Sarilumab (polymyalgia rheumatica)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

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Medical and scientific advice

- Mathias Mäurer, Klinik für Neurologie am Klinikum Würzburg Mitte (Clinic of Neurology at Würzburg Central Hospital), Würzburg; Germany

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by two persons.

IQWiG thanks the respondents and the Deutsche Rheuma-Liga for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents and the Deutsche Rheuma-Liga were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Christof Dücker
- Tatjana Herrmanns
- Michaela Florina Kerekes
- Stefan Kobza
- Mandy Kromp
- Daniela Preukschat
- Anke Schulz
- Claudia Selbach
- Pamela Wronski

Part I: Benefit assessment

I Table of contents

Page

I List of tables I.3
I List of abbreviations I.4
I 1 Executive summary of the benefit assessment I.5
I 2 Research question I.13
I 3 Information retrieval and study pool I.14
I 3.1 Studies included I.14
I 3.2 Study characteristics I.14
I 4 Results on added benefit I.23
I 4.1 Outcomes included I.23
I 4.2 Risk of bias I.28
I 4.3 Results I.30
I 4.4 Subgroups and other effect modifiers I.36
I 5 Probability and extent of added benefit I.37
I 5.1 Assessment of added benefit at outcome level I.37
I 5.2 Overall conclusion on added benefit I.39
I 6 References for English extract I.41

I List of tables[2]

Page

Table 2: Research question for the benefit assessment of sarilumab I.5
Table 3: Sarilumab – probability and extent of added benefit I.12
Table 4: Research question for the benefit assessment of sarilumab I.13
Table 5: Study pool – RCT, direct comparison: sarilumab compared with ACT I.14
Table 6: Characteristics of the study included – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone I.15
Table 7: Characteristics of the interventions – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone I.16
Table 8: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone I.20
Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone I.22
Table 10: Matrix of outcomes – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone I.24
Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone I.29
Table 12: Results (mortality, morbidity; health-related quality of life, side effects, dichotomous) – RCT, direct comparison: sarilumab + prednisone with placebo + prednisone I.31
Table 13: Results (morbidity, continuous) – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone I.33
Table 14: Extent of added benefit at outcome level: sarilumab (+ corticosteroids) in comparison with corticosteroids I.37
Table 15: Positive and negative effects from the assessment of sarilumab (+ corticosteroids) in comparison with corticosteroids I.39
Table 16: Sarilumab – probability and extent of added benefit I.40

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
CRP	C-reactive protein
csDMARDs	conventional synthetic disease-modifying antirheumatic drugs
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAQ-DI	Health Assessment Questionnaire - Disability Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	mental component summary
MTX	methotrexate
NRI	non-responder imputation
PCS	physical component summary
PMR	polymyalgia rheumatica
RCT	**randomized** controlled trial
SAE	serious adverse event
SMD	standardized mean difference
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug sarilumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 04 February 2025.

Research question

The aim of this report was to assess the added benefit of sarilumab in comparison with systemic corticosteroids and the combination of corticosteroids with methotrexate (MTX) as ACT in patients with polymyalgia rheumatica (PMR) who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of sarilumab

Therapeutic indication	**ACT**[a]
Adults with PMR who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper	Treatment of physician's choice, taking into account systemic corticosteroids and the combination of corticosteroids with methotrexate[b]

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- A single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
- If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
- A subgroup analysis according to MTX add-on therapy (yes/no) is considered helpful for the early benefit assessment and should be submitted with the dossier.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PMR: polymyalgia rheumatica

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for deriving any added benefit.

Study pool and study design

The benefit assessment of sarilumab used the EFC15160 study (hereinafter referred to as SAPHYR).

The SAPHYR study is a randomized, double-blind, parallel, multicentre study for the comparison of sarilumab + prednisone with placebo + prednisone. The study had a total randomized treatment phase of 52 weeks.

The study included adult patients with a diagnosis of active PMR according to the classification criteria of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). Before the start of the study, patients also had to have received treatment with at least 10 mg/day prednisone (or equivalent) for at least 8 weeks. In addition, they had to have experienced at least 1 PMR relapse within 12 weeks prior to screening while attempting to taper off a dose of at least 7.5 mg/day prednisone (or equivalent). In addition, patients had to have received treatment with at least 7.5 mg/day and a maximum of 20 mg/day prednisone (or equivalent) upon screening and during the screening phase. Patients with a diagnosis of giant cell arteritis, concurrent rheumatoid arthritis or other connective tissue diseases or active fibromyalgia were excluded from participation in the study. Patients with an unstable MTX dose or an MTX dose of more than 15 mg/week within 3 weeks prior to randomization were also excluded from participation in the study. The MTX dose had to remain stable throughout the study. Reduction and discontinuation were possible for safety reasons.

The study included a total of 118 patients who were randomly assigned in a 1:1 ratio to sarilumab + prednisone (N = 60) or placebo + prednisone (N = 58). Treatment with sarilumab in the intervention arm was largely in compliance with the specifications of the Summary of Product Characteristics (SPC).

Before the start of the study, corticosteroid therapy should be optimized in both arms in order to reduce the risk of serious adverse events (SAEs) when tapering the corticosteroids. As a starting dose for the first 2 weeks of treatment with prednisone, 15 mg/day prednisone was then used for all patients in both treatment arms. In both study arms, prednisone was then tapered according to fixed tapering schedules, with prednisone administration in the intervention arm being gradually reduced to 1 mg/day by Week 13, followed by prednisone placebo from Week 14, while in the control arm it was gradually tapered to 1 mg/day by Week 52. At the investigator’s discretion, treatment with a maximum of 5 mg/day of unblinded additional prednisone could be administered in both study arms in the event of one PMR relapse up to Week 12. In case of 1 PMR relapse during the regular prednisone tapering (up to Week 12) despite administration of additional prednisone of up to 5 mg/day, the tapering regimen had to be discontinued and the patient received a commercial rescue corticosteroid

as decided by the investigator. In this case, blinded treatment with sarilumab or placebo should be continued, unless this was contraindicated due to safety concerns. If symptoms persisted during treatment with rescue corticosteroids, other treatment options including conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) could be used. In these cases, the study medication had to be discontinued.

Primary outcome of the study was sustained remission at Week 52, with secondary outcomes including morbidity, health-related quality of life and adverse events (AEs).

Limitations of the SAPHYR study

Patients who have responded inadequately to corticosteroids were not included

Patients who did not respond adequately to corticosteroids were not included in the SAPHYR study.

Therapy with MTX only in stable doses

According to the now expired "S3 guideline for the treatment of PMR" from 2017, administration of MTX in addition to corticosteroid therapy should be considered at an early stage, especially in patients at high risk of relapse and/or of a long treatment duration, as well as in patients with risk factors, comorbidities and/or concomitant medications in whom corticosteroid-induced side effects are more likely to occur. Since, according to this guideline, there is no prototypical clinical situation in PMR that undoubtedly requires the use of MTX, this decision must be made on a very individualized or patient-specific basis. The "S2e guideline for the treatment of PMR: Update 2024", only considers MTX as an alternative to interleukin 6 receptor blocking substances in patients with a recurrent course and in selected patients with new-onset disease and at high risk of corticosteroid-induced side effects.

The 2024 French guideline "Recommendations of the French Society of Rheumatology for the management in current practice of patients with polymyalgia rheumatica" points out that the data on the efficacy of MTX in patients with PMR relapse in general and with PMR relapse during corticosteroid taper in particular come exclusively from observational studies. The efficacy of MTX in PMR is also called into question by the results of the recently published PMR MODE study, even if this does not relate to use for relapses.

Patients on MTX therapy were only included in the SAPHYR study if their MTX dose was at most 15 mg/week and this dose had been stable in the 3 months prior to the start of the study. Moreover, the MTX dose had to remain stable throughout the study. In this context, a reduction of the MTX dose and MTX discontinuation was possible for safety reasons. In case of PMR recurrence and insufficient effect of additional prednisone and, if necessary, rescue corticosteroids, treatment with csDMARDs (i.e. also with MTX) was permitted as rescue medication. In this case, the study treatment had to be discontinued and the patients

concerned were classified as non-responders for the primary outcome. Concomitant treatment with MTX was therefore only possible to a limited extent in the study. Of the patients included, a maximum of 5 (8%) in the intervention arm and a maximum of 10 (17%) in the control arm had received prior treatment with MTX. 12 (20%) and 17 (29%) of the patients received concomitant therapy with MTX (MTX add-on). However, it is unclear whether this only includes patients who were included in the study with a stable MTX dose or whether it also includes patients who received MTX as emergency therapy as part of the study. It is unclear what percentage of patients received rescue therapy with csDMARDs in general and MTX in particular; information is only available on the percentage of patients who received rescue corticosteroids, which was 32% and 59% respectively. The inclusion criteria show that the concomitant MTX therapy used in about a quarter of the patients was not initiated to treat the relapse immediately preceding the inclusion in the study, but already existed before this relapse. In conclusion, the results of the SAPHYR study can only be used to make statements about patients for whom the physician considers corticosteroids to be the appropriate therapy for relapse treatment. The extent to which an additional administration of MTX or an increase of the MTX dose would have been indicated for the treatment of the relapse in the study population remains unclear. This uncertainty has been taken into account in the assessment of the certainty of conclusions.

Treatment with prednisone not individualized

According to guidelines for the treatment of PMR, the dosage of corticosteroid therapy should be adjusted individually for each patient. In the SAPHYR study, however, corticosteroid therapy was given to all patients with a starting dose of 15 mg/day of prednisone. Although corticosteroid therapy should be optimized before the start of the study in order to reduce the risk of SAEs when tapering corticosteroids, no data are available on the extent to which this optimization took place before randomization. It can therefore not be ruled out that the starting dose of 15 mg/day prednisone was too high for individual patients. The use of additional prednisone also indicates that the starting dose of 15 mg/day prednisone was too low for some patients. In addition, prednisone was tapered in both study arms according to a fixed tapering schedule with a fixed treatment duration. This does not comply with the recommendations of the guideline. The resulting uncertainties regarding the transferability of the results to the German health care context are taken into account when assessing the reliability of the results.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes was rated as low for the SAPHYR study.

The risk of bias of the results on the outcome overall survival was rated as low. For the effect estimates based on AE recordings - exclusively discontinuation due to AEs -, the effect estimates on duration of morning stiffness and mobility of upper limbs, the effect estimates

on symptoms and the effect estimates on health-related quality of life, there is a high potential for bias. Although the risk of bias for the effect estimate on discontinuation due to AEs is low, the certainty of results for this effect estimate is limited.

Taking into account all uncertainties described above in the results of the SAPHYR study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

Results

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome all-cause mortality. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome all-cause mortality; an added benefit is therefore not proven.

Morbidity

Remission

No suitable data are available for the outcome remission. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for this outcome; an added benefit is therefore not proven.

Duration of morning stiffness

For the outcome duration of morning stiffness, a statistically significant difference between the treatment arms with regard to the change in the duration of morning stiffness in minutes was shown when considering the mean differences over the duration of the study. However, the lower limit of the 95% confidence interval (CI) is 5.77 minutes, which appears too low for baseline values of over one hour to rate the observed effect as clinically relevant. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome duration of morning stiffness; an added benefit is therefore not proven.

Mobility of the upper limbs

For the outcome mobility of upper limbs, a statistically significant difference between the treatment arms was shown when considering the mean differences over the duration of the study. The standardized mean difference (SMD) was analysed to examine the relevance of the result. The 95% CI of SMD was not completely below the irrelevance threshold of -0.2. It can therefore not be inferred that the effect is relevant; an added benefit is therefore not proven.

Pain

No statistically significant difference between treatment arms was shown for the outcome pain. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome pain; an added benefit is therefore not proven.

Physical functioning

There is no statistically significant difference between treatment arms for the outcome physical functioning. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome physical functioning; an added benefit is therefore not proven.

Patient assessment of disease activity

There was no statistically significant difference between the treatment arms for the outcome patient assessment of disease activity. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome patient assessment of disease activity; an added benefit is therefore not proven.

Fatigue

No statistically significant difference between treatment arms was found for the outcome of fatigue. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome fatigue; an added benefit is therefore not proven.

Health status

No statistically significant difference between the treatment arms was shown for the outcome health status. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome health status; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded using the Physical Component Summary (PCS) and the Mental Component Summary (MCS) of the Short Form (36) – version 2 (SF-36v2). Statistically significant differences between the treatment arms were not shown for both summary scores. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome health-related quality of life; an added benefit is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome SAEs. For the outcome SAEs, there was therefore no hint of greater or lesser harm from

sarilumab in comparison with corticosteroids; therefore, there is no proof of greater or lesser harm.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome discontinuation due to AEs. For the outcome discontinuations due to AEs, there was therefore no hint of greater or lesser harm from sarilumab in comparison with corticosteroids; therefore, greater or lesser harm is not proven.

Infections (System Organ Class [SOC], AE)

No statistically significant difference between treatment arms was shown for the outcome infections. For the outcome infections, there was therefore no hint of greater or lesser harm from sarilumab in comparison with corticosteroids; therefore, greater or lesser harm is not proven.

Serious infections (SOC, SAEs)

No statistically significant difference between the treatment arms was shown for the outcome serious infections. For the outcome serious infections, there was therefore no hint of greater or lesser harm from sarilumab in comparison with corticosteroids; therefore, greater or lesser harm is not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug sarilumab in comparison with the ACT is assessed as follows:

There are neither positive nor negative effects from the assessment of sarilumab in comparison to corticosteroids.

In summary, there is no hint of added benefit of sarilumab over the ACT for patients with PMR who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3 presents a summary of the probability and extent of the added benefit of sarilumab.

Table 3: Sarilumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with PMR who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper	Treatment of physician's choice, taking into account systemic corticosteroids and the combination of corticosteroids with methotrexate[b]	Patients for whom corticosteroids are the appropriate treatment of physician's choice[c]: added benefit not proven
		Patients for whom the combination of corticosteroids with methotrexate is the appropriate treatment of physician's choice: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:
- A single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
- If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
- A subgroup analysis according to MTX add-on therapy (yes/no) is considered helpful for the early benefit assessment and should be submitted with the dossier.

c. The SAPHYR study only included patients who had experienced a relapse during corticosteroid taper. It remains unclear whether the observed effects can be extrapolated to patients who have had an inadequate response to corticosteroids.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PMR: polymyalgia rheumatica

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report was to assess the added benefit of sarilumab in comparison with systemic corticosteroids and the combination of corticosteroids with MTX as ACT in patients with PMR who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of sarilumab

Therapeutic indication	**ACT[a]**
Adults with PMR who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper	Treatment of physician's choice, taking into account systemic corticosteroids and the combination of corticosteroids with methotrexate[b]

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- A single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
- If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
- A subgroup analysis according to MTX add-on therapy (yes/no) is considered helpful for the early benefit assessment and should be submitted with the dossier.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MTX: methotrexate; PMR: polymyalgia rheumatica

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for deriving any added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on sarilumab (status: 22 November 2024)
- Bibliographical literature search on sarilumab (last search on 22 November 2024)
- Search in trial registries/trial results databases for studies on quizartinib (last search on 22 November 2024)
- Search on the G-BA website for sarilumab (last search on 22 November 2024)

To check the completeness of the study pool:

- Search in trial registries for studies on sarilumab (last search on 27 February 2025); for search strategies, see I Appendix A of the full dossier assessment

The review did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: sarilumab compared with ACT

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
EFC15160 (SAPHYR[d])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SAPHYR	RCT, double-blind, parallel	Adults with active PMR according to EULAR/ACR classification criteria ▪ with an erythrocyte sedimentation rate (ESR) ≥ 30 mm/h or a CRP value ≥ 10 mg/L as a sign of disease activity within 12 weeks prior to screening ▪ ≥ 8 weeks of treatment with ≥ 10 mg prednisone (or equivalent) per day before the start of the study ▪ ≥ 1 PMR relapse[b] when attempting to taper off a dose of ≥ 7.5 mg prednisone (or equivalent) per day within 12 weeks prior to screening ▪ for screening and during the screening phase: treatment with ≥ 7.5 mg/day and ≤ 20 mg/day prednisone (or equivalent)	Sarilumab + prednisone (N = 60) placebo + prednisone (N = 58)	Screening: ≤ 4 weeks treatment: 52 weeks follow-up: 6 weeks	70 centres in: Argentina, Australia, Belgium, Canada, Estonia, France, Germany, Hungary, Israel, Italy, Japan, Netherlands, Russia, Spain, Switzerland, United Kingdom, United States 10/2018–05/2021	Primary: sustained remission at Week 52 secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes comprise exclusively data on relevant available outcomes for this benefit assessment/based on the information provided by the company in Module 4 B.
b. PMR relapse was defined as pain in the shoulder and/or hip girdle associated with inflammatory stiffness.

ACR: American College of Rheumatology; AE: adverse event; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; N: number of randomized patients; PMR: polymyalgia rheumatica; RCT: randomized controlled trial

Table 7: Characteristics of the interventions – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone

Study	Intervention	Comparison
SAPHYR	Sarilumab 200 mg every 2 weeks, SC	Placebo, every 2 weeks, SC
	Dose adjustments, treatment interruptions a reduction of the dose to 150 mg every 2 weeks, SC, or an interruption for up to 30 consecutive days was possible in the event of neutropenia, thrombocytopenia or an increased liver values depending on the laboratory values.	
	Prednisone[a]	
	▪ Starting dose: 15 mg/day within the first 2 weeks ▪ from Week 3: gradual tapering to 1 mg/day by Week 13 ▪ prednisone placebo from Week 14 in patients without relapse ▪ for 1 PMR relapse up to Week 12, supplementation of the current prednisone dose with ≤ 5 mg/day of unblinded additional prednisone was permitted at the investigator's discretion	▪ Starting dose: 15 mg/day within the first 2 weeks ▪ from Week 3: gradual tapering to 1 mg/day by Week 52 ▪ for 1 PMR relapse up to Week 12, supplementation of the current prednisone dose with ≤ 5 mg/day of unblinded additional prednisone was permitted at the investigator's discretion
	Disallowed pretreatment: ▪ immunosuppressants including JAK inhibitors (4 weeks prior to randomization), abatacept (8 weeks prior to randomization), TNF inhibitors (depending on the drug, 2 to 8 weeks prior to randomization or after at least 5 half-lives have elapsed, whichever was longer), cyclosporin, azathioprine, mycophenolate mofetil or leflunomide (4 weeks prior to randomization), anakinra (1 week prior to randomization), alkylating agents (6 months prior to randomization) **allowed concomitant treatment** ▪ corticosteroids as rescue therapy[b] ▪ MTX ≤ 15 mg/week, if dose had been stable within the last 3 months before the start of the study; the dose also had to be kept stable for the duration of the study, with reduction and discontinuation being possible for safety reasons ▪ non-systemic corticosteroids in other indications (intranasal, inhaled, ophthalmic and topical application) ▪ NSAIDs **disallowed concomitant treatment[c]:** ▪ DMARDs except MTX (see above)	

a. The exact tapering schedules for prednisone in both study arms are shown in I Appendix B.
b. Discontinuation of tapering and use of a commercial corticosteroid as rescue therapy.
c. The study medication had to be discontinued in the event of PMR relapse and insufficient efficacy of additional prednisone and rescue therapy with the need to take disallowed medication.

DMARD: disease-modifying antirheumatic drug; JAK: Janus kinase; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; PMR: polymyalgia rheumatica; RCT: randomized controlled trial; SC: subcutaneous; TNF: tumour necrosis factor

Study design

The SAPHYR study is a randomized, double-blind, parallel, multicentre study for the comparison of sarilumab + prednisone with placebo + prednisone. The study had a total randomized treatment phase of 52 weeks.

The study included adult patients with a diagnosis of active PMR according to the classification criteria of the EULAR and the ACR [7]. In the study, an abnormal C-reactive protein (CRP) value or an abnormal erythrocyte sedimentation rate (ESR) were defined as a CRP value of at least 10 mg/L or an ESR of at least 30 mm/h within 12 weeks prior to screening. Before the start of the study, patients also had to have received treatment with at least 10 mg/day prednisone (or equivalent) for at least 8 weeks. In addition, they had to have experienced at least 1 PMR relapse within 12 weeks prior to screening while attempting to taper off a dose of at least 7.5 mg/day prednisone (or equivalent). In addition, patients had to have received treatment with at least 7.5 mg/day and a maximum of 20 mg/day prednisone (or equivalent) upon screening and during the screening phase. Patients with a diagnosis of giant cell arteritis, concurrent rheumatoid arthritis or other connective tissue diseases or active fibromyalgia were excluded from participation in the study. Patients with an unstable MTX dose or an MTX dose of more than 15 mg/week within 3 weeks prior to randomization were also excluded from participation in the study. The MTX dose had to remain stable throughout the study. Reduction and discontinuation were possible for safety reasons.

The study included a total of 118 patients who were randomly assigned in a 1:1 ratio to sarilumab + prednisone (N = 60) or placebo + prednisone (N = 58). Treatment with sarilumab in the intervention arm was largely in compliance with the specifications of the SPC [8].

Before the start of the study, corticosteroid therapy should be optimized in both arms in order to reduce the risk of SAEs when tapering the corticosteroids. As a starting dose for the first 2 weeks of treatment with prednisone, 15 mg/day prednisone was then used for all patients in both treatment arms. In both study arms, prednisone was then tapered according to fixed tapering schedules (see I Appendix B), with prednisone administration in the intervention arm being gradually reduced to 1 mg/day by Week 13, followed by prednisone placebo from Week 14, while in the control arm it was gradually tapered to 1 mg/day up to Week 52. At the investigator's discretion, treatment with a maximum of 5 mg/day of unblinded additional prednisone could be administered in both study arms in the event of one PMR relapse up to Week 12. In case of 1 PMR relapse during the regular prednisone tapering (up to Week 12) despite administration of additional prednisone of up to 5 mg/day, the tapering regimen had to be discontinued and the patient received a commercial rescue corticosteroid as decided by the investigator. In this case, blinded treatment with sarilumab or placebo should be continued, unless this was contraindicated due to safety concerns. If symptoms persisted

during treatment with rescue corticosteroids, other treatment options including csDMARDs could be used. In these cases, the study medication had to be discontinued.

Primary outcome of the study was sustained remission at Week 52, with secondary outcomes including morbidity, health-related quality of life and AEs.

Limitations of the SAPHYR study

Patients who have responded inadequately to corticosteroids were not included

Patients who did not respond adequately to corticosteroids were not included in the SAPHYR study.

Therapy with MTX only in stable doses

According to the now expired "S3 guideline for the treatment of PMR" from 2017, administration of MTX in addition to corticosteroid therapy should be considered at an early stage, especially in patients at high risk of relapse and/or of a long treatment duration, as well as in patients with risk factors, comorbidities and/or concomitant medications in whom corticosteroid-induced side effects are more likely to occur. Since, according to this guideline, there is no prototypical clinical situation in PMR that undoubtedly requires the use of MTX, this decision must be made on a very individualized or patient-specific basis [9]. The "S2e guideline for the treatment of PMR: Update 2024", only considers MTX as an alternative to interleukin 6 receptor blocking substances in patients with a recurrent course and in selected patients with new-onset disease and at high risk of corticosteroid-induced side effects [10].

The 2024 French guideline "Recommendations of the French Society of Rheumatology for the management in current practice of patients with polymyalgia rheumatica" points out that the data on the efficacy of MTX in patients with PMR relapse in general and with PMR relapse during corticosteroid taper in particular come exclusively from observational studies [11]. The efficacy of MTX in PMR is also called into question by the results of the PMR MODE study only published as an abstract to date, even if this does not relate to use for relapses [12,13].

Patients on MTX therapy were only included in the SAPHYR study if their MTX dose was at most 15 mg/week and this dose had been stable in the 3 months prior to the start of the study. Moreover, the MTX dose had to remain stable throughout the study. In this context, a reduction of the MTX dose and MTX discontinuation was possible for safety reasons. In case of PMR recurrence and insufficient effect of additional prednisone and, if necessary, rescue corticosteroids, treatment with csDMARDs (i.e. also with MTX) was permitted as rescue medication. In this case, the study treatment had to be discontinued and the patients concerned were classified as non-responders for the primary outcome. Concomitant treatment with MTX was therefore only possible to a limited extent in the study. Of the patients included, a maximum of 5 (8%) in the intervention arm and a maximum of 10 (17%)

in the control arm had received prior treatment with MTX. 12 (20%) and 17 (29%) of the patients received concomitant therapy with MTX (MTX add-on). However, it is unclear whether this only includes patients who were included in the study with a stable MTX dose or whether it also includes patients who received MTX as emergency therapy as part of the study. It is unclear what percentage of patients received rescue therapy with csDMARDs in general and MTX in particular; information is only available on the percentage of patients who received rescue corticosteroids, which was 32% and 59% respectively. The inclusion criteria (stable MTX dose for 3 months, relapse during the last 12 weeks prior to the start of the study) show that the concomitant MTX therapy used in about a quarter of the patients was not initiated to treat the relapse immediately preceding the inclusion in the study, but already existed before this relapse. In conclusion, the results of the SAPHYR study can only be used to make statements about patients for whom the physician considers corticosteroids to be the appropriate therapy for relapse treatment. The extent to which an additional administration of MTX or an increase of the MTX dose would have been indicated for the treatment of the relapse in the study population remains unclear. The remaining uncertainty has been taken into account in the assessment of the certainty of conclusions.

Treatment with prednisone not individualized

According to guidelines for the treatment of PMR, the dosage of corticosteroid therapy should be adjusted individually for each patient. The dosage of corticosteroid therapy should always be as high as necessary but as low as possible. The duration of corticosteroid therapy should also be adapted to the individual patient, whereby the duration of treatment should be as long as necessary but as short as possible [9,10]. In the SAPHYR study, however, corticosteroid therapy was given to all patients with a starting dose of 15 mg/day of prednisone. Although corticosteroid therapy should be optimized before the start of the study in order to reduce the risk of SAEs when tapering corticosteroids, no data are available on the extent to which this optimization took place before randomization. It can therefore not be ruled out that the starting dose of 15 mg/day prednisone was too high for individual patients. The use of additional prednisone (7 patients in the placebo arm and 4 patients in the sarilumab arm) also indicates that the starting dose of 15 mg/day prednisone was too low for some patients. In addition, prednisone was tapered in both study arms according to a fixed tapering schedule with a fixed treatment duration (see I Appendix B of the full dossier assessment). This does not comply with the recommendations of the guidelines. The resulting uncertainties regarding the transferability of the results to the German health care context are taken into account when assessing the reliability of the results (see Section I 4.2).

Characteristics of the study population

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone (multipage table)

Study characteristic category	Sarilumab + prednisone N = 60	Placebo + prednisone N = 58
SAPHYR		
Age [years], mean (SD)	69 (8)	69 (9)
Sex [F/M], %	75/25	64/36
Geographical region, n (%)		
Western countries	47 (78)	44 (76)
South America	5 (8)	4 (7)
Rest of the world	8 (13)	10 (17)
Morning stiffness, n (%)	47 (78)	45 (78)
Morning stiffness [min], MD [Q1; Q3]	60 [45; 120]	90 [60; 180]
Shoulder pain, n (%)	43 (72)	48 (83)
Restricted shoulder mobility, n (%)	34 (57)	37 (64)
Hip pain, n (%)	40 (67)	37 (64)
Restricted hip mobility, n (%)	24 (40)	21 (36)
Prednisone dose (or equivalent) during PMR relapse [mg], MD [Q1; Q3]	10.0 [7.5; 12.5]	10.0 [7.5; 10.0]
Number of previous PMR relapses per patient, MD [Q1; Q3]	2 (1; 3)	2 (1; 3)
Last prednisone dose (or equivalent) before baseline visit [mg/day], MD [Q1; Q3]	11.3 [9.5; 15.0]	10.0 [8.0; 15.0]
Duration of PMR from diagnosis to baseline [days], MD [Q1; Q3]	292 [160; 865]	310 [144; 883]
CRP at baseline [mg/L], MD [Q1; Q3]	6.8 [2.0; 15.1]	5.7 [2.2; 9.5]
ESR at baseline [mm/h], MD [Q1; Q3]	25.0 [12.5; 40.0]	22.0 [15.0; 35.0]
Prior bDMARDs, n (%)	1 (2)	1 (2)
Adalimumab	1 (2)	0 (0)
Tocilizumab	0 (0)	1 (2)
Previous non-biologic DMARDs, n (%)	6 (10)	11 (19)
Methotrexate	2 (3)	9 (16)
Methotrexate sodium	3 (5)	1 (2)
Leflunomide	2 (3)	1 (2)
Azathioprine	0 (0)	1 (2)
Hydroxychloroquine	0 (0)	1 (2)
Hydroxychloroquine sulphate	1 (2)	0 (0)
Concomitant methotrexate, n (%)	12 (20)[a]	17 (29)
Treatment discontinuation, n (%)[b]	17 (28)	22 (38)
Study discontinuation, n (%)[c]	15 (25)	15 (26)

Table 8: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone (multipage table)

Study characteristic category	Sarilumab + prednisone N = 60	Placebo + prednisone N = 58

a. Institute's calculation.
b. Common reasons for treatment discontinuation in the intervention arm versus the control arm were the following (percentages based on randomized patients): AE (12% versus 7%), lack of efficacy (7% versus 16%), and patient decision (5% versus 7%). In addition, 1 randomized patient in the sarilumab arm did not start treatment.
c. The most common reason for study discontinuation in the intervention vs. the control arm was the following (percentages refer to randomized patients): AE (10% versus 2%). For 15% vs. 24%, the reason for study discontinuation is not known.

AE: adverse event; bDMARD: biologic DMARD; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; f: female; m: male; MD: median; n: number of patients in the category; N: number of randomized patients; PMR: polymyalgia rheumatica; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the patients are largely balanced between both treatment arms of the SAPHYR study. The mean age of the patients was 69 years; the majority of them were female and were predominantly included in the study in the Western countries. The majority of patients in both arms had morning stiffness, with the median duration of morning stiffness at the start of the study being clearly shorter in the intervention arm than in the comparator arm. In both arms, the median number of previous PMR relapses per patient was 2. The median duration of PMR diagnosis at the start of the study was 292 days in the intervention arm and 310 days in the control arm. A maximum of 5 (8%) patients in the intervention arm and a maximum of 10 patients (17%) in the control arm had received prior treatment with MTX.

Treatment was discontinued less frequently in the intervention arm than in the control arm (28% vs. 38%). AEs presented the most common reason for treatment discontinuation in the intervention arm, while the most common reason for treatment discontinuation in the control arm was lack of efficacy. About 25% of the patients discontinued the study.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
SAPHYR	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the SAPHYR study.

Transferability of the study results to the German health care context

The company states that a total of 77.1% of patients in the SAPHYR study were recruited and treated in Western countries, that the median age of the total population at the start of the study was 69.5 years and that 69.5% of patients were women. Here, the company sees agreement with the German/Austrian/Swiss S3 guideline on the treatment of PMR, which states that the onset of the disease occurs almost exclusively in people over the age of 50, with a ratio of affected women to men of 3:1 [9]. It also points out that the administration of sarilumab in the SAPHYR study was carried out in accordance with the marketing authorization [8]. It could therefore be assumed that the study population reflects the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Section I 4.2.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - remission
  - duration of morning stiffness, measured as part of the PMR activity score (PMR-AS)
  - mobility of the upper limbs, recorded as part of the PMR-AS
  - pain, recorded using a visual analogue scale (VAS) of the Health Assessment Questionnaire - Disability Index (HAQ-DI)
  - physical functioning, recorded using the HAQ-DI
  - patient global assessment of disease activity, record3ed using a HAQ-DI VAS
  - fatigue, recorded using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
  - health status recorded with the EQ-5D VAS
- Health-related quality of life
  - recorded with the SF-36v2
- Side effects
  - serious AEs (SAEs)
  - discontinuation due to AEs
  - infections (SOC, AE)
  - serious infections (SOC, SAEs)
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 B).

Table 10 shows for which outcomes data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone

Study	Outcomes														
	All-cause mortality[a]	Remission	Duration of morning stiffness[b]	Mobility of the upper limbs[c]	Pain (VAS)[d]	Physical functioning status[e]	Patient-reported global assessment of the disease activity[f] (VAS)	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Infections (SOC, AE)	Serious infections (SOC, SAE)	Other specific AEs
SAPHYR	Yes	No[g]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[h]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. The duration of morning stiffness was recorded as part of the PMR-AS.
c. Mobility of the upper limbs was recorded as part of the PMR-AS.
d. Pain was recorded using the VAS of the HAQ-DI.
e. Physical functioning was recorded as part of the HAQ-DI.
f. The patient-reported global assessment of disease activity was recorded as part of the HAQ-DI.
g. No suitable data available; for reasoning, see Section I 4.1 of this dossier assessment.
h. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; PMR: polymyalgia rheumatica; PMR-AS: PMR activity score; RCT: randomized controlled trial; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Primary study outcome: sustained remission at Week 52

The company presented analyses on the composite outcome sustained remission at Week 52 and on its individual components as separate outcomes. Here, the sustained remission at Week 52 comprises the following individual components:

- Remission (resolution of signs and symptoms of PMR and CRP normalization) by Week 12 at the latest
- No relapse (recurrence of signs and symptoms or increase in ESR, associated with active PMR requiring an increase of the corticosteroid dose) from Weeks 12 to 52
- Sustained CRP reduction from Weeks 12 to 52
- Successful prednisone tapering from Weeks 12 to 52 (no need for rescue medication)

A relapse was defined as recurrence of signs and symptoms or as ESR increase, associated with active PMR requiring an increase of the corticosteroid dose). An increase in the corticosteroid dose was any dose increase during protocol-compliant prednisone tapering or renewed corticosteroid administration after completion of protocol-compliant tapering. The use of a fixed tapering scheme for corticosteroid therapy does not comply with the recommendations of the guidelines, according to which corticosteroid tapering should be individualized for each patient. Adherence to a fixed tapering schedule is not patient-relevant and is therefore not used for this assessment. An increase in ESR is not patient-relevant, therefore the component no relapse from Weeks 12 to 52, which includes the ESR increase and the increase of the corticosteroid dose, is not patient-relevant.

Successful prednisone tapering meant no need for rescue medication. The use of additional prednisone with a maximum cumulative dose of 100 mg (or equivalent), i.e. in excess of the intended dose in the tapering phase, for example for the treatment of AEs not related to PMR, was possible. As different standardized tapering schemes (see Table 17 in I Appendix B) were predefined for each arm, the analyses presented for this individual component of the composite outcome cannot be interpreted and are not suitable for the benefit assessment.

The composite outcome includes laboratory parameters and dose adjustments that are not necessarily associated with noticeable symptoms for the patient. The composite outcome and all individual components were therefore disregarded in the benefit assessment.

In summary, a suitable operationalization for the recording of the outcome remission was not predefined in the SAPHYR study. A suitable analysis on remission should record the symptoms independently of laboratory parameters and could also take into account a steroid threshold value (see e.g. A24-113 [14]), whereby the level of the selected steroid threshold was to be justified. If a steroid threshold value is anchored in the remission outcome, it should generally be possible for almost all patients to fall below this threshold value from the selected time point onwards, based on the specified dose reduction regimens. Steroid reduction (below a relevant threshold value) should exist for a relevant period of time and not just at a single point in time.

Time to first PMR relapse after clinical remission

The company presents the outcome time to first PMR relapse after clinical remission. A relapse is defined here as described above for the individual component no relapse. For the reasons described above, the outcome is not used for the benefit assessment.

Changes of PMR-AS at Week 52

The company presents the PMR-AS and its individual components as outcomes. The PMR-AS records the following individual components:

- pain assessment by the patient
- disease assessment by the investigator
- the CRP value
- duration of morning stiffness
- mobility of the upper limbs

The PMR-AS sum score is not relevant to the patient, as the CRP value is a laboratory parameter without noticeable symptoms. The individual components duration of morning stiffness and mobility of the upper limbs are used (see the following sections). In this benefit assessment, the pain assessment by the patient is used as a single component of the HAQ-DI, as the pain assessment was recorded within the framework of the PMR-AS using the HAQ-DI VAS. The individual component disease assessment by the investigator is not used, as the patient-reported global assessment of disease activity via the HAQ-DI VAS already reflects the patient-relevant disease assessment.

Duration of morning stiffness

The company presented analyses on the duration of morning stiffness as individual component of the PMR-AS. For the analyses presented, however, it remains unclear whether the duration of morning stiffness records a patient-reported morning stiffness for the day of the survey or a patient-reported average morning stiffness over a period prior to the survey. The duration of morning stiffness is a patient-relevant outcome; the analyses are used for this assessment.

Change in mobility of the upper limbs at Week 52

The company presented analyses of the mobility of the upper limbs as an individual component of the PMR-AS recorded on a 4-level scale (3 = no mobility of the upper limbs, 2 = mobility of the upper limbs up to below the shoulder girdle, 1 = mobility of the upper limbs up to the shoulder girdle, 0 = mobility of the upper limbs up to above the shoulder girdle). The mobility of the upper limbs is patient-relevant; the analyses are used for this assessment.

Consideration of the improvement in the responder analyses in the categories morbidity and health-related quality of life

In the dossier, the company presented responder analyses on the improvement of symptoms for outcomes in the categories morbidity and health-related quality of life; these were not predefined. The response criteria used in the analyses presented by the company fulfil the requirements for response criteria of reflecting with sufficient certainty a change that is perceivable for patients, as described in the *General Methods* of the Institute [1]. Since the patients included in the SAPHYR study were symptomatic (active PMR) at baseline and additional treatment with sarilumab could therefore in principle improve symptoms, the

analyses on improvement are considered for the responder analyses in the categories morbidity and health-related quality of life.

Imputation of missing values in responder analyses

The patient-reported outcomes were analysed using responder analyses at Week 52. Due to high proportions of missing values (approx. 30% in the experimental intervention arm vs. approx. 40% in the control arm), it is necessary to impute missing values. For this purpose, the company presented analyses with a non-responder imputation (NRI). For patients with a missing value at Week 52, the assumption is made that they have no response - regardless of how they were doing at the previous examination time points. There is only limited information available on the reasons for the lack of values at Week 52. The extent to which the chosen imputation of missing values is appropriate for this analysis remains unclear. This is considered in the assessment of the risk of bias (see Section I 4.2).

Moreover, the company on the one hand stated that it used logistic regression from the SAS procedure GLIMMIX, which would result in an odds ratio (OR); on the other hand, its own results were consistent with those of the company when the sample calculation was performed via the SAS procedure GLIMMIX using a logarithm as a link function, which results in a relative risk (RR). This sample calculation shows that the additional uncertainty in the data caused by the imputation of missing values in the estimation of the variance was not taken into account by a correction. Since such a variance correction is expected to result in wider CIs, this has no consequences for the benefit assessment against the background of the data specifically available (no statistically significant differences despite the lack of correction).

Analyses with a mixed-effects model repeated measures (MMRM) and the relevance assessment of the related results

In the present benefit assessment, the MD presented by the company, which was determined by means of an MMRM is used for the assessment of morning stiffness and mobility of the upper limbs. The estimated effect represents the difference in changes (compared to baseline) between the treatment groups at Week 52. In the MMRM standard model, all persons can be considered with a baseline and a post-baseline value. This means that all patients who have both a baseline value and a value at another time point - Week 12, Week 24 or Week 52 - can and should be included in the parameter estimation step before the effect estimate at Week 52. However, the company only included randomized patients in the analysis for whom a survey was available both at baseline and at Week 52. The proportion of patients included in the analysis is nevertheless sufficient, so that the company's analyses were used for the benefit assessment.

At the start of the study, the medians and mean values of the patient characteristic morning stiffness, as well as the observed standard deviations of the two arms, differed significantly.

The extent to which the present effect estimate was influenced by this is unclear. The company should remove implausible values for sensitivity analyses, such as a 24-hour morning stiffness. For this purpose, an accurate descriptive presentation of the baseline values on the duration of morning stiffness (e.g. histogram in addition to the summarizing parameters) should be presented before and after removing implausible values. The uncertainties with regard to the present analysis are taken into account in the assessment of the certainty of conclusions (see Section I 4.2).

There is a statistically significant MD for the mobility of the upper limbs. An SMD is used to assess the clinical relevance. The company presented calculations for this, which it referred to as “Hedges’ g”. The company did not sufficiently describe how the calculation was performed; in particular, it did not explain how the estimate of the standard deviation pooled across the treatment groups, which is included in the original Hedges' g, is replaced. Thus, the results were checked through the Institute's calculation. For this purpose, an SMD was determined using the MD estimated from the MMRM analysis, the corresponding 95% CI as well as the number of patients included in the analysis. There was broad agreement with the company's calculations; in particular, there was no difference in the assessment of clinical relevance, and the company's calculations are presented in this assessment and labelled as SMD.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone

Study		Outcomes														
	Study level	All-cause mortality[a]	Remission	Duration of morning stiffness[b]	Mobility of the upper limbs[c]	Pain (VAS)[d]	Physical functioning status[e]	Patient-reported global assessment of the disease activity[f] (VAS)	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Infections (SOC, AEs)	Serious infections (SOC, SAEs)	Other specific AEs
SAPHYR	L	L	–	H[g]	H[g]	H[h]	H[h]	H[h]	H[h]	H[h]	H[h]	H[h]	L	H[h]	H[h]	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b. The duration of morning stiffness was recorded as part of the PMR-AS.
c. Mobility of the upper limbs was recorded as part of the PMR-AS.
d. Pain was recorded using the VAS of the HAQ-DI.
e. Physical functioning was recorded as part of the HAQ-DI.
f. The patient-reported global assessment of disease activity was recorded as part of the HAQ-DI.
g. High proportion of patients excluded from the analysis (> 10%).
h. Shortened observation period for potentially informative reasons.

AE: adverse event; FACIT: Functional Assessment of Chronic Illness Therapy; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; L: low; PMR: polymyalgia rheumatica; PMR-AS: PMR activity score; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results on the outcome overall survival was rated as low.

The effect estimates based on AE surveys - with the exception of all-cause mortality and discontinuation due to AEs - have a high risk of bias, as the consideration of AEs was linked to treatment discontinuation (+ 60 days) and the reasons given for treatment discontinuations are potentially informative.

The fact that 20% of patients are missing in the analysis leads to a high risk of bias in the effect estimates on duration of morning stiffness and mobility of the upper limbs.

For the other effect estimates on symptoms and the effect estimates on health-related quality of life, there is also a high risk of bias: According to the protocol, a survey should take place on Day 1, Week 12, Week 24 and Week 52, regardless of the premature end of treatment.

However, the responses rates decrease sharply over the course of the study, so that when calculating the RR at Week 52, around 35% of patients have missing values, which are imputed by non-response.

Although the risk of bias for the effect estimate on discontinuation due to AEs is low, the certainty of results for this effect estimate is limited. Premature treatment discontinuation for reasons other than AEs represents a competing event for the discontinuations due to AEs to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion “discontinuation” can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Summary assessment of the certainty of conclusions

Apart from the aspects described above regarding the risk of bias at outcome level, the following uncertainties affecting the certainty of the results of the SAPHYR study exist, as described in Section I 3.2:

- Uncertainty as to whether additional administration of MTX or an increase in the MTX dose would have been indicated for the study population
- Uncertainty due to the lack of individualized corticosteroid tapering schemes as required by the guidelines

Taking into account all mentioned uncertainties in the results of the SAPHYR study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

I 4.3 Results

Table 12 and Table 13 summarize the results on the comparison of sarilumab + prednisone with placebo + prednisone in patients with PMR. Where necessary, IQWiG calculations are provided to supplement the data from the company’s dossier.

Table 12: Results (mortality, morbidity; health-related quality of life, side effects, dichotomous) – RCT, direct comparison: sarilumab + prednisone with placebo + prednisone (multipage table)

Study outcome category outcome time point	Sarilumab + prednisone		Placebo + prednisone		Sarilumab + prednisone vs. placebo + prednisone
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
SAPHYR					
Mortality					
All-cause mortality[b]	60	0 (0)	58	0 (0)	–
Morbidity					
Remission	No suitable data[c]				
Pain (HAQ-DI VAS – improvement[d])	60	20 (33)	58	20 (34)	0.97 [0.58; 1.61] 0.896
Physical functioning status (HAQ-DI - improvement [e])	60	19 (32)	58	10 (17)	1.84 [0.93; 3.63]; 0.081
Patient-reported global assessment of disease activity (HAQ-DI VAS - improvement[f])	60	21 (35)	58	14 (24)	1.45 [0.81; 2.58]; 0.208
Fatigue (FACIT-Fatigue – improvement[g])	60	24 (40)	58	17 (29)	1.36 [0.82; 2.28]; 0.233
Health status (EQ-5D VAS – improvement[h])	60	16 (27)	58	9 (16)	1.72 [0.82; 3.60]; 0.152
Health-related quality of life					
SF-36v2					
Physical component summary (improvment[i])	60	14 (23)	58	10 (17)	1.35 [0.65; 2.82]; 0.419
Mental component summary (improvement[i])	60	11 (18)	58	5 (9)	2.13 [0.78; 5.80]; 0.141
Side effects					
AEs (supplementary information)	59	56 (95)	58	49 (84)	–
SAEs	59	8 (14)	58	12 (21)	0.66 [0.29; 1.50]; 0.316
Discontinuation due to AEs	59	7 (12)	58	4 (7)	1.72 [0.53; 5.63]; 0.370
Infections (SOC, AEs)	59	22 (37)	58	29 (50)	0.75 [0.49; 1.14]; 0.173
Serious infections (SOC, SAEs)	59	3 (5)	58	3 (5)	0.98 [0.20; 4.75]; 0.983

Table 12: Results (mortality, morbidity; health-related quality of life, side effects, dichotomous) – RCT, direct comparison: sarilumab + prednisone with placebo + prednisone (multipage table)

Study outcome category outcome time point	Sarilumab + prednisone		Placebo + prednisone		Sarilumab + prednisone vs. placebo + prednisone
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]

a. RR, CI and p-value: On the one hand, the company stated that it used logistic regression from the SAS procedure GLIMMIX, which would result in an odds ratio (OR); on the other hand, its own results were consistent with those of the company when the sample calculation was performed via the SAS procedure GLIMMIX using a logarithm as a link function, which results in a relative risk (RR) (see Section I 4.1). In responder analyses for patient-reported outcomes, non-responder imputation presumably was done for 18 vs. 23 patients. They were therefore categorized as non-responders in the absence of a value at Week 52 or at baseline.
b. The results on all-cause mortality are based on the data on fatal AEs.
c. No suitable data available; for justification see Section I 4.1 of this dossier assessment.
d. A score decrease by ≥ 1.5 points from baseline to Week 52 is considered a clinically relevant improvement (scale range: 0 to 10).
e. A score decrease by ≥ 0.45 points from baseline to Week 52 is considered a clinically relevant improvement (scale range: 0 to 3).
f. A score decrease by ≥ 15 points from baseline to Week 52 is considered a clinically relevant improvement (scale range: 0 to 100).
g. A score increase by ≥ 7.8 points from baseline to Week 52 is considered a clinically relevant improvement (scale range: 0 to 52).
h. A score increase by ≥ 15 points from baseline to Week 52 is considered a clinically relevant improvement (scale range: 0 to 100).
i. A score increase by ≥ 10 points from baseline to Week 52 is considered a clinically relevant improvement (scale range: 0 to 100).

AE: adverse event; CI: confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; n: number of patients with (at least 1) event; N: number of analysed patients; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; VAS: visual analogue scale

Table 13: Results (morbidity, continuous) – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone

Study outcome category outcome	Sarilumab + prednisone			Placebo + prednisone			Sarilumab + prednisone vs. placebo + prednisone
	N	values at baseline mean (SD)	mean change at Week 52 mean[a] (SE)	N	values at baseline mean (SD)	mean change at Week 52 mean[a] (SE)	MD [95% CI]; p-value[a]
SAPHYR							
Morbidity							
Duration of morning stiffness[b] [min]	48	66.35 (64.86)	-75.61 (5.87)	46	106.30 (216.84)	-53.18 (5.98)	-22.43 [-39.09; -5.77]; 0.009
Mobility of the upper limbs[c]	48	0.52 (0.80)	-0.47 (0.06)	46	0.46 (0.62)	-0.23 (0.06)	-0.24 [0.40; 0.08]; 0.004 SMD: -0.60 [-1.00; -0.19]

a. MW and SE (per treatment group) as well as MD, CI and p-value (between-group comparison): MMRM with change from baseline as dependent variable and baseline value, treatment group, visit and interactions between baseline value and visit as well as between treatment and visit as covariables. Effect represents the difference in changes (compared to baseline) between the treatment groups at Week 52.
b. The duration of morning stiffness was recorded as part of the PMR-AS.
c. Mobility of the upper limbs was recorded as part of the PMR-AS. Lower values mean better symptoms; negative effects mean an advantage for the intervention (scale range: 0 to 3).

CI: confidence interval; MMRM: mixed-effects model with repeated measures; N: number of analysed patients with values at baseline and at Week 52; PMR: polymyalgia rheumatica; PMR-AS: PMR activity score; RCT: randomized controlled trial; SD: standard deviation; SDM: standardized mean difference; SE: standard error

On the basis of the available information, at most hints, e.g. of an added benefit, can be given for all outcomes; the reasons for this are presented in Section I 4.2 and in the Section Limitations of the SAPHYR study (page I.20).

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome all-cause mortality. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome all-cause mortality; an added benefit is therefore not proven.

Morbidity

Remission

No suitable data are available for the outcome remission. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for this outcome; an added benefit is therefore not proven.

Duration of morning stiffness

For the outcome duration of morning stiffness, a statistically significant difference between the treatment arms with regard to the change in the duration of morning stiffness in minutes was shown when considering the mean differences over the duration of the study. However, the lower limit of the 95% CI is only 5.77 minutes, which appears too low for baseline values of over one hour to rate the observed effect as clinically relevant. Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome duration of morning stiffness; an added benefit is therefore not proven.

Mobility of the upper limbs

For the outcome mobility of upper limbs, a statistically significant difference between the treatment arms was shown when considering the mean differences over the duration of the study. The SMD was considered to check the relevance of the result. The 95% CI of SMD was not completely below the irrelevance threshold of -0.2. It can therefore not be inferred that the effect is relevant; an added benefit is therefore not proven.

Pain

No statistically significant difference between treatment arms was shown for the outcome pain (improvement in the HAQ-DI VAS for pain recording by ≥ 1.5 points). Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome pain; an added benefit is therefore not proven.

Physical functioning

No statistically significant difference between the treatment arms was shown for the outcome physical functioning (improvement in HAQ-DI by ≥ 0.45 points). Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome physical functioning; an added benefit is therefore not proven.

Patient assessment of disease activity

No statistically significant difference between treatment arms was shown for the outcome patient-reported global assessment of the disease activity (improvement in the HQ-DI VAS for the assessment of the disease activity by ≥ 15 points). Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome patient assessment of disease activity; an added benefit is therefore not proven.

Fatigue

No statistically significant difference between the treatment arms was shown for the outcome fatigue (improvement in FACIT-Fatigue by ≥ 7.8 points). Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome fatigue; an added benefit is therefore not proven.

Health status

No statistically significant difference between the treatment arms was shown for the outcome health status (improvement in EQ-5D VAS by ≥ 15 points). Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome health status; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded using the PCS and the MCS of the SF-36v2. There were no statistically significant differences between the treatment arms for either summary score (each recording an improvement by ≥ 10 points). Consequently, there is no hint of added benefit of sarilumab in comparison with corticosteroids for the outcome health-related quality of life; an added benefit is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome SAEs. For the outcome SAEs, there was therefore no hint of greater or lesser harm from sarilumab in comparison with corticosteroids; therefore, there is no proof of greater or lesser harm.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome discontinuation due to AEs. For the outcome discontinuations due to AEs, there was therefore no hint of greater or lesser harm from sarilumab in comparison with corticosteroids; therefore, greater or lesser harm is not proven.

Infections (SOC, AE)

No statistically significant difference between treatment arms was shown for the outcome infections. For the outcome infections, there was therefore no hint of greater or lesser harm from sarilumab in comparison with corticosteroids; therefore, greater or lesser harm is not proven.

Serious infections (SOC, SAEs)

No statistically significant difference between the treatment arms was shown for the outcome serious infections. For the outcome serious infections, there was therefore no hint of greater or lesser harm from sarilumab in comparison with corticosteroids; therefore, greater or lesser harm is not proven.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for this benefit assessment:

- Age (< 70 years versus ≥ 70 years)
- Sex (male versus female)
- Number of relapses before screening (1 relapse vs. > 1 relapse)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

There was 1 statistically significant interaction for the characteristic number of relapses before screening in the outcome physical functioning and 1 statistically significant interaction for the characteristic age in the outcome fatigue.

The data in the subgroups are not considered suitable for an effect estimate; this is explained below. However, the problems discussed in Section I 4.2 due to the many values imputed by NRI is reinforced in the subgroup analyses. Especially for the subgroup characteristics age and number of relapses before screening, the proportion of total replaced values increases even further in at least one subgroup compared to the analysis of the total population, or the difference in imputed values between the arms is even more pronounced. Isolated statistically significant interaction tests for these characteristics are therefore not considered robust and the results are not used for the benefit assessment.

In addition to the potential effect modifiers mentioned above, the G-BA pointed out that subgroup analyses with the subgroup characteristic MTX add-on therapy (yes/no) would be helpful. There were no effect modifications with statistically significant interaction between treatment and the subgroup characteristic MTX add-on therapy, whereby, as explained above under Limitations of the study (section on the therapy with MTX only at stable doses, page I.20), it is unclear whether MTX add-on represents a pure baseline characteristic.

It should be noted that the company did not use the above-mentioned criteria with regard to AEs and treatment discontinuation due to AEs for the decision as to whether interaction tests are calculated. It is unclear whether the above criteria would require a calculation.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is assessed based on the results presented in Chapter I 4 (see Table 14).

Table 14: Extent of added benefit at outcome level: sarilumab (+ corticosteroids) in comparison with corticosteroids (multipage table)

Outcome category **outcome**	**Sarilumab + prednisone vs. placebo + prednisone** **proportion of events (%) or mean change** **effect estimation [95% CI];** **p-value** **probability** [a]	**Derivation of extent** [b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser/added benefit not proven
Morbidity		
Remission	No suitable data	Lesser/added benefit not proven
Duration of morning stiffness [min]	Mean: −75.61 vs. −53.18 MD: −22.43 [−39.09; -5.77] p = 0.009	Lesser/added benefit not proven [c]
Mobility of the upper limbs	mean: -0.47 vs. -0.23 MD: 0.24 [-0.40; -0.08]; p = 0.004 SMD: -0.60 [-1.00; -0.19] [d]	Lesser/added benefit not proven
Pain (HAQ-DI VAS – improvement)	33% vs. 34% RR: 0.97 [0.58; 1.61]; p = 0.896	Lesser/added benefit not proven
Physical functioning (HAQ-DI - improvement)	32% vs. 17% RR: 1.84 [0.93; 3.63]; p = 0.081	Lesser/added benefit not proven
Patient-reported global assessment of disease activity (HAQ-DI VAS - improvement at Week 52 ≥ 15)	35% vs. 24% RR: 1.45 [0.81; 2.58]; p = 0.208	Lesser/added benefit not proven

Table 14: Extent of added benefit at outcome level: sarilumab (+ corticosteroids) in comparison with corticosteroids (multipage table)

Outcome category **outcome**	**Sarilumab + prednisone vs. placebo + prednisone** **proportion of events (%) or mean change** **effect estimation [95% CI];** **p-value** **probability** [a]	**Derivation of extent** [b]
Fatigue (FACIT-Fatigue – improvement)	40% vs. 29% RR: 1.36 [0.82; 2.28]; p = 0.233	Lesser/added benefit not proven
Health status (EQ-5D VAS, improvement)	27% vs. 16% RR: 1.72 [0.82; 3.60]; p = 0.152	Lesser/added benefit not proven
Health-related quality of life		
SF-36v2		
Physical component summary (improvement)	23% vs. 17% RR: 1.35 [0.65; 2.82]; p = 0.419	Lesser/added benefit not proven
Mental component summary (improvement)	18% vs. 9% RR: 2.13 [0.78; 5.80]; p = 0.141	Lesser/added benefit not proven
Side effects		
SAEs	14% vs. 21% RR: 0.66 [0.29; 1.50]; p = 0.316	Greater/lesser harm not proven
Discontinuation due to AEs	12% vs. 7% RR: 1.72 [0.53; 5.63]; p = 0.370	Greater/lesser harm not proven
Infections (SOC, AE)	37% vs. 50% RR: 0.75 [0.49; 1.14]; p = 0.173	Greater/lesser harm not proven
Serious infections (SOC, SAEs)	5% vs. 5% RR: 0.98 [0.20; 4.75]; p = 0.983	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_l).
c. See Section I 4.3 of the present dossier assessment for the reasoning.
d. If the CI for the SMD is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.

AE: adverse event; CI: confidence interval; CI_l: lower limit of confidence interval; CI_u: upper limit of confidence interval; MD: mean difference; RR: relative risk; SMD: standardized mean difference; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account for the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of sarilumab (+ corticosteroids) in comparison with corticosteroids

Positive effects	**Negative effects**
–	–
No suitable data are available for the outcome remission.	

Based on the SAPHYR study, there are neither positive nor negative effects from the assessment of sarilumab in comparison with corticosteroids. The study provides suitable data for the benefit assessment on patients for whom the physician considers corticosteroids to be the appropriate therapy for relapse treatment.

For patients for whom the physician considers the combination of corticosteroids with MTX to be the appropriate therapy for relapse treatment, there are no suitable data for the assessment.

Patients who have had an inadequate response to corticosteroids were not investigated in the SAPHYR study.

In summary, there is no hint of added benefit of sarilumab over the ACT for patients with PMR who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper.

The result of the assessment of the added benefit of sarilumab in comparison with the ACT is summarized in Table 16.

Table 16: Sarilumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with PMR who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper	Treatment of physician's choice, taking into account systemic corticosteroids and the combination of corticosteroids with methotrexate[b]	Patients for whom corticosteroids are the appropriate treatment of physician's choice[c]: added benefit not proven
		Patients for whom the combination of corticosteroids with methotrexate is the appropriate treatment of physician's choice added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:
- A single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
- If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
- A subgroup analysis according to MTX add-on therapy (yes/no) is considered helpful for the early benefit assessment and should be submitted with the dossier.

c. The SAPHYR study only included patients who had experienced a relapse during corticosteroid taper. It remains unclear whether the observed effects can be extrapolated to patients who have had an inadequate response to corticosteroids.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PMR: polymyalgia rheumatica

The assessment described above deviates from that of the company, which derived an indication of a considerable added benefit for adult patients with PMR who have responded inadequately to corticosteroids or who experienced a relapse during the tapering off of corticosteroids.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under
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