weeks up to the end of the study (extension week). No estimand definitions were provided for the secondary efficacy objectives.

As already mentioned, the chosen combination of design and endpoint for this indication is understood but methodologically problematic. It is a “soft” endpoint in an open-label, single-arm setting.

Study participants were assessed “according to the treatment that they actually received”. This statement is understood to refer to the portion 1 of the trial, as all patients received the same dose in portions 2 and 3. Such an approach would not be in line with ITT, but it is acceptable considering the scope of portion1 of the trial.

It was not explicitly stated in the protocol/SAP whether participants who, in portion 1, received doses 1 and 3, would have eventually been analysed as recipients of dose 2 in the subsequent portions of the study (which would have been problematic). However, this does not seem to have occurred, as results in the CSR dated 07-Jun-2023 were presented according to “Efficacy evaluation on the Dose 2” and “Efficacy evaluation of Doses 1 and 3 up to Week 24 from baseline and after Dose adjustment”.Considering the drop-out rates and the numbers recommended by the health authority recommendations, the study seems to have underestimated the number of patients to be included. As presented in the study report, indeed 101 participants were treated, but only 89 of them concluded the core treatment phase and could be analysed. However, considering that no formal hypothesis testing is conducted and that the order of magnitude is in the range recommended by the health authorities, this was accepted by the CHMP.

Although not explicitly stated in the protocols, efficacy data from participants originally assigned to dose 1 and 3 (20 patients) were eventually analysed separately from the participants who received dose 2 from the beginning (73 patients). This is endorsed by the CHMP.

Dose finding analysis:

No explicit definitive criteria were planned for the selection of the doses, rather the choices appear to be ad-hoc, but overall reasonable

The analysis was conducted using a while-on-treatment approach, meaning that the main analysis was conducted only on patients who complete the core treatment. This was not endorsed by the CHMP, as it may introduce a potential selection bias which enhances the estimated response rates. The MAH provided upon request additional analyses based on all treated participants. These are considered more robust, in particular since the majority of those who discontinued prematurely did so because of AEs (4/7).

Efficacy data and additional analyses

The demographic characteristics had similar distribution across the 3 doses within each BW group.

In general, pcJIA participants enrolled in the study had long lasting disease, with a relative high proportion of RF+ pJIA subtype considering its incidence in the general population (Macaubas C, 2009), high disease activity at baseline, and a significant proportion of participants who had already failed one bDMARD.

Initially the MAH applied for a broad indication, without mentioning the subtype of pJIA, the concomitant use of medicine and the line of therapy. Upon CHMP request, the MAH updated the requested indication to mention the subtypes of pJIA that were included in the clinical trial (RF- and RF+ pJIA subtype and extended oJIA), and that patients should have responded inadequately to previous therapy with conventional synthetic DMARDs in line with the population included in the clinical trial. In addition, in line with the clinical trial population and the RA adult population the MAH mentioned that sarilumab can be used as monotherapy or in combination with methotrexate. This was endorsed by the CHMP.

Week 12 data

The 3 sarilumab dose regimens evaluated showed improving signs and symptoms of disease activity, with a JIA ACR30 response rate with the "as observed while on-treatment" approach of 100% at Week 12 in all 3 doses in both BW groups. Based on these data that demonstrated a more rapid and generally more pronounced improvement in signs and symptoms of pcJIA in Dose 2 and Dose 3

compared to Dose 1 and considering PK, PD and safety data, Dose 2 was selected for enrolling subsequent participants in Portions 2 and 3.

In addition:

- At Week 12, as observed while on-treatment, the JIA ACR70 response rates were 50.0%, 61.5%, and 100% in Dose 1, 2, and 3, respectively.
- As observed while on-treatment, the JIA ACR30 response rates plateaued to 100% achievement within the first 2 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 non-responder imputation approach, 76.9%, 92.9%, and 73.3% of patients achieved JIA ACR30 in Doses 1, 2, and 3, respectively. As calculated by LOCF approach, 84.6%, 1 and 86.7% 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 participants completed Week 12 with no active arthritis (4 each with Doses 1 and 2, and 5 with Dose 3). Overall, the CHAQ-DI scores and mean hs-CRP decreased for patients in all doses for both BW groups throughout the 12-week core treatment phase. The largest mean decrease at Week 12 was observed for participants in Group B, Dose 2 (mean change of 1.0 for CHAD-DI and -15.2 mg/L for hs-CRP).
- The decrease in disease activity was seen in all dose and BW groups as early as Week 2 with a mean change in JADAS-27 from baseline at Week 12 of -17.2, -14.7, and -19.7 in Dose 1, 2, and 3, respectively.

Portions 1, 2 and 3: One-year data analysis

Participants enrolled in Dose 2

All participants had JIA ACR30 response at Week 12 and improvement continued up to Week 48 as seen with the JIA ACR70 response rate that was achieved by 80.9% of participants at Week 12 and 93.8% at Week 48.

As already mentioned above, the MAH provided upon request additional analyses based on all treated participants. Overall, the responder proportions were smaller compared to the previously reported results: the proportion of patients with JIA ACR 70 response rate were 76.7% and 87.7%at Week 12 and Week 48, respectively when not excluding participants who discontinued treatment. Of note, one enrolled but untreated participant was still excluded from these analysis. Upon CHMP request, the MAH explained that the untreated patient was excluded as he did not meet the inclusion criteria at the baseline visit and therefore this constitutes a reasonable exclusion. The proportion of patients with JIA ACR 90 response rate were 42.5% and 69.9% at Week 12 and Week 48, respectively.

The newly provided 'ITT approach' analyses are more robust than the previously reported ones and therefore these numbers have been included in section 5.1 of the SmPC instead of the previously included results.

In addition, change from baseline in JADAS-27 CRP was -17.46 at Week 12 and -20.75 at Week 48 for the patients on the recommended dose. At Week 48, 51.6% of patients on the recommended dose were in remission (inactive disease per Wallace criteria for 6 consecutive months).

Participants enrolled in Doses 1 or 3 who had their dose adjusted to Dose 2

A total of 20 participants initially enrolled to receive Doses 1 or 3 had their dose adjusted to Dose 2. In participants on Dose 1 and Dose 3 before dose adjustment, the JIA ACR30, 50 and 70 were 100% 6 weeks after dose adjustment for participants who switched from Dose 1 and were 100% from the time

of dose adjustment for those who switched from Dose 3. No discernible changes in JIA ACR response rates were observed in participants who switched from Dose 1 (the lowest dose) or Dose 3 (the highest dose) to the selected Dose 2.

Descriptive comparison between adults and paediatric patients

JIA ACR30/50/70 in participants with pJIA at Dose 2 (Study DRI13925) and ACR20/50/70 in adult participants with RA at 200 mg q2w (Study EFC11072) at Week 12 in the efficacy population and JIA ACR30/50/70 at Week 12 (non-responder imputation approach) in participants with pJIA at Dose 2 (Study DRI13925) and in adult participants with RA at 200 mg q2w (Study EFC11072 Part B) in PK population suggest both greater proportion of responders in paediatric patients with pJIA than in adults patients with RA.

2- and 3-year efficacy results (results presented in the CSR 3)

The MAH provided long term data up to 3 years. Patients received as defined in the protocol Dose 2. The improvement in efficacy parameters was maintained / further improved throughout the observation period. A slightly better outcome in group B was observed, the reason remains unclear. The CHMP agreed with the MAH that the observation can be explained by the disease characteristics of Group A, the patients baseline characteristics suggest that that Group A were slightly more diseased. Moreover, the data did not raise any concern.

2.6.7. Conclusions on the clinical efficacy

There were limitations of the design and conduct of the study, in particular related to the efficacy analysis, Howeve as the primary objective was to describe the PK profile, the efficacy data are only supportive. The key secondary objective was to describe the efficacy of sarilumab in participants with pJIA. All participants had JIA ACR30 response at Week 12 and improvement continued up to Week 48 as seen with the JIA ACR70 response rate that was achieved by 76.7% of participants at Week 12 and 87.7% at Week 48. The proportion of patients with JIA ACR 90 response rate were 42.5% and 69.9% at Week 12 and Week 48, respectively.

In addition, change from baseline in JADAS-27 CRP was -17.46 at Week 12 and -20.75 at Week 48 for the patients on the recommended dose. At Week 48, 51.6% of patients on the recommended dose were in remission (inactive disease per Wallace criteria for 6 consecutive months).

The MAH provided long term data up to 3 years. The improvement in efficacy parameters was maintained / further improved throughout the observation period.

Since extrapolation from adults to children has been demonstrated, clinical efficacy is considered demonstrated.

The CHMP concluded that the efficacy data available supports the following indication :

Polyarticular juvenile idiopathic arthritis

Kevzara is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA; rheumatoid factor positive or negative polyarthritis and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with conventional synthetic DMARDs (csDMARDs). Kevzara may be used as monotherapy or in combination with MTX.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Data from 101 participants who received at least one dose of sarilumab administered at one of the evaluated 3 dose regimens and who were treated for at least 52 weeks (1 year) have been included in the safety analysis.

2.6.8.2. Adverse events

Among the 93 participants who received at least 1 dose of Dose 2, 89 (95.7%) participants experienced at least 1 treatment non-emergent adverse event (TEAE). No notable difference in the incidence of any TEAEs was observed in the 93 participants compared to the 73 participants who received Dose 2 from baseline.

During the entire treatment period, the most frequently reported TEAEs (≥5.0% at preferred term [PPT] level) were in the system organ classes (SOCs): Infections and Infestations (80.6% [75/93 participants]), Blood and Lymphatic System Disorders (36.6% [34/93]), Gastrointestinal Disorders (33.3% [31/93]), Investigations (26.9% [25/93]), Injury, poisoning and procedural complications (26.9% [25/93]), and General Disorders and Administration Site Conditions (22.6% [21/93 participants]).

TEAEs were more frequent in Group B (<30 kg) than in Group A (≥30 kg): 87.8% versus 75.0% for Infections and Infestations, 48.8% versus 26.9% for Blood and Lymphatic System Disorders, 43.9% versus 25% for Gastrointestinal Disorders, 29.3% versus 17.3% for General disorders and administration site conditions, respectively.

At PT level, the most frequent reported TEAEs were:

- Nasopharyngitis (36.6%) (28.8% in Group A and 46.3% in Group B). The exposure adjusted event rate for the 93 participants who received at least one dose of Dose 2 was 35.5/100 PYs
- Neutropenia (31.2%) (21.2% in Group A and 43.9% in Group B). The exposure-adjusted event rate for the 93 participants who received at least one dose of Dose 2 was 52.2/100 PYs
- Upper Respiratory Tract Infections (14.0%) (17.3% in Group A and 9.8% in Group B). The exposure-adjusted event rate for the 93 participants who received at least one dose of Dose 2 was 12.5/100 PYs.

Other frequent PTs, all reported by 9.7% (9/93 participants) in Dose 2 were: pharyngitis, alanine aminotransferase increased (ALT increased), COVID-19, and injection site erythema.

Among the 42 treated participants (safety population), included in the ascending dose-finding portion, 12 participants (28.5%) experienced Grade 3 or 4 neutropenia (decrease in absolute neutrophil count) during the 12-week core-treatment period, with a higher incidence of neutropenia in Dose 3 (6/12 participants) compared to the 2 other doses (3/12 participants in each dose cohort) and in Group B (8/12 participants) compared to Group A (4/12 participants). However, none of the Grade 3 or 4 neutropenia events were associated with infections or severe infections and all resolved within a few days.

Final study report:

Among the 93 participants who received at least one dose of selected Dose 2 during the entire treatment period, 89 (95.7%) participants experienced at least 1 TEAE. The types of TEAEs were

equally distributed between the BW groups. The incidence of TEAEs was most frequent in SOC Infections and infestations with a higher frequency in Group B (87.8%) compared to Group A (76.9%). The most commonly reported PTs were either known reactions due to PD effect of sarilumab (neutropenia) or events that are commonly seen in general paediatric population, such as nasopharyngitis and upper respiratory tract infections. The most commonly reported injection site reactions were injection site erythema.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events and death

During the 52-week treatment period, a total of 7 SAEs were reported in 4 participants, who were all on Dose 2 at the time of event. During the entire treatment period (up to Week 156), among the 93 participants who received Dose 2, 6 participants reported 9 SAEs, all of which were considered by the Investigator as not related to the IMP. Each event term was reported once.

During the 12-week treatment period (up to Week 12), 1 participant on Dose 2 in Group B reported 3 SAEs, bone tuberculosis, pancreatic pseudocyst, pancreatitis acute.

Between Week 13 and Week 24, 1 additional participant on Dose 2 in Group A reported 1 SAE of a ligament rupture.

Between Week 25 and Week 52, 2 additional participants in Group B, Dose 2 reported 2 SAEs; 1 participant reported inguinal hernia and the other participant reported tonsillar hypertrophy. During this period, another SAE of meniscus injury occurred for the patient who already had the SAE of ligament rupture between Week 13 and Week 24.

After the 52-week treatment period, 2 additional participants in Group A, Dose 2, reported 2 additional SAEs: an acute sinusitis and a serious event reported as juvenile idiopathic arthritis (worsening of underlying condition).

None of the 20 participants who switched from Dose 1 or Dose 3 to the selected Dose 2 experienced an SAE afterward.

No deaths occurred in the DRI13925 study.

Adverse events of special interest

During the entire treatment period, among the 93 participants who received Dose 2, 14 (15.1%) participants reported adverse events of special interest (AESIs). The AESIs reported were infections, neutropenia and ALT increased. Per BW group, more AESIs were reported in Group B (11 participants) compared to Group A participants (3 participants). All participants were on Dose 2 from baseline, except for 1 participant previously on Dose 3 (the AESI was collected after switching to Dose 2).

The most frequent AESI was neutropenia, which occurred during the 52-week treatment period in 10 (10.8%) participants, all of whom were on Dose 2 from baseline (3 in Group A and 7 in Group B). All participants recovered within a median duration of 14 days after IMP discontinuation.

Final study report:

Events qualifying as AESIs were reported in 3 participants, of which 'opportunistic infections' were reported in 1 participant (herpes zoster) and 'ALT increase (≥3× upper limit of normal)' was reported in 2 participants.

There were no events of GI perforations, malignancies and/or severe hypersensitivity reactions reported. No deaths were reported in this study.

Rate of infections in the context of neutropenia occurrence

In order to assess whether neutropenia had an impact on the occurrence of infections, the numbers (%) of participants who experienced at least 1 infection and serious infection were compared between the neutropenic period (period with confirmed Grade 3 or Grade 4 ANC decrease) and the non-neutropenic period (ANC > 1 Giga/L).

Overall, no serious or opportunistic infections occurred during the neutropenic period (for all Grades) and the percentages of participants with at least 1 infection were similar in the group of participants with normal ANC (85.7%) and in the group of participants with at least 1 ANC<LLN (81.8%) (Grades 3 and 4). Rate of infections in the Group B during the neutropenic period was numerically lower compared to corresponding rates in the non-neutropenic period, while rate of infections in Group A was numerically higher during the neutropenic period compared to the corresponding rates in Group B; however, this difference could be attributed to the very short neutropenic period occurring in Group A. No clear correlation between neutropenia and infection has been observed in the paediatric population under study. All neutropenia episodes recovered in a median time of 14 days.

No notable differences were observed between the percentages of participants with at least 1 infection and normal ANC (85.7%) and participants with at least one infection and Grade 1 neutropenia (75.0%), or Grade 2 neutropenia (76.2%), or Grade 3 neutropenia (81.5%), or Grade 4 neutropenia (92.9%).

No relationship was observed between incidence of serious infection and ANC decrease. There were 3 participants with at least 1 serious infection and among them, 1 participant was in the group of participants with normal ANC and 2 participants were in the group of participants who had Grade 3 neutropenia. For the 2 participants with Grade 3 neutropenia, the infection (1 participant had serious acute sinusitis; 1 participant had infectious mononucleosis) was not reported at a time close to the neutropenic event; in both instances, neutropenia was considered to be related to the IMP by the Investigator.

Final study report:

Grade 3 or 4 neutropenia have been reported in 30 (32.3%) of the 93 participants who received at least one dose of selected Dose 2 (10 [19.2%] in Group A and 20 [48.8%] in Group B). No events of neutropenia were reported as serious. Neutropenia meeting AESI criteria occurred more frequently in Group B (7 participants) compared to Group A (3 participants). Neutropenia mostly occurred during the first 12 weeks and longer exposure to sarilumab did not result in increasing the neutropenic burden in this population and Grade 3 or 4 neutropenia were observed most frequently in the first 4 weeks of treatment. These events of neutropenia were all reversible and median time to recovery following treatment interruption was 14 days. Decrease in ANC is an expected PD effect with an anti-IL-6R mAb. The reduction of neutrophils is believed to be primarily due to margination into rapidly mobilizable noncirculating pools (e.g., liver, spleen, and bone marrow) and not from myelotoxicity. The Nadir occurs several days after the sarilumab administration before neutrophils return to baseline value. The observed higher incidence of neutropenia in paediatric participants compared to adults may be due to the inability of paediatric patients to transfer neutrophils from the bone marrow to the peripheral blood (ineffective production) or increased margination-sequestration (which leads to pseudoneutropenia). Importantly and like the neutropenia observed with sarilumab in the adult RA population, events of neutropenia observed in Study DRI13925 were not associated with an increased risk of infection, and no serious nor opportunistic infection occurred during the neutropenic period.

Local tolerability

During the entire treatment period, 13/93 (14.0%) participants treated with at least 1 dose of the selected Dose 2 (all from baseline) experienced injection site reactions. For 12/13 participants, the events were related to the IMP. The most frequently reported PT was injection site erythema (9/13 participants). No participants reported injection site reactions after their switch from either Dose 1 or Dose 3 to the selected Dose 2.

No notable differences were observed between the 2 BW groups in the incidence or type of reported injection site reaction. The majority of infection site reactions were mild in severity.

2.6.8.4. Laboratory findings

A mean decrease in WBC count, predominantly due to a decrease in ANC, was observed in both BW groups, however, this decrease was more profound in Group B participants compared to Group A participants.

Events or laboratory parameters of platelet count decrease were not observed in any participant during the conduct of the trial.

No cases of potential Hy's Law (ALT >3 × ULN and bilirubin >2 × ULN) and no cases of hepatic failure were reported. During the entire treatment period, 2 participants treated with at least 1 dose of the selected Dose 2 had ALT increase leading to permanent discontinuation, of which 1 participant was treated with Dose 2 from baseline and another participant had dose adjusted from Dose 3 to Dose 2 – both events occurred after Week 52.

There were no clinically significant changes observed in mean cholesterol, LDL, HDL, and triglyceride levels at any timepoints for all doses. During the entire treatment period for 93 participants on Dose 2 from baseline, 3 participants reported non-clinically significant hypertriglyceridemia (3.2%).

Final study report:

Besides a decrease in ANC, laboratory abnormalities in Study DRI13925 were not associated with clinical consequences: elevations in transaminases were not associated with hepatotoxicity (no Hy's Law and/or hepatic failure events), and lipid imbalances were limited to 3 events of hypertriglyceridemia without any changes in low-density lipoprotein (LDL) or high-density lipoprotein (HDL) cholesterol, which did not lead to major cardiovascular events.

2.6.8.5. Safety in special populations

The evaluation of infections within the SOC Infections and infestations showed a higher incidence of events in younger participants (<6 years) and those with a lower BW than older participants (≥6 years) and those with a higher BW, during 12-week and 52-week treatment periods. Nasopharyngitis and other URTI were the most commonly reported TEAEs in this SOC.

Severe and serious neutropenia

Neutropenia mostly occurred during the initiation phase of sarilumab treatment and longer exposure to sarilumab did not add to the neutropenic burden on these participants.

The evaluation of 'severe or serious neutropenia' showed a higher incidence in younger participants (<6 years) and those with a lower BW than older participants (>6 years) and with a higher BW. This difference was evident during both the 12-week treatment period and the 52-week treatment period.

However, the incidence of neutropenia observed in the 52-week treatment period was comparable to the 12-week core-treatment period, indicating that the majority of neutropenia occurred in the treatment initiation phase of sarilumab (12-week core-treatment period).

In the age group ≥6 to 12 years old, the incidence of severe or serious neutropenia did not change between the 12-week core treatment period and the 52-week treatment period and it slightly increased (3.6% increment difference) between the 2 treatment periods for participants aged ≥ 12 years of age.

ANC <1.0 Giga/L

Incidence of ANC <1.0 Giga/L was higher in younger participants (<6 years) and those with a lower BW than older participants (>6 years) and with a higher BW. This difference was evident during the 12-week core-treatment period and the 52-week treatment period.

Following CHMP's request, more granular age groups were defined: 2 to ≤3, 4 to ≤6, 7 to ≤9, 10 to ≤ 12, 13 to ≤15, and ≥16 years.

Table 12: Summary of safety profile (TEAEs) by age groups – Participants on the selected dose (Dose 2)

	0-12 weeks (N=73)	0-52 weeks (N=73)
Any TEAE by age groups (year)		
2-3	12/13 (92.3%)	13/13 (100%)
4-6	6/6 (100%)	6/6 (100%)
7-9	8/15 (53.3%)	13/15 (86.7%)
10-12	11/18 (61.1%)	16/18 (88.9%)
13-15	6/11 (54.5%)	8/11 (72.7%)
≥ 16	8/10 (80.0%)	8/10 (80.0%)
Any serious TEAE by age groups (year)		
2-3	0/13 (0%)	1/13 (7.7%)
4-6	0/6 (0%)	0/6 (0%)
7-9	0/15 (0%)	1/15 (6.7%)
10-12	0/18 (0%)	0/18 (0%)
13-15	1/11 (9.1%)	2/11 (18.2%)
≥ 16	0/10 (0%)	0/10 (0%)
Any discontinuation due to TEAE by age groups (year)		
2-3	1/13 (7.7%)	2/13 (15.4%)
4-6	0/6 (0%)	1/6 (16.7%)
7-9	0/15 (0%)	0/15 (0%)
10-12	0/18 (0%)	0/18 (0%)
13-15	1/11 (9.1%)	1/11 (9.1%)
≥ 16	1/10 (10.0%)	1/10 (10.0%)

Extracted from PGM=PRODOPS/SAR153191/DRI13925/CSR_1YEAR/EXPLO/PGM/tems_se_overview_age_s_1.sas OUT=EXPLO/OUTPUT/tems_se_overview_age_s_1_1.rtf (18MAY2024 - 4:16)

Taking into consideration limited number of participants, review of granular age groups did not identify new patterns. The safety profile observed during the 12-week and 52-week treatment period did not change until end of the study, i.e. up to week 156 (final DRI13925 Clinical Study Report; dated on 22 April 2024).

A summary of the safety profile by these additional age groups is provided in Table 13.

Table 13: Summary of infections, neutropenia, and ANC<1.0 Giga/L by age groups – Participants on the selected dose (Dose 2)

	0-12 weeks (N=73)	0-52 weeks (N=73)
Any infections by age groups (year)		
2-3	10/13 (76.9%)	13/13 (100%)
4-6	3/6 (50.0%)	5/6 (83.3%)
7-9	6/15 (40.0%)	8/15 (53.3%)
10-12	8/18 (44.4%)	12/18 (66.7%)
13-15	2/11 (18.2%)	6/11 (54.5%)
≥ 16	5/10 (50.0%)	6/10 (60.0%)
Any serious infections by age groups (year)		
2-3	0/13 (0%)	0/13 (0%)
4-6	0/6 (0%)	0/6 (0%)
7-9	0/15 (0%)	0/15 (0%)
10-12	0/18 (0%)	0/18 (0%)
13-15	1/11 (9.1%)	1/11 (9.1%)
≥ 16	0/10 (0%)	0/10 (0%)
Neutropenia (PT; severe or serious) by age groups (year)		
2-3	3/13 (23.1%)	4/13 (30.8%)
4-6	2/6 (33.3%)	2/6 (33.3%)
7-9	3/15 (20.0%)	3/15 (20.0%)
10-12	2/18 (11.1%)	3/18 (16.7%)
13-15	0/11 (0%)	0/11 (0%)
≥ 16	1/10 (10.0%)	1/10 (10.0%)
ANC<1.0 Giga/L by age groups (year)		
2-3	5/13 (38.5%)	6/13 (46.2%)
4-6	3/6 (50.0%)	3/6 (50.0%)
7-9	4/15 (26.7%)	6/15 (40.0%)
10-12	3/18 (16.7%)	4/18 (22.2%)
13-15	0/11 (0%)	0/11 (0%)
≥ 16	2/10 (20.0%)	2/10 (20.0%)

Extracted from PGM=PRODOP5/SAR153191/DRI13925/C5R_1YEAR/EXPLO/PGM/ema_ae_overview_age_s_t.sas OUT=EXPLO/OUTPUT/ema_ae_overview_age_s_t_i.rtf (15MAY2024 - 4:16)

The evaluation of PTs in the SOC Infections and Infestations showed the highest incidence of any infections in participants in the 2 to ≤3 age category, followed by participants in the 4 to ≤6 and ≥16 age categories during the 12-week treatment period. Similar patterns have been observed in the 52-week treatment period.

The evaluation of 'ANC <1.0 Giga/L' revealed that the highest incidence occurred in the 4 to ≤6 age category, followed by participants in the 2 to ≤3 and 7 to ≤9 age categories. This difference was consistently observed during both the 12-week and 52-week treatment periods. Notably, during the 52- week treatment period, one additional participant in each 2 to ≤3, 7 to ≤9 and 10 to ≤12 age categories had 'ANC <1.0 Giga/L'.

Taking into consideration the limited number of participants, the review of granular age groups did not identify new patterns.

2.6.8.6. Discontinuation due to adverse events

Participants on Dose 2 discontinued treatment due to TEAEs less frequently than those in the non-selected doses, and this was observed during the first 12 weeks, the first 6 months (24 weeks) and the first year (52 weeks) of exposure to sarilumab. The majority of discontinuations occurred during the 12-week core-treatment period. The exposure-adjusted event rate for TEAEs leading to treatment

discontinuation was lower in Dose 2 compared to the 2 non-selected doses: 7.4/100 PYs in Dose 2 versus 29.5/100 PYs in Dose 3 and 18.9/100 PYs in Dose 1.

During the entire treatment period, among the 93 participants who received Dose 2, 8 (8.6%) participants (7 on Dose 2 from baseline and 1 previously on Dose 3) reported TEAEs leading to treatment discontinuation.

The most common TEAE leading to treatment discontinuation was neutropenia (5 participants treated in Dose 2 from baseline [1 in Group A, 4 in Group B]). Overall, Group B participants discontinued treatment due to TEAE more frequently than Group A participants.

2.6.8.7. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

A total of 101 participants have been treated with sarilumab in study DRI13925. The pivotal safety data is based on a total of 93 participants who received at least 1 dose of the selected Dose 2 during the entire treatment period. Data from the 20 participants who had their dose regimen adjusted to the Dose 2 regimen are included in the analysis. Due to the rarity of the disease, in some ages groups the patient numbers are small and thus the database is limited. During the procedure, the MAH submitted the final study report providing long-term data of up to 3 years. The 2- and 3 -year safety data reported were consistent with the safety data previously provided. There were no new safety concerns or signals observed in the final analysis.

Among the 93 participants who received at least 1 dose of Dose 2, 89 (95.7%) participants experienced at least 1 treatment non-emergent adverse event (TEAE).

During the entire treatment period, the most frequently reported TEAEs (≥5.0% at preferred term [PPT] level) were in the system organ classes (SOCs): Infections and Infestations (80.6% [75/93 participants]), Blood and Lymphatic System Disorders (36.6% [34/93]), Gastrointestinal Disorders (33.3% [31/93]), Investigations (26.9% [25/93]), Injury, poisoning and procedural complications (26.9% [25/93]), and General Disorders and Administration Site Conditions (22.6% [21/93 participants]).

TEAEs were more frequent in Group B (<30 kg) than in Group A (≥30 kg): 87.8% versus 75.0% for Infections and Infestations, 48.8% versus 26.9% for Blood and Lymphatic System Disorders, 43.9% versus 25% for Gastrointestinal Disorders, 29.3% versus 17.3% for General disorders and administration site conditions, respectively. Patients in Group B received a higher dose than patients in Group A, the effect might be dose related. However, an age-related effect couldn't be excluded e.g. children with lower weight might be younger.

Therefore, upon CHMP request, more granular subgroups were defined as follows: 2 to ≤3, 4 to ≤6, 7 to ≤9, 10 to ≤12, 13 to ≤15, and ≥16 years, and the MAH provided data for these different age groups.

The younger age groups had a higher incidence of TAEs than the older groups. Participants aged 4 to ≤ 6 years had the highest incidence of any TEAE (6/6 [100%]), followed by the 2 to ≤3 years age group (12/13 [92.3%]). The trend was also observed in the 52-week treatment period, although the differences across the age groups were less pronounced.

The incidence of serious TEAEs was low and all events were unrelated to the product. With regard to reports of serious TEAE, by age group the highest incidence was seen for the 0-12 weeks period, as well as for the 0-52 weeks period, in higher age groups.

The occurrence of TEAEs leading to treatment discontinuation was low across all age groups and treatment periods (0-12 weeks and 0-52 weeks). No clear pattern was observed.

The interpretation of the data is hampered by the small sample size and lack of control. Nevertheless, the review of the granular age groups did not identify a safety signal for any of the groups.

The AESIs reported were infections, neutropenia and ALT increased. No serious or opportunistic infections occurred during the neutropenic period (for all Grades) and the percentages of participants with at least 1 infection were similar in the group of participants with normal ANC (85.7%) and in the group of participants with at least 1 ANC<LLN (81.8%) (Grades 3 and 4).

Injection site reactions were seen in 13/93 (14.0%) participants treated with at least 1 dose of the selected Dose 2 (all from baseline). For 12/13 participants, the events were related to the IMP. The most frequently reported PT was injection site erythema (9/13 participants). No safety concerns were raised.

The rate of infections was 146.6 events per 100 patient-years. The most common infections observed were nasopharyngitis (36.6%) and upper respiratory tract infections (14.0%). The majority were mild.

These information have been reflected in section 4.8 of the SmPC.

The AESI profile did not raise a concern, the observed AESIs are expected and occurred with a low frequency.

The incidence of infections, neutropenia and ANC <1.0 Giga/L was higher in the younger patients (< 6 years). Decreases in neutrophil counts below 1 x 10^9/L occurred in 10/52 (19.2%) patients weighing ≥30 kg and 20/41 (48.8%) patients weighing 10 to <30 kg. As stated by the MAH the majority of infections were driven by upper respiratory tract infections in the younger age group. These findings are consistent with the expected epidemiological background in this population.

The granular review of age groups did not identify new patterns for severe or serious neutropenia. The highest incidence was seen in the 4 to ≤6 age category, followed by participants in the 2 to ≤3 and 7 to ≤9 age categories. Only one additional patient experienced neutropenia during the 52-week treatment period. Similar pattern was seen for evaluation of 'ANC <1.0 Giga/L'.

The decrease on neutrophil count was not linked to the occurrence of serious infection.

The highest incidence of any infections was in participants in the 2 to ≤3 age category, followed by participants in the 4 to ≤6 and ≥16 age categories during the 12-week treatment period with similar pattern observed in the 52-week treatment period. This was consistent with the epidemiological background in the paediatric population.

The interpretation of the data is hampered by the small sample size and lack of control. Taking this into consideration the granular review of the age groups did not identify a safety signal for any of the groups.

No death occurred during the conduct of the study.

The most common adverse drug reaction that resulted in permanent discontinuation of therapy with sarilumab was neutropenia (5.4%). This information has been added in section 4.8 of the SmPC.

Regarding laboratory abnormalities, a mean decrease in WBC count, predominantly due to a decrease in ANC, was observed in both BW groups, however, this decrease was more profound in Group B

participants compared to Group A participants. Decrease in monocyte counts occurred in 4 (4.3%) patients and were mild in severity and non-serious.

During the entire treatment period, 2 participants treated with at least 1 dose of the selected Dose 2 had ALT increase leading to permanent discontinuation, of which 1 participant was treated with Dose 2 from baseline and another participant had dose adjusted from Dose 3 to Dose 2 – both events occurred after Week 52.

There were no clinically significant changes observed in mean cholesterol, LDL, HDL, and triglyceride levels at any timepoints for all doses. During the entire treatment period, 3 participants reported non-clinically significant hypertriglyceridemia (3.2%) (1 patient experienced triglyceride levels ≥150 mg/dL (1 x ULN)). A summary of these data has been included in section 4.8 of the SmPC.

Overall, the most common observed adverse reactions were the following: Neutropenia, ALT increase, Infection (upper respiratory tract and nasopharyngitis) and Injection site reactions. From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

Data from a small single arm study were provided. Thus, the safety database is small, however the observed safety data are in general consistent with the known safety profile of Kevzara.

No new safety concerns were identified during the development program in the clinical trial population.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	Serious infections Neutropenia Gastrointestinal perforations
Important potential risks	Thrombocytopenia and potential risk of bleeding Clinically evident hepatic injury Lipid abnormalities and increased risk of major cardiovascular events Malignancy
Missing information	None

2.7.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Safety surveillance program using existing EU RA registries (OBS15180 in Germany, 6R88-RA-1720 in Spain, OBS15220 in Sweden, 6R88-RA-1634 in UK) Ongoing Category 3	To monitor the safety of sarilumab and evaluate the risk of selected outcomes of interest with long term use in patients with RA in real-world clinical practice.	• Serious infections • Lipid abnormalities and increased risk of major CV events • Gastrointestinal perforations • Malignancy	Study progress report Final report of study results: • Final country report for Sweden • Final study report (with final country reports for UK, Germany, Spain) • Amended Swedish report and Amended Final study report.	Annually (2020-2022) and biennially (every other year) (2023-2028), first report (sarilumab cohort only) Mar-2020 Q4-2028 Q4-2029 Q4-2030

CV: Cardiovascular; EU: European Union; Q: Quarter; RA: Rheumatoid Arthritis; UK: United Kingdom.

2.7.3. Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infections	Routine risk minimization measures: • SmPC: Labeled in sections 4.2, 4.4 and 4.8 • Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA. Additional risk minimization measures: Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Safety surveillance program using existing EU RA registries
Neutropenia	Routine risk minimization measures: • SmPC: Labeled in sections 4.2, 4.4, 4.8 and 5.1 • Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA. Additional risk minimization measures: Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Gastrointestinal perforations	Routine risk minimization measures: • SmPC: Labeled in sections 4.4 and 4.8 • Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA. Additional risk minimization measures: Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Safety surveillance program using existing EU RA registries
Thrombocytopenia and potential risk of bleeding	Routine risk minimization measures: • SmPC: Labeled in sections 4.2, 4.4 and 4.8 • Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Clinically evident hepatic injury	Routine risk minimization measures: • SmPC: Labeled in sections 4.2, 4.4 and 4.8 • Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Lipid abnormalities and increased risk of major cardiovascular events	Routine risk minimization measures: • SmPC: Labeled in sections 4.4 and 4.8 • Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Safety surveillance program using existing EU RA registries
Malignancy	Routine risk minimization measures: • SmPC: Labeled in sections 4.4 and 4.8 • Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Safety surveillance program using existing EU RA registries

EU: European Union; HCP: Healthcare Professional; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 5.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Kevzara 150mg and 200mg. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Juvenile idiopathic arthritis (JIA) as defined by International League of Associations for Rheumatology (ILAR) classification is an arthritis of unknown aetiology that begins before 16 years of age and persists for at least 6 weeks with other known conditions excluded.

The following subtypes of JIA are collectively referred to as polyarticular-course juvenile idiopathic arthritis pJIA since they present similar clinical features (affecting 5 or more joints and ultimately evolving to permanent joint damage):

- Oligoarticular JIA (oJIA) 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 4 joints (typically large joints, such as knees, ankles, wrists) and is not associated with constitutional findings such as fever, weight loss, fatigue or systemic signs of inflammation. Disease onset ranges from 1 to 5 years and peaks at 2 to 3 years. If greater than 4 joints become affected after the first 6 months of

disease, it is designated as extended oligoarthritis (e-oJIA) in contrast to persistent oJIA that features only up to 4 joints throughout the course of the disease. Oligoarticular JIA carries a risk for developing chronic anterior uveitis, especially when antinuclear antibody is present and disease onset is in early childhood.

- Polyarticular JIA (pJIA) that is defined as an arthritis affecting 5 or more joints during the first 6 months of disease. Both large (e.g., hips and knees) and small (e.g., joints of the hand) joints can be involved, and often in symmetric bilateral distribution. Low grade fever can accompany the arthritis. Presence of Rheumatoid Factor (RF) differentiates 2 forms of pJIA:

  - Rheumatoid Factor-positive (RF+) pJIA is diagnosed in only 3% to 5% 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: it represents 11% to 28% of all children and adolescents with JIA. It presents at a younger age (in late childhood, 6 to 12 years) with respect to the RF+ pJIA. Radiologic changes in RF-negative disease occur later than in RF-positive disease and it may not be as destructive and persistent.

JIA is the most common rheumatic disease of childhood with a global prevalence estimated to range from 3.8 to 400/100,000 persons with an incidence of 1.6 to 23/100,000 persons-year. JIA affects primarily females (3:1 female/male ratio)

3.1.2. Available therapies and unmet medical need

As a first line treatment, patients with pJIA who have no systemic manifestations can be treated with either non-steroidal anti-inflammatory drugs (NSAIDs) or intra-articular injections of glucocorticoids (GCs). If patients do not respond to the first line of treatment, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX) that are immunosuppressive and immunomodulatory, targeting intracellular or extracellular elements of an inflammation pathway, can be administered. Since the demonstration of its efficacy for treatment of JIA in 1992, MTX has become the systemic drug of choice for the disease.

According to international guidelines and recommendations, addition of biologic disease modifying antirheumatic drugs (bDMARDs) are suggested if moderate or high disease activity persists after 3 months of treatment with MTX. The 2019 ACR guidelines recommend changing or adding biologic DMARDs to MTX if no or minimal response is observed after 6-8 weeks with MTX.

Biologic DMARDs approved for pJIA are TNF-α antagonists, selective T-cell costimulator modulator, humanized mAb against IL- 6R and janus kinase (JAK) inhibitor.

3.1.3. Main clinical studies

Study DRI13925 was a multinational, multicentre, open-label, 2-phase, study in children and adolescents aged 2 to 17 years with pJIA who had inadequate response to or who were intolerant to current therapy or who were considered as candidates for a bDMARD.

Study DRI13925 consisted of 3 subsequent portions: one dose-finding portion, and two expansion portions. Each portion had a 12-week core phase and an extension phase. The extension phase was up to 144 weeks for participants enrolled in Portion 1 and Portion 2, and up to 84 weeks for the participants enrolled in Portion 3. For Portions 1 and 2, only participants who responded (i.e., those

who have reached a JIA ACR30 response) at Week 12 were permitted to continue in the extension phase while all participants enrolled in Portion 3 were allowed to continue in the extension phase irrespective of their JIA ACR response level.

The patient population selected for Study DRI13925 was a RF- or RF+ pJIA subtype or extended oJIA subtype as defined by ILAR 2001 JIA Classification Criteria.

3.2. Favourable effects

In study DRI13925, the primary endpoint was to assess the PK exposure of sarilumab from baseline to week 12 to identify the dose and regimen for adequate treatment of paediatric participants with pJIA.

The data from Study DRI13925 were used for the Pop PK analysis and the E-R analyses (for the key efficacy and safety endpoints) in the pJIA population, and compared with those in adults with RA. Even though there are some remaining uncertainties pertaining to limited underlying data, the observed PK data and Pop PK analysis were consistent and ultimately the data package on clinical pharmacology overall supports the proposed posology based on cohort 2 (3 mg/kg q2w for participants with bodyweight > 30 kg and < 60 kg and 4 mg/kg q2w for bodyweight < 30 kg and > 10 kg) and a positive benefit-risk relationship of Kevzara in pJIA patients.

The key secondary objective was to describe the efficacy of sarilumab in participants with pJIA. All participants had JIA ACR30 response at Week 12 and improvement continued up to Week 48 as seen with the JIA ACR70 response rate that was achieved by 76.7% of participants at Week 12 and 87.7% at Week 48. The proportion of patients with JIA ACR 90 response rate were 42.5% and 69.9% at Week 12 and Week 48, respectively.

In addition, change from baseline in JADAS-27 CRP was -17.46 at Week 12 and -20.75 at Week 48 for the patients on the recommended dose. At Week 48, 51.6% of patients on the recommended dose were in remission (inactive disease per Wallace criteria for 6 consecutive months).

The MAH provided long term data up to 3 years. The improvement in efficacy parameters was maintained / further improved throughout the observation period.

3.3. Uncertainties and limitations about favourable effects

Initially, the MAH applied for a broad indication, without mentioning the subtype of pJIA, the concomitant use of medicine and the line of therapy. Upon CHMP request, the MAH updated the requested indication to mention the subtypes of pJIA that were included in the clinical trial (RF- and RF+ pJIA subtype and extended oJIA), and that patients should have responded inadequately to previous therapy with conventional synthetic DMARDs which is consistent with the population included in the clinical trial. In addition, in line with the inclusion criteria and the RA adult indication, the MAH mentioned that sarilumab can be used as monotherapy or in combination with methotrexate. This was endorsed by the CHMP.

As such there are no self-standing data that demonstrate robust efficacy. The provided efficacy data are descriptive as they are derived from an uncontrolled, open-label, single-arm setting with the purpose of dose finding. Nevertheless, they are considered supportive for the overall extrapolation concept.

In addition, the MAH used a while-on-treatment approach, introducing a bias with the chosen analysis, upon CHMP request the analysis were reperformed using an ITT approach, these results were considered more realistic and are the one reflected in section 5.1 of the SmPC.

3.4. Unfavourable effects

Overall the safety profile in paediatric pJIA patients appears to be comparable to the already established safety profile of sarilumab in adults RA patients. The most important observed adverse events have been described in section 4.8 of the SmPC and were the following:

- Neutropenia (no serious or opportunistic infections occurred during the neutropenic period)
- ALT increase
- Infection (upper respiratory tract and nasopharyngitis)
- Injection site reactions

3.5. Uncertainties and limitations about unfavourable effects

Only a single arm trial was performed with a small sample size which limits the data collected on unfavourable effects.

3.6. Effects Table

Table 14: Effects Table for Kevzara, pJIA (data cut-off: 09 Feb 2023).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Secondary endpoint Efficacy analysis at Week 12: Portions 1-3, selected dose (dose 2) ALL	JIA-ACR70	%	76.7	None	Overall consistent picture as regards efficacy endpoints (JIA-ACR 30/50/70/90), only supportive for the extrapolation (secondary endpoint, single arm trial)	Study DRI13925
Secondary endpoint Efficacy analysis at Week 12: Portions 1-3, selected dose (dose 2) ALL	JIA-ACR90	%	45.2	None	Overall consistent picture as regards efficacy endpoints (JIA-ACR 30/50/70/90), only supportive for the extrapolation (secondary endpoint, single arm trial)	Study DRI13925
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Neutropenia	Decreases in neutrophils	%	31.2		Single arm study, small sample size	Study DRI13925
ALT increase		%	9.7		Single arm study, small sample size	Study DRI13925
Infections(upper respiratory tract)		%	14		Single arm study, small sample site	Study DRI13925
nasopharyngitis		%	36.6		Single arm study, small sample site	Study DRI13925
Injection site reaction		%	14.0		Single arm study, small sample site	Study DRI13925

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Given the limitations of the design and conduct of the study in particular a “soft” endpoint in an open-label, single-arm setting, the efficacy and safety data are only descriptive. All participants had JIA ACR30 response at Week 12 and improvement in efficacy parameters was maintained or further improved throughout the observation period (up to 3 years). The overall incidence of adverse events was low. The observed safety data in pJIA patients were in general consistent with the known safety profile of sarilumab in RA patients. No new safety concerns were identified during the development program in the clinical trial population. The long-term safety will be followed up in the post marketing setting.

Overall, the efficacy and safety results are considered supportive for the extrapolation concept.

In addition, upon CHMP request, the MAH updated the indication to better reflect the clinical trial population: kevzara is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA; rheumatoid factor positive or negative polyarthritis and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with conventional synthetic DMARDs (csDMARDs). Kevzara may be used as monotherapy or in combination with MTX. This was endorsed by the CHMP.

3.7.2. Balance of benefits and risks

The provided efficacy data provide some indication that disease control can be achieved at Week 12 and maintained over a period of at least 48 weeks. These data cannot be considered robust due to the design of this dose finding trial which was uncontrolled, open-label, with a small sample size and using a “soft” endpoint.

Although the aetiology and pathogenesis of JIA are not fully understood, it is accepted that pJIA shares many of the pathological abnormalities that have been identified in adult RA. Different products each

with distinct mechanisms of action that were initially developed for and are effective in adult RA have also been demonstrated to be effective in pJIA.

The PD markers collected in the pJIA study DRI13925 (CRP, ESR, IL-6 and sIL-6R) were similar to those collected in the RA studies. In addition, it can be assumed that increased IL-6 concentration in patients with pJIA or RA, plays an important role in both the pathologic inflammation and joint destruction. Therefore, an extrapolation concept for exposure bridging, as agreed by the Paediatric Committee in 2017 for this study, is generally accepted in this disease setting and may be sufficient for waiving a formal efficacy study in order to spare children from unnecessary trials. Overall, observed data on clinical pharmacology and the analyses conducted on this basis, as well as the clinical data, indicate that there are differences in PK comparability and foremost in exposure-response relationships between the paediatric population (pJIA) and adult population (RA). The MAH presented parameter estimations of predicted exposures after single and multiple dose for patients with pJIA and comparisons with paediatric patients for Groups A and B. While limited numbers of observed exposures are available to compare with, they are reasonably well aligned with the estimated parameters for the analysed dose levels and groups presented. Furthermore, the simulations regarding comparability of exposures after steady state doses between the different groups of paediatric patients with adult participants with RA showed that exposures for groups A and B fell between the exposures of 150 mg and 200 mg. The difference in exposure is not expected to exceed the safe exposure range observed so far in adults. Therefore, there are no specific concerns regarding safety. This lower exposure following dose cohort 2 in paediatrics is not expected to be linked to a significant drop or loss in efficacy, as greater responsiveness in paediatrics is indicated at similar drug levels. Moreover, effectiveness and a tolerable safety profile of sarilumab was observed for the recommended dose regimen of 3 mg/kg Q2W and 4 mg/kg Q2W for pJIA participants. The median Ctrough of dose cohort 2 was at least within the range of the Ctrough in adult participants with RA who received 150 mg q2w or 200 mg q2w. In addition, based on the data of all tested dosing regimens for paediatric patients with pJIA in this study, the recommended dose regimen of 3 mg/kg Q2W (capped at 200 mg Q2W) dose for participants with body weight ≥30 kg and 4 mg/kg Q2W for participants with body weight ≥ 10 kg and <30 kg, respectively, most closely matched the dose regimen of adults with RA, supporting a positive benefit-risk balance of Kevzara in pJIA patients.

In summary, even though there are some remaining uncertainties to ultimately confirm the validity of the extrapolation exercise the data overall support a favourable benefit-risk balance for the proposed posology and indication.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Kevzara is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the benefit-risk balance of, Kevzara 175 mg/ml solution for injection in vial is favourable in the following

indication:

Polyarticular juvenile idiopathic arthritis

Kevzara is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA; rheumatoid factor positive or negative polyarthritis and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with conventional synthetic DMARDs (csDMARDs). Kevzara may be used as monotherapy or in combination with MTX.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Kevzara subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

- Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Prior to launch of Kevzara in each Member State the MAH must agree about the content and format of patient card, including communication media, distribution modalities, and any other aspects, with the National Competent Authority.

The MAH shall ensure that in each Member State where Kevzara is marketed, all healthcare professionals who are expected to prescribe Kevzara have access to the patient card.

The patient card shall contain the following key messages:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Kevzara.
- That Kevzara treatment may increase the risks of serious infections, neutropenia and intestinal perforation.
- Educate patients and/or parents/caregivers on signs or symptoms that could represent serious infections or gastrointestinal perforations to seek for medical attention immediately.

- Contact details of the prescriber for Kevzara.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0067/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A

Extension application to add a new strength of 175 mg/ml solution for injection in vial, grouped with an extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older for KEVZARA, based on results from study DRI13925; this is a multinational, multi-center, open-label, 2 phase, 3 portions study to describe the PK profile as well as safety and efficacy of sarilumab. As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3, 6.5 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP has also been approved. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.