Sarilumab (Polymyalgia rheumatica)

Addendum to Project A25-18 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

Project: A25-83 Version: 1.0 Status: 10 Jul 2025 DOI: 10.60584/A25-83_en

[1] Translation of the addendum *Sarilumab (Polymyalgia rheumatica) – Addendum zum Projekt A25-18 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Sarilumab (Polymyalgia rheumatica) – Addendum to Project A25-18

Commissioning agency

Federal Joint Committee

Commission awarded on

24 June 2025

Internal Project No.

A25-83

https://doi.org/10.60584/A25-83_en

Address of publisher

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

Recommended citation

Institute for Quality and Efficiency in Health Care. Sarilumab (Polymyalgia rheumatica); Addendum to Project A25-18 (dossier assessment) [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-83_en.

Keywords

Sarilumab, Polymyalgia Rheumatica, Benefit Assessment, NCT03600818

IQWiG employees involved in the addendum

- Christof Dücker
- Michaela Florina Kerekes
- Daniela Preukschat
- Anke Schulz
- Claudia Selbach

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MTX	methotrexate
PMR	polymyalgia rheumatica
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 24 June 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-18 (Sarilumab – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of remission data from the SAPHYR study [2-5]. For the assessment, the data presented by the pharmaceutical company (hereinafter referred to as "the company") in the dossier [6] and in the commenting procedure [7] were considered.

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The randomized controlled trial (RCT) SAPHYR was used to assess the added benefit of sarilumab in comparison with systemic corticosteroids and the combination of corticosteroids with methotrexate (MTX) as appropriate comparator therapy (ACT) in patients with polymyalgia rheumatica (PMR) who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper. A detailed description of the study can be found in dossier assessment A25-18 [1]. As commissioned, this addendum comprises the assessment of the following analyses:

- Sustained remission at Week 52
- Sustained remission at Week 52 without C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
- Time to first PMR relapse after clinical remission

2.1 Analysis "Sustained remission at Week 52" and "Sustained remission at Week 52 without CRP and ESR" presented by the company

For the benefit assessment, the company presented the primary outcome of the SAPHYR study "sustained remission at Week 52" in Module 4B. According to this operationalization, patients were only considered to be responders if all 4 outcome components had been fulfilled (AND operation). The 4 individual components and other relevant information are shown in detail in Table 1.

As part of the comments, the company presented a sensitivity analysis on "Sustained remission at Week 52 without CRP and ESR", in which the laboratory values marked *in italics* in Table 1 were not decisive for the achievement of a remission. Patients were therefore responders in this analysis if all 3 detailed components (without *italicised* criteria) had been fulfilled

Table 1: Individual components of the outcomes “Sustained remission at Week 52" and "Sustained remission at Week 52 without CRP and ESR"

Outcome component	**Details**
Remission by Week 12 at the latest, defined as: resolution of the signs and symptoms of the PMR[a] *and CRP normalization* [b]	Patients who received rescue medication up to Week 12 were categorized as non-responders in the component. Up to Week 12, in case of signs and symptoms of PMR, treatment with a maximum of 5 mg/day of unblinded additional prednisone could be given once at the investigator's discretion (applies to n = 4 in the sarilumab arm and n = 7 in the comparator arm). Any corticosteroid treatment beyond this was considered rescue medication. By Week 12, 6 patients in the sarilumab arm and 12 patients in the comparator arm had received such rescue medication.
No relapse from Weeks 12 to 52, where relapse is defined as: recurrence of signs and symptoms that required an increase in the corticosteroid dose (prednisone) *or* *increase in ESR[c] associated with active PMR requiring an increase in corticosteroid dose)*	Patients with relapse were those for whom the "rescue therapy" field was selected on the "Steroid Medication" page in the eCRF and for whom "Active PMR" or "Elevated ESR Attributable to Active PMR" was selected under "If Rescue Therapy, please specify". by considering ESR values, active PMR was potentially more likely to be detected in the comparator arm than in the sarilumab arm, which may lead to an overestimation of the effect in favour of sarilumab. any PMR-related dose increase between Weeks 12 and 52 (= rescue medication) during protocol-compliant prednisone tapering resulted in a non-responder rating.
Sustained CRP reduction from Weeks 12 to 52[d]	
Successful prednisone tapering from Weeks 12 to 52 (no need for rescue medication)[e]	Patients with PMR-related dose increase between Weeks 12 and 52 (= rescue medication) were unable to achieve a response in the component. These were 13 in the sarilumab arm and 22 in the comparator arm. patients requiring rescue medication as decided by the investigator should receive corticosteroids as first-line rescue medication. If symptoms persist despite treatment with rescue corticosteroids, non-biological immunosuppressive drugs should be used as rescue medication.
Outcome criteria that are not included in the sensitivity analysis without laboratory values (ESR and CRP) are shown in *italics*	
a. Assessment of signs and symptoms of PMR includes, but is not limited to: morning stiffness and/or pain in the neck, shoulder and/or pelvic girdle; limited range of motion in the shoulders and/or pelvic girdle; constitutional symptoms such as fatigue, weight loss and mild fever; other abnormalities that, in the investigator's opinion, indicate a PMR relapse. b. CRP normalization to values below 10 mg/L, without subsequent increases to at least 10 mg/L. A single CRP increase (≥ 10 mg/L) was not considered a failure to achieve remission unless the CRP value remained elevated (≥ 10 mg/L) for 2 subsequent study visits. c. There is no information available on how an increase in ESR was defined. d. Sustained CRP reduction was defined as normalization of CRP to < 10 mg/L without successive increases to ≥ 10 mg/L. e. The administration of additional prednisone, for example for the treatment of AEs that were not associated with PMR, was permitted in a maximum cumulative dose of 100 mg. AE: adverse event; CRP: C-reactive protein; eCRF: electronic case report form; ESR: erythrocyte sedimentation rate; PMR: polymyalgia rheumatica	

The reasons for the unsuitability of both outcome definitions are described in detail below, with particular reference to the sensitivity analysis subsequently submitted with the comments. Since the assessment of the outcome is closely related to the tapering scheme applied in the study, the information on this aspect subsequently submitted by the company in the comments is first categorized.

Lack of individuality of the tapering scheme in the comparator arm

In the SAPHYR study, prednisone tapering followed a rigid tapering schedule in both study arms with a fixed treatment duration (see dossier assessment A25-18 Appendix B). As already described in A25-18, this does not comply with the guidelines, which recommend continuous reduction with monitoring of disease activity and side effects [8,9]. In the intervention arm, complete discontinuation of prednisone was specified for Week 14, while in the comparator arm the prednisone dose was 1 mg/day from Week 44 until the end of treatment (Week 52) according to the scheme. In the comments [7], the company states that the fixed tapering schemes with a fixed treatment duration are an adequate implementation of individualized corticosteroid therapy in the context of a controlled study design. Even in everyday life, an individualized treatment is not completely customized, but should be interpreted as a reactive adaptation of an otherwise standardized therapy depending on the patient's individual therapeutic needs. The company also emphasises the individual adaptability of the therapy in the study through the possibility of administering additional prednisone in the first 12 weeks of the treatment phase and also through the possibility of administering rescue medication over the entire duration of the study. With regard to the permitted single administration of additional prednisone at a maximum dose of 5 mg/day in addition to the protocol-defined tapering scheme, it should be noted, as already stated by the G-BA [10], that the approach chosen in the study for the subsequent tapering of the additional prednisone does not comply with the recommendations of the guideline. In the event of a relapse, the guideline recommends increasing the prednisone dose to at least the pre-relapse dose during corticosteroid taper. This dose should then be gradually reduced to the dose at which the relapse occurred within 4 to 8 weeks after the symptoms have subsided. In the study, however, the additional prednisone against signs and symptoms of PMR had to be stopped before the Week 12, so that a slow reduction over 4- to 8-week was not possible. With regard to the customizability of treatment through the administration of rescue medication, it should be noted that reactive adaptation by means of rescue medication based on the need for treatment in the study led to the patients being classified as non-responders. They therefore no longer had the opportunity to be included in the assessment as responders. The results of the outcome sustained remission at Week 52 therefore also reflect adherence to a rigid tapering scheme defined by the protocol.

Dossier assessment A25-18 described that corticosteroid therapy was administered to all patients with a starting dose of 15 mg/day prednisone and it remains unclear whether the

starting dose of 15 mg/day prednisone was too high or too low for individual patients. With its comments, the company provides information on how many patients were titrated up or down to 15 mg/day prednisone at the start of the study: A total of 35 (58.3%) patients in the sarilumab arm and 37 (63.8%) patients in the comparator arm underwent up-titration. The dose was reduced for 7 (11.7%) patients in the sarilumab arm and 2 (3.4%) patients in the comparator arm. Thus, the starting dose of 15 mg/day was potentially too low for only a few patients. However, the use of additional prednisone (4 patients in the sarilumab arm and 7 patients in the comparator arm) still suggests that, particularly for some patients in the comparator arm, either the starting dose of 15 mg/day prednisone was too low or the tapering schedule was not optimally chosen. In the comments, the company explained that a standardized corticosteroid starting dose was necessary for the comparability of the arms, including comparability with regard to the cumulative corticosteroid dose. However, a standardized corticosteroid starting dose does not increase the comparability of the study arms for that reason alone that the tapering schemes of the two arms are fundamentally different.

Even after the commenting procedure, criticism of the remission outcomes presented by the company remains, as individualized therapy was only possible to a limited extent and this limitation had a direct impact on outcomes, as explained in the following sections.

Remission outcome sustained remission presented by the company and sensitivity analysis not suitable for the benefit assessment

Component: remission by Week 12 at the latest

Besides the need for resolution of the PMR signs and symptoms, the component "remission by Week 12 at the latest" includes a necessary normalization of CRP. The laboratory value CRP is not necessarily accompanied by noticeable symptoms. In addition, interleukin-6 receptor antagonists such as sarilumab are characterized by the fact that inflammatory parameters such as the CRP value or ESR can be within the normal range regardless of the disease activity and therefore cannot be interpreted or can only be interpreted to a very limited extent [11]. It is also known from clinical studies on rheumatoid arthritis that when comparing interleukin-6 receptor antagonists with therapies without direct effects on inflammatory parameters, outcomes that include the laboratory values CRP or ESR in addition to recording clinical disease activity are associated with systematic overestimates of the effect sizes in favour of the interleukin-6 receptor antagonists [12]. The component "remission by Week 12 at the latest", taking into account the CRP value, therefore potentially leads to an overestimation of the effect in favour of sarilumab. Based on the sensitivity analysis subsequently submitted by the company (see Table 2), it can be seen that 1 patient per arm was ultimately assessed as not being in remission due to elevated CRP values. The criterion of an elevated CRP value therefore only had a minor influence on the analysis.

As described above, there is still uncertainty as to whether the use of rescue medication could have been avoided, particularly in the patients in the comparator arm, with an individually adjusted starting dose or an individually adjusted tapering schedule (rescue medication defined as medication in excess of the one-time permitted additional prednisone [maximum 5 mg/day], see Table 1). This is particularly important because patients who received rescue medication up to Week 12 were categorized as non-responders in the "remission by Week 12 at the latest" component. This affected 6 in the intervention arm and 12 patients in the comparator arm. It remains unclear whether these patients achieved remission, i.e. the absence of PMR symptoms at a relevantly low steroid dose, during the course of the study. An individually necessary adjustment of the corticosteroid therapy beyond the one-time permitted additional prednisone was therefore possible within the scope of the study, but this reactive individualization was regarded as rescue medication and inevitably led to a non-responder classification. This potentially disadvantages the comparator arm in particular, in which patients were particularly dependent on optimally selected and flexible corticosteroid therapy due to the lack of a standardized additional add-on therapy (such as sarilumab).

In summary, the narrow remission definition in the SAPHYR study potentially prevents an assessment as a responder up to Week 12, potentially to the disadvantage of the comparator arm. In contrast, a remission definition based on the absence of PMR signs and symptoms towards the end of the study and a sustained steroid reduction below a relevant threshold value (or steroid freedom, if achievable) is considered adequate for the benefit assessment. Such outcome operationalization ensures that the long-term side effects associated with the use of corticosteroids are avoided to a relevant extent with a high degree of certainty. In contrast, a mere reduction of corticosteroid doses during tapering without falling below the threshold value is not sufficiently informative in terms of the benefit assessment, as it is unclear to what extent this prevents long-term side effects to a relevant extent.

Component: no relapse from Weeks 12 to 52

For the component no relapse from Weeks 12 to 52, relapse was defined as recurrence of PMR signs and symptoms or an increase in ESR (increase associated with active PMR) requiring an increase in corticosteroid dose. Patients can only be included in the no relapse component if they have previously been in remission. It remains unclear whether the time point of remission (up to Week 12) is relevant for the achievement of this component and whether the use of rescue medication up to Week 12 may not be included here. Since more patients fulfilled the no relapse component than are included in the remission at Week 12 component, it is assumed that a previous remission at any time or regardless of rescue medication up to Week 12 was sufficient to achieve this component.

As described above, the ESR can be within the normal range during treatment with sarilumab regardless of the disease activity. Thus, the absence of an ESR increase is not patient-relevant

and the classification as non-response may also lead to an overestimation of the effect in favour of sarilumab, whereby the results of the sensitivity analysis show (Table 2) that the proportion of patients with event remains unchanged if the ESR is not included. The prescribed connection with an active PMR should counteract the assessment based solely on a laboratory parameter. Nevertheless, the study protocol stipulated that ESR values could be requested by the investigator or determined in the local laboratory if required. In its comments, the German Society for Rheumatology and Clinical Immunology states that the investigator was informed in the event of an elevated ESR value [13]. Therefore, an active PMR was potentially more likely to be detected in the comparator arm than in the sarilumab arm, which may lead to an overestimation of the effect in favour of sarilumab.

In addition, the relapse component includes an increase in the corticosteroid dose as a required criterion. This is particularly problematic because, as described above, the tapering schemes in the study were not individualized for each patient. Any deviation from the prescribed scheme in the sense of reactive individualization (i.e. any PMR-related dose increase) thus inevitably led to a non-responder rating in the no relapse component. This appears too rigid and potentially disadvantages the comparator arm, which is particularly dependent on this flexibilization of the corticosteroid dose without an additional therapy (such as sarilumab) (see previous text section on the tapering scheme).

Thus, the operationalization of the component no relapse showed that patients with disease activity (and possibly ESR increase) and subsequent increase in the corticosteroid dose could no longer be recorded as responders, even at later time points in the study. 13 (22%) patients in the intervention arm and 22 (38%) patients in the comparator arm received an increase of the corticosteroid dose (= rescue medication) between Weeks 12 and 52. However, it is conceivable that these patients showed remission after disease activity (and ESR increase) and subsequent deviation from the corticosteroid scheme in the further course of the study. The number of responders is therefore potentially underestimated due to the company's operationalization, particularly in the comparator arm.

Component: Successful tapering

Successful prednisone tapering was defined as no need for rescue medication. The use of additional prednisone with a cumulative dose of ≤ 100 mg (or equivalent), i.e. in excess of the dose intended in the tapering phase, for example for the treatment of AEs not related to PMR, was possible (see Table 1). As already noted analogously for the component no relapse, the component successful prednisone tapering from Weeks 12 to 52 is not a suitable component of a remission outcome in the present operationalization. It is not the adherence to a rigid regimen that is ultimately decisive, but whether the patient in remission can remain steroid-free or (if freedom cannot be achieved) below a relevant steroid threshold. In the consultation, the G-BA also pointed out that not every reduced consumption of

corticosteroids is directly relevant to patients; in the G-BA's opinion, the reduction of corticosteroids below the so-called Cushing's threshold is regarded as a relevant surrogate for the avoidance of corticosteroid-induced side effects and the selected operationalization and rationale for choosing the drug threshold should be justified in the dossier.

Further notes

Irrespective of the aforementioned points of criticism regarding the primary operationalization of sustained remission presented by the company, missing values for 13 vs. 9 patients (22% vs. 16%) were imputed for the analysis. Here, patients who discontinued the study before Week 52 and did not experience a relapse before discontinuation were categorized as non-responders. Likewise, patients for whom data were missing, so that the achievement of a sustained remission could not be assessed, were categorized as non-responders. This aspect alone leads to a high risk of bias for the results of this outcome.

Results (supplementary presentation)

In accordance with the commission, the results of the outcome sustained remission at Week 52 submitted by the company and the sensitivity analysis are presented as supplementary information.

Table 2: Results (sustained remission at Week 52) – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone

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					
Morbidity					
Sustained remission	60	17 (28.3)	58	6 (10.3)	2.74 [1.15; 6.52]; 0.023
Remission by Week 12[b] at the latest	ND[c]	28 ND	ND[c]	22 ND	
No relapse from Weeks 12 to 52[d]	ND[c]	33 ND	ND[c]	19 ND	
Sustained CRP reduction from Weeks 12 to 52[e]	ND[c]	40 ND	ND[c]	26 ND	
Successful prednisone tapering from Weeks 12 to 52[f]	ND[c]	30 ND	ND[c]	14 ND	
Sustained remission (sensitivity analysis[g])	60	19 (31.7)	58	8 (13.8)	2.30 [1.08; 4.86]; 0.030
Remission by Week 12[h] at the latest	ND[c]	29 (48.3)	-[c]	23 (39.7)	
No relapse from Weeks 12 to 52[i]	ND[c]	33 (ND)	ND[c]	19 (ND)	
Successful prednisone tapering from Weeks 12 to 52[f]	ND[c]	30 (ND)	ND[c]	14 (ND)	

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). Patients who completed the study before Week 52 and did not experience a relapse before discontinuation were categorized as non-responders. This applied to 13 vs. 9 patients (22% vs. 16%) for both the main and sensitivity analyses.
b. Defined as resolution of PMR signs and symptoms and CRP normalization (< 10 mg/L), see Table 1 for details.
c. According to the company, no missing values were imputed in the components. As values were imputed in the main analysis and the sensitivity analysis, the patient numbers of 60 vs. 58 stated by the company for each of the components are not the number of analysed patients.
d. Defined as either the absence of a recurrence of signs and symptoms requiring an increase of the corticosteroid dose or as absence of an increase of ESR (associated with active PMR) requiring an increase of the corticosteroid dose.
e. Defined as CRP < 10 mg/L without subsequent increases to ≥ 10 mg/L at two or more visits after Week 12 up to Week 52.
f. Defined as no need for rescue medication, see Table 1 for details.
g. Sensitivity analysis: sustained remission without inclusion of CRP and ESR values.
h. Defined as resolution of the PMR signs and symptoms.
i. Defined as absence of a recurrence of signs and symptoms that required an increase in the corticosteroid dose.

CI: confidence interval; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; n: number of patients with event; N: number of analysed patients; ND: no data; PMR: polymyalgia rheumatica; RCT: randomized controlled trial; RR: relative risk

The analysis sustained remission at Week 52 presented by the company and the sensitivity analysis without consideration of the laboratory parameters showed a statistically significant effect in favour of sarilumab.

2.2 The analysis time to first PMR relapse after clinical remission presented by the company

For the benefit assessment, the company presented an analysis of the time to first PMR relapse after clinical remission. This analysis is not suitable for deriving the added benefit, as remission at Week 12 at the latest and no relapse were defined identically to the outcome sustained remission at Week 52 (see Section 2.1).

Irrespective of this, 31 vs. 13 patients were censored in the event time analysis (52% vs. 22%). This aspect is considered to be so distorting that meaningful interpretation of the result is no longer possible. Patients who did not achieve remission over the 52-week observation period were included in the analysis as patients with an event at the time of randomization. Therefore, the outcome includes the component time to first PMR relapse on the one hand and the component no remission on the other, and is therefore referred to below as time to first PMR relapse or no remission.

In accordance with the commission, this analysis is presented as supplementary information in Table 3. The corresponding Kaplan-Meier curve can be found in Appendix B.

Table 3: Results (time to first PMR relapse) – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone

Study outcome category outcome	Sarilumab + prednisone		Placebo + prednisone		Sarilumab + prednisone vs. placebo + prednisone
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
SAPHYR					
Morbidity					
Time to first PMR relapse or no remission[b]	60	NA [93.0; NC] 29 (48.3)[c]	58	99.0 [1.0; 154.0] 45 (77.6)[c]	0.56 [0.35; 0.90]; 0.015
PMR relapse		10 (16.7)		17 (29.3)	-
No remission		19 (31.7)		28 (48.3)	-

a. HR, CI, and p-value: Cox model. 31 (52%) vs. 13 (22%) were censored in the course of the study.
b. A relapse was defined as either recurrence of signs and symptoms requiring an increase of the corticosteroid dose or as increase of ESR (associated with active PMR) requiring an increase of the corticosteroid dose. A relapse required a previous remission up to Week 12. Remission was defined as resolution of PMR signs and symptoms and CRP normalization (< 10 mg/L), for detailed information see Table 1. Patients without clinical remission during the course of the study were regarded as patients with PMR relapse upon randomization.
c. Institute's calculation.

CI: confidence interval; CRP: C-reactive protein; CS: corticosteroid; ESR: erythrocyte sedimentation rate; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial

The analysis "Time to first PMR relapse after clinical remission" showed a statistically significant difference in favour of sarilumab over placebo.

2.3 Description of an operationalization suitable for the benefit assessment

As in dossier assessment A25-18, a suitable analysis on remission was to 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.

Analyses of this kind would certainly have been possible in the SAPHYR study: A threshold value of 5 mg/day (as stated as a therapy goal by the clinical experts at the hearing, [15]) would have been achievable in both study arms of the SAPHYR study at Week 24.

In addition, a certain degree of individualization should be possible in the tapering scheme without deviations being directly assessed as non-response. In the present data situation, it is

unclear whether additional patients, particularly in the comparator arm, would have been assessed as "in sustained remission" in the SAPHYR study if a suitable outcome operationalization had been applied and to what extent this would have influenced the effects. In principle, however, a potential bias to the disadvantage of the comparator arm can be assumed for the available results. Based on additional results in the publication on the SAPHYR study, however, this potential bias can be further categorized below.

In the publication on the SAPHYR study, data on steroid-free clinical remission at Week 52 (see Appendix A, Figure 1) [5] can be found in Figure S4 of the Supplement; the outcome steroid-free clinical remission at Week 52 includes those patients with resolution of the PMR signs and symptoms (clinical remission) and steroid freedom at Week 52. Thus, the bias due to the rigid tapering scheme is no longer included in this analysis. However, this only reflects a time point and not a relevant period for a steroid-free remission.

Information on the outcome at Week 52 was not available for 18 versus 22 patients, i.e. 30% vs. 38% of the randomized patients. For the analysis, patients without a value were categorized as non-responders. Maintaining the non-responder imputation from the analyses of sustained remission enables a better comparison of the operationalizations and the associated analyses. This results in a high risk of bias.

In addition, Figure S2 of the Supplement of the publication on the SAPHYR study contains data (see Appendix A, Figure 2) that allow an analysis of the individual component clinical remission at Week 52. No data were available for 12 vs. 12 patients, i.e. 20% vs. 21% of the randomized patients. For the analysis, these patients without a value were categorized as non-responders.

The results for the analysis on steroid-free clinical remission at Week 52 and the component clinical remission at Week 52 are provided as supplementary information in Table 4

Table 4: Results (steroid-free remission at Week 52) – RCT, direct comparison: sarilumab + prednisone in comparison with placebo + prednisone

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					
Morbidity					
Steroid-free clinical rmission at Week 52[b]	60	27 (45.0[c])	58	8 (13.8[c])	3.26 [1.35; 7.88]; 0.009
Clinical remission at Week 52[d]	60	39 (65.0[c])	58	26 (44.8[c])	1.45 [0.99; 2.12]; 0.057

a. RR, CI and p-value: own calculation with variance correction for substituted values. Patients with missing values were categorized as non-responders. For steroid-free clinical remission at Week 52, this applied to 18 vs. 22 patients (30% vs. 38%), for the clinical remission at Week 52 presented as supplementary information, this applied to 12 vs. 12 patients (20% vs. 21%).
b. Defined as resolution of PMR signs and symptoms and steroid freedom.
c. Institute's calculation.
d. Defined as resolution of the PMR signs and symptoms.

CI: confidence interval; n: number of patients with event; N: number of randomized patients; PMR: polymyalgia rheumatica; RCT: randomized controlled trial; RR: relative risk

For the steroid-free clinical remission at Week 52, there was a statistically significant difference between the treatment arms in favour of sarilumab.

The analysis of steroid-free clinical remission at Week 52 is not in itself suitable for the benefit assessment, as only a point in time and not a relevant period of steroid freedom is considered here. However, based on the results of the analysis on steroid-free clinical remission at Week 52, it can be concluded with sufficient certainty that, overall, the significant effects of all the analyses presented in this addendum are not caused by bias alone.

Overall, a hint of non-quantifiable added benefit of sarilumab compared to prednisone can therefore be derived in this special data situation in the outcome remission.

It is taken into account that subgroup analyses are not available for this analysis, just as for the sensitivity analysis of the company. However, the subgroup analyses on the primary outcome sustained remission also showed no indications of effect modifications relevant to the conclusion.

2.4 Summary

Based on this addendum, a hint of a non-quantifiable added benefit of sarilumab over corticosteroids can be derived in the outcome remission for patients with PMR who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper. Overall, there is also a hint of a non-quantifiable added benefit of sarilumab compared with glucocorticoids since this positive effect is not offset by any negative effects (see dossier assessment).

The following Table 5 shows the result of the benefit assessment of sarilumab taking into account both dossier assessment A25-18 and the present addendum.

Table 5: 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]: hint of non-quantifiable added benefit
		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 G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Sarilumab (Polymyalgia rheumatica); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2025 [Accessed: 25.06.2025]. URL: https://doi.org/10.60584/A25-18.

2. Sanofi. Evaluation of the Efficacy and Safety of Sarilumab in Patients With Polymyalgia Rheumatica [online]. 2022 [Accessed: 11.04.2025]. URL: https://clinicaltrials.gov/study/NCT03600818.

3. Sanofi-Aventis. A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with polymyalgia rheumatica; EFC15160; Clinical Study report [unpublished]. 2021.

4. Sanofi-Aventis Recherche & Développement. A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with polymyalgia rheumatica [online]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002989-42.

5. Spiera RF, Unizony S, Warrington KJ et al. Sarilumab for Relapse of Polymyalgia Rheumatica during Glucocorticoid Taper. N Engl J Med 2023; 389(14): 1263-1272. https://doi.org/10.1056/NEJMoa2303452.

6. Sanofi-Aventis. Sarilumab (Kevzara); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2025 [Accessed: 03.07.2025]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1161/#dossier.

7. Sanofi-Aventis. Stellungnahme zum IQWiG-Bericht Nr. 2005: Sarilumab (Polymylagia rheumatica); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Demnächst verfügbar unter: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1161/#beschluesse in the document "Zusammenfassende Dokumentation"].

8. Deutsche Gesellschaft für Rheumatologie, Österreichischen Gesellschaft für Rheumatologie und Rehabilitation, Schweizerischen Gesellschaft für Rheumatologie. S3-Leitlinie zur Behandlung der Polymyalgia rheumatica [online]. 2017. URL: https://register.awmf.org/assets/guidelines/060-006l_S3_Polymyalgia-rheumatica_2018-05-abgelaufen.pdf.

9. Deutsche Gesellschaft für Rheumatologie und Klinische Immunologie, Österreichische Gesellschaft für Rheumatologie und Rehabilitation, Schweizerische Gesellschaft für Rheumatologie. S2e -Leitlinie zur Behandlung der Polymyalgia rheumatica; Update 2024 [online]. 2024. URL: https://register.awmf.org/assets/guidelines/060-006l_S2e_Behandlung-der-Polymyalgia-rheumatica_2025-04.pdf.

10. Gemeinsamer Bundesausschuss. Niederschrift (finale Fassung) zum Beratungsgespräch gemäß § 8 Am-NutzenV; Beratungsanforderung 2023-B-266 [unpublished]. 2023.

11. Reisch M, Dejaco C. Methoden zur Erfassung der Krankheitsaktivität der Polymyalgia rheumatica. Z Rheumatol 2023; 82(5): 368-379. https://doi.org/10.1007/s00393-023-01358-x.

12. Janke K, Kiefer C, McGauran N et al. A systematic comparison of different composite measures (DAS 28, CDAI, SDAI, and Boolean approach) for determining treatment effects on low disease activity and remission in rheumatoid arthritis. BMC Rheumatol 2022; 6(1): 82. https://doi.org/10.1186/s41927-022-00314-7.

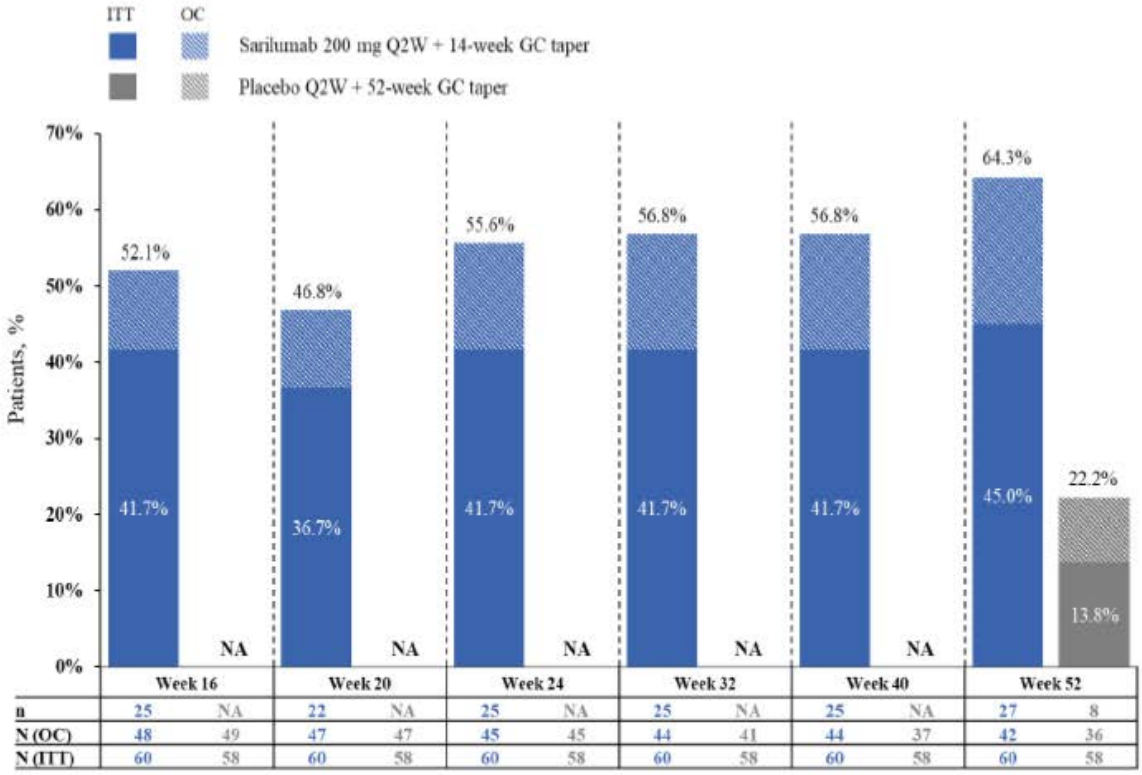
13. Deutsche Gesellschaft für Rheumatologie und Klinische Immunologie. Stellungnahme zum IQWiG-Bericht Nr. 2005: Sarilumab (Polymylagia rheumatica); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1161/#beschluesse im Dokument "Zusammenfassende Dokumentation"].

14. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Benralizumab (eosinophile Granulomatose mit Polyangiitis); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2025 [Accessed: 04.03.2025]. URL: https://doi.org/10.60584/A24-113.

15. Gemeinsamer Bundesausschuss. Sarilumab (D-1141): mündliche Anhörung gemäß § 35 a Abs. 3 Satz 2 SGB V; stenografisches Wortprotokoll [online]. 2025 [Accessed: 03.07.2025]. URL: https://www.g-ba.de/downloads/91-1031-1161/2025-06-24_Wortprotokoll_Sarilumab_D-1141.pdf.

Appendix A Appendix A Figures S4 and S2 from the publication on the SAPHYR study

Figure S4. Patients Without Any PMR Signs and Symptoms, off Prednisone Taper, and Not on Rescue Therapy

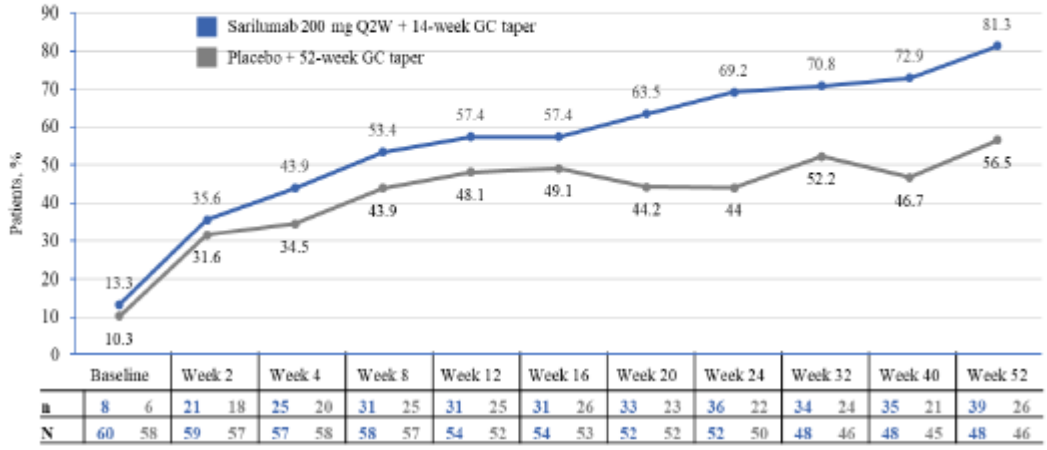


Figures presents data on the proportion of patients without any PMR signs and symptoms, off prednisone taper, and not on rescue therapy. The observed cases are based on patients who had PMR assessments at each visit, not including PMR assessments performed after treatment discontinuation. The first scheduled clinical assessment after completion of protocolized prednisone taper was at week 16 in the sarilumab arm and week 52 in the comparator arm.

GC, glucocorticoid; ITT, intent-to-treat; N, number of patients evaluable; n, number of patients with GC-free resolution of PMR signs and symptoms; NA, not applicable; OC, observed cases (of the evaluable patients at that timepoint); PMR, polymyalgia rheumatica; Q2W, every 2 weeks.

Figure 1: Figure S4 from the publication on the SAPHYR study

Figure S2. Patients Without Any PMR Signs and Symptoms by Visit



	Baseline		Week 2		Week 4		Week 8		Week 12		Week 16		Week 20		Week 24		Week 32		Week 40		Week 52	
n	8	6	21	18	25	20	31	25	31	25	31	26	33	23	36	22	34	24	35	21	39	26
N	60	58	59	57	57	58	58	57	54	52	54	53	52	52	52	50	48	46	48	45	48	46

Figure shows the proportion of patients without any PMR signs and symptoms based on the number of patients assessed at each visit from baseline up to week 52. "N" is the number of patients who had PMR assessments at each visit, including PMR assessments performed after treatment discontinuation; "n" is the number of patients without any PMR signs and symptoms.

GC, glucocorticoid; PMR, polymyalgia rheumatica; Q2W, every 2 weeks.

Figure 2: Figure S2 from the publication on the SAPHYR study

Appendix B Appendix B Cumulative incidence curve for the outcome time to first PMR relapse from Module 4B

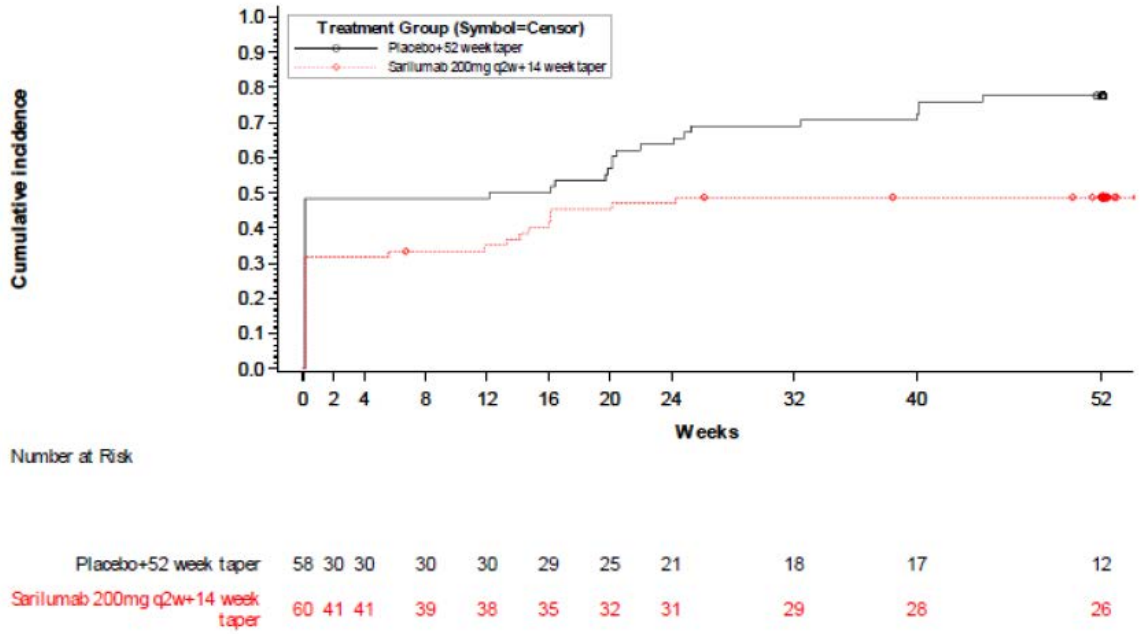


Abbildung 4-2: Kaplan-Meier-Kurve für den Endpunkt „Zeit bis zum ersten PMR-Schub nach klinischer Remission“ aus RCT (Studie SAPHYR) mit dem zu bewertenden Arzneimittel (ITT-Population)

Die Zeit (Tage) wurde von der Randomisierung bis zum ersten PMR-Schub nach klinischer Remission bis Woche 52 berechnet.

ITT: Intention-To-Treat; PMR: Polymyalgia rheumatica; q2w: Alle zwei Wochen; RCT: Randomisierte, kontrollierte Studie (Randomized Controlled Trial).

Figure 4-2: Kaplan-Meier curve for the outcome "time to first PMR relapse after clinical remission" from RCT (SAPHYR study) with the drug to be assessed (ITT population)

The time (days) was calculated from randomization to the first PMR relapse after clinical remission up to Week 52.

ITT: intention to treat; PMR: polymyalgia rheumatica; Q2W every two weeks; RCT: randomized controlled trial

Figure 3: Cumulative incidence curve according to Kaplan-Meier for the outcome time to first PMR recurrence