EU-RISK MANAGEMENT PLAN FOR KEVZARA® (SARILUMAB)

Data Lock Point (DLP)	09-FEB-2023
Risk Management Plan (RMP) Version number	Version 5.0
Date of final sign-off	22-OCT-2024

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Risk Management Plan v4.0 is submitted in line with the regulatory submission of a new indication: polymyalgia rheumatica (PMR) in adult population. The RMP is updated to v4.1 to align the PMR indication wording and posology as per the CHMP recommendations (procedure number: EMEA/H/C/004254/II/0044). The RMP v3.0 is submitted in line with the regulatory submission of a new pediatric indication (active polyarticular-course juvenile idiopathic arthritis [pcJIA]) in patients 2 years of age and older. The RMP is updated to v5.0 to align the polyarticular juvenile idiopathic arthritis (pJIA) indication wording as per the Committee for Medicinal Products for Human Use (CHMP) recommendations (procedure number: EMEA/H/C/004254/X/0043/G). This RMP includes information related to PMR (approved in EU RMP v4.1) and the pJIA indication.
Summary of significant changes in this RMP	Update of the DLP (09-Feb-2023). All relevant parts/modules have been updated using this DLP. All relevant parts/modules (Part II Modules SIII, SIV, SVII and Part VI) have been updated with data from Study EFC15160 (PMR indication) and DRI13925 (pJIA indication). Polymyalgia Rheumatica indication wording has been updated in Part I and Part II Module SI, and the dosage information has been updated in Part I (RMP v4.1). Minor updates have been made in Part II Module SIV, Module SVII and Part III (RMP v4.1). Additional risk minimization measures have been updated to cover the pediatric populations (RMP v3.0). Polyarticular juvenile idiopathic arthritis indication wording has been updated in Part I and Part II Module SI. Additionally, in all relevant places throughout the RMP, pcJIA has been updated to pJIA (RMP v5.0). Minor updates have been made in Part II Module SIII, Module SIV, Module SVII and Part V (RMP v5.0). In line with the comments provided on the Summary of Product Characteristics (SmPC), the term “Patient Alert card” has been updated to “Patient Card” in RMP Part V and Annex 6 (RMP v5.0).

CHMP: Committee for Medicinal Products for Human Use; DLP: Data Lock Point; EU-RMP: European Union Risk Management Plan; pcJIA: Polyarticular-Course Juvenile Idiopathic Arthritis; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	4.1
Approved with procedure	EMEA/H/C/004254/II/0044
Date of approval (opinion date)	17-Oct-2024

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	Johanne-Sophie Depont-Seiller[a], [redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

A/G ratio:	Albumin/Globulin ratio
ACR:	American College of Rheumatology
AE:	Adverse Event
ALP:	Alkaline Phosphatase
ALT:	Alanine Aminotransferase
AMA:	Anti-Mitochondrial Autoantibody
ANA:	Anti-Nuclear Antibody
ANC:	Absolute Neutrophil Count
ANOVA:	Analysis of Variance
AS:	Ankylosing Spondylitis
AST:	Aspartate Aminotransferase
ATC:	Anatomical Therapeutic Chemical
ATP III:	Adult Treatment Panel III
bDMARD:	Biological Disease Modifying Anti-Rheumatic Drug
BMI:	Body Mass Index
CAC:	Cardiovascular Adjudication Committee
CBILI:	Conjugated Bilirubin
CD-1:	Cluster of Differentiate-1
CD-19:	Cluster of Differentiate-19
CD-20:	Cluster of Differentiate-20
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CNS:	Central Nervous System
COVID-19:	Coronavirus Disease-2019
CRP:	C-Reactive Protein
CS:	Corticosteroid
csDMARD:	Conventional Synthetic Disease Modifying Anti-Rheumatic Drug
CTCAE:	Common Terminology Criteria for Adverse Event
CTLA-4:	Cytotoxic T-Lymphocyte Associated Antigen-4
C_{trough}:	Plasma Trough Concentration
CV:	Cardiovascular
DBL:	Data Base Lock
DDD:	Defined Daily Dose
DLP:	Data Lock Point
DMARD:	Disease Modifying Anti-Rheumatic Drug
EEA:	European Economic Area
EMA:	European Medicines Agency
eoJIA:	Extended Oligoarticular Juvenile Idiopathic Arthritis
EPAR:	European Public Assessment Report

ePPND:	Enhanced Pre-/Postnatal Development
E-R:	Exposure-Response
EU:	European Union
EULAR:	European League Against Rheumatism
EU-RMP:	European Union Risk Management Plan
FDA:	Food and Drug Administration
GCA:	Giant Cell Arteritis
GD:	Gestational Day
GI:	Gastrointestinal
GVP:	Good Pharmacovigilance Practices
HbA1c:	Glycated Hemoglobin
HCP:	Healthcare Professional
HDL:	High Density Lipoprotein
HIV:	Human Immunodeficiency Virus
HL:	Hodgkin's Lymphoma
HLA:	Human Leukocyte Antigen
HLA-A2:	Human Leukocyte Antigen-Alpha 2
HLA-DRB1:	Human Leukocyte Antigen Class II Histocompatibility, D Related Beta Chain 1
HR:	Hazard Ratio
IBD:	Inflammatory Bowel Disease
IFU:	Instructions for Use
IgG:	Immunoglobulin G
IgG2a:	Immunoglobulin G Gamma 2A Chain C Region, A Allele
IgM:	Immunoglobulin M
IL-1:	Interleukin-1
IL-6:	Interleukin-6
IL-6R:	Interleukin-6 Receptor
IL-6Rα:	Alpha subunit of Interleukin-6 Receptor
ILAR:	International League of Associations for Rheumatology
ILD:	Interstitial Lung Disease
IMP:	Investigational Medicinal Product
INN:	International Nonproprietary Name
IR:	Incidence Rate
IRR:	Incidence Rate Ratio
ISS:	Integrated Safety Summary
IV:	Intravenous
JAK:	Janus Kinase
JIA:	Juvenile Idiopathic Arthritis
KLH:	Keyhole Limpet Hemocyanin
LDL:	Low Density Lipoprotein
LLN:	Lower Limit of Normal
MACE:	Major Adverse Cardiovascular Event
MAH:	Marketing Authorization Holder

MARCO:	Margin Consolidated
Max:	Maximum
MedDRA:	Medical Dictionary for Regulatory Activities
Min:	Minimum
MN:	Minnesota
MTX:	Methotrexate
n:	Number of Patient
N:	Total Number of Patient
NCEP:	National Cholesterol Education Program
NHL:	Non-Hodgkin's Lymphoma
NIU:	Non-Infectious Uveitis
NMSC:	Non-Melanoma Skin Cancer
NOAEL:	No Observed Adverse Effect Level
NSAID:	Nonsteroidal Anti-Inflammatory Drug
OI:	Opportunistic Infection
oJIA:	Oligoarticular Juvenile Idiopathic Arthritis
P:	Probability
PARC:	Performance Analysis Reporting Center
PBRER:	Periodic Benefit-Risk Evaluation Report
pcJIA:	Polyarticular-Course Juvenile Idiopathic Arthritis
PCSA:	Potentially Clinically Significant Abnormalities
PFP:	Pre-Filled Pen
PFS:	Pre-Filled Syringe
PIP:	Pediatric Investigation Plan
pJIA:	Polyarticular Juvenile Idiopathic Arthritis
PK:	Pharmacokinetic
PMR:	Polymyalgia Rheumatica
PND:	Post-Natal Day
poJIA:	Persistent Oligoarticular Juvenile Idiopathic Arthritis
PPV:	Pneumococcal Polysaccharides Vaccine
PSUR:	Periodic Safety Update Report
PT:	Preferred Term
PTC:	Product Technical Complaint
PY:	Patient-Year
Q:	Quarter
q2w:	Once Every Two Weeks
q4w:	Once Every Four Weeks
QPPV:	Qualified Person Responsible for Pharmacovigilance
qw:	Once Every Week
RA:	Rheumatoid Arthritis
RCT:	Randomized Control Trial
RF:	Rheumatoid Factor
RF-:	Rheumatoid Factor-Negative

RF+:	Rheumatoid Factor-Positive
RMP:	Risk Management Plan
RR:	Risk Ratio
SC:	Subcutaneous
SD:	Standard Deviation
SEER:	Surveillance, Epidemiology, and End Results Program
SI:	Serious Infection
SIR:	Standardized Incidence Ratio
sJIA:	Systemic-Juvenile Idiopathic Arthritis
SmPC:	Summary of Product Characteristics
SMQ:	Standardized MedDRA Query
TB:	Tuberculosis
TBILI:	Total Bilirubin
TC:	Total Cholesterol
TCZ:	Tocilizumab
TEAE:	Treatment-Emergent Adverse Event
TG:	Triglyceride
THIN:	The Health Improvement Network
TNF:	Tumor Necrosis Factor, Tumor Necrosis Factor
TNF-α:	Tumor Necrosis Factor-Alpha
TTV:	Tetanus Toxoid Vaccine
UK:	United Kingdom
ULN:	Upper Limit of Normal
US:	United States
US FDA:	United States Food and Drug Administration
USA:	United States of America
WHO:	World Health Organization
WIG2:	Scientific Institute for Health Economics and Health System Research

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Sarilumab
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	L04AC14
Marketing Authorization Holder	Sanofi Winthrop Industrie
Medicinal products to which this RMP refers	1
Invented name(s) in the (European Economic Area [EEA])	Kevzara
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Kevzara, also referred to as sarilumab, SAR153191, or REGN88, is a recombinant human monoclonal antibody of the Immunoglobulin G (IgG) kappa isotype directed against the alpha subunit of the Interleukin-6 (IL-6) receptor (Alpha subunit of Interleukin-6 Receptor [IL-6Rα]).
	Summary of mode action: Interleukin-6 is a key cytokine with a wide range of biological activities, including regulation of immune reactivity, the acute phase response, inflammation, oncogenesis, and hematopoiesis. Overproduction of IL-6 has been found to play pathological roles in chronic inflammatory diseases, including rheumatoid arthritis (RA) and PMR. By binding to IL-6Rα with high affinity, sarilumab blocks the binding of IL-6 and interrupts the cytokine-mediated signaling cascade.
	Important information about its composition: Recombinant human monoclonal antibody of the IgG kappa isotype.
Hyperlink to the product information	Refer to sequence 0093-module 1.3.1 Summary of Product Characteristics (SmPC), labelling and package leaflet.
Indication(s) in the EEA	Current: *Rheumatoid arthritis* *Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.*

	Polymyalgia rheumatica *Kevzara is indicated for the treatment of polymyalgia rheumatica (PMR) in adult patients who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper.*
	Proposed: *Rheumatoid arthritis* *Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.* *Polymyalgia rheumatica* *Kevzara is indicated for the treatment of polymyalgia rheumatica (PMR) in adult patients who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper.* Polyarticular juvenile idiopathic arthritis (pJIA) *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*.
Dosage in the EEA	Current: RA The recommended therapeutic dose for sarilumab is 200 mg administered subcutaneously once every two weeks (q2w). The dose may be decreased to 150 mg q2w for the management of certain laboratory abnormalities. PMR The recommended dose of sarilumab is 200 mg administered subcutaneously q2w, in combination with a tapering course of systemic corticosteroids, after which sarilumab can be continued as monotherapy.
	Proposed: RA The recommended therapeutic dose for sarilumab is 200 mg administered subcutaneously once every two weeks (q2w). The dose may be decreased to 150 mg q2w for the management of certain laboratory abnormalities. PMR The recommended dose of sarilumab is 200 mg administered subcutaneously q2w, in combination with a tapering course of systemic corticosteroids, after which sarilumab can be continued as monotherapy. pJIA The recommended dose of sarilumab for pJIA patients ≥30 kg is 3 mg/kg subcutaneous (SC) injection q2w and for patients ≥10 to <30 kg is 4 mg/kg SC injection q2w. Dose is capped at 200 mg q2w for patients weighing ≥63 kg.
Pharmaceutical form(s) and strength(s)	Current: RA and PMR

	Sarilumab is supplied in two single-use pharmaceutical forms, pre-filled syringe (PFS) and pre-filled pen (PFP), containing 150 mg or 200 mg of sarilumab in 1.14 mL solution for subcutaneous (SC) injection (at a concentration of 131.6 mg/mL and 175 mg/mL respectively).
	Proposed: RA and PMR Sarilumab is supplied in two single-use pharmaceutical forms, PFS and PFP, containing 150 mg or 200 mg of sarilumab in 1.14 mL solution for SC injection (at a concentration of 131.6 mg/mL and 175 mg/mL, respectively). pJIA Sarilumab is supplied as a single-dose vial containing 270 mg of sarilumab in 1.54 mL solution for SC injection (at a concentration of 175 mg/mL).
Is/will the product (be) subject to additional monitoring in the European Union (EU)?	No

ATC: Anatomical Therapeutic Chemical; csDMARD: Conventional Synthetic Disease Modifying Anti-Rheumatic Drug; DMARD: Disease Modifying Anti-Rheumatic Drug; EEA: European Economic Area; EU: European Union; IgG: Immunoglobulin G; IL-6: Interleukin-6; IL-6Rα: Alpha subunit of Interleukin-6 Receptor; INN: International Nonproprietary Name; MTX: Methotrexate; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PFS: Pre-Filled Syringe; PFP: Pre-Filled Pen; PMR: Polymyalgia Rheumatica; q2w: Once Every Two Weeks; RA: Rheumatoid Arthritis; RMP: Risk Management Plan; SC: Subcutaneous; SmPC: Summary of Product Characteristics.

RISK MANAGEMENT PLAN – PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

Kevzara is also indicated for the treatment of polymyalgia rheumatica (PMR) in adult patients who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper.

Additionally, 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 epidemiology of RA, PMR and pJIA is summarized in the following sections.

Rheumatoid Arthritis:

Rheumatoid arthritis is a chronic, inflammatory disease affecting the synovium, leading to joint damage and bone destruction, causing severe disability and increased mortality. Several prevalence and incidence studies during the past decades have suggested considerable variations in disease occurrence in different geographical regions, among different populations and over time. (1)

Table 6 - Epidemiology of Rheumatoid arthritis

<table>
<tr><th>Indication</th><th>Rheumatoid arthritis</th></tr>
<tr><td>Incidence</td><td>In a recent 2022 review paper, the age- and sex-standardized incidence rate (IR) of RA was calculated between 1998-2018 to be 35.5 (95% confidence interval (CI): 35.1-35.9) per 100 000 person-years, while the prevalence rate was 35.2 (95% CI: 34.8-35.5) per 100 000 individuals. The IR was found to be twice as high for women compared to men. (2)
The country specific estimated incidence of RA are also described in the Table 6a below:
Table 6a
<table>
<tr><th>Country
(Year of the publication)</th><th>Incidence cases/1000 inhabitants</th><th>Population Age</th></tr>
<tr><td>United States (US) (2002) (1)</td><td>0.5</td><td>≥18</td></tr>
<tr><td>Sweden (2010) (3)</td><td>0.5</td><td>≥20</td></tr>
<tr><td>Canada (2014) (4)</td><td>0.5</td><td>≥15</td></tr>
<tr><td>US (2010) (5)</td><td>0.4</td><td>≥18</td></tr>
</table></td></tr>
</table>

Indication	Rheumatoid arthritis

Finland (2003) (1)	0.4	≥16
Sweden (2013) (6)	0.4	≥18
United Kingdom (UK) (2012) (7)	0.4	≥16
Finland (2000) (1)	0.3	≥16
Finland (2001) (1)	0.3	≥16
Italy (2014) (8)	0.3	≥18
Norway (2000) (1)	0.3	≥20
Greece (1997) (1)	0.2	>15
Sweden (2002) (1)	0.2	≥16
UK (2005) (1)	0.2	≥15
France (1994) (1)	0.1	20-70
Spain (2008) (9)	0.1	≥16
Japan (1999) (1)	0.1	All ages

UK: United Kingdom; US: United States.

A 2016 literature review has shown that the activity and deleterious effects of RA have diminished over time, in conjunction with recent therapeutic advances (new drugs and improved patient selection). However, there seems to be no decrease in the frequency of RA, which continues to induce significant excess mortality. (10) In a US study, the incidence of RA overall was stable during 2005-2014 compared with the previous decade, with a decreasing incidence of rheumatoid factor (RF)+ RA and increasing incidence of RF- RA in 2005-2014 as compared with the previous decades. (11)

Prevalence

A recent meta-analysis performed for 67 studies on the incidence and prevalence of RA in 41 countries revealed a combined prevalence of 0.46% (95% CI: 0.37-0.57%). In the same review paper, the data from 2017 Global Burden of Disease study indicated variations in the prevalence of RA across regions. Specifically, higher prevalence rates of 0.26% were observed in North Africa and the Middle East, compared to 0.14% in western sub-Saharan Africa. Similar trends were observed in the IRs, with 37 per 100 000 patient year (PYs) in North Africa and the Middle East, and 23 per 100 000 PYs in western sub-Saharan Africa. (2)

In Europe and North America, the prevalence of RA varies between 3 to 10 cases per 1000 inhabitants as shown in Table 6b below:

Table 6b

Country (year of the article)	Prevalence cases/1000 inhabitants	Population Age
Finland (2001) (1)	18	65-85
US (1999) (1)	10.7	≥35
Turkey (2010) (12)	10	≥20
England (2002) (1)	8.5	≥16
UK (2005) (13)	8.1	≥15

Indication	Rheumatoid arthritis

Finland (1993) (1)	8	≥16
US (2010) (5)	7.2	≥18
Greece (2003) (1)	7	≥18
Sweden (2010) (3)	6.6	≥20
Spain (2002) (1)	5	≥20
Norway (2000) (1)	4.7	≥20
Estonia (2013) (14)	4.4	≥20
Spain (2014) (15)	4.2	≥15
Italy (1998) (1)	3.3	≥16
Italy (2014) (8)	3.2	≥18
France (2005) (1)	3.1	≥18
Denmark (2011) (16)	3	≥15
China (2003) (1)	2.8	≥16
Argentina (2002) (1)	2	≥16
Japan (1999) (1)	1.7	All ages

UK: United Kingdom; US: United States.

Demographics of the population in the authorized/proposed indication

In adults, both the prevalence and incidence are reportedly about 2- to 4-fold higher in women than in men, and symptoms appear to be more severe in women. (6) Rheumatoid arthritis may present at any age and increases with age. Patients are most commonly diagnosed in the third to sixth decade of life. The prevalence peaked at age 70-79 years (women = 2.1%, men = 1.1%) before dropping in those aged 80 years and above. (3) Rheumatoid arthritis is a multifactorial disease with genetic, environmental, and demographic components. Sex, age, genetic predisposition, and smoking are recognized as risk factors for RA. Fifty (50%) of the risk for development of RA is attributable to genetic factors. Smoking is the main environmental risk, and doubles the risks of developing RA. (17)

Main existing treatment options

Current guidelines, including those from European League against Rheumatism (EULAR) and American College of Rheumatology (ACR), for the treatment of patients with RA emphasize the importance of close monitoring and frequent adjustment or switching of therapy to achieve the therapeutic target, focusing on the absence of or minimal presence of signs and symptoms of inflammatory disease activity, improvement in physical function and prevention of the progression of structural damage. (18)(19) The goal is to achieve these objectives within three to six months after starting therapy. Without effective treatment, joint damage progresses chronically and irreversibly (20)(21), and results in impaired physical function and disability.

Consequently, therapies that provide sustained benefit over long periods of time are necessary. Conventional Synthetic DMARDs, such as MTX are the first line of therapy for RA. Treatment with a Biological Disease Modifying Anti-Rheumatic Drug (bDMARD) or Janus Kinase (JAK) inhibitor as add-on or as monotherapy is the recommended next line of treatment. Approved second line therapies include bDMARDs targeting the tumor necrosis factor alpha (TNF-α) (infliximab, adalimumab, etanercept, golimumab, certolizumab), B-cell antigen Cluster of Differentiate-20 (CD)-20 (rituximab), Cytotoxic T Lymphocyte Associated Antigen-4 (CTLA-4) (abatacept), the pro-inflammatory cytokine

Indication	Rheumatoid arthritis
	Interleukin-1 (IL-1) (anakinra) or the IL-6 receptor (Tocilizumab [TCZ], sarilumab) and the JAK inhibitors.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Rheumatoid arthritis is a chronic, progressive condition that leads to sustained joint damage, physical disfigurement, disability, consequent reduced functions and quality of life, and increased morbidity and mortality. The cause of RA is complex and multifactorial and remains poorly understood. The following factors have been identified to play a role in the patient's risk for development of the disease. • Genetic factors: Certain genetic variations and predispositions are believed to contribute to the development of RA. Family history, the genetic factor for a "shared epitope" and specific genetic markers, such as the Human Leukocyte Antigen Class II Histocompatibility, D Related Beta Chain 1 (*HLA-DRB1)* gene, have been associated with an increased risk of developing the disease. (22) • Autoimmune dysfunction: The exact triggers for this autoimmune response are still not fully understood. (23) • Environmental factors: This includes infections or exposure to certain substances which may play a role in the development of RA, such as tobacco smoke. (23) • Hormonal factors: Hormonal changes, especially in women, have been linked to an increased risk of developing RA. The disease often improves during pregnancy but can flare up after childbirth, suggesting a hormonal influence. (22) Studies conducted over the past four decades have found that RA is associated with increased mortality in comparison with the general population of the same age and gender. Most studies indicate that the main causes of death in RA patients are cardiovascular (CV), infectious, hematological, gastrointestinal (GI), and pulmonary complications. A meta-analysis from Toledano et al. (24) revealed that the overall standardized mortality ratio ranged from 1.25 to 4.58. Recent studies among various populations in North America and the UK have reported standardized mortality ratios of 1.22 to 2.1 (25), while studies in Sweden and Netherlands reported values of 1.61 and 1.40, respectively. (24)
Important co-morbidities	Rheumatoid arthritis is linked to numerous extra-articular manifestations and co-existing conditions. The individuals with RA face twice the likelihood of experiencing a myocardial infarction and an elevated risk of CV mortality, reaching up to 50% higher than that of the general population. (26) In a case-control study involving a total of 3276 participants from the Mayo Clinic Biobank, consisting of 821 cases with RA and 2455 control individuals, RA co-morbidities were identified prior to and post-diagnosis. There was a correlation identified between RA and pre-existing co-morbidities like Inflammatory Bowel Disease (IBD), type 1 diabetes, epilepsy, and venous thromboembolism. (27)

ACR: American College of Rheumatology; bDMARD: Biological Disease Modifying Anti-Rheumatic Drug; CI: Confidence Interval; CV: Cardiovascular; CD-20: Cluster of Differentiate-20; CTLA-4: Cytotoxic T Lymphocyte Associated Antigen-4; DMARD: Disease Modifying Anti-Rheumatic Drug; EULAR: European League Against Rheumatism; GI: Gastrointestinal; HLA-DRB1: Human Leukocyte Antigen Class II Histocompatibility, D Related Beta Chain 1; IBD: Inflammatory Bowel Disease; IL-1: Interleukin-1; IL-6: Interleukin-6; IR: Incidence Rate; JAK: Janus Kinase; MTX: Methotrexate; PY: Patient-Year; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; RF+: Rheumatoid Factor-Positive; RF-: Rheumatoid Factor-Negative; TCZ: Tocilizumab; TNF-α; Tumor Necrosis Factor-Alpha; UK: United Kingdom; US: United States.

Polymyalgia rheumatica:

Polymyalgia rheumatica is a chronic, inflammatory disease of unknown etiology characterized by pain and morning stiffness of the shoulder, neck, and pelvic girdle and is frequently associated with low-grade fever, fatigue, malaise, and weight loss. The debilitating effect of the disease can significantly affect the quality of life of PMR patients. (28)

Table 7 - Epidemiology of Polymyalgia rheumatica (PMR)

Indication	Polymyalgia rheumatica (PMR)
Incidence	The incidence of PMR is highest in Scandinavian countries and in people of northern European descent (29) with rates almost ten-fold higher in northern Europe (33.6 to 113 per 100 000 adults >50 years) compared to southern Europe (3.15 to 27.43 per 100 000 adults >50 years). (30) In Italy, the annual rate of incidence of PMR is between 12 and 23 cases/100 000 inhabitants. (31) In Germany, the annual age- and sex-standardized IRs of PMR in adults >40 years from 2011 to 2019 were 18.6/100 000 persons with a higher incidence in women than in men (21.8/100 000 versus 12.8/100 000 persons per year). (32) Reported rates for the UK were significantly higher with an overall IR of 96/100,000. In the UK, the incidence of PMR was highest in women, older age groups and those living in the South of England. (33)
Prevalence	Estimates of the prevalence of PMR vary widely depending on the incidence in the population and the case definition used, namely whether patients who have achieved remission are counted as prevalent cases. Although heterogeneity exists, PMR remains a common inflammatory rheumatological disease in the elderly Caucasian population. In Italy, the prevalence ranged from 37 to 62 cases/100 000 adults aged over 50 years. (31) In Germany, the annual age- and sex-standardized prevalence rate of PMR in adults >40 years from 2011 to 2019 was 138.8/100 000. (32) The reported prevalence rate in the UK was significantly higher at 850/100 000. (33)
Demographics of the population in the authorized/proposed indication	The lifetime risk of PMR stands at 2.4% for women and 1.7% for men. (34) The average age of onset is slightly over age 70, and approximately 75% of patients are women. PMR is almost exclusively a disease of adults over the age of 50, with a prevalence that increases progressively with advancing age. The peak incidence of PMR occurs between ages 70 and 80. (35) Polymyalgia rheumatica predominantly affects individuals with North European heritage, but it can also manifest in individuals from various, other ethnic backgrounds. (29)
Main existing treatment options	Per the 2015 ACR/EULAR guidelines, corticosteroid (CS) remains the standard of care therapy with a recommended minimum effective starting dose within the range of 12.5 to 25 mg of prednisone (or equivalent) daily. (36) Treatment duration ranges from approximately 1 to 3 years, (37) during which CS should be tapered. Therapies, other than CS, have shown limited efficacy in the treatment of PMR. Methotrexate has been assessed in a small number of randomized trials with inconsistent results. An expert ACR/EULAR panel conditionally recommended MTX for early use in patients at high risk of prolonged CS use and/or CS-related adverse event (AEs) and during follow-up for patients who have had a relapse, have not had significant response to CS, or are experiencing CS-related side effects. No other recommendation could be made for use of other non-biologic agents, and the expert panel strongly recommended against the use of TNF-α blocking agents for the treatment of PMR. (38)
Natural history of the indicated condition in the untreated population including mortality and morbidity	Polymyalgia rheumatica presents with sudden-onset pain in both shoulders accompanied by morning stiffness as a primary characteristic. In less frequent instances, it may also affect the neck, pelvic girdle, and upper thighs. Constitutional symptoms are frequently reported, but any fever experienced is usually of low intensity. Patients may experience limitations in their active joint range of motion, even though no weakness is typically observed. (34) In a 2021 retrospective study to investigate if diagnosed PMR is linked to early mortality (among 18 943 patients with PMR; 87 801 controls), PMR did not show a higher risk of mortality (adjusted mortality rate ratio of 1.00 [95% CI: 0.97-1.03]) when compared to a group of matched controls. (39)

Indication	Polymyalgia rheumatica (PMR)
Important co-morbidities	In 10% to 21% of PMR cases, there is an association with giant cell arteritis (GCA). This condition is characterized by symptoms such as headaches, alterations in vision, jaw claudication, and tenderness in the temporal artery. Complications of GCA can lead to irreversible vision impairment. (34) In a systematic literature review, positive associations were found between PMR diagnosis and stroke, CV disease, peripheral arterial disease, diverticular disease and hypothyroidism. A positive association between PMR and the overall malignancy rate has been reported, in addition to the association between PMR and specific types of cancer, such as leukemia, lymphoma, myeloproliferative disease and specified solid tumors. However, data are inconsistent, and others found either no or negative association between cancer and PMR. (40)

ACR: American College of Rheumatology; AE: Adverse Event; CI: Confidence Interval; CS: Corticosteroid; CV: Cardiovascular; EULAR: European League Against Rheumatology; GCA: Giant Cell Arteritis IR: Incidence Rate; PMR: Polymyalgia Rheumatica; MTX: Methotrexate; TNF-α: Tumor Necrosis Factor-Alpha; UK: United Kingdom.

Polyarticular juvenile idiopathic arthritis:

Juvenile idiopathic arthritis (JIA) is defined by International League of Associations for Rheumatology (ILAR) classification as an arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks with other known conditions excluded. (41) Juvenile idiopathic arthritis affects primarily females (3:1 female/male) (42)(43) and comprises 7 subtypes categorized by age of onset and disease characteristics in the first 6 months after onset. (41)

Among them:

Oligoarticular JIA (oJIA) subtype (44), 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. Oligoarticular JIA carries a risk for developing chronic anterior uveitis, especially when antinuclear antibodies are present and disease onset is in early childhood. If greater than 4 joints become affected after the first 6 months of disease, it is designated as extended oJIA in contrast to persistent oJIA that features only up to 4 joints involved throughout the course of the disease.

Polyarticular JIA is defined as arthritis affecting 5 or more joints during the first 6 months of disease. Both large (eg, hips and knees) and small (eg, joints of the hand) joints can be involved, and often in symmetric bilateral distribution. Low grade fever can accompany the arthritis. Presence of RF differentiates 2 forms of pJIA: (41)

- Rheumatoid Factor-positive pJIA is diagnosed in only 3% to 5% of children and adolescents with JIA. Features of RF+ pJIA include a mean onset at 12 to 14 years old and a marked female gender predominance (13:1 female/male ratio).
- Rheumatoid Factor-negative pJIA represents 11% to 28% of all children and adolescents with JIA. It presents at a younger age (in late childhood, 7 to 9 years) with respect to the

RF+ pJIA. Radiologic changes in RF- disease occur later than in RF+ disease and it may not be as destructive and persistent.

The extended oJIA, RF+ and RF- pJIA are referred to collectively as pJIA considering they present similar clinical features (affecting 5 or more joints and ultimately evolving to permanent joint damage). The pJIA resembles adult RA based on its similar clinical features.

Table 8 - Epidemiology of Polyarticular juvenile idiopathic arthritis (pJIA)

<table>
<tr><th>Indication</th><th>Polyarticular juvenile idiopathic arthritis (pJIA)</th></tr>
<tr><td>Incidence</td><td>Large epidemiologic studies of polyarticular juvenile arthritis were summarized in a literature review including the percentage of patients with pJIA by country, RF+ and RF-. Overall, the incidence of RF- pJIA disease has been calculated to range from 0.28-6.5 per 100 000 and RF+ pJIA disease from 0.1-0.9 per 100 000 person-years. (43)
Table 8a - Incidence (per 100 000 person-years) of pJIA by Country (43)
<table>
<tr><th></th><th>Year</th><th>RF-</th><th>RF+</th><th>Polyarticular (%) of all arthritis[a]</th></tr>
<tr><td>Germany</td><td>2001</td><td>0.28</td><td>-</td><td>9.0%</td></tr>
<tr><td>US (Minnesota [MN])</td><td>1993</td><td>1.67</td><td>-</td><td>12.0%</td></tr>
<tr><td>Spain</td><td>2010</td><td>0.7</td><td>0.1</td><td>12.4%</td></tr>
<tr><td>US (MN)</td><td>1996</td><td>2</td><td>-</td><td>17.0%</td></tr>
<tr><td>Finland</td><td>2001</td><td>4</td><td>-</td><td>20.0%</td></tr>
<tr><td>France</td><td>2006</td><td>0.71</td><td>-</td><td>22.4%</td></tr>
<tr><td>Costa Rica</td><td>1995</td><td>1.24</td><td>-</td><td>23.0%</td></tr>
<tr><td>Estonia</td><td>2007</td><td>4.4</td><td>0.9</td><td>25.0%</td></tr>
<tr><td>Egypt</td><td>2013</td><td>-</td><td>0.72</td><td>29.5%</td></tr>
<tr><td>Canada</td><td>1995</td><td>1.85</td><td>-</td><td>34.9%</td></tr>
<tr><td>Sweden</td><td>1995</td><td>2.24</td><td>0.46</td><td>35.0%</td></tr>
<tr><td>Czech Republic</td><td>2006</td><td>6.5</td><td>-</td><td>50.0%</td></tr>
</table>
a Including only RF-, RF+ subtypes
MN: Minnesota; pJIA: Polyarticular Juvenile Idiopathic Arthritis; RF: Rheumatoid Factor; RF+: Rheumatoid Factor-Positive; RF-: Rheumatoid Factor-Negative; US: United States.
The distribution of patients with JIA, by subtype, was described in a 2-year (2004-2006), prospective, population-based study to determine the incidence of JIA in Catalonia, Spain. Of the patients identified, the incidence of extended oligoarticular juvenile idiopathic arthritis (eoJIA) was observed to be 0.4 (95% CI: 0.2-0.7). Subtypes were identified according to the ILAR (Edmonton revision) classification. (45) In a long-term, prospective longitudinal cohort study identifying consecutive JIA cases within Denmark, Finland, Sweden and Norway, patients were identified with disease onset between January 1997 to June 2000 and followed for median 98 months. Of the 435 children with JIA observed in the Nordic cohort, 17.9% of the JIA cohort was comprised of eoJIA, and the distribution of the remaining subtypes were as follows: systemic JIA 4.1%; oligoarticular persistent 30.1%; polyarticular RF- 18.4%; polyarticular RF+ 0.7%; juvenile psoriatic arthritis 3.2%; enthesitis-related arthritis 11.0%; undifferentiated arthritis 14.5%. (46)</td></tr>
<tr><td>Prevalence</td><td>The prevalence of JIA was summarized in a literature review, including the percentage of patients with polyarticular JIA by country, RF+ and RF-. Spanning different populations, the prevalence of</td></tr>
</table>

Indication	Polyarticular juvenile idiopathic arthritis (pJIA)
	RF- disease varies from 1.64-33.4 per 100 000 and RF+ disease from 0.28-10.3 per 100 000 person-years. (43)

Table 8b – Prevalence (per 100 000 person-years) of pJIA by Country (43)

	Year	RF-	RF+	Polyarticular (%) of all arthritis
Germany	2001	1.64	-	9.0%
US (MN)	1993	13.6	-	12.0%
Spain	2010	3.7	0.7	12.4%
France	2010	2.6	0.31	18.7%
Belgium	1993	33.4	-	20.0%
France	2006	4.4	-	22.4%
Estonia	2007	16.3	3.8	24.0%
Egypt	2013	-	0.28	29.5%
Sweden	1995	18.7	10.3	35.0%

MN: Minnesota; pJIA: Polyarticular Juvenile Idiopathic Arthritis; RF: Rheumatoid Factor; RF+: Rheumatoid Factor-Positive; RF-: Rheumatoid Factor-Negative; US: United States.

In a national, non-interventional, multi-center, retrospective study conducted in four pediatric rheumatology clinics across three cities in Turkey, oJIA was the most common type observed, accounting for 38.8% of the patients (n = 194) using the ILAR Criteria. Following oJIA, enthesitis-related arthritis was the next common subtype, comprising 23.2% of the cases (n = 116). Among those with oJIA, the majority (90.7% or n = 176) fell into the persistent subtype persistent oligoarticular juvenile idiopathic arthritis (poJIA), while a smaller percentage (9.3% or n = 18) were classified as having the extended subtype eoJIA. (47) In a Canadian study of prevalence of JIA across different populations using survey data of 1082 patients, approximately 859 (79.4%) patients returned responses. Of all JIA patients, 9.2% had eoJIA, whereas the remaining subtypes were as follows: 29.4% Persistent; 20.6% RF-; 3.1% RF+; 14.5% Systemic; 11.3% Psoriatic; 10.6% Enthesitis; and 1.3% other JIA. (48)

Demographics of the population in the authorized/proposed indication

Gender

The incidence of pJIA is higher in girls, with a ratio of two to four times more often than boys. The gender gap is even more pronounced when the disease starts during teenage years. (43)

Age

Polyarticular JIA may onset at any point prior to the age of 16, although it is uncommon for it to occur before the first year of life. The onset of the RF- subtype follows a bimodal distribution, with the first peak occurring between 1-3 years of age, and the second peak occurring in later childhood between 9-14 years of age. RF+ JIA tends to affect older children, with the onset of the disease occurring between the ages of 10 and 13 years. (43)

Ethnicity/Race

In a database study of the Division of Rheumatology at The Hospital for Sick Children in Toronto, JIA had been identified in 1605 patients between 01-Jul-1984 and 30-Jun-2002. Based on the questionnaire responses, patients were categorized into seven ethnic groups: European (including individuals of European or West Asian origin), Black (including those of Black African, African American, or Caribbean origin), Native North American, Latin American (including Central or South American origin), Asian (including Southeast Asian, Chinese, Japanese, or Pacific Islands origin), Indian Subcontinent, and Arab (including individuals of North African or Arabic origin). Patients in the Table 8c below were compared and grouped in two categories: European origin and non-European origin. Of this population, 758 patients (European = 599, non-European = 159) qualified for the final cohort following the survey and cohort entry criteria.

The characteristics were described among the JIA cohort, which included patients with oJIA (extended, persistent, all) and polyarticular JIA (RF-, RF+), as well as systemic JIA, psoriatic JIA, enthesitis-related JIA, and other JIA. The distribution of JIA by ethnic descent (European versus non-European) among each subtype as follows:

- Systemic (European: 75.7%; Non-European: 24.3%);
- Oligoarticular - persistent (80.3%; 19.7%);
- Oligoarticular Extended (88.6%; 11.4%);
- Rheumatoid Factor-negative polyarticular (82%; 18%);
- Rheumatoid Factor-positive polyarticular (48.1%; 51.9%);
- Enthesitis-related (67.2%;32.8%);
- Psoriatic (87.8%;12.2%);
- Young-onset anti-nuclear antibody (ANA) positive (83.3%; 16.7%).

In summary, the majority of subtypes were present in the European cohorts, with the exception of RF+ pJIA. (48)

The Table 8c depicts the distribution of ethnicities among the non-European cohort (N = 159), within the JIA subtypes. (48)

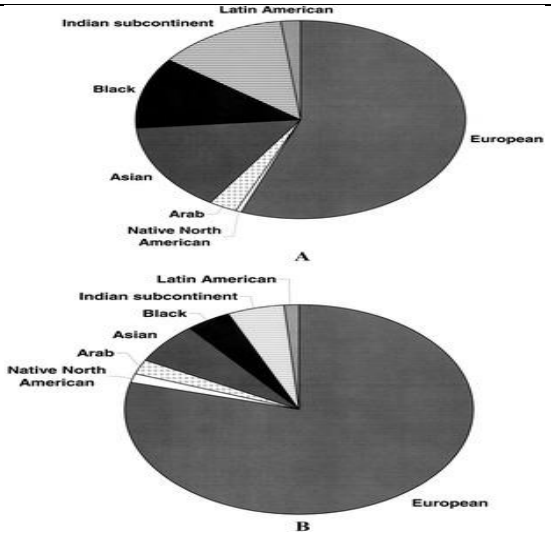
Table 8c - Distribution of JIA subtypes by specific non-European versus European ethnic groups, each column representing a percentage of the reference sample header (N) listed (48)

JIA subtype	JIA study cohort (n = 758)	European (n = 599)	Non-European (N =159)						
			All (n = 159)	Asian (n = 50)	Indian subcontinent (n = 40)	Black (n = 31)	Arab (n = 17)	Latin American (n = 11)	Native North American (n = 10)
RF-negative polyarticular	22.2 %	23.1 %	18.9 %	20%	12.5%	19.4%	17.7 %	18.2%	40%
RF-positive polyarticular	3.3%	2.2%	8.8 %	4%	7.5%	16.1%	0%	18.2%	20%
Extended oJIA	9.3%	11.8 %	6.3 %	2.0%	10.0%	9.7%	0%	0%	10%

Note: As other JIA subtype (ie, systemic, psoriatic, persistent oligoarticular, Enthesitis-related) is not shown in table, these numbers do not add to 100%.
JIA: Juvenile Idiopathic Arthritis; N: Total Number of Patient; n: Number of Patient; oJIA: Oligoarticular Juvenile Idiopathic Arthritis; RF: Rheumatoid Factor.

Distribution of ethnic groups with JIA are represented in the Figure 1 below.

Figure 1 - Ethnicity distribution among children and adolescents in the Toronto metro area (A) provided by Statistics Canada in the 2001 census and (B) In the study cohort of 758 JIA patients (48)

Indication	Polyarticular juvenile idiopathic arthritis (pJIA)
	 Patients of European origin had a significantly younger age at diagnosis for JIA compared to those of non-European origin. The mean age at diagnosis for patients of European origin was 6.5 years (95% CI: 6.1-6.8 years), whereas for those of non-European origin, it was 7.8 years (95% CI: 7.1-8.4 years) (Probability[P] = 0.005 by one-way ANOVA). (48)
Main existing treatment options	Current pJIA treatment paradigm consists of early adoption of systemic treatments and patient-centered approach with definition of target clinical remission or at least low disease activity and ensure adequate growth and development by avoiding long-term systemic glucocorticoid administration. (49) The 2019 ACR guidelines recommend initiating the therapy with a csDMARD such as MTX and to change the csDMARD or to add a bDMARD, if no or minimal response is observed after 6 to 8 weeks with MTX alone, then to change of bDMARD if the desired response is not reached. (50) he currently approved bDMARDs (or assimilated) for pJIA belong to the classes of anti-tumor necrosis factor (TNF) alpha (adalimumab, etanercept), T-cell blocker (abatacept), anti-IL-6 (TCZ), and the JAKi tofacitinib. The 2019 guidelines also acknowledge that biologics may be appropriate initial therapy for some patients with risk factors and involvement of high-risk joints (eg, cervical spine, hip, and wrist), high disease activity, and/or for those judged by their physician to be at high risk of disabling joint damage.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Juvenile idiopathic arthritis is arthritis of unknown etiology, typically in children below 16 years of age and lasts for at least six weeks. Polyarticular JIA involves at least 5 joints. Patients with RF+ pJIA are less likely to go into remission but more likely to have worse outcomes or be treated with steroids or biologic agents than other subtypes. (51) The subtypes as defined in the ILAR include systemic; oligoarthritis (persistent, extended); polyarthritis (RF-/RF+); psoriatic arthritis; enthesitis-related arthritis; undifferentiated (fits no specific category; fits more than one category). According to the ILAR classification, patients initially diagnosed with systemic-onset JIA, psoriatic arthritis, enthesitis-related arthritis, and oligoarticular arthritis, who later develop arthritis in multiple joints (known as eoJIA), can all exhibit polyarticular disease. However, despite having polyarticular features, they are excluded from the polyarticular JIA subgroups as per the ILAR classification criteria. (43) Studies have estimated the prevalence of joint damage among patients with JIA at different rates for various subtypes. In eoJIA, it ranges from 8% to 27%. For polyarticular JIA, the prevalence is estimated to be between 35% and 67%. Among those with RF+ pJIA, the prevalence of joint damage can be as high as 80%. (52) Polyarticular juvenile idiopathic arthritis is a severely disabling disease. Like adult RA, it is a chronic, progressive condition that may lead to irreversible joint damage, physical disfigurement, disability, consequent impaired physical function and reduced quality of life, and increased morbidity and mortality. Various subtypes of JIA exhibit distinct immunopathological mechanisms.

Indication	Polyarticular juvenile idiopathic arthritis (pJIA)
	The introduction of biologic drugs in the clinical management of JIA has significantly enhanced the prognosis for children affected by this disease. (53)
Important co-morbidities	The most common comorbidities in polyarticular JIA (RF+ and RF-) are chronic secondary pain syndrome, uveitis, autoimmune thyroiditis. (54) In a German polyarticular JIA study of patients including the ILAR categories polyarthritis (RF+ and RF- polyarticular JIA) and eoJIA identified from the administrative database Scientific Institute for Health Economics and Health System Research (WIG2), the most common comorbidities were described as follows in this group: (55) • Uveitis (18%) • Atopic dermatitis (13%) • Allergic rhinitis (11%) • Persistent somatoform pain (8%) • Lack of expected normal (4%) • Psoriasis (5%) • Depression/anxiety disorders (4%) Risk factors for JIA include maternal smoking during pregnancy. For example, in a cohort of 58 841 Finnish children followed from birth, 31 cases of JIA were identified. There was a 2-fold higher risk of JIA development during the initial 7 years of life in children of mothers who smoked over 10 cigarettes per day compared to children of non-smoking mothers. (56) In terms of pJIA, human leukocyte antigen-alpha 2 (HLA-A2) has been associated with early-onset RF- disease, but this association is not as strong as its link to oJIA. On the other hand, polymorphisms in class II Human Leukocyte Antigen (HLA) alleles are highly correlated with the development of pJIA. (43)

ACR: American College of Rheumatology; ANA: Anti-Nuclear Antibody; ANOVA: Analysis of Variance; bDMARD: Biological Disease Modifying Anti-Rheumatic Drug; CI: Confidence Interval; csDMARD: Conventional Synthetic Disease Modifying Anti-Rheumatic Drug; eoJIA: Extended Oligoarticular Juvenile Idiopathic Arthritis; HLA: Human Leukocyte Antigen; HLA-A2: Human Leukocyte Antigen-Alpha 2; IL-6: Interleukin-6; ILAR: International League of Associations for Rheumatology; JAKi: Janus Kinase Inhibitor; JIA: Juvenile Idiopathic Arthritis; MN: Minnesota; MTX: Methotrexate; N: Total Number of Patient; n: Number of Patient; oJIA: Oligoarticular Juvenile Idiopathic Arthritis; P: Probability; pJIA: Polyarticular Juvenile Idiopathic Arthritis; poJIA: Persistent Oligoarticular Juvenile Idiopathic Arthritis; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; RF+: Rheumatoid Factor-Positive; RF-: Rheumatoid Factor-Negative; TCZ: Tocilizumab; TNF: Tumor Necrosis Factor; US: United States; WIG2: Scientific Institute for Health Economics and Health System Research.

RISK MANAGEMENT PLAN - PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Introduction

This section presents a summary of the important non-clinical safety findings for sarilumab. Overall, these results support that sarilumab can be safely administered at a dosage of 200 mg q2w in humans. In vitro binding studies determined that in addition to binding human monomeric IL-6Rα with high affinity, sarilumab also cross-reacts with cynomolgus monkey monomeric IL-6Rα with high affinity. Because sarilumab does not bind to mouse IL-6Rα, a surrogate murine monoclonal antibody against mouse IL-6Rα, REGN844, was generated to conduct pharmacology, and reproductive and developmental toxicology studies in wild-type mice. The non-clinical safety profile of sarilumab was evaluated in the following in vivo and in vitro studies:

- Repeat-dose general toxicology studies with sarilumab up to 6 months duration using the intravenous (IV) route in cynomolgus monkeys;
- Repeat-dose general toxicology studies with sarilumab up to 13 weeks duration using the SC route in cynomolgus monkeys;
- Repeat-dose general toxicology studies with REGN844 up to 4 weeks duration using the IV and SC routes in adult Cluster of Differentiate-1 (CD-1) mice;
- An enhanced pre-/postnatal development (ePPND) toxicology study with sarilumab in cynomolgus monkeys using the IV route;
- A combined male/female fertility study with REGN844 using the SC route in adult CD-1 mice;
- Repeat-dose general toxicology studies with REGN844 up to 9 weeks duration using the IV and SC routes in juvenile CD-1 mice; and
- An in vitro tissue-cross reactivity study in human and cynomolgus monkey tissues with biotinylated sarilumab.

Sarilumab-related findings are described below and in Table 9.

Sarilumab was well-tolerated in repeat-dose general toxicology monkey studies at the highest doses tested following either IV administration up to 26 weeks in duration at doses up to 50 mg/kg/week, or SC administration up to 13 weeks in duration at doses up to 100 mg/kg/week. The highest doses administered were the no observed adverse effect level (NOAEL).

Safety pharmacology endpoints for the central nervous system (CNS), CV system, or respiratory system were evaluated as part of the toxicology studies conducted in cynomolgus monkeys, in which sarilumab was administered at doses up to 100 mg/kg/week SC for 13 weeks, or up to 50 mg/kg/week IV for 6 months. No sarilumab-related effects were observed in these organ systems in these repeat-dose toxicity studies.

The main sarilumab-related effects were consistent with the known pharmacological mechanism of action of inhibiting IL-6 signaling. Related to the immune system, there were transient, mostly minimal to moderate, reversible or partially reversible decreases in absolute neutrophil

count (ANC), and slightly lower primary and secondary IgG responses following antigen challenge with keyhole limpet hemocyanin (KLH). Other pharmacologically-mediated findings included transient, mostly minimal to moderate, reversible or partially reversible decreases in serum fibrinogen, and/or serum C-reactive protein (CRP) concentrations as well as reversible elevations in circulating IL-6 concentrations. These findings and other sporadic findings noted in some studies (decreased white blood cell counts, monocytes, total protein, and albumin/globulin [A/G] ratio) that may have been associated with sarilumab treatment were not considered adverse because of the large variability and similarity to control and/or pretest values, the reversibility/partial reversibility of the finding, and the lack of associated clinical signs or anatomic pathology findings.

No deaths in the toxicology program were considered related to sarilumab treatment. Two monkeys in repeat-dose IV studies with sarilumab ≥13 weeks in duration died or were euthanized because of either an infection and/or inflammation in the large intestine. Spontaneous GI disease is a relatively common finding in macaques where the large intestine is more commonly affected. The Sponsor did not consider the deaths in these mid-dose monkeys to be related to sarilumab based on their sporadic occurrence, and the absence of similar findings in the high-dose groups.

Adult CD-1 mice were treated for 4 weeks with a murine surrogate antibody against IL-6Rα (REGN844) in an exploratory study. There was a dose-dependent increase in absolute and relative adrenal gland weight in males at ≥50 mg/kg/week SC and 25 mg/kg/week IV; however, there were no macroscopic or microscopic correlates to the increase in adrenal gland weight. Therefore, the effects on adrenal gland weight were not considered adverse.

The potential effects of IL-6 inhibition on the reproductive system were studied by using REGN844 in CD-1 mice to evaluate fertility and early embryonic development, and by using the clinical candidate (sarilumab) in cynomolgus monkeys to evaluate embryo-fetal and pre-/postnatal development. Inhibition of IL-6 receptor did not impair fertility in male and female mice using REGN844 (NOAEL for fertility and early embryonic effects of 200 mg/kg/week). Relative to controls, sarilumab did not produce teratogenicity or increase abortions/stillbirths in pregnant monkeys up to 50 mg/kg/week when administered from gestation day (GD) 20 to natural birth (approximately GD 165). No effects were noted in the infant monkeys from the treated females when evaluated up to 1 month after birth. Lastly, in a 9 week pivotal study, juvenile mice administered REGN844 SC starting on Post-Natal Day (PND) 14, the NOAEL was considered to be 200 mg/kg/week, the highest dose evaluated.

In an immunohistochemistry tissue-cross reactivity study with biotinylated sarilumab, the staining pattern of biotinylated-sarilumab in human tissues was very similar to that noted in cynomologus monkey tissues. Specific staining was almost exclusively detected in the cytoplasm and/or cytoplasmic granules in human and monkey tissue elements. Membrane staining was not observed in any of the human tissues and cell surface staining was only observed in mammary gland epithelium tissue from one monkey. The potential toxicological consequences of cytoplasmic and cytoplasmic granular staining are considered low as the accessibility of cytoplasmic sites is questionable in intact cells in vivo. Since no AEs following sarilumab dosing in monkeys were observed, the cell surface staining of mammary gland tissue from one monkey is not considered toxicologically relevant.

The key non-clinical findings are presented in the following table.

Table 9 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • Key issues identified from acute or repeat-dose toxicity studies - **Reversible decreases in circulating neutrophil counts in monkeys**. This effect is non-adverse and related to the mechanism of action of sarilumab. No effects on bone marrow in the repeat-dose toxicity studies.	The finding is relevant to human use since the occurrence of decreased neutrophils has been observed with other IL-6 inhibitors and is a known pharmacologic effect. Therefore, neutropenia is considered as an important identified risk. (See Part II SVII)
- **Slightly lower primary and secondary IgG response**. In adult monkeys administered sarilumab after an antigen challenge (keyhole lympet hemocyanin). This effect is non-adverse and related to the mechanism of action of sarilumab. It should be noted that the IgG responses at all doses, although lower than controls, were still robust. Slightly lower IgG responses in the dosing and early recovery periods in juvenile male mice administered REGN844 after an antigen challenge with keyhole lympet hemocyanin. It should be noted that the IgG responses, although lower than controls, were still robust. This effect is reversible, non-adverse, and related to the mechanism of action of IL-6 inhibition.	This finding is relevant to human use due to potential concern on patient's ability to generate a sufficient humoral immune response to vaccines. Studies that specifically assess the effects of RA therapy on humoral immune response have been conducted with other biologic drugs. (57)(58)(59) Most relevant to sarilumab are the vaccine studies conducted with TCZ, a drug that targets the same cytokine receptor as sarilumab. A randomized controlled trial of TCZ conducted in patients with moderate to severe RA evaluated humoral immune responses to T cell dependent and T cell independent antigens, Tetanus Toxoid Vaccine (TTV) and 23 valent pneumococcal polysaccharide vaccine, respectively. In this study, patients were randomized to receive TCZ 8 mg/kg IV every 4 weeks plus MTX or MTX alone, and then vaccinated 3 weeks later with Pneumococcal Polysaccharides Vaccine (PPV23) (Pneumovax; Merck and Co) and TTV (Adsorbed; Aventis Pasteur). Five weeks after vaccination, at study week 8, 60.0% of TCZ plus MTX patients and 70.8% of patients receiving MTX alone responded to ≥6 of 12 PPV23 serotypes, with insufficient evidence for any difference in treatments (10.8% [95% CI: 33.7-12.0]). At the same time point, 42.0% of TCZ plus MTX patients and 39.1% of patients receiving MTX alone responded to TTV. (60) Another study conducted in RA patients evaluated administration of inactivated trivalent influenza vaccine (Biken HA, Mistubishi Tanabe Pharm Corporation) to RA patients receiving TCZ 8 mg/kg (for at least 4 weeks), and/or MTX (for at least 12 weeks). This study demonstrated that geometric mean titers increased significantly for all strains post-vaccination without evidence of a decreased effect due to TCZ. (61) The available data from TCZ support that protection is still achieved in the majority of vaccinated patients after short-term TCZ use. Given the similar mechanism of action between sarilumab and TCZ, no difference is expected in the immune response to vaccination in humans.
- **Gastrointestinal tract in monkeys**. Two monkeys in repeat-dose IV studies with sarilumab ≥13 weeks in duration died or were euthanized because of either an infection and/or	Spontaneous GI disease is a relatively common finding in macaques where the large intestine is more commonly affected. (62)(63) Although these infections in the GI tract were considered spontaneous, break through infections

Key Safety Findings	Relevance to human usage
inflammation in the large intestine. The mortalities were attributed to amoebiasis (female) and typhlocolitis (male). One female monkey on 10 mg/kg/week sarilumab in the 3-month IV study was found dead approximately 5 weeks into the recovery period (Day 123). There were no notable changes in clinical pathology parameters in week 13 (including neutrophil counts which were within control range for that week) and no body weight changes up to week 17 as well as no notable clinical signs until just before death. The CRP was elevated throughout the study (including the highest CRP concentration during pretest) suggestive of a pre-existing inflammatory process that was possibly secondary to a pre-existing infection. Microscopic lesions including multifocal, mucosal ulceration within the large intestine, associated with inflammation, bacterial overgrowth and numerous amoebae were noted. Small and large intestinal mucosal proliferation was noted as well, characterized by marked elongation of crypts. One male monkey on 15 mg/kg/week sarilumab in 6-month IV study was humanely euthanized in week 19 (Day 133) of the dosing period. Decreases in body weight were noted starting in Week 7, diarrhea was noted starting in week 12 and other clinical signs (eg, thin, inappetence, and/or hunched posture) were noted starting in week 16. However, there were no notable changes in clinical pathology parameters during the study in this monkey. Microscopic findings of ulceration, hemorrhage, mucosal abscessation, and generalized inflammation of the large intestine, consistent with the reported antemortem clinical signs of diarrhea, poor food consumption, and body weight loss were noted. Although the relationships of the animal deaths to sarilumab are listed as unclear in the study report, the death in these monkeys were not considered related to sarilumab based on the weight of evidence of the data in the study including immune endpoints and the lack of deaths in the high-dose group where exposures to sarilumab were higher.	unrelated to sarilumab treatment, infections, including serious infection (SI), may occur with sarilumab based on its mechanism of action. Serious infection is considered as an important identified risk. (See Part II SVII)
- **Injection site (subcutis) in monkeys**. No macroscopic findings at the SC injection site related to sarilumab were noted. Microscopically, there were non-adverse minimal to moderate reversible inflammatory infiltrates at the SC injection sites at all dose-levels, including vehicle control to a lesser degree. These inflammatory	This finding is relevant to human use since injection site reactions have been associated with medications administered subcutaneously. Injection site reactions are listed as adverse reactions in SmPC.

Key Safety Findings	Relevance to human usage
infiltrates identified at SC injection sites were considered representative of a localized reaction to the SC injection of concentrated human proteinaceous material.	
• Reproductive/developmental toxicity studies - **Fertility**: There were no effects on male and female reproductive indices (mating, fertility, and pregnancy) in mice administered REGN844. In a combined male/female fertility study, REGN844 was administered at doses up to 200 mg/kg/week SC in adult mice. There were no REGN844-related effects on organ weights or macroscopic findings. There were no REGN844-related microscopic observations in the testes, epididymides, ovary, or vagina. In females, sarilumab-related microscopic findings were observed in the uterus in which there was at least one implantation site with degeneration observed microscopically in the uterus of 1/24 control mouse, 2/24 mice at 50 mg/kg/week and 6/24 mice at 200 mg/kg/week. However, in the absence of any test article-related effects on other male and female reproductive indices (mating, fertility, and pregnancy), the toxicological significance of the increased incidence of implantation site degeneration at 200 mg/kg/week observed microscopically is not known.	Based on these non-clinical studies, the risks regarding human reproductive parameters and teratogenicity are considered to be low. There is limited clinical experience with the use of sarilumab in pregnant women. In addition, sarilumab should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Embryo-fetal and Developmental toxicology**: In an ePPND toxicology study in cynomolgus monkeys, sarilumab was administered intravenously at doses up to 50 mg/kg/week IV to pregnant female monkeys from GD20 through natural delivery (approximately GD165). Maternal toxicity endpoints both before and after delivery were assessed. Monitoring of offspring for approximately 28 days after delivery was performed. Administration of sarilumab to pregnant monkeys did not cause any embryo-fetal effects or effects on gestation length. The incidences of these embryo-fetal loss and stillbirths in the sarilumab groups were similar to those of the control group and the testing facility's historical incidence data. It was concluded that sarilumab did not affect either maintenance of pregnancy or natural delivery. In addition, no sarilumab-related effects on the neonates were noted up to one month after birth in clinical observations, body weight, or in parameters of functional or morphological development including skeletal findings, coagulation, serum chemistry,	No sarilumab related effects on monkey neonates were noted. However, since sarilumab was detected in the serum of neonates up to one month and based on the safety observations of sarilumab use in humans and adult monkeys, sarilumab possesses the potential to cause immunosuppressive effects in the infants of mothers treated with sarilumab during their pregnancy. Sarilumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab.

Key Safety Findings	Relevance to human usage
immunophenotyping of peripheral blood lymphocytes, organ weights, macroscopic observations, and microscopic evaluations. These neonates were exposed to sarilumab through the time of necropsy 30 days after birth at all doses evaluated. In samples taken from neonates, sarilumab mean serum concentrations were dependent on the dose received by their respective mother; mean sarilumab concentrations in the offspring increased in a dose proportional manner.	
• Genotoxicity: None	-
• Carcinogenicity A carcinogenicity risk assessment was conducted. Based on the weight of evidence from the animal toxicology studies and tumor pharmacology studies with sarilumab and the literature assessment of the IL-6/IL-6Rα pathway, the data support the conclusion that chronic administration of sarilumab does not pose an increased risk of cancer. After review of the Sponsor's risk assessment, the carcinogenic risk was considered sufficiently characterized by the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA). No specific non-clinical studies were requested to assess the carcinogenic potential of sarilumab.	In the clinical development program, there was no increase in the rate of malignancy in patients on sarilumab compared to the general population or patients with RA. The rates and types of malignancies observed were not unexpected given the demographics of the population. However, treatment with immunosuppressants may result in an increased risk of malignancies and, therefore, malignancies is being considered an important potential risk. (See Part II SVII)
Safety pharmacology • Cardiovascular system, nervous system and respiratory system: Safety pharmacology endpoints for the CNS, CV system, or respiratory system were evaluated as part of the toxicology studies conducted in cynomolgus monkeys, in which sarilumab was administered at doses up to 100 mg/kg/week SC for 13 weeks, or up to 50 mg/kg/week IV for 6 months. No sarilumab-related effects were observed in these organ systems in these repeat-dose toxicity studies.	There were no effects in the non-clinical studies on CNS, CV, or respiratory safety pharmacology endpoints noted with sarilumab. The value of nonclinical safety pharmacology endpoints is limited given the current stage of Life Cycle Management and available human data/experience with sarilumab.
Other toxicity-related information or data • Drug Abuse and Liability Assessment: Based on a review of non-clinical findings, there was no evidence of CNS activity or signs suggestive of drug abuse. • Safety findings in special populations - Juvenile toxicity: To support the investigation of sarilumab in patients less than two years of age, juvenile toxicity studies with the murine surrogate REGN844 in mice were performed. In juvenile mice, no adverse effects were observed in a 4-week exploratory SC study up to 200 mg/kg/week when dosing was initiated at PND 14. In a 9-week pivotal study, juvenile mice were administered REGN844 SC up to 200 mg/kg/week starting on PND 14. There was no evidence of an increase in infections or	No relevant literature and clinical data suggested a potential drug abuse for sarilumab. As noted, these findings were considered associated with the injection of proteinaceous material and/or self-trauma secondary to minor inflammation at the injection site as well as a local response to inflammation at the injection site (lymph node and bone marrow) rather than evidence of systemic effects of REGN844. The microscopic findings were reversed at the end of the 13-week recovery period. The NOAEL was considered to be 200 mg/kg/week. This is consistent with literature in which juvenile mice treated with a monoclonal antibody to block the IL-6 receptor did

Key Safety Findings	Relevance to human usage
any effects on body weight and food consumption throughout the study. There were no microscopic findings in the male and female sex organs at approximately PND 78-79 when the mice were sexually mature at the end of the dosing phase. There were slightly lower titer responses in IgG in male mice at all doses after antigen challenge with KLH in the dosing and early recovery periods, increased serum IgG concentrations at 60 and 200 mg/kg/week in males and females, and slightly higher Immunoglobulin M (IgM) serum concentration in females at 200 mg/kg/week. These changes in IgG responses and IgG concentrations were reversed at the end of the 13-week recovery period. It should be noted that the IgG titer responses to KLH in juvenile mice, although lower than controls, were still robust. It should also be noted that the serum detection assay used for serum IgG concentrations was not specific to endogenous IgG and would also detect REGN844, a murine Immunoglobulin G Gamma-2A (IgG2a); therefore, the increase in serum IgG was considered a combination of both endogenous IgG and REGN844. There were microscopic findings at the injection site (minimal to moderate inflammation) and axillary lymph nodes (slight to minimal lymphoid hyperplasia) at all doses and femoral/sternal bone marrow (minimally increased hemopoiesis) at 60 and 200 mg/kg/week. These findings were considered associated with injection of proteinaceous material and/or self-trauma secondary to minor inflammation at the injection site as well as a local response to inflammation at the injection site rather than evidence of systemic effects of REGN844. These were reversed at the end of the 13-week recovery period. The NOAEL was considered to be 200 mg/kg/day.	not demonstrate any adverse findings that impacted their development. (64)(65)

CI: Confidence Interval; CNS: Central Nervous System: CRP: C-Reactive Protein; CV: Cardiovascular; EMA: European Medicines Agency; ePPND: Enhanced Pre-/Postnatal Development; FDA: Food and Drug Administration; GD: Gestational Day; GI: Gastrointestinal; IgG: Immunoglobulin G; IgG2a: Immunoglobulin G Gamma-2A Chain C Region, A Allele; IgM: Immunoglobulin M; IL-6: Interleukin-6; IL-6Rα: Alpha subunit of Interleukin-6 Receptor; IV: Intravenous; KLH: Keyhole Limpet Hemocyanin; MTX: Methotrexate; NOAEL: No-Observed Adverse Effect Level; PND: Postnatal Day; PPV: Pneumococcal Polysaccharides Vaccine; RA: Rheumatoid Arthritis; SC: Subcutaneous; SI: Serious Infection; SmPC: Summary of Product Characteristics; TCZ: Tocilizumab; TTV: Tetanus Toxoid Vaccine; US FDA: United States Food and Drug Administration.

No additional non-clinical data have been collected on the use of sarilumab in any special populations.

Cumulative exposure in patients with RA

In the Phase 1 studies, 225 RA patients and 53 healthy subjects received sarilumab.

In the Phase 2 and 3 studies conducted in patients with RA, ankylosing spondylitis (AS), and non-infectious uveitis (NIU), 3933 patients received sarilumab (3595 in RA patients from 11 studies, 289 patients with AS and 49 patients with NIU).

Eight international Phase 2 and 3 RA studies are included in the integrated safety database and all had final database locks prior to March 2021. In this integrated safety database, a total of 3358 patients received at least 1 dose of sarilumab ± DMARD in the Phase 2 and 3 global RA clinical development program, providing 11 728.5 PYs) of cumulative exposure (Table 10). This includes 471 patients treated with sarilumab as monotherapy for a total exposure of 1721.0 PY (Table 12). Based on exposure at any time during sarilumab treatment, a total of 2617 patients received at least one dose of 200 mg q2w for a total of 8622.1 PY of exposure and 1727 patients received at least one dose of 150 mg q2w for a total of 2827.7 PY of exposure (Table 10).

Table 10 - Duration of exposure with sarilumab with or without DMARD in rheumatoid arthritis

	Sarilumab 150 mg q2w[a]	**Sarilumab 200 mg q2w**[b]	**All doses (N = 3358)**[c]
	Any exposure (N = 1727)[d]	**Any exposure (N = 2617)**[d]	
Overall			
Number of patients	1727	2617	3358
Total exposure (PY)	2827.7	8622.1	11 728.5
Number of patients with duration of treatment by category (n [%])			
≥12 weeks	1554 (90.0%)	2358 (90.1%)	3067 (91.3%)
≥24 weeks	1201 (69.5%)	2122 (81.1%)	2743 (81.7%)
≥48 weeks	840 (48.6%)	1839 (70.3%)	2357 (70.2%)
≥96 weeks	396 (22.9%)	1536 (58.7%)	1927 (57.4%)
≥144 weeks	341 (19.7%)	1347 (51.5%)	1743 (51.9%)
≥192 weeks	296 (17.1%)	1200 (45.9%)	1604 (47.8%)
≥240 weeks	235 (13.6%)	991 (37.9%)	1397 (41.6%)
≥264 weeks	195 (11.3%)	855 (32.7%)	1187 (35.3%)
≥288 weeks	157 (9.1%)	641 (24.5%)	974 (29.0%)
≥312 weeks	136 (7.9%)	489 (18.7%)	788 (23.5%)
≥336 weeks	107 (6.2%)	394 (15.1%)	628 (18.7%)
≥360 weeks	80 (4.6%)	308 (11.8%)	503 (15.0%)
≥384 weeks	49 (2.8%)	239 (9.1%)	414 (12.3%)
≥408 weeks	35 (2.0%)	162 (6.2%)	337 (10.0%)
≥432 weeks	21 (1.2%)	101 (3.9%)	241 (7.2%)

	Sarilumab 150 mg q2w[a]	Sarilumab 200 mg q2w[b]	All doses (N = 3358)[c]
	Any exposure (N = 1727)[d]	Any exposure (N = 2617)[d]	
≥456 weeks	7 (0.4%)	32 (1.2%)	114 (3.4%)
≥480 weeks	5 (0.3%)	1 (<0.1%)	62 (1.8%)
≥504 weeks	2 (0.1%)	0	27 (0.8%)

This table includes all patients who received sarilumab from the phase 2 and 3 studies that have been included in the integrated safety summary (ISS) (EFC11072, EFC10832, SFY13370, EFC11574, EFC13752, EFC14092, MSC12665, LTS11210).

a Includes both 150 mg q2w plus DMARD and 150 mg q2w monotherapy

b Includes both 200 mg q2w plus DMARD and 200 mg q2w monotherapy

c Includes all sarilumab doses: 100 mg once every week (qw), 100 mg q2w, 150 mg qw, 150 mg q2w, and 200 mg q2w

d Exposure at any time

Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/cdc_exposure_all_s_t.sas OUT=REPORT/OUTPUT/cdc_exposure_all_s_t_x.rtf (10JUN2021 - 17:48)

DMARD: Disease Modifying Anti-Rheumatic Drug; ISS: Integrated Safety Summary; N: Total Number of Patient; n: Number of Patient; PY: Patient-Year; qw: Once Every Week; q2w: Once Every Two Weeks.

The exposure in the sarilumab plus DMARD population and sarilumab monotherapy population is summarized in Table 11 and Table 12 respectively. The sarilumab plus DMARD safety population consists of all patients who received any dose of sarilumab in Studies EFC11072 Part A, EFC11072 Part B, EFC10832, SFY13370, EFC11574 (main-study and sub-study), MSC12665 (including both the initial study and extension safety periods) and LTS11210. The monotherapy population consists of all patients who received any dose of sarilumab in Studies EFC13752, EFC14092, and LTS11210 (includes only patients receiving sarilumab as monotherapy who entered from EFC13752 study). It was evaluated separately to allow for an assessment of the safety of sarilumab when administered without concomitant DMARDs. This population however is assessed for consistency with the concomitant DMARD population.

Table 11 - Duration of exposure - Sarilumab plus DMARD Population

	Sarilumab plus DMARD
	Any Dose (N = 2887)
Cumulative exposure to treatment (PY)	10 007.6
Duration of study treatment (days)	
Number	2887
Mean (standard deviation [SD])	1266.1 (1101.4)
Median	952.0
Min:Max	7:3701
Number of patients with duration of study treatment by category (n [%])	
≥1 day	2887 (100%)
>12 weeks	2570 (89.0%)
>24 weeks	2259 (78.2%)
>48 weeks	1960 (67.9%)
>96 weeks	1562 (54.1%)
>144 weeks	1415 (49.0%)
>192 weeks	1298 (45.0%)

	Sarilumab plus DMARD
	Any Dose (N = 2887)
>240 weeks	1171 (40.6%)
>264 weeks	1010 (35.0%)
>288 weeks	874 (30.3%)
>312 weeks	755 (26.2%)
>336 weeks	614 (21.3%)
>360 weeks	489 (16.9%)
>384 weeks	407 (14.1%)
>408 weeks	332 (11.5%)
>432 weeks	240 (8.3%)
>456 weeks	114 (3.9%)
>480 weeks	62 (2.1%)
>504 weeks	27 (0.9%)

Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/cdc_exposure_s_t_p2.sas OUT=REPORT/OUTPUT/cdc_exposure_s_t_p2_x.rtf (10JUN2021 - 17:50)
DMARD: Disease Modifying Anti-Rheumatic Drug; Max: Maximum; Min: Minimum; N: Total Number of Patient; n: Number of Patient; PY: Patient-Year; SD: Standard Deviation.

Table 12 - Duration of exposure - Sarilumab monotherapy Population

	Sarilumab
	Any Dose (N = 471)
Cumulative exposure to treatment (PY)	1721.0
Duration of study treatment (days)	
Number	471
Mean (SD)	1334.6 (705.1)
Median	1596.0
Min:Max	14:2269
Number of patients with duration of study treatment by category (n [%])	
≥1 day	471 (100%)
>12 weeks	433 (91.9%)
>24 weeks	416 (88.3%)
>36 weeks	403 (85.6%)
>48 weeks	391 (83.0%)
>60 weeks	384 (81.5%)
>72 weeks	376 (79.8%)
>84 weeks	368 (78.1%)
>96 weeks	357 (75.8%)

	Sarilumab
	Any Dose (N = 471)
>120 weeks	337 (71.5%)
>144 weeks	326 (69.2%)
>168 weeks	319 (67.7%)
>192 weeks	292 (62.0%)
>216 weeks	248 (52.7%)
>240 weeks	222 (47.1%)
>264 weeks	145 (30.8%)
>288 weeks	49 (10.4%)
>312 weeks	15 (3.2%)
>324 weeks	2 (0.4%)

Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/cdc_exposure_s_t_p3.sas OUT=REPORT/OUTPUT/cdc_exposure_s_t_p3_x.rtf (10JUN2021 - 17:51)
Max: Maximum; Min: Minimum; N: Total Number of Patient; n: Number of Patient; PY: Patient-Year; SD: Standard Deviation.

The exposure by dose at any time during treatment for the sarilumab plus DMARD population and sarilumab monotherapy population is summarized in Table 13 and Table 14 respectively.

Table 13 - Exposure by dose - Sarilumab plus DMARD long term safety population

	All Sarilumab plus DMARD (Any exposure N = 2887)				
	150 mg q2w (N = 1615)	**200 mg q2w (N = 2157)**	**100 mg q2w (N = 80)**	**100 mg qw (N = 79)**	**150 mg qw (N = 328)**
Cumulative exposure to treatment (PY)	2661.6	7117.4	19.4	17.0	242.2
Duration of study treatment (Day)					
Number	1615	2157	80	79	328
Mean (SD)	590.6 (777.8)	1205.2 (1023.2)	88.5 (26.8)	78.4 (33.1)	269.7 (148.2)
Median	281.0	980.0	91.0	91.0	255.5
Min:Max	13:3555	7:3363	14:173	7:177	14:610
Number of patients with duration of study treatment by category (n [%])					
≥1 day	1615 (100%)	2157 (100%)	80 (100%)	79 (100%)	328 (100%)
>12 weeks	1407 (87.1%)	1846 (85.6%)	61 (76.3%)	49 (62.0%)	274 (83.5%)
>24 weeks	1002 (62. %)	1700 (78.8%)	1 (1.3%)	1 (1.3%)	224 (68.3%)
>48 weeks	785 (48.6%)	1467 (68.0%)	0	0	105 (32.0%)
>96 weeks	351 (21.7%)	1210 (56.1%)	0	0	0
>144 weeks	302 (18.7%)	1062 (49.2%)	0	0	0

	All Sarilumab plus DMARD (Any exposure N = 2887)				
	150 mg q2w (N = 1615)	200 mg q2w (N = 2157)	100 mg q2w (N = 80)	100 mg qw (N = 79)	150 mg qw (N = 328)
>192 weeks	265 (16.4%)	935 (43.3%)	0	0	0
>240 weeks	219 (13.6%)	806 (37.4%)	0	0	0
>264 weeks	183 (11.3%)	701 (32.5%)	0	0	0
>288 weeks	152 (9.4%)	584 (27.1%)	0	0	0
>312 weeks	135 (7.1%)	470 (21.8%)	0	0	0
>336 weeks	104 (6.4%)	386 (17.9%)	0	0	0
>360 weeks	77 (4.8%)	297 (13.8%)	0	0	0
>384 weeks	47 (2.9%)	225 (10.4%)	0	0	0
>408 weeks	35 (2.2%)	153 (7.1%)	0	0	0
>432 weeks	18 (1.1%)	97 (4.5%)	0	0	0
>456 weeks	7 (0.4%)	32 (1.5%)	0	0	0
>480 weeks	5 (0.3%)	1 (<0.1%)	0	0	0
>504 weeks	2 (0.1%)	0	0	0	0

Note: Patients are counted under each dose based on the treatment actually received; for patients who received different doses, they are counted multiple times under each corresponding dose.
Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/cdc_exposure_dose_s_t_p2.sas OUT=REPORT/OUTPUT/cdc_exposure_dose_s_t_p2_x.rtf (10JUN2021 - 17:48)
DMARD: Disease Modifying Anti-Rheumatic Drug; Max: Maximum; Min: Minimum; N: Total Number of Patient; n: Number of Patient; PY: Patient-Year; qw: Once Every Week; q2w: Once Every Two Weeks; SD: Standard Deviation.

Table 14 - Exposure by dose - Sarilumab monotherapy population

	All Sarilumab (Any exposure N = 471)	
	150 mg q2w (N = 112)	200 mg q2w (N = 460)
Cumulative exposure to treatment (PY)	216.1	1504.7
Duration of study treatment (Day)		
Number	112	460
Mean (SD)	704.7 (701.1)	1194.8 (721.7)
Median	175.0	1428.0
Min:Max	14:2169	14:2269
Number of patients with duration of study treatment by category (n [%])		
≥1 day	112 (100%)	460 (100%)
>12 weeks	103 (92.0%)	419 (91.1%)
>24 weeks	72 (64.3%)	405 (88.0%)
>36 weeks	51 (45.5%)	378 (82.2%)
>48 weeks	51 (45.5%)	360 (78.3%)
>60 weeks	49 (43.8%)	344 (74.8%)

	All Sarilumab (Any exposure N = 471)	
	150 mg q2w (N = 112)	200 mg q2w (N = 460)
>72 weeks	48 (42.9%)	331 (72.0%)
>84 weeks	46 (41.1%)	321 (69.8%)
>96 weeks	45 (40.2%)	313 (68.0%)
>120 weeks	42 (37.5%)	293 (63.7%)
>144 weeks	38 (33.9%)	282 (61.3%)
>168 weeks	31 (27.7%)	276 (60.0%)
>192 weeks	30 (26.8%)	249 (54.1%)
>216 weeks	21 (18.8%)	208 (45.2%)
>240 weeks	15 (13.4%)	183 (39.8%)
>264 weeks	10 (8.9%)	107 (23.3%)
>288 weeks	5 (4.5%)	20 (4.3%)
>312 weeks	0	3 (0.7%)
>324 weeks	0	1 (0.2%)

Note: Patients are counted under each dose based on the treatment actually received; for patients who received different doses, they are counted multiple times under each corresponding dose.
Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/cdc_exposure_dose_s_t_p3.sas OUT=REPORT/OUTPUT/cdc_exposure_dose_s_t_p3_x.rtf (10JUN2021 - 17:49)
Max: Maximum; Min: Minimum; N: Total Number of Patient; n: Number of Patient; PY: Patient-Year; q2w: Once Every Two Weeks; SD: Standard Deviation.

The demographic and baseline patient characteristics of the sarilumab plus DMARD population and sarilumab monotherapy population are shown in Table 15 and Table 16 respectively.

In the sarilumab plus DMARD and sarilumab monotherapy populations, the majority of patients were <65 years, female and Caucasian.

Patients with severe renal impairment were excluded from the study. The majority of patients had normal renal function.

Table 15 - Exposure by age, age/gender, race, ethnicity, renal impairment - Sarilumab plus DMARD population

	Any dose (N = 2887)
Age	
<65 years	
N	2464
Patient-years	8861.5
≥65 and <75 years	
N	378

	Any dose (N = 2887)
Patient-years	1063.0
≥75 and <85 years	
N	42
Patient-years	79.8
≥85 years	
N	3
Patient-years	3.3
Gender	
Male	
N	541
Patient-years	1878.0
Female	
N	2346
Patient-years	8129.6
Age by gender	
Age <65 years and Female	
N	2014
Patient-years	7210.1
Age ≥65 and <75 years and Female	
N	299
Patient-years	854.2
Age ≥75 and <85 years and Female	
N	32
Patient-years	63.0
Age ≥85 years and Female	
N	1
Patient-years	2.3
Age <65 years and Male	
N	450
Patient-years	1651.4
Age ≥65 and <75 years and Male	
N	79
Patient-years	208.8

	Any dose (N = 2887)
Age ≥75 and <85 years and Male	
N	10
Patient-years	16.8
Age ≥85 years and Male	
N	2
Patient-years	1.0
Race	
Caucasian/White	
N	2463
Patient-years	8659.3
Black	
N	75
Patient-years	235.7
Asian/Oriental	
N	127
Patient-years	376.3
Other	
N	222
Patient-years	736.3
Ethnicity	
Hispanic	
N	996
Patient-years	3797.5
Non-Hispanic	
N	1891
Patient-years	6210.1
Renal impairment (creatinine clearance at baseline)[a]	
<30 mL/min (severe renal impairment)	
N	1
Patient-years	0.5
≥30 - <60 mL/min (moderate renal impairment)	
N	121
Patient-years	324.3

	Any dose (N = 2887)
≥60 - <90 mL/min (mild renal impairment)	
N	685
Patient-years	2314.3
≥90 mL/min (normal)	
N	1990
Patient-years	7149.7

Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/cdc_exposure_subgroup_s_t_p2.sas OUT=REPORT/OUTPUT/cdc_exposure_subgroup_s_t_p2_x.rtf (10JUN2021 - 17:52)

a Not all patients had renal measurement at baseline.

DMARD: Disease Modifying Anti-Rheumatic Drug; N: Total Number of Patient.

Table 16 - Exposure by age, age/gender, race, ethnicity, renal impairment - Sarilumab monotherapy population

	Any Dose (N = 471)
Age	
<65 years	
N	387
Patient-years	1441.3
≥65 and <75 years	
N	78
Patient-years	251
≥75 and <85 years	
N	6
Patient-years	28.6
≥85 years	
N	0
Patient-years	0
Gender	
Male	
N	82
Patient-years	293.4
Female	
N	389
Patient-years	1427.6

	Any Dose (N = 471)
Age by gender	
Age <65 years and Female	
N	320
Patient-years	1195.1
Age ≥65 and <75 years and Female	
N	63
Patient-years	203.8
Age ≥75 and <85 years and Female	
N	6
Patient-years	28.6
Age ≥85 years and Female	
N	0
Patient-years	0
Age <65 years and Male	
N	67
Patient-years	246.1
Age ≥65 and <75 years and Male	
N	15
Patient-years	47.2
Age ≥75 and <85 years and Male	
N	0
Patient-years	0
Age ≥85 years and Male	
N	0
Patient-years	0
Race	
Caucasian/White	
N	437
Patient-years	1608.30
Black	
N	3
Patient-years	4.2
Asian/Oriental	
N	12
Patient-years	35.5

	Any Dose (N = 471)
Other	
N	19
Patient-years	73.04
Ethnicity	
Hispanic	
N	96
Patient-years	342.0
Non-Hispanic	
N	375
Patient-years	1378.9
Renal impairment (creatinine clearance at baseline)	
<30 mL/min (severe renal impairment)	
N	0
Patient-years	0
≥30 - <60 mL/min (moderate renal impairment)	
N	23
Patient-years	64.6
≥60 - <90 mL/min (mild renal impairment)	
N	139
Patient-years	548.7
≥90 mL/min (normal)	
N	309
Patient-years	1107.7

Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/cdc_exposure_subgroup_s_t_p3.sas OUT=REPORT/OUTPUT/cdc_exposure_subgroup_s_t_p3_x.rtf (10JUN2021 - 17:53)
N: Total Number of Patient.

Cumulative exposure in patients with Coronavirus Disease 2019 (COVID-19)

Sanofi Sponsored study:

In the Phase 3 study conducted in patients with COVID-19, a total of 416 patients were randomized and treated in EFC16844, where 332 patients have been exposed to sarilumab (Table 17).

Table 17 - Cumulative patient exposure in Phase 3 COVID-19 clinical study[a]

Treatment[b]	Number of Subjects
Sarilumab 200 mg IV	159

Treatment[b]	Number of Subjects
Sarilumab 400 mg IV	173
Placebo	84

a This is the number of exposed patients from unblinded study EFC16844 as of 12-Jan-2021; Data base lock (DBL) date: 24-Sep-2020.

b Patients are randomized to sarilumab 200 mg IV or sarilumab 400 mg IV or placebo IV in a ratio of 2:2:1.

Extracted from: PGM=PRODOPS/SAR153191/OVERALL/DSUR_JAN_2021/REPORT/PGM/dsur_cumexp_s_t.sas OUT=REPORT/OUTPUT/dsur_cumexp_covid_s_t_i.rtf (27JAN2021 - 19:54)

COVID-19: Coronavirus Disease-2019; DBL: Data Base Lock; IV: Intravenous.

Regeneron Sponsored study:

Study 6R88COV-2040 was a Phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in adults who were hospitalized with COVID-19 and who had evidence of pneumonia. There were 1456 patients exposed to sarilumab.

Table 18 - Cumulative patient exposure in Phase 2/3 COVID-19 clinical study

Randomized and Treated	Placebo	Sarilumab 200 mg IV	Sarilumab 400 mg IV	Sarilumab 800 mg IV
Phase 2	90	187	180	-
Phase 3 Cohort 1	294	489	582	-
Phase 3 Cohort 2	15	-	-	16
Phase 3 Cohort 3	6	-	-	2
Total	405	676	762	18

COVID-19: Coronavirus Disease-2019; IV: Intravenous.

Cumulative exposure in participants with PMR:

In the completed phase 3 EFC15160 study (SAPHYR) conducted in participants with PMR, there were 117 participants treated with study drug: 59 participants in the sarilumab 200 mg + 14-week taper group and 58 participants in the placebo + 52-week taper group. The cumulative exposure to treatment was 47.37 PYs for the sarilumab 200 mg + 14-week taper group and 45.36 PYs for the placebo + 52-week taper group (Table 19).

Table 19 - Extent of exposure to subcutaneous investigational medicinal product - Safety population EFC15160 study

	Placebo + 52-week taper (N=58)	Sarilumab 200 mg q2w + 14-week taper (N=59)	All (N=117)
Cumulative exposure to treatment (PYs)	45.36	47.37	92.73
Duration of study treatment (days)			
Number	58	59	117
Mean (SD)	285.6 (115.8)	293.3 (124.0)	289.5 (119.6)

	Placebo + 52-week taper (N=58)	Sarilumab 200 mg q2w + 14-week taper (N=59)	All (N=117)
Median	363.0	363.0	363.0
Min:Max	27:371	13:373	13:373
Duration of study treatment by category (n[%])			
>0 and ≤4 weeks	1 (1.7)	2 (3.4)	3 (2.6)
>4 and ≤8 weeks	5 (8.6)	6 (10.2)	11 (9.4)
>8 and ≤12 weeks	2 (3.4)	0	2 (1.7)
>12 and ≤16 weeks	1 (1.7)	3 (5.1)	4 (3.4)
>16 and ≤20 weeks	1 (1.7)	1 (1.7)	2 (1.7)
>20 and ≤24 weeks	3 (5.2)	2 (3.4)	5 (4.3)
>24 and ≤32 weeks	4 (6.9)	0	4 (3.4)
>32 and ≤40 weeks	2 (3.4)	1 (1.7)	3 (2.6)
>40 and <52 weeks	32 (55.2)	34 (57.6)	66 (56.4)
≥52 weeks	7 (12.1)	10 (16.9)	17 (14.5)
Number of patients with duration of study treatment by category (n[%])			
>0 week	58 (100)	59 (100)	117 (100)
>4 weeks	57 (98.3)	57 (96.6)	114 (97.4)
>8 weeks	52 (89.7)	51 (86.4)	103 (88.0)
>12 weeks	50 (86.2)	51 (86.4)	101 (86.3)
>16 weeks	49 (84.5)	48 (81.4)	97 (82.9)
>20 weeks	48 (82.8)	47 (79.7)	95 (81.2)
>24 weeks	45 (77.6)	45 (76.3)	90 (76.9)
>32 weeks	41 (70.7)	45 (76.3)	86 (73.5)
>40 weeks	39 (67.2)	44 (74.6)	83 (70.9)
≥52 weeks	7 (12.1)	10 (16.9)	17 (14.5)

Note: Patients are considered in the treatment group they actually received.
Duration is defined as last dose date - first dose date + 14 days, regardless of unplanned intermittent discontinuations.
Extracted from: PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/cdc_exposure_s_t.sas
OUT=REPORT/OUTPUT/cdc_exposure_s_t_x.rtf (27JUL2021 5:13).
Max: Maximum; Min: Minimum; N: Total Number of Patient; n: Number of Patient; PY: Patient-Year; q2w: Once Every Two Weeks; SD: Standard Deviation.

Exposure on sarilumab by age range, gender, and racial group is provided in Table 20 and Table 21.

Table 20 - Number of Participants Exposed on Sarilumab in EFC15160 study by Age and Sex

	Number of participants		Exposure in person-years	
Age Group	**Female**	**Male**	**Female**	**Male**

	Number of participants		Exposure in person-years	
≥50 - <65	11	5	8.70	3.67
≥65 - <75	25	8	20.02	7.34
≥75 - <85	8	1	6.19	0.46
≥85	1	0	0.99	0
Total	**45**	**14**	**35.90**	**11.47**

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/cdc_exposure_subgrp_age_s_t.sas
OUT=REPORT/OUTPUT/cdc_exposure_subgrp_age_s_t_i.rtf (21JUL2023 8:22).

Table 21 - Number of Participants Exposed on Sarilumab in EFC15160 study by Racial Group

Racial Group	Number of participants	Exposure in PYs
Caucasian	50	40.22
Black	0	0
Asian/Oriental	1	0.96
Unknown	0	0
Not Reported	8	6.20
Total	**59**	**47.37**

Race as "Not Reported": 8 patients from France as it is not permitted to collect race information in France.
PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/cdc_exposure_subgrp_race_s_t.sas
OUT=REPORT/OUTPUT/cdc_exposure_subgrp_race_s_t_i.rtf (21JUL2023 8:22).
PY: Patient-Year.

Cumulative exposure in participants with polyarticular juvenile idiopathic arthritis (pJIA)

There were 3 dose regimens tested in DRI13925 study, referred as Dose 1, 2 and 3, defined as follows (Table 22):

- Doses 1 and 2 targeting pharmacokinetic (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).

The recommended/selected dose of sarilumab for pJIA patients is Dose regimen 2.

Table 22 - Dose by body weight and dose regimen - Study DRI13925

Body weight	Dose Regimen 1	Dose Regimen 2	Dose Regimen 3
Group A ≥30 kg and ≤60 kg	2 mg/kg q2w	3 mg/kg q2w	2 mg/kg qw
Group B <30 kg and ≥10 kg	2.5 mg/kg q2w	4 mg/kg q2w	2.5 mg/kg qw

qw: Once Every Week; q2w: Once Every Two Week.

At the time of the cut-off date of 13 January 2023, in study DRI13925 conducted in pediatric participants aged 2 to 17 years old with pJIA, 101 participants have been exposed to sarilumab (administered as open-label treatment), and the cumulative treatment exposure was 214.4 PY.

There were 13 participants exposed to dose regimen 1 (19.0 participant-years) before dose adjustment to the selected dose 2, 73 participants exposed to dose regimen 2 from baseline (155.4 participants-years), and 15 participants exposed to dose regimen 3 (11.2 participant-years) before dose adjustment to the selected dose 2 (Table 23).

There were 9 participants in Dose 1 and 11 participants in dose 3 which had their dose adjusted to the selected dose 2. The cumulative exposure on the selected dose 2 after dose adjustment was 9.9 and 18.8 participant-years for participants who were on dose 1 and dose 3 before dose adjustment, respectively (Table 24).

Exposure by age range, gender, and race is provided in Table 25 and Table 26.

Table 23 - Exposure to investigational medicinal product during the entire treatment period – Safety population

	Dose Regimen Cohort											
	1			**2**			**3**			**Any Dose**		
Weight Group	**≥30 kg (N = 7)**	**<30 kg (N = 6)**	**All (N = 13)**	**≥30 kg (N = 42)**	**<30 kg (N = 31)**	**All (N = 73)**	**≥30 kg (N = 6)**	**<30 kg (N = 9)**	**All (N = 15)**	**≥30 kg (N = 55)**	**<30 kg (N = 46)**	**All (N = 101)**
Cumulative exposure to treatment (participant years)	10.6	8.5	19.0	90.8	64.6	155.4	7.6	3.7	11.2	121.3	93.0	214.4
Duration of study treatment (Day)												
Number	7	6	13	42	31	73	6	9	15	55	46	101
Mean (SD)	550.6 (365.8)	516.8 (222.8)	535.0 (296.5)	789.7 (307.8)	760.8 (389.5)	777.4 (342.6)	461.8 (70.2)	148.6 (133.4)	273.9 (192.8)	805.7 (331.0)	738.8 (430.4)	775.2 (379.0)
Median	757.0	589.5	595.0	673.0	1092.0	675.0	503.5	217.0	273.0	689.0	1091.0	1078.0
Min:Max	14:840	67:672	14:840	14:1112	14:1101	14:1112	336:504	7:343	7:504	14:1112	7:1101	7:1112
Duration of study treatment by category (n[%])												
>0 and <4 weeks	1 (14.3%)	0	1 (7.7%)	1 (2.4%)	2 (6.5%)	3 (4.1%)	0	3 (33.3%)	3 (20.0%)	2 (3.6%)	5 (10.9%)	7 (6.9%)
≥4 and <8 weeks	1 (14.3%)	0	1 (7.7%)	2 (4.8%)	0	2 (2.7%)	0	1 (11.1%)	1 (6.7%)	3 (5.5%)	1 (2.2%)	4 (4.0%)
≥8 and <12 weeks	0	1 (16.7%)	1 (7.7%)	0	0	0	0	0	0	0	1 (2.2%)	1 (1.0%)
≥12 weeks	5 (71.4%)	5 (83.3%)	10 (76.9%)	39 (92.9%)	29 (93.5%)	68 (93.2%)	6 (100%)	5 (55.6%)	11 (73.3%)	50 (90.9%)	39 (84.8%)	89 (88.1%)

	Dose Regimen Cohort											
	1			2			3			Any Dose		
Weight Group	≥30 kg (N = 7)	<30 kg (N = 6)	All (N = 13)	≥30 kg (N = 42)	<30 kg (N = 31)	All (N = 73)	≥30 kg (N = 6)	<30 kg (N = 9)	All (N = 15)	≥30 kg (N = 55)	<30 kg (N = 46)	All (N = 101)
Entire study, including extension												
<12 weeks	2 (28.6%)	1 (16.7%)	3 (23.1%)	3 (7.1%)	2 (6.5%)	5 (6.8%)	0	4 (44.4%)	4 (26.7%)	5 (9.1%)	7 (15.2%)	12 (11.9%)
≥12 and <24 weeks	0	0	0	0	2 (6.5%)	2 (2.7%)	0	0	0	0	2 (4.3%)	2 (2.0%)
≥24 and <36 weeks	0	0	0	0	0	0	0	3 (33.3%)	3 (20.0%)	0	0	0
≥36 and <48 weeks	0	0	0	0	0	0	0	1 (11.1%)	1 (6.7%)	0	0	0
≥48 and <52 weeks	0	0	0	0	1 (3.2%)	1 (1.4%)	1 (16.7%)	1 (11.1%)	2 (13.3%)	0	1 (2.2%)	1 (1.0%)
≥52 and <72 weeks	0	0	0	1 (2.4%)	3 (9.7%)	4 (5.5%)	2 (33.3%)	0	2 (13.3%)	1 (1.8%)	4 (8.7%)	5 (5.0%)
≥72 and <96 weeks	1 (14.3%)	4 (66.7%)	5 (38.5%)	9 (21.4%)	4 (12.9%)	13 (17.8%)	3 (50.0%)	0	3 (20.0%)	11 (20.0%)	4 (8.7%)	15 (14.9%)
≥96 and <120 weeks	2 (28.6%)	1 (16.7%)	3 (23.1%)	11 (26.2%)	2 (6.5%)	13 (17.8%)	0	0	0	11 (20.0%)	2 (4.3%)	13 (12.9%)
≥120 and <144 weeks	2 (28.6%)	0	2 (15.4%)	0	1 (3.2%)	1 (1.4%)	0	0	0	0	1 (2.2%)	1 (1.0%)
≥144 and <156 weeks	0	0	0	4 (9.5%)	0	4 (5.5%)	0	0	0	5 (9.1%)	3 (6.5%)	8 (7.9%)
≥156 weeks	0	0	0	14 (33.3%)	16 (51.6%)	30 (41.1%)	0	0	0	22 (40.0%)	22 (47.8%)	44 (43.6%)

	Dose Regimen Cohort											
	1			2			3			Any Dose		
Weight Group	≥30 kg (N = 7)	<30 kg (N = 6)	All (N = 13)	≥30 kg (N = 42)	<30 kg (N = 31)	All (N = 73)	≥30 kg (N = 6)	<30 kg (N = 9)	All (N = 15)	≥30 kg (N = 55)	<30 kg (N = 46)	All (N = 101)
Number of participants with duration of study treatment by category (n[%])												
≥1 day	7 (100%)	6 (100%)	13 (100%)	42 (100%)	31 (100%)	73 (100%)	6 (100%)	9 (100%)	15 (100%)	55 (100%)	46 (100%)	101 (100%)
≥4 weeks	6 (85.7%)	6 (100%)	12 (92.3%)	41 (97.6%)	29 (93.5%)	70 (95.9%)	6 (100%)	6 (66.7%)	12 (80.0%)	53 (96.4%)	41 (89.1%)	94 (93.1%)
≥8 weeks	5 (71.4%)	6 (100%)	11 (84.6%)	39 (92.9%)	29 (93.5%)	68 (93.2%)	6 (100%)	5 (55.6%)	11 (73.3%)	50 (90.9%)	40 (87.0%)	90 (89.1%)
≥12 weeks	5 (71.4%)	5 (83.3%)	10 (76.9%)	39 (92.9%)	29 (93.5%)	68 (93.2%)	6 (100%)	5 (55.6%)	11 (73.3%)	50 (90.9%)	39 (84.8%)	89 (88.1%)
≥24 weeks	5 (71.4%)	5 (83.3%)	10 (76.9%)	39 (92.9%)	27 (87.1%)	66 (90.4%)	6 (100%)	5 (55.6%)	11 (73.3%)	50 (90.9%)	37 (80.4%)	87 (86.1%)
≥36 weeks	5 (71.4%)	5 (83.3%)	10 (76.9%)	39 (92.9%)	27 (87.1%)	66 (90.4%)	6 (100%)	2 (22.2%)	8 (53.3%)	50 (90.9%)	37 (80.4%)	87 (86.1%)
≥48 weeks	5 (71.4%)	5 (83.3%)	10 (76.9%)	39 (92.9%)	27 (87.1%)	66 (90.4%)	6 (100%)	1 (11.1%)	7 (46.7%)	50 (90.9%)	37 (80.4%)	87 (86.1%)
≥52 weeks	5 (71.4%)	5 (83.3%)	10 (76.9%)	39 (92.9%)	26 (83.9%)	65 (89.0%)	5 (83.3%)	0	5 (33.3%)	50 (90.9%)	36 (78.3%)	86 (85.1%)
≥72 weeks	5 (71.4%)	5 (83.3%)	10 (76.9%)	38 (90.5%)	23 (74.2%)	61 (83.6%)	3 (50.0%)	0	3 (20.0%)	49 (89.1%)	32 (69.6%)	81 (80.2%)
≥96 weeks	4 (57.1%)	1 (16.7%)	5 (38.5%)	29 (69.0%)	19 (61.3%)	48 (65.8%)	0	0	0	38 (69.1%)	28 (60.9%)	66 (65.3%)
≥120 weeks	2 (28.6%)	0	2 (15.4%)	18 (42.9%)	17 (54.8%)	35 (47.9%)	0	0	0	27 (49.1%)	26 (56.5%)	53 (52.5%)

	Dose Regimen Cohort											
	1			2			3			Any Dose		
Weight Group	≥30 kg (N = 7)	<30 kg (N = 6)	All (N = 13)	≥30 kg (N = 42)	<30 kg (N = 31)	All (N = 73)	≥30 kg (N = 6)	<30 kg (N = 9)	All (N = 15)	≥30 kg (N = 55)	<30 kg (N = 46)	All (N = 101)
≥144 weeks	0	0	0	18 (42.9%)	16 (51.6%)	34 (46.6%)	0	0	0	27 (49.1%)	25 (54.3%)	52 (51.5%)
≥156 weeks	0	0	0	14 (33.3%)	16 (51.6%)	30 (41.1%)	0	0	0	22 (40.0%)	22 (47.8%)	44 (43.6%)

Note: Duration of sarilumab exposure is defined as: last dose date - first dose date + 14 days (+ 7 days for cohort 3). 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.
Note: Summaries on the non-selected doses (ie, Dose 1 and Dose 3) only include the data collected prior to the first dose adjustment to the selected dose; summaries under the "Any Dose" columns include all the sarilumab exposure regardless of the dose adjustment.
PGM=PRODOPS/SAR153191/DRI13925/CSR_1YEAR/REPORT/PGM/cdc_exposure_s_t.sas OUT=REPORT/OUTPUT/cdc_exposure_s_t_i.rtf (10MAR2023 - 6:57)
Max: Maximum; Min: Minimum; N: Total Number of Patient; n: Number of Patient; SD: Standard Deviation.

Table 24 - Exposure on the selected Dose 2 after dose adjustment - For participants who were on non-selected doses prior to dose selection

	On Dose regimen 1 before dose adjustment			On Dose regimen 3 before dose adjustment			Combined		
Weight Group	≥30 kg (N = 4)	<30 kg (N = 5)	All (N = 9)	≥30 kg (N = 6)	<30 kg (N = 5)	All (N = 11)	≥30 kg (N = 10)	<30 kg (N = 10)	All (N = 20)
Cumulative exposure to treatment (participant years)	3.2	6.7	9.9	9.2	9.7	18.8	12.4	16.3	28.7
Duration of study treatment (Day)									
Number	4	5	9	6	5	11	10	10	20
Mean (SD)	293.8 (48.2)	487.0 (38.0)	401.1 (109.4)	557.2 (177.2)	705.6 (340.4)	624.6 (260.9)	451.8 (191.6)	596.3 (255.8)	524.1 (232.1)
Median	293.5	504.0	419.0	588.0	868.0	590.0	462.0	504.5	504.5

	On Dose regimen 1 before dose adjustment			On Dose regimen 3 before dose adjustment			Combined		
Weight Group	**≥30 kg (N = 4)**	**<30 kg (N = 5)**	**All (N = 9)**	**≥30 kg (N = 6)**	**<30 kg (N = 5)**	**All (N = 11)**	**≥30 kg (N = 10)**	**<30 kg (N = 10)**	**All (N = 20)**
Min:Max	252:336	419:505	252:505	225:764	98:875	98:875	225:764	98:875	98:875
Duration of study treatment by category (n[%])									
>0 and <4 weeks	0	0	0	0	0	0	0	0	0
≥4 and <8 weeks	0	0	0	0	0	0	0	0	0
≥8 and <12 weeks	0	0	0	0	0	0	0	0	0
≥12 and <24 weeks	0	0	0	0	1 (20.0%)	1 (9.1%)	0	1 (10.0%)	1 (5.0%)
≥24 and <36 weeks	0	0	0	1 (16.7%)	0	1 (9.1%)	1 (10.0%)	0	1 (5.0%)
≥36 and <48 weeks	3 (75.0%)	0	3 (33.3%)	0	0	0	3 (30.0%)	0	3 (15.0%)
≥48 and <52 weeks	1 (25.0%)	0	1 (11.1%)	0	0	0	1 (10.0%)	0	1 (5.0%)
≥52 and <72 weeks	0	2 (40.0%)	2 (22.2%)	0	0	0	0	2 (20.0%)	2 (10.0%)
≥72 and <96 weeks	0	3 (60.0%)	3 (33.3%)	4 (66.7%)	0	4 (36.4%)	4 (40.0%)	3 (30.0%)	7 (35.0%)
≥96 and <120 weeks	0	0	0	1 (16.7%)	1 (20.0%)	2 (18.2%)	1 (10.0%)	1 (10.0%)	2 (10.0%)
≥120 weeks	0	0	0	0	3 (60.0%)	3 (27.3%)	0	3 (30.0%)	3 (15.0%)
Number of participants with duration of study treatment by category (n[%])									
≥1 day	4 (100%)	5 (100%)	9 (100%)	6 (100%)	5 (100%)	11 (100%)	10 (100%)	10 (100%)	20 (100%)
≥4 weeks	4 (100%)	5 (100%)	9 (100%)	6 (100%)	5 (100%)	11 (100%)	10 (100%)	10 (100%)	20 (100%)
≥8 weeks	4 (100%)	5 (100%)	9 (100%)	6 (100%)	5 (100%)	11 (100%)	10 (100%)	10 (100%)	20 (100%)
≥12 weeks	4 (100%)	5 (100%)	9 (100%)	6 (100%)	5 (100%)	11 (100%)	10 (100%)	10 (100%)	20 (100%)
≥24 weeks	4 (100%)	5 (100%)	9 (100%)	6 (100%)	4 (80.0%)	10 (90.9%)	10 (100%)	9 (90.0%)	19 (95.0%)

	On Dose regimen 1 before dose adjustment			On Dose regimen 3 before dose adjustment			Combined		
Weight Group	≥30 kg (N = 4)	<30 kg (N = 5)	All (N = 9)	≥30 kg (N = 6)	<30 kg (N = 5)	All (N = 11)	≥30 kg (N = 10)	<30 kg (N = 10)	All (N = 20)
≥36 weeks	4 (100%)	5 (100%)	9 (100%)	5 (83.3%)	4 (80.0%)	9 (81.8%)	9 (90.0%)	9 (90.0%)	18 (90.0%)
≥48 weeks	1 (25.0%)	5 (100%)	6 (66.7%)	5 (83.3%)	4 (80.0%)	9 (81.8%)	6 (60.0%)	9 (90.0%)	15 (75.0%)
≥52 weeks	0	5 (100%)	5 (55.6%)	5 (83.3%)	4 (80.0%)	9 (81.8%)	5 (50.0%)	9 (90.0%)	14 (70.0%)
≥72 weeks	0	3 (60.0%)	3 (33.3%)	5 (83.3%)	4 (80.0%)	9 (81.8%)	5 (50.0%)	7 (70.0%)	12 (60.0%)
≥96 weeks	0	0	0	1 (16.7%)	4 (80.0%)	5 (45.5%)	1 (10.0%)	4 (40.0%)	5 (25.0%)
≥120 weeks	0	0	0	0	3 (60.0%)	3 (27.3%)	0	3 (30.0%)	3 (15.0%)

Note: Duration of sarilumab exposure is defined as: last dose date - first dose date + 14 days (+ 7 days for cohort 3).
PGM=PRODOPS/SAR153191/DRI13925/CSR_1YEAR/REPORT/PGM/cdc_exposure_sl_s_t.sas OUT=REPORT/OUTPUT/cdc_exposure_sl_s_t_x.rtf (10MAR2023 - 6:58)
Max: Maximum; Min: Minimum; N: Total Number of Patient; n: Number of Patient; SD: Standard Deviation.

Table 25 - Number of Participants Exposed on Sarilumab in DRI13925 study by Age and Sex

	Number of participants		Exposure in person-years	
Age group	Female	Male	Female	Male
2-5 years	19	7	38.66	15.54
6-11 years	30	7	55.74	19.81
12-17 years	28	10	64.74	19.88
Total	**77**	**24**	**159.14**	**55.23**
Overall Total	**101**			

	Number of participants		Exposure in person-years	
Age group	**Female**	**Male**	**Female**	**Male**

PGM=PRODOPS/SAR153191/DRI13925/CSR_1YEAR/REPORT/PGM/cdc_exposure_subgrp_age_s_t.sas OUT=REPORT/OUTPUT/cdc_exposure_subgrp_age_s_t_i.rtf (04APR2023 - 8:35)

Table 26 - Number of Participants Exposed on Sarilumab in DRI13925 study by Racial Group

Racial Group	Number of participants	Exposure in patient-years
Caucasian	88	182.60
Black	0	0
Asian	1	2.99
Unknown	5	13.76
Not Reported	7	15.01
Total	**101**	**214.36**

Race as "Unknown": 4 patients were from Mexico and 1 patient was from Germany.
Race as "Not Reported": 4 patients were from France and 3 patient was from Mexico.
PGM=PRODOPS/SAR153191/DRI13925/CSR_1YEAR/REPORT/PGM/cdc_exposure_subgrp_race_s_t.sas OUT=REPORT/OUTPUT/cdc_exposure_subgrp_race_s_t_i.rtf (04APR2023 - 8:35)

RISK MANAGEMENT PLAN - PART II MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 27 - Important exclusion criteria in pivotal studies in the development program

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients with a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug	General measure for patient's safety.	No	The absence of data in this population does not constitute a safety concern. This is covered in contra-indications section of the SmPC.
Infections • Invasive Opportunistic Infection (OI's) • Fever or chronic, persistent, or recurring infections requiring active treatment within 4 weeks prior to screening • Recurrent or active Herpes Zoster • Untreated, incompletely treated, or suspected tuberculosis (TB)	These exclusion criteria were considered because immunosuppressive drugs, such as those used to treat RA and PMR, are associated with an increased risk of infection, including viral reactivation, OI's, and SI's.	No	The absence of data in this population does not constitute a safety concern. Active, severe infections" are covered in contraindications section of the SmPC. "Active infection, including localized infections" are covered in special warnings and precautions for use" section of the SmPC.
Autoimmune or inflammatory systemic or localized joint disease(s) other than the condition studied in respective clinical trials (for RA programme)	This exclusion criterion was considered for methodological reasons as these underlying conditions could have confounded the evaluation of the efficacy endpoints.	No	Product indicated for RA patients as per SmPC.
For pJIA program: • Diagnosis of JIA subtypes except polyarticular RF+ or RF- JIA or eoJIA.			This corresponds to target population.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Juvenile idiopathic arthritis or arthritis onset prior to age 16 (for RA programme)	This exclusion criterion was considered because the target population is adults.	No	Product indicated for adult patients as per SmPC. Additionally, a Pediatric Investigation Plan (PIP) has been approved for sarilumab. One clinical study (DRI13925; polyarticular-course juvenile idiopathic arthritis) in pediatric population has been completed (last participant last visit: 27-Dec-2023). One clinical study (DRI13926; systemic juvenile idiopathic arthritis) in pediatric indication is ongoing.
For pJIA program: • Aged <2 and >17 years old. • Body weight <10 kg or >60 kg for patients enrolled in portion 1 in 3 ascending dose selection cohorts, then body weight <10 kg for patients subsequently enrolled in portion 2 and 3 at the selected dose 2 regimen.	This exclusion criterion was considered because the target population is pediatric.	No	This corresponds to target population.
Severe active systemic RA, including but not limited to vasculitis, pulmonary fibrosis, and/or Felty's syndrome (for RA program).	This exclusion criterion was considered for methodological reasons as these severe conditions could have confounded the evaluation of the safety and efficacy endpoints.	No	Sarilumab is indicated in combination with DMARDs or as monotherapy for the treatment of moderately to severely active RA in adult patients who responded inadequately or were intolerant to DMARDs.
Interstitial lung disease	This exclusion criterion was considered for methodological reasons, to prevent biases on the efficacy/safety endpoints evaluation as interstitial lung disease is associated with significant morbidity and mortality and could result in increased occurrence of premature study discontinuations. In addition, patients with Interstitial Lung Disease (ILD) may be receiving other immunosuppressive therapies that would	No	Extensive clinical safety data did not show any safety signal in patients with underlying pulmonary disease.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	confound evaluation of safety/efficacy endpoints.		
Malignancy within the past 5 years other than adequately-treated carcinoma in-situ of the cervix, non-metastatic squamous cell or basal cell carcinoma of the skin	This exclusion criterion was considered for methodological reasons, to prevent biases on the efficacy/safety endpoints evaluation as recent or ongoing cancers could result in increased occurrence of premature study discontinuations. Patients with recent or ongoing cancers are also at greater risk of receiving anticancer intervention(s) which could interfere with their participation in a study with an investigational medicine product.	No	No safety signal related to cancers emerged from the extensive clinical safety data. Statements mentioning that the impact of treatment with sarilumab is not known but treatment with immunosuppressants may result in an increased risk of malignancies is included in "Special warnings and precautions for use" section of SmPC.
Stage III or IV cardiac failure according to the New York Heart Association classification	This exclusion criterion was considered for methodological reasons, to prevent biases on the efficacy/safety endpoints evaluation as Stage III or IV cardiac failure could result in increased occurrence of premature study discontinuations.	No	Extensive clinical safety data did not show any safety signal in patients with less severe underlying cardiac failure (ie, Stage I or II).
Patients with calculated creatinine clearance <30 mL/minute (using Cockroft-Gault formula)	This exclusion criterion was considered for methodological reasons to prevent biases on the safety endpoints evaluation as a decline in renal function may be associated with increase of AEs.	No	Based on a population pharmacokinetic analysis, mild to moderate renal impairment did not have any appreciable effect on the pharmacokinetics of sarilumab. Consequently, no dosage adjustment is required in patients with mild to moderate renal impairment. Statement that patients with severe renal impairment were not studied is displayed in SmPC (eg, Use in special populations, Pharmacokinetic properties).
Pregnant or lactating females			
Pregnant or breast-feeding women and patients of child	These exclusion criteria were considered due to methodological	No	Considered as missing information in the initial EU-RMP and has been removed from the list of safety

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
bearing potential who did not agree to use effective methods of contraception	considerations, to prevent any potential direct or indirect harmful effects on pregnancy, embryo-fetal development, birth or postnatal development in the absence of information on the use of sarilumab during pregnancy or lactation in humans.		concerns in EU-RMP update version 2.0 onwards.
Exclusion criteria related to sarilumab use			
Hepatitis B/hepatitis C virus infected patients	These exclusion criteria were considered because immunosuppressive drugs, such as those used to treat RA and PMR, are associated with an increased risk of infection, including viral reactivation.	No	Considered as missing information in the initial EU-RMP and has been removed from the list of safety concerns in EU-RMP update version 2.0 onwards.
Human Immunodeficiency Virus (HIV) infected patients	These exclusion criteria were considered because immunosuppressive drugs, such as those used to treat RA and PMR, are associated with an increased risk of infection, including viral reactivation.	No	Considered as missing information in the initial EU-RMP and has been removed from the list of safety concerns in EU-RMP update version 2.0 onwards.
Use of live vaccines	This exclusion criterion was considered because live vaccines should not be administered concurrently with immunosuppressive drugs as clinical safety has not been established.	No	Considered as missing information in the initial EU-RMP and has been removed from the list of safety concerns in EU-RMP update version 2.0 onwards.
Diabetes mellitus (Glycated Hemoglobin [HbA1c] $\geq$9%)	This exclusion criterion was considered for methodological reasons, to prevent biases on the safety endpoints, such as those related to infections and CV disease.	No	Data were obtained from extensive clinical safety and did not show any safety signal related to diabetes mellitus.
Inflammatory bowel disease or severe diverticulitis or previous GI perforation	These exclusion criteria were considered because of existing data from TCZ and the concomitant use of medications in these patients known to be associated with GI	No	Gastrointestinal perforation is considered an important identified risk. Summary of product characteristics mentions in “special warnings and precautions” section that sarilumab should be used with

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	perforation (ie, Nonsteroidal Anti-Inflammatory Drug [NSAIDs], steroids).		caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with new onset abdominal symptoms such as persistent pain with fever should be evaluated promptly.
Patients with significant laboratory abnormalities before randomization			
• Hemoglobin <8.5 g/dL (<7 g/dL for pJIA). • White blood cells <3 x 10^9/l • Neutrophils <2 x 10^9/l • Platelet count <150 x 10^3/µl • Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) >1.5 x upper limit of normal (ULN) • Hypercholesterolemia (>350 mg/dL, 9.1 mmol/L) • Hypertriglyceridemia (>500 mg/dL, 5.6 mmol/L)	These exclusion criteria were considered because of existing data from another Interleukin-6 Receptor (IL-6R) antagonist which demonstrated laboratory abnormalities related to hematologic, liver function testing, and lipid parameters. These exclusion criteria were considered, to prevent biases on the efficacy/safety endpoint evaluation and because they could result in an increased risk of premature study discontinuation.	No	Summary of product characteristics statements in "special warnings and precautions for use" section recommends not to administer sarilumab in patients with neutrophil count <2 x 10^9/l, platelet count <150 x 10^3/µl or ALT or AST >1.5 x ULN. Prescribers are advised to manage patients according to clinical guidelines for the management of hyperlipidemia.
Patients with prior or concomitant immunosuppressive therapy			
Other immunosuppressive agents prior to randomization • Etanercept, anakinra within 28 days • Infliximab, adalimumab, golimumab, certolizumab pegol, abatacept within 42 days • Rituximab or other cell-depleting agents within 6 months prior to randomization or until total lymphocyte count and Cluster of Differentiate-19 (CD-19) plus	These exclusion criteria were considered due to methodological reasons as other immunosuppressive agents could have confounded the evaluation of the efficacy/safety endpoint evaluations.	No	Statement in the section "interactions with other medicinal products and other forms of interaction" of the SmPC mentions that Kevzara has not been investigated in combination with JAK inhibitors or biological DMARDs such as Tumor Necrosis Factor (TNF) antagonists.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
lymphocyte count are normalized • Prednisone >10 mg or equivalent per day, parenteral or intra-articular glucocorticoid injection within 4 weeks • Prior treatment with anti-IL-6 or IL-6R antagonist therapies • Prior treatment with a JAK inhibitor			

AE: Adverse Event; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CD-19: Cluster of Differentiate-19; CV: Cardiovascular; DMARD: Disease Modifying Anti-Rheumatic Drug; eoJIA: Extended Oligoarticular Juvenile Idiopathic Arthritis; EU: European Union; GI: Gastrointestinal; HbA1c: Glycated Hemoglobin; HIV: Human Immunodeficiency Virus; ILD: Interstitial Lung Disease; IL-6: Interleukin-6; IL-6R: Interleukin-6 Receptor; JAK: Janus Kinase; JIA: Juvenile Idiopathic Arthritis; NSAID: Nonsteroidal Anti-Inflammatory Drug; OI: Opportunistic Infection; PIP: Pediatric Investigation Plan; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; RF: Rheumatoid Factor; RF+: Rheumatoid Factor Positive; RF-: Rheumatoid Factor Negative; RA: Rheumatoid Arthritis; RMP: Risk Management Plan; SI: Serious Infection; SmPC: Summary of Product Characteristics; TB: Tuberculosis; TCZ: Tocilizumab; TNF: Tumor Necrosis Factor; ULN: Upper Limit of Normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency and adverse reactions caused by prolonged or cumulative exposure.

The limitations are due to the limited exposure in clinical development programs. These limitations are mitigated by the postmarketing exposure, see Section SV.1.1.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 28 - Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant or Breast-feeding women	As of 09-Feb-2023, there have been 34 pregnancies in 26 sarilumab-treated RA female patients and in 8 partners of male sarilumab-treated RA patients reported in clinical trials and retrieved from the pharmacovigilance database (22 from LTS11210, 2 from 6R88-COV-2040, 2 from ACT13480, 2 from EFC14092, 1 from EFC10832, 1 from EFC11072, 1 from EFC11574, 1 from LTS13618, 1 from MSC12665, and 1 from TDU11373).

Type of special population	Exposure
	The female patient pregnancies have resulted in 6 spontaneous abortions, 1 imminent abortion (spontaneous abortion), 1 anembryonic gestation, 2 induced abortions, 1 missed abortion, 14 live births without congenital anomalies (including 2 premature births) and 1 case with no information on pregnancy outcome. Two female patients received sarilumab in off label use for COVID-19 while already pregnant. The 8 partner pregnancies have resulted in 6 live births without congenital anomalies, 1 induced abortion (family reason), and 1 unknown pregnancy outcome. As per SmPC, sarilumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab. Women of childbearing potential should use effective contraception during and up to 3 months after treatment. As of 09-Feb-2023, 8 cases of exposure via breast milk were reported with no associated AEs. It is not known whether sarilumab is present in human milk. However, it is known that IgG is excreted in human milk in small amounts.
Patients with relevant comorbidities	
• Patients with hepatic impairment	No formal study of the effect of hepatic impairment on the pharmacokinetics of sarilumab was conducted because the disposition of sarilumab, an IgG antibody, is not expected to be impacted by hepatic impairment. In the clinical development program (RA and PMR study [adults] and pJIA study [pediatrics]), patients with an ALT >1.5 x ULN, or patients who were at risk for reactivation of hepatitis B were excluded from the studies. During the studies patients were monitored for increases in transaminases, and recommendations were provided on dose modification (RA and PMR study [adults]) or dose discontinuation (pJIA study [pediatrics]). No patient in the pJIA study had hepatic impairment at screening. Due to the elevations in hepatic transaminases that may occur with sarilumab administration, treatment with sarilumab is not recommended in patients with active hepatic disease or hepatic impairment. This sub-population is not considered an outstanding safety concern, as sarilumab is not recommended in these patients.
• Patients with renal impairment	No formal study of the effect of renal impairment on the pharmacokinetics of sarilumab was conducted because the disposition of sarilumab, an IgG antibody, is not expected to be impacted by renal impairment. Per protocol for RA and PMR study (EFC15160), adult patients with severe renal impairment (calculated creatinine clearance <30 mL/minute [using Cockcroft-Gault formula]) were excluded from these clinical studies. Sarilumab has not been studied in patients with severe renal impairment. Most of the patients had normal renal function or mild renal impairment. Per the protocol for the pJIA study, pediatric patients with estimated glomerular filtration rate <30 mL/min/1.73m2 (using the modified Schwartz formula) were excluded from the study. Of the total number of patient in the phase 2 or 3 studies on sarilumab with/without DMARD, 24.5% (822 patients) had mild renal impairment (≥60 to <90 mL/min) at baseline and 4.3% (144 patients) had moderate renal impairment (≥30 to <60 mL/min) at baseline. Total PY exposure was 1424.7 PY in patients who had mild renal impairment and 217.9 PY in patients who moderate renal impairment. No patient in the pJIA study had renal impairment at screening. Based on a population pharmacokinetic analysis, mild to moderate renal impairment did not have any appreciable effect the pharmacokinetics of sarilumab. Consequently, no dosage adjustment is required in patients with mild to moderate renal impairment.

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td colspan="2">Other</td></tr>
<tr><td>Elderly</td><td>No obvious trend in functional sarilumab exposure with age was observed in patients with RA in clinical studies. Population pharmacokinetic analysis (Study POH0428) with data from patients from 18 to 88 years (14% of 2186 patients with RA in the data set were >65 years) did not identify age as a significant covariate influencing sarilumab pharmacokinetics.
Of the total number of patient (N = 3358) in the phase 2 or 3 studies on sarilumab with and without DMARD, 15.1% (507 patients) were 65 years and over (equivalent to 1425.7 PY of exposure). Of the patients over 65 years of age, 1.5% (51 patients) were 75 years and over (equivalent to 111.7 PY of exposure), including 3 patients 85 years of age and over.
Although the data are limited, particularly in the subgroup of patients 75 years and older, no overall differences in safety and efficacy were observed in patients ≥65 years old compared to those <65 years old.
No obvious trend in sarilumab exposure with age was observed in patients with PMR in Study EFC15160. Population pharmacokinetic analysis (Study POH0139) with data from patients from 51 to 88 years (16 (27%) patients with <65 years of age, 33 (56%) patients with 65 to 75 years of age, and 10 (17%) patients with >75 years) suggested the lack of impact of age on sarilumab pharmacokinetics. Therefore, no dose adjustments are recommended for elderly patients.
Elderly patients are at an increased risk for infection, (66) and a numerically higher incidence of SI's was observed in patients ≥65 years old in both the sarilumab and placebo groups. Therefore, caution should be used when treating the elderly population as shown in below Table 28a.
Table 28a - Summary of SI by subgroups during the entire Treatment-Emergent Adverse Event (TEAE period) - Placebo controlled safety population
<table>
<tr><th></th><th>Placebo plus DMARD (N = 661)
n (%)[a]</th><th colspan="2">Sarilumab</th></tr>
<tr><th></th><th></th><th>150 mg q2w plus DMARD (N = 660)
n (%)[a]</th><th>200 mg q2w plus DMARD (N = 661)
n (%)[a]</th></tr>
<tr><td colspan="4">Age</td></tr>
<tr><td><65 years</td><td>10/573 (1.7%)</td><td>8/574 (1.4%)</td><td>15/569 (2.6%)</td></tr>
<tr><td>≥65 and <75 years</td><td>2/84 (2.4%)</td><td>4/79 (5.1%)</td><td>4/82 (4.9%)</td></tr>
<tr><td>≥75 years</td><td>0/4 (0.0%)</td><td>0/7 (0.0%)</td><td>0/10 (0.0%)</td></tr>
</table>
a % serious infections
Including 2 patients ≥85 years of age on sarilumab, one in each dose group.
DMARD: Disease Modifying Anti-Rheumatic Drug; N: Total Number of Patient; q2w: Once Every Two Weeks; SI: Serious Infection; TEAE: Treatment-Emergent Adverse Event.</td></tr>
</table>

AE: Adverse Event; ALT: Alanine Aminotransferase; COVID-19: Coronavirus Disease-2019; DMARD: Disease Modifying Anti-Rheumatic Drug; IgG: Immunoglobulin G; N: Total Number of Patient; n: Number of Patient; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; PY: Patient-Year; q2w: Once Every Two Weeks; RA: Rheumatoid Arthritis; SI: Serious Infection; SmPC: Summary of Product Characteristics; TEAE: Treatment-Emergent Adverse Event; ULN: Upper Limit of Normal.

Pregnant or breast-feeding women

Sarilumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab. It is unknown whether sarilumab is excreted in human milk. The excretion of sarilumab in milk has not been studied in animals. Because IgG1 are excreted in human milk, a decision should be made whether to discontinue breast-feeding or to discontinue

sarilumab therapy considering the benefit of breast-feeding for the child and the benefit of therapy for the woman. As part of routine surveillance, a standard data collection form will be utilized for documenting pregnancy reports. Attempts to collect drug exposure via parent information are to be done at time of exposure and delivery or outcome/termination of the pregnancy.

Patients with hepatic impairment

In summary, sarilumab use has not been studied in patients with underlying hepatic impairment. Due to the elevations in hepatic transaminases that may occur with sarilumab administration, treatment with sarilumab is not recommended in patients with active hepatic disease or hepatic impairment. This sub-population has not showed any significant difference in the safety profile comparing to general population.

Patients with renal impairment

In summary, there are limited data in moderate and no data in severe renal impairment; however, in the absence of effects of renal impairment on the pharmacokinetics of sarilumab, this is not considered as an at-risk sub-population.

Elderly

There are limited data in patients ≥65 years old. However, there is no expectation that future pharmacovigilance activity could further characterize the use of sarilumab in this population, for which specificities are deemed adequately addressed in product labelling.

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

The Marketing Authorization Holder (MAH) is currently utilizing the Margin Consolidated (MARCO) application for reporting of sales data from postmarketing experience since December 2019. The MARCO application data reporting by country is not limited by subscription agreements and therefore represents the sales data from a greater number of countries than was available in performance analysis reporting center (PARC). For this reason, increases in the reporting of postmarketing exposure is observed due to the expansion in the availability of data utilized to estimate patient exposure. The MARCO application collects data monthly, as a result, the data may not correspond precisely to the current reporting interval.

Methodology

- Calculating total sales in mg by multiplying number of syringes/autoinjectors with their respective strength.
- The total sales in mg was divided by World Health Organization (WHO) defined daily dose (DDD) of 14.3 mg for parenteral formulations to estimate number of patient days.
- Patient days were divided by 365 to estimate number of PYs.

SV.1.2 Exposure

Exposure from the cumulative experience is available from MARCO for the period from 01 July 2015 to 31 December 2022.

A total of 2.5 million pre-filled syringes/autoinjectors were sold worldwide cumulatively corresponding to 34.1 million patient days and 93 554 PYs.

Detailed usage data are not available therefore presentation of patient exposure by age, sex, and indication is not possible.

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The properties of Sarilumab do not indicate a potential for misuse for illegal purposes.

There is no evidence that a peripherally administered monoclonal antibody targeting IL-6 receptor can affect central mechanisms or produce behavioral alterations, further diminishing any concern for an abuse liability potential. The molecule structure, known mechanism of action and pharmacokinetic effects of sarilumab do not predispose it to become subject to drug abuse or dependence. Nonclinical and clinical data did not yield events raising a concern of drug dependence or abuse.

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

This section is not applicable as the initial RMP for sarilumab was submitted prior to the implementation of GVP module V Rev 2.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns or reclassification have been considered since RMP version 4.1.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for sarilumab:

- 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

SVII.3.1 Presentation of important identified risks and important potential risks

Table 29 - Identified risk: Serious infections

Identified Risk	Serious infections
Potential mechanism	Interleukin-6 has a role in B- and T-cell differentiation and acute phase reactants and, therefore, an increase in risk of infection.
Evidence source(s) and strength of evidence	The important risk was defined based on in-depth review of the literature on IL-6, review, and analysis of non-clinical findings, as well as of clinical safety data observed with sarilumab during the clinical development program. Consistent with the mechanism of

Identified Risk	Serious infections
	action, sarilumab administration is associated with an increase in the rate of infections, including SI's.
Characterization of the risk	**Frequency with 95% CI** RA studies: Placebo-controlled population (Pool 1): The rate of SI infections in the entire-placebo-controlled population was 3.1 events per 100 PY (95% CI: 1.62-5.48) in the placebo group compared to 3.0 events per 100 PY (95% CI: 1.57-5.04) and 4.3 events (95% CI: 2.59-6.72) in the 150 mg q2w and 200 mg q2w sarilumab groups, respectively. Sarilumab plus DMARD long-term safety population (Pool 2): In the sarilumab plus DMARD long-term safety population, the SI event rate was 3.3 events per 100 PY and remained constant over time. Sarilumab monotherapy population (Pool 3): In the sarilumab monotherapy population, the SI event rate was 1.5 events per 100 PY (95% CI). PMR study (EFC15160): The incidence of patients with SI's was similar in the sarilumab 200 mg q2w + 14-week taper group (5.1%) compared to the placebo + 52-week taper group (5.2%). pJIA study (DRI13925): pJIA (open label non-comparative study): There were two participants (2.2%) with serious infections during the entire treatment period on the selected dose 2 (one participant in the weight group A [≥30 kg] and one participant in the weight group B [≥10kg - <30 kg]). The rate of serious infections in the pJIA study during the entire treatment period on the selected dose 2 was 1.0 event per 100 PY. **Severity and nature of risk** Serious infections required treatment with antibacterial, antivirals and/or antifungals. Serious infections generally required hospitalization and, depending on severity, had required management in the intensive care unit. Some SI were fatal in the adult RA population, however there were no deaths in the clinical trial with pediatric patients. **Seriousness/outcomes** RA studies: Pool 1: No fatal infections were reported during the placebo-controlled period. Pool 2: Of the 268 patients on sarilumab plus DMARD with a SI, 245 patients were hospitalized of which 15 patients had a fatal outcome. Of the 15 patients in Pool 2 who had a fatal outcome, 5 patients had pneumonia, 3 patients with septic shock, 2 patients with sepsis, 1 patient had a gangrene, 1 patient had a histoplasmosis disseminated, 1 patient with infectious pleural effusion, 1 patient with psoas abscess and 1 with viral pneumonia. Pool 3: In the monotherapy population, 21 patients had a SI, for which 20 patients were hospitalized and of these 2 patients had a fatal outcome due to *Clostridium difficile* infection and peritonitis. PMR study (EFC15160): Of the 59 patients in the sarilumab 200 mg q2w + 14-week taper group, 3 (5.1%) patients had SI. The three SI's were intervertebral discitis, pneumonia, and urinary tract infection bacterial. Sarilumab treatment was permanently discontinued due to intervertebral discitis and due to pneumonia. None of the infections led to fatal outcome. pJIA study (DRI13925): In the pediatric study, 2 out of 93 participants (2.2%) on selected dose 2 had serious infection. One participant (1.1%) was diagnosed with the SI of Pott's disease (bone

<table>
<tr><th>Identified Risk</th><th>Serious infections</th></tr>
<tr><td></td><td>
tuberculosis) three days after first sarilumab administration despite a non-reactive QuantiFERON test at screening, while the other participant (1.1%) had acute sinusitis.
<u>Postmarketing safety experience (RA indication)</u>
The most frequently reported infections include Nasopharyngitis/Sinusitis/Upper respiratory tract infection, Pneumonia/Bronchitis, Influenza/COVID-19, Urinary tract infection, Herpes Zoster, and Cellulitis. Opportunistic infections, mostly TB, are reported occasionally. Ongoing monitoring of the postmarketing data up to DLP did not reveal any new emerging information impacting the characterization of this risk.
<u>Background incidence/prevalence</u>
The rate of infections, in general, is increased in RA patients compared with other diseases. In a study from the Olmstead County cohort, (67) the incidence of infection in 609 RA patients was 19.64 per 100 PY and the RR was 1.53 (1.41-1.65) compared to non-RA population.
The rate of specific OI is increased, such as TB, (around four-fold). The incidence Risk Ratio (RR) of pulmonary TB in patients with RA compared to the general population is 3.68 (95% CI: 2.36-5.92). (68)
The increased rates are related to both the immunosuppressant drugs used in the treatment of RA and to the level of systemic inflammation. (69)
<u>Serious infections</u>
A cohort study in United States of America (USA) of patients with incident RA had found a rate of all SI's of 6.6 per 100 PY. (70) A Canadian study of RA patients aged 66 or older estimated that the rate of infections requiring hospitalization, or an emergency room visit was 4.6 per 100 PY. (71)
The incidence of SI's across all studies evaluating biologic DMARDs were in the range of 2-11 per 100 PY, and the majority of studies reported a narrower range of 2 to 6 per 100 PY. (72) Among observational study participants, the ranges of incidence of SI's associated with TNF inhibitors and biologic DMARDs were 2.2-10.4 per 100 PY and 4.6-7.0 per 100 PY, respectively.
These data were consistent with results of a meta-analysis of 18 Randomized Control Trial (RCTs) in more than 8800 RA patients that reported the incidence of SI's associated with TNF inhibitors to be 3.6 per 100 PY. (73) The corresponding incidence associated with MTX ranged from 1.0 to 8.8 per 100 PY (Table 29a), which was not different from the range observed for non-biologic DMARDs as a group (1.3-9.6 per 100 PY). (72)
Table 29a - Range of incidence density of serious infections, opportunistic infections, and tuberculosis in rheumatoid arthritis patients receiving biologic disease modifying antirheumatic drugs - data from randomized clinical trial, open-label extension, and observational studies ([Extracted from Tran et al. 2013] 72)
<table>
<tr><th rowspan="2">Drugs</th><th colspan="3">Incidence per 100 PY (range)</th></tr>
<tr><th>SI</th><th>OI</th><th>TB</th></tr>
<tr><td>Rituximab</td><td>2.0-5.2</td><td>-</td><td>-</td></tr>
<tr><td>Etanercept</td><td>2.6-11.1</td><td>0.01-0.12</td><td>0.01-0.11</td></tr>
<tr><td>Adalimumab</td><td>2.0-8.7</td><td>0.03-1.12</td><td>0.08-0.56</td></tr>
<tr><td>Abatacept</td><td>1.6-4.3</td><td>0.2</td><td>0.18</td></tr>
<tr><td>Infliximab</td><td>3.9-10.3</td><td>0.29-2.6</td><td>0.05-2.6</td></tr>
<tr><td>Anakinra</td><td>1.0-5.4</td><td>0.13</td><td>-</td></tr>
<tr><td>Certolizumab</td><td>4.0-7.3</td><td>-</td><td>0.7-2.5</td></tr>
</table>
</td></tr>
</table>

Identified Risk	Serious infections

TCZ	3.1-9.1	0.15-1.1	0.08-0.09
Golimumab	2.5-10.0	-	0.46-1.4
TNF inhibitors	2.2-10.4	0.15-3.0	-
Biologic DMARDs	4.6-7.0	-	-
MTX	1.0-8.8	-	-
Nonbiologic DMARDs and corticoid	1.3-9.6	-	-

DMARD: Disease Modifying Anti-Rheumatic Drug; MTX: Methotrexate; OI: Opportunistic Infection; PY: Patient-Year; SI: Serious Infection; TB: Tuberculosis; TCZ: Tocilizumab; TNF: Tumor Necrosis Factor.

Data from the British Society for Rheumatology Biologics Register: Incidence rate for SI's was 4.14 per 100 PY for DMARD users and 5.23 for anti-TNFs. After adjusting for age, sex, disease severity, comorbidities, extra-articular manifestations, baseline glucocorticoid use, and smoking, Incidence Rate Ratio (IRR) of all SI's in patients treated with anti-TNF-α agents was not significant at 1.0 (CI: 0.7-1.6) except for skin and soft tissue infections, which were significantly increased (adjusted IRR: 4.3; 95% CI: 1.1-17.2). Serious infections of lower respiratory tract infections were most common, followed by skin and soft tissue, musculoskeletal (ie, bone, joint) and urinary tract infection. (74)

In a large retrospective English cohort study of PMR or GCA, a total of 22 234 (55.7%) people had an infection during 138 412 person-years of follow-up; the median duration of follow-up per patient was 4.8 (Interquartile range 2.2-8.5) years. The incidence of all-cause infection was 160.7 (95% CI: 159.3-162.2) per 1000 person-years. (75)

In a RCT assessing the safety and efficacy of TCZ in patients with active pJIA, the IR of severe infection was 4.9 per 100 person-years (in all exposed group [N = 188]). Common AEs were pneumonia, reported in four (2.1%) patients (three in the 8 mg/kg for 30 kg or more group, one in the 10 mg/kg for the less than 30 kg group), followed by bronchitis in two (1.1%) patients (both in the 10 mg/kg for less than 30 kg group) and cellulitis in two (1.1%) patients (both in the 8 mg/kg for 30 kg or more group). (76)

A pharmacovigilance registry called Pharmachild (NCT01399281) was established in 2011 to analyze the safety profile of biologic drugs on an international cohort of JIA patients. The combined data coming from the Pharmachild registry and the national registries from Germany (BiKeR) and Sweden, regarding more than 15 000 JIA patients, have been recently published. Infection and infestations were the most frequent reported AEs (29.4-30.1%). (77)

Opportunistic infections including tuberculosis

Incidence data for OI and TB were reported far less frequently than for SI. Among trials that reported OI and TB, the incidence of OI and TB ranged from 0.03 to 2.6/100 PY and 0.04 to 2.5/100 PY, respectively. Two observational studies reported an incidence of OI (including TB) of 2.5-3.0/100 PY and of non-TB OI of 0.15/100 PY among those receiving TNF inhibitors. (72) See Table 29a.

Impact on individual patient

A SI can be life threatening and result in death if not appropriately treated.

Risk factors and risk groups	Known risk factors for infections include increased age, medical history of diabetes or chronic obstructive pulmonary disease, smoking, use of concomitant immunosuppressant (eg, MTX). (66)

Identified Risk	Serious infections
Preventability	Complications of SI can be prevented with early detection (diagnosis) of infection leading to early action (identification of infectious etiology/agent involved and treatment). Sarilumab dosing should be stopped during a SI. All patients should be tested for latent TB prior to starting sarilumab and, if positive, treated prior to starting sarilumab. Monitoring for active TB should continue during sarilumab treatment.
Impact on the benefit-risk balance of the product	The benefit-risk balance remained positive for patients treated with respect to the valid labeling recommendations.
Public health impact	Serious infections may lead to hospitalization and/or prolonged hospitalization, and thus, to increased public health care spending, loss of economic productivity and potentially loss of work-force due to potential risk of SI's leading to fatal outcomes.

Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/ae_infection_s_t_p2.sas OUT=REPORT/OUTPUT/ae_infection_s_t_sae_p2_x.rtf (11JUN2021 - 7:05)
Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/ae_infection_s_t_p3.sas OUT=REPORT/OUTPUT/ae_infection_s_t_sae_p3_x.rtf (11JUN2021 - 7:06)
Postmarketing safety experience information has been aligned with PBRER DLP 12 Jan 2023.
AE: Adverse Event; CI: Confidence Interval; COVID-19: Coronavirus Disease 2019; DLP: Data Lock Point; DMARD: Disease Modifying Anti-Rheumatic Drug; IL-6: Interleukin-6; IRR: Incidence Rate Ratio; MTX: Methotrexate; N: Total number of Patient; OI: Opportunistic Infection; PBRER: Periodic Benefit-Risk Evaluation Report; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; PY: Patient-Year; q2w: Once Every Two Weeks; RA: Rheumatoid Arthritis; RCT: Randomized Control Trial; RR: Risk Ratio; SI: Serious Infection; TB: Tuberculosis; TCZ: Tocilizumab; TNF: Tumor Necrosis Factor; USA: United States of America.

Table 30 - Identified Risk: Neutropenia

Identified Risk	Neutropenia
Potential mechanism	Based on non-clinical and clinical findings, reversible decreases in neutrophil count have been observed as a consequence of IL-6 inhibition. Analysis of neutrophil responses in a single-dose pharmacokinetic study (PKM12058) demonstrated that while the number of neutrophils is decreased, the neutrophils present maintain normal functionality.
Evidence source(s) and strength of evidence	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of non-clinical findings, as well as of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with laboratory abnormality of decreased neutrophil count, consistent with its mechanism of action. Neutropenia was not associated with increased incidence of infection.
Characterization of the risk	**Frequency with 95% CI** Incidence of neutropenia: RA studies: During the entire treatment period in the placebo-controlled population (Pool 1), the incidence of ANC <1.0 Giga/L was 0.2% in placebo plus DMARD group, 6.1% in the 150 mg q2w plus DMARD group and 9.2% in the 200 mg q2w plus DMARD group, and the incidence of ANC <0.5 Giga/L was 0.0% in placebo plus DMARD group, 1.2% in 150 mg q2w plus DMARD group and 0.9% in the 200 mg q2w plus DMARD group. In the sarilumab plus DMARD long-term safety population (Pool 2), the incidence of ANC <1 Giga/L was 13.1%. In the Sarilumab monotherapy population (Pool 3), the incidence of ANC <1 Giga/L was 16.3.

Identified Risk	Neutropenia

Table 30a - Number (%) of patients with decrease in absolute neutrophil count during the entire TEAE period by maximum grade - Placebo-controlled safety population (Pool 1)

		Sarilumab	
Laboratory parameter criteria n/N1 (%)	**Placebo + DMARD (N = 661)**	**150 mg q2w + DMARD (N = 660)**	**200 mg q2w + DMARD (N = 661)**
Absolute neutrophil count			
Grade 1: ≥1.5 Giga/L – Lower Limit of Normal (LLN)	24/661 (3.6%)	89/660 (13.5%)	107/658 (16.3%)
Grade 2: ≥1-1.5 Giga/L	7/661 (1.1%)	82/660 (12.4%)	99/658 (15.0%)
Grade 3: ≥0.5-1 Giga/L	1/661 (0.2%)	32/660 (4.8%)	55/658 (8.4%)
Grade 4: <0.5 Giga/L	0/661	8/660 (1.2%)	6/658 (0.9%)

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed during the TEAE period.
PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/lab_pcsa_s_t_p2.sas OUT=REPORT/OUTPUT/lab_pcsa_wbc_s_t_p2_x.rtf (11JUN2021 – 10:04)
PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/lab_pcsa_s_t_p3.sas OUT=REPORT/OUTPUT/lab_pcsa_wbc_s_t_p3_x.rtf (11JUN2021 – 10:11)
DMARD: Disease Modifying Anti-Rheumatic Drug; LLN: Lower Limit of Normal; q2w: Once Every Two Weeks; TEAE: Treatment-Emergent Adverse Event.

PMR study (EFC15160):

During the treatment period in the sarilumab 200 mg q2w + 14-week taper group, the incidence of ANC <1.0 Giga/L (grade 3 and grade 4 combined) was 12.1%, while no patients in the placebo + 52-week taper group had ANC <1.0 Giga/L. The incidence of ANC <0.5 Giga/L (grade 4) was 3.4% in the sarilumab 200 mg q2w + 14-week taper group and 0.0% in placebo + 52-week taper group.

Table 30b - Number (%) of patients with neutrophil count decreased during the TEAE period by maximum grade - Safety population - Study EFC15160

Laboratory parameter Common Terminology Criteria for Adverse Event (CTCAE)	**Placebo + 52-week taper (N=58)**	**Sarilumab 200 mg q2w + 14-week taper (N=59)**	**All (N=117)**
Neutrophil count decreased			
Grade 1	0/57	13/58 (22.4)	13/115 (11.3)
Grade 2	0/57	11/58 (19.0)	11/115 (9.6)
Grade 3	0/57	5/58 (8.6)	5/115 (4.3)
Grade 4	0/57	2/58 (3.4)	2/115 (1.7)

Neutrophil count decreased: Grade 1: < LLN - 1.5*10^9/L (G/L), Grade 2: <1.5 - 1.0*10^9/L (G/L), Grade 3: <1.0 - 0.5*10^9/L (G/L), Grade 4: <0.5*10^9/L (G/L)
Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once during treatment. The denominator (/N1) for each

Identified Risk	Neutropenia
	parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline. PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/adhoc_lab_ctcae_s_t.sas OUT=REPORT/OUTPUT/adhoc_lab_ctcae_neut_s_t_x.rtf (01JUN2022 5:06). CTCAE: Common Terminology Criteria for Adverse Event; LLN: Lower Limit of Normal; N: Total Number of Patient; q2w: Once Every Two Weeks; TEAE: Treatment-Emergent Adverse Event. pJIA study (DRI13925): During the entire treatment period in the pediatric participants on the selected dose 2, the incidence of ANC <1 Giga/L was 37.0% (54.8% in the weight group B [≥10 kg to <30 kg]; 23.4% in the weight group A [≥30 kg]). **Neutropenia and infection** RA studies: There were no clinically meaningful differences between the rates of infections or SI's in patients with decrease in ANC <LLN and patients whose ANC remained ≥LLN. The incidence of patients with infection was similar in patients with Grade 1-3 neutropenia and Grade 4 neutropenia, with a numerically lower incidence of infection reported in patients with Grade 4 neutropenia. PMR study (EFC15160): No infections were associated with the low neutrophil count. The rate of infection was higher in the placebo + 52-week taper group in the PMR study compared to in the sarilumab 200 mg q2w + 14-week taper group, despite higher incidence of neutropenia in the sarilumab 200 mg q2w + 14-week taper group. pJIA study (DRI13925): During entire treatment period in pediatric participants on the selected dose 2, rates of infections or SI's were comparable between the patients with or without ANC <LLN (77.8% versus 82.1% for infections, 2.2% versus 3.6% for SI's). **Severity and nature of risk** RA and PMR: Sarilumab administration is associated with a dose-dependent decrease in ANCs which has not been associated with an increased risk of infection including SI's. The decrease in ANC <1.0 Giga/L was transient with the ANC trending to normal or baseline during or after discontinuation of sarilumab. pJIA: In the pJIA study, all neutropenia events were non-serious. **Seriousness/outcomes** RA studies: The number (%) of patients with treatment-emergent serious AEs of neutropenia and number per 100 PY were 24 (0.8%) and 0.2, respectively. In the sarilumab plus DMARD long-term safety population, the time to onset of ANC <1.0 Giga/L, which appears highest within 6 months of initiating therapy, and the time to onset of SI, which appears constant over time, there appears to be no association between decrease in neutrophil count and the risk of SI. Of the 377 patients on any dose of sarilumab in the long-term safety population (Pool 2) who had an ANC <1.0 Giga/L, 271 patients (71.88%) normalized on-treatment (ie, at least one ANC value was normal within ≤17 days after last dose of sarilumab), 83 patients (22.02%) normalized after discontinuation of sarilumab, and 23 patients (6.10%) had not normalized as of the last available assessment. The mean duration between first normal value and last dose of sarilumab was 43.98 days and median duration was 33 days. In the 23 patients who had not normalized, none of

Identified Risk	Neutropenia
	the patients were still enrolled in the studies and continued receiving sarilumab therapy. Overall, the occurrence of ANC <1.0 Giga/L in patients treated with sarilumab + DMARD was transient. PMR study (EFC15160): The incidence of laboratory value decrease of ANC was higher in the sarilumab 200 mg + 14-week taper group (31 [53.4%]) compared to the placebo + 52-week taper group (0%). The majority of occurrences were either Grade 1 or 2. Seven participants (12.1%) reported ANC decrease of Grade ≥3 severity, of whom 2 participants had a Grade 4 ANC decrease (Table 30b). The mean neutrophil count decrease from baseline to week 52 was 4.784 Giga/L for the sarilumab 200 mg + 14-week taper group and 1.225 Giga/L for the placebo + 52-week taper group. There were no infections associated with the low neutrophil count. pJIA study (DRI13925): During the entire treatment period in the pediatric participants on the selected dose 2, the incidence of ANC <1 Giga/L was 37.0% (54.8% in the weight group B [≥10 kg to <30 kg]; 23.4% in the weight group A [≥30 kg]). Neutropenia led to permanent treatment discontinuation in 5 patients (6.8%), of which four patients were in the weight group B. The time to onset of neutropenia in pediatric patients appeared highest within first 3 months (12 weeks), neutropenia was transient, judged as non-serious by the treating Investigators and there was no apparent association between decreased neutrophil count and the risk of SI's. The median duration of neutropenia was 14 days from onset of event occurrence. **Postmarketing safety experience (RA indication)** Approximately two-thirds of the reported postmarketing cases of neutropenia were considered serious. No associated infections were reported in almost all cases. Ongoing monitoring of the postmarketing data up to DLP did not reveal any new emerging information impacting the characterization of this important identified risk. **Background incidence/prevalence** In a 12-month prospective, observational study carried out in 40 Spanish centers of 379 adult patients with moderate or severe RA who initiated treatment with TCZ, the frequency at follow-up of neutropenia was 5.8%. (78) In 6-month-controlled phase III studies in RA patients, the frequency of neutropenia (Neutrophils <1000 Giga/L) was, 0.1% for patients on placebo and DMARDs, 3.4% for patient on TCZ 8 mg and DMARDs, and 1.8% for patients on TCZ 4 mg q4w IV plus MTX. (79) In a single center, open-label study of PMR patients administering tocilizumab monotherapy, neutropenia and elevated serum low-density lipoprotein cholesterol levels were observed in all patients during the study, but none of these events were serious. (80) The results of two clinical trials (NCT00642460; NCT00988221) describe the frequency of neutropenia in patients with pJIA (5.9%) comparable to that reported in patients with RA. In both systemic-juvenile idiopathic arthritis (sJIA) and pJIA, children in the lower weight category had a higher frequency of grade 3 neutropenia; analysis of the relationship between lowest neutrophil count and several variables showed a significant association only for age and only in patients with sJIA. (81) **Impact on individual patient** Infections can be a result of neutropenia which can be serious/life threatening and can result in death.

Identified Risk	Neutropenia
Risk factors and risk groups	RA and PMR: Subgroup analyses on the placebo-controlled population (Pool 1) and sarilumab + DMARD long-term safety population (Pool 2) were conducted for ANC <1.0 Giga/L according to age, gender, race, ethnicity, body mass index (BMI), weight, geographic region, RA duration of disease, RA functional class, prior biologic use, baseline steroid use MTX dose, concomitant DMARD use (ie, MTX or non-MTX), and baseline ANC <5.99 Giga/L. As anticipated due to the mean decrease in ANC in patients on sarilumab, a numerically higher incidence of ANC <1.0 Giga/L was observed in patients with baseline ANC <5.99 Giga/L in both the placebo-controlled population and sarilumab + DMARD long-term safety population. A numerically higher incidence of ANC <1.0 Giga/L was also observed in patients with weight <60 kg. Weight has been observed as a covariate on the pharmacokinetics of sarilumab with higher drug exposure at lower body weight. In the EFC15160 study (PMR), the exposure-response (E-R) relationship was evaluated between proportion of participants (%) ANC <1.0 Giga/L (included CTCAE Grade 3 and 4) and sarilumab steady-state plasma trough concentration (C_{trough}) in participants with PMR. The proportion of participants with ANC <1.0 Giga/L was similar among the low, medium, and high exposure tertiles, with no trend of increase with increasing concentration of sarilumab. The E-R relationship of ANC is consistent in patients with PMR and in patients with RA. No specific subgroup analyses were conducted in the PMR Study EFC15160 according to age, gender, race, ethnicity, body mass index, and weight. pJIA: In the DRI13925 (pJIA study), a higher incidence of ANC <1.0 Giga/L was observed in patients with body weight <30 kg. However, this group did not have higher rate of infections compared to patients of the same body weight without neutropenia.
Preventability	Initiation of sarilumab is not recommended if ANC is <2.0 Giga/L. Routine monitoring of neutrophil counts for early detection and guidance for dosing modifications (reduction/interruption/discontinuation) according to neutrophil count.
Impact on the benefit-risk balance of the product	The benefit-risk balance remained positive for patients treated in respect to the valid labeling recommendations.
Public health impact	Neutropenia may lead to the possibility of SI in susceptible patients (with underlying medical conditions) that may lead to hospitalization and/or prolonged hospitalization, and thus, to increased public health care spending, loss of economic productivity and potentially loss of work-force for the duration of hospitalization.

Postmarketing safety experience information has been aligned with PBRER DLP 12 Jan 2023.
AE: Adverse Event; ANC: Absolute Neutrophil Count; BMI: Body Mass Index; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Event; C_{trough}: Plasma Trough Concentration; DLP: Data Lock Point; DMARD: Disease Modifying Anti-Rheumatic Drug; E-R: Exposure-Response; IL-6: Interleukin-6; IV: Intravenous; LLN: Lower Limit of Normal; MTX: Methotrexate; N: Total Number of Patient; PBRER: Periodic Benefit-Risk Evaluation Report; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; PY: Patient-Year; q2w: Once Every Two Weeks; q4w: Once Every Four Weeks; RA: Rheumatoid Arthritis; SI: Serious Infection; sJIA: Systemic-Juvenile Idiopathic Arthritis; TCZ: Tocilizumab; TEAE: Treatment-Emergent Adverse Event.

Table 31 - Identified risk: Gastrointestinal perforations

Identified Risk	Gastrointestinal perforations
Potential mechanism	Interleukin-6 is produced in part by GI intraepithelial lymphocytes at the onset of an inflammatory injury for epithelial proliferation and wound repair. (82)
Evidence source(s) and strength of evidence	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Gastrointestinal perforations were primarily reported as

<table>
<tr><th>Identified Risk</th><th>Gastrointestinal perforations</th></tr>
<tr><td></td><td>complications of diverticulitis, including lower GI perforation and abscess and were generally confounded by the use of concomitant steroids or NSAIDs.</td></tr>
<tr><td>Characterization of the risk</td><td>
<u>Frequency with 95% CI</u>
<u>RA studies</u>:
<u>Placebo-controlled population (Pool 1)</u>: One patient on sarilumab experienced a GI perforation (0.11 events per 100 PY [95% CI: 0.00-0.63]). The patient was randomized to the 150 mg q2w treatment arm. No event occurred in patients on placebo plus DMARD.
<u>Sarilumab plus DMARD long-term safety population (Pool 2)</u>: A total of 10 patients on sarilumab plus DMARD, which includes 1 patient from the placebo-controlled population, had either complicated diverticulitis or GI perforation not secondary to surgical complication. All cases of complicated diverticulitis (ie, diverticulitis with evidence of abscess, perforation [including microperforation]) were considered as cases of lower GI perforation. All but one patient was on concomitant NSAID (including low dose aspirin or steroids). The event rates (with 95% CIs) for GI perforation are provided in Table 31a.
Table 31a - Number of patients on sarilumab + DMARD with gastrointestinal perforation during the TEAE period
<table>
<tr><th>Event</th><th>Sarilumab + DMARD (any dose)
N = 2887
10 322.0 PY
Number of events/100 PY (95% CI)</th></tr>
<tr><td>Lower gastrointestinal perforation</td><td>7 patients 0.07 (0.03, 0.14)</td></tr>
<tr><td>Upper gastrointestinal perforation</td><td>3 patients 0.03 (0.01, 0.08)</td></tr>
<tr><td>All gastrointestinal perforations</td><td>10 patients 0.10 (0.05, 0.18)</td></tr>
</table>
Gastrointestinal perforation events as assessed by clinical review.
CI: Confidence Interval; DMARD: Disease-Modifying Anti-Rheumatic Drug; N: Total Number of Patient; PY: Patient-Year; TEAE: Treatment-Emergent Adverse Event.
In Pool 2 total number of diverticulitis/potential GI perforations was 42 (0.4 per 100 PY), and total number of serious Diverticulitis/potential GI perforations was 31 (0.3 per 100 PY). None of the patients died and 16 patients (0.6%) permanently discontinued sarilumab.
<u>Sarilumab monotherapy population (Pool 3):</u> In sarilumab monotherapy population, total number of diverticulitis/potential GI perforations was 3 (0.2 per 100 PY), and total number of serious Diverticulitis/potential GI perforations was 2 (0.1 per 100 PY). One patient on the 200 mg q2w dose died 0.2%) and 2 patients (0.4%) on 200 mg q2w dose permanently discontinued sarilumab.
<u>PMR study (EFC15160)</u>:
No cases of GI perforation with or without diverticulitis were reported in the PMR Study EFC15160.
<u>pJIA study (DRI13925)</u>:
No pediatric patient experienced GI perforation in the pJIA study.
<u>Severity and nature of risk</u>
The events of GI perforation were primarily due to complications of diverticulitis and were generally confounded by the use of concomitant steroids or NSAIDs. The rate of GI perforations observed with sarilumab is within the range for these events observed for RA patients receiving CSs and/or TNF inhibitors based on estimates from large healthcare databases. (83) However, since patients with an increased risk of GI perforation (ie, history of inflammatory bowel disease, severe diverticulitis, or previous GI perforation) were excluded from the sarilumab studies there may be a baseline
</td></tr>
</table>

difference in the populations used for comparison. The contribution of these concomitant medications relative to sarilumab in the development of GI perforations is not known.

PMR study (EFC15160):

No cases of GI perforation with or without diverticulitis were reported in the PMR Study EFC15160.

pJIA study (DRI13925):

No pediatric patient experienced GI perforation in the pJIA study.

Seriousness/outcomes

RA studies:

All patients required hospitalization and 4 patients required surgical intervention. One patient experienced respiratory complications post-operatively and died 13 days after surgery. One patient in pool 3 with peritonitis with a fatal outcome; cause of death was pancreatic necrosis.

PMR study (EFC15160):

No cases of GI perforation with or without diverticulitis were reported in the PMR Study EFC15160.

pJIA study (DRI13925):

No pediatric patient experienced GI perforation in the pJIA study.

Postmarketing safety experience (RA indication)

Ongoing monitoring of the postmarketing data up to DLP did not reveal any new emerging information impacting the characterization of this risk.

Background incidence/prevalence

A retrospective cohort study on claims data showed that among 143 433 RA patients, the rate of perforation was 1.70 per 1000 PY (95% CI: 1.58-1.83) and most perforations (83%) occurred in the lower GI tract. The rate of perforation was lower when a more specific GI perforation definition was used (0.87, 95% CI: 0.78-0.96 per 1000 PY). Among various RA medication groups, and compared to MTX, the risk of GI perforation was highest among patients with exposure to concomitant non-biologic DMARDs and glucocorticoids. Biologics without glucocorticoid exposure was not a risk factor for perforation. (84) (See Table 31b) The reported rate of GI perforations for CSs and anti-TNF-α agents in the United Health Care database was 0.39/100 PY (95% CI: 0.31-0.48) and 0.13/100 PY (95% CI: 0.08-0.19), respectively. (83)

Table 31b - Incidence rate of gastrointestinal perforation, by medication exposure, in total study population (Extracted from Curtis, et al. 2012 [84])

	Sensitive gastrointestinal perforation definition N = 143 433		Specific gastrointestinal perforation definition N = 143 433	
Medication Exposure group	**IR/1000 PY**	**95% CI**	**IR/1000 PY**	**95% CI**
Biologics with glucocorticoids	1.87	1.46-2.35	0.91	0.63-1.26
Biologics without glucocorticoids	1.02	0.80-1.29	0.47	0.32-0.66
Methotrexate with glucocorticoids	2.24	1.82-2.74	1.25	0.94-1.63

Identified Risk	Gastrointestinal perforations

Methotrexate without glucocorticoids	1.08	0.86-1.35	0.47	0.33-0.66
All other DMARDs[a] with glucocorticoids	3.03	2.34-3.85	1.65	1.16-2.29
All other DMARDs[a] without glucocorticoids	1.71	1.34-2.16	0.66	0.44-0.96
Glucocorticoids without DMARDs or biologics	2.86	2.27-3.56	2.15	1.64-2.76
No DMARDs biologics or glucocorticoids	1.68	1.44-1.96	0.81	0.64-1.01
Overall	1.70	1.58-1.83	0.87	0.78-0.96

a Azathioprine, chloroquine, hydroxychloroquine, D-penicillamine, leflunomide, sulfasalazine, gold compounds.
CI: Confidence Interval; DMARD: Disease Modifying Anti-Rheumatic Drug;
IR: Incidence Rate; PY: Patient-Year.

Patients with PMR and RA face an increased risk of lower GI perforation when using tocilizumab. Nonetheless, there is a scarcity of data regarding its occurrence rate or frequency. (85)

A pharmacovigilance registry called Pharmachild (NCT01399281) was established in 2011 to analyze the safety profile of biologic drugs on an international cohort of JIA patients. The combined data coming from the Pharmachild registry and the national registries from Germany (BiKeR) and Sweden, regarding more than 15 000 JIA patients, have been recently published. Gastrointestinal disorders were reported in 11.5-19.6% of these patients. (77) Of the total events of special interest identified in Pharmachild (2022 events) and BiKeR (1697 events) registries, GI perforation was identified in 17 (0.8%) patients of the Pharmachild registry and 4 (0.2%) patients of the BiKeR registry.

Impact on individual patient

Gastrointestinal perforation can be life threatening and can result in death.

Risk factors and risk groups	Age, history of diverticulitis, use of glucocorticoids, and/or prescription NSAIDs, concomitant NSAID or steroid use. (83)
Preventability	Use with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis should be evaluated promptly for early identification of diverticulitis which can be associated with GI perforation.
Impact on the benefit-risk balance of the product	The benefit-risk balance remained positive for patients treated in respect to the valid labeling recommendations.
Public health impact	Gastrointestinal perforations may lead to hospitalization and/or prolonged hospitalization, and thus, to increased public health care spending, loss of economic productivity and potentially loss of work-force due to potential risk of SI. Gastrointestinal perforations may be potentially fatal if not adequately treated in a timely manner.

Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/ae_aesi_gastro_s_t_p2.sas OUT=REPORT/OUTPUT/ae_aesi_divgiperfo_s_t_p2_x.rtf (11JUN2021 - 7:32)
Extracted from: PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/ae_aesi_gastro_s_t_p3.sas OUT=REPORT/OUTPUT/ae_aesi_divgiperfo_s_t_p3_x.rtf (11JUN2021 - 7:34)
Postmarketing safety experience information has been aligned with PBRER DLP 12-Jan-2023.
CI: Confidence Interval; CS: Corticosteroid; DLP: Data Lock Point; DMARD: Disease Modifying Anti-Rheumatic Drug;
GI: Gastrointestinal; IL-6: Interleukin-6; IR: Incidence Rate; JIA: Juvenile Idiopathic Arthritis; MTX: Methotrexate; N: Total Number of Patient; NSAID: Nonsteroidal Anti-Inflammatory Drug; PBRER: Periodic Benefit-Risk Evaluation Report; pJIA: Polyarticular Juvenile

Identified Risk	Gastrointestinal perforations

Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; PY: Patient-Year; q2w: Once Every Two Weeks; RA: Rheumatoid Arthritis; SI: Serious Infection; TEAE: Treatment-Emergent Adverse Event; TNF: Tumor Necrosis Factor.

Table 32 - Potential risk: Thrombocytopenia and potential risk of bleeding

Potential Risk	Thrombocytopenia and potential risk of bleeding
Potential mechanism	Interleukin-6 administered to humans has been associated with increasing platelet counts. Mechanism is not clear although it may be affected via thrombopoietin. (86)
Evidence source(s) and strength of evidence	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with laboratory abnormality of decreased platelet count, consistent with its mechanism of action.
Characterization of the risk	**Frequency with 95% CI** Incidence of thrombocytopenia: RA studies: Platelet count <100 Giga/L was observed in 0 patients in the placebo plus DMARD group, in 4 patients (0.6%) in 150 mg q2w sarilumab plus DMARD group and in 11 (1.7%) patients in the 200 mg q2w sarilumab plus DMARD group during the entire treatment period in placebo-controlled population (Pool 1). Pool 2: A total of 124 (4.3%) patients in the sarilumab plus DMARD long-term safety population experienced thrombocytopenia. Only five of the patients (0.2%) experienced serious thrombocytopenia, 17 (0.6%) patients had permanently discontinued treatment due to thrombocytopenia and one patient had a fatal outcome. A total of 93 (3.2%) patients in sarilumab plus DMARD long term safety population experienced a platelet count <100 Giga/L. Fifteen patients (0.5%) had platelet count <50 Giga/L. Of the 93 patients on any dose of sarilumab who had a platelet count <100 Giga/L, 52 patients (1.8%) normalized on-treatment (ie, at least one platelet count was normal within ≤17 days after last dose of sarilumab), 21 patients (0.7%) normalized after discontinuation of sarilumab, and 20 patients (0.7%) had not normalized after sarilumab discontinuation as of the last available assessment. In the 20 patients who not had normalized, no patients were still enrolled in the studies (ie, sarilumab therapy was continuing). Of the 20 patients who had permanently discontinued sarilumab therapy and had not normalized, ten patients had platelet count >100 Giga/L but <LLN and nine patients had platelet count ≥50-100 Giga/L and the one remaining patient had a platelet <50 Giga/L at the last available assessment. Overall, the decrease in platelet count was transient. (Pool 3): In the sarilumab monotherapy safety population, there were 10 patients (2.1%) with a platelet count of <100 Giga/L, and 7 patients with thrombocytopenia. None of the patients permanently discontinued treatment or died due to thrombocytopenia. All patients normalized on treatment. PMR study (EFC15160): The incidence of platelet count decrease was higher in the sarilumab 200 mg + 14-week taper group (10 [17.2%]) compared to the placebo + 52-week taper group (3 [5.3%]). All incidences in both groups were of Grade 1 severity. At week 52, a mean decrease of 75.7 Giga/L from baseline was observed in the sarilumab 200 mg + 14-week taper group compared to a mean decrease of 15.8 Giga/L from baseline in the placebo + 52-week taper group. The mean platelet count remained within the normal range in both regimens. pJIA study (DRI13925):

Potential Risk	Thrombocytopenia and potential risk of bleeding
	No pediatric patient had platelet count <100 Giga/L in the pJIA study. **Thrombocytopenia and hemorrhage** RA studies: A total of 9 patients from Pool 2 and 3 patients from Pool 3 with platelet count of <100 Giga/L had a TEAE within the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) Hemorrhages. Pool 2: A total of 9 patients with platelet count of <100 Giga/L had a TEAE within the SMQ Hemorrhages. In 6 patients, the events were not concurrent, and therefore the decrease in platelet count was not a potential cause for the event. In the 2 out of the remaining 3 patients, there were non-serious events, assessed as mild in intensity, of injection site ecchymosis with a platelet count between 58-91 Giga/L and left arm hematoma with a platelet count between 60-93 Giga/L. The patient with left arm hematoma had prior AEs of intermittent hematoma in the upper arms which occurred without concurrent decrease in platelet count, making it unlikely that this event was related to the platelet count <100 Giga/L and the third patient had a non-site-specific GI bleed. Pool 3: A total of 3 patients with platelet count of <100 Giga/L had a TEAE within the SMQ Hemorrhages. In all 3 patients, the events were not concurrent, and therefore the decrease in platelet count was not a potential cause for the events. Metrorrhagia, pre-treatment epistaxis happened almost two years after the platelet count decrease, and alveolar hemorrhage was a year or more after the platelet count decrease. In summary, sarilumab administration was associated with a decrease in platelet count but has not been associated with bleeding. PMR study (EFC15160): There were 2 participants in the sarilumab 200 mg + 14-week taper group with a platelet count <100 Giga/L from week 2 onwards (1 participant with a platelet count of 99 Giga/L and another participant with a platelet count of 77 Giga/L). These laboratory results did not warrant permanent discontinuation of study drug. For these 2 participants, all prior and subsequent platelet counts were >200 Giga/L, the 2 independent low platelet counts were single occurrences without clinical manifestations or consequences. pJIA study (DRI13925): No pediatric patient had platelet count <100 Giga/L. **Severity and nature of risk** RA and PMR: Sarilumab administration is associated with a decrease in platelet count which has not been associated with bleeding. The decrease in platelet <100 Giga/L was transient with the platelet count trending to normal or baseline during or after discontinuation of sarilumab. pJIA: No pJIA patient had platelet count <100 Giga/L. **Seriousness/outcomes** Decrease in platelet count was not associated with a bleeding event requiring hospitalization or transfusion. **Postmarketing safety experience (RA indication)** Ongoing monitoring of the post marketing data up to DLP did not reveal any new emerging information impacting the characterization of this risk.

Potential Risk	Thrombocytopenia and potential risk of bleeding
	Background incidence/prevalence In a cross-sectional study in Pakistan, among 140 RA patients treated with low dose MTX, thrombocytopenia was found in 2.1 % of patients. (87) In a 12-month prospective, observational study carried out in 40 Spanish centers of 379 adult patients with moderate or severe RA who initiated treatment with TCZ, at follow-up the frequency of thrombocytopenia was 1.1%. (78) In 6-month-controlled phase III studies, the frequency of thrombocytopenia (platelet counts <100 000) was 1.7% for patient on TCZ 8 mg and DMARDs, 1.3% for patients on TCZ 4 mg + MTX and 0.5% for patients on placebo and DMARDs. (79) A recent study on JIA aimed to evaluate the effectiveness of TCZ in the short and long-term follow-up of severe uveitis. This multicenter study was conducted involving 25 patients who exhibited an inadequate response to conventional treatment, including corticosteroids and at least one conventional immunosuppressive drug, such as biological therapy. The primary adverse effects observed included severe autoimmune thrombocytopenia, autoimmune anemia, thrombocytopenia, pneumonia, viral conjunctivitis, and bullous impetigo, with each of these complications occurring in one patient. (88) **Impact on individual patient** Thrombocytopenia can result in bleeding which can range from minor to life threatening/death.
Risk factors and risk groups	Rarely does bleeding occur in patients with platelet counts >50 Giga/L. Purpura may occur in patients with platelet counts between 30-50 Giga/L. Platelet counts <5 Giga/L may result in spontaneous bleeding. (89)
Preventability	Initiation of sarilumab is not recommended if platelet count is <150 Giga/L. Routine monitoring of platelet and dosing modifications (reduction/ interruption/ discontinuation) is recommended based on platelet counts.
Impact on the benefit-risk balance of the product	The benefit-risk balance remained positive for patients treated in respect to the valid labeling recommendations.
Public health impact	Serious bleeding may lead to hospitalization and/or prolonged hospitalization, and thus, to increased public health care spending, loss of economic productivity and potential loss of work-force. If not treated adequately in a timely manner, serious bleeding may potentially cause fatal outcomes.

Postmarketing safety experience information has been aligned with PBRER DLP 12-Jan-2023.
AE: Adverse Event; CI: Confidence Interval; DLP: Data Lock Point; DMARD: Disease Modifying Anti-Rheumatic Drug; GI: Gastrointestinal; IL-6: Interleukin-6; LLN: Lower Limit of Normal; MedDRA: Medical Dictionary for Regulatory Activities; MTX: Methotrexate; PBRER: Periodic Benefit-Risk Evaluation Report; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; q2w: Once Every Two Weeks; RA: Rheumatoid Arthritis; SMQ: Standardized MedDRA Query; TCZ: Tocilizumab; TEAE: Treatment-Emergent Adverse Event.

Table 33 - Potential risk: Clinically evident hepatic injury

Potential Risk	Clinically evident hepatic injury
Potential mechanism	Interleukin-6 induces hepatic acute phase proteins. In animal models, IL-6 has been shown to have hepatoprotective effects against various forms of liver injury and to promote hepatic regeneration; therefore, anti-IL-6 effect could lead to increased hepatocyte susceptibility to hepatotoxic insults. (90)
Evidence source(s) and strength of evidence	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with laboratory

<table>
<tr><th>Potential Risk</th><th>Clinically evident hepatic injury</th></tr>
<tr><td></td><td>abnormalities of increased hepatic transaminases, consistent with its mechanism of action.</td></tr>
<tr><td>Characterization of the risk</td><td>
<u>Frequency with 95% CI</u>
<u>RA studies</u>:
<u>Placebo-controlled population (pool 1)</u>:
Table 33a provides the maximum elevated value of ALT in patients in the placebo controlled-studies. The incidence of ALT elevation was greater in the sarilumab plus DMARD groups than in the placebo plus DMARD group, with similar occurrence between the 2 sarilumab treatment groups. The majority of ALT and AST elevations were <3x ULN. The elevations in AST followed a similar trend to ALT although the overall occurrence was lower.
Table 33a - Number (%) patients with abnormalities (Potentially Clinically Significant Abnormalities [PCSA]) during the entire TEAE period - Placebo-controlled safety population
<table>
<tr><th></th><th></th><th colspan="2">Sarilumab</th></tr>
<tr><th>Laboratory parameter
PCSA criteria
n/N1 (%)</th><th>Placebo + DMARD
(N = 661)</th><th>150 mg
q2w + DMARD
(N = 660)</th><th>200 mg
q2w + DMARD
(N = 661)</th></tr>
<tr><td colspan="4">ALT</td></tr>
<tr><td>>1 - 1.5 ULN</td><td>127/661 (19.2%)</td><td>163/659 (24.7%)</td><td>178/657 (27.1%)</td></tr>
<tr><td>>1.5 - 3 ULN</td><td>70/661 (10.6%)</td><td>124/659 (18.8%)</td><td>162/657 (24.7%)</td></tr>
<tr><td>>3 and ≤5 ULN</td><td>10/661 (1.5%)</td><td>36/659 (5.5%)</td><td>31/657 (4.7%)</td></tr>
<tr><td>>5 and ≤10 ULN</td><td>1/661 (0.2%)</td><td>9/659 (1.4%)</td><td>10/657 (1.5%)</td></tr>
<tr><td>>10 and ≤20 ULN</td><td>0/661</td><td>4/659 (0.6%)</td><td>1/657 (0.2%)</td></tr>
<tr><td>>20 ULN</td><td>0/661</td><td>0/659</td><td>1/657 (0.2%)</td></tr>
<tr><td colspan="4">AST</td></tr>
<tr><td>>1 - 1.5 ULN</td><td>86/661 (13.0%)</td><td>153/659 (23.2%)</td><td>149/657 (22.7%)</td></tr>
<tr><td>>1.5 - 3 ULN</td><td>37/661 (5.6%)</td><td>82/659 (12.4%)</td><td>92/657 (14.0%)</td></tr>
<tr><td>>3 and ≤5 ULN</td><td>3/661 (0.5%)</td><td>12/659 (1.8%)</td><td>15/657 (2.3%)</td></tr>
<tr><td>>5 and ≤10 ULN</td><td>0/661</td><td>4/659 (0.6%)</td><td>3/657 (0.5%)</td></tr>
<tr><td>>10 and ≤20 ULN</td><td>0/661</td><td>3/659 (0.5%)</td><td>0/657</td></tr>
<tr><td>>20 ULN</td><td>0/661</td><td>0/659</td><td>1/65 (0.2%)</td></tr>
<tr><td colspan="4">Alkaline phosphatase</td></tr>
<tr><td>>1.5 ULN</td><td>19/661 (2.9%)</td><td>18/659 (2.7%)</td><td>14/657 (2.1%)</td></tr>
<tr><td>Total bilirubin</td><td></td><td></td><td></td></tr>
<tr><td>>1.5 ULN</td><td>1/661 (0.2%)</td><td>17/659 (2.6%)</td><td>18/657 (2.7%)</td></tr>
<tr><td>>2 ULN</td><td>1/661 (0.2%)</td><td>5/659 (0.8%)</td><td>5/657 (0.8%)</td></tr>
<tr><td colspan="4">ALT and total bilirubin</td></tr>
</table>
</td></tr>
</table>

Potential Risk	Clinically evident hepatic injury

ALT>3 ULN and Total Bilirubin (TBILI) >2 ULN	1/661 (0.2%)	2/659 (0.3%)	1/657 (0.2%)
Conjugated bilirubin			
>1.5 ULN	1/661 (0.2%)	1/659 (0.2%)	2/657 (0.3%)
>2 ULN	1/661 (0.2%)	0/659	2/657 (0.3%)
Unconjugated bilirubin			
>1.5 ULN	10/661 (1.5%)	33/658 (5.0%)	50/657 (7.6%)
>2 ULN	1/661 (0.2%)	17/658 (2.6%)	24/657 (3.7%)

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed during the TEAE period.

PGM=PRODOPS/SAR153191/OVERALL/CSS_EU/REPORT/PGM/lab_pcsa_liver_s_t_int_p1.sas OUT=REPORT/OUTPUT/lab_pcsa_liver_s_t_p1_int_i.rtf (15MAR2016 - 11:14)

ALT: Alanine Transaminase; AST: Aspartate Transaminase; DMARD: Disease Modifying Anti-Rheumatic Drug; N: Total Number of Patient; PCSA: Potentially Clinically Significant Abnormalities; TBILI: Total Bilirubin; TEAE: Treatment-Emergent Adverse Event; ULN: Upper Limit of Normal.

Pool 2: As expected with the longer observation time, the incidence of liver function PCSAs was numerically higher in the long-term safety population (Table 33b), but overall, the observations on liver function tests were consistent with what was seen in the placebo-controlled population, with the majority of elevations in ALT >1-3 x ULN.

Table 33b - Number (%) of patients with abnormalities (PCSA) - Sarilumab + DMARD long-term safety population (Pool 2)

	Sarilumab + DMARD
Laboratory parameter PCSA criteria n/N1 (%)	**Any Dose (N = 2887) (9892.5 PY)**
ALT	
>1 - 1.5 ULN	762/2876 (26.5%)
>1.5 - 3 ULN	816/2876 (28.4%)
>3 and ≤5 ULN	228/2876 (7.9%)
>5 and ≤10 ULN	73/2876 (2.5%)
>10 and ≤20 ULN	8/2876 (0.3%)
>20 ULN	4/2876 (0.1%)
AST	
>1 - 1.5 ULN	832/2876 (28.9%)
>1.5 – 3 ULN	538/2876 (18.7%)
>3 and ≤5 ULN	98/2876 (3.4%)
>5 and ≤10 ULN	27/2876 (0.9%)
>10 and ≤20 ULN	5/2876 (0.2%)
>20 ULN	4/2876 (0.1%)

Potential Risk	Clinically evident hepatic injury

Total bilirubin	
>1.5 ULN	139/2876 (4.8%)
>2 ULN	49/2876 (1.7%)
ALT and total bilirubin	
ALT >3 ULN and TBILI >2 ULN	10/2876 (0.3%)
Unconjugated bilirubin	
>1.5 ULN	318/2875 (11.1%)
>2 ULN	138/2875 (4.8%)

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed during the TEAE period.
PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/lab_pcsa_liver_s_t_p2.sas OUT=REPORT/OUTPUT/lab_pcsa_liver_s_t_p2_x.rtf (11JUN2021 - 9:57)

ALT: Alanine Transaminase; AST: Aspartate Transaminase; DMARD: Disease Modifying Anti-Rheumatic Drug; N: Total Number of Patient; PCSA: Potentially Clinically Significant Abnormalities, TBILI: Total Bilirubin; TEAE: Treatment-Emergent Adverse Event; ULN: Upper Limit of Normal.

Sarilumab monotherapy population (pool 3):

Table 33c provides maximum elevation of ALT in patients on sarilumab monotherapy. Consistent with administration of sarilumab in the absence of concomitant MTX or other DMARDs with the potential for hepatotoxicity, the incidence of patients with ALT elevations was lower in the sarilumab monotherapy population than in the population receiving sarilumab with concomitant DMARDs.

Table 33c - Number (%) of patients with ALT abnormalities (PCSA) - Sarilumab monotherapy safety population (Pool 3)

Laboratory parameter PCSA criteria n/N1 (%)	Sarilumab Monotherapy Any Dose
ALT	
>1 - 1.5 ULN	116/469 (24.7%)
>1.5 - 3 ULN	99/469 (21.1%)
>3 and ≤5 ULN	30/469 (6.4%)
>5 and ≤10 ULN	7/469 (1.5%)
>10 and ≤20 ULN	2/469 (0.4%)
>20 ULN	2/469 (0.4%)

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed during TEAE period.

PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/lab_pcsa_liver_s_t_p3.sas OUT=REPORT/OUTPUT/lab_pcsa_liver_s_t_p3_x.rtf (11JUN2021 - 9:58)

ALT: Alanine Transaminase; PCSA: Potentially Clinically Significant Abnormalities; TEAE: Treatment-Emergent Adverse Event; ULN: Upper Limit of Normal.

Table 33d - Liver function - Number (%) of patients with abnormalities (PCSA) during the entire TEAE period - Sarilumab monotherapy safety population (Pool 3)

Laboratory parameter PCSA criteria n/N1 (%)	Sarilumab Monotherapy Any Dose
Laboratory parameter	Any
PCSA criteria n/N1 (%)	Dose
	(N = 471)
AST	
>1 - 1.5 ULN	94/469 (20.0%)
>1.5 - 3 ULN	62/469 (13.2%)
>3 and ≤5 ULN	12/469 (2.6%)
>5 and ≤10 ULN	4/469 (0.9%)
>10 and ≤20 ULN	0/469
>20 ULN	1/469 (0.2%)
Alkaline phosphatase	
>1.5 ULN	4/469 (0.9%)
Total bilirubin	
>1.5 ULN	27/469 (5.8%)
>2 ULN	8/469 (1.7%)
Conjugated bilirubin	
>1.5 ULN	0/469
Unconjugated bilirubin	
>1.5 ULN	61/469 (13.0%)
>2 ULN	33/469 (7.0%)
ALT and total bilirubin	
ALT >3 ULN and TBILI >2 ULN	1/469 (0.2%)
Conjugated and total bilirubin	
Conjugated Bilirubin (CBILI) >35% TBILI and TBILI >1.5 ULN	0/469

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed during TEAE period.

PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/lab_pcsa_liver_s_t_p3.sas OUT=REPORT/OUTPUT/lab_pcsa_liver_s_t_p3_x.rtf (11JUN2021 - 9:58)

ALT: Alanine Transaminase; AST: Aspartate Transaminase; CBILI: Conjugated Bilirubin; DMARD: Disease Modifying Anti-Rheumatic Drug; N: Total Number of Patient; PCSA: Potentially Clinically Significant Abnormalities, TBILI: Total Bilirubin; TEAE: Treatment-Emergent Adverse Event; ULN: Upper Limit of Normal.

PMR study (EFC15160):

In the sarilumab 200 mg + 14-week taper group, all episodes of ALT or AST increase were Grade 1. None of the PMR participants had ALT or AST increased >3x ULN. No

Potential Risk	Clinically evident hepatic injury

cases of potential Hy's Law (ALT >3x ULN and bilirubin >2x ULN) and no cases of hepatic failure were reported. In the placebo + 52-week taper group, three participants had liver transaminase abnormalities; one participant had Grade 3 AST increase, one participant had Grade 2 ALT increase, and one participant had Grade 3 ALT increase.

Three participants had an Alkaline Phosphatase (ALP) increase, two in the placebo + 52-week taper group and one in the sarilumab 200 mg + 14-week taper group (all were Grade 1). Incidence of blood bilirubin increase was similar between 2 groups.

Table 33e - Number (%) of patients with Alanine Aminotransferase Increased during the TEAE period by maximum grade - Safety population - Study EFC15160

Laboratory parameter (CTCAE)	Placebo + 52-week taper (N=58)	Sarilumab 200 mg q2w + 14-week taper (N=59)	All (N=117)
Alanine Aminotransferase Increased			
Grade 1	8/58 (13.8)	20/58 (34.5)	28/116 (24.1)
Grade 2	1/58 (1.7)	0/58	1/116 (0.9)
Grade 3	1/58 (1.7)	0/58	1/116 (0.9)
Grade 4	0/58	0/58	0/116

Alanine aminotransferase increased: Grade 1: >ULN - 3.0x ULN, Grade 2: >3.0 - 5.0x ULN, Grade 3: >5.0 - 20.0x ULN, Grade 4: >20.0x ULN

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline.

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/adhoc_lab_ctcae_s_t.sas OUT=REPORT/OUTPUT/adhoc_lab_ctcae_alt_s_t_x.rtf (01JUN2022 5:05).

CTCAE: Common Terminology Criteria for Adverse Event; N: Total Number of Patient; q2w: Once Every Two Weeks; ULN: Upper Limit of Normal

pJIA study (DRI13925):

During the entire treatment period, one (1.1%) participant on the selected dose 2 had ALT >3 x ULN. No participant had concurrent ALT >3 x ULN and bilirubin >2 x ULN. No Hy's law cases were identified in the pJIA study.

Severity and nature of risk

RA studies:

Sarilumab administration was associated with a higher incidence of transaminase elevations, with the majority of ALT elevation <3x ULN. Elevations in transaminases were not associated with clinically meaningful increases in CBILI or clinical evidence of hepatitis or hepatic insufficiency. No cases met the criteria for Hy's Law. Alanine Aminotransferase elevations >3x ULN were generally transient, and the majority of these patients continued with sarilumab therapy. Consistent with administration in the absence of MTX or other DMARDs, a lower incidence of ALT elevations, including elevations >3x ULN, was observed in the monotherapy population than in the sarilumab plus DMARD populations.

PMR study (EFC15160):

In the EFC15160 study, none of the participants in sarilumab group had ALT or AST increased >3x ULN.

pJIA study (DRI13925):

Potential Risk	Clinically evident hepatic injury
	During the entire treatment period, one (1.1%) participant on the selected dose 2 had ALT >3 x ULN. No participant had concurrent ALT >3 x ULN and bilirubin >2 x ULN. No Hy's law cases were identified in the pJIA study. **Seriousness/outcomes** RA studies: There were no fatal cases. In the sarilumab long-term safety population, there were 10 patients who had ALT >3x ULN and TBILI >2x ULN and did not meet criteria for Hy's law (ie, concomitant elevation with no plausible alternative explanation). The occurrences of ALT >10x ULN was infrequent (0.4% [12 patients]). All 12 patients in the sarilumab plus DMARD long-term safety population with ALT >10x ULN had alternative explanations for their transaminases increase or confounding factors; none of the cases were suggestive of drug induced hepatic insufficiency or hepatic failure. The elevation in ALT was transient. Of the 313 patients on any dose of sarilumab who had an ALT >3x ULN, 176 (61%) patients normalized on-treatment (ie, at least 1 ALT value was normal within ≤17 days after last dose of sarilumab), 72 (25%) patients normalized after discontinuation of sarilumab, and 65 (23%) patients had not normalized as of the last available assessment. In the 65 patients who had not normalized, none of the patients were still enrolled in the studies and continued receiving sarilumab therapy. Of the patients who had permanently discontinued sarilumab, but normalization was not documented, the median time of the ALT last value from their last dose of sarilumab was 37 days. In the majority of these patients, the last measured ALT value was <3x ULN with over one-third between 1-1.5x ULN, suggesting that the patient was trending toward normalization. In the 11 patients whose last value was >3x ULN, the median follow-up time was 15 days from the last Investigational Medicinal Product (IMP) which did not allow for adequate follow-up time to assess for normalization. Overall, the occurrence of ALT >3x ULN in patients treated with sarilumab plus DMARD was transient. Similar to the concomitant DMARD population, there were no fatal events or cases that met Hy's Law criteria in the monotherapy population. In summary, patients experienced elevations in transaminases that were not associated with clinically meaningful increases in CBILI or clinical evidence of hepatitis or hepatic insufficiency. No cases met Hy's Law criteria (ie, ALT >3x ULN and total bilirubin >2x ULN with no plausible alternative explanation). PMR study (EFC15160): In the EFC15160 study, none of the participants in sarilumab group had ALT or AST increased >3x ULN. pJIA study (DRI13925): In the pJIA study, during the entire treatment period, one (1.1%) participant on the selected dose 2 had ALT >3 x ULN. No participant had concurrent ALT >3 x ULN and bilirubin >2 x ULN. No Hy's law cases were identified in the pJIA study. **Postmarketing safety experience (RA indication)** Ongoing monitoring of the postmarketing data up to DLP did not reveal any new emerging information impacting the characterization of this important potential risk. **Background incidence/prevalence** Liver dysfunction is observed in 18% to 50% of RA patients and in most cases liver dysfunction is induced by anti-rheumatic drugs used for treatment of RA. (91) In a cross sectional study in Pakistan among 140 RA patients treated with low dose MTX, liver toxicity was found in 8.6% of patients. (87) In a 12-month prospective, observational study carried out in 40 Spanish centers of 379 adult patients with moderate or severe RA who initiated treatment with TCZ, the frequency of elevation of liver transaminases at follow-up was 4.7%. (78)

Potential Risk	Clinically evident hepatic injury
	The incidence rate of serious hepatic events in patients with RA is 4.9 per 10 000 per year, and the incidence rate of non-serious hepatic events in patients with RA is 80.0 per 10 000 per year. There was no increase in the rate of serious hepatic events with either leflunomide (RR: 0.9; 95% CI: 0.2-4.9) or traditional DMARDs (2.3; 0.8-6.5). However, the rate was increased with biologic DMARDs (5.5; 1.2-24.6). The rate of non-serious hepatic events was also increased with biologic DMARDs (1.5; 1.0-2.3), but not with leflunomide (0.9; 0.7-1.3) and traditional DMARDs (1.1; 0.8-1.4). (92) There are potential immune-mediated origins of liver damage in patients with PMR. In fact, certain researchers have noted a rise in Anti-Mitochondrial Autoantibody (AMA) in as many as 30% of individuals with PMR. (93) In patients with PMR and GCA, liver involvement, particularly of a cholestatic nature, may be observed and often resolves with the administration of glucocorticoid therapy. (93) RA and pJIA patients administering TCZ should caution hepatic AEs. For example, rates of severe hepatic AEs occurred in approximately 0.04/100 PYs in the TCZ population. (94) **Impact on individual patient** Effects on liver can range from clinically insignificant to fulminant hepatic failure resulting in death.
Risk factors and risk groups	RA and PMR: A higher incidence of ALT >3x ULN was seen in patients whose baseline ALT was >ULN in the placebo-controlled population and the sarilumab plus DMARD long-term safety population compared to patients whose baseline ALT values were not >ULN. pJIA: In the pJIA study, no Hy's Law cases were identified.
Preventability	Initiation of sarilumab is not recommended for patients with ALT or AST >1.5x ULN. Routine monitoring of liver enzymes for early detection and dose modification (reduction/interruption/discontinuation) according to ALT level is recommended.
Impact on the benefit-risk balance of the product	The benefit-risk balance remained positive for patients treated in respect to the valid labeling recommendations.
Public health impact	Hepatic injury may lead to hospitalization and/or prolonged hospitalization, and thus, to increased public health care spending, loss of economic productivity and potentially loss of work-force due to potential risk of serious hepatic injury, which may lead to fatal outcomes if not treated on time and adequately.

Postmarketing safety experience information has been aligned with PBRER DLP 12-Jan-2023.
AE: Adverse Event; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AMA: Anti-Mitochondrial Autoantibody; AST: Aspartate Aminotransferase; CBILI: Conjugated Bilirubin; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Event; DLP: Data Lock Point; DMARD: Disease Modifying Anti-Rheumatic Drug; GCA: Giant Cell Arteritis; IL-6: Interleukin-6; IMP: Investigational Medicinal Product; MTX: Methotrexate; N: Total Number of Patient; PBRER: Periodic Benefit-Risk Evaluation Report; PCSA: Potentially Clinically Significant Abnormalities; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; q2w: Once Every Two Weeks; RA: Rheumatoid Arthritis; RR: Risk Ratio; TBILI: Total Bilirubin; TCZ: Tocilizumab; TEAE: Treatment-Emergent Adverse Event; ULN: Upper Limit of Normal.

Table 34 - Potential risk: Lipid abnormalities and increased risk of major cardiovascular adverse events

Potential Risk	Lipid abnormalities and increased risk of major cardiovascular adverse events
Potential mechanism	Interleukin-6 reduces total cholesterol and triglycerides in animals and humans. The exact mechanism by which IL-6 induces these changes still remains unknown. However, IL-6 may affect lipid metabolism by stimulating lipid uptake via very low-density

Potential Risk	Lipid abnormalities and increased risk of major cardiovascular adverse events
	lipoprotein receptor induction, increasing hepatic and adipose tissue lipolysis and decreasing hepatic lipid synthesis. Interleukin-6 blockade normalizes reduced lipid levels caused by IL-6 but does not affect normal lipid metabolism. (95)
Evidence source(s) and strength of evidence	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with laboratory abnormalities of increased lipids, consistent with its mechanism of action and may increase the risk of major adverse cardiovascular event (MACE).
Characterization of the risk	**Frequency with 95% CI** RA studies: **Lipids** A mean increase from baseline in low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides was observed in the sarilumab plus DMARD treatment groups compared to placebo plus DMARD, with similar increases observed between the 2 sarilumab doses. This increase was observed 4 weeks after initiation of therapy (ie, first time point measured). In the sarilumab plus DMARD groups at Week 4, the mean increase in LDL was approximately 14 mg/dL (16%) and the mean increase in triglycerides was approximately 23 mg/dL (23%), and then both remained stable. The mean increase in HDL was approximately 3 mg/dL (6%). Although increases were observed, mean values remained in the normal range. Similar to the sarilumab plus DMARD populations, a mean increase from baseline in LDL, HDL, and triglycerides was observed at 4 weeks after initiation of sarilumab monotherapy (ie, first time point measured). At week 4 the mean increase in LDL was approximately 0.32 mmol/L (13%), mean increase in HDL was approximately 0.03 mmol/L (3%) and the mean increase in triglycerides was approximately 0.32 mmol/L (29%). Although increases were observed, mean values remained in the normal range. Based on average of post-baseline LDL values, the majority of patients did not have a shift in National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) LDL classification during sarilumab plus DMARD treatment. Of those who shifted up a NCEP ATP III LDL classification, the majority shifted up 1 classification, with a numerically higher incidence observed in the sarilumab treatment groups compared to placebo. A numerically higher incidence of patients on sarilumab initiated statins compared to placebo with no difference observed between the 2 doses of sarilumab (3 [0.5%] in the placebo-controlled population, 16 patients [2.4%] in 150 mg q2w, and 16 patients [2.4%] in 200 mg q2w). pJIA study: In the pediatric study (in the safety population), a mean decrease from baseline in LDL and triglycerides, and a mean increase from baseline in HDL was observed 4 weeks after initiation of sarilumab treatment. At week 4, the mean decrease from baseline in LDL was 0.05 mmol/L, the mean decrease from baseline in triglycerides was 0.03 mmol/L and the mean increase in HDL was 0.045. A similar pattern was observed in later weeks for LDL and HDL, while an increase in triglycerides was observed from week 12 to week 20. At week 20, a decrease in triglycerides was observed again. Although an increase in triglycerides was observed, values remained in the normal range. No MACE were observed in the study. **Major adverse cardiovascular event** RA studies:

Potential Risk	Lipid abnormalities and increased risk of major cardiovascular adverse events

An external Cardiovascular Adjudication Committee (CAC) was utilized in the Phase 3 studies. The CAC reviewed and adjudicated all deaths and serious CV AEs in a blinded fashion to identify events of MACE (primary), which were defined as CV death (including undetermined cause of death), myocardial infarction, stroke, hospitalization for unstable angina, or hospitalization for transient ischemic attack. Serious CV AEs sent for adjudication were identified by a list of SMQs as specified in the CAC Charter. In addition, any non-serious AE requiring a CV procedure was sent for adjudication.

Placebo-controlled population (Pool 1): No events were observed in placebo, and 2 events of MACE were observed in each of the sarilumab treatment groups (incidence rate [95% CI] in each group: 0.5 [0.05, 1.63]); Sarilumab plus DMARD long-term safety population (Pool 2): The incidence (95% CI) of MACE (primary) was 0.5 patients/100 PY (0.35, 0.64).

Table 34a provides the number of events of MACE as adjudicated by category.

Note: Patient may have had more than 1 MACE event and included in more than one category.

Table 34a - Number (%) patients with adjudicated treatment-emergent CV events and number of events during the entire TEAE period - sarilumab plus DMARD long-term safety population (Pool 2)

	Sarilumab + DMARD	
CV Events Category	**Any Dose (N = 2887)**	**Any Dose (PY = 10322.0) nE (nE/100 PY)**
MACE (primary)	50 (1.7%)	54 (0.5)
MACE (narrow)	45 (1.6%)	47 (0.5)
CV Death	16 (0.6%)	16 (0.2)
Myocardial infarction	2 (<0.1%)	1 (0.0)
Heart Failure	3 (0.1%)	3 (0.0)
Stroke	3 (0.1%)	3 (0.0)
Other CV Causes	7 (0.2%)	7 (0.1)
Undetermined cause of Death	1 (<0.1%)	1 (0.0)
Myocardial infarction (non-fatal)	17 (0.6%)	17 (0.2)
Hospitalization for unstable angina (non-fatal)	2 (<0.1%)	2 (0.0)
Stroke (non-fatal)	14 (0.5%)	15 (0.2)
Hospitalization for transient ischemic attack (non-fatal)	4 (0.1%)	5 (0.1)

Potential Risk	Lipid abnormalities and increased risk of major cardiovascular adverse events

MACE (primary) includes CV Death, Myocardial infarction, Stroke, Hospitalization for unstable angina or Hospitalization for Transient Ischemic Attack.
MACE (narrow) includes CV Death, Myocardial infarction, or Stroke.
n (%) = number and percentage of patients with at least one adjudicated treatment-emergent CV event.
nE(nE /100 PY) = number of events and number of events per 100 PY.
PY for a treatment group is the total treatment duration of the treatment group.
PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/ae_cv_adj_summ_s_t_p2.sas OUT=REPORT/OUTPUT/ae_cv_adj_summ_s_t_p2_x.rtf (11JUN2021 - 7:59)
CV: Cardiovascular, DMARD: Disease Modifying Anti-Rheumatic Drug; MACE: Major Adverse Cardiovascular Event; N: Total Number of Patient; PY: Patient-Year; TEAE: Treatment Emergent Adverse Event.

Table 34b provides the number of events of MACE as adjudicated by category.

Note: Patient may have had more than 1 MACE event and included in more than one category.

Table 34b - Number (%) patients with adjudicated treatment-emergent CV events and number of events during the entire TEAE period - sarilumab monotherapy safety population (Pool 3)

	Sarilumab	
CV Events Category	**Any Dose (N = 471)**	**Any Dose (PY = 1768) nE (nE/100 PY)**
MACE (primary)	7 (1.5%)	7 (0.4)
MACE (narrow)	7 (1.5%)	7 (0.4)
CV Death	3 (0.6%)	3 (0.2)
Stroke	2 (0.4%)	2 (0.1)
Other CV Causes	1 (0.2%)	1 (0.1)
Myocardial infarction (non-fatal)	1 (0.2%)	1 (0.1)
Hospitalization for unstable angina (non-fatal)	0	0
Stroke (non-fatal)	3 (0.6%)	3 (0.2)
Hospitalization for transient ischemic attack (non-fatal)	0	0

MACE (primary) includes CV Death, Myocardial infarction, Stroke, Hospitalization for unstable angina or Hospitalization for Transient Ischemic Attack.
MACE (narrow) includes CV Death, Myocardial infarction, or Stroke.
n (%) = number and percentage of patients with at least one adjudicated treatment-emergent CV event.
nE(nE /100 PY) = number of events and number of events per 100 PY.
PY for a treatment group is the total treatment duration of the treatment group.
PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/ae_cv_adj_summ_s_t_p3.sas OUT=REPORT/OUTPUT/ae_cv_adj_summ_s_t_p3_x.rtf (11JUN2021 - 7:59)
CV: Cardiovascular; DMARD: Disease Modifying Anti-Rheumatic Drug; MACE: Major Adverse Cardiovascular Event; N: Total Number of Patient; PY: Patient-Year; TEAE: Treatment Emergent Adverse Event.

PMR study (EFC15160):

	At Week 52, a mean change from baseline of approximately 0.699 mmol/L in mean LDL and 0.034 mmol/L in triglycerides was observed in the sarilumab 200 mg + 14-week taper group compared to no changes observed in the placebo + 52-week taper group. Both LDL and triglycerides remained within the normal range. Mean HDL did not present significant differences between placebo and sarilumab groups. The HDL levels remained within the normal range throughout the study. pJIA study (DRI13925): No MACE was observed in the pediatric study (pJIA). **Severity and nature of risk** RA studies: Sarilumab administration is associated with elevation in lipids. The observed rate for MACE in the patients receiving sarilumab plus DMARD was not higher than the background rate for the RA population. PMR study (EFC15160): In the EFC15160 study (PMR), no lipid increases over time resulted in clinically meaningful AEs. No events of MACE were reported in the sarilumab arm of the PMR Study. pJIA study (DRI13925): No MACE was observed in pJIA population. **Seriousness/outcomes** RA studies: A total of 54 events were adjudicated as MACE (primary) in 50 patients. Of these 50 patients, the mean age was 60.1 years, and the majority of patients had underlying CV risk factors (ie, hypertension, diabetes, dyslipidemia, coronary artery disease, ischemic cerebrovascular disease, and/or family history of coronary artery disease). Sixteen patients had fatal outcome. PMR study (EFC15160): In the EFC15160 study (PMR), no lipid increases over time resulted in clinically meaningful AEs. pJIA study (DRI13925): No MACE was observed in pJIA population. **Postmarketing safety experience (RA indication)** Ongoing monitoring of the postmarketing data up to DLP did not reveal any new emerging information impacting the characterization of this risk. **Background incidence/prevalence** In a population-based longitudinal cohort study performed in The Health Improvement Network (THIN), the overall incidence rate of MACE (narrow) (CV death, non-fatal myocardial infarction, stroke) was 1.11 patients/100 PY in RA patients on DMARDs. The rate of CV death was 0.46 patients/100 PY, non-fatal myocardial infarction was 0.51 patients/100 PY, and stroke was 0.42 patients/100 PY. (96) Investigations examining the role of dyslipidemia in RA are somewhat contradictory but suggest that serum lipids oscillate according to the duration of disease and/or severity of disease. In severe active RA, patients have been reported to have significantly lower serum levels of total cholesterol, HDL and LDL. In contrast, RA patients with early, untreated disease, show significant declines in HDL with concomitant elevations in LDL and total cholesterol/HDL ratios, lipid profiles known to correlate with an increased incidence of CV disease. (25) In the US, a study based on electronic medical record from 2005 RA subjects from 2 large academic medical centers showed that women with RA compared to the general population had a significantly lower total

Potential Risk	Lipid abnormalities and increased risk of major cardiovascular adverse events

cholesterol (186 versus 200 mg/dL; P ≤0.002) and LDL cholesterol (105 versus 118 mg/dL; P ≤0.001). High density lipoprotein cholesterol was not significantly different in the 2 groups. RA patients appear to have an overall lower total cholesterol and LDL cholesterol than the general population despite the general overall increased risk of CV disease from observational studies. (97)

In the US, a population-based cohort study of 603 RA and 603 non-RA subjects was conducted and found that at baseline the prevalence of dyslipidemia was 49% (in RA group) and 52% (in non-RA group), respectively. The incidence of dyslipidemia was significantly different in RA patients (2.71/100 PY) and in non-RA (3.64/100 PY).

Although the reasons and the clinical significances of changes in lipid profiles in the RA population are not clear, it is assumed that it may increase the overall CV risk in the RA population. Plasma lipid changes in RA patients are often detected in clinical tests, the systemic inflammatory status and drug treatment of RA patients can interact with the metabolic level of the body. (98)

The Hazard Ratio (HR) for CV disease in patients with PMR is 1.47 (95% CI: 1.40 to 1.54) compared to matched controls. (99)

Another study including data from a recent national cohort study from the UK support the increased risk of vascular disease (adjusted HR 1.23 [95% CI: 1.19-1.28]) after PMR diagnosis. However, this may have been impacted by surveillance bias. (100)

In a prospective study in 28 patients with pJIA from Brazil who all fulfilled the ILAR criteria for JIA, the lipoprotein levels showed a mean total cholesterol (TC) level of 150.3 ± 26.0 mg/dL, LDL level of 83.6 ± 23.1 mg/dL, HDL level of 50.6 ± 11.6 mg/dL, and triglyceride (TG) level of 81.6 ± 49.4 mg/dL (Values are expressed as the mean ± SD) (Table 34c). When compared to age-adjusted normal lipoprotein levels, 57% of the subjects (16 out of 28) had decreased HDL levels. However, abnormal TC, LDL, and TG levels were only observed in 7% (2 out of 28), 18% (5 out of 28), and 14% (4 out of 28) of the patients, respectively. Notably, male patients had lower HDL levels compared to female patients (42.6 ± 12.6 mg/dL versus 53.3 ± 10.1 mg/dL, respectively; p<0.05). (101)

Table 34c - Characteristics and lipid profiles of 28 patients with polyarticular JIA (101)

Variable	JIA patients (N=28)	Female gender (N=21)	Male gender (N=7)	p-value
Age, years	19.86 ± 5.79 (5-29)	20.00 ± 5.64	19.43 ± 6.68	0.826
Age at diagnosis, years	10.00 ± 5.03 (1-16)	9.62 ± 4.96	11.14 ± 5.43	0.498
Disease duration, years	9.36 ± 5.41 (1-25)	9.71 ± 5.12	8.29 ± 6.52	0.555
TC, mg/dl	150.29 ± 26.04 (104-206)	150.71 ± 26.44	149.00 ± 26.78	0.883
TG, mg/dl	81.61 ± 49.36 (33-255)	72.62 ± 35.00	108.57 ± 75.82	0.265
HDL, mg/dl	50.61 ± 11.55 (30-74)	53.29 ± 10.11	42.57 ± 12.62	0.031

Potential Risk	Lipid abnormalities and increased risk of major cardiovascular adverse events
	<table><tr><td>LDL, mg/dl</td><td>83.61 ± 23.06 (41-138)</td><td>83.29 ± 22.49</td><td>84.57 ± 26.58</td><td>0.901</td></tr><tr><td>CV risk factor, number</td><td>0.96 ± 0.92 (0-4)</td><td>0.90 ± 0.89</td><td>1.14 ± 1.07</td><td>0.64</td></tr></table> Note: Data are expressed as mean ± standard deviation; the values in parentheses indicate the range. CV: Cardiovascular; HDL: High-Density Lipoprotein; JIA: Juvenile Idiopathic Arthritis; LDL: Low-Density Lipoprotein; N: Total Number of Patient; TC: Total Cholesterol; TG: Triglyceride. **Impact on individual patient** Cardiovascular events may be life threatening or result in death.
Risk factors and risk groups	Rheumatoid arthritis is associated with increased CV morbidity and mortality, related not only to traditional CV risk factors (eg, age, gender, diabetes, hyperlipidemia, and hypertension), but also to a chronic inflammatory state. (102) The results in a publication from a randomized, parallel-group, multicenter, non-inferiority, Phase 4 clinical trial to asses CV safety of TCZ (IL-6 inhibitor) were compared with etanercept in RA, showed that 83 MACE occurred over 4900 PYs in the TCZ arm versus 78 over 4891 PYs in the etanercept arm (HR 1.05; 95% CI: 0.77-1.43). (103) As of now, there remains uncertainty in the available evidence regarding the risk of vascular disease among individuals with PMR. Several biologically plausible mechanisms connecting PMR to vascular disease have been proposed. These mechanisms encompass factors such as the inflammatory load associated with the condition, subclinical arteritis, stenosis or aneurysms, and the adverse effects of long-term CS treatment (eg, diabetes, hypertension, and dyslipidemia). These combined factors contribute to the complex relationship between PMR and vascular disease. (104) In pJIA, abnormal lipid levels and atherogenic indices could be associated with disease activity in JIA. (105)
Preventability	Monitor lipid parameters and manage elevations as per NCEP guidelines.
Impact on the benefit-risk balance of the product	The benefit-risk balance remained positive for patients treated in respect to the valid labeling recommendations.
Public health impact	Lipid abnormalities may result in CV (MACE) events that may lead to hospitalization and/or prolonged hospitalization, and thus, to increased public health care spending, loss of economic productivity and potentially loss of work-force due to potential risk of serious MACE events leading to fatal outcomes and/or premature deaths vs. the background population without the indication (eg, RA, which carries an increased risk of MACE - background rate in untreated RA patients, see risk factors and risk groups section).

Postmarketing safety experience information has been aligned with PBRER DLP 12-Jan-2023.
AE: Adverse Event; ATP III: Adult Treatment Panel III; CAC: Cardiovascular Adjudication Committee; CI: Confidence Interval; CS: Corticosteroid; CV: Cardiovascular; DMARD: Disease Modifying Anti-Rheumatic Drug; HDL: High Density Lipoprotein; HR: Hazard Ratio; IL-6: Interleukin-6; ILAR: International League of Associations for Rheumatology; IR: Incidence Rate; JIA: Juvenile Idiopathic Arthritis; LDL: Low Density Lipoprotein; MACE: Major Adverse Cardiovascular Event; NCEP: National Cholesterol Education Program; PBRER: Periodic Benefit-Risk Evaluation Report; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; PY: Patient-Year; q2w: Once Every Two Weeks; RA: Rheumatoid Arthritis; SD: Standard Deviation; SMQ: Standardized MedDRA Query; TEAE: Treatment Emergent Adverse Event; TC: Total Cholesterol; TCZ: Tocilizumab; TG: Triglyceride; THIN: The Health Improvement Network; UK: United Kingdom; US: United States.

Table 35 - Potential risk: Malignancy

<table>
<tr><th>Potential Risk</th><th>Malignancy</th></tr>
<tr><td>Potential mechanism</td><td>The immunomodulatory effects of biologic DMARDs used in the treatment of RA may result in an increased risk of malignancies.</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of non-clinical findings, as well as of clinical safety data observed with sarilumab during the clinical development program. Due to the immunomodulatory effects of biologic DMARDs used in the treatment of RA, treatment may result in an increased risk of malignancies. Since a higher rate of malignancy was not observed in patients treated with sarilumab compared to the general population or patients with RA, this is considered an important potential risk.</td></tr>
<tr><td>Characterization of the risk</td><td><u>Frequency with 95% CI</u>
<u>RA studies</u>:
<u>Placebo-controlled population (Pool 1)</u>: The exposure-adjusted event rate of any malignancy including Non-Melanoma Skin Cancer (NMSC) was similar between the 3 treatment groups (ie, 1.0 events/100 PY in placebo, 1.1 events/100 PY in 150 mg q2w, and 0.9 events/100PY in 200 mg q2w).
Sarilumab plus DMARD long-term safety population (Pool 2): The event rate of any malignancy was 0.6 events/100 PY and the rate of any malignancy excluding NMSC was 0.5 events/100 PY. Table 35b provides the total number of malignancies during the TEAE period.
Sarilumab monotherapy population (Pool 3): The event rate of any malignancy was 0.8 events/100 PY and the rate of malignancy excluding NMSC was 0.7 events/100 PY. Table 35c provides the total number of malignancies during the TEAE period. Table 35a compares the number of events of malignancy observed in the sarilumab plus DMARD long-term safety population to the expected number of patients in the study population in the Surveillance, Epidemiology, and End Results Program (SEER) database. Based on Standardized Incidence Ratio (SIRs) using the SEER database, the rates observed in clinical development program are consistent with the overall rate in observed in the general population. No definitive conclusions can be made regarding the cause for the small number of events of renal and renal pelvic cancer (3 events) and small intestinal cancer (1 event), respectively.
Table 35a - Standard incidence ratios for malignancies in sarilumab + DMARD long-term safety population: general population (SEER database 2003-2012)
<table>
<tr><th>Malignancy</th><th>Observed Number of Events in Sarilumab + D MARD (any dose)</th><th>Expected Number of Events Based on the Incidence Rates in general population patients in SEER database[a]</th><th>SIR[b] (95% CI)</th></tr>
<tr><td>Any malignancy</td><td>47</td><td>40.52</td><td>1.16 (0.87 - 1.54)</td></tr>
<tr><td>Non-melanoma skin cancer</td><td>15</td><td>Not included in SEER</td><td>Not calculated</td></tr>
<tr><td>Breast cancer</td><td>6</td><td>10.47</td><td>0.57 (0.26 - 1.28)</td></tr>
<tr><td>Colorectal cancer</td><td>4</td><td>3.48</td><td>1.15 (0.43 - 3.07)</td></tr>
<tr><td>Lung cancer</td><td>3</td><td>4.78</td><td>0.63 (0.20 - 1.95)</td></tr>
</table>
</td></tr>
</table>

Potential Risk	Malignancy

Malignant melanoma	3	1.71	1.75 (0.56 - 5.43)
Renal and renal pelvic cancer	3	1.22	2.46 (0.79 - 7.63)
Bladder	2	1.06	1.88 (0.47 - 7.51)
Thyroid cancer	2	1.46	1.37 (0.34 - 5.48)
Appendiceal cancer	1	Not available	Not calculated
Cervical cancer	1	0.60	1.66 (0.23-11.82)
Pancreatic cancer	1	0.88	1.13 (0.16 - 8.05)
Prostate	1	3.42	0.29 (0.04 - 2.07)
Small intestinal cancer	1	0.18	5.50 (0.77 - 39.02)
Tumor of unspecified malignancy	1	Not available	Not calculated
Hematologic	3	Not available	Not calculated

a SEER database did not provide incidence rate when some age groups had <16 cases. Hence for such categories incidence was considered as zero.

b SIR adjusted for age and gender

CI: Confidence Interval; DMARD: Disease Modifying Anti-Rheumatic Drug; SEER: Surveillance, Epidemiology, and End Results Program; SIR: Standardized Incidence Ratio.

Table 35b - Overview of malignancy TEAEs by site: number (%) patients and events - Sarilumab + DMARD long-term safety population (Pool 2)

	Sarilumab + DMARD
	(Any Dose)
Total number of patients	**2887**
Total treatment duration in PY	10 322.0
Treatment duration up to the first event in PY[a]	10 268.6
Total patients with ≥1 Malignancy (%)	63 (2.2%)
Number of patients with ≥1 Malignancy per 100 PY	0.6
Total number of Malignancy (per 100 PY)	67 (0.7)
Non-melanoma skin cancer - total number of events (events/100 PY)	0
Total patients with ≥1 Malignancy excluding NMSC (%)	49 (1.7%)
Number of patients with ≥1 Malignancy excluding NMSC per 100 PY	0.5
Total number of Malignancy excluding NMSC (per 100 PY)	49 (0.5)

Potential Risk	Malignancy

Solid tumors excluding NMSC - total number of events (events/100 PY)	46 (0.5)
Breast cancer	8 (0.1)
Lung cancer	7 (0.1)
Colorectal cancer	5 (0.1)
Renal and renal pelvic cancer	4 (0.0)
Malignant melanoma	3 (0.0)
Prostate	3 (0.0)
Bladder cancer	2 (0.0)
Cervical cancer	2 (0.0)
Pancreatic cancer	2 (0.0)
Thyroid cancer	2 (0.0)
Ovarian	2 (0.0)
Appendiceal cancer	1 (0.0)
Gallbladder cancer	1 (0.0)
Lip and oral cavity	1 (0.0)
Rectal cancer	1 (0.0
Small intestinal cancer	1 (0.0)
Tumor of unspecified malignancy	1 (0.0)
Hematologic - total number of events (events/100 PY)	3 (0.1)
B-cell lymphoma	1 (0.0)
Lymphoproliferative disorder	1 (0.0)
Plasmacytoma	1 (0.0)

MedDRA 23.1
Search criteria: SMQ Malignant or unspecified tumours. Table sorted by decreasing frequency of Preferred Term (PT) in the any dose treatment group.

a For patients with no such event, the duration is up to the end of the treatment duration.

PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/ae_aesi_malign_s_t_p2.sas OUT=REPORT/OUTPUT/ae_aesi_malign_s_t_p2_int_x.rtf (11JUN2021 - 9:05)

MedDRA: Medical Dictionary for Regulatory Activities; NMSC: Non-Melanoma Skin Cancer; PT: Preferred Term; PY: Patient-Year; SMQ: Standard MedDRA Query; TEAE: Treatment-Emergent Adverse Event.

Table 35c - Overview of malignancy TEAEs by site: number (%) patients and events - Sarilumab monotherapy safety population (Pool 3)

	Sarilumab
	Any Dose
Total number of patients	471
Total treatment duration in PY	1768.9

Potential Risk	Malignancy

Treatment duration up to the first event in PY[a]	1760.6
Total patients with ≥1 Malignancy (%)	12 (2.5%)
Number of patients with ≥1 Malignancy per 100 PY	0.7
Total number of Malignancy (per 100 PY)	14 (0.8)
Non-melanoma skin cancer - total number of events (events/100 PY)	0
Total patients with ≥1 Malignancy excluding NMSC (%)	11 (2.3%)
Number of patients with ≥1 Malignancy excluding NMSC per 100 PY	0.6
Total number of Malignancy excluding NMSC (per 100 PY)	13 (0.7)
Solid tumors excluding NMSC - total number of events (events/100 PY)	11 (0.7)
Lung cancer	2 (0.1)
Tumor of unspecified malignancy	1 (0.1)
Embryo	1 (0.1)
Gallbladder cancer	1 (0.1)
Gastrointestinal	1 (0.1)
Mesenterium	1 (0.1)
Malignant melanoma	1 (0.1)
Peritoneum	1 (0.1)
Skin	1 (0.1)
Ureter	1 (0.1)
Hematologic - total number of events (events/100 PY)	2 (0.1)
Chronic lymphocytic leukaemia	1 (0.1)
Metastases to pleura	1 (0.1)

MedDRA 23.1

Search criteria: SMQ Malignant or unspecified tumours. Table sorted by decreasing frequency of PT in the any dose treatment group.

a For patients with no such event, the duration is up to the end of the treatment duration.

PGM=PRODOPS/SAR153191/OVERALL/CSS_2021/REPORT/PGM/ae_aesi_malign_s_t_p3.sas OUT=REPORT/OUTPUT/ae_aesi_malign_s_t_p3_int_x.rtf (11JUN2021 - 9:05) MedDRA: Medical Dictionary for Regulatory Activities; NMSC: Non-Melanoma Skin Cancer; PT: Preferred Term; PY: Patient-Year; SMQ: Standard MedDRA Query; TEAE: Treatment-Emergent Adverse Event.

PMR study (EFC15160):

Three cases were reported each in the sarilumab 200 mg + 14-week taper group (5.1%) and the placebo + 52-week taper group (5.2%). In the sarilumab 200 mg + 14-week taper group, two cases of benign neoplasms of thyroid gland and one case (1.7%) of basal cell carcinoma were reported. In the placebo + 52-week taper group, there was a single case each (1.7%) of basal cell carcinoma, colon adenoma, and Erdheim-Chester disease. None of these events led to fatal outcome.

pJIA study (DRI13925):

Potential Risk	Malignancy
	No patient experienced malignancy in the pediatric study (pJIA). **Severity and nature of risk** RA and PMR: Based on SIRs, an increase rate of malignancy was not observed in patients on sarilumab compared to the general population. The rates and types of malignancies observed in the clinical development program are not unexpected given the demographics of the population. pJIA study: No malignancy was reported in the pJIA study. **Seriousness/outcomes** RA studies: Seven patients on sarilumab plus DMARD died due to malignancy (Cervix cancer metastatic, Colorectal cancer metastatic, Ductal adenocarcinoma of pancreas, Lung adenocarcinoma, Metastatic bronchial carcinoma, Non-small cell lung cancer, Gallbladder cancer metastatic). PMR study (EFC15160): No deaths were observed in the EFC15160 (PMR) study. pJIA study (DRI13925): No malignancy was reported in the pJIA study. **Postmarketing safety experience (RA indication)** Ongoing monitoring of the postmarketing data up to DLP did not reveal any new emerging information impacting the characterization of this risk. **Background incidence/prevalence** **Malignancies** According to a recent meta-analysis that investigated the pooled data from previous cohort studies, the overall risk of developing malignancy is slightly increased in RA patients. Regarding site-specific risk, the risk of lymphoma and lung cancer was particularly increased, and it is postulated that a shared etiology such as smoking or chronic persistent immune activation may play a role in the development of neoplasms. (106) In an international cross-sectional study, among 3920 RA patients recruited in 17 participating countries, the past and current frequency of solid malignancies (excluding basal cell skin cancers) was 4.5% (95% CI: 3.9%-5.2%) and ranged from 0.3% in Egypt to 12.5% in the USA. (107) Taken as a whole, the incidence of cancer is very slightly increased in RA. A recent meta-analysis (108) showed a pooled SIR of 1.09 (1.06-1.13). However, the rates vary depending on the type of cancer. (109) Generally, the rate of malignancy in patients with pJIA is unknown; however children generally have fewer co-morbidities, concomitant medications, and lower baseline risks of malignancy. (110) A pharmacovigilance registry called Pharmachild (NCT01399281) was established in 2011 to analyze the safety profile of biologic drugs on an international cohort of JIA patients. The combined data coming from the Pharmachild registry and the national registries from Germany (BiKeR) and Sweden in more than 15 000 JIA patients showed that malignancies occurred in a limited number of patients. (77) **Lymphoma** According to many studies, there is a general agreement that Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL) are increased in RA. The incidence of NHL in RA is approximately 100 per 100 000 PY. (111) The pooled SIRs from a recent meta-analysis

Potential Risk	Malignancy
	(108) were 2.08 (1.80-2.39) for malignant lymphoma, 3.29 (2.56-4.22) for Hodgkin disease and 1.95 (1.70-2.24), for NHL. **Lung cancer** In the recent meta-analysis, (108) the risk of lung cancer in patients with RA compared with the general population was 1.63 (1.43-1.87). Smoking seems to be a factor contributing to both the risk of development of RA and the risk of lung cancer. **Skin cancer** In the recent meta-analysis, (108) the risk of melanoma in patients with RA compared with the general population was 1.23 (1.01-1.49). **Breast cancer** In the recent meta-analysis, (108) the risk of breast cancer in patients with RA compared with the general population was 0.86 (0.73-1.01). There is no clear explanation for this finding, however TNF plays a role in the pathogenesis of breast cancer and estrogen changes occurring in RA have been hypothesized to play a possible role. (111) **Colorectal cancer** In the recent meta-analysis, the risk of colorectal cancer in patients with RA compared with the general population was 0.78 (0.71-0.86). This decreased risk may be due to the increased use of NSAIDs which are known to decrease the risk. In a groundbreaking exploratory study and the first of its kind to prospectively examine the incidence of new malignancies in patients with PMR/GCA over a 40-week follow-up period, the prevalence of malignancies in an age and gender-matched control population from the same region were compared. Among the 77 individuals recently diagnosed with PMR and GCA, four cases of solid cancer were identified, representing a prevalence of 5.2% (95% CI: 1.4-12.8%). (112) **Impact on individual patient** Depending on the nature of malignancy, the prognosis can be variable and can result in chronic treatments and morbidity-mortality.
Risk factors and risk groups	Adult population: Age, duration/severity of RA and PMR and other risk factors based on type (eg, smoking history, family history). Pediatric population (pJIA): Underlying medical conditions, inherited gene mutations, developmental issues, exposure to infections (eg, Epstein-Barr virus), exposure to radiation and previous cancer treatment.
Preventability	No preventative measure is anticipated.
Impact on the benefit-risk balance of the product	The benefit-risk balance remained positive for patients treated in respect to the valid labeling recommendations.
Public health impact	Malignancies may lead to hospitalization and/or prolonged hospitalization or require chronic treatments, and thus, to increased public health care spending, loss of economic productivity and potentially loss of work-force due to potential risk of fatal outcomes and/or premature deaths vs. the background population without the indication (eg, RA).

Postmarketing safety experience information has been aligned with PBRER DLP 12-Jan-2023.

CI: Confidence Interval; DLP: Data Lock Point; DMARD: Disease Modifying Anti-Rheumatic Drug; GCA: Giant Cell Arteritis; HL: Hodgkin's Lymphoma; JIA: Juvenile Idiopathic Arthritis; IL-6: Interleukin-6; MedDRA: Medical Dictionary for Regulatory Activities; NHL: Non-Hodgkin's Lymphoma; NMSC: Non-Melanoma Skin Cancer; NSAID: Nonsteroidal Anti-Inflammatory Drug; PBRER: Periodic Benefit-Risk Evaluation Report; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; PT: Preferred Term; PY: Patient-Year; q2w: Once Every Two Weeks; RA: Rheumatoid Arthritis; SEER: Surveillance, Epidemiology, and End Results Program; SIR: Standardized Incidence Ratio; SMQ: Standardized MedDRA Query; TEAE: Treatment-Emergent Adverse Event; TNF: Tumor Necrosis Factor; USA: United States of America.

SVII.3.2 Presentation of the missing information

Not applicable

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the 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

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of sarilumab.

The safety profile of sarilumab has been characterized based on the extensive data collected during both non-clinical and clinical development programs. The cumulative clinical safety data indicated a consistent safety profile across Phase 2 to 3 studies and allowed characterization of the important identified and potential risks. This safety profile will continue to be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports, product technical complaints (PTCs) associated with an AE, and signal detection. These routine pharmacovigilance activities remain a recognized method for detecting rare and unexpected adverse drug reactions.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

A safety surveillance program using RA registries is ongoing to evaluate the long-term safety of RA patients exposed to sarilumab in real-world clinical practice with a follow-up for 5 years. This program assesses important identified and potential risks that require a longer duration to manifest.

Table 36 - Additional pharmacovigilance activities (category 1 to 3) summary

Safety surveillance program using existing EU RA registries (OBS15180 in Germany, 6R88-RA-1720 in Spain, OBS15220 in Sweden, 6R88-RA-1634 in United Kingdom) (Cat. 3)
Study short name and title Post-authorization safety surveillance program for sarilumab using existing European Rheumatoid Arthritis Registries in Germany, Spain, Sweden and UK.
Rationale and study objectives 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, this safety study is being conducted in four European countries with the following selected outcomes of interest: • Serious infections, • Malignancies, • MACE, • GI perforations. ▪ The primary objectives: • To monitor long-term safety of sarilumab by estimating incidence rates of outcomes of interest among patients treated with sarilumab, including SI's, malignancies, GI perforations and MACE in real-world clinical practice in each study country. • To estimate HRs of the outcomes of interest in the sarilumab cohort as compared to the bDMARDs or JAK cohort in real-world clinical practice in each study country.

- The secondary objectives:
- To provide additional background information for the sarilumab and bDMARDs/JAK inhibitors cohorts by estimating incidence rates of the outcomes of interest in a cohort of patients who are exposed to Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug (csDMARDs) in real-world clinical practice in each study country, except Spain.
- To conduct a meta-analysis to estimate the pooled HRs from the four registries (sarilumab cohort vs bDMARDs/JAK inhibitors cohort).

Study design

Composed of four individual non-interventional studies of similar design using existing RA registries in four European countries: Germany, UK, Sweden and Spain. Each study is an observational cohort study with a designed follow up of 5 years.

Study populations

This safety surveillance program will target the adult patients with active RA who have been treated with one or more DMARDs. The following three cohorts of patients with RA aged 18 years of age or older with an enrollment period of approximately 4 years in Sweden (until the 31-Dec-2022), and approximately 5 years in Germany, Spain and the UK (until 31-Dec-2023) are included:

- Sarilumab cohort: Patients who are newly treated with sarilumab with or without concomitant csDMARDs per the SmPC.
- Biological disease modifying anti-rheumatic drug/JAK inhibitors cohort: Patients who had been treated with a bDMARD/JAK inhibitor other than sarilumab, with or without concomitant csDMARDs and never exposed to sarilumab, matched to patients treated with sarilumab on the number of bDMARDs/JAK inhibitors used prior to initiation of sarilumab treatment. The number of prior bDMARD/JAK inhibitor treatments are categorized into 0, 1, or 2 or more.
- Conventional synthetic disease-modifying anti rheumatic drug cohort: Patients who have been treated with at least one csDMARDs and start a new csDMARD, and never been exposed to any bDMARDs or JAK inhibitors during the study observation period. The cohort is adapted to provide background info and event rates in patients treated with csDMARD, but not for formal comparison with sarilumab cohort in multivariate analyses due to the concerns about inadequate control for confounding related to the differences in RA severity, comorbidities, and concomitant treatment, etc, between the 2 cohorts. No csDMARDs cohort is available in Spain.

Milestones

Start of data collection: Launch date of sarilumab in each country for sarilumab cohort (but even earlier for the other cohorts)

End of data collection: Dec-2028

Study progress report: Annually (2020-2022) and biennially (every other year) (2023-2028), first report (sarilumab cohort only) Mar-2020

Final report of study results:

- Final country report for Sweden: Quarter (Q)4-2028
- Final study report (with final country reports for UK, Germany, Spain): Q4-2029

Amended Swedish report and Amended Final study report: Q4-2030

bDMARD: Biological Disease Modifying Anti-Rheumatic Drug; csDMARD: Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug; DMARD: Disease-Modifying Anti-Rheumatic Drug; EU: European Union; GI: Gastrointestinal; HR: Hazard Ratio; JAK: Janus Kinase; MACE: Major Adverse Cardiovascular Event; Q: Quarter; RA: Rheumatoid Arthritis; SI: Serious Infection; SmPC: Summary of Product Characteristics; UK: United Kingdom.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 37 - Ongoing and planned additional pharmacovigilance activities

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.

RISK MANAGEMENT PLAN PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for sarilumab.

RISK MANAGEMENT PLAN- PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Sarilumab is available as a prescription only medication. Treatment should be initiated by Healthcare Professionals (HCPs) experienced in the diagnosis and treatment of RA or PMR or active pJIA. The routine risk minimization activities consist of appropriate safety information/statements provided in the SmPC directed to the HCP and in the patient leaflet. Both HCPs and RA or PMR patients will also be provided with packaging information relative to the use of medical device, such as instructions for use (IFU), to convey key messages for optimal use of the medical device. These are important tools for routine risk minimization as they constitute a controlled and standardized format for informing HCPs and patients about sarilumab.

Table 38 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Serious infections	**Routine risk communication:** Labeled in section 4.8 of SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Labeled in sections 4.2 and 4.4 of SmPC. **Other routine risk minimization measures beyond the Product Information:** Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA.
Neutropenia	**Routine risk communication:** Labeled in section 4.8 of SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Labeled in sections 4.2, 4.4 and 5.1 of SmPC. **Other routine risk minimization measures beyond the Product Information:** Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA.
Gastrointestinal perforations	**Routine risk communication:** Labeled in section 4.8 of SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Labeled in section 4.4 of SmPC. **Other routine risk minimization measures beyond the Product Information:** Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA.
Thrombocytopenia and potential risk of bleeding	**Routine risk communication:** Labeled in section 4.8 of SmPC.

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: Labeled in sections 4.2 and 4.4 of SmPC. **Other routine risk minimization measures beyond the Product Information:** Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA.
Clinically evident hepatic injury	**Routine risk communication:** Labeled in section 4.8 of SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Labeled in sections 4.2 and 4.4 of SmPC. **Other routine risk minimization measures beyond the Product Information:** Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA.
Lipid abnormalities and increased risk of major cardiovascular events	**Routine risk communication:** Labeled in section 4.8 of SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Labeled in section 4.4 of SmPC. **Other routine risk minimization measures beyond the Product Information:** Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA.
Malignancy	**Routine risk communication:** Labeled in section 4.8 of SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Labeled in section 4.4 of SmPC. **Other routine risk minimization measures beyond the Product Information:** Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA or PMR or pJIA.

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

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 39 - Additional risk minimization measures

Patient Card	
Objectives	The objective of the Patient Card is to educate patients and/or parents/caregivers on specific actions to take to minimize the risk of SI's, neutropenia and GI perforations.
Rationale for the additional risk minimization activity	To remind patients and/or parents/caregivers and HCPs involved in their treatment that the patient is being treated with sarilumab. To educate patients and/or parents/caregivers on specific risks related to the use of sarilumab.

Patient Card	
	To remind patients and/or parents/caregivers to show the Patient Card to doctors/HCPs involved with their medical care (especially in case of medical emergencies and/or if new doctors/HCPs are involved).
Target audience and planned distribution path	Target audience Patients and/or parents/caregivers Distribution path In countries where the Patient Card is used, it would be a credit-card size folded card carried by the patient and/or parents/caregivers. The prescribing HCP is expected to fill-in their contact details and then give the card to the patient and/or parents/caregivers. Replacement Patient Cards could be provided to patients and/or parents/caregivers by the HCPs. Channel of distribution may be adapted to the local environment.
Plans to evaluate the effectiveness of the interventions and criteria for success	Plans to evaluate the effectiveness of the interventions Routine pharmacovigilance Criteria for success Number and severity of cases reported

GI: Gastrointestinal; HCP: Healthcare Professional; SI: Serious Infection.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 40 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

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
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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: Patient Card	**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.

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for KEVZARA (Sarilumab)

This is a summary of the RMP for Kevzara. The RMP details important risks of Kevzara how these risks can be minimized, and how more information will be obtained about Kevzara's risks and uncertainties (missing information).

Kevzara's SmPC and its package leaflet give essential information to HCPs and patients on how Kevzara should be used.

This summary of the RMP for Kevzara should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Kevzara's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Kevzara in combination with methotrexate (MTX) is authorized for the treatment of moderately to severely active rheumatoid Arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more Disease Modifying Anti-Rheumatic Drug (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. Kevzara is also indicated for the treatment of polymyalgia rheumatica (PMR) in adult patients who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper. Additionally, 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. (see SmPC for the full indication). It contains sarilumab as the active substance and it is given by subcutaneous route.

Further information about the evaluation of Kevzara's benefits can be found in Kevzara's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/kevzara

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Kevzara, together with measures to minimize such risks and the proposed studies for learning more about Kevzara's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Kevzara, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Kevzara are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kevzara. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 41 - List of important risks and missing information

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

II.B Summary of important risks

Table 42 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Serious infections

Serious infections	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of non-clinical findings, as well as of clinical safety data observed with sarilumab during the clinical development program. Consistent with the mechanism of action, sarilumab administration is associated with an increase in the rate of infections, including SI's.
Risk factors and risk groups	Known risk factors for infections include increased age, medical history of diabetes or chronic obstructive pulmonary disease, smoking, use of concomitant immunosuppressant (eg, MTX). (66)
Risk minimization measures	**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
Additional pharmacovigilance activities	Safety surveillance program using existing EU RA registries

EU: European Union; HCP: Healthcare Professional; IL-6: Interleukin-6; MTX: Methotrexate; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; RA: Rheumatoid Arthritis; SI: Serious Infection; SmPC: Summary of Product Characteristics.

Table 43 - Important identified risk with corresponding risk minimization activities: Neutropenia

Neutropenia	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of non-clinical findings, as well as of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with laboratory abnormality of decreased neutrophil count, consistent with its mechanism of action. Neutropenia was not associated with increased incidence of infection.
Risk factors and risk groups	RA and PMR: Subgroup analyses on the placebo-controlled population (Pool 1) and sarilumab + DMARD long-term safety population (Pool 2) were conducted for ANC <1.0 Giga/L according to age, gender, race, ethnicity, BMI, weight, geographic region, RA duration of disease, RA functional class, prior biologic use, baseline steroid use MTX dose, concomitant DMARD use (ie, MTX or non-MTX), and baseline ANC <5.99 Giga/L. As anticipated due to the mean decrease in ANC in patients on sarilumab, a numerically higher incidence of ANC <1.0 Giga/L was observed in patients with baseline ANC <5.99 Giga/L in both the placebo-controlled population and sarilumab + DMARD long-term safety population. A numerically higher incidence of ANC <1.0 Giga/L was also observed in patients with weight <60 kg. Weight has been observed as a covariate on the pharmacokinetics of sarilumab with higher drug exposure at lower body weight. In the EFC15160 study (PMR), the E-R relationship was evaluated between proportion of participants (%) ANC <1.0 Giga/L (included CTCAE Grade 3 and 4) and sarilumab steady-state C_{trough} in participants with PMR. The proportion of

Neutropenia	
	participants with ANC <1.0 Giga/L was similar among the low, medium, and high exposure tertiles, with no trend of increase with increasing concentration of sarilumab. The E-R relationship of ANC is consistent in patients with PMR and in patients with RA. No specific subgroup analyses were conducted in the PMR Study EFC15160 according to age, gender, race, ethnicity, body mass index, and weight. pJIA: In the DRI13925 (pJIA study), a higher incidence of ANC <1.0 Giga/L was observed in patients with body weight <30 kg. However, this group did not have higher rate of infections compared to patients of the same body weight without neutropenia.
Risk minimization measures	**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

ANC: Absolute Neutrophil Count; CTCAE: Common Terminology Criteria for Adverse Event; C_{trough}: Plasma Trough Concentration; E-R: Exposure-Response; BMI: Body Mass Index; DMARD: Disease Modifying Anti-Rheumatic Drug; HCP: Healthcare Professional; IL-6: Interleukin-6; MTX: Methotrexate; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 44 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Gastrointestinal perforations

Gastrointestinal perforations	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Gastrointestinal perforations were primarily reported as complications of diverticulitis, including lower GI perforation and abscess and were generally confounded by the use of concomitant steroids or NSAIDs.
Risk factors and risk groups	Age, history of diverticulitis, use of glucocorticoids, and/or prescription NSAIDs, concomitant NSAID or steroid use. (83)
Risk minimization measures	**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
Additional pharmacovigilance activities	Safety surveillance program using existing EU RA registries

EU: European Union; GI: Gastrointestinal; HCP: Healthcare Professional; IL-6: Interleukin-6; NSAID: Nonsteroidal Anti-Inflammatory Drug; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 45 - Important potential risk with corresponding risk minimization activities: Thrombocytopenia and potential risk of bleeding

Thrombocytopenia and potential risk of bleeding	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with laboratory abnormality of decreased platelet count, consistent with its mechanism of action.
Risk factors and risk groups	Rarely does bleeding occur in patients with platelet counts >50 Giga/L. Purpura may occur in patients with platelet counts between 30-50 Giga/L. Platelet counts <5 Giga/L may result in spontaneous bleeding. (89)
Risk minimization measures	**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

HCP: Healthcare Professional; IL-6: Interleukin-6; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 46 - Important potential risk with corresponding risk minimization activities: Clinically evident hepatic injury

Clinically evident hepatic injury	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with transient laboratory abnormalities of increased hepatic transaminases, consistent with its mechanism of action.
Risk factors and risk groups	RA and PMR: A higher incidence of ALT >3x ULN was seen in patients whose baseline ALT was >ULN in the placebo-controlled population and the sarilumab plus DMARD long-term safety population compared to patients whose baseline ALT values were not >ULN. pJIA: In the pJIA study, no Hy's Law cases were identified.
Risk minimization measures	**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

ALT: Alanine Aminotransferase; DMARD: Disease Modifying Anti-Rheumatic Drug; HCP: Healthcare Professional; IL-6: Interleukin-6; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics; ULN: Upper Limit of Normal.

Table 47 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Lipid abnormalities and increased risk of major cardiovascular events

Lipid abnormalities and increased risk of major cardiovascular events	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with laboratory abnormalities of increased lipids, consistent with its mechanism of action and may increase the risk of MACE.
Risk factors and risk groups	Rheumatoid arthritis is associated with increased CV morbidity and mortality, related not only to traditional CV risk factors (eg, age, gender, diabetes, hyperlipidemia, and hypertension), but also to a chronic inflammatory state. (102) The results in a publication from a randomized, parallel-group, multicenter, non-inferiority, Phase 4 clinical trial to assess CV safety of TCZ (IL-6 inhibitor) were compared with etanercept in RA, showed that 83 MACE occurred over 4900 PYs in the TCZ arm versus 78 over 4891 PYs in the etanercept arm (HR 1.05; 95% CI: 0.77-1.43). (103) As of now, there remains uncertainty in the available evidence regarding the risk of vascular disease among individuals with PMR. Several biologically plausible mechanisms connecting PMR to vascular disease have been proposed. These mechanisms encompass factors such as the inflammatory load associated with the condition, subclinical arteritis, stenosis or aneurysms, and the adverse effects of long-term CS treatment (eg, diabetes, hypertension, and dyslipidemia). These combined factors contribute to the complex relationship between PMR and vascular disease. (104) In pJIA, abnormal lipid levels and atherogenic indices could be associated with disease activity in JIA. (105)
Risk minimization measures	**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
Additional pharmacovigilance activities	Safety surveillance program using existing EU RA registries

CI: Confidence Interval; CS: Corticosteroid; CV: Cardiovascular; EU: European Union; HCP: Healthcare Professional; HR: Hazard Ratio; IL-6: Interleukin-6; JIA: Juvenile Idiopathic Arthritis; MACE: Major Adverse Cardiovascular Event; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; PY: Patient-Year; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics; TCZ: Tocilizumab.

Table 48 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Malignancy

Malignancy	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of non-clinical findings, as well as of clinical safety data observed with sarilumab during the clinical development program. Due to the immunomodulatory effects of biologic DMARDs used in the treatment of RA, treatment may result in an increased risk of malignancies. Since a higher rate of malignancy was not observed in patients treated with sarilumab compared to the

Malignancy	
	general population or patients with RA, this is considered an important potential risk.
Risk factors and risk groups	Adult population: Age, duration/severity of RA and PMR and other risk factors based on type (eg, smoking history, family history). Pediatric population (pJIA): Underlying medical conditions, inherited gene mutations, developmental issues, exposure to infections (eg, Epstein-Barr virus), exposure to radiation and previous cancer treatment.
Risk minimization measures	**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
Additional pharmacovigilance activities	Safety surveillance program using existing EU RA registries

DMARD: Disease Modifying Anti-Rheumatic Drug; EU: European Union; HCP: Healthcare Professional; IL-6: Interleukin-6; pJIA: Polyarticular Juvenile Idiopathic Arthritis; PMR: Polymyalgia Rheumatica; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Kevzara.

II.C.2 Other studies in post-authorization development plan

Table 49 - Other studies in post-authorization development plan

Safety surveillance program using existing EU RA registries (OBS15180 in Germany, 6R88-RA-1720 in Spain, OBS15220 in Sweden, 6R88-RA-1634 in United Kingdom) (Cat. 3)
Purpose of the study: 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.

EU: European Union; RA: Rheumatoid Arthritis.

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RISK MANAGEMENT PLAN - PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Proposed key messages of the additional risk minimization measures

1. Healthcare professionals (HCPs) educational material

The HCPs educational materials include the following elements:

- The Summary of Product Characteristics.
- Patient Card.

1.1 Patient Card:

- 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.

2. Patient educational material

The patients educational materials include the following element:

- The Patient Information Leaflet.