17 October 2024
EMA/509012/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kevzara

International non-proprietary name: Sarilumab

Procedure No. EMEA/H/C/004254/II/0044

Note

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

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List of abbreviations

ACR/EULAR:	American College of Rheumatology/European League against Rheumatism
ADA:	anti-drug antibody
ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interest
AIS:	aggregate improvement score
ALT:	alanine transferase
ANC:	absolute neutrophil count
ANCOVA:	analysis of covariance
AST:	aspartate transaminase
BMI:	body mass index
CI:	confidence interval
COVID-19:	coronavirus disease of 2019
CRP:	C-reactive protein
CS:	corticosteroids
CSR:	clinical study report, clinical study report
Ctrough:	concentration observed before drug administration during repeated dosing
CWS:	cumulative worsening score, cumulative worsening score
DMARDs:	disease-modifying antirheumatic drugs
EMA:	European Medicines Agency
EQ-5D-3L:	EuroQol 5 dimension questionnaire; 3-level version
E-R:	exposure response
ESR:	erythrocyte sedimentation rate
EU:	European Union
FACIT-Fatigue:	functional assessment of chronic illness therapy fatigue
GCA:	giant cell arteritis
GiACTA:	giant cell arteritis acterma
GTI:	glucocorticoid toxicity index
HAQ:	health assessment questionnaire
IMP:	investigational medicinal product
IL-6R:	interleukin-6 receptor
IRT	interactive response technology
ITT:	intent-to-treat
IV:	intravenous
LS means:	least-square means
MA:	marketing authorization
MCS:	mental component scores
MD-VAS:	physician global assessment of disease activity-visual analog scale
Nab:	neutralizing antibody
NCA:	non compartmental analysis
PCS:	physical component scores
PD:	pharmacodynamic
PFS:	prefilled syringe
PK:	pharmacokinetic
PMR:	polymyalgia rheumatica
PMR-AS:	PMR activity score
PRO:	patient-reported outcome

PSUR:	periodic safety update report
PT:	preferred term
PY:	patient-year
RA:	rheumatoid arthritis
SA:	sensitivity analyses
SAE:	serious adverse event
SC:	subcutaneous
SD:	standard deviation
SE:	standard error
SF-362v:	short form 36-item questionnaire version 2
SmPC:	summary of product characteristic
SoC:	standard of care
SOC:	system organ class
TB:	tuberculosis
TEAE:	treatment-emergent adverse event
TNF:	tumor necrosis factor
TNF-α:	tumor necrosis factor-alpha
ULN:	upper limit of normal
VAS:	visual analog scale
WBC:	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 28 November 2023 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of Polymyalgia Rheumatica (PMR) in adult patients who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper for Kevzara, based on results from study EFC15160; this is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with polymyalgia rheumatica; As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP is also submitted. As part of the application, the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0356/2018 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 21 April 2017 (EMEA/H/SA/1143/4/2017/II & EMEA/H/SA/1143/5/2017/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: n/a

Timetable	Actual dates
Submission date	28 November 2023
Start of procedure:	23 December 2023
CHMP Rapporteur Assessment Report	21 February 2024
PRAC Rapporteur Assessment Report	23 February 2024
PRAC RMP advice and assessment overview adopted by PRAC	7 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 March 2024
Request for supplementary information (RSI)	21 March 2024
CHMP Rapporteur Assessment Report	27 June 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur Assessment Report	18 July 2024
2nd Request for supplementary information (RSI)	25 July 2024
CHMP Rapporteur Assessment Report	23 Sept 2024
CHMP members comments	07 October 2024
Updated CHMP Rapporteur Assessment Report	10 October 2024
CHMP opinion:	17 October 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Polymyalgia rheumatica (PMR) is an inflammatory disease of unknown aetiology characterised 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 patients with PMR. PMR typically affects individuals ≥50 years of age, with prevalence varying by age and population.

The MAH's initially claimed therapeutic indication was:

Kevzara is indicated for the treatment of polymyalgia rheumatica (PMR) in adult patients who have had an inadequate response to corticosteroids (CS) or who cannot tolerate CS taper.

Epidemiology

PMR is the most common inflammatory rheumatological disease in the elderly Caucasian population. The average age of onset is slightly over age 70, and approximately 75% of patients are women. PMR is rarely diagnosed in persons under the age of 50, with prevalence increasing with advancing age.

The annual incidence and prevalence of PMR is highest in Scandinavian countries and in people of northern European descent. A recent systematic literature review confirmed that PMR incidence rates are 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).

Heterogeneity also exists in the persistence of CS use among patients with PMR due to factors such as differences in study periods, clinical practice, and patient populations. Published data from literature reviews suggest the persistence rate is 69% to 90% at 1 year and 47% to 76% at 2 years. A published meta-analysis examining CS discontinuation in PMR indicated that, at 1 year, 77% of patients were still taking CS and, at 2 years, 51% of patients have persistent CS use.

Biologic features

PMR is an inflammatory disease with elevated inflammatory markers, such as erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP). Numerous different cytokines, such as serum B-cell activating factor (BAFF), chemokine ligand-9 (CXCL9), TNF-α, and IL-6 have been implicated as potentially pathogenic in PMR (38); however, the most consistently reported link is between the IL-6 cytokine and PMR.

Numerous studies have confirmed that IL-6 concentrations are elevated in PMR. Dasgupta et. al. in 1990 first demonstrated elevated serum IL-6 levels in 15 untreated patients (12 patients with PMR and 3 patients with giant cell arteritis (GCA)) at sequential visits for 1 year. This observation was subsequently confirmed by Roche et. al., who established that IL-6 levels were elevated in 32 untreated patients (13 patients with PMR and 19 patients with GCA). In both of these studies and others, the investigators were also able to show that administration of CS rapidly reduced the levels of circulating IL-6 in patients who had a clinical response. Elevation of IL-6 has also been documented in the muscle and synovial fluid of PMR patients.

Genetic analysis has demonstrated a potential link between IL-6 and PMR. For example, Boiardi et. al. demonstrated that PMR patients with a polymorphism within the IL-6 promotor have higher concentrations of IL-6 and are at higher risk of relapse and recurrence than those without the polymorphism; however, additional work is needed to confirm this association.

A recent analysis of FinnGen, a public-private collaborative Finnish database that combines genome information with digital health care data, indicated that polymorphisms within the IL-6 cytokine family signal transducer (IL-6ST) gene locus may also impact the risk of developing PMR.

Management

Per the 2015 American College of Rheumatology/European League against Rheumatology (ACR/EULAR) guidelines, corticosteroid (CS) remains the standard of care (SoC) therapy with a recommended minimum effective starting dose within the range of 12.5 to 25 mg of prednisone (or equivalent) daily. Treatment duration ranges from approximately 1 to 3 years, during which CS should be tapered. Although CS with a slow taper will reduce symptoms rapidly for most patients, numerous reports have demonstrated a significant number of patients cannot taper CS successfully and do not achieve remission.

Therapies, other than CS, have shown limited efficacy in the treatment of PMR. An expert ACR/EULAR panel conditionally recommended methotrexate for early use in patients at high risk of prolonged CS use and/or CS-related 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 tumour necrosis factor-alpha (TNF-α) blocking agents for the treatment of PMR.

Patients who are unable to taper CS, in addition to inadequately controlled disease, are also at higher risk of complications due to the long-term exposure associated with CS therapy.

As there is no approved option, besides CS, for the treatment of the population with PMR, there is an unmet medical need in patients who have had an inadequate response to CS or who experience a relapse during corticosteroid taper.

2.1.2. About the product

Sarilumab is an IL-6 receptor antagonist that binds to both sIL-6R and membrane-bound IL-6 receptors (mIL-6R) and has been shown to inhibit IL-6-mediated signaling through these receptors.

In the European Union (EU) sarilumab is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease modifying antirheumatic drugs (DMARDs).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received Scientific advice from the CHMP on 21 April 2017 (EMEA/H/SA/1143/4/2017/II & EMEA/H/SA/1143/5/2017/II). The Scientific advice pertained to clinical aspects of the dossier. There are deviations from the proposed protocol / CHMP recommendations. The most pertinent points are discussed below in the relevant sections.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

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

2.2.2. Discussion and conclusion on non-clinical aspects

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

According to the current CHMP guideline on environmental risk assessment (CHMP/SWP/4447/00 corr 2), for products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment. As a monoclonal antibody, sarilumab falls within the scope of this provision. The MAH provided a justification for not performing a detailed ERA for sarilumab, which is considered acceptable by the CHMP. The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, sarilumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The clinical development program to assess sarilumab for use in PMR included one pivotal Phase 3 study (study EFC15160), a multinational, multicentre, randomised, double-blind, placebo-controlled, 52-week, Phase 3 study that evaluated the efficacy and safety of sarilumab in the treatment of participants with PMR who were resistant to CS tapering.

In July 2020, due to a combination of prolonged recruitment timelines and the impact of the COVID-19 pandemic, enrolment was discontinued by the MAH. All randomly assigned participants were allowed to complete the study. A total of 118 (117 treated) patients of the intended 280 was enrolled.

The data for the PMR indication provided by the pivotal study EFC15160 are further supplemented by safety data from placebo-controlled studies conducted in the study EFC15068 in patients with GCA and studies conducted in the RA population.

For study EFC15068 (in patients with GCA) enrolment was discontinued by the MAH in July 2020, due to a combination of prolonged recruitment timelines and the impact of the COVID-19 pandemic. The study was completed on 24 November 2020. The study enrolled 83 participants out of the 360 planned participants with 36 participants completing the 52-week treatment period.

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of study	- Study identifier - Location of study report - Coordinating Investigator (and center) - Number of centers	- Objective(s) of study - Study design and type of control	Test product(s): - Formulation - Dosage regimen - Route of administration	Reference therapy: - Formulation - Dosage regimen - Route of administration	Number of study participants - Total[a, b, c] - Gender[a] (M/F) - Race[a] (W/B/O) - Age[a] mean ± SD (range) - Treatment group[b]	Healthy study participants or diagnosis of study participants	Duration of treatment	Study status Type of report
Study reports of controlled clinical studies pertinent to the claimed indication								
Efficacy and safety	[EFC15160] Module 5.3.5.1 Pr J Morel (Centre Hospitalo-universitaire, Montpellier, France) 70 active centers	Efficacy and safety of sarilumab in patients with PMR Double-blind, placebo-controlled study with 2 parallel groups (1:1, sarilumab 200 mg + 14 CS taper :placebo + 52-week CS taper)	Sarilumab - 175 mg/mL (200 mg) solution or in case of dose reduction (option only for patients who had laboratory abnormality): 131,6 mg/mL (150 mg) solution - q2W - SC Prednisone - 1 and/or 5 mg encapsulated tablet - daily - oral	SC placebo - solution - q2W - SC Oral placebo - encapsulated tablet - daily - oral	- 118/117/78 - 36/82 - 98/0/20 - 68.9 ± 8.1 (51-88) years - sarilumab 200 mg q2W + 14-week CS taper group: 60 - placebo + 52-week CS taper group: 58	Study participants with PMR	52 weeks	Complete Full
Other study reports								
Efficacy and safety	[EFC15068] Module 5.3.5.4 Pr W. Schmidt (Immanuel Krankenhaus Berlin, Standort Berlin-Buch, Germany) 61 active centers	Efficacy and safety of sailumab in patients with GCA Double-blind, placebo-controlled study with 4 parallel groups (2:1:1:2, sarilumab 200 mg q2W + 26-week CS taper, sarilumab 150 mg q2W + 26-week CS taper, placebo + 26-week CS taper, placebo + 52-week CS taper)	Sarilumab - 175 mg/mL (200 mg) solution - 131,6 mg/mL (150 mg) solution - q2W - SC Prednisone - 5 and 20 mg tablet And - 1 and 5 mg capsule - daily - oral	SC placebo - solution - q2W - SC Oral placebo - capsule - daily - oral	83/83/29 - 16/67 - 72/1/10 - 71.0 ± 7.9 (51-89) years - sarilumab 200 mg q2W + 26-week CS taper group: 27 - sarilumab 150 mg q2W + 26-week CS taper group: 14 - placebo + 26-week CS taper group: 14 - placebo + 52-week CS taper group: 28	Study participants with GCA	52 weeks	Complete Abbreviated[d]

2.3.2. Pharmacokinetics

The pharmacokinetics (PK) of sarilumab has previously been described in the adult RA patient population and healthy participants indicating nonlinear PK of sarilumab with target-mediated drug disposition. With regards to this application, PK and pharmacodynamics (PD) of sarilumab were primarily collected and assessed in adult patients with steroid resistant active PMR in study EFC15160. Data from adult patients with new onset and steroid resistant GCA (study EFC15068) are regarded as supportive (Table 1).

Table 1 Sarilumab pharmacokinetic and pharmacodynamic assessments in clinical studies and analyses

Study type	Study code	Dose or dose range Duration of intervention	Number of study patients randomized	PK sampling
PK and PD assessments in efficacy/safety studies in patients with PMR				
Repeated SC dose, pivotal Phase 3 study (52 weeks)	EFC15160	Sarilumab 200 mg q2w for 52 weeks with a 14-week taper of CS or placebo q2w for 52 weeks with a 52-week taper of CS	60 sarilumab 58 placebo[a]	Sparse sampling[b]
PK and PD assessments in efficacy/safety studies in patients with GCA[c]				
Repeated SC dose, pivotal Phase 3 study (52 weeks)	EFC15068	Sarilumab 200 mg q2w for 52 weeks with a 26-week taper of CS Sarilumab 150 mg q2w for 52 weeks with a 26-week taper of CS Placebo q2w for 52 weeks with a 26-week taper of CS or placebo q2w for 52 weeks with a 52-week taper of CS	27 sarilumab 200 mg q2w+26W taper 14 sarilumab 150 mg q2w+26W taper 14 placebo+26W taper 28 placebo+52W taper	Sparse sampling[b]
Pop PK analysis, pooled Phase 3 data in patients with PMR and GCA				
Pop PK	POH1039	Data from Phase 3 studies (EFC15160 and EFC15068)	58+40[d]	Sparse sampling

CS: corticosteroid; GCA: giant cell arteritis; PD: pharmacodynamic; PK: pharmacokinetic; PMR: polymyalgia rheumatica; Pop PK: population pharmacokinetic; q2w: every 2 weeks; SC: subcutaneous

a In July 2020, due to a combination of prolonged recruitment timelines and the impact of the COVID-19 pandemic, enrollment was discontinued. All patients in Study EFC15160 have completed the 52-week study intervention period.

b Samples collected at predose, baseline (Week 0), during treatment (Weeks 2, 4, 12, 16, 24, and 52), and follow-up period (Week 58) as well as postdose 4-7 days after Week 24 dosing.

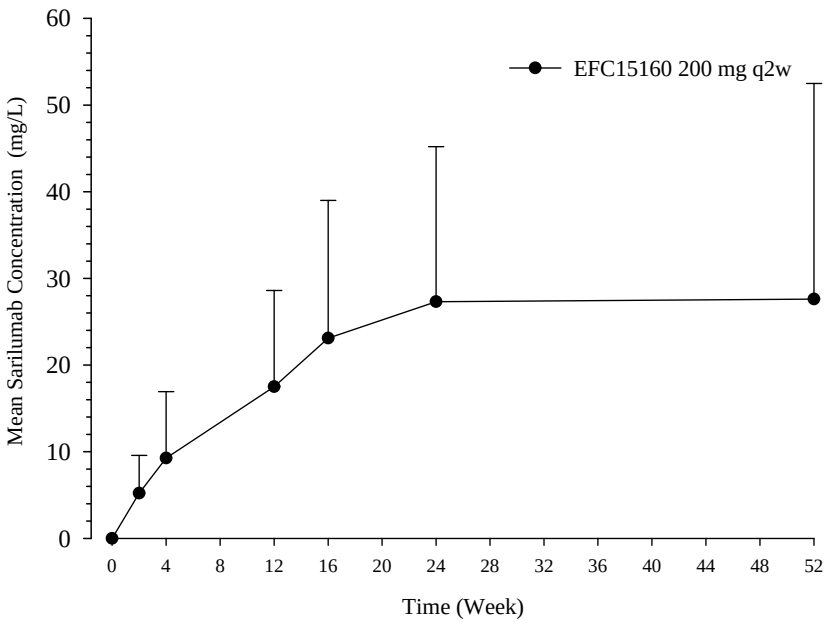
c In July 2020, due to a combination of prolonged recruitment timelines and the impact of the COVID-19 pandemic, enrollment was discontinued by the Applicant. All randomized patients in Study EFC15068 had to stop the treatment.

d Fifty-eight patients with PMR in Study EFC15160+40 patients with GCA in Study EFC15068. Patients with samples missing or below the limit of quantification were not in the Pop PK analysis dataset.

Pivotal Phase 3 Study EFC15160

Sarilumab concentrations in serum were measured in study using sparse sampling (samples collected at predose, baseline [Week 0], during treatment at Weeks 2, 4, 12, 16, 24, and 52 before sarilumab administration, and follow-up period at Week 58 as well at post dose 4-7 days after Week 24 dosing). The concentration-time profile is depicted below.

Figure 1 – Mean (±SD) concentrations of sarilumab following repeated SC administration in patients with PMR – Study EFC15160



N=58 (Week 0), 56 (Week 2), 50 (Week 4), 46 (Week 12), 42 (Week 16), 40 (Week 24), and 33 (Week 52)

Descriptive statistics were used to summarize the concentration data over time in patients with PMR in the Phase 3 study (EFC15160).

Table 2 Summary of serum sarilumab trough concentrations at each visit during the TEAE period – PK population

Parameter (unit)	Sarilumab 200mg q2w+14 week taper (N=58)
Functional Concentration (ng/mL)	
Baseline	
Number	58
Mean (SD)	0.00 (0.00)
SE	0.000
CV	NC
Geometric Mean	NC
Median	0.00
Min ; Max	0.0 ; 0.0
V3/Week 2	
Number	56
Mean (SD)	5209.02 (4357.37)
SE	582.278
CV	83.650
Geometric Mean	2912.25
Median	4395.00
Min ; Max	156.3 ; 18600.0
V4/Week 4	
Number	50
Mean (SD)	9259.25 (7668.95)
SE	1084.554
CV	82.825
Geometric Mean	5715.82
Median	7815.00
Min ; Max	156.3 ; 42000.0
V6/Week 12	
Number	46
Mean (SD)	17494.20 (11146.33)
SE	1643.437
CV	63.714
Geometric Mean	12742.00
Median	17850.00
Min ; Max	853.0 ; 43000.0
V7/Week 16	
Number	42
Mean (SD)	23082.86 (15878.92)
SE	2450.171
CV	68.791
Geometric Mean	17603.96
Median	20800.00
Min ; Max	1680.0 ; 77800.0
V9/Week 24	
Number	40
Mean (SD)	27289.75 (17927.73)
SE	2834.624
CV	65.694
Geometric Mean	20784.43
Median	23450.00
Min ; Max	1830.0 ; 84300.0
V12/Week 52	
Number	33
Mean (SD)	27604.95 (24880.13)
SE	4331.074
CV	90.129
Geometric Mean	13708.10
Median	23500.00
Min ; Max	156.3 ; 98200.0

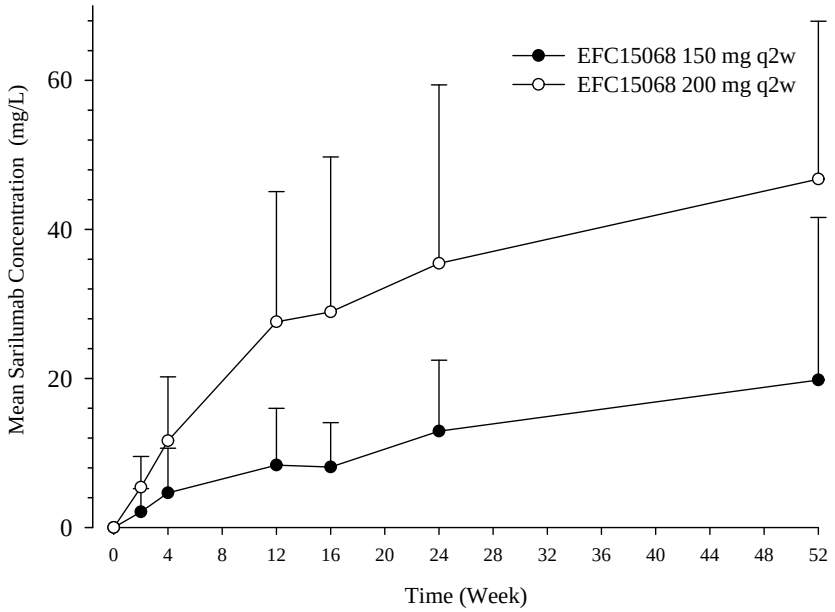
Table 2 bis: Summary of serum sarilumab post-dose concentrations at Week 24 during the TEAE period - PK population

Functional Concentration (ng/mL)	
V9/Week 24	
Number	26
Mean (SD)	35757.69 (15353.96)
SE	3011.160
CV	42.939
Geometric Mean	32164.47
Median	36850.00
Min ; Max	12600.0 ; 70300.0

Supportive: EFC15068 (GCA patient data)

Study EFC15068 enrolled 83 participants out of the 360 planned participants, with 36 patients completing the 52-week treatment period. The concentration-time profile is depicted below.

Figure 2 – Mean (±SD) concentrations of sarilumab following repeated SC administration in patients with GCA – Study EFC15068



150 mg q2w N=14 (Week 0), 14 (Week 2), 13 (Week 4), 13 (Week 12), 12 (Week 16), 12 (Week 24), and 6 (Week 52)
200 mg q2w N=26 (Week 0), 25 (Week 2), 25 (Week 4), 20 (Week 12), 17 (Week 16), 19 (Week 24), and 9 (Week 52)

Analysis of PK Data

Due to the fact that only sparse PK sampling has been conducted in the pivotal study, non-compartmental PK analysis is not feasible. PK data was used to update pop PK modelling that was originally established based on PK data collected from RA patients, in order to characterize PK in the target population.

Population PK Analysis

A Pop PK analysis was conducted by pooling the data from the Phase 3 study in patients with PMR (Study EFC15160) and the supportive study in patients with GCA (Study EFC15068). The main objective of this study was to characterize the PK of sarilumab in patients with PMR/GCA and to assess the influence of intrinsic and extrinsic factors on sarilumab PK in patients with PMR/GCA via post-hoc assessment.

Model development

A previously established Pop PK model for participants with RA served as the basis for Pop PK model development for the current application. The Pop PK model for patients with PMR and GCA was developed by re-estimating parameters from the Pop PK model in patients with RA. The final dataset

included 58 patients with PMR with 341 sarilumab concentrations and 40 patients with GCA with 241 sarilumab concentrations. The Pop PK analysis was performed with NONMEM (version 7.5.1).

First, single fixed effect parameters (Vm, Km, Vc/F, CL0/F, Q/F, and Vp/F) were examined. A single fixed effect was re-estimated by fixing all but the fixed effect parameter from the RA pop PK model. Second, paired fixed-effect parameters from the RA Pop PK model were examined and re-estimated.

All covariate effects were fixed to the effects of the RA Pop PK model using median covariates in the patients with RA. Models including Ka were considered post-hoc based on the limited information to fit absorption-related parameters in the data of patients with PMR and GCA, with an implicit covariate of disease estimated based on the final parameter selected.

The final pop PK model parameters are presented below.

Table 3 – Population pharmacokinetic parameters of sarilumab final model in patients with PMR/GCA (Study POH1039)

Parameter	Estimate	RSE (%)	Median [95%CI]
Vm, (mg/day)	10.2	3.76	10.2 [9.58; 10.8]
Km, (mg/L)	0.939	Fixed	NE
Vc/F, (L)	2.08	Fixed	NE
CL_O/F, (L/day)	0.172	12.3	0.170 [0.143; 0.207]
Ka, (day^{-1})	0.136	Fixed	NE
Q/F, (L/day)	0.156	Fixed	NE
Vp/F, (L)	5.23	Fixed	NE
WT effect on CL_O/F	0.885	Fixed	NE
WT effect on Vm	0.516	Fixed	NE
ALBR effect on Vm	-0.844	Fixed	NE
CLCRN effect on Vm	0.212	Fixed	NE
C1P2F2 effect on Ka[a]	0.663	Fixed	NE
ADA effect on CL_O/F[b]	1.43	Fixed	NE
Sex effect on CL_O/F	0.846	Fixed	NE
BLCRP effect on Vm	0.0299	Fixed	NE
Interindividual variability (CV %)			
Vm[c]	28.5	25.9	NE
CL_O/F[c]	95.6	16.3	94.7 [78.0; 112]
Block Vm- CL_O/F[d]	-0.195	28.2	-0.192 [-0.300; -0.0968]
Residual variability			
σ^2[e]	0.387	1.77	0.387 [0.364; 0.415]

ADA: anti-drug antibody; ALBR: albumin normalized to upper limit of normal; BLCRP: baseline C-reactive protein; CLCRN: BSA normalized creatinine clearance; CL_O/F: apparent linear clearance from central compartment; Ka: absorption rate constant; Km: Michaelis-Menten constant; NE: Not evaluable; Q/F: apparent inter-compartmental clearance; RSE: percentage of Relative Standard Error (100 x SE/Estimate); V_c/F: apparent central volume of distribution; V_m: maximum elimination rate from central compartment; V_p/F: apparent peripheral volume of distribution; WT: body weight; 95% CI: 95% confidence interval (ie, 2.5th and 97.5th percentile).

a Drug product C1P1F1 was used in Phase 1 studies only. C1P2F2 was used in some Phase 1 studies and in the dose-ranging Phase 2 study. C2P1F3 was used in the pivotal Phase 3 studies and is planned-to-be-marketed drug product

b ADA was time-varying.

c inter-individual variability are expressed as coefficient of variation (CV%).

d estimate of covariance between two variances is expressed as correlation coefficient.

e Variance of residual error is based on the Log-transformed dependent variable (ie, sarilumab concentration).

With the final model, individual sarilumab exposure up to the last dose was determined using an empirical Bayesian estimation approach for the patients with PMR from Study EFC15160 and patients with GCA from Study EFC15068.

The simulations included visualizations of the concentration-time profile and noncompartmental analysis (NCA) parameters at steady state. The NCA parameters were summarized: area under the concentration-time curve over 14-day time period at steady state (AUC0-14 days ss), maximum concentration at steady state (Cmax ss), and trough concentration at steady state (Ctrough,ss).

Figure 3 Model diagnostics (Vm and CL/F with correlated IIV model)

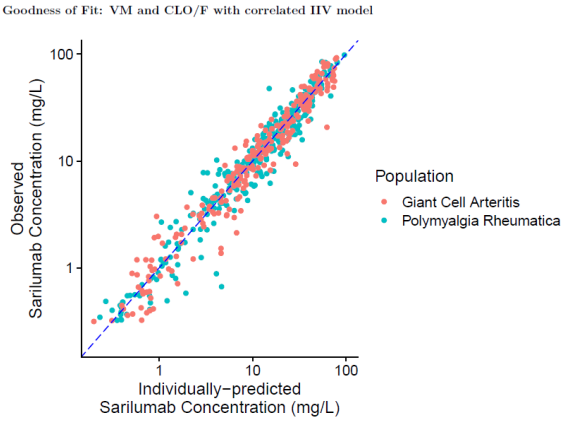


Figure 22: Goodness of fit, VM and CLO with correlated IIV model: observed vs individual-predicted concentrations

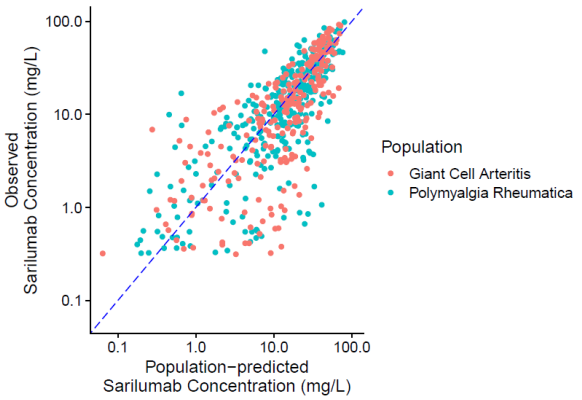


Figure 23: Goodness of fit, VM and CLO with correlated IIV model: observed vs population-predicted concentrations

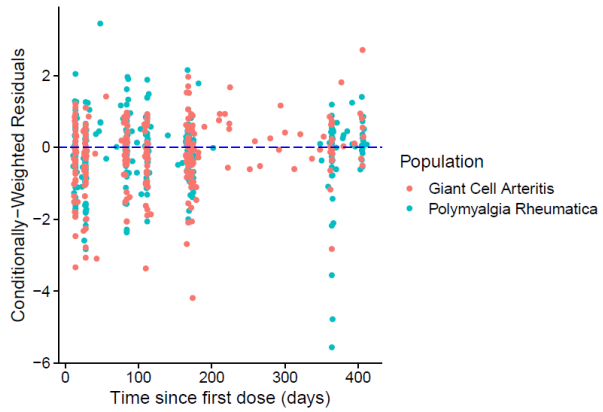


Figure 24: Goodness of fit, VM and CLO with correlated IIV model: conditionally-weighted residuals vs time

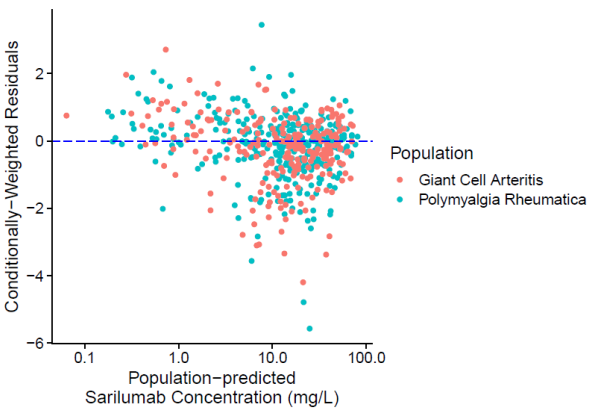
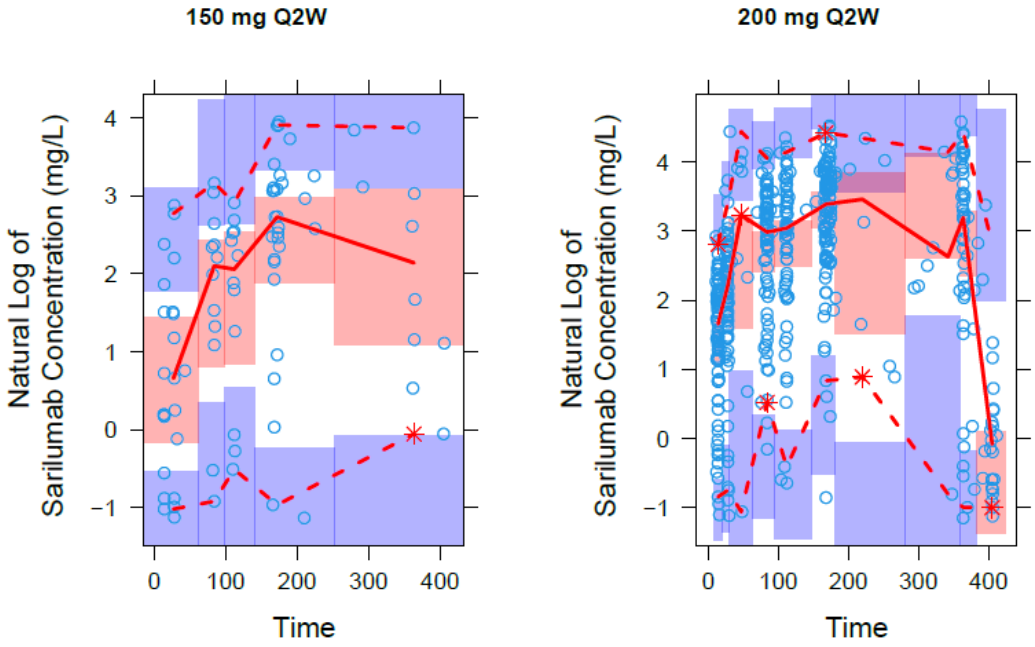


Figure 25: Goodness of fit, VM and CLO with correlated IIV model: conditionally-weighted residuals vs population-predicted concentrations

Figure 4 Visual predictive checks for VM, CLO (with correlated IIV for VM and CLO) model



Cross Study Comparison

PK parameters at steady state obtained via post-hoc estimation with the Pop PK models in patients with PMR, GCA, and RA, along with observed trough concentrations, are summarized in the table below.

Table 4 – Mean (SD) sarilumab pharmacokinetic parameters in serum, following repeated SC administrations of sarilumab to patients with PMR, GCA, and RA

Population (Study identifier)	Dose	N	C_{max} (mg/L)	$AUC_{0\text{-}14\ days}$ (mg•day/L)	C_{trough} (mg/L)		
			Predicted[a]	Predicted[a]	Predicted[a]	N	Observed
PMR (EFC15160)	200 mg q2w	59	46.5 (23.0)	551 (321)	27.0 (21.5)	40	27.3 (17.9)
GCA (EFC15068)	150 mg q2w	15	29.3 (17.9)	336 (247)	14.9 (16.3)	12	12.9 (9.51)
	200 mg q2w	27	50.2 (24.5)	604 (340)	31.0 (22.1)	19	35.5 (24.0)
RA (EFC11072 Part B)	150 mg q2w	366	20.4 (9.23)	207 (119)	6.57 (7.53)	274	7.63 (9.73)
	200 mg q2w	426	35.9 (15.5)	400 (213)	16.9 (14.5)	266	18.8 (16.3)
RA (EFC10832)	150 mg q2w	181	19.0 (9.11)	192 (122)	5.89 (7.58)	115	6.97 (8.98)
	200 mg q2w	183	34.8 (14.5)	384 (194)	15.5 (12.9)	114	19.3 (16.7)
RA (SFY13370)	150 mg q2w	47	23.3 (10.0)	249 (140)	9.41 (9.41)	40	11.3 (12.6)
	200 mg q2w	51	40.6 (18.6)	474 (254)	21.7 (16.8)	41	26.9 (25.1)
RA (MSC12665)	150 mg q2w	48	21.7 (9.94)	226 (121)	7.48 (6.46)	47	6.29 (7.46)
	200 mg q2w	51	39.3 (20.3)	450 (266)	19.7 (15.6)	48	16.9 (15.4)
RA (EFC13752)	150 mg q2w	65	19.9 (7.47)	193 (101)	5.29 (6.31)	54	7.35 (8.03)
	200 mg q2w	66	33.3 (12.0)	357 (173)	13.0 (12.2)	52	17.2 (15.9)
RA Pool 1[b]	200 mg q2w	-	-	-	-	561	17.2 (15.7)
RA Pool 1 Subgroup[c]	200 mg q2w	-	-	-	-	78	15.7 (14.9)

$AUC_{0\text{-}14\ days}$: AUC[Week 22 – Week 24] for 200 mg q2w or 150 mg q2w; C_{max}: maximum concentration; C_{trough}: represents the mean trough concentration at Week 24; CS: corticosteroid; GCA: giant cell arteritis; MTX: methotrexate; N: number of patients; PMR: polymyalgia rheumatica; q2w: every 2 weeks; RA: rheumatoid arthritis; SC: subcutaneous; TNF: tumor necrosis factor

a Predicted: summary statistics of post-hoc estimates of exposure parameters in Study POH01039 (PMR and GCA) and Study POH0428 (RA).

b RA Pool 1 Population: A placebo controlled pooled population from clinical studies evaluated sarilumab for the treatment of patients with moderately to severely active RA who had an inadequate response to MTX or TNF antagonists.

c RA Pool 1 Subgroup: A subgroup of patients with RA (50 to 87 years of age) in RA Pool Population with a similar age-range and CS use as patients with PMR (50 to 88 years of age).

Sources: 5.3.3.5 Study POH1039 Pop PK analysis report; Study POH0428 Pop PK analysis report; 5.3.5.1 Study EFC15160, Appendix 16.2.5; 5.3.5.4 Study EFC15068, Appendix 16.2.5

Data indicate that the observed variability in Ctrough after SC dose of sarilumab in patients with PMR, GCA, and RA was high. The observed mean Ctrough in patients with RA ranged from 16.9 to 26.9 mg/L, indicating variabilities between trials at 200 mg q2w. At Week 24, individual exposures (Ctrough) overlapped among the populations despite a higher mean PK exposure in patients with PMR and GCA than that in patients with RA.

Model-based individual exposures (AUC0-14 days, Cmax, and Ctrough) at steady state following 200 mg Q2W are presented in box plots (Figure 5) and overlapped among the 3 populations. A higher mean PK exposure was estimated in patients with PMR and GCA than in patients with RA, individual exposures at steady state in patients with PMR and GCA were within the range (min-max) of those in patients with RA after 200 mg q2w SC doses. The simulations are driven by the differences in estimated CL.

Table 5 – Population pharmacokinetic parameters of sarilumab in patients with PMR and RA

PK parameter	Study POH1039 (PMR)		Study POH0428 (RA)	
	Estimate (unit)*	RSE (%)	Estimate (unit)	RSE (%)
CL_0/F (apparent linear clearance) (L/day)	0.162[a]	NA	0.260	5.36
V_c/F (apparent central volume of distribution) (L)	2.08	Fixed	2.08	3.20
Q/F (intercompartmental clearance) (L/day)	0.156	Fixed	0.156	3.87
V_p/F (apparent peripheral volume of distribution) (L)	5.23	Fixed	5.23	5.98
V_m (maximum rate of clearance) (mg/day)	8.53[a]	NA	8.06	1.96
K_m (Michaelis Menten rate constant) (mg/L)	0.939	Fixed	0.939	4.38
K_a (absorption rate constant) (day^{-1})	0.136	Fixed	0.136	2.53

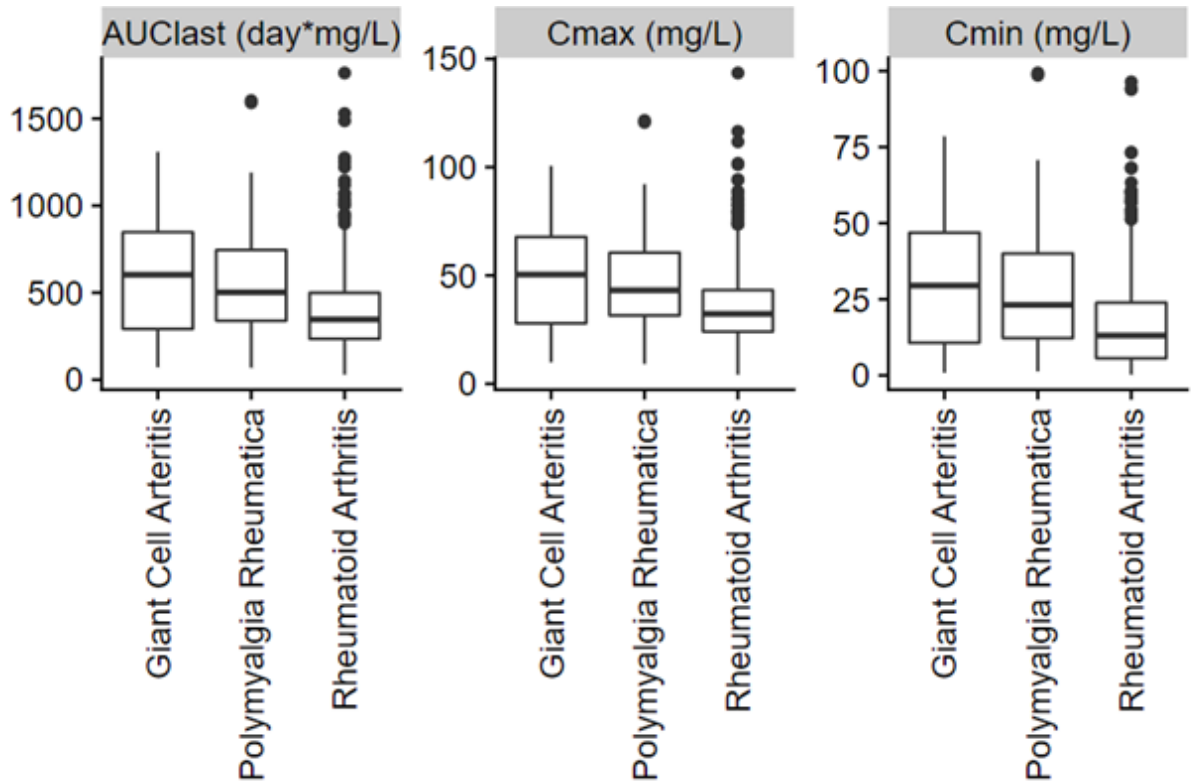
NA: not applicable; PMR: polymyalgia rheumatica; RA: rheumatoid arthritis; RSE: relative standard error

* All covariate effects were fixed to the effects in the RA Pop PK model using median covariates in the patients with RA.

a Mean population post-hoc estimation for patients with PMR.

Source: 5.3.3.5 Study POH1039 Pop PK analysis report; Study POH0428 Pop PK analysis report

Figure 5 - Box plot of sarilumab steady-state PK parameters at 200 mg q2w in patients with PMR, GCA, and RA (Studies POH1039 and POH0428)



AUC_{last}=$AUC_{0\text{-}14\ days}$: AUC (area under the serum concentration versus time curve at steady state) with 14 days dosing interval; GCA: giant cell arteritis; C_{max}: maximum concentration; C_{min}=C_{trough}: represents the mean trough concentration at steady state; PMR: polymyalgia rheumatica; q2w: every 2 weeks; RA: rheumatoid arthritis

Absorption

Sarilumab is well-absorbed in patients with RA after SC administration, with the maximum concentration of sarilumab achieved at a median tmax of 2 to 4 days after the first dose and an estimated absolute bioavailability of 80% based on the previous Pop PK analysis in the original marketing application.

Distribution

The estimated volume of distribution at steady state (Vss/F) for the RA population from the Pop PK model, with an estimated Vc/F of 2.08 L and Vp/F of 5.23 L, was 7.31 L (the sum of Vc/F and Vp/F).

These parameters were fixed in the PMR/GCA pop PK model to that from the RA Pop PK model assuming that the volume of distribution is the same.

Elimination

As in patients with RA, the elimination of sarilumab in patients with PMR is biphasic and is characterized by an initial elimination half-life of 10 days and a terminal half-life of 4 days at steady state after 200 mg q2w SC sarilumab doses (Study POH1039).

Based on the Pop PK model, sarilumab concentrations after the last steady state dose were expected to be measurable up to a median time of 48 days for 200 mg q2w in patients with PMR. The population mean CL0/F for patients with PMR was 38% lower (Study POH1039) compared to that for RA patients (0.260 L/day) when all covariate effects were fixed to the effects in the RA Pop PK model using median covariates in the patients with RA (Table 5).

Dose proportionality and time dependencies

Only one dose (200 mg Q2W) was studied in patients with PMR so no information on dose proportionality in the target population is available. A greater than proportional exposure was noted in patients in the related disease of GCA (150 mg and 200 mg Q2W SC were tested).

After multiple SC administrations of sarilumab 200 mg q2w, the observed trough concentrations of functional sarilumab increased over time from Week 0 to Week 24. Pharmacokinetic steady state appeared to be reached by Week 24 (27.3 mg/L) and was sustained at the steady-state level throughout the treatment period (up to Week 52).

There was accumulation following SC administration of sarilumab 200 mg q2w, with an accumulation ratio of approximately 5-6 fold based on the mean trough concentrations.

Special populations

The observed total variability (coefficient of variation) after 200 mg q2w SC dose of sarilumab in patients with PMR was 63.7% to 90.1% for Ctrough.

The post-hoc individual steady-state exposure values in patients with PMR (Study EFC15160), based on the Pop PK model, are summarized by covariates in the table below, followed by a table comparing the demographics and baseline characteristics across populations.

Table 6 - Mean (SD) for post-hoc estimates of steady state exposure of sarilumab in patients with PMR from Study EFC15160 by covariates tested in population pharmacokinetic analysis (Study POH1039)

Intrinsic and extrinsic factors		N	$C_{max,ss}$ (mg/L)	$AUC_{0\text{-}14\ days\ ss}$ (mg.day/L)	$C_{trough,ss}$ (mg/L)
All (200 mg q2w)		59	46.5 (23.0)	551 (321)	27.0 (21.5)
Age (year)	<65 years	16	39.4 (17.5)	450 (244)	20.0 (16.2)
	65 to 75 years	33	47.7 (22.2)	567.(311)	28.0 (21.0)
	>75 years	10	54.0 (31.6)	659 (437)	34.8 (28.8)
Weight (kg)	<60 kg	9	76.7 (28.0)	972 (393)	55.8 (27.1)
	60 to <100 kg	47	42.5 (17.1)	494 (237)	23.0 (15.5)
	≥100 kg	3	19.9 (5.42)	182 (65.4)	2.95 (1.77)
Sex	Male	14	38.7 (14.4)	441 (200)	19.5 (12.8)
	Female	45	49.0 (24.7)	585 (345)	29.3 (23.2)
Albumin (g/L)	<43 g/L	34	45.8 (22.1)	541 (307)	26.3 (20.5)
	≥43 g/L	25	47.5 (24.7)	564 (346)	27.9 (23.3)
CL_{CR} (mL/min)	Normal	22	34.0 (13.4)	374 (186)	15.0 (12.2)
	Mild RI	25	48.3 (17.0)	574 (237)	28.3 (15.7)
	Moderate RI	12	65.9 (33.1)	824 (458)	46.2 (30.6)
CRP	≤6.8 mg/L	29	48.8 (18.5)	582 (257)	29.1 (16.9)
	>6.8 mg/L	30	44.4 (26.8)	521 (375)	24.9 (25.3)
ADA	Negative ADA*	52	48.6 (23.2)	580 (324)	29.0 (21.6)
	Positive ADA	3	22.3 (1.60)	208 (23.6)	2.90 (1.84)

* 3 patients with missing ADA status and 1 patient had pre-existing ADA at baseline.
ADA: anti-drug antibody; $AUC_{0\text{-}14days,ss}$: area under concentration-time curve from time 0 to 14 days at steady state; CL_{cr}: creatinine clearance; $C_{max,ss}$: maximum concentration at steady state; CRP: c-reactive protein; $C_{trough,ss}$: concentration observed before drug administration during repeated dosing at steady state; PMR: polymyalgia rheumatica; q2w: every 2 weeks
Source: 5.3.3.5 Study POH1039 Pop PK analysis report

Table 7 Comparison of demographics and baseline characteristics across populations

	Giant Cell Arteritis	Polymyalgia Rheumatica	Rheumatoid Arthiritis
	(N=41)	(N=59)	(N=1935)
Age (yr)			
Mean (SD)	71.3 (8.83)	68.7 (7.82)	51.6 (12.2)
Median [Min, Max]	73.0 [52.0, 89.0]	69.0 [51.0, 88.0]	53.0 [18.0, 87.0]
Interquartile range [Q25, Q75]	[66.0, 76.0]	[64.0, 73.0]	[43.0, 61.0]
Sex			
Male	5 (12.2%)	14 (23.7%)	350 (18.1%)
Female	36 (87.8%)	45 (76.3%)	1585 (81.9%)
Albumin normalized concentration; ALBR (ALB/upper limit of normal)			
Mean (SD)	0.909 (0.0565)	0.907 (0.0581)	0.767 (0.0784)
Median [Min, Max]	0.908 [0.781, 1.02]	0.903 [0.783, 1.04]	0.776 [0.408, 1.08]
Interquartile range [Q25, Q75]	[0.872, 0.957]	[0.874, 0.935]	[0.714, 0.816]
Albumin concentration; ALB (g/L)			
Mean (SD)	42.6 (2.81)	42.9 (2.73)	37.4 (3.78)
Median [Min, Max]	42.5 [37.8, 50.0]	43.0 [36.0, 49.5]	38.0 [20.0, 53.0]
Interquartile range [Q25, Q75]	[41.0, 44.8]	[41.1, 44.3]	[35.0, 40.0]
Body weight; WT (kg)			
Mean (SD)	69.9 (15.2)	74.3 (15.4)	74.9 (18.2)
Median [Min, Max]	67.2 [44.3, 103]	72.8 [44.0, 125]	72.0 [31.5, 177]
Interquartile range [Q25, Q75]	[57.0, 82.3]	[64.9, 84.6]	[62.0, 85.3]
Estimated creatinine clearance; CLCR (mL/min)			
Mean (SD)	68.1 (21.0)	85.4 (30.3)	111 (35.5)
Median [Min, Max]	63.5 [37.9, 129]	84.6 [32.6, 193]	106 [36.6, 321]
Interquartile range [Q25, Q75]	[56.2, 74.9]	[63.6, 102]	[86.1, 131]
Body surface area; BSA (m^2)			
Mean (SD)	1.72 (0.188)	1.80 (0.198)	1.85 (0.248)
Median [Min, Max]	1.70 [1.36, 2.23]	1.79 [1.38, 2.29]	1.82 [1.13, 3.01]
Interquartile range [Q25, Q75]	[1.58, 1.85]	[1.66, 1.94]	[1.67, 2.00]
Baseline C-reactive protein; BLCRP (mg/L)			
Mean (SD)	5.91 (9.20)	10.1 (9.79)	22.5 (25.8)
Median [Min, Max]	1.77 [0.100, 37.4]	6.82 [0.450, 38.2]	14.5 [0.0720, 218]
Interquartile range [Q25, Q75]	[1.10, 5.20]	[2.22, 15.1]	[6.75, 29.2]
Anti-drug antibody at any time; ADA			
Negative	37 (90.2%)	52 (88.1%)	1537 (79.4%)
Positive	1 (2.4%)	4 (6.8%)	396 (20.5%)
Missing	3 (7.3%)	3 (5.1%)	2 (0.1%)
Anti-drug antibody at baseline; ADA			
Negative	38 (92.7%)	55 (93.2%)	1872 (96.7%)
Positive	0 (0%)	1 (1.7%)	37 (1.9%)
Missing	3 (7.3%)	3 (5.1%)	26 (1.3%)

Body weight

Previous PK assessment has shown that body weight was the most influential covariate that described the variability in sarilumab exposure in patients with RA. Similar to patients with RA, a trend of decrease in sarilumab concentrations with increase in body weight was noted in patients with PMR in Study EFC15160 (Table 8, Figure 6).

Table 8 - Sarilumab exposure by body weight category in patients with PMR following SC administrations of 200 mg q2w in Study EFC15160

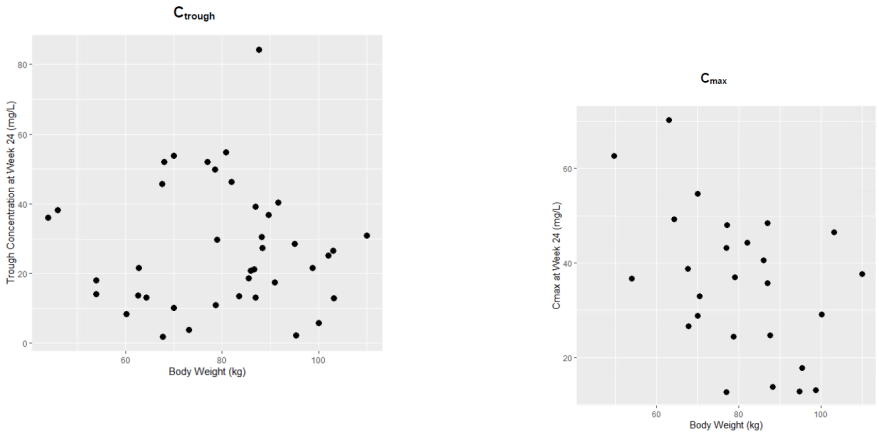
Body weight	N	C_{max} (mg/L)	$AUC_{0\text{-}14\ days}$ (mg•day/L)	C_{trough} (mg/L)
<60 kg	9	76.7 (28.0)	972 (393)	55.8 (27.1)
60 to <100 kg	47	42.5 (17.1)	494 (237)	23.0 (15.5)
≥100 kg	3	19.9 (5.42)	182 (65.4)	2.95 (1.77)

Note: Descriptive statistics are mean (standard deviation) for pharmacokinetic parameters for Study EFC15160.

$AUC_{0\text{-}14\ days}$: area under concentration-time curve from time 0 to 14 days; C_{max}: maximum concentration; C_{trough}: concentration observed before drug administration during repeated dosing; PMR: polymyalgia rheumatica; SC: subcutaneous

Source: 5.3.3.5 Study POH1039 Pop PK analysis report

Figure 6 Scatter plot of concentrations of sarilumab at Week 24 versus patient body weight in patients with PMR (Study EFC15160)



Patients with PMR had a similar body weight in study EFC15160 (median: 72.8 kg; 25th to 75th percentile: 65 kg to 85 kg) compared to patients with RA in the Phase 3 studies in the original marketing application (median: 71 kg; 25th to 75th percentile: 62 kg to 83 kg).

Gender

Former population PK analysis of sarilumab concentration data from 304 male and 1466 female patients with RA identified gender as a significant covariate impacting CL0/F. The effect of gender was translated into 14% lower sarilumab steady state exposures (AUC0-14 days) after repeated 200 mg q2w administrations, respectively, for a typical male patient, as compared to a typical female patient. The results of post-hoc assessment (Study POH1039) of data from 45 (76%) female and 14 (24%) male patients with PMR were consistent with the findings in patients with RA. Accordingly, no dose adjustments were recommended in patients with PMR based on gender.

Age

Former population PK analysis of sarilumab in patients with RA did not identify age as a significant covariate. The patients with PMR in the Pop PK analysis data set were 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. After accounting for body weight differences, no obvious trend in sarilumab exposure with age from patients from 51 to 88 years was observed in patients with PMR in study EFC15160. The Pop PK analysis suggested the lack of impact of age on sarilumab PK. No dose adjustments based on age were recommended for patients with PMR.

Race

The Pop PK analysis data set in patients with PMR included 50 Caucasian (83%) and 1 Asian (1.7%) patients. Nine (15%) patients did not report the race. Thus, there was insufficient data to evaluate the race effect in patients with PMR. Former population PK analysis in patients with RA did not identify race (Caucasian versus non-Caucasian) as a significant covariate influencing functional sarilumab PK. No dose adjustments based on race were recommended for patients with PMR.

Renal and hepatic impairment

As in patients with RA, the Pop PK analysis data set in patients with PMR included 22 (37%) patients with normal renal function, 25 (42%) patients with mild renal impairment, and 12 (20%) patients with moderate renal impairment (Table 9). Creatinine clearance (based on the Cockcroft-Gault formula normalized by BSA) was a statistically significant covariate for nonlinear maximum rate of clearance (Vm) in the Pop PK analysis; the impact of CLcr on Vm did not translate into an appreciable effect on functional sarilumab exposure (AUC0-14 days) at steady state.

In a categorical analysis by renal impairment category, individual post-hoc predicted sarilumab exposures (AUC0-14 days) after repeated 200 mg, q2w, SC doses were greater by 53% in patients with mild renal impairment (CLcr of 60 to 90 mL/min) and by 120% in moderate renal impairment (CLcr of 30 to 60 mL/min), as compared to patients with normal renal function. This larger difference in the post-hoc parameters compared the Pop PK model estimated effect is likely due to the body weight difference between subgroups in addition to the impact of CLcr. The mean body weight was 87.6 kg, 71.1 kg, and 55.9 kg in the normal renal function, mild renal impairment, and moderate renal impairment subgroups, respectively. Since the subgroups are not balanced across all covariates, this univariate assessment may not allow for a fair comparison.

Table 9 - Sarilumab exposure by renal function category in patients with PMR following SC administrations of 200 mg q2w in Study EFC15160

Category of Renal Function	N	C_{max} (mg/L)	$AUC_{0\text{-}14\ days}$ (mg•day/L)	C_{trough} (mg/L)
Normal (≥90 mL/min)	22	34.0 (13.4)	374 (186)	15.0 (12.2)
Mild (60 to 90 mL/min)	25	48.3 (17.0)	574 (237)	28.3 (15.7)
Moderate (30 to 60 mL/min)	12	65.9 (33.1)	825 (458)	46.2 (30.6)

Descriptive statistics are mean (standard deviation) of pharmacokinetic parameters for Study EC15160.

$AUC_{0\text{-}14\ days}$: area under concentration-time curve from time 0 to 14 days; C_{max}: maximum concentration; C_{trough}: concentration observed before drug administration during repeated dosing; PMR: polymyalgia rheumatica; q2w: every 2 weeks; SC: subcutaneous

Source: 5.3.3.5 Study POH1039 Pop PK analysis report

The laboratory test values for hepatic function (aspartate transaminase [AST], alanine transaminase, or total bilirubin levels) did not have a clinically meaningful effect on sarilumab PK, which is consistent with patients with RA.

Serum albumin

Although serum albumin was a statistically significant covariate for nonlinear maximum rate of clearance (Vm) in the Pop PK analysis of data from patients with serum albumin ranging from 36.0 to 49.5 g/L, it did not translate into an appreciable change in sarilumab exposure (AUC0-14 days) at steady state (Table 6). Low albumin would correlate with faster sarilumab clearance (and hence lower sarilumab exposure). Of note, patients with PMR had higher mean baseline albumin levels (43 g/L in patients with PMR and 38 g/L in patients with RA) resulting in an apparently lower clearance and higher sarilumab exposure than patients with RA.

Baseline C-reactive protein level

In patients with RA, baseline CRP level was a statistically significant covariate of nonlinear Vm of sarilumab in the Pop PK analysis. This did not result meaningful change in functional sarilumab steady state exposure. Because sarilumab is eliminated in part through target-mediated clearance and the baseline CRP level reflects disease activity in patients. Patients with the higher CRP exhibited higher clearance. Of note, patients with PMR had lower mean baseline CRP levels than patients with RA, resulting in lower clearance and higher sarilumab exposure than patients with RA.

Disease populations

Disease population was not evaluated as a covariate in the Pop PK analyses and was assessed by a cross-study comparison (see sections above). Among the significant covariates identified by the Pop PK analysis (body weight, sex, baseline albumin, CLcr, and baseline CRP), patients with PMR had higher albumin, lower CLcr, and lower CRP than patients with RA.

Effects of corticosteroids (CS) on sarilumab pharmacokinetics

Patients with PMR were receiving moderate to high dose CS at the time of entry into the clinical study 15160. A comparison of the effect of concomitant administration of CS with sarilumab by CS dose subgroup (0, >0 and <7.5 mg/day, and ≥7.5 mg/day) showed similar and considerable overlap in sarilumab concentrations across subgroups in patients with RA, suggesting that there is no relevant effect of CS on sarilumab PK.

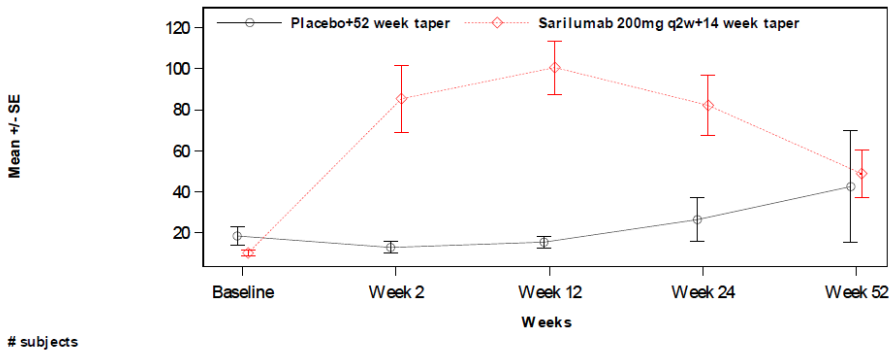
2.3.3. Pharmacodynamics

Several PD biomarkers were assessed in clinical studies in patients with PMR and GCA, including IL-6, sIL-6Rα, and inflammatory markers (acute phase reactants CRP and ESR).

Results from Pivotal Study EFC15160

IL-6 and sIL-6r

Figure 7 Mean IL-6 (ng/L) during the 52-week treatment period - Safety population



subjects

	Baseline	Week 2	Week 12	Week 24	Week 52
Placebo+52 week taper	49	54	41	42	7
Sarilumab 200mg q2w+14 week taper	50	54	44	40	7

Figure 8 - Mean soluble interleukin-6 receptor (ng/mL) during the 52-week treatment period - Safety population

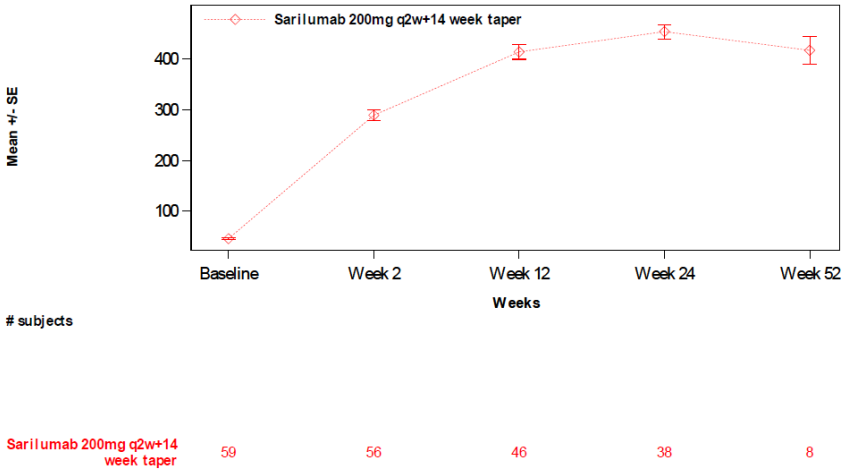
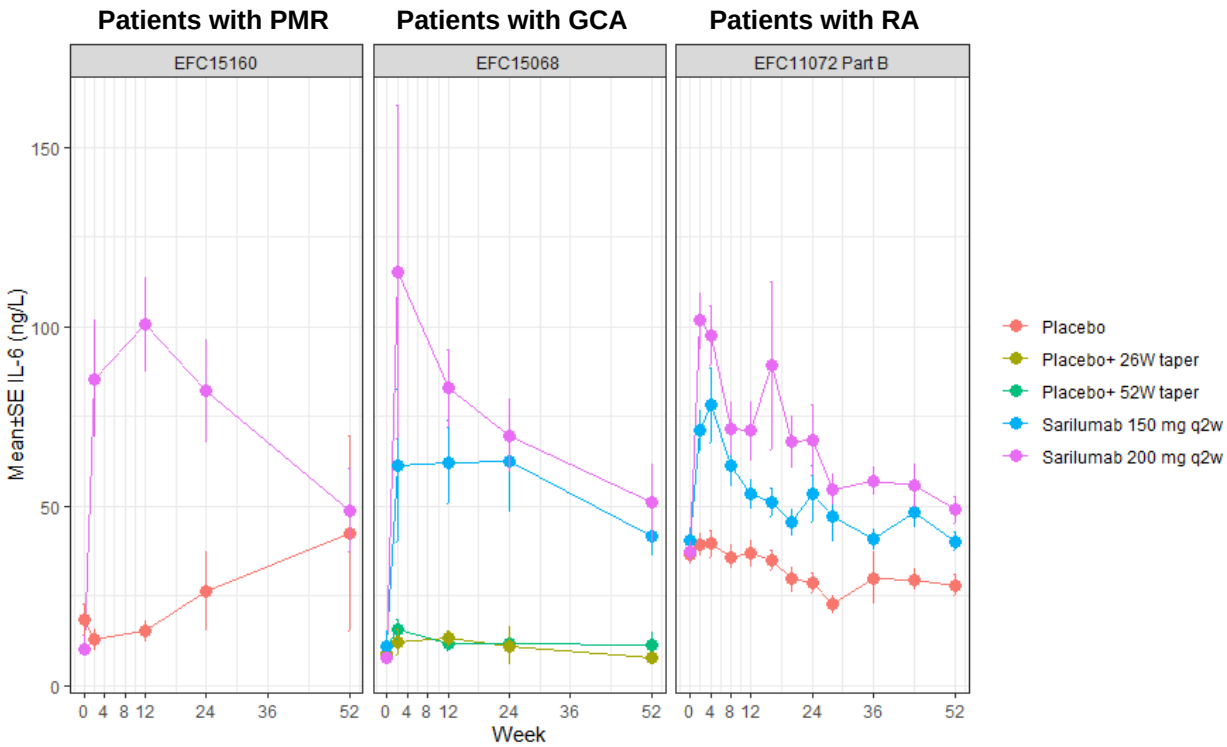


Figure 9 - Concentrations of IL-6 following repeated SC administration in patients with PMR, GCA, and RA



IL-6: interleukin-6; GCA: giant cell arteritis; PMR: polymyalgia rheumatica; q2w: every 2 weeks; RA: rheumatoid arthritis; SC: subcutaneous; W: week

Serum IL-6 levels are elevated in patients with PMR compared to IL-6 levels in the healthy population.

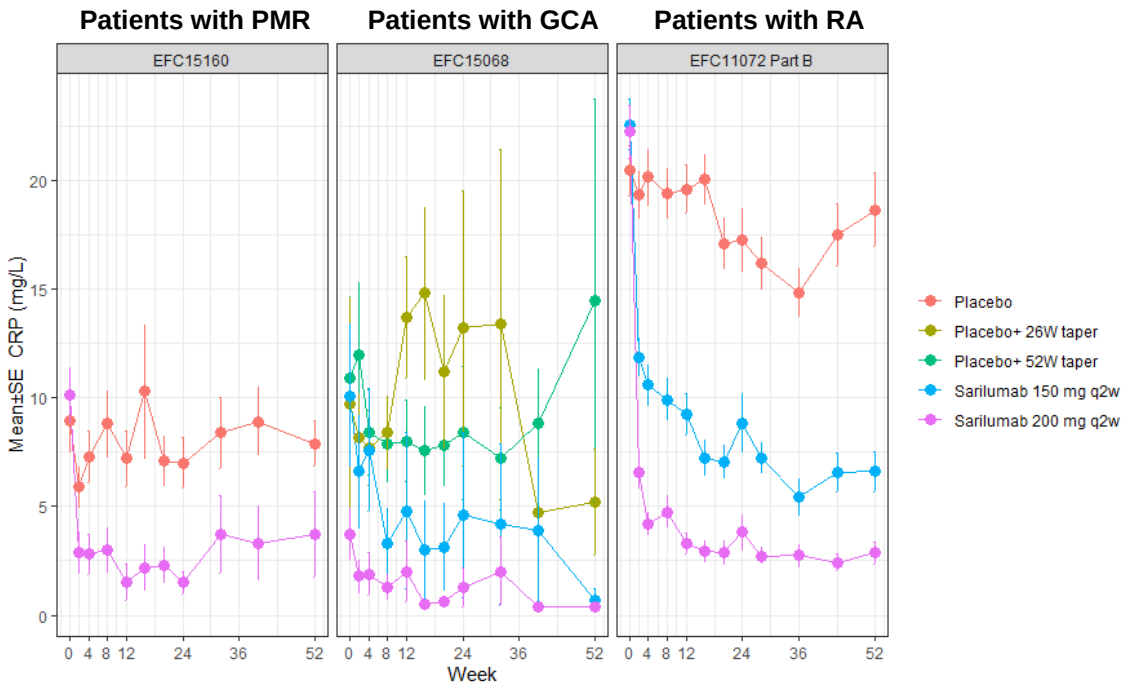
In patients with PMR, mean IL-6 concentrations in serum increased to peak levels at Week 12 and then declined after further treatment; mean total sIL-6Rα concentration increased as early as Week 2, and reached peak levels by Week 24. The baseline IL-6 levels in patients with PMR were lower than those observed in patients with RA (Figure 9). This may be attributed to high dose CS at the time of entry

into clinical studies prior to the baseline, which would have suppressed the acute phase reactants. For baseline total sIL-6Rα levels in serum, levels were similar in patients with PMR and RA.

Sarilumab treatment resulted in an overall similar effect on IL-6 profiles and sIL-6R profiles over time in PMR and RA patients following 200 mg Q2W.

C-reactive protein

Figure 10 - Concentrations of C-reactive protein following repeated SC administration in patients with PMR, GCA, and RA



CRP: C-reactive protein; GCA: giant cell arteritis; PMR: polymyalgia rheumatica; q2w: every 2 weeks; RA: rheumatoid arthritis; SC: subcutaneous; W: week

Baseline serum CRP levels in patients with PMR were lower than those observed in patients with RA (Figure 10). This may be attributed to high dose CS at the time of entry into clinical studies prior to the baseline.

A rapid and larger decrease from baseline in mean CRP level was observed following sarilumab 200 mg q2w, that is to an overall comparable extent compared wo the RA population.

Mechanism of action

PMR is an inflammatory disease with elevated inflammatory markers, such as erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP). Interleukin-6 is a known pivotal mediator of the acute phase response which is characterized by elevations of ESR and CRP. IL-6 could thus be considered a potentially relevant driver of inflammation and pathophysiology of PMR.

Sarilumab binds specifically to IL-6Rα and inhibits IL-6 mediated signaling, leading to an increase in concentration of total sIL-6Rα and normalization of levels of acute phase proteins and inflammatory markers (CRP) in patients with PMR.

2.3.4. PK/PD and exposure-response analyses

Descriptive PK-PD and exposure-response analyses

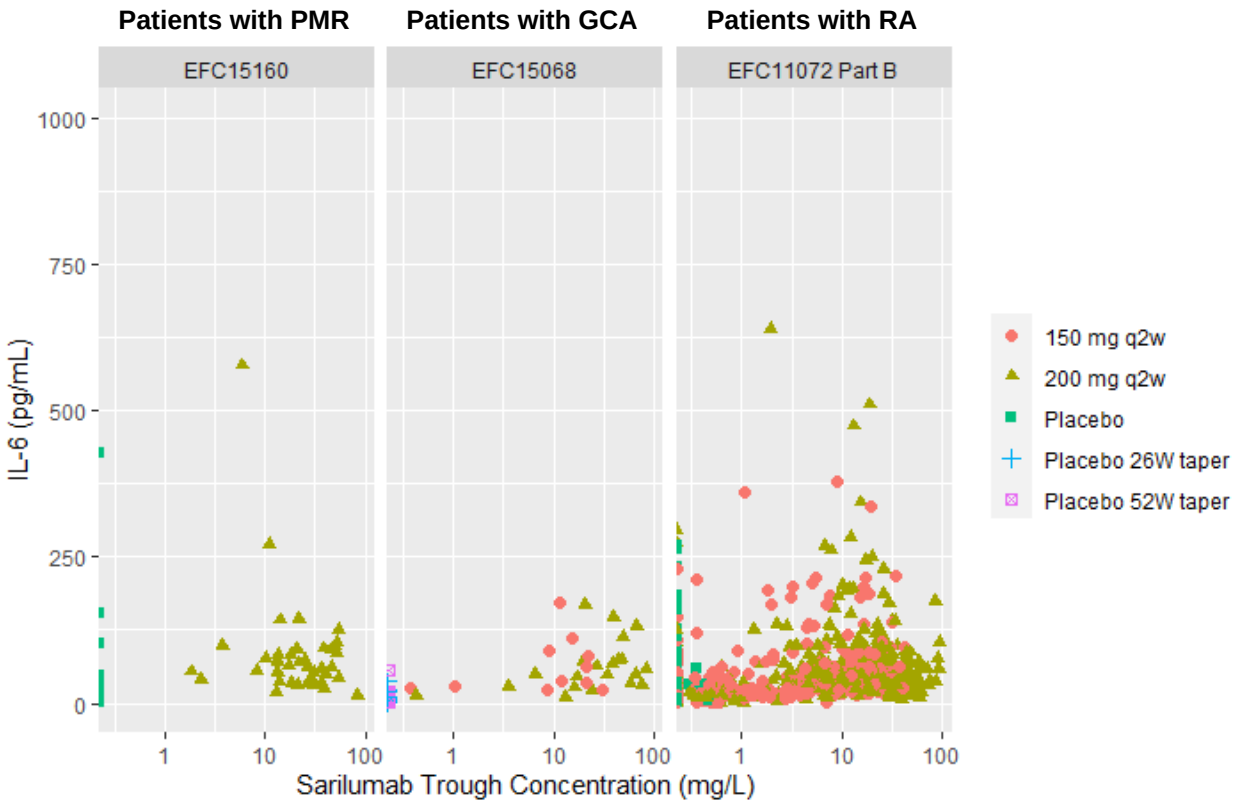
The relationships of sarilumab concentrations with the PD biomarkers in patients with PMR (Study EFC15160) and in patients with GCA (Study EFC15068) were explored graphically and compared with those in patients with RA (Study EFC11072 Part B). The exposure-response relationship for the key efficacy and safety endpoints in the PMR Population was assessed using a descriptive E-R analysis by exposure tertiles with data from Study EFC15160.

The key clinical efficacy endpoints were proportion (%) of patients achieving sustained remission at Week 52, and cumulative proportion (%) of patients who had rescue therapy during the 52-week treatment period. The key clinical safety endpoints included TEAE, SAE, AESI, and ANC levels.

Biomarkers

The variability of IL-6 level was high in patients with PMR, GCA, and RA who received placebo and sarilumab treatments. There was no obvious relationship between individual IL-6 levels and sarilumab trough concentrations in patients with PMR (Study EFC15160), GCA (Study EFC15068), and RA (Study EFC11072 Part B, original marketing application) as shown in the figure below.

Figure 11 - Relationship between steady-state trough concentration of sarilumab and IL-6 after 24 weeks of sarilumab treatment in patients with PMR, GCA, and RA



Not included 3 outliers (IL-6 >2000 pg/mL) in EFC11072 Part B.
GCA: giant cell arteritis; IL-6: interleukin-6; PMR: polymyalgia rheumatica; q2w: every 2 weeks; RA: rheumatoid arthritis

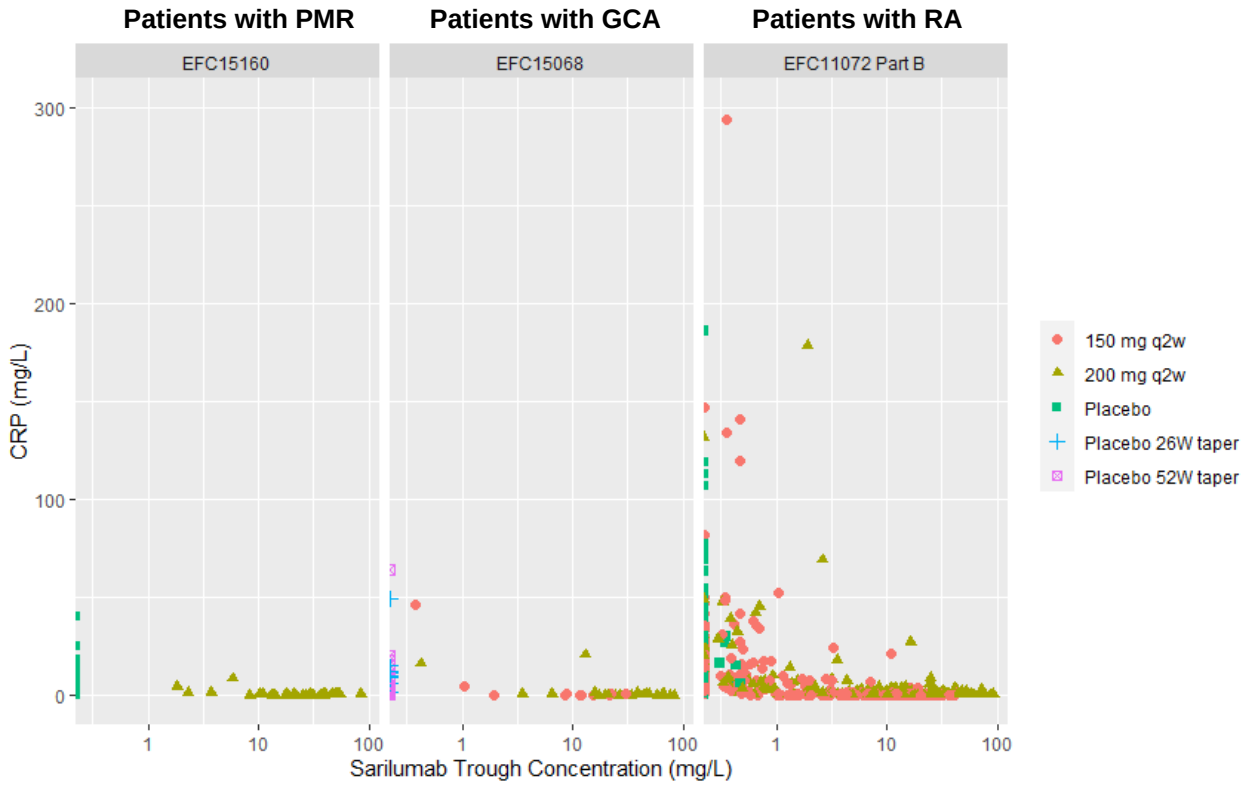
Total sIL-6Rα increased with increasing sarilumab trough concentrations after repeated 200 mg q2w doses in patients with PMR in Study EFC15160, plateauing overall above ~25 mg/L (ctrough).

Figure 12 - Relationship between steady-state trough concentration of sarilumab and total sIL-6R after 24 weeks of sarilumab treatment in patients with PMR, GCA, and RA

GCA: giant cell arteritis; PMR: polymyalgia rheumatica; q2w: every 2 weeks; RA: rheumatoid arthritis; sIL6R: soluble interleukin-6 receptor

The reductions in CRP increased with increasing sarilumab trough concentrations after repeated 200 mg q2w doses in patients with PMR, with CRP levels reaching the normal range (<10 mg/L) at Week 24 (Study EFC15160).

Figure 13 - Relationship between steady-state trough concentration of sarilumab and CRP after 24 weeks of sarilumab treatment in patients with PMR, GCA, and RA



CRP: C-reactive protein; GCA: giant cell arteritis; PMR: polymyalgia rheumatica; q2w: every 2 weeks; RA: rheumatoid arthritis

Efficacy endpoints

The descriptive analyses indicated that the key efficacy endpoints were in general similar in the low, medium, and high tertiles of sarilumab exposure in patients with PMR.

There was a small increase of proportion of patients with sustained remission at week 52 (primary efficacy endpoint) from the low to the medium tertile and the treatment effect approached a plateau over the concentration range following the sarilumab 200 mg q2w dosing regimen. The cumulative number (%) of patients who received rescue therapy was statistically significantly lower in the sarilumab treated patients. There was no clear trend of decrease in proportion (%) of patients who had rescue therapy with increased exposure (Table 10).

Table 10 – Key efficacy endpoints by steady-state Ctrough tertile (study EFC15160)

n(%)	Placebo	Sarilumab 200 mg q2w		
		Low (1st tertile)	Medium (2nd tertile)	High (3rd tertile)
	N=58	N=15	N=19	N=14
Range of C_{trough} (min, max, mg/L)	-	0.88, 13.6	13.8, 30.5	30.8, 84.3
Mean C_{trough} (mg/L)	-	7.50	22.4	47.2
Proportion of patients with sustained remission at Week 52	6 (10.3)	4 (26.7)	7 (36.8)	5 (35.7)
Proportion of patients with sustained remission excluding CRP at Week 52	8 (13.8)	6 (40.0)	7 (36.8)	5 (35.7)
Cumulative proportion (%) of patients who had rescue therapy	34 (58.6)	5 (33.3)	5 (26.3)	6 (42.9)

CRP = c-reactive protein; C_{trough} = concentration observed before drug administration during repeated dosing; min = minimum; max = maximum; proportion of patients: number of patients (%); q2w = every 2 weeks
Source: scp-appx1-pmr-us-eu [1.1.1.1], [1.3.1.1], [1.3.1.2], and [1.3.2.1]

The baseline disease characteristics of PMR including prednisone (or equivalent) dose for PMR at baseline, prednisone (or other CS) dose at time of PMR flare and baseline ESR were in general balanced in each exposure tertile, while baseline CRP and duration of PMR showed numerical differences by exposure tertiles. The patients in the low tertile had higher baseline CRP and longer duration of PMR disease. Additionally, body weight was higher in the patients in the lowest exposure tertile, which is expected since body weight is one of the main sources of PK variability. The unbalanced distribution of baseline values in each exposure tertile is a potentially confounding factor and likely contributed to the difference observed across tertiles (Table 11).

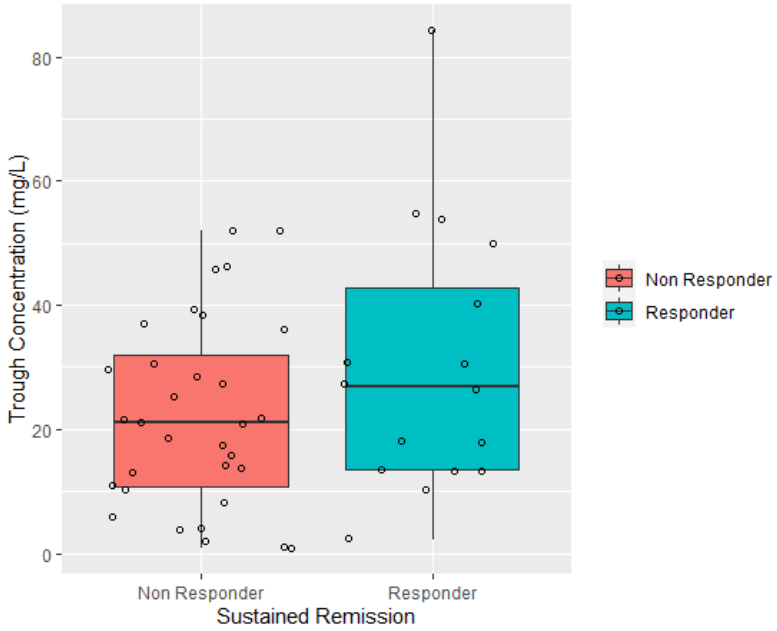
Table 11 Patient disease characteristics at baseline by steady-state Ctrough tertile in patients with PMR (Study EFC15160)

		Sarilumab 200 mg q2w		
	Placebo	Low (1st tertile)	Medium (2nd tertile)	High (3rd tertile)
	N=58	N=15	N=19	N=14
Range of C_{trough} (min, max, mg/L)	-	0.88, 13.6	13.8, 30.5	30.8, 84.3
Mean C_{trough} (mg/L)	-	7.50	22.4	47.2
Duration of PMR from diagnosis date to baseline (days)	600.2 (680.5)	1179.1 (1194.8)	451.7 (402.4)	549.3 (830.3)
Prednisone or equivalent dose for PMR at baseline (mg/day)	11.31 (3.29)	10.42 (3.01)	13.50 (4.50)	12.68 (3.60)
Dose (mg) of prednisone (or other corticosteroid) at time of PMR flare	10.23 (4.16)	9.40 (2.83)	11.24 (4.47)	10.39 (3.62)
Baseline CRP (mg/L)	8.92 (11.20)	13.57 (11.65)	10.22 (9.74)	8.41 (9.12)
Baseline ESR (mm/hour)	26.93 (17.09)	28.47 (20.27)	31.42 (32.30)	29.00 (16.74)
Baseline body weight (kg)	83.49 (16.42)	86.22 (14.97)	78.26 (12.74)	63.73 (9.42)

C_{trough} tertile: 1 (0.88-13.6 mg/L), 2 (13.8-30.5 mg/L), 3 (30.8-84.3 mg/L)
CRP: C-reactive protein; C_{trough}: concentration observed before drug administration during repeated dosing; ESR: erythrocyte sedimentation rate; PMR: polymyalgia rheumatica; q2w: every 2 weeks
Source: scp-appx1-pmr-eu [1.1.1.1], [1.2.1], and [1.2.2]

With an appreciable overlap in the confidence intervals, the mean Ctrough in the responders was slightly higher than that in the nonresponders (Figure 14), with more patients having sarilumab concentrations above 25 mg/L in the responders (56%) compared to nonresponders (41%) (sIL-6R changes reached a plateau at sarilumab concentration of 25 mg/L).

Figure 14 - Box plot of sarilumab steady-state C_{trough} in individual patients with PMR by sustained remission responder status (Study EFC15160)



Sustained remission at Week 52.

The boxplot was generated with the whiskers of maximum 1.5 interquartile range (IQR). From above the upper quartile (75%), a distance of 1.5 times the IQR is measured out and a whisker is drawn up to the largest observed point from the dataset that falls within this distance. Similarly, a distance of 1.5 times the IQR is measured out below the lower quartile (25%) and a whisker is drawn up to the lower observed point from the dataset that falls within this distance.

Safety endpoints

Descriptive analysis for TEAE, SAE, and AESI is provided in the table below. From these data there were no noticeable consistent patterns in the incidence of individual TEAEs, treatment-emergent SAEs, TEAEs leading to permanent treatment discontinuation, and AESIs observed that suggested a correlation of E-R of safety endpoints. Nevertheless, the sample size is considered low. No apparent trend of increasing TEAE incidence with increasing concentration of sarilumab could be detected.

In addition, a descriptive exposure-safety analysis by quartiles of sarilumab steady-state Ctrough (at Week 24) was conducted to examine the relationships of the incidence of TEAEs, SAEs, TEAE leading to permanent treatment discontinuation, and AESIs with the steady-state Ctrough of sarilumab in patients with RA. The descriptive quartile analysis for RA Pool 1 Population showed a flat relationship between TEAE incidences and exposure in patients with RA.

Although a higher mean PK exposure was observed in patients with PMR than patients with RA at Week 24, individual exposures (Ctrough) overlapped between the 2 populations supporting the comparisons of safety data from patients with PMR study and safety data from the original marketing application submitted for the RA indication.

The E-R relationship was also evaluated between ANC at Week 24 and sarilumab steady-state Ctrough in patients with PMR (Study EFC15160). When compared with the placebo group, a lower mean ANC level and a greater mean change from baseline in the ANC in the sarilumab 200 mg q2w treatment group was noted (Table 12).

Table 12 – ANC and proportion of patients with ANC<1.0 Giga/L by steady-state C_{trough} tertile in patients with PMR (Study EFC15160)

		Sarilumab 200 mg q2w[a]		
	Placebo	Low (1st tertile)	Medium (2nd tertile)	High (3rd tertile)
	N=58	N=15	N=19	N=14
Range of C_{trough} (min, max, mg/L)	-	0.88, 13.6	13.8, 30.5	30.8, 84.3
Mean C_{trough} (mg/L)	-	7.50	22.4	47.2
Mean (SD) ANC (Giga/L)	5.564 (2.111)	2.927 (1.410)	2.565 (1.576)	2.752 (1.400)
Mean (SD) ANC change from baseline (Giga/L)[b]	-0.986 (2.209)	-3.611 (2.613)	-5.765 (3.523)	-4.496 (2.196)
ANC<1.0 Giga/L n(%)[c]	0	1 (6.7)	2 (10.5)	0

ANC: absolute neutrophil count; C_{trough}: concentration observed before drug administration during repeated dosing; q2w: every 2 weeks

a Based on C_{trough} value at Week 24; for patients with missing C_{trough} at Week 24, the closest non-missing value measured at Week 12, 16, or 52 is used.

b ANC change from baseline at Week 24.

c During the TEAE period.

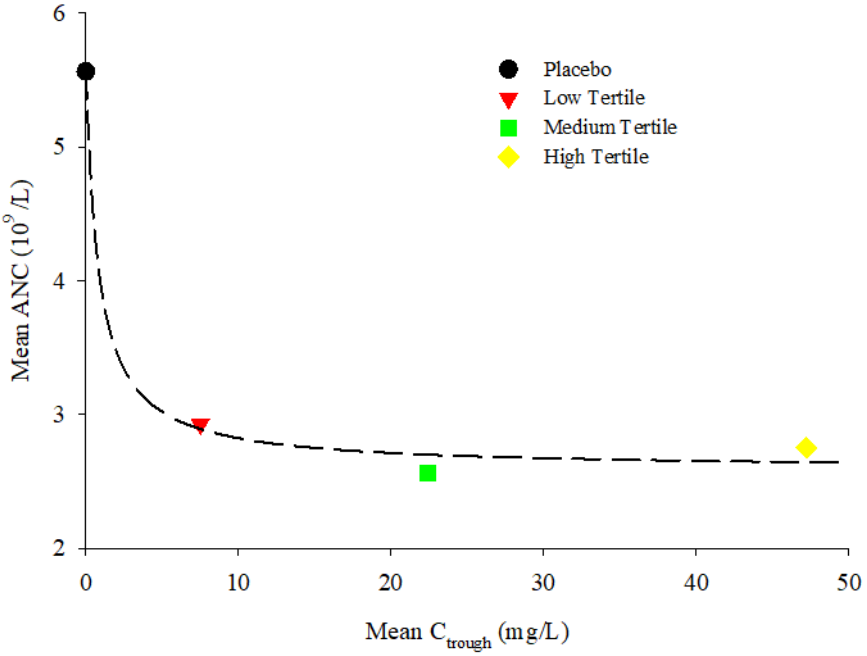
Source: scp-appx1-pmr-eu [1.1.1.1], [1.5.1.1], and [1.5.2.1]

The E-R relationship was evaluated between the proportion of patients (%) with ANC <1.0 Giga/L and sarilumab steady-state Ctrough in patients with PMR (Study EFC15160). The proportion of patients 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. Nevertheless, the sample size is regarded low.

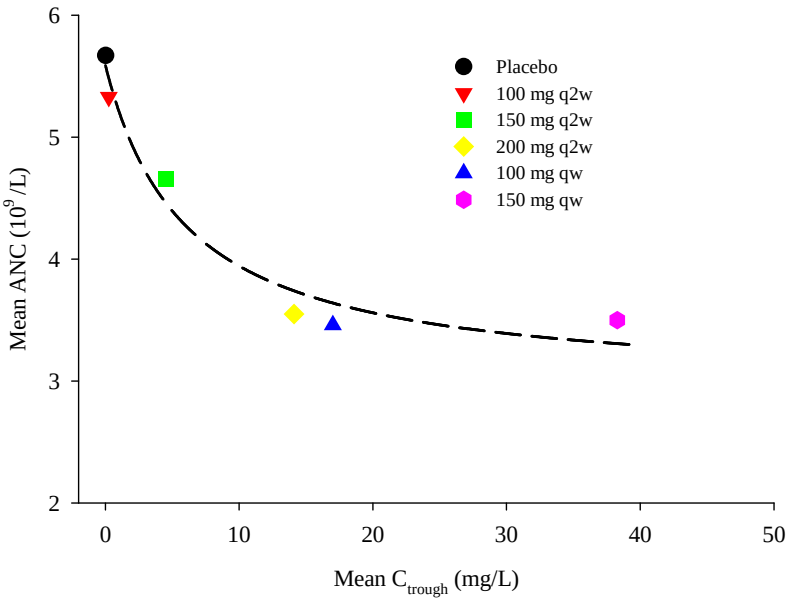
The mean ANC level and ANC change from baseline increased with increasing sarilumab Ctrough from the low tertile to the medium tertile, and the treatment effect approached a plateau over concentration range of the medium to high tertiles following the 200 mg q2w dosing regimen in patients with PMR.

Figure 15 - ANC versus trough concentration of sarilumab in patients with PMR and RA

Patients with PMR (Study EFC15160)



Patients with RA (Study EFC11072 Part A)



ANC: absolute neutrophil count; C_{trough}: concentration observed before drug administration during repeated dosing; PMR: polymyalgia rheumatica; q2w: every 2 weeks; qw: every week; RA: rheumatoid arthritis

Study EFC15160 at Week 24

Study EFC11072 Part A at Week 12 (in the original marketing application).

Dash line is presented to illustrate an E_{max} type relationship.

2.3.5. Discussion on clinical pharmacology

The proposed dose recommendation for sarilumab in patients with PMR is primarily based on key efficacy and safety endpoints in study EFC15160, with supportive PD, PK/PD and exposure-response data from this study as well as from patients with GCA (Study EFC15068).

PK

Overall, PK data and model-based population PK analysis indicated comparability with RA patients, whose PK has been described previously. Sarilumab exhibited nonlinear PK with target-mediated drug disposition. Trough concentrations at steady state in patients with PMR were within the range of those observed in patients with RA. As only sparse PK sampling has been conducted in studies EFC15160 and EFC15068, non-compartmental PK analysis was not deemed feasible. Pooled PK data was used to update the pop PK modelling that had originally been established based on PK data collected from RA patients, in order to characterise PK in the target population. The model development process lacked a prespecified plan that would explain why the MAH chose fitting of selected parameter (CL/F and Vm) to pooled, imbalances data with high variability over e.g. external validation of PMR PK data or combined PMR/GCA PK data. With the current process, interindividual variability of CL/F increased three-fold. Of note, all covariate effects were fixed to those from the RA PK model, which might be one source of inflating IIV. Fixing included also characteristics such as ALB, CLCRN, BLCRP – that were distributed differently between the RA and PMR populations. Pooling of GCA and PMR for pop PK was chosen, although GCA trough concentrations indicated a higher degree of accumulation and longer time to steady state compared to PMR observed trough concentrations. Of note, sample size and amount of PK and PD collected were lower than originally planned. The final dataset included 58 patients with PMR with 341 sarilumab concentrations and 40 patients with GCA with 241 sarilumab concentrations for pop PK analysis. Predicted mean Ctrough at week 24 and 52 (both considered at steady state) for PMR patients were comparable with observed Ctrough values, however, time to steady state and degree of accumulation (Ctrough) were deviating between observation and prediction, with a trend in higher predicted accumulation ratio and longer time to steady state than observed. The description of PK in PMR patients initially proposed for SmPC Section 5.2 was highly relying on the final pop PK model based on pooled data. At the CHMP request, the MAH amended the SmPC statement in Section 5.2, taking observed Ctrough from PMR patients into account.
The CHMP agreed that analyses of sparse Ctrough PK samples including model-based analysis did not warrant dose adaptation for the PMR target population.

PD

In patients with PMR, mean IL-6 concentrations in serum increased to peak levels at Week 12 and then declined after further treatment; mean total sIL-6Rα concentration increased as early as Week 2, and reached peak levels by Week 24. The baseline IL-6 levels in patients with PMR were lower than those observed in patients with RA. This may be attributed to high dose corticosteroids at the time of entry into clinical studies prior to the baseline, which would have suppressed the acute phase reactants. For baseline total sIL-6Rα levels in serum, levels were similar in patients with PMR and RA.
Although PD marker CRP and ESR were used to support the posology in PMR and comparability over patient populations PMR, GCA, and RA, reporting was regarded sufficient to conclude overall comparability, also based on a very flat exposure response relationships with regard to efficacy and safety. Sarilumab treatment for PMR patients taking 200 mg once every 2 weeks has a similar effect compared to RA patients on the PD biomarker profiles (CRP and ANC) over time. This information has been reflected in section 5.1 of the SmPC.

The relationships of sarilumab concentrations with the PD biomarkers in patients with PMR (Study EFC15160) and in patients with GCA (Study EFC15068) were explored graphically and compared with

those in patients with RA (Study EFC11072 Part B). The exposure-response relationship for the key efficacy and safety endpoints in the PMR Population was assessed using a descriptive E-R analysis by exposure tertiles with data from Study EFC15160. Results indicated no obvious relationship between individual IL-6 levels and sarilumab trough concentrations in patients with PMR (Study EFC15160). Total sIL-6Rα increased with increasing sarilumab trough concentrations after repeated 200 mg q2w doses in patients with PMR in Study EFC15160, plateauing overall above ~25 mg/L (ctrough).

The descriptive analyses indicated that the key efficacy endpoints were in general similar in the low, medium, and high tertiles of sarilumab exposure in patients with PMR. There was a small increase of proportion of patients with sustained remission at week 52 (primary efficacy endpoint) from the low to the medium tertile and the treatment effect approached a plateau over the concentration range following the sarilumab 200 mg q2w dosing regimen.

No clear E-R relationships were observed in patients with PMR between increasing concentrations of sarilumab and the proportion of patients experiencing TEAEs or the proportion of patients with ANC<1.0 Giga/L. This was consistent with observations for patients with RA.

2.3.6. Conclusions on clinical pharmacology

PK and PD data from the pivotal study in PMR patients (Study EFC15160) and from patients with GCA (Study EFC15068) support the approval of sarilumab 200 mg once every 2 weeks by SC administration for the treatment of adult patients with PMR, in combination with a tapering course of systemic corticosteroids, after which sarilumab can be continued as monotherapy.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response studies were performed.

2.4.2. Main study

Study EFC15160: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with polymyalgia rheumatica. (Short title: Evaluation of the Efficacy and Safety of Sarilumab in Patients With Polymyalgia Rheumatica (SAPHYR))

Methods

Study participants

Study participants 50 years and older who were diagnosed with PMR according to the ACR/EULAR criteria were included in the study. Participants were unable to taper CS successfully without flare and had to have had at least 1 episode of unequivocal PMR flare while attempting to taper prednisone at a dose that was ≥7.5 mg day (or equivalent) within the past 12 weeks prior to screening. They also had to have had a history of being treated for at least 8 weeks with prednisone ≥10 mg/day or equivalent.

As these patients were resistant to CS taper, they were required to be taking prednisone of ≥7.5 mg/day (or equivalent) and not exceeding 20 mg/day during the screening period.

Patients with giant cell arthritis or rheumatoid arthritis or other inflammatory arthritis or other connective tissue diseases were excluded from the study.

Table 13 - Key inclusion and exclusion criteria

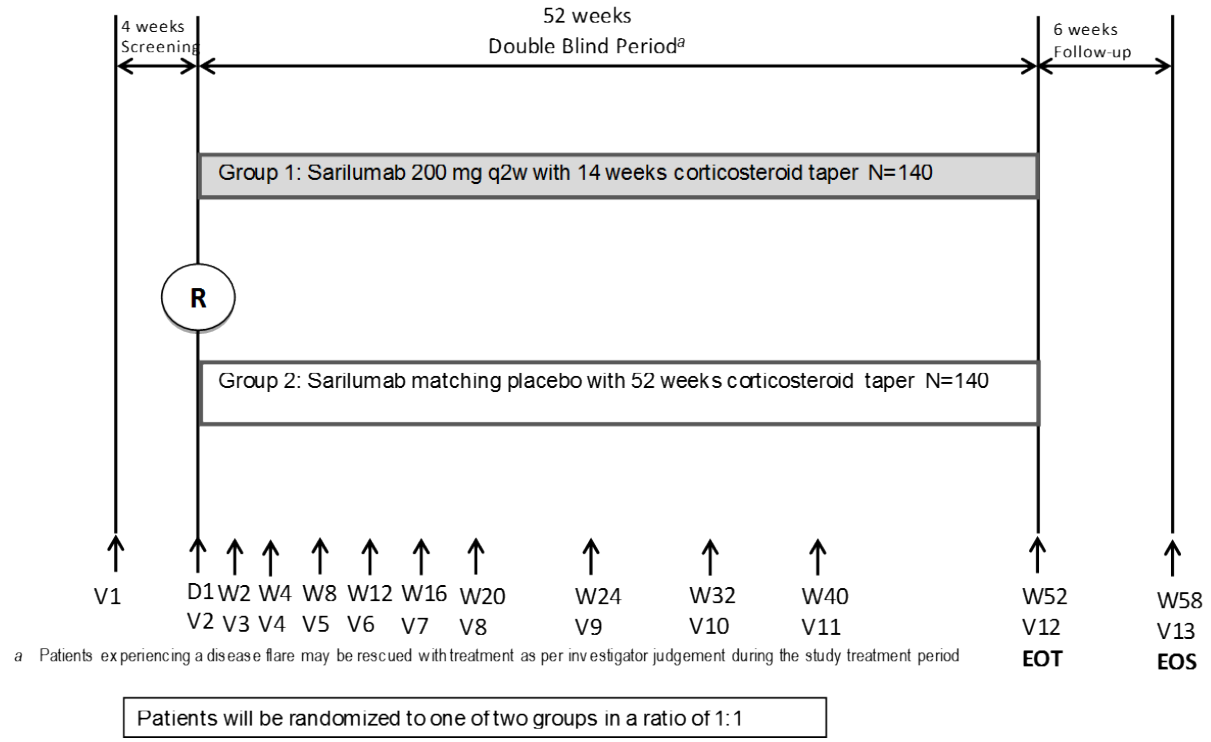
Inclusion criteria	
Diagnostic criteria	• Diagnosis of PMR according to the ACR/EULAR classification criteria as follows (satisfied all criteria): - Age ≥50 years at time of diagnosis. - Bilateral shoulder pain. - Elevated acute phase reactants (CRP >10 mg/L and/or ESR >30 mm/hr). AND one of the following: 1. A score ≥4 at the time of diagnosis based on the following (without ultrasound): - Duration of morning stiffness >45 minutes: 2 points. - Hip pain or limited range of motion: 1 point. - Seronegative for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP): 2 points. - Absence of other joint involvement: 1 point. OR 2. A score ≥5 at the time of diagnosis based on the following (with ultrasound): - Duration of morning stiffness >45 minutes: 2 points. - Hip pain or limited range of motion: 1 point. - Seronegative for RF and anti-CCP: 2 points. - Absence of other joint involvement: 1 point. - At least 1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least 1 hip with synovitis and/or trochanteric bursitis: 1 point (confirmed with ultrasound). - Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis: 1 point. (confirmed with ultrasound). • Patient must have had ESR ≥30 mm/hr or CRP ≥10 mg/L associated with PMR disease activity within 12 weeks prior to screening.
Prednisone use	• Patients were required to be taking prednisone of ≥7.5 mg/day (or equivalent) and not exceeding 20 mg/day at screening and during the screening period. • Patient must have had a history of being treated for at least 8 weeks with prednisone ≥10 mg/day or equivalent.
PMR flare	• Patient must have had at least 1 episode of unequivocal PMR flare while attempting to taper prednisone at a dose that was ≥7.5 mg/day (or equivalent) within the past 12 weeks prior to screening: - Unequivocal symptoms of PMR flare defined as shoulder and/or hip girdle pain associated with inflammatory stiffness.

Exclusion criteria	
Diagnosis	• Diagnosis of GCA (eg, persistent or recurrent localized headache, temporal artery or scalp tenderness, jaw claudication, extremity claudication, blurry or loss of vision, symptoms of stroke). • Concurrent RA or other inflammatory arthritis or other connective tissue diseases, such as but not limited to systemic lupus erythematosus, systemic sclerosis, vasculitis, myositis, mixed connective tissue disease, ankylosing spondylitis.
Prior treatment	• Any prior (within the defined periods below) or concurrent use of immunosuppressive therapies including but not limited to the following: - JAK inhibitor (eg, tofacitinib) within 4 weeks of baseline. - Cell-depletion agents (eg, anti-CD20) without evidence of recovery of B cells to baseline level. - Anakinra within 1 week of baseline. - Abatacept within 8 weeks of baseline. - TNF inhibitors within 2-8 weeks (etanercept within 2 weeks, infliximab, certolizumab, golimumab, or adalimumab within 8 weeks), or after at least 5 half-lives had elapsed, whichever was longer. - Alkylating agents including cyclophosphamide (CYC) within 6 months of baseline. - Cyclosporine A (CsA), azathioprine (AZA) or mycophenolate mofetil (MMF) or leflunomide within 4 weeks of baseline. • Therapeutic failure, including inadequate response or intolerance, or contraindication, to biological IL-6 antagonist (prior IL-6 antagonist treatment that was terminated for reasons unrelated to therapeutic failure at least 3 months before baseline was not excluded). • Unstable methotrexate (MTX) dose and/or MTX dose >15 mg/week within 3 months of baseline.

Abbreviations: ACR/EULAR = American College of Rheumatology/European League against Rheumatism; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GCA = Giant Cell Arteritis; JAK = Janus kinase; PMR = polymyalgia rheumatic; TNF-α = Tumor necrosis factor-alpha

Treatments

Figure 16 - Graphical study design



Abbreviations: D= Day; EOT=end of treatment; EOS=end-of-study; q2w=every 2 weeks; R=randomization; V=Visit; W= Week

Participants were randomized to 1 of the following 2 parallel treatment groups in a 1:1 ratio:

- Group 1: Sarilumab 200 mg q2w with a 14-week taper of CS (subsequently referred as "sarilumab 200 mg q2w+14-week taper")
- Group 2: Sarilumab matching placebo q2w with a 52-week taper of CS (subsequently referred as "placebo+52-week taper")

All participants received sarilumab 200 mg or placebo for 52 weeks. Sarilumab 200 mg dose could be reduced to 150 mg q2w in a blinded manner for management of predefined laboratory abnormalities such as neutropenia, thrombocytopenia, and elevated liver enzymes as recommended in the Summary of Product Characteristics (SmPC) for the RA indication.

All patients received prednisone treatment with different regimen depending on the assigned group. Patients received prednisone and/or prednisone matching placebo in order to ensure the double-blind CS tapering regimen as defined below was maintained. The initial dose of prednisone for both groups was 15 mg/day for the first 2 weeks after randomisation.

- Group 1: From Week 2 to Week 13, patients received gradually decreasing dose levels of prednisone (prednisone or combination of prednisone and placebo to prednisone). From Week 14 onwards, patients without flare received prednisone matching placebo.
- Group 2: From Week 2 to Week 51, patients received gradually decreasing dose levels of prednisone (prednisone or combination of prednisone and placebo to prednisone).

A 6-week post treatment follow up period followed the 52-weeks.

Objectives, outcomes/endpoints

Table 14 Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of KEVZARA® (sarilumab) in patients with PMR as assessed by proportion of patients with sustained remission at Week 52 for sarilumab with a 14-week CS tapering regimen as compared to placebo with a 52-week CS tapering regimen.	• Primary efficacy endpoint: - Proportion of patients achieving sustained remission at Week 52
Secondary	
• To demonstrate the efficacy of sarilumab (with 14 week taper of CS) compared to placebo (with 52 week taper of CS) in patients with PMR with regards to: - Clinical responses (such as components of sustained remission, disease remission rates, time to first disease flare) over time - Cumulative corticosteroid (including prednisone) exposure	• Secondary efficacy endpoints: - Components of sustained remission composite measured at Week 52 - Total cumulative corticosteroid (including prednisone) dose over 52 weeks - Time to first PMR flare
• To assess the effect of sarilumab on reducing glucocorticoid toxicity as measured by the composite GTI questionnaire	• GTI aggregate improvement score (AIS) at Week 52 • GTI cumulative worsening score (CWS) at Week 52
• To assess the safety (including immunogenicity) and tolerability of sarilumab in patients with PMR	• Safety endpoints: - Adverse events - Laboratory safety variables - Vital signs variables - Antinuclear antibodies - Immunogenicity variables
• To measure sarilumab concentrations from serum of patients with PMR	• Functional sarilumab concentrations in serum
Other	
• To assess the effect of sarilumab on physician assessment of disease activity as measured by MD-VAS	• Physician global assessment of disease activity as measured by MD-VAS
• To assess the effect of sarilumab on a variety of PRO concepts, including fatigue (as measured by FACIT-Fatigue scale), health status (as measured by EQ-5D-3L and SF-36v2), physical function (as measured by HAQ-DI), pain (as measured via HAQ-DI by a VAS) and patient assessment of disease activity (as measured via HAQ-DI by a VAS).	• PROs - The functional assessment of chronic illness therapy fatigue scale - EQ-5D-3L - SF-36v2 - HAQ-DI

Objectives	Endpoints
• To assess the impact of ESR/CRP levels on remission status	• Changes in ESR and CRP from baseline through Week 52
• To characterize the disease activity of PMR patients while on steroid taper or sarilumab treatment in a subset of patients using comprehensive approaches to evaluate circulating immune cell types	• Changes in IL-6 level and sIL-6R through Week 52
• To characterize the disease activity of PMR patients while on steroid taper or sarilumab treatment by evaluating circulating proteins, genetics and gene expression in patients who consent for this optional part of the study.	• Changes in markers of inflammation and disease activity over time as assessed in circulating immune cell types, circulating proteins, and gene expression changes.

Abbreviations: CRP, C-reactive protein; CS, corticosteroid; EQ-5D-3L, EuroQol 5 dimension questionnaire, 3-level version; ESR, erythrocyte sedimentation rate; FACIT, functional assessment of chronic illness therapy; GTI, glucocorticoid toxicity index; HAQ-DI, Health Assessment Questionnaire Disability Index; IL-6, interleukin 6; PMR, polymyalgia rheumatica; PRO, patient reported outcome; SF-36v2, Short-Form 36-item questionnaire; sIL-6, soluble IL-6 receptor; VAS, visual analogue scale

The primary endpoint proportion of patients achieving sustained remission at Week 52 is a composite endpoint, sustained remission at Week 52 is defined by having met all of the following parameters:

1. Achievement of disease remission no later than Week 12

AND

2. Absence of disease flare from Week 12 through Week 52

AND

3. Sustained reduction of CRP (to <10 mg/L, with an absence of successive elevations to ≥10 mg/L) from Week 12 through Week 52

AND

4. Successful adherence to the prednisone taper from Week 12 through Week 52.

Successful adherence to the prednisone taper may include the use of any excess prednisone (beyond the per protocol CS tapering regimen) with a cumulative dose of less than or equal to 100mg (or equivalent), such as those employed to manage an AE not related to PMR.

Disease remission is defined as resolution of signs and symptoms of PMR, and normalization of CRP (<10 mg/L). Note: A single CRP elevation (≥10 mg/L) is not considered absence of remission unless CRP remains elevated (≥10 mg/L) at 2 consecutive study visits.

Evaluation for clinical signs and symptoms by the Efficacy Assessor at every study visit according to the schedule of assessment should include, but are not limited to, the following:

- Morning stiffness and/or pain, in the neck, shoulder and/or hip girdles
- Limited range of motion of the shoulders and/or hip girdles
- Constitutional symptoms, such as fatigue, weight loss and low-grade fever
- Other features judged by the clinician-investigator to be consistent with a PMR flare

Flare is defined as recurrence of signs and symptoms attributable to active PMR requiring an increase in CS dose, or elevation of ESR attributable to active PMR plus an increase in CS dose. Increase in CS dose is defined as:

- Any dose increases during the protocol defined steroid taper.

- Re-initiation of prednisone therapy after the protocol defined taper has been completed.

Note: During the initial 12 weeks of prednisone taper, treatment for one flare before Week 12 is permitted if it can be successfully treated with a ≤5 mg/day prednisone add-on taper regimen (completed prior to Week 12) and provided that all other sustained remission parameters are met.

Sample size

The total expected number of participants (280 participants) to be randomized was changed to 118 participants as a result of the inability to recruit due to the COVID19 pandemic and the study was terminated prematurely.

The original sample size of 280 patients (140 per group) was based on the following assumptions:

- Expected difference of 25% (no prior data available, thus based on expected clinical relevance)
- "assuming 5% to 50% placebo + 52-week prednisone taper response rate"
- 90% power
- Two-sided alpha of 0.01
- Using chi-squared ($\chi 2$) test.

Following the protocol amendment, the alpha level was increased from 0.01 to 0.05 and the sample size reduced from 140 to 59 per group. The sample size of 59 per group provides at least 85% and 95% power to detect a 25% and 30% difference in response rates between sarilumab + 14-week prednisone taper and placebo + 52-week prednisone taper groups respectively, assuming response rates between 5% to 15% in the placebo + 52-week prednisone taper group based on two-sided $\chi 2$ test at a significance level of 0.05.

Table 15 Power calculations based on total sample size of 118 randomized patients

Assumed sustained remission rate for placebo+ 52-week prednisone taper	Sample Size per group	Power assuming an absolute 25% between group difference	Power assuming an absolute 30% between group difference
5%	59	95.6%	98.8%
10%	59	91.2%	97.2%
15%	59	86.9%	95.4%

Randomisation

The randomization treatment kit number was planned to be generated centrally by Sanofi. The investigational medicinal products (IMPs) were planned to be packaged in accordance with this list. Patients were planned to be randomized to one of the two treatment groups via an interactive response technology (IRT). Both the randomization and treatment kit lists were planned to be loaded into the IRT. A patient was be considered randomized when the treatment number has been provided by the IRT.

Patients who meet the entry criteria were planned to be randomized to one of the two treatment groups at a ratio of 1:1. No stratification was planned.

Blinding (masking)

The list of treatment kit numbers was planned to be generated by the Sanofi Clinical Supplies Department. A patient randomization list was planned to be generated by the IRT.

Based on the double blinded study design, the investigators and patients were planned to be blinded to the allocation of the active sarilumab and placebo treatment arms.

Sarilumab and matching placebo were planned to be provided in matching glass prefilled syringes in kits. For example, every 2 weeks, the patient allocated to Group 1 will receive 1 sarilumab prefilled syringe (PFS), the patient allocated to Group 2 will receive a sarilumab matching placebo PFS.

The treatment kit numbers were planned to be obtained by the Investigator at the time of patient randomization and subsequent patient scheduled visits via IRT that would be available 24 hours a day.

Standard measures to break the blind in case of safety issues were described in the protocol.

Statistical methods

Analysis Sets

ITT was used for all efficacy analysis. No per-protocol population was prespecified, but several sensitivity analyses were planned (see below). Safety and PK sets were defined as standard and used for the respective analyses.

Primary Endpoint

Fisher's exact test at 5% significance level was performed to test the null hypothesis that the proportion of patients who achieved sustained remission at Week 52 in each treatment group (Group 1 = sarilumab + 52-week prednisone taper; Group 2 = placebo + 14-week prednisone taper) is the same, against the alternative hypothesis that the proportion is not the same between the treatment groups:

$H0$: $\rho_{Group1} - \rho_{Group2} = 0$

$H1$: $\rho_{Group1} - \rho_{Group2} \neq 0$

The number and proportion of patients achieving sustained remission at Week 52 in each treatment group was presented, with the 95% exact confidence interval for the proportion difference and p-value from Fisher's exact test (2-sided).

Patients who did not achieve remission, received rescue treatment with open label prednisone (or equivalent), withdrew from the study before Week 52, or having missing data that prevented assessment of the primary endpoint were considered as non-responders.

Sensitivity Analyses (SA) for Primary Endpoint

The sensitivity analyses were performed in the same fashion as for the primary endpoint. Descriptive statistics (i.e., counts and percentages) were provided for the three individual components.

1) *Sensitivity analysis excluding acute phase reactants:*

Sensitivity analysis was performed for the primary endpoint by removing the acute phase reactants (CRP and ESR) from the definition to mitigate against the possibility of biasing the results due to the known PD effect of sarilumab on acute phase reactants.

Patients achieving sustained remission at Week 52 excluding acute phase reactants were defined by having met all of the following parameters:

- Achievement of disease remission not later than Week 12. Disease remission was defined as resolution of signs and symptoms of PMR.
- Absence of disease flare from Week 12 through Week 52. Flare was defined as recurrence of signs and symptoms attributable to active PMR plus an increase in CS dose due to PMR.
- Successful adherence to the prednisone taper from Week 12 through Week 52.

2) Sensitivity analysis excluding patients who discontinued treatment as they were incorrectly diagnosed as PMR or newly diagnosed as RA while on study:

The diagnosis of PMR can be challenging as symptom characteristics often overlap, making it difficult to decipher differential diagnosis of PMR. Sensitivity analysis of primary endpoint was performed to remove patients who discontinued study treatment due to a change in PMR disease diagnosis.

3) Sensitivity analyses for missing data in the primary endpoint:

Tipping point analysis was performed. The number of responders to impute in each treatment group varied from zero to up to the total number of patients with missing primary endpoint outcomes. For each imputation combination, a p-value based on Fisher's exact test was calculated. The goal was to identify scenarios leading to non-significant results (p-value ≥0.05).

Patients who received rescue therapy were considered as non-responders. Withdrawn patients who had a disease flare prior to withdrawal were also considered as non-responders as this represents the true outcome had they remained in the study. Withdrawn patients who did not experience a disease flare prior to withdrawal were considered as missing and were sequentially imputed for the tipping point analysis.

Secondary Endpoints

Key secondary endpoint: Total cumulative corticosteroid (including prednisone) dose

Descriptive statistics including the number of subjects, mean, and median of the total cumulative prednisone (or equivalent) dose were presented for each treatment group. The difference between the medians and the corresponding 95% non-parametric confidence interval along with p-value from the non-parametric Wilcoxon rank-sum test between the treatment groups was also provided.

Both expected and actual cumulative CS dose were presented. Patients who received increased prednisone or equivalent in rescue therapy were included in their original treatment groups.

Other secondary endpoints:

- Components of sustained remission composite measure at Week 52 (primary endpoint, 4 components) (descriptive only)
- Time to first PMR flare during the treatment period (descriptive and Hazard Ratio)
- GTI (descriptive and ANCOVA / least-square means)

Multiplicity

Hierarchical strategy including only the primary and key secondary endpoint.

Subgroup Analyses

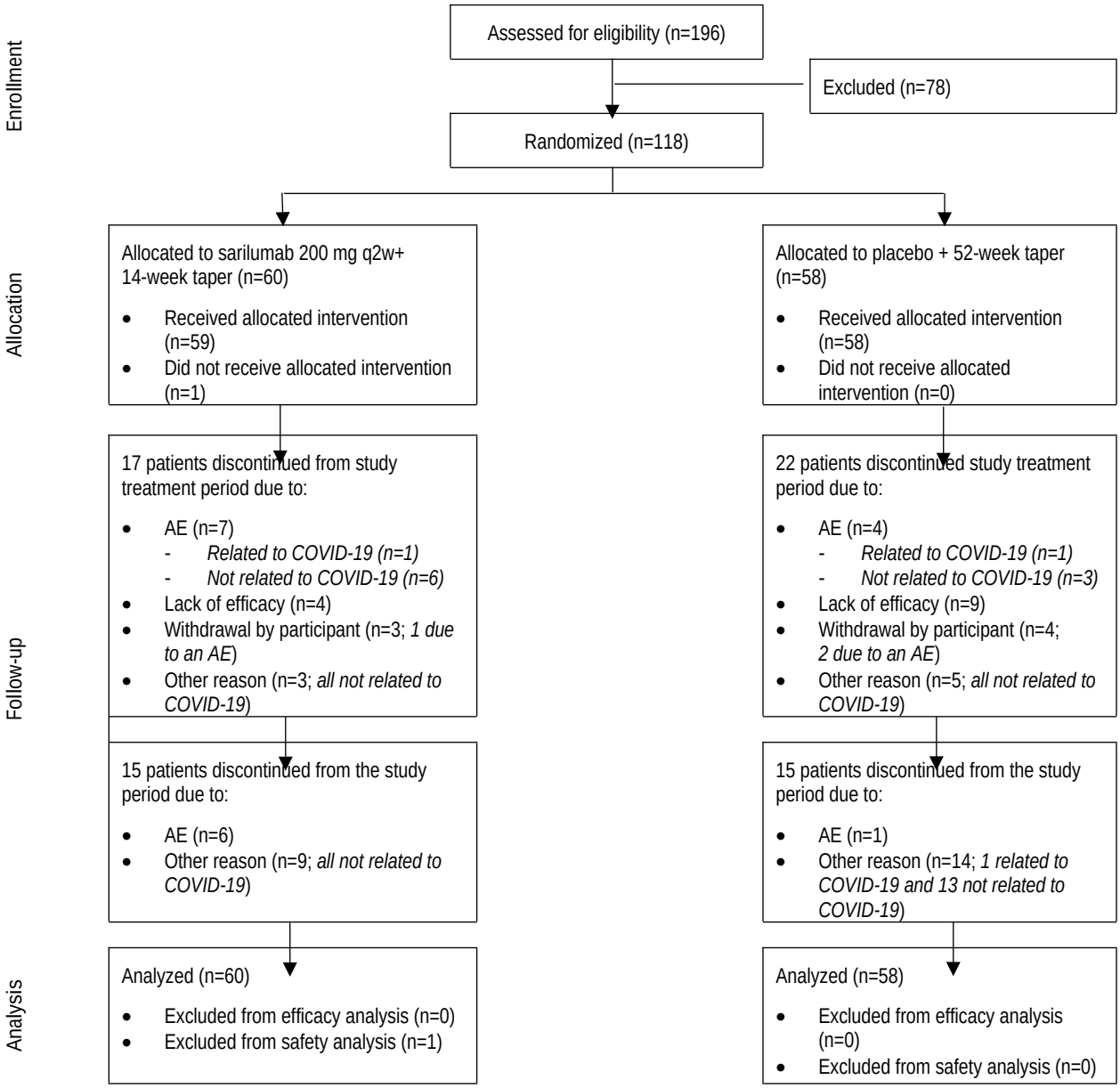
To assess the consistency in treatment effects across subgroup levels, subgroup analyses were conducted for the primary endpoint with respect to:

- Gender (Male versus Female)
- Race (Caucasian/White versus all other races)
- Region (Region 1 [Western countries], Region 2 [South America], Region 3 [Rest of the world])
- Age (<70, ≥70)
- Baseline weight (<60, ≥60 and <100, ≥100 kg)
- BMI (<25, ≥25 and <30, ≥30 kg/m2)
- Baseline CRP (≤median, >median)
- Baseline ESR (≤median, >median)
- Baseline CS dose (≤median, >median)
- Number of relapses prior to screening (1, > 1 relapse)
- COVID-19 impacted population (Yes, No) –only performed if >10% of patients were impacted by COVID-19. The population without trial impact (disruption) due to COVID-19 was defined as patients without any critical or major deviation related to COVID-19 or did not permanently discontinue study treatment due to COVID-19.

Results

Participant flow

Figure 17 - Disposition diagram



Abbreviations: AE=adverse event; COVID-19=coronavirus disease of 2019; q2w=once every 2 weeks
Source: 5.3.5.1 Study EFC15160 [Figure 2]

Recruitment

Participants were randomized at 60 sites located in Australia, Argentina, Belgium, Canada, Estonia, France, Germany, Hungary, Israel, Italy, Japan, the Netherlands, Russia, Spain, Switzerland, the UK, and the US.

Conduct of the study

The total expected number of participants (280 participants) to be randomized was changed to 118 participants as a result of the inability to recruit due to the COVID19 pandemic and the study was terminated prematurely.

Due to the change in the total expected number of participants, the statistical significance level was changed from 0.01 to 0.05, and the power calculations were revised.

Overall 58 (49.2%) participants had any critical or major deviations; of these, 26 (43.3%) participants in the sarilumab 200 mg q2w+14-week taper group and 32 (55.2%) participants in the placebo+52-week taper group had critical or major protocol deviations. None of these participants were excluded from the efficacy or safety analyses.

Baseline data

Randomised patients had a median age of 69.5 years with the majority of patients in the range of n≥ 65 to <75 years. The patients were primarily female (69.5%) and White (83.1%).

Demographic and participant characteristics at baseline were generally similar between treatment groups with a slightly higher number of participants in the ≥75 to <85 years age group and a slightly lower number of participants in the ≥65 to <75 years age group in the placebo+52-week taper group compared to the sarilumab 200 mg q2w+14-week taper group.

There was a slightly higher proportion of participants in the ≥100 kg weight group in the placebo+52-week taper group compared to the sarilumab 200 mg q2w+14-week taper group.

Table 16 - Demographics and patient characteristics at screening or baseline - Randomized population

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)	All (N=118)
Age (years)			
Number	58	60	118
Mean (SD)	69.1 (8.5)	68.8 (7.8)	68.9 (8.1)
Median	70.0	69.0	69.5
Q1; Q3	64.0; 75.0	64.0; 73.0	64.0; 74.0
Min; Max	52; 88	51; 88	51; 88
Age group (years) [n (%)]			
Number	58	60	118
≥50 - <65	15 (25.9)	16 (26.7)	31 (26.3)
≥65 - <75	26 (44.8)	34 (56.7)	60 (50.8)
≥75 - <85	16 (27.6)	9 (15.0)	25 (21.2)
≥85	1 (1.7)	1 (1.7)	2 (1.7)
Sex [n (%)]			
Number	58	60	118
Male	21 (36.2)	15 (25.0)	36 (30.5)
Female	37 (63.8)	45 (75.0)	82 (69.5)
Race [n (%)]			
Number	58	60	118
White	48 (82.8)	50 (83.3)	98 (83.1)
Black or African American	0	0	0
Asian	2 (3.4)	1 (1.7)	3 (2.5)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Unknown	0	0	0
Not Reported[a]	8 (13.8)	9 (15.0)	17 (14.4)
Ethnicity [n (%)]			
Number	58	60	118
Hispanic or Latino	7 (12.1)	6 (10.0)	13 (11.0)
Not Hispanic or Latino	43 (74.1)	45 (75.0)	88 (74.6)
Unknown	0	0	0
Not Reported[a]	8 (13.8)	9 (15.0)	17 (14.4)
Region [n (%)]			
Number	58	60	118
Western countries	44 (75.9)	47 (78.3)	91 (77.1)
South America	4 (6.9)	5 (8.3)	9 (7.6)
Rest of the World	10 (17.2)	8 (13.3)	18 (15.3)
Weight (kg)			
Number	58	60	118
Mean (SD)	83.49 (16.42)	74.44 (15.28)	78.89 (16.42)
Median	83.50	73.15	77.70
Q1; Q3	70.00; 94.00	64.65; 84.75	67.80; 88.30
Min; Max	57.0; 127.3	44.0; 125.0	44.0; 127.3
Weight group (kg) [n (%)]			
Number	58	60	118

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)	All (N=118)
<60	4 (6.9)	9 (15.0)	13 (11.0)
≥60 - <100	43 (74.1)	48 (80.0)	91 (77.1)
≥100	11 (19.0)	3 (5.0)	14 (11.9)
BMI (kg/m^2)			
Number	58	60	118
Mean (SD)	29.90 (4.63)	27.81 (5.42)	28.84 (5.14)
Median	30.27	27.21	28.51
Q1; Q3	26.67; 32.01	23.75; 30.79	25.39; 31.77
Min; Max	21.2; 43.8	18.6; 44.8	18.6; 44.8

Region: Western Countries = Australia, Belgium, Canada, Estonia, France, Germany, Hungary, Italy, Netherlands, Spain, Switzerland, United Kingdom, United States; South American = Argentina; Rest Of The World = Russia, Israel, Japan.

a Race and ethnicity information are not allowed to be collected in France.

Note: Number = Number of patients assessed. Percentages are calculated using number of patients assessed as denominator.

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/dem_demo_r_t.sas OUT=REPORT/OUTPUT/dem_demo_r_t_x.rtf (27JUL2021 5:11)

Disease characteristics of PMR at baseline

The median (range) duration of PMR was 300 (66 to 3992) days for all participants. At baseline, participants were taking a median dose of 10 mg of prednisone or prednisone equivalent. All of the participants reported a PMR flare in the 6 months prior to screening with a median dose of 10 mg of prednisone or prednisone equivalents at the time of flare. Erythrocyte sedimentation rate and CRP were mildly elevated with median value of 23.50 mm/hour and 6.12 mg/L, respectively.

Table 17 - Disease characteristics of PMR at screening or baseline - Randomized population

	Placebo+52-week taper (N=58)	Sarilumab 200 mg q2w+14-week taper (N=60)	All (N=118)
Duration of PMR from diagnosis date to baseline (days)			
Number	50	54	104
Mean (SD)	600.2 (680.5)	660.0 (818.0)	631.3 (752.0)
Median	309.5	291.5	300.0
Q1; Q3	144.0; 883.0	160.0; 865.0	150.0; 870.5
Min; Max	66; 2784	78; 3992	66; 3992
Prednisone or equivalent dose for PMR at baseline (mg/day) [a]			
Number	58	60	118
Mean (SD)	11.31 (3.29)	12.33 (3.90)	11.83 (3.63)
Median	10.00	11.25	10.00
Q1; Q3	8.00; 15.00	9.50; 15.00	9.00; 15.00
Min; Max	7.5; 20.0	7.5; 20.0	7.5; 20.0
Number of patients with prior PMR flares [n (%)] [b]			
Number	58	60	118
≤ 6 months prior to screening	58 (100)	60 (100)	118 (100)
6 to 12 months prior to screening	19 (32.8)	22 (36.7)	41 (34.7)
> 12 months prior to screening	18 (31.0)	15 (25.0)	33 (28.0)
Number of prior flares per patient [c]			
Number	58	60	118
Mean (SD)	2.9 (3.2)	2.8 (2.6)	2.8 (2.9)
Median	2.0	2.0	2.0

	Placebo+52-week taper (N=58)	Sarilumab 200 mg q2w+14-week taper (N=60)	All (N=118)
Q1; Q3	1.0; 3.0	1.0; 3.0	1.0; 3.0
Min; Max	1; 22	1; 14	1; 22
Dose (mg) of prednisone (or other corticosteroid) at time of PMR flare[d]			
Number	58	60	118
Mean (SD)	10.23 (4.16)	10.53 (3.70)	10.38 (3.92)
Median	10.00	10.00	10.00
Q1; Q3	7.50; 10.00	7.50; 12.50	7.50; 12.00
Min; Max	1.0; 30.0	5.0; 20.0	1.0[e]; 30.0
Baseline CRP (mg/L)			
Number	58	60	118
Mean (SD)	8.92 (11.20)	9.97 (9.79)	9.45 (10.47)
Median	5.69	6.76	6.12
Q1; Q3	2.24; 9.45	1.99; 15.10	2.06; 12.70
Min; Max	0.1; 62.3	0.5; 38.2	0.1; 62.3
Baseline ESR (mm/hour)			
Number	58	60	118
Mean (SD)	26.93 (17.09)	31.15 (24.55)	29.08 (21.23)
Median	22.00	25.00	23.50
Q1; Q3	15.00; 35.00	12.50; 40.00	13.00; 37.00
Min; Max	5.0; 85.0	2.0; 115.0	2.0; 115.0

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

a Based on last dose prior to baseline visit.

b Each patient could have more than one prior PMR flare and can be categorized to more than one category.

c Number of patients with prior flare. This value is used as denominator to compute mean number of flares per patient.

d Dose of prednisolone at time of PMR flare was collected for the episode of flare within the past 12-weeks prior to screening. No patients had multiple flares within that period.

e 2 patients did not meet inclusion criteria.

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Numbers analysed

The primary efficacy analysis population was the intent-to-treat (ITT) population, which consisted of all randomized patients. All patients were analysed according to the treatment to which they were randomised. The ITT population for the efficacy analyses consisted of all 118 randomized participants.

Table 18 Analysis populations

n(%)	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w+14 week taper (N=60)	All (N=118)
Randomized Population	58 (100)	60 (100)	118 (100)
Efficacy Population			
Intent-to Treat (ITT)	58 (100)	60 (100)	118 (100)
Pharmacokinetic (PK) Population	0	58 (96.7)	58 (49.2)
Antidrug antibody (ADA) Population	55 (94.8)	56 (93.3)	111 (94.1)
Population with trial impact (disruption) due to COVID-19	5 (8.6)	5 (8.3)	10 (8.5)
Population without trial impact (disruption) due to COVID-19	53 (91.4)	55 (91.7)	108 (91.5)
Safety Population	58 (100)	59 (98.3)	117 (99.2)

COVID-19: Coronavirus Disease 2019

Note: Percentages are calculated using the number of randomized patients as denominator.

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Outcomes and estimation

An overall summary of the efficacy endpoints is provided below.

Multiplicity was controlled by a hierarchical testing procedure. The only secondary endpoint included in the hierarchy was the endpoint of total cumulative CS dose; P-values for the rest of the secondary and exploratory endpoints were not adjusted and only considered nominally.

Primary efficacy endpoint

The study met its primary endpoint as the proportion of participants achieving sustained remission at Week 52 was higher in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group; this difference was statistically significant.

Table 19 - Number (%) of patients achieving sustained remission at Week 52 - ITT population

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)
Number	58	60
Yes	6 (10.3)	17 (28.3)
Proportion difference (95% CI) for sarilumab vs. placebo		18.0 (4.15 ,31.82)
p-value[a]		0.0193

CI: Confidence interval

a P-value from Fisher's exact test

Note: Patients who did not achieve remission, received rescue treatment with open-label prednisone (or equivalent), withdrew from the study before Week 52, or had missing data that prevented assessment of the primary endpoint were considered as nonresponders.

Source: 5.3.5.1 Study EFC15160 CSR Table 16

There were 17 (28.3%) participants in the sarilumab 200 mg q2w+14-week taper group and 6 (10.3%) participants in the placebo+52-week taper group who achieved sustained remission at Week 52 with a proportion difference of 18.0 (95% CI: 4.15, 31.82). The difference was statistically significant with p-value of 0.0193 (Table 19). This endpoint was achieved despite the fact that

sarilumab-treated participants had an accelerated CS taper compared to those in the placebo group and required less steroid use.

Primary endpoint sensitivity analyses

The following sensitivity analyses were performed for the primary endpoint:

Sensitivity analysis excluding acute phase reactants

Table 20 - Sensitivity analysis: Number (%) of patients achieving sustained remission at Week 52 excluding acute phase reactants - ITT population

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)
Number	58	60
Yes	8 (13.8)	19 (31.7)
Proportion difference (95% CI) for sarilumab vs. placebo		17.9 (3.13 ,32.61)
p-value[a]		0.0280

CI: Confidence interval

a P-value from Fisher's exact test

Note: Patients who did not achieve remission, received rescue treatment with open-label prednisone (or equivalent), withdrew from the study before Week 52, or had missing data that prevented assessment of the primary endpoint were considered as nonresponders.

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_primary_i_t.sas OUT=REPORT/OUTPUT/eff_primary_sens_wk52_i_t_x.rtf (09SEP2021 4:01)

The proportion of participants achieving sustained remission at Week 52 excluding the acute phase reactants CRP and ESR was statistically significantly greater in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group (19 [31.7%] participants and 8 [13.8%] participants, respectively; p=0.0280) with a proportion difference of 17.9 (95% CI: 3.13, 32.61)

Sensitivity analysis excluding patients who discontinued treatment as they were incorrectly diagnosed as PMR or newly diagnosed as RA while on study

Table 21 - Sensitivity analysis: Number (%) of patients achieving sustained remission at Week 52 excluding those with incorrect PMR diagnosis - ITT population

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)
Number	55	58
Yes	6 (10.9)	17 (29.3)
Proportion difference (95% CI) for sarilumab vs. placebo		18.4 (4.08 ,32.72)
p-value[a]		0.0193

CI: Confidence interval

a P-value from Fisher's exact test

Note: Patients who did not achieve remission, received rescue treatment with open-label prednisone (or equivalent), withdrew from the study before Week 52, or had missing data that prevented assessment of the primary endpoint were considered as nonresponders.

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_primary_i_t.sas OUT=REPORT/OUTPUT/eff_primary_wk52_exclupmr_i_t_x.rtf (09SEP2021 4:01)

During Study EFC15160, 5 participants had their initial diagnosis of PMR revised to a different diagnosis, with 4 participants diagnosed with RA and 1 participant diagnosed with Erdheim-Chester Disease. All 5 participants (2 in the sarilumab 200 mg q2w+14-week taper group and 3 in the placebo+52-week taper group) were non-responders in the initial analysis. The proportion of participants achieving sustained remission at Week 52 excluding those with an incorrect PMR diagnosis was statistically significantly higher in the sarilumab 200 mg q2w+14-week taper group compared to

the placebo+52-week taper group (17 [29.3%] participants and 6 [10.9%] participants, respectively; p=0.0193) with a proportion difference of 18.4 (95% CI: 4.08, 32.72).

Sensitivity analysis for missing data for primary endpoint

Summary of missing data for the components of the primary endpoint

The primary endpoint of sustained remission at Week 52 was a composite endpoint consisting of 4 components. The 4 components of the primary endpoint were derived based on 3 main measurements: PMR clinical assessments, CRP, and rescue medication, where the rescue medication was not subject to missing data. Twenty-two patients in the placebo group and 17 in the Kevzara group had missing data at week 52/at the last study visit.

The proportions of missing PMR clinical assessments and CRP measurements were balanced between the treatment groups. Missing data were due to early treatment discontinuation, and patients who discontinued treatment prior to Week 52 or who were randomized but not treated were considered as non-responders for the primary endpoint.

Summary of missing data for the primary endpoint

For the primary endpoint, patients who permanently withdrew from the study treatment prior to Week 52 or who were randomized but not treated were considered as non-responders. Withdrawn patients who had a disease flare prior to withdrawal were true non-responders as this represented the true outcome had they remained in the study. Withdrawn patients who did not experience a disease flare prior to withdrawal (including the patient who was randomized but not treated) were considered as "missing" and were sequentially imputed for the sensitivity analyses

Table 22 - Primary endpoint: Patient accountability at Week 52 - ITT population

Sustained remission at Week 52 (primary endpoint)	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)
Completed treatment at Week 52 visit	36 (62.1)	42 (70.0)
Responders	6	17
Non-responders[a]	30	25
Did not complete treatment at Week 52 visit	22 (37.9)	18 (30.0)
Non-responders[b]	13	5
Missing[c]	9	13

a Patients who did not achieve remission or receive rescue treatment with open-label prednisone (or equivalent) are considered as non-responders.

b Patients who received rescue treatment.

c Patients who withdrew from the study before Week 52 and did not experience a disease flare prior to withdrawal are considered as missing and where sequentially imputed for the tipping point analysis.

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_tipping_i_t.sas OUT=REPORT/OUTPUT/eff_tipping_summ_i_t_x.rtf (19JUL2021 8:44)

Sensitivity analysis for the primary endpoint: control-based multiple imputation

Sensitivity analyses using the conservative control-based multiple imputations were conducted to assess the robustness of the conclusion of the primary endpoint. Data from all 22 participants (9 from the placebo group and 13 from sarilumab group) who withdrew from the study before Week 52 and did not experience a disease flare prior to withdrawal (including the participants who was randomized but not treated) were considered as missing. The missing data for all 22 participants were imputed using the logistic regression method where only observations in the placebo group were used to derive the imputation model for the binary response, and the process was repeated 100 times. Each complete dataset was analysed using logistic regression for the binary responder outcome with treatment as

covariate. The model parameter estimates obtained from each analysed dataset was then combined using Rubin's rules for inference.

The results from the control-based multiple imputation approach were statistically significant with a proportion difference of 19.1 (95% CI: 4.54, 33.56; p=0.0257) and were consistent with the results from the primary analysis approach. Furthermore, 3 participants in the placebo group who prematurely discontinued from study treatment were due to lack of efficacy. Considering these 3 placebo participants as non-responders, the p-value from the control-based multiple imputation approach was 0.0177.

Tipping point analysis

In the primary analysis, patients who did not complete the study, withdrew or were lost to follow up were considered non-responders. In this tipping point analysis, the robustness of the results in case responders had been wrongly assigned to being non-responder was investigated. In most of the investigated combinations (up to 9 responders with missing data in the placebo group and 13 responders with missing data in the sarilumab group), the results stopped being significant (0.05) when the difference in actual responders in the placebo group vs. in the sarilumab group was more than two, which corresponds to an estimated difference (point estimate) of 14-17% (Table 23; Table 24).

Table 23 - Tipping point analysis: P-values for sustained remission at Week 52 - ITT population

Number of responders in Sarilumab 200mg q2w+14-week taper patients with missing primary endpoint	Number of responders in Placebo+52-week taper patients with missing primary endpoint									
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
0	0.0193	0.0389	0.0714	0.1207	0.1902	0.2817	0.3953	0.5287	0.6779	0.8372
1	0.0112	0.0236	0.0453	0.0799	0.1310	0.2015	0.2932	0.4059	0.5374	0.6840
2	0.0063	0.0140	0.0280	0.0515	0.0879	0.1404	0.2118	0.3035	0.4153	0.5451
3	0.0035	0.0081	0.0169	0.0324	0.0574	0.0953	0.1491	0.2212	0.3128	0.4237
4	0.0019	0.0046	0.0100	0.0198	0.0366	0.0631	0.1023	0.1571	0.2296	0.3211
5	0.0010	0.0025	0.0057	0.0119	0.0227	0.0407	0.0683	0.1087	0.1643	0.2372
6	0.0005	0.0014	0.0032	0.0069	0.0138	0.0256	0.0445	0.0733	0.1146	0.1708
7	0.0003	0.0007	0.0018	0.0039	0.0081	0.0157	0.0283	0.0482	0.0778	0.1199
8	0.0001	0.0004	0.0009	0.0022	0.0047	0.0094	0.0175	0.0308	0.0515	0.0820
9	<.0001	0.0002	0.0005	0.0012	0.0026	0.0054	0.0105	0.0192	0.0333	0.0547
10	<.0001	<.0001	0.0002	0.0006	0.0014	0.0031	0.0062	0.0117	0.0209	0.0355
11	<.0001	<.0001	0.0001	0.0003	0.0008	0.0017	0.0035	0.0069	0.0128	0.0224
12	<.0001	<.0001	<.0001	0.0002	0.0004	0.0009	0.0020	0.0040	0.0076	0.0138
13	<.0001	<.0001	<.0001	<.0001	0.0002	0.0005	0.0011	0.0022	0.0044	0.0083

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_tipping_i_t.sas OUT=REPORT/OUTPUT/eff_tipping_pval_i_t_x.rtf (19JUL2021 8:44)

Table 24 - Tipping point analysis: Difference in proportions of patients achieving sustained remission at Week 52 between treatment groups (sarilumab against placebo) - ITT population

Number of responders in Sarilumab 200mg q2w+14-week taper patients with missing primary endpoint	Number of responders in Placebo+52-week taper patients with missing primary endpoint									
	0	1	2	3	4	5	6	7	8	9
0	17.99%	16.26%	14.54%	12.82%	11.09%	9.37%	7.64%	5.92%	4.20%	2.47%
1	19.66%	17.93%	16.21%	14.48%	12.76%	11.03%	9.31%	7.59%	5.86%	4.14%
2	21.32%	19.60%	17.87%	16.15%	14.43%	12.70%	10.98%	9.25%	7.53%	5.80%
3	22.99%	21.26%	19.54%	17.82%	16.09%	14.37%	12.64%	10.92%	9.20%	7.47%
4	24.66%	22.93%	21.21%	19.48%	17.76%	16.03%	14.31%	12.59%	10.86%	9.14%
5	26.32%	24.60%	22.87%	21.15%	19.43%	17.70%	15.98%	14.25%	12.53%	10.80%
6	27.99%	26.26%	24.54%	22.82%	21.09%	19.37%	17.64%	15.92%	14.20%	12.47%
7	29.66%	27.93%	26.21%	24.48%	22.76%	21.03%	19.31%	17.59%	15.86%	14.14%
8	31.32%	29.60%	27.87%	26.15%	24.43%	22.70%	20.98%	19.25%	17.53%	15.80%
9	32.99%	31.26%	29.54%	27.82%	26.09%	24.37%	22.64%	20.92%	19.20%	17.47%
10	34.66%	32.93%	31.21%	29.48%	27.76%	26.03%	24.31%	22.59%	20.86%	19.14%
11	36.32%	34.60%	32.87%	31.15%	29.43%	27.70%	25.98%	24.25%	22.53%	20.80%
12	37.99%	36.26%	34.54%	32.82%	31.09%	29.37%	27.64%	25.92%	24.20%	22.47%
13	39.66%	37.93%	36.21%	34.48%	32.76%	31.03%	29.31%	27.59%	25.86%	24.14%

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/adhoc_eff_tipping_diff_i_t.sas
OUT=REPORT/OUTPUT/adhoc_eff_tipping_diff_i_t_x.rtf (13MAY2022 4:30)

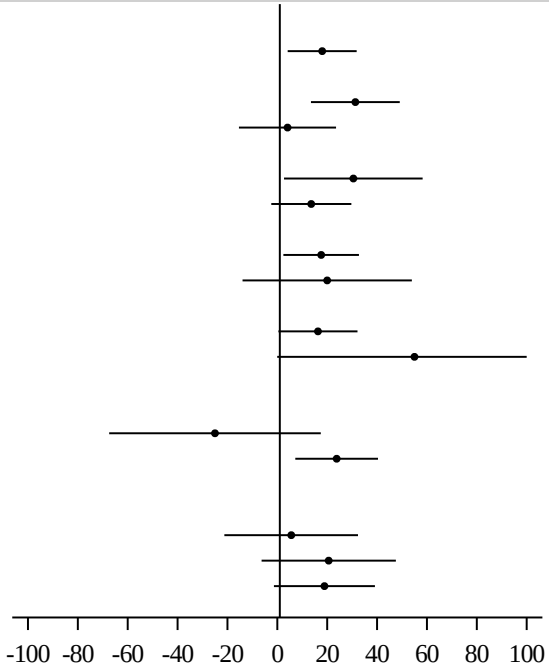
Subgroup analyses

Overall, subgroup analyses performed for the primary endpoint demonstrated the consistency in treatment effects. These results showed a numerical trend in favour of the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group in all measured subgroups (age, sex, race, region, and BMI) except in participants with a baseline weight <60 kg. The sample size was very small (n=1) in this subgroup of participants with a baseline weight <60 kg.

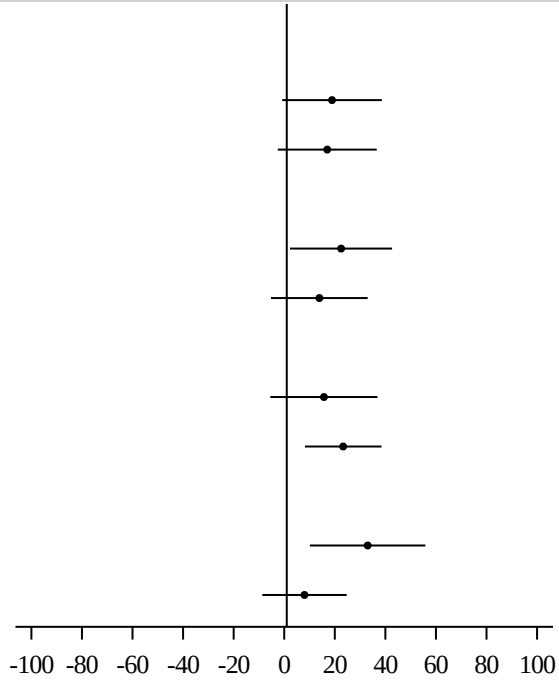
There was no statistically significant interaction effect between each subgroup and treatment group as confidence intervals overlapped and subgroup efficacy was generally directionally consistent.

Figure 18 - Forest plot for subgroup analysis of proportion of patients achieving sustained remission at Week 52 - ITT population

Subgroup	Placebo	SAR 200	Difference (95% CI)
All patients, n/N (%)	6/58 (10.3%)	17/60 (28.3%)	18.0 (4.15 to 31.82)
Age group			
>=50 and <70 years	1/25 (4.0%)	12/34 (35.3%)	31.3 (13.49 to 49.10)
>=70 years	5/33 (15.2%)	5/26 (19.2%)	4.1 (-15.39 to 23.55)
Sex			
Male	2/21 (9.5%)	6/15 (40.0%)	30.5 (2.69 to 58.27)
Female	4/37 (10.8%)	11/45 (24.4%)	13.6 (-2.42 to 29.69)
Race			
Caucasian/White	5/48 (10.4%)	14/50 (28.0%)	17.6 (2.43 to 32.73)
All other races	1/10 (10.0%)	3/10 (30.0%)	20.0 (-13.95 to 53.95)
Region			
Western countries	5/44 (11.4%)	13/47 (27.7%)	16.3 (0.44 to 32.15)
South America	1/4 (25.0%)	4/5 (80.0%)	55.0 (-0.04 to 100.00)
Rest of the World	0/10	0/8	NE (NE to NE)
Baseline weight, kg			
<60	1/4 (25.0%)	0/9	-25.0 (-67.43 to 17.43)
>=60 - <100	5/43 (11.6%)	17/48 (35.4%)	23.8 (7.21 to 40.37)
>=100	0/11	0/3	NE (NE to NE)
BMI, kg/m2			
<25	1/9 (11.1%)	3/18 (16.7%)	5.6 (-21.24 to 32.35)
>=25 - <30	4/19 (21.1%)	10/24 (41.7%)	20.6 (-6.31 to 47.54)
>=30	1/30 (3.3%)	4/18 (22.2%)	18.9 (-1.36 to 39.14)



Subgroup	Placebo	SAR 200	Difference (95% CI)
Baseline CRP			
<=median	3/31 (9.7%)	8/28 (28.6%)	18.9 (-0.81 to 38.60)
>median	3/27 (11.1%)	9/32 (28.1%)	17.0 (-2.56 to 36.59)
Baseline ESR			
<=median	3/31 (9.7%)	9/28 (32.1%)	22.5 (2.28 to 42.65)
>median	3/27 (11.1%)	8/32 (25.0%)	13.9 (-5.23 to 33.01)
Baseline CS dose			
<=median	6/34 (17.6%)	10/30 (33.3%)	15.7 (-5.50 to 36.87)
>median	0/24	7/30 (23.3%)	23.3 (8.20 to 38.47)
Number of relapses prior to screening			
1	2/23 (8.7%)	10/24 (41.7%)	33.0 (10.13 to 55.81)
>1	4/35 (11.4%)	7/36 (19.4%)	8.0 (-8.66 to 24.70)



Secondary efficacy endpoints

Multiplicity was controlled by a hierarchical testing procedure. The only secondary endpoint included in the hierarchy was the endpoint of total cumulative CS dose. P-values for the rest of the secondary and exploratory endpoints were considered as nominal.

Components of sustained remission composite endpoint measured at Week 52

The components of sustained remission by treatment group were described with descriptive statistics

Table 25 - Components of sustained remission composite measure at Week 52 - ITT population

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)
Achievement of disease remission no later than Week 12[a]		
Number	58	60
Yes	22 (37.9)	28 (46.7)
No	36 (62.1)	32 (53.3)
Absence of disease flare from Week 12 through Week 52[b]		
Number	58	60
Yes	19 (32.8)	33 (55.0)
No	39 (67.2)	27 (45.0)
Sustained reduction of CRP from Week 12 through Week 52[c]		
Number	58	60
Yes	26 (44.8)	40 (66.7)
No	32 (55.2)	20 (33.3)
Successful adherence to the prednisone taper from Week 12 through Week 52[d]		
Number	58	60
Yes	14 (24.1)	30 (50.0)
No	44 (75.9)	30 (50.0)

a Disease remission is defined as resolution of signs and symptoms of PMR, and normalization of CRP (<10 mg/L).

b Flare is defined as either 1) recurrence of signs and symptoms attributable to active PMR plus an increase in CS dose due to PMR, or 2) elevation of ESR attributable to active PMR plus an increase in CS dose due to PMR.

c The status of normalization of CRP from Week 12 through Week 52 was determined based on the CRP values measured at Week 16, Week 20, Week 24, Week 32, Week 40 and Week 52. If there were 2 or more consecutive visits with CRP>=10 mg/L, then it was categorized as no normalization of CRP.

d Successful adherence to the prednisone taper from Week 12 through Week 52 is defined as patients who did not take rescue therapy from Week 12 through Week 52 and might include the use of any excess prednisone (beyond the per protocol CS tapering regimen) with a cumulative dose of <=100 mg (or equivalent), such as those employed to manage AE not related to PMR. The cumulative dose of excess prednisone use was counted from baseline to Week 52.

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_second_composite_i_t.sas
OUT=REPORT/OUTPUT/eff_sec_composite_w52_i_t_x.rtf (27JUL2021 5:20)

There was a higher proportion of participants achieving each component of the sustained remission endpoint in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group.

The proportion of participants who achieved disease remission within 12 weeks was higher in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group (28 [46.7%] participants and 22 [37.9%] participants, respectively).

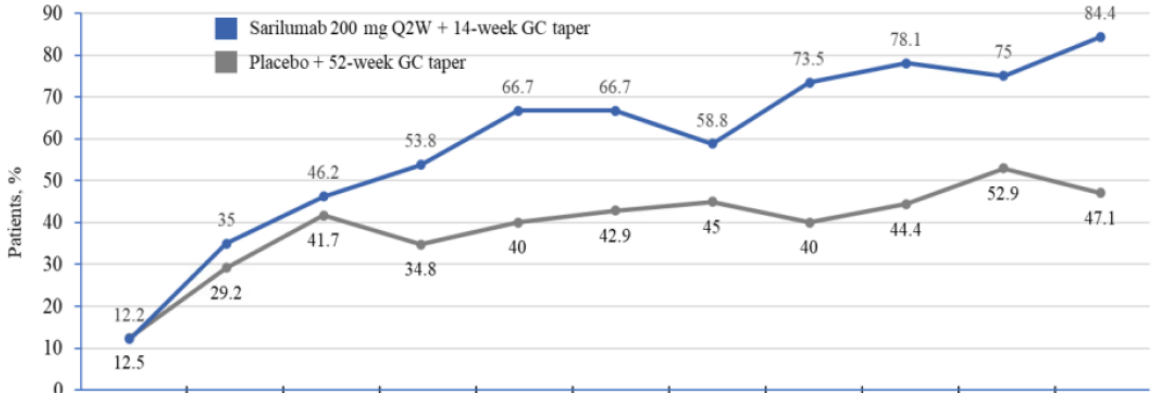
The proportion of participants with absence of disease flare from Week 12 through Week 52 was higher in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group (33 [55.0%] participants and 19 [32.8%] participants, respectively).

The proportion of participants who achieved sustained reduction of CRP from Week 12 through Week 52 was higher in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group (40 [66.7%] participants and 26 [44.8%] participants, respectively).

The proportion of participants who achieved successful adherence to the prednisone taper from Week 12 through Week 52 was higher in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group (30 [50.0%] participants and 14 [24.1%] participants, respectively).

After the baseline visit, the number (%) of participants without any PMR signs and symptoms (excluding participants who had received rescue therapy) was higher at each visit in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group. At the end of treatment (Week 52), 27 (84.4%) participants in the sarilumab 200 mg q2w+14-week taper group and 8 (47.1%) participants in the placebo+52-week taper group did not have any PMR signs and symptoms (excluding participants who had received rescue therapy

Figure 5 - Patients without any PMR signs and symptoms by visit – ITT population excluding patients who had rescue therapy



	Baseline		Week 2		Week 4		Week 8		Week 12		Week 16		Week 20		Week 24		Week 32		Week 40		Week 52	
n	5	3	14	7	18	10	21	8	24	8	24	9	20	9	25	8	25	8	24	9	27	8
N	41	24	40	24	39	24	39	23	36	20	36	21	34	20	34	20	32	18	32	17	32	17

"N" is the number of patients who performed PMR assessments at each visit (including PMR assessments performed after treatment discontinuation), excluding patients who received rescue therapy;

"n" is the number of patients without any PMR signs and symptoms among these patients

Components of the sensitivity analyses of the sustained remission at Week 52 excluding acute phase reactants of both CRP and ESR are summarised below. Results on the components excluding acute phase reactants are almost identical to that on the components of the sustained remission at Week 52, which demonstrates that the treatment effect on the primary endpoint was primarily driven by the improvement on the PMR signs and symptoms and reduction in CS use in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group, not by the acute phase reactants.

Table 26 - Components of sustained remission composite measure at Week 52 excluding acute phase reactants (CRP and ESR) - ITT population

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)
Achievement of disease remission no later than Week 12[a]		
Number	58	60
Yes	23 (39.7)	29 (48.3)
No	35 (60.3)	31 (51.7)
Absence of disease flare from Week 12 through Week 52[b]		
Number	58	60
Yes	19 (32.8)	33 (55.0)
No	39 (67.2)	27 (45.0)
Successful adherence to the prednisone taper from Week 12 through Week 52 [c]		
Number	58	60
Yes	14 (24.1)	30 (50.0)
No	44 (75.9)	30 (50.0)

a Disease remission is defined as resolution of signs and symptoms of PMR

b Flare is defined as recurrence of signs and symptoms attributable to active PMR plus an increase in CS dose due to PMR

c Successful adherence to the prednisone taper from Week 12 through Week 52 is defined as patients who did not take rescue therapy from Week 12 through Week 52 and might include the use of any excess prednisone (beyond the per protocol CS tapering regimen) with a cumulative dose of ≤100 mg (or equivalent), such as those employed to manage AE not related to PMR. The cumulative dose of excess prednisone use was counted from baseline to Week 52.

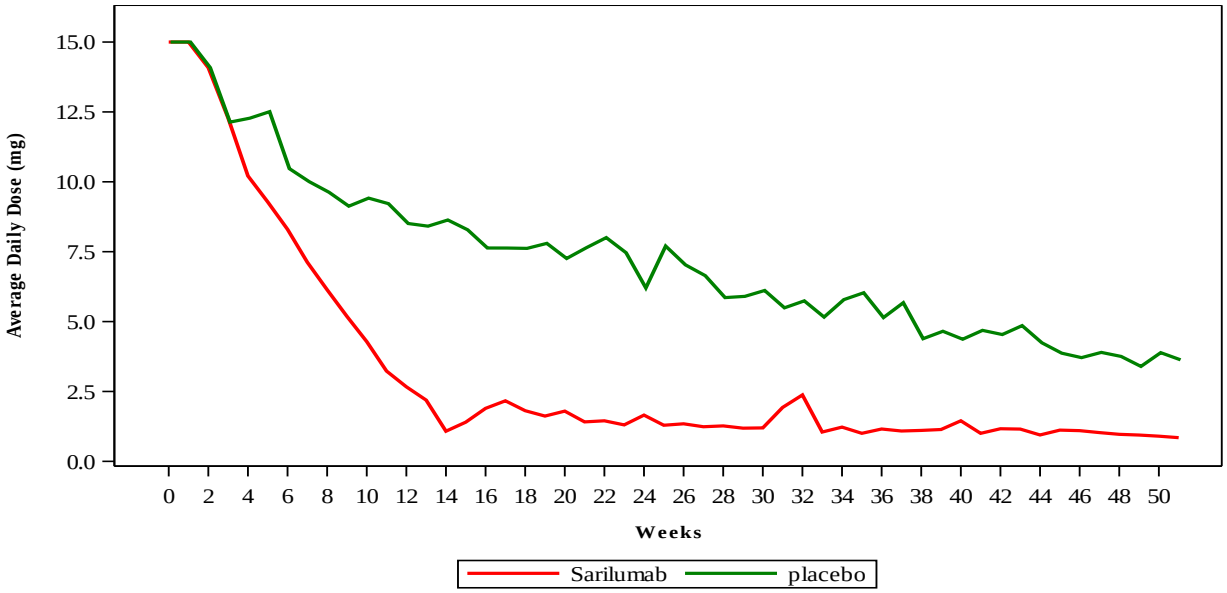
PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_second_composite2_i_t.sas
OUT=REPORT/OUTPUT/eff_sec_composite2_w52_i_t_i.rtf (08FEB2023 20:16)

Total cumulative corticosteroid (including prednisone) dose over 52 weeks

The study assessed both expected and actual CS doses. Expected CS dose was defined as the per protocol CS taper. Actual CS dose was defined as the CS taken during the study (e.g., prednisone taper regimen per protocol; add-on prednisone prior to Week 12, CS use due to rescue, or use of commercial prednisone during the study treatment period such as that employed to manage an AE not related to PMR).

The median actual cumulative CS dose (prednisone or CS dose equivalents) taken over the 52-week treatment period was 777 mg in the sarilumab 200 mg q2w+14 weeks taper group compared to 2044 mg in the placebo+52-week taper group (p<0.0001).

Figure 19 - Actual mean daily CS dose (mg) taken during double-blind study treatment period – ITT population



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The placebo+52-week taper group had a larger than expected cumulative CS dose compared to the sarilumab 200 mg q2w+14-week taper group due to the differences in the duration of the CS taper between the 2 groups. When comparing the actual versus expected CS use in this study, a favourable reduction in CS use was observed in the sarilumab 200 mg q2w+14-week taper group, driven by the increased flare rate in the placebo+52-week taper group (Table 27). The median of the difference between the actual and expected cumulative CS dose was also significantly lower in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group (0.0 mg versus 199.5 mg; p=0.0189).

Table 27 - Cumulative corticosteroid dose during treatment period - ITT population

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)
Expected cumulative CS dose (mg)[a]		
Number	58	59
Mean (SD)	1780.6 (478.3)	741.9 (99.9)
SE	62.81	13.00
Median (95% CI)	2044.0 (2031.0, 2044.0)	777.0 (777.0, 777.0)
Q1; Q3	1780.0; 2044.0	777.0; 777.0
Min; Max	404; 2044	224; 777
Actual cumulative CS dose (mg)[b]		
Number	58	59
Mean (SD)	2235.8 (839.4)	1039.5 (612.2)
SE	110.21	79.70
Median (95% CI)	2044.0 (2044.0, 2455.0)	777.0 (777.0, 777.0)
Q1; Q3	1950.0; 2840.0	777.0; 1018.5
Min; Max	404; 3676	224; 2885
p-value vs. placebo[c]		<.0001
Difference between actual and expected cumulative CS dose (mg)		
Number	58	59
Mean (SD)	455.1 (548.1)	297.6 (588.7)
SE	71.97	76.64
Median (95% CI)	199.5 (0.0, 496.0)	0.0 (0.0, 0.0)
Q1; Q3	0.0; 846.0	0.0; 245.0
Min; Max	-57; 1632	-13; 2108
p-value vs. placebo[c]		0.0189

CS: Corticosteroids, CI: Confidence interval, SE: standard error

a Expected cumulative dose based on CS tapering regimen up to end of treatment, assuming that the taper was continued without error.

b Cumulative dose of CS up to the end of treatment, including expected prednisone in tapering regimen per protocol, add-on prednisone, CS used in rescue therapy and the use of commercial prednisone.

c P-value from Wilcoxon rank-sum test.

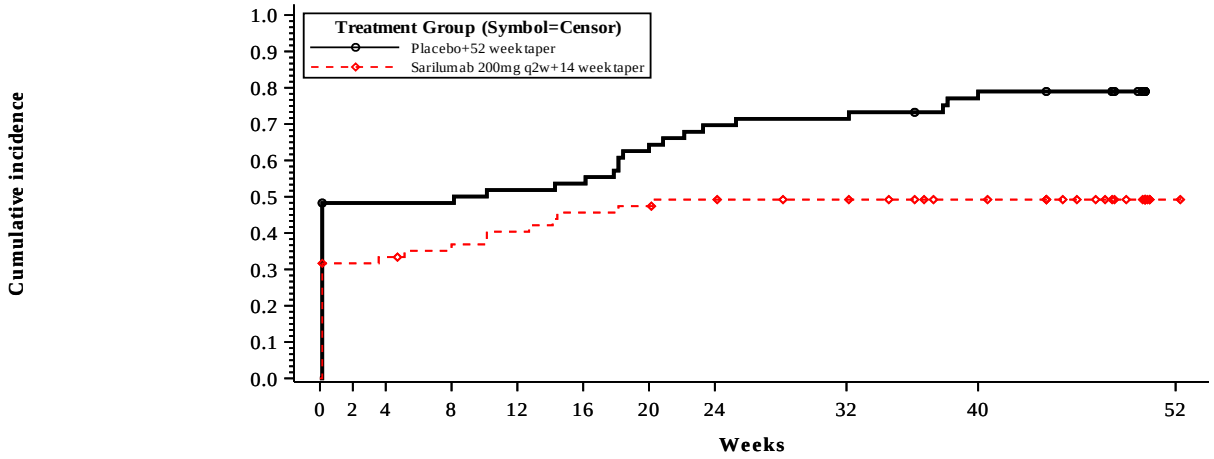
PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/dem_cortico_i_t.sas OUT=REPORT/OUTPUT/dem_cortico_i_t_x.rtf (09OCT2021 5:29)

Time to first PMR flare

The time to first PMR flare was statistically significantly longer in sarilumab treated participants than in placebo-treated participants in both analyses (main analysis: starting from clinical remission, post-hoc analysis: starting from randomisation). In the main analysis, patients who never achieve remission were considered as having had a flare at randomization day (Day 1), hence time to event was considered 0. Forty-one (68.3%) participants in the sarilumab 200 mg q2w+14-week taper group and 30 (51.7%) participants in the placebo+52-week taper group achieved clinical remission during the 52-week treatment period. Of the patients who achieved clinical remission, twice the proportion of participants subsequently flared in the placebo combined with CS use over 52 weeks (17/30; 56.7%) when compared with the sarilumab 200 mg q2w+14-week taper group (10/41; 24.4%). Participants in the sarilumab 200 mg q2w+14-week taper group were less likely to have a PMR flare after achieving clinical remission compared to participants in the placebo+52-week taper group (16.7% versus 29.3%) with a hazard ratio of 0.56 (95% CI: 0.35 to 0.90; p=0.0153). The median value was not reached in the sarilumab 200 mg q2w+14-week taper group.

The post-hoc analysis results were consistent with the analyses for total time to first PMR flare calculated from the randomization day.

Figure 20 – Post-hoc analysis: Kaplan-Meier plot for time to first PMR flare after clinical remission up to 52 weeks - ITT population



Number at Risk

Placebo+52 week taper	58	29	29	29	27	26	21	17	16	12	0
Sarilumab 200mg q2w+14 week taper	60	40	39	37	34	31	30	28	26	21	1

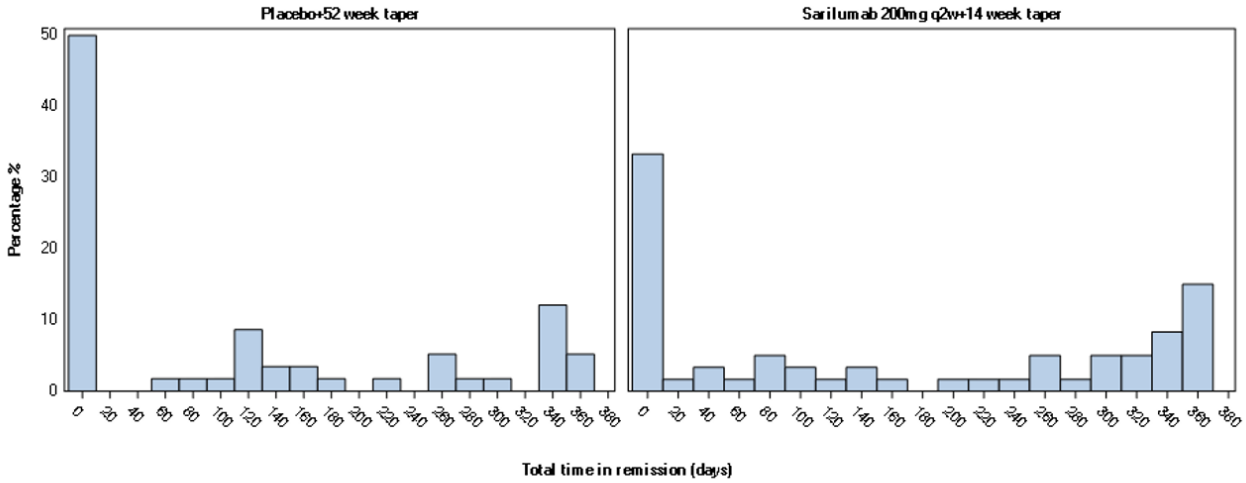
Note: Time (days) is calculated from clinical remission date to first PMR flare up to Week 52.
PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_km_time2pmr_remi_i_f.sas
OUT=REPORT/OUTPUT/eff_km_time2pmr_remi_i_f_x.rtf (29OCT2021 4:33)

Total time in remission (post-hoc analysis)

To aid the interpretation of the secondary endpoint of time to first PMR flare after remission, a post-hoc analysis of the total time in remission as a continuous endpoint was performed

The distributions of total time in remission by treatment group are presented below, which show that the total time in remission was not normally distributed. As a result, this endpoint was analysed non-parametrically with p-value from Wilcoxon rank-sum test between the treatment groups provided.

Figure 21 Post-hoc analysis: Histogram of total time in remission by treatment group - ITT population



PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_tottime_remis_i_f.sas OUT=REPORT/OUTPUT/eff_tottime_remis_i_f_i.rtf (26MAR2022 14:48)

Results showed that the sarilumab 200 mg q2w+14-week taper group had a numerically longer total time in remission compared to the placebo+52-week taper group with a median of 133.0 days versus 28.0 days (p=0.064). This is consistent with the totality of data suggesting that sarilumab-treated participants had improvement in their PMR when compared to placebo.

Table 28 - Post-hoc analysis: Total time in remission (days) - ITT population

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)
Number	58	60
Mean (SD)	114.9 (137.0)	160.3 (148.3)
SE	17.98	19.14
Median (95% CI)	28.0 (0.0 , 128.0)	133.0 (35.0 , 260.0)
Q1 ; Q3	0.0 ; 252.0	0.0 ; 325.0
Min ; Max	0 ; 350	0 ; 365
p-value vs. placebo[a]		0.0640

a P value from Wilcoxon rank-sum test

Note: Total time in remission is calculated as time from clinical remission to first flare for patients who achieved remission and had a flare, time from remission up to end of treatment date or Week 52 for patients who achieved remission and never flared, and time in remission is 0 for patients who never achieved remission.

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_tottime_remis_i_t.sas OUT=REPORT/OUTPUT/eff_tottime_remis_i_t_i.rtf (26MAR2022 14:48)

Cumulative worsening score and aggregate improvement score at Week 52

The GTI is a composite scale designed to assess glucocorticoid related morbidity.

The GTI-CWS captures cumulative glucocorticoid toxicity regardless of whether it is permanent or transient. The GTI-CWS can only increase or remain the same over time. A lower score indicates lower glucocorticoid toxicity.

The GTI-AIS captures both worsening and improvement in glucocorticoid toxicity. New or worsening toxicities contribute to a positive score and improvements in existing toxicities contribute to a negative score. A lower score indicates lower glucocorticoid toxicity.

There was a numerical trend towards the sarilumab 200 mg q2w+14-week taper group having lesser cumulative worsening and greater aggregate improvement compared to the placebo+52-week taper

group. However, there was no significant difference in the CWS between the sarilumab 200 mg q2w+14 week taper group and the placebo+52 week taper group with LS mean difference (SE) versus placebo+52 week taper was -4.90 (9.375) (95% CI: -23.477, 13.669; p=0.6020)

Table 29 - Summary of cumulative worsening score during 52-week treatment period - ITT population

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)
Number	57	60
Mean (SD)	57.9 (51.9)	51.7 (48.4)
SE	6.87	6.25
Median	55.0	39.0
Min; Max	0; 257	0; 195
LS Mean (SE)[a]	57.22 (6.678)	52.32 (6.507)
LS Mean difference (SE) vs. placebo[a]		-4.90 (9.375)
95% CI		(-23.477 ,13.669)
p-value		0.6020

CI: Confidence interval; LS: Least squares; SD: Standard deviation; SE: Standard error of the mean.

Smaller cumulative worsening score implies less glucocorticoid toxicity.

a Analysis of covariance (ANCOVA) model includes treatment groups and baseline glucocorticoid toxicity score as fixed effects.

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_gti_ancova_i_t.sas
OUT=REPORT/OUTPUT/eff_gti_ancova_ws_wk52_i_t_x.rtf (27JUL2021 5:25)

There was no significant difference in the AIS between the sarilumab 200 mg q2w+14-week taper group and the placebo+52 week taper group with LS mean deference (SE) versus placebo+52 week taper was – 6.59 (8.811) (95% CI: –24.047,10.862; p=0.4559).

Table 30 - Summary of aggregate improvement score during 52-week treatment period - ITT population

	Placebo+52-week taper (N=58)	Sarilumab 200mg q2w+14-week taper (N=60)
Number	57	60
Mean (SD)	-0.5 (57.1)	-1.1 (44.6)
SE	7.56	5.76
Median	0.0	0.5
Min ; Max	-283 ; 122	-122 ; 86
LS Mean (SE)[a]	2.57 (6.275)	-4.02 (6.115)
LS Mean difference (SE) vs. placebo[a`]		-6.59 (8.811)
95% CI		(-24.047 ,10.862)
p-value		0.4559

CI: Confidence interval; LS: Least squares; SD: Standard deviation; SE: Standard error of the mean.

Smaller aggregate improvement score implies less glucocorticoid toxicity.

a Analysis of covariance (ANCOVA) model includes treatment groups and baseline glucocorticoid toxicity score as fixed effects.

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/eff_gti_ancova_i_t.sas
OUT=REPORT/OUTPUT/eff_gti_ancova_is_wk52_i_t_x.rtf (27JUL2021 5:25)

Exploratory endpoints

Multiplicity was controlled by a hierarchical testing procedure. Exploratory endpoints were not included in the hierarchy so p-values for exploratory endpoints were considered as nominal.

Table 31 Summary of secondary/exploratory endpoints – ITT population

	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w +14 week taper (N=60)	P-value vs. Placebo
Other secondary/exploratory endpoints			
Components of sustained remission at Week 52, n (%)			
Achievement of disease remission no later than Week 12[f]	22 (37.9)	28 (46.7)	-
Absence of disease flare from Week 12 through Week 52[g]	19 (32.8)	33 (55.0)	-

	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w +14 week taper (N=60)	P-value vs. Placebo
Sustained reduction of CRP from Week 12 through Week 52[h]	26 (44.8)	40 (66.7)	-
Successful adherence to the prednisone taper from Week 12 through Week 52[i]	14 (24.1)	30 (50.0)	-
Time to first PMR flare after clinical remission up to 52 weeks[j]			
Number (%) of patients with PMR flare after clinical remission	17 (29.3)	10 (16.7)	
Kaplan-Meier estimates in days, Median (95%CI)[k]	99.00 (1.000 ; 154.000)	NC (93.000 ; NC)	
Hazard ratio (95% CI)[l]		0.56 (0.35,0.90)	0.0153
Glucocorticoid toxicity index (GTI) scores			
Cumulative worsening score (CWS) at Week 52			
LS mean (SE)[n]	57.22 (6.678)	52.32 (6.507)	
LS mean difference vs. placebo (95%CI)[m]		-4.90 (-23.477, 13.669)	0.6020
Aggregate improvement score (AIS) at Week 52			
LS mean (SE)[n]	2.57 (6.275)	-4.02 (6.115)	
LS mean difference vs. placebo (95%CI)[m]		-6.59 (-24.047, 10.862)	0.4559
PMR activity score (PMR-AS) at Week 52			
LS mean change from baseline (SE)[n]	-10.27 (0.97)	-15.57 (0.94)	
LS mean difference for change from baseline vs. placebo (95%CI)[n]		-5.302 (-8.006, -2.597)	0.0002
Quality of life endpoints			
EQ-5D – Single Index Utility at Week 52			
LS mean change from baseline (SE)[n]	-0.02 (0.04)	0.11 (0.04)	
LS mean difference for change from baseline vs. placebo (95%CI)[n]		0.130 (0.010, 0.250)	0.0336
SF-36 Physical Component Summary Score at Week 52			
LS mean change from baseline (SE)[n]	2.87 (1.45)	7.65 (1.34)	
LS mean difference for change from baseline vs. placebo (95%CI)[n]		4.784 (0.865, 8.703)	0.0172
SF-36 Mental Component Summary Score at Week 52			
LS mean change from baseline (SE)[n]	-1.71 (1.57)	3.04 (1.47)	
LS mean difference for change from baseline vs. placebo (95%CI)[n]		4.748 (0.484, 9.013)	0.0295
MD-VAS at Week 52			
LS mean change from baseline (SE)[n]	-30.49 (3.46)	-40.58 (3.40)	
LS mean difference for change from baseline vs. placebo (95%CI)[n]		-10.097 (-19.775, -0.419)	0.0411
FACIT-Fatigue at Week 52 (0-52)			

	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w +14 week taper (N=60)	P-value vs. Placebo
LS mean change from baseline (SE)[n]	4.17 (1.42)	7.91 (1.33)	
LS mean difference for change from baseline vs. placebo (95%CI)[n]		3.740 (-0.108, 7.588)	0.0567
HAQ-DI standardized score at Week 52			
LS mean change from baseline (SE)[n]	-0.15 (0.09)	-0.39 (0.09)	
LS mean difference for change from baseline vs. placebo (95%CI)[n]		-0.246 (-0.496, 0.005)	0.0543

Abbreviations: ANCOVA, analysis of covariance; AIS, aggregate improvement score; CI, Confidence interval; CRP, C-reactive protein; CS, Corticosteroids; CWS, cumulative worsening score; EQ-5D-3L, EuroQol 5 dimension questionnaire, 3-level version; ESR, erythrocyte sedimentation rate; FACIT, functional assessment of chronic illness therapy; GTI, glucocorticoid toxicity index; HAQ-DI, Health Assessment Questionnaire Disability Index; ITT, intent-to-treat; LS, Least squares; MMRM, mixed-effect model repeated measure; NC, Not able to calculate; NA: Not applicable; PMR, polymyalgia rheumatica; PMR-AS, PMR activity score; q2w, every 2 weeks; SE, standard error; SF-36, Short-Form 36-item questionnaire; VAS, visual analogue scale.

a Patients who did not achieve remission, received rescue treatment with open label prednisone (or corticosteroid dose equivalents), withdrew from the study before Week 52, or had missing data that prevented assessment of the primary endpoint were considered as non-responders.

b P-value from Fisher's exact test.

c Expected cumulative dose based on the CS tapering regimen up to the end of treatment, assuming that the taper was continued without error.

d Cumulative dose of CS up to the end of treatment, including expected prednisone in the tapering regimen per protocol, add-on prednisone, CS used in rescue therapy and the use of commercial prednisone.

e P value from the Wilcoxon rank-sum test.

f Disease remission is defined as the resolution of signs and symptoms of PMR, and normalization of CRP (<10 mg/L).

g Flare is defined as either 1) recurrence of signs and symptoms attributable to active PMR plus an increase in CS dose due to PMR, or 2) elevation of ESR attributable to active PMR plus an increase in CS dose due to PMR.

h The status of normalization of CRP from Week 12 through Week 52 was determined based on the CRP values measured at Week 16, Week 20, Week 24, Week 32, Week 40 and Week 52. If there were 2 or more consecutive visits with CRP>=10 mg/L, then it was categorized as no normalization of CRP.

i Successful adherence to the prednisone taper from Week 12 through Week 52 is defined as participants who did not take rescue therapy from Week 12 through Week 52 and might include the use of any excess prednisone (beyond the per protocol CS tapering regimen) with a cumulative dose of ≤100 mg (or corticosteroid dose equivalents)), such as those employed to manage an AE not related to PMR. The cumulative dose of excess prednisone use was counted from baseline to Week 52.

j Time (days) is calculated from randomization to first PMR flare after clinical remission up to Week 52.

k Patients who never achieved remission were censored at the randomization day, and those who achieved clinical remission and never flared were censored at the end of treatment assessment date up to Week 52. The two-sides 95% CI was computed by the Brookmeyer and Crowley method (log transformation).

l From the Cox proportional hazards model.

m The analysis of covariance (ANCOVA) model includes the treatment groups and baseline glucocorticoid toxicity score as fixed effects.

n Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, visit, and treatment-by-visit interaction, and baseline-by-visit interaction. Patients who had a baseline and at least 1 post-baseline value at Week 12, Week 24, or Week 52 were included in the MMRM analysis.

Note: Smaller cumulative worsening score implies less glucocorticoid toxicity. Smaller aggregate improvement score implies less glucocorticoid toxicity.

Exploratory efficacy endpoints demonstrated consistent benefit to sarilumab-treated patients in the study as measured by alternate efficacy assessments and physician and patient-reported endpoints

Ancillary analyses

Summary of main study

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

Table 32 Summary of Efficacy for trial EFC15160

Title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with polymyalgia rheumatica (PMR).			
Study identifier	Study number: EFC15160 IND Number(s): 100632 EudraCT number: 2017-002989-42 NCT: NTC03600818 WHO universal trial number: U1111-1201-0777		
Design	This is a multi-center, randomized, double-blind, placebo-controlled 52-week study with a 6-week post-treatment follow-up phase, evaluating the efficacy and safety of sarilumab in patients with PMR. Adult patients with active corticosteroid-refractory PMR will be randomized 1:1 to one of 2 parallel treatment groups: • sarilumab 200 mg q 2w x 52 weeks plus 14-week corticosteroid taper • matching placebo q2w x 52 weeks plus 52-week corticosteroid taper		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks up to 4-week screening period N/A
Hypothesis	Superiority		
Treatments groups	Sarilumab group		Sarilumab 200 mg once every 2 weeks (q2w) with a 14-week taper of corticosteroids, 60 randomized patients
	Placebo group		Sarilumab matching placebo q2w with 52-week taper of corticosteroids, 58 randomized patients
Endpoints and definitions	Primary efficacy endpoint	Proportion of patients achieving sustained remission at Week 52	To evaluate the efficacy of KEVZARA® (sarilumab) in patients with PMR as assessed by proportion of patients with sustained remission at Week 52 for sarilumab with a 14-week CS tapering regimen as compared to placebo with a 52-week CS tapering regimen. Sustained remission is defined as: - Achievement of disease remission no later than Week 12, AND - Absence of disease flare from Week 12 through Week 52, AND - Sustained reduction of CRP (to <10 mg/L, with an absence of successive elevations to ≥10 mg/L) from Week 12 through Week 52, AND - Successful adherence to the prednisone taper from Week 12 through Week 52

	Secondary efficacy endpoints	• Components of sustained remission composite measured at Week 52 • Total cumulative corticosteroid (including prednisone) dose over 52 weeks • Time to first PMR flare	To demonstrate the efficacy of sarilumab (with 14-week taper of CS) compared to placebo (with 52-week taper of CS) in patients with PMR with regards to: - Clinical responses (such as components of sustained remission, disease remission rates, time to first disease flare) over time - Cumulative CS (including prednisone) exposure
		• GTI Aggregate improvement score (AIS) at Week 52 • CTI Cumulative worsening score (CWS) at Week 52	To assess the effect of sarilumab on reducing glucocorticoid toxicity as measured by the composite glucocorticoid toxicity index (GTI) questionnaire.
	Other endpoint	Physician global assessment of disease activity as measured by MD-VAS	To assess the effect of sarilumab on physician assessment of disease activity as measured by a visual analogue scale (MD-VAS)
		PROs • The functional assessment of chronic illness therapy fatigue scale • EQ-5D-3L • SF-36 physical component score v2 • SF-36 mental component score v2 • HAQ-DI	To assess the effect of sarilumab on a variety of patient reported outcome (PRO) concepts, including fatigue (as measured by functional assessment of chronic illness therapy fatigue [FACIT-fatigue] scale), health status (as measured by EuroQol 5 dimension questionnaire; 3-level version [EQ-5D-3L] and short form 36-item questionnaire [SF-36v2]), physical function (as measured by Health Assessment Questionnaire Disability Index [HAQ-DI]), pain (as measured via HAQ-DI by a visual analogue scale [VAS]) and patient assessment of disease activity (as measured via HAQ-DI by a VAS).
Database lock	07-July-2021		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat population, defined as the randomized population analysed according to the treatment group allocated by randomization. Week 52		
Descriptive statistics and estimate variability	Treatment group	Sarilumab group	Placebo group
	Number of subject	60	58
	Primary efficacy endpoint Proportion of patients achieving sustained remission at Week 52 o Proportion	28.3%	10.3%

	Secondary efficacy endpoints • Components of sustained remission composite measured at Week 52: a) Achievement of disease remission no later than Week 12 b) Absence of disease flare from Week 12 through Week 52 c) Sustained reduction of CRP from Week 12 through Week 52 d) Successful adherence to prednisone taper from Week 12 through Week 52 • Total cumulative corticosteroid (including prednisone) dose over 52 weeks • Time to first PMR flare o Proportion o Median o Median	• a) 46.7% b) 55.0% c) 66.7% d) 50.0% • 777 mg • Not able to calculate	• a) 37.9% b) 32.8% c) 44.8% d) 24.1% • 2044 mg • 99 days
	o Standard deviation o 95% CI o 95% CI	• a) 6.4% b) 6.4% c) 6.1% d) 6.5% • (777.0, 777.0) • (93, Not able to calculate)	• a) 6.4% b) 6.2% c) 6.5% d) 5.6% • (2044.0, 2455.0) • (1.0, 154.0)
	Secondary efficacy endpoint • GTI Aggregate improvement score (AIS) at Week 52 • GTI Cumulative worsening score (CWS) at Week 52 o LS mean	• -4.02 • 52.32	• 2.57 • 57.22
	o Standard error	• 6.115 • 6.507	• 6.275 • 6.678
	Other endpoint Physician global assessment of disease activity as measured by MD-VAS o LS mean change from baseline	-40.58	-30.49
	o Standard error	3.40	3.46

	Other endpoint PROs • The functional assessment of chronic illness therapy fatigue scale • EQ-5D-3L • SF-36 physical component score v2 • SF-36 mental component score v2 • HAQ-DI o LS mean change from baseline	• 7.91 • 0.11 • 7.65 • 3.04 • -0.39	• 4.17 • -0.02 • 2.87 • -1.71 • -0.15
	o Standard error	• 1.33 • 0.04 • 1.34 • 1.47 • 0.09	• 1.42 • 0.04 • 1.45 • 1.57 • 0.09

Effect estimate per comparison	Primary efficacy endpoint Proportion of patients achieving sustained remission at Week 52	Comparison groups	Sarilumab group VS Placebo group
		Difference	18.0%
		95% CI	(4.15, 31.82)
		P-value Fisher's exact test	0.0193
	Secondary efficacy endpoints • Time to first PMR flare	Comparison groups	Sarilumab group VS Placebo group
		Hazard ratio	0.56
		95% CI	(0.35, 0.90)
		P-value Cox regression	0.0153
	Secondary efficacy endpoint • GTI Aggregate improvement score (AIS) at Week 52 • GTI Cumulative worsening score (CWS) at Week 52	Comparison groups	Sarilumab group VS Placebo group
		LS mean difference	• -6.59 • -4.90
		95% CI	• (-24.047, 10.862) • (-23.477, 13.669)
		P-value ANCOVA	• 0.4559 • 0.6020
	Other endpoint Physician global assessment of disease activity as measured by MD-VA	Comparison groups	Sarilumab group VS Placebo group
		LS mean difference	-10.097

		95% CI	(-19.775, -0.419)
		P-value MMRM	0.0411
	Other endpoint PROs • The functional assessment of chronic illness therapy fatigue scale • EQ-5D-3L • SF-36 physical component summary score v2 • SF-36 mental component summary score v2 • HAQ-DI	Comparison groups	Sarilumab group VS Placebo group
		LS mean difference	• 3.740 • 0.130 • 4.784 • 4.748 • -0.246
		95% CI	• (-0.108, 7.588) • (0.010, 0.250) • (0.865, 8.703) • (0.484, 9.013) • (-0.496, 0.005)
		P-value MMRM	• 0.0567 • 0.0336 • 0.0172 • 0.0295 • 0.0543

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

A single pivotal study was submitted to support the new indication in patients with PMR. The MAH sought scientific advice on this matter. Overall, the approach was agreed by CHMP and some modifications were proposed. However, the MAH finally deviated from the proposal, the most salient issues are discussed below.

Patients 50 years and older who were diagnosed with PMR according the ACR/EULAR criteria were eligible. Participants were unable to taper CS successfully without flare and had to have had at least 1 episode of unequivocal PMR flare while attempting to taper prednisone at a dose that was ≥7.5 mg day (or equivalent) within the past 12 weeks prior to screening.

Initially, the indication proposed by the MAH was: Kevzara is indicated for the treatment of polymyalgia rheumatica (PMR) in adult patients who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper. As the word tolerance implies a population that cannot endure corticosteroid taper due to adverse safety reactions, rather than, as intended, a population that experiences disease recurrence upon corticosteroid taper, at the CHMP request, the MAH amended the wording of the indication to describe more accurately the intended population. Therefore, the final agreed indication is: 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.

Participants were randomized in a 1:1 ratio to receive sarilumab 200 mg or placebo for 52 weeks. Randomization was not stratified. Sarilumab 200 mg dose could be reduced to 150 mg q2w in a blinded manner for management of predefined laboratory abnormalities. All patients were planned to receive prednisone treatment with different regimen depending on the assigned group. The tapering

regimen applied in the study was consistent with the EULAR/ACR guidance (2015 Recommendations for the Management of Polymyalgia Rheumatica). In the Scientific advice, the following treatment regimen was proposed: sarilumab 200 mg q2w SC or placebo q2w SC and treated for 52 weeks. Beginning at Week 2, patients would undergo a protocol-defined steroid taper of 6 weeks duration. During the taper (Weeks 2-8), patients who experienced a relapse of PMR would be allowed to increase the dose of prednisone or equivalent to the dose level that the patient was receiving prior to the relapse and then return to the protocol defined tapering schedule. The CHMP proposed to add a second placebo arm (secondary comparison) with steroid tapering over 52 weeks. This was foreseen to facilitate the interpretation of the outcomes, especially the steroid sparing potential of sarilumab. The MAH followed the scientific advice but instead of adding a second placebo arm, replaced the 6-week CS taper placebo arm to a 52-week CS taper to provide a more stringent comparator placebo arm representative of standard of care than the initially proposed 6 week, whereby patients would be less likely to experience flares due to a rapid steroid taper and thus to allow for more meaningful clinical comparisons with current standard of care. This was endorsed by the CHMP.

The primary objective of the study was to evaluate the efficacy in patients with PMR as assessed by proportion of patients with sustained remission at Week 52 for sarilumab with a 14-week CS tapering regimen as compared to placebo with a 52-week CS tapering regimen.

After the start of the study the protocol was amended once. As a result of the inability to recruit due to the COVID19 pandemic, the study was terminated prematurely resulting in a change in the total expected number of patients. As a consequence, the statistical analysis plan was modified. The total expected number of participants (280 participants) to be randomized was reduced to 118 participants. The final sample size, based on a premature termination of the trial, was deemed sufficient by the MAH to show a clinically relevant difference of 25% following the modifications in the assumptions: (1) increase of alpha from 0.01 to 0.05; (2) reduction of response rates in placebo group from 5-50% to 5-15%.

The original alpha, planned at 0.01 level, had been endorsed during the SA, in order to generate “statistically compelling” results, in alignment with the guidance on single pivotal trials (CPMP/EWP/2330/99). The threshold has then been increased to 0.05 after the early termination of recruitment (only 42% of the originally planned number of participants was recruited). While 0.05 is the commonly used acceptable significance level, these changes were major and raised uncertainty on the robustness of results. The protocol amendment in which the alpha was increased also included a dramatic change in the assumption regarding the placebo response rate.

At the CHMP request, the MAH provided additional justification that the changes in the SAP were not prompted by an unblinded data analysis. The MAH explained that a higher alpha was chosen in order to have “a reasonable power for the study” given the reduced sample size, due to the premature termination of the study because of the COVID-19 pandemic. In other words, the MAH has accepted a higher risk of false positive results to compensate the higher insecurity associated with the smaller population. In summary, both the increase of alpha and the amended placebo rate were implemented as reaction to issues arising during the conduct of the trial and which could not have been appropriately addressed during the planning stage. The issue was not further pursued by the CHMP, additional analyses were requested by the CHMP to support the robustness of the results (see section below).

Efficacy data and additional analyses

Of the 196 participants who were screened, 78 participants were screen failures and 118 participants were randomized. There were 117 participants treated: 59 participants in the sarilumab 200 mg

q2w+14-week taper group and 58 participants in placebo+52-week taper group. Of these, 78 (66.1%) participants completed the study treatment period and 39 (33.1%) participants discontinued from the study treatment.

Demographic and participant characteristics at baseline were generally similar between treatment groups with a slightly higher number of participants in the ≥75 to <85 years age group and a slightly lower number of participants in the ≥65 to <75 years age group in the placebo+52-week taper group compared to the sarilumab 200 mg q2w+14-week taper group. There was a slightly higher proportion of participants in the ≥100 kg weight group in the placebo+52-week group.

The proportion of participants achieving sustained remission at Week 52 was higher in the sarilumab 200 mg q2w+14-week taper group compared to placebo+52-week taper group. There were 17 (28.3%) participants in the sarilumab 200 mg q2w+14-week taper group and 6 (10.3%) participants in the placebo+52-week taper group who achieved sustained remission at Week 52 with point estimate and 95% CI: 18.0 (4.15 ,31.82), p = 0.0193.

As only a single pivotal trial, limited in size and impacted by several changes in the protocol was performed, additional analyses were requested by the CHMP to support the robustness of the results. To better understand the estimated treatment effect the MAH provided an additional sensitivity analysis of the primary endpoint in which patients were not automatically treated as non-responders if they received rescue treatment. To address the concern that the primary result may be strongly dependent on unsuccessful tapering in the control arm, the MAH provided an analysis in which the criterion “successful adherence to the prednisone taper from Week 12 through week 52 ” was removed, and only the remaining three criteria were assessed for the definition of response.

Additional analyses of the primary endpoint and its component indicate that the treatment effect estimate is not artificially inflated by counting nonadherence to the corticosteroid tapering as non-response. In addition, the data suggest that sarilumab treatment facilitate tapering. However, since rapid tapering may increase the risk of flares, some uncertainty remains. While the interplay of response and tapering may remain somewhat uncertain (i.e. to which extent the benefit of sarilumab manifests in achieving response or in allowing reduced corticosteroid use), the previously raised concern whether too strict tapering may have driven the results does no longer preclude the conclusion of a clinically relevant benefit.

Subgroup analyses performed for the primary endpoint suggested a consistent treatment effect. However, numbers were small. Randomization was not stratified. Results showed a numerical trend in favour of the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group across all reported subgroups (age, sex, race, region, and BMI) except in participants with a baseline weight <60 kg. The sample size was very small (n=1) in this subgroup of participants with a baseline weight <60 kg. In some subgroups no effect could be estimated due to small numbers (region: Rest of World, baseline weight ≥100kg).

There was a higher proportion of participants achieving each component a) achievement of disease remission no later than Week 12, b) absence of disease flare from Week 12 through Week 52 c) sustained reduction of CRP from Week 12 through Week 52 and d) successful adherence to prednisone taper from Week 12 through Week 52 of the sustained remission endpoint in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group.

A 6-week post treatment follow-up was planned to follow the 52-weeks treatment period. Although the CHMP considered the length adequate from the efficacy and safety perspective, it seemed too short to evaluate the extent of relapses. Thus, a follow-up period to at least 6 months was recommended. The MAH clarified that they followed the patients until the main part of sarilumab was excreted (degraded), i.e. for at least 5 half-lives after the last dose in line with the CHMP scientific advice. However no data

beyond one year are available. And currently it is not known when treatment should be discontinued therefore the MAH updated section 4.2 of the SmPC to mention that data are available for patients that were treated for up to 1 year and that treatment beyond 52 weeks should be guided by disease activity, physician discretion and patient choice. In addition, the CHMP recommended the MAH to investigate the necessary treatment duration. The MAH confirmed that they will conduct a cohort study with the primary objective of evaluating treatment patterns and outcomes associated with sarilumab in patients with polymyalgia rheumatica. Specifically, the study will aim to provide insights into the appropriate duration of sarilumab treatment, as well as to examine the effects of treatment discontinuation in patients who achieve a response.

For the other Secondary efficacy endpoints, multiplicity was controlled by a hierarchical testing procedure. The only secondary endpoint included in the hierarchy was the endpoint of total cumulative CS dose. P-values for the rest of the secondary and exploratory endpoints were considered as nominal

Secondary endpoints included total cumulative corticosteroid (including prednisone) dose over 52 weeks. Of relevance is larger actual cumulative CS. The placebo+52-week taper group had a larger actual cumulative CS dose due to the differences in the duration of the CS taper between the placebo+52-week taper group and the sarilumab 200 mg q2w+14-week taper group. The total median cumulative prednisone dose over the 52-week treatment period (i.e., actually taken by participants) was 777 mg in the sarilumab 200 mg q2w+1- week taper group, as compared to 2044 mg in the placebo+52-week taper group.

The median of the difference between the actual and expected cumulative CS dose was significantly lower in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group (0.0 mg versus 199.5 mg; p=0.0189). The MAH explained the difference between the actual and expected cumulative CS dose with the rescue therapy received by participants for PMR. The cumulative number (%) of participants who received rescue therapy due to PMR was lower in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group. During the 52-week treatment period, there were 34 (58.6%) participants in the placebo+52-week taper group and 19 (32.2%) participants in the sarilumab 200 mg q2w+14-week taper group who received rescue therapy due to PMR.

Exploratory efficacy endpoints except GTI score indicated favourable functional and symptomatic benefits from sarilumab treatment in combination with rapid 14-week corticosteroid taper versus 52-week corticosteroid taper in placebo.

2.4.4. Conclusions on the clinical efficacy

Efficacy has been demonstrated, superiority of Kevzara on top of 14-week steroid taper vs placebo on top of 52-week steroid taper was shown, the primary and key secondary endpoints were met.

The CHMP concluded that the clinical efficacy has been demonstrated for use of Kevzara in the following indication:

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.

2.5. Clinical safety

Introduction

The primary assessment of sarilumab safety in adult participants with PMR is from the pivotal, placebo-controlled Phase 3 Study EFC15160 (SAPHYR).

In order to provide a robust evaluation of safety to support this Type II variation, the MAH presented supporting safety data from studies evaluating sarilumab in patients with related rheumatological conditions, GCA (EFC15068), and RA. The RA studies are those that supported the original RA MA (granted on 23 June 2017 in the EU). In addition, at the CHMP request, the MAH presented pooled results of the RA and PMR studies.

Patient exposure

Study EFC15160 evaluated 118 participants with PMR (117 treated) over a 52-week treatment period with 59 participants receiving sarilumab and 58 participants receiving placebo.

Adverse events

The table below provides an overview of the TAEs in the safety population.

Table 33 – Overview of treatment-emergent adverse events - Safety population

n (%)	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w+14 week taper (N=59)	All (N=117)
Patients with any TEAE	49 (84.5)	56 (94.9)	105 (89.7)
Patients with any treatment emergent SAE	12 (20.7)	8 (13.6)	20 (17.1)
Patients with any TEAE leading to death	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	4 (6.9)	7 (11.9)	11 (9.4)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event

n (%) = number and percentage of patients with at least one TEAE

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The table below presents TEAEs by primary SOC and PT for the safety population in ≥5% of participants in any treatment group.

As seen in the table below, the overall incidence of TEAEs was slightly higher in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group (56 [94.9%] and 49 [84.5%] participants, respectively), with infections and infestations and musculoskeletal and connective tissue disorders being the most frequently reported TEAEs by SOC in both treatment groups.

The most frequently reported TEAEs (≥20%) in the sarilumab 200 mg q2w+14-week taper group were in the SOCs Musculoskeletal and connective tissue disorders, Infections and infestations, Gastrointestinal disorders, Skin and subcutaneous tissue disorders, Injury, poisoning and procedural complications, Blood and lymphatic system disorders, and General disorders and administration site conditions.

The most frequently reported TEAEs (≥20%) in the placebo+52-week taper group were in the SOCs Infections and infestations, Musculoskeletal and connective tissue disorders, Skin and subcutaneous tissue disorders, Nervous system disorders, Psychiatric disorders, and Injury, poisoning and procedural complications.

The most frequently reported TEAEs by PT (≥10%) in the sarilumab 200 mg q2w+14-week taper group were neutropenia (15.3%), arthralgia (15.3%), diarrhoea (11.9%), and insomnia, hypertension, and osteoarthritis (each 10.2%). The most frequently reported TEAEs by PT (≥10%) in the placebo+52-week taper group were insomnia (15.5%) and nasopharyngitis, depression, and fall (each 10.3%).

The incidence of neutropenia was higher in the sarilumab 200 mg q2w+14-week taper group (15.3%) compared to the placebo+52-week taper group (0%). The rate of infections and infestations was higher in the placebo+52-week taper group (50.0%) compared to the sarilumab 200 mg q2w+14-week taper group (37.3%).

Out of the total 105 (89.7%) participants who had at least 1 TEAE, 40 (34.2%) participants had at least 1 TEAE that was related to the IMP. The incidence of TEAEs related to the IMP was higher in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group (25 [42.4%] and 15 [25.9%] participants, respectively).

Table 34 - Number (%) of patients with common TEAE(s) (≥5% in any treatment group) by Primary SOC and PT - Safety population

Primary System Organ Class Preferred Term n(%)	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w+14 week taper (N=59)	All (N=117)
Any event	49 (84.5)	56 (94.9)	105 (89.7)
INFECTIONS AND INFESTATIONS	29 (50.0)	22 (37.3)	51 (43.6)
Cystitis	3 (5.2)	2 (3.4)	5 (4.3)
Gastroenteritis	3 (5.2)	2 (3.4)	5 (4.3)
Nasopharyngitis	6 (10.3)	2 (3.4)	8 (6.8)
Upper respiratory tract infection	5 (8.6)	2 (3.4)	7 (6.0)
Influenza	4 (6.9)	0	4 (3.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	5 (8.6)	15 (25.4)	20 (17.1)
Neutropenia	0	9 (15.3)	9 (7.7)
Increased tendency to bruise	4 (6.9)	4 (6.8)	8 (6.8)
Leukopenia	0	4 (6.8)	4 (3.4)
PSYCHIATRIC DISORDERS	13 (22.4)	11 (18.6)	24 (20.5)
Insomnia	9 (15.5)	6 (10.2)	15 (12.8)
Depression	6 (10.3)	5 (8.5)	11 (9.4)
Mania	3 (5.2)	2 (3.4)	5 (4.3)
NERVOUS SYSTEM DISORDERS	15 (25.9)	11 (18.6)	26 (22.2)
Cognitive disorder	4 (6.9)	4 (6.8)	8 (6.8)
Sciatica	1 (1.7)	3 (5.1)	4 (3.4)
Headache	5 (8.6)	1 (1.7)	6 (5.1)
EYE DISORDERS	10 (17.2)	9 (15.3)	19 (16.2)
Dry eye	4 (6.9)	0	4 (3.4)
VASCULAR DISORDERS	10 (17.2)	9 (15.3)	19 (16.2)
Hypertension	2 (3.4)	6 (10.2)	8 (6.8)

Primary System Organ Class Preferred Term n(%)	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w+14 week taper (N=59)	All (N=117)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9 (15.5)	7 (11.9)	16 (13.7)
Cough	1 (1.7)	4 (6.8)	5 (4.3)
GASTROINTESTINAL DISORDERS	11 (19.0)	25 (42.4)	36 (30.8)
Diarrhoea	1 (1.7)	7 (11.9)	8 (6.8)
Constipation	0	4 (6.8)	4 (3.4)
Gastrooesophageal reflux disease	2 (3.4)	3 (5.1)	5 (4.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	15 (25.9)	16 (27.1)	31 (26.5)
Pruritus	1 (1.7)	3 (5.1)	4 (3.4)
Rash pruritic	0	3 (5.1)	3 (2.6)
Skin striae	4 (6.9)	0	4 (3.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	27 (46.6)	26 (44.1)	53 (45.3)
Arthralgia	3 (5.2)	9 (15.3)	12 (10.3)
Osteoarthritis	5 (8.6)	6 (10.2)	11 (9.4)
Myalgia	0	4 (6.8)	4 (3.4)
Back pain	2 (3.4)	3 (5.1)	5 (4.3)
Tendonitis	2 (3.4)	3 (5.1)	5 (4.3)
Bursitis	5 (8.6)	2 (3.4)	7 (6.0)
Rotator cuff syndrome	3 (5.2)	2 (3.4)	5 (4.3)
Polymyalgia rheumatica	3 (5.2)	1 (1.7)	4 (3.4)
Pain in extremity	3 (5.2)	0	3 (2.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (10.3)	12 (20.3)	18 (15.4)
Fatigue	0	3 (5.1)	3 (2.6)
Injection site pruritus	0	3 (5.1)	3 (2.6)
Oedema peripheral	5 (8.6)	3 (5.1)	8 (6.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	12 (20.7)	16 (27.1)	28 (23.9)
Accidental overdose	1 (1.7)	3 (5.1)	4 (3.4)
Fall	6 (10.3)	3 (5.1)	9 (7.7)
Skin laceration	3 (5.2)	1 (1.7)	4 (3.4)
Limb injury	3 (5.2)	0	3 (2.6)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term, MedDRA: Medical Dictionary for Regulatory Activities. MedDRA 24.0
n (%) = number and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT within a SOC in the Sarilumab 200mg q2w treatment group.
The SOCs with at least one PT ≥ 5% in any treatment group are presented.
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Serious adverse event / deaths / other significant events

No deaths occurred in this study.

A higher incidence of SAEs was observed in the placebo+52-week taper group (20.7%) compared to the sarilumab 200 mg q2w+14-week taper group (13.6%).

The most frequently reported SAEs occurred in the Infections and infestations SOC, 3 (5.1%) participants in the sarilumab 200 mg+14-week taper group (all of which were cases of bacterial infections) and 3 (5.2%) participants in the placebo+52-week taper group (all of which were cases of COVID-19 infection). All other SOCs had no more than 1 SAE reported across the treatment groups with the exception of Blood and lymphatic system disorders (neutropenia: 2 [3.4%] participants in sarilumab 200 mg q2w+14-week taper group), Vascular disorders (giant cell arteritis: 1 participant in each treatment group), and Musculoskeletal and connective tissue disorders (polymyalgia rheumatica: 1 participant in each treatment group). There were no SAEs of infection associated with or preceded by neutropenia.

Table 35 - Number (%) of patients with treatment-emergent SAE(s) presented by primary SOC and PT - Safety population

Primary System Organ Class Preferred Term n(%)	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w+14 week taper (N=59)	All (N=117)
Any class	12 (20.7)	8 (13.6)	20 (17.1)
INFECTIONS AND INFESTATIONS	3 (5.2)	3 (5.1)	6 (5.1)
Intervertebral discitis	0	1 (1.7)	1 (0.9)
Pneumonia	0	1 (1.7)	1 (0.9)
Urinary tract infection bacterial	0	1 (1.7)	1 (0.9)
COVID-19	2 (3.4)	0	2 (1.7)
COVID-19 pneumonia	1 (1.7)	0	1 (0.9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (3.4)	0	2 (1.7)
Basal cell carcinoma	1 (1.7)	0	1 (0.9)
Erdheim-Chester disease	1 (1.7)	0	1 (0.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	2 (3.4)	2 (1.7)
Neutropenia	0	2 (3.4)	2 (1.7)
NERVOUS SYSTEM DISORDERS	1 (1.7)	0	1 (0.9)
Syncope	1 (1.7)	0	1 (0.9)
VASCULAR DISORDERS	3 (5.2)	2 (3.4)	5 (4.3)
Aortic intramural haematoma	0	1 (1.7)	1 (0.9)
Giant cell arteritis	1 (1.7)	1 (1.7)	2 (1.7)
Hypertensive emergency	1 (1.7)	0	1 (0.9)
Orthostatic hypotension	1 (1.7)	0	1 (0.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (1.7)	0	1 (0.9)
Pulmonary embolism	1 (1.7)	0	1 (0.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (5.2)	1 (1.7)	4 (3.4)
Polymyalgia rheumatica	1 (1.7)	1 (1.7)	2 (1.7)
Intervertebral disc protrusion	1 (1.7)	0	1 (0.9)
Lumbar spinal stenosis	1 (1.7)	0	1 (0.9)
RENAL AND URINARY DISORDERS	1 (1.7)	0	1 (0.9)
Pollakiuria	1 (1.7)	0	1 (0.9)

Primary System Organ Class Preferred Term n(%)	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w+14 week taper (N=59)	All (N=117)
INVESTIGATIONS	1 (1.7)	0	1 (0.9)
Alanine aminotransferase increased	1 (1.7)	0	1 (0.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (1.7)	1 (0.9)
Femur fracture	0	1 (1.7)	1 (0.9)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term, MedDRA: Medical Dictionary for Regulatory Activities.
MedDRA 24.0
n (%) = number and percentage of patients with at least one SAE.
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in the Sarilumab 200mg q2w treatment group.
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Adverse events of special interest

During the sarilumab development program and consistent with IL-6 blockade, the following potential risks and laboratory abnormalities and the possible consequent clinical outcomes of these risks were identified:

- Clinically significant infections including confirmed diagnosis of opportunistic infections, active/latent TB or initiation of medications for suspected TB, infections requiring prolonged medication, and infections requiring any parenteral treatment
- The following laboratory abnormalities:
    - ALT increase leading to permanent discontinuation
    - ANC decrease leading to permanent discontinuation
    - Thrombocytopenia leading to permanent discontinuation
- Elevations in hepatic transaminases (increase in ALT ≥3×ULN) and potential hepatic impairment

Table 36 - Number (%) of patients with at least one treatment-emergent AESI during the TEAE period by category and PT - Safety population

AESI Preferred Term n(%)	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w+14 week taper (N=59)	All (N=117)
Number of patients with AESIs	5 (8.6)	7 (11.9)	12 (10.3)
Opportunistic infections[a]	2 (3.4)	2 (3.4)	4 (3.4)
Herpes zoster	1 (1.7)	2 (3.4)	3 (2.6)
COVID-19	1 (1.7)	0	1 (0.9)
Tuberculosis	0	0	0
Infections requiring Prolonged Medication	2 (3.4)	2 (3.4)	4 (3.4)
Cystitis bacterial	0	1 (1.7)	1 (0.9)
Intervertebral discitis	0	1 (1.7)	1 (0.9)
COVID-19	1 (1.7)	0	1 (0.9)
Erysipelas	1 (1.7)	0	1 (0.9)
Infections requiring parenteral treatment	2 (3.4)	1 (1.7)	3 (2.6)
Intervertebral discitis	0	1 (1.7)	1 (0.9)
COVID-19	1 (1.7)	0	1 (0.9)
COVID-19 pneumonia	1 (1.7)	0	1 (0.9)
ALT increase leading to permanent discontinuation	1 (1.7)	0	1 (0.9)
Alanine aminotransferase increased	1 (1.7)	0	1 (0.9)
ANC decrease leading to permanent discontinuation	0	3 (5.1)	3 (2.6)
Neutropenia	0	3 (5.1)	3 (2.6)
Thrombocytopenia leading to permanent discontinuation	0	0	0
ALT increase >= 3 ULN	2 (3.4)	0	2 (1.7)
Alanine aminotransferase increased	2 (3.4)	0	2 (1.7)
Pregnancy or partner pregnancy	0	0	0
Symptomatic Overdose	0	0	0

TEAE: Treatment emergent adverse event, AESI: Adverse event of special interest, ALT: Alanine aminotransferase, ANC: Absolute neutrophil count, ULN: Upper limit of normal, MedDRA: Medical Dictionary for Regulatory Activities.

a Per PI judgment.

MedDRA 24.0

n (%) = number and percentage of patients with at least one AESI.

Table sorted by decreasing frequency of PT in Sarilumab 200mg q2w group within each AESI category.

Note: The same patients may be presented in more than one category.

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Alanine transaminase increase

Two participants in the placebo+52 week-taper group had a TEAE of ALT increase (≥3 × ULN). One of these participants experienced ALT increase leading to permanent discontinuation of the IMP.

Neutropenia

Three participants in the sarilumab 200 mg q2w+14-week taper group permanently discontinued the IMP due to neutropenia. Two participants had a neutrophil count <0.5 Giga/L. None of the events of neutropenia were associated with infections.

Thrombocytopenia

No AEs of thrombocytopenia were reported. Two participants had a platelet count within range of ≥75 Giga/L to 100 Giga/L.

Laboratory findings

White blood cells (WBC)

A mean decrease in WBC count was observed in the sarilumab 200 mg+14-week taper group. There was a mean decrease from baseline to Week 52 of 5.47 Giga/L and 1.30 Giga/L for the sarilumab 200 mg+14-week taper group and the placebo+52-week taper group, respectively, predominantly due to a decrease in the ANC. There were no clinically meaningful changes in other WBC counts, including lymphocytes. The mean WBC count remained within the normal range in both regimens.

Neutrophils

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 [12.0%] reported ANC decrease of Grade ≥3 severity, of whom 2 participants had a Grade 4 ANC decrease. There were no infections associated with the low neutrophil count.

Table 37 - Number (%) of patients with neutrophil count decreased during the TEAE period by maximum grade - Safety population - Study EFC15160

Laboratory parameter (CTCAE)	Placebo+52 week taper (N=58)	Sarilumab 200mg 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)

LLN: Lower limit of normal
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 parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline.
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Lymphocytes

The incidence of laboratory value decrease of lymphocyte count was higher in the sarilumab 200 mg+14-week taper group (8 [13.8%]) compared to the placebo+52-week taper group (2 [3.5%]). All cases of lymphocyte count decreased in the sarilumab 200 mg+14-week taper group were Grade 2 except for 1 patient with Grade 3.

Platelets

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

Haemoglobin

The mean values of haemoglobin remained within the normal range in both regimens.

Liver function

No cases of potential Hy's law (ALT >3 × ULN and bilirubin >2 × ULN) and no cases of hepatic failure were reported. None of the participants in the sarilumab 200 mg+14-week taper group had ALT or aspartate transaminase (AST) increase >Grade 1.

There were no clinically significant changes observed in mean low-density lipoprotein and triglyceride levels at any timepoints in the sarilumab 200 mg+14-week taper group.

Safety in special populations

Study EFC15160 (PMR)

In the PMR Study EFC15160, age groups were categorized by participants <65, ≥65 to <75, ≥75 to <85, and ≥85 years of age.

For patients <65 years of age, events for patients with any TEAE were balanced between the sarilumab 200 mg+14-week taper group (14/16=87.5%) and the placebo+52-week taper group (13/15=86.7%). In this age group, TEAE leading to permanent treatment discontinuation occurred in one more patient in the placebo+52-week taper group (2/15= 13.3%) compared to the sarilumab 200 mg+14-week taper group (1/16=6.3%).

For those ≥65 and <75 years of age, the proportion of patients with any TEAE was higher in the sarilumab 200 mg+14-week taper group (32/33=97.0%) compared to the placebo+52-week taper group (22/26=84.6%). In this age group, TEAE leading to permanent treatment discontinuation was higher in the sarilumab 200 mg+14-week taper group (4/33=12.1%) compared to the placebo+52week taper group (1/26= 3.8%). These observations were mainly due to neutropenia.

Proportions of patients with any treatment emergent SAE were balanced between the sarilumab 200 mg+14-week taper group (5/33=15.2%) and the placebo+52-week taper group (4/26=15.4%). For those ≥75 and <85 years of age, the proportion of patients with any TEAE was higher in the sarilumab 200 mg+14-week taper group (9/9=100%) compared to the placebo+52-week taper group (13/16=81.3%). In this age group, TEAE leading to permanent treatment discontinuation was more frequent in the sarilumab 200 mg+14-week taper group (2/9=22.2%) compared to the placebo+52-week taper group (1/16= 6.3%). Events for patients with any treatment emergent SAE were balanced between the sarilumab 200 mg+14-week taper group (3/9=33.3%) and the placebo+52-week taper group (5/16=31.3%).

Table 38 - Number (%) of patients with TEAE(s) by primary SOC by age categories - Safety population - Study EFC15160

Primary System Organ Class n(%)	Placebo+52 week taper (N=58)				Sarilumab 200mg q2w+14 week taper (N=59)			
	Age < 65	Age >= 65 to <75	Age >= 75 to <85	Age >= 85	Age < 65	Age >= 65 to <75	Age >= 75 to <85	Age >= 85
Number	15	26	16	1	16	33	9	1
Infections and infestations	10 (66.7)	11 (42.3)	7 (43.8)	1 (100)	5 (31.3)	14 (42.4)	2 (22.2)	1 (100)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (7.7)	1 (6.3)	0	1 (6.3)	1 (3.0)	1 (11.1)	0
Blood and lymphatic system disorders	1 (6.7)	2 (7.7)	2 (12.5)	0	1 (6.3)	9 (27.3)	5 (55.6)	0
Immune system disorders	0	0	0	0	0	1 (3.0)	0	0
Endocrine disorders	1 (6.7)	0	0	0	1 (6.3)	1 (3.0)	0	0
Metabolism and nutrition disorders	0	3 (11.5)	3 (18.8)	0	2 (12.5)	2 (6.1)	0	0
Psychiatric disorders	2 (13.3)	6 (23.1)	4 (25.0)	1 (100)	4 (25.0)	6 (18.2)	1 (11.1)	0
Nervous system disorders	4 (26.7)	9 (34.6)	2 (12.5)	0	6 (37.5)	5 (15.2)	0	0
Eye disorders	1 (6.7)	7 (26.9)	2 (12.5)	0	3 (18.8)	5 (15.2)	1 (11.1)	0
Ear and labyrinth disorders	1 (6.7)	2 (7.7)	0	0	1 (6.3)	1 (3.0)	0	0
Cardiac disorders	1 (6.7)	3 (11.5)	0	0	0	4 (12.1)	1 (11.1)	0
Vascular disorders	1 (6.7)	7 (26.9)	2 (12.5)	0	3 (18.8)	5 (15.2)	1 (11.1)	0
Respiratory, thoracic and mediastinal disorders	2 (13.3)	4 (15.4)	3 (18.8)	0	3 (18.8)	4 (12.1)	0	0
Gastrointestinal disorders	4 (26.7)	3 (11.5)	4 (25.0)	0	5 (31.3)	17 (51.5)	3 (33.3)	0
Hepatobiliary disorders	0	1 (3.8)	0	0	1 (6.3)	0	0	0
Skin and subcutaneous tissue disorders	2 (13.3)	9 (34.6)	4 (25.0)	0	3 (18.8)	9 (27.3)	4 (44.4)	0
Musculoskeletal and connective tissue disorders	6 (40.0)	11 (42.3)	9 (56.3)	1 (100)	8 (50.0)	14 (42.4)	4 (44.4)	0
Renal and urinary disorders	0	3 (11.5)	1 (6.3)	1 (100)	1 (6.3)	0	0	1 (100)
Reproductive system and breast disorders	1 (6.7)	1 (3.8)	0	0	0	0	0	0
General disorders and administration site conditions	1 (6.7)	3 (11.5)	2 (12.5)	0	4 (25.0)	5 (15.2)	3 (33.3)	0
Investigations	4 (26.7)	0	2 (12.5)	0	0	1 (3.0)	0	0
Injury, poisoning and procedural complications	2 (13.3)	4 (15.4)	5 (31.3)	1 (100)	2 (12.5)	9 (27.3)	4 (44.4)	1 (100)

TEAE: Treatment-emergent adverse event, SOC: System organ class
n (%) = number and percentage of patients with at least one TEAE in each age category
Note: Table sorted by SOC internationally agreed order.
PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/adhoc_ae_soc_byagegr1_s_t.sas
OUT=REPORT/OUTPUT/adhoc_ae_soc_byagegr1_s_t_i.rtf (03AUG2023 11:20)

Discontinuation due to adverse events

A higher incidence of TEAEs leading to permanent treatment discontinuation was observed in the sarilumab 200 mg q2w+14-week taper group (7 [11.9%] participants) compared with the placebo+52-week taper group (4 [6.9%] participants). The most frequently reported TEAEs leading to discontinuation occurred in the following SOCs (Table 39):

- Infections and infestations (5.1% in the sarilumab 200 mg q2w+14 week taper group and 1.7% in the placebo+52 week taper group)
- Blood and lymphatic system disorders (5.1% in the sarilumab 200 mg q2w+14 week taper group and 0% in the placebo+52 week taper group)

The most frequently reported events leading to a treatment discontinuation in the sarilumab 200 mg q2w+14-week taper group were in the SOC Blood and lymphatic system disorders, with 3 (5.1%) participants reported with an event of neutropenia.

There was 1 participant in the sarilumab 200 mg q2w+14-week taper group who had a dose modification due to neutropenia.

Table 39 - Number (%) of patients experiencing TEAE(s) leading to treatment discontinuation by primary SOC and PT - Safety population

Primary System Organ Class Preferred Term n(%)	Placebo+52 week taper (N=58)	Sarilumab 200mg q2w+14 week taper (N=59)	All (N=117)
Any class	4 (6.9)	7 (11.9)	11 (9.4)
INFECTIONS AND INFESTATIONS	1 (1.7)	3 (5.1)	4 (3.4)
COVID-19	1 (1.7)	1 (1.7)	2 (1.7)
Intervertebral discitis	0	1 (1.7)	1 (0.9)
Pneumonia	0	1 (1.7)	1 (0.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	3 (5.1)	3 (2.6)
Neutropenia	0	3 (5.1)	3 (2.6)
VASCULAR DISORDERS	1 (1.7)	0	1 (0.9)
Giant cell arteritis	1 (1.7)	0	1 (0.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (1.7)	0	1 (0.9)
Pulmonary embolism	1 (1.7)	0	1 (0.9)
RENAL AND URINARY DISORDERS	0	1 (1.7)	1 (0.9)
Nephrolithiasis	0	1 (1.7)	1 (0.9)
INVESTIGATIONS	1 (1.7)	0	1 (0.9)
Alanine aminotransferase increased	1 (1.7)	0	1 (0.9)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term, MedDRA: Medical Dictionary for Regulatory Activities.

MedDRA 24.0

n (%) = number and percentage of patients with at least one TEAE leading to permanent treatment discontinuation

Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing frequency in the Sarilumab 200mg q2w treatment group.

PGM=PRODOPS/SAR153191/EFC15160/CSR/REPORT/PGM/ae_socpt_s_t.sas OUT=REPORT/OUTPUT/ae_socpt_ltdisc_s_t_x.rtf (27JUL2021 5:29)

Supportive data

The MAH submitted supporting safety data from studies evaluating sarilumab in patients with related rheumatological conditions, GCA (EFC15068), and RA.

Study EFC15068 evaluated 83 participants with GCA over a 52-week treatment period with 27 participants receiving sarilumab 200 mg every 2 weeks (q2w)+26-week taper, 14 participants receiving sarilumab 150 mg q2w+26-week taper, 14 participants receiving placebo+26-week taper, and 28 participants receiving placebo+52-week taper.

The studies in RA that supported the original RA marketing application provided a larger group of patients with RA who received sarilumab.

Two RA safety populations, RA Pool 1 and RA Pool 2, are based on studies in the integrated safety database used in the original RA marketing application:

- RA Pool 1 Population: Placebo-controlled population. There were 1982 patients with RA over a 12-week to 52-week treatment period with 1321 patients receiving sarilumab and 661 patients receiving placebo.
- RA Pool 2 Population: Sarilumab+DMARD long-term safety population. There were 2887 patients with RA over a 12-week to 5-year treatment period with all 2887 patients receiving sarilumab. Long-term safety data from the RA Pool 2 will only be described in a summarised manner in the sections describing long-term exposure

The results were assessed for RA in the initial MA and the results from study EFC15068 did not raise a new signal.

In addition, at the CHMP request, the MAH pooled the data from the RA studies with the PMR study, the results are presented below:

The most frequent adverse reactions were neutropenia (14.3%), upper respiratory infections (6.8%), increased ALT (6.3%), urinary tract infections (5.3%), and injection site erythema (5.0%). The most common serious adverse reactions were infections (3.1%). In this analysis, the MAH pooled 4 studies that informed the safety profiles in the original MAA/original filings for the indication RA and the filing for the new indication PMR. This included 4 completed randomized, placebo controlled clinical trials as listed in Table 40. These studies involved 720 patients receiving sarilumab and 719 patients receiving placebo during the placebo-controlled treatment period. Adverse events (AEs) from the on-treatment period were included in this analysis.

Table 40 Studies included in the pooled analysis Study

Study code	Study title	Included dose levels
RA	EFC11072 Part A (12 weeks) EFC11072 Part B (52 weeks) a EFC10832 (24 weeks) a) Only data from Pool 1 (placebo-controlled studies in RA treated with sarilumab 200 mg q2w)	**200mg Sarilumab** **200mg Placebo**
PMR	Study EFC15160	**200mg Sarilumab** **200mg Placebo**

All TEAEs from all indicated Studies in Table 40, were evaluated to identify all ADRs (Table 41). ADRs were determined by a sequential process, initially by applying a threshold as the objective criteria, followed by clinical assessment to determine if a reasonable relationship could be established. A TEAE that did not meet the threshold was also identified for additional review based on clinical relevance (e.g., pneumonia or cellulitis).

Potential events for ADR consideration were identified from TEAEs (Table 41) according to the following criteria: ≥5% occurrence in the sarilumab 200 mg group and the difference compared with the placebo 200mg group is greater than 2%.

Clinical assessment for ADRs focused on the following considerations: 1) a plausible mechanism of action, 2) presence of confounders and/or alternative explanation, 3) a plausible dose/exposure relationship, and 4) consistency of evidence across studies and patient groups.

The potential events meeting the objective criteria for additional clinical review, such as those events already listed in the initially approved RA Indication (SmPC Section 4.8) have also been considered

even if their combined percentage was less than 5% or the difference was less than 2% compared to placebo, based upon clinical relevance and medical judgement.

Following the review of all TEAEs of the combined pooled data, no reported adverse events have been identified as new ADRs and no new serious events have been identified to warrant updated Warnings or Precautions.

Table 41: Results of Pooled Safety Data and Proposal for Consolidated ADR Table – Changes Noted in Bold

MedDRA System Organ Class (SOC)	Frequency in Indication-Specific ADR Tables (Per Current SmPC)	Current ADR	Proposed Frequency for Consolidated ADR Table	Proposed ADR	Summary of Change and/or Justification
Infections and infestations	Common	Upper respiratory tract infection	Common	Upper respiratory tract infection	ADRs retained; no change in frequency.
Infections and infestations		Urinary tract infection	Common	Urinary tract infection	ADRs retained; no change in frequency.
Infections and infestations		**Nasopharyngitis**	**Uncommon**	**Nasopharyngitis (no change to ADR term)**	**Frequency change to 0.7% thus changing the frequency from common to uncommon.**
Infections and infestations		Oral herpes	Common	Oral herpes	ADRs retained; no change in frequency.
Infections and infestations	Uncommon	**Pneumonia**	**Common**	**Pneumonia (no change to ADR term)**	**Frequency change to 1.3% thus changing the frequency from uncommon to common.**
Infections and infestations		**Cellulitis**	**Common**	**Cellulitis (no change to ADR term)**	**Frequency change to 1.4% thus changing the frequency from uncommon to common.**
Infections and infestations		Diverticulitis	Uncommon	Diverticulitis	ADRs retained; no change in frequency.
Blood and lymphatic system disorders	Very common	Neutropenia	Very common	Neutropenia	ADRs retained; no change in frequency. Footnote added to

					the SmPC to note that this event also occurred in PMR
Blood and lymphatic system disorders	Common	Thrombocytopenia	Common	Thrombocytopenia	ADRs retained; no change in frequency.
Blood and lymphatic system disorders		Leukopenia	Common	Leukopenia	ADRs retained; no change in frequency. Footnote added to the SmPC to note that this event also occurred in PMR
Metabolism and nutrition disorders	Common	Hypercholesterolemia	Common	Hypercholesterolemia	ADRs retained; no change in frequency.
Metabolism and nutrition disorders		Hypertriglyceridemia	Rare	Hypertriglyceridemia	ADRs retained; no change in frequency.
Gastrointestinal disorders	Rare	Gastrointestinal perforation	Rare	Gastrointestinal perforation	ADRs retained; no change in frequency.
Hepatobiliary disorders	Common	Transaminases increased	Common	Transaminases increased	ADRs retained; no change in frequency.
General disorders and administration site conditions	Common	Injection site erythema	Common	Injection site erythema	ADRs retained; no change in frequency.
General disorders and administration site conditions		Injection site pruritus	Common	Injection site pruritus	ADRs retained; no change in frequency. Footnote added to the SmPC to note that this event also occurred in PMR

Based on the pooled analyses, the calculated frequencies for some ADRs were updated: nasopharyngitis, pneumonia and cellulitis.

Nasopharyngitis had its frequency decreased to “uncommon” based on the pooled data. Pneumonia and cellulitis (although these MedDRA PTs did not meet numerical criteria for inclusion in the consolidated ADR table, these 2 ADRs have been retained based on medical judgement). Footnotes to the consolidated ADR table have been added to indicate that Neutropenia, Leukopenia and Injection site pruritis occurred in patients with PMR as well, however the other ADRs were not reported in the 59 PMR participants or the frequency for inclusion was not met.

Post marketing experience

There is no significant marketing experience with sarilumab in the PMR indication as sarilumab was only recently approved for the treatment of PMR in the US. However, sarilumab has been approved for treatment of adult participants with moderately to severely active RA who have had an inadequate response or intolerance to one or more DMARDs since 12 January 2017 (international birth date) and is currently approved in over 41 countries globally.

Cumulative patient exposure from post marketing experience up to 30 June 2023 was estimated to be 107,932 PYs.

In post marketing experience, the safety profile of sarilumab is consistent with the known safety profile of the drug observed in prior and ongoing studies. No new safety concerns have been identified from the post-marketing data as stated in the most recently submitted Periodic Safety Update Report (PSUR) covering the period from 13 January 2021 to 12 January 2023.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis during the PSUR reporting interval, the benefit-risk balance of sarilumab in the approved indication of RA remains positive.

2.5.1. Discussion on clinical safety

The assessment of sarilumab safety is based on adult participants with PMR from the pivotal, placebo-controlled Phase 3 Study EFC15160 (SAPHYR). The study was terminated prematurely due to low recruitment resulting in a change in the total expected number of patients. Thus, the database is smaller, there were only 118 participants with PMR (117 treated) included in the study. Patients were treated over a 52-week treatment period with 59 participants receiving sarilumab and 58 participants receiving placebo.

The MAH further supplemented these data with data from an equally small study in GCA patients and the data from the RA population. They are largely in line with the safety profile of IL-6 antagonists. The GCAs study did not add substantial patient numbers, and no new safety signal was identified.

In study EFC15160 (SAPHYR), the overall incidence of TEAEs was slightly higher in the sarilumab 200 mg+14-week taper group compared to the placebo+52-week taper group treatment-emergent. No deaths were reported in either group during the study. A higher incidence of SAEs was observed in the placebo+52-week taper group (20.7%) compared to the sarilumab 200 mg q2w+14-week taper group (13.6%). The most frequently reported SAEs occurred in the Infections and Infestations SOC in a similar frequency between treatment groups. Serious adverse events of neutropenia occurred in 2 participants (3.4%) in the sarilumab 200 mg+14-week taper group compared to none in the placebo+52-week taper group. In both cases of neutropenia, the participants experienced Grade 4 ($<0.5 \times 10^9$/L) decreases in neutrophils without any infections and resolved following permanent discontinuation of study drug.

Adverse events of special interest were evaluated to assess their potential association with sarilumab treatment. The rate of infections and infestations was higher in the placebo+52-week taper group (50.0%) compared to the sarilumab 200 mg q2w+14-week taper group (37.3%). The number of participants who experienced any treatment-emergent AESI in the safety population was low.

More patients discontinued treatment in the sarilumab 200 mg+14-week taper group than in the placebo+52-week taper group. The most common TEAE leading to treatment discontinuation was neutropenia. For AESI, 4 participants reported opportunistic infection AESIs with 2 in each group. Three participants in the sarilumab 200 mg+14-week taper group permanently discontinued the study drug due to neutropenia not associated with infection. Two participants in the placebo+52-week taper group had an AESI of ALT increase ($\geq 3 \times$ ULN). One of these participants experienced ALT increase leading to permanent discontinuation of the study drug. These information have been added in section 4.8 of the SmPC. There were no events of serious hypersensitivity reactions, GI perforations and/or malignancies reported.

Haematology data and laboratory results did not show a safety signal. As expected reduction in neutrophil count was observed. Seven participants (12.0%) in the sarilumab group reported ANC

decrease of Grade ≥3 severity, of whom 2 participants (3.4%) had a Grade 4 ANC decrease. This information has been included in section 4.8 of the SmPC. In addition as only limited safety data were collected in patients with laboratory abnormalities (neutropenia, thrombocytopenia…) the MAH updated section 4.2 of the SmPC to recommend discontinuation of sarilumab if patients develop laboratory abnormalities. A post-approval study to further evaluate the safety of sarilumab in PMR patients is planned by the MAH and the results will be submitted when available.

Age groups were categorized by participants <65, ≥65 to <75, ≥75 to <85, and ≥85 years of age. In summary, any TEAEs in <65 and ≥85 age group were balanced between both groups, whereas in age groups ≥65 and <75 and ≥75 and <85, there were minor variations in the sarilumab group, mostly driven by neutropenia. In certain age groups in the placebo group, variations were higher than in the similar age groups in the sarilumab group, mostly driven by psychiatric, neurological, ocular, vascular and respiratory AEs. Of note, due to the small patient numbers no firm conclusion could be drawn. The MAH proposed to collect safety data in the higher age groups from post-marketing spontaneous adverse event reporting (per the approved scheduled PSUR, the MAH will report on all age-groups, incl. higher age groups and incl. all available data for these age groups), solicited reporting (continuous reporting to the MAH), and retrospective studies using claims data or electronic health records, in jurisdictions where sarilumab is approved for PMR. This approach was considered acceptable by the CHMP.

The ADA response in patients with PMR was low. Three (5.4%) patients in the 200 mg q2w group and one (1.8%) patient in the placebo group had treatment-emergent positive ADA responses. All the ADA responses were transient with a low titre (50) except 1 patient (1.8%) in the sarilumab 200 mg q2w+14-week taper group who had persistent ADA response with a low titre. In the 200 mg q2w group, the 3 patients with treatment-emergent positive ADA responses were also positive for NAb. Patients with treatment-emergent positive ADA responses exhibited lower sarilumab exposure than patients who were ADA negative. None of the patients who had treatment-emergent positive ADA responses experienced anaphylaxis, serious and/or clinically significant hypersensitivity reactions, or injection site reactions. In the 200 mg q2w group, all 3 patients who had treatment-emergent positive ADA responses were non-responders for the primary endpoint. This information has been included in section 4.8 of the SmPC.

The MAH provided the requested pooled safety data for the RA indication and PMR indication. For this purpose, the data of 4 clinical studies (3 in RA and 1 in PMR) were pooled. The methodology applied for pooling the data was deemed acceptable by the CHMP. Based on the pooled analyses, the calculated frequencies for some ADRs were updated: nasopharyngitis, pneumonia and cellulitis, and section 4.8 of the SmPC has been updated. In addition the ADRs reported in the PMR patients: neutropenia, leukopenia and injection site pruritus were mentioned. Overall, the MAH's conclusion that there are no new safety concerns identified and the benefit-risk profile of sarilumab remains favourable, was endorsed by the CHMP.

2.5.2. Conclusions on clinical safety

The safety database in PMR is small, however the observed safety data are in general consistent with the data presented in the RA population.

Overall, no new safety concerns or signals were identified during the development program in the clinical trial population.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

The list of safety concerns remains unchanged:

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

Pharmacovigilance plan

The pharmacovigilance plan remains unchanged:

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				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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 minimisation measures

The risk minimisation measures remain unchanged:

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 and PMR. Additional risk minimization measures: Patient Alert 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 and PMR. Additional risk minimization measures: Patient Alert 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 and PMR. Additional risk minimization measures: Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Safety surveillance program using existing EU RA registries

Safety concern	Risk minimization measures	Pharmacovigilance activities
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 and PMR. 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 and PMR. 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 and PMR. 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 and PMR. 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; PMR: Polymyalgia Rheumatica; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current excipients guideline, which were reviewed and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package

leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The recommended dosage in the present variation for the treatment of adult patients with PMR is the same as the one approved for RA: 200 mg given every 2 weeks (Q2W) administered as a SC injection. The package leaflet has only been updated to add the PMR extension of indication and none of the changes affect the instruction for use (IFU).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Polymyalgia rheumatica is an inflammatory disease of unknown aetiology 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 patients with PMR. Polymyalgia rheumatica typically affects individuals ≥50 years of age, with prevalence varying by age and population. In addition to the signs and symptoms of PMR, patients with PMR often require long-term CS use, with CS-related AEs adding to the morbidity of their disease.

3.1.2. Available therapies and unmet medical need

Per the 2015 American College of Rheumatology/European League against Rheumatology (ACR/EULAR) guidelines, corticosteroid (CS) remains the standard of care (SoC) therapy with a recommended minimum effective starting dose within the range of 12.5 to 25 mg of prednisone (or equivalent) daily. Treatment duration ranges from approximately 1 to 3 years, during which CS should be tapered. Although CS with a slow taper will reduce symptoms rapidly for most patients, numerous reports have demonstrated a significant number of patients cannot taper CS successfully and do not achieve remission. Patients who are unable to taper CS, in addition to inadequately controlled disease, are also at higher risk of complications due to the long-term exposure associated with CS therapy.

Therapies, other than CS, have shown limited efficacy in the treatment of PMR. An expert ACR/EULAR panel conditionally recommended methotrexate for early use in patients at high risk of prolonged CS use and/or CS-related 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 tumour necrosis factor-alpha (TNF-α) blocking agents for the treatment of PMR. There is therefore an unmet medical need for alternative treatment for patients who have had an inadequate response to CS or who experience a relapse during corticosteroid taper.

3.1.3. Main clinical study

A single pivotal study (Study EFC15160) in adult participants with PMR was performed. The study was a multinational, multicentre, randomized, double-blind, placebo-controlled, 52-week, study evaluating the efficacy and safety of sarilumab in the treatment of patients with active PMR resistant to CS tapering.

The primary endpoint was the proportion of patients achieving sustained remission at Week 52, a composite endpoint defined by having met all of the following 4 components: (1) achievement of disease remission no later than Week 12; (2) absence of disease flare from Week 12 through Week 52; (3) sustained reduction of CRP (to <10 mg/L, with an absence of successive elevations to ≥10 mg/L) from Week 12 through Week 52; and (4) successful adherence to the prednisone taper from Week 12 through Week 52.

The study population for EFC15160 consisted of participants 50 years and older who were diagnosed with PMR according the ACR/EULAR criteria. Participants were unable to taper CS successfully without flare They also had to have had a history of being treated for at least 8 weeks with prednisone ≥10 mg/day or equivalent. As these patients were resistant to CS taper, they were required to be taking prednisone of ≥7.5 mg/day (or equivalent) and not exceeding 20 mg/day during the screening period.

3.2. Favourable effects

The primary endpoint was met: the proportion of participants achieving sustained remission at Week 52 was higher in the sarilumab 200 mg q2w+14-week taper group compared to placebo+52-week taper group. There were 17 (28.3%) participants in the sarilumab 200 mg q2w+14-week taper group and 6 (10.3%) participants in the placebo+52-week taper group who achieved sustained remission at Week 52 with point estimate and 95% CI: 18.0 (4.15 ,31.82), p = 0.0193.

There was a higher proportion of participants achieving each component a) achievement of disease remission no later than Week 12 (46.7% vs 37.9%), b) absence of disease flare from Week 12 through Week 52 (55% vs 32.8%) c) sustained reduction of CRP from Week 12 through Week 52 (66.7% vs 44.8%) and d) successful adherence to prednisone taper from Week 12 through Week 52 (50% vs 24.1%) of the sustained remission endpoint in the sarilumab 200 mg q2w+14-week taper group compared to the placebo+52-week taper group.

The key secondary endpoint was also achieved: the total median cumulative prednisone dose over the 52-week treatment period (i.e., actually taken by participants) was 777 mg in the sarilumab 200 mg q2w+1- week taper group, as compared to 2044 mg in the placebo+52-week taper group.

Exploratory efficacy endpoints except GTI score indicated favourable functional and symptomatic benefits from sarilumab treatment in combination with rapid 14-week corticosteroid taper versus 52 - week corticosteroid taper in placebo.

3.3. Uncertainties and limitations about favourable effects

The population in the pivotal trial consisted of participants who were unable to taper CS successfully without flare. The MAH initially proposed an indication for patients who have had an inadequate response to corticosteroids (CS) or who cannot tolerate CS taper, this did not accurately reflect the trial's population. Therefore at the CHMP request, the MAH revised the wording of the indication to specify usage in patients who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper.

Due to COVID-19, the MAH had issue with recruiting patients (only 118 participants were randomized of the 280 initially planned) and the trial was terminated prematurely. Due to the change in the total expected number of participants, the statistical significance level was changed from 0.01 to 0.05, and the power calculations were revised. While 0.05 is the commonly used acceptable significance level, these changes were major and raised uncertainty on the robustness of results. The MAH explained that a higher alpha was chosen in order to have "a reasonable power for the study" given the reduced sample size. Both the increase of alpha and the amended placebo rate were implemented as reaction

to issues arising during the conduct of the trial and which could not have been appropriately addressed at planning stage. This was considered acceptable and the issue was not further pursued by the CHMP.

As only a single pivotal trial, limited in size and impacted by several changes in the protocol was performed, additional analyses were requested by the CHMP to support the robustness of the results. To better understand the estimated treatment effect the MAH provided an additional sensitivity analysis of the primary endpoint in which patients were not automatically treated as non-responders if they received rescue treatment. To address the concern that the primary result may be strongly dependent on unsuccessful tapering in the control arm, the MAH provided an analysis in which the criterion “successful adherence to the prednisone taper from Week 12 through week 52” was removed, and only the remaining three criteria were assessed for the definition of response. Additional analyses of the primary endpoint and its component indicate that the treatment effect estimate is not artificially inflated by counting nonadherence to the corticosteroid tapering as non-response. In addition, the data suggest that sarilumab treatment facilitates tapering.

No data beyond one year are available, therefore it is not known when treatment should be discontinued. In order to address this uncertainty, the MAH updated section 4.2 of the SmPC to mention that data are available for patients that were treated for up to 1 year and to recommend that treatment beyond 52 weeks should be guided by disease activity, physician discretion and patient choice. In addition, the CHMP recommended the MAH to investigate the necessary treatment duration. The MAH confirmed that they will conduct a post-authorisation study with the primary objective of evaluating treatment patterns and outcomes associated with sarilumab in patients with PMR. Specifically, the study will provide insights into the appropriate duration of sarilumab treatment, and examine the effects of treatment discontinuation in patients who achieve a response.

3.4. Unfavourable effects

The safety profile of sarilumab in the PMR population was consistent with the RA population. No new risks have been identified in the PMR population.

The reported ADRs in the study in PMR patients were neutropenia, leukopenia and injection site pruritus.

There was overall a higher incidence of SAEs in the placebo+52-week taper group (20.7%) compared to the sarilumab 200 mg+14-week taper group (13.6%).

The most frequently reported SAEs occurred in the Infections and Infestations SOC in a similar frequency between treatment groups. SAEs of neutropenia occurred in 2 participants (3.4%) in the sarilumab 200 mg+14-week taper group compared to none in the placebo+52-week taper group.

3.5. Uncertainties and limitations about unfavourable effects

Due to the early termination of the trial the sample size was smaller than expected. In addition the study lasted only 52 weeks therefore there is limited long term data. Further safety data will be collected in the post-marketing setting.

Limitations also included sparse safety data in patients with laboratory abnormalities (neutropenia, thrombocytopenia…) therefore the MAH updated section 4.2 of the SmPC to recommend discontinuing sarilumab if patients develop laboratory abnormalities.

Finally, as PMR is a disease that is occurring mainly in patients older than 50 years, the PMR population is older than the RA population. Therefore the MAH will collect further safety data in the higher age groups in the post-marketing setting.

3.6. Effects Table

Table 42: Effects Table for Kevzara, PMR (data cut-off:07 July 2021).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint	Proportion of participants achieving sustained remission at Week 52	Person/ patient (%)	17 (28.3%)	6 (10.3%)	Point estimate and 95% CI: 18.0 (4.15 ,31.82), p = 0.0193 Limitations: (1) the point estimate is smaller than expected, (2) results depend on small numbers (3) the level of significance has been increased from 0.01 to 0.05 in a late amendment	Clinical study report of study EFC15160
Key secondary endpoint	Total actual cumulative corticosteroid (including prednisone) dose over 52 weeks	Mg	777.0	2044.0	p <.0001 Strength: multiplicity corrected (hierarchical testing) Limitation: Point estimate not reported in the clinical study reports (only the difference between the actual and expected cumulative CS dose, which was itself statistically significant at p =0.0189).	Clinical study report of study EFC15160
Unfavourable Effects						
Infections and Infestations		%	5.1	5.2		Clinical study report of study EFC15160
Neutropenia	Decreases in neutrophils	%	3.4	0		Clinical study report of study EFC15160

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoint and secondary endpoint were met. Results indicate that with sarilumab treatment patients may achieve response and reduce corticosteroid doses. As only a single pivotal trial, limited in size and impacted by several changes in the protocol was performed, the robustness of the results was questioned. Further analysis performed by the MAH provided reassurance on the efficacy of sarilumab.

Although it is acknowledged that there are still uncertainties regarding optimal treatment duration,

further data are expected to be gained through post-marketing experience. In the meantime, the recommendation that treatment beyond 52 weeks should be guided by disease activity, physician discretion and patient choice in section 4.2 of SmPC is considered sufficient.

The overall incidence of adverse events was low and in general comparable between the groups. The observed safety profile in the PMR population is largely consistent with the known RA safety profile. As, the safety data base in PMR is small, further safety data will be collected in the post-marketing setting.

3.7.2. Balance of benefits and risks

In the single pivotal trial, the primary and key secondary endpoints were met, demonstrating efficacy in the treatment of PMR in adult patients who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper. Results indicate that sarilumab treatment may facilitate corticosteroid taper.

In addition, although the pivotal trial was small, a favourable safety profile was observed and is in line with the known safety profile in RA. Further safety data will be collected in the post-marketing setting.

3.8. Conclusions

The overall B/R of Kevzara is positive in the following indication:

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.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA, IIIB and IV

Extension of indication to include treatment of Polymyalgia Rheumatica (PMR) in adult patients who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper, based on results from study EFC15160; this is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with polymyalgia rheumatica. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.1 of the SmPC are updated. The Package Leaflet and the labelling are updated in accordance. Furthermore, the PI is brought in line with the latest excipients guideline. Version 4.1 of the RMP is also approved.

The variation leads to amendments to the Summary of Product Characteristics, labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Kevzara-H-C-004254-II-0044’

Attachments

1. SmPC, Labelling, Package Leaflet and Annex IV (changes highlighted) as adopted by the CHMP on 17 October 2024.