Article linked on page 8

KEVZARA®
(sarilumab) injection
200 mg

Sarilumab for Relapse of Polymyalgia Rheumatica (PMR) during Glucocorticoid Taper

Spiera RF, Unizony S, Warrington KJ, et al. *The New England Journal of Medicine.* 2023

The SArilumab in Patients witH polYmyalgia Rheumatica (SAPHYR) study compared the efficacy and safety of KEVZARA 200 mg Q2W + 14-week corticosteroid (CS) taper with placebo Q2W + 52-week CS taper in patients with PMR who flared with CS taper[1,2]

Q2W=once every 2 weeks.

INDICATION

KEVZARA® (sarilumab) is indicated for treatment of adult patients with polymyalgia rheumatica (PMR) who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper.[2]

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with KEVZARA are at increased risk for developing serious infections that may lead to hospitalization or death. Opportunistic infections have also been reported in patients receiving KEVZARA. Most patients who developed infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Avoid use of KEVZARA in patients with an active infection.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before KEVZARA use and during therapy. Treatment for latent infection should be initiated prior to KEVZARA use.**
- **Invasive fungal infections, such as candidiasis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

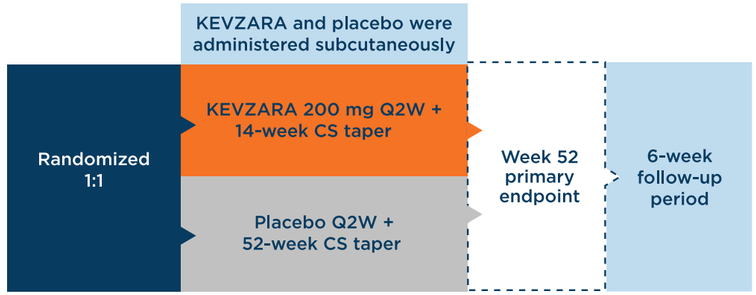
Closely monitor patients for signs and symptoms of infection during treatment with KEVZARA. If a serious infection develops, interrupt KEVZARA until the infection is controlled.

Consider the risks and benefits of treatment with KEVZARA prior to initiating therapy in patients with chronic or recurrent infection.

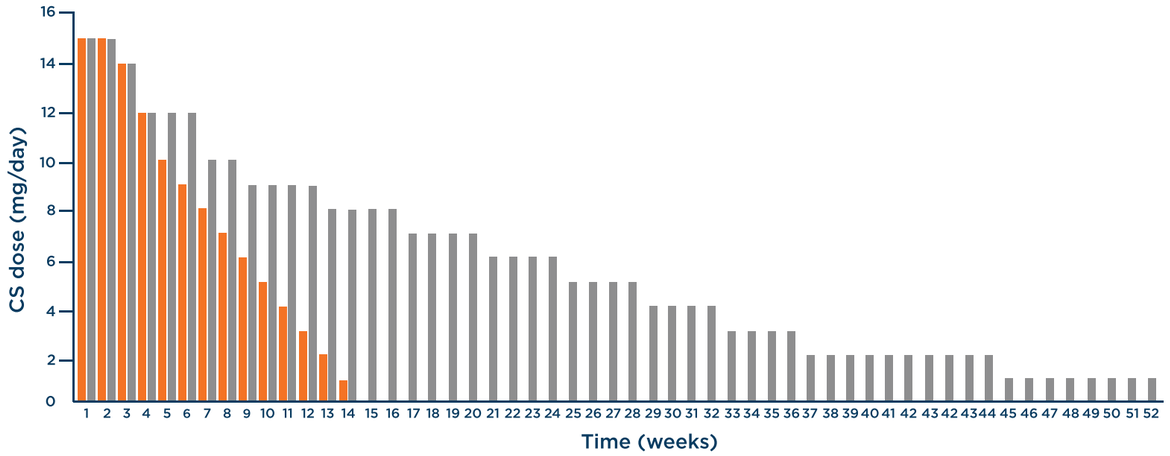
Please see Important Safety Information throughout and click here to see full Prescribing Information, including Boxed WARNING.

SAPHYR—a double-blind, placebo-controlled, 52-week, multicenter clinical trial[1-3]

In the phase 3 trial, 118 patients with PMR* were randomized to receive KEVZARA 200 mg every 2 weeks with a predefined 14-week CS taper (n=60) or placebo every 2 weeks with a predefined 52-week CS taper (n=58).[1-3†]



The predefined CS taper schedule[1-3]



*Polymyalgia rheumatica (PMR) was diagnosed based on ACR/EULAR criteria.[1]
†One patient was randomized but not treated in the KEVZARA + 14-week CS taper arm.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATION

Do not use KEVZARA in patients with known hypersensitivity to sarilumab or any of the inactive ingredients.

WARNINGS AND PRECAUTIONS

- ***Infections.*** Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including KEVZARA. Among opportunistic infections, TB, candidiasis, and pneumocystis were reported with KEVZARA. The most frequently observed serious infections with KEVZARA in RA patients included pneumonia and cellulitis.
  - Hold treatment with KEVZARA if a patient develops a serious infection or an opportunistic infection.
  - Patients with latent TB should be treated with standard antimycobacterial therapy before initiating KEVZARA. Consider anti-TB therapy prior to initiation of KEVZARA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but having risk factors for TB infection.

The primary endpoint was a composite endpoint of 4 metrics[1,2]

Primary endpoint[1,2]

- Proportion of patients with sustained remission at Week 52. Sustained remission was defined as achievement of all 4 components:
  - Absence of signs and symptoms and CRP <10 mg/L (disease remission*) no later than Week 12
  - Absence of disease flare† from Week 12 through Week 52
  - Sustained reduction of CRP (<10 mg/L) from Week 12 through Week 52
  - Successful adherence to prednisone taper from Week 12 though Week 52

Select secondary endpoints[1,2]

- Components of sustained remission composite endpoint at Week 52
- Total cumulative CS dose over 52 weeks
- Safety endpoints

Other Analysis[1,4]

- CS-free resolution of PMR signs and symptoms

*Disease remission is defined as the resolution of signs and symptoms of PMR, and normalization of CRP (<10 mg/L).[1]
†Flare is defined as recurrence of signs and symptoms attributable to active PMR requiring an increase in corticosteroid dose, or elevation of ESR attributable to active PMR plus an increase in corticosteroid dose.[1,2]

Select baseline demographics and patient characteristics[1,3]

Parameter	KEVZARA 200 mg Q2W + 14-week CS taper (n=60)	Placebo Q2W + 52-week CS taper (n=58)
Median age, years‡	69 (51–88)	70 (52–88)
Sex (female), n (%)	45 (75)	37 (64)
Median PMR duration (days)‡§	292 (78–3992)	310 (66–2784)
Median no. of prior flares/patient‡	2 (1–14)	2 (1–22)
Race, n (%)		
Caucasian	50 (83)	48 (83)
Asian	1 (2)	2 (3)
Not reported	9 (15)	8 (14)
Prior immunosuppression, n (%)		
Methotrexate	2 (3)	9 (16)
Methotrexate sodium	3 (5)	1 (2)
Leflunomide	2 (3)	1 (2)
Azathioprine	0	1 (2)
Hydroxychloroquine	0	1 (2)
Hydroxychloroquine sulfate	1 (2)	0
Adalimumab	1 (2)	0
Tocilizumab	0	1 (2)
Median CRP, mg/L‡	6.8 (0.5–38.2)	5.7 (0.1–62.3)
Median ESR, mm/h‡	25.0 (2.0–115.0)	22.0 (5.0–85.0)

‡Median values presented as median (range).[1]
§Diagnosis date to baseline. Placebo Q2W + 52-week CS taper (n=50), sarilumab 200 mg Q2W + 14 CS taper (n=54).[1]

ACR=American College of Rheumatology; CRP=C-reactive protein; CS=corticosteroid; ESR=erythrocyte sedimentation rate; EULAR=European Alliance of Associations for Rheumatology; PMR=polymyalgia rheumatica; Q2W=once every 2 weeks; SAPHYR=SArliumab in Patients witH polYmyalgia Rheumatica.

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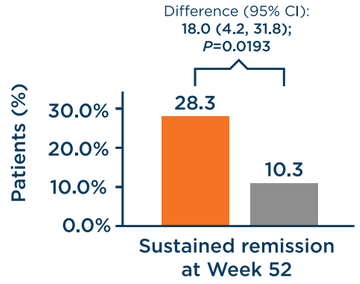
KEVZARA demonstrated statistically significant sustained remission at Week 52[1,2]

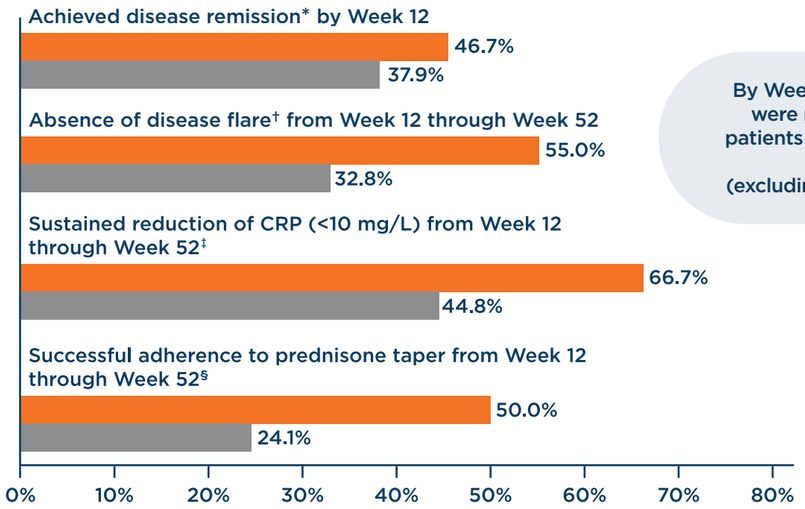
Primary endpoint: Proportion of patients achieving sustained remission at Week 52[1,2]



With sustained remission, patients achieved disease remission no later than Week 12 and maintained disease remission through Week 52.[1,2]

KEVZARA 200 mg Q2W + 14-week CS taper (n=60) | Placebo Q2W + 52-week CS taper (n=58)

KEVZARA showed improvement across all components of sustained remission[1,2]*

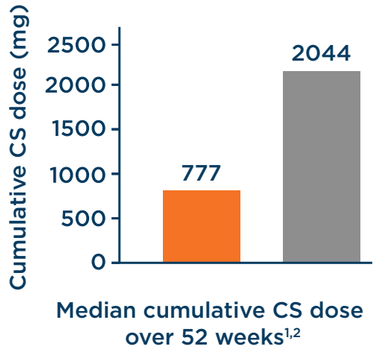


By Week 12, patients in the KEVZARA arm were receiving 3 mg of daily CSs while patients in the placebo-controlled arm were receiving 9 mg of daily CSs (excluding rescue CSs, per study protocol).[3]

KEVZARA 200 mg Q2W + 14-week CS taper (n=60) | Placebo Q2W + 52-week CS taper (n=58)

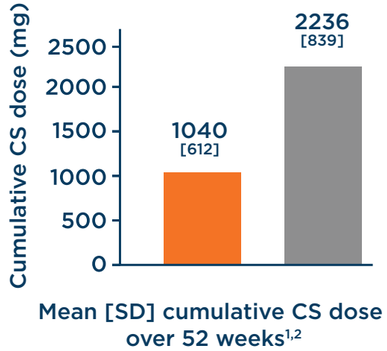
*Disease remission is defined as the resolution of signs and symptoms of PMR and normalization of CRP (<10 mg/L).[2]
†Flare is defined as recurrence of signs and symptoms attributable to active PMR requiring an increase in corticosteroid dose, or elevation of ESR attributable to active PMR plus an increase in corticosteroid dose.[2]
‡The status of normalization of CRP from Week 12 through Week 52 was determined based on the CRP values measured at Week 16, Week 20, Week 32, Week 40, and Week 52. If there were 2 or more consecutive visits with CRP ≥10 mg/L, then it was categorized as no normalization of CRP.[3]
§Successful adherence to the prednisone taper from Week 12 through Week 52 is defined as patients who did not take rescue therapy from Week 12 through Week 52 and might include the use of any excess prednisone (beyond the per-protocol CS-tapering regimen) with a cumulative dose of ≤100 mg (or equivalent), such as those employed to manage AEs not related to PMR. The cumulative dose of excess prednisone use was counted from baseline to Week 52.[3]

Steroid-sparing effect: Patients received a lower cumulative CS dose during the 52-week treatment period in the KEVZARA arm compared to the placebo-controlled arm[1,2]



The median of the difference between the actual and expected cumulative CS dose based on the prednisone taper assigned was 0 mg in the KEVZARA arm vs 199 mg in the comparator arm (>50% patients in the KEVZARA arm had the same actual and expected cumulative CS dose).[1]

KEVZARA 200 mg Q2W + 14-week CS taper (n=60) | Placebo Q2W + 52-week CS taper (n=58)



The mean [SD] difference between the actual and expected cumulative CS dose was 298 [589] mg in the KEVZARA arm vs 455 [548] mg in the placebo arm.[3]

KEVZARA 200 mg Q2W + 14-week CS taper (n=60) | Placebo Q2W + 52-week CS taper (n=58)

AE=adverse event; CI=confidence interval; CRP=C-reactive protein; CS=corticosteroid; ESR=erythrocyte sedimentation rate; PMR=Polymyalgia rheumatica; Q2W=once every 2 weeks; SD=standard deviation.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ***Infections.*** **(cont'd)**
  - Consider the risks and benefits of treatment prior to initiating KEVZARA in patients who have: chronic or recurrent infection, a history of serious or opportunistic infections, underlying conditions that may predispose them to infection, been exposed to TB, or lived in or traveled to areas of endemic TB or endemic mycoses.
  - Viral reactivation has been reported with immunosuppressive biologic therapies. Cases of herpes zoster were observed in clinical studies with KEVZARA.

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KEVZARA® (sarilumab) injection 200 mg

CS-free resolution of PMR signs and symptoms data[1,4]

ITT Population Analysis[1,4]

At Week 52, 27/60 (45%) of patients in the KEVZARA arm vs 8/58 (14%) in the comparator arm had CS-free resolution of PMR signs and symptoms.

64%

Analysis of Observed Cases[1,4]*

In evaluable patients at Week 52 who completed treatment, 27/42 (64%) in the KEVZARA arm vs 8/36 (22%) in the comparator arm had CS-free resolution of PMR signs and symptoms.

Limitations:

- **Analyses based on observed cases or evaluable patients are restricted to a subset of patients defined based on a post-randomization variable, leading to potentially biased comparisons between treatment arms and limiting the interpretability of the results**
- **Difficult to determine whether any differences observed are due to the effects of the treatment or to differences in patient characteristics between the subsets of randomized patients on the two arms**

Results are descriptive. No definitive conclusions can be made as data were not multiplicity controlled.

*The observed cases are based on patients with PMR assessments at each visit (PMR assessments after treatment discontinuation were not included), with the first assessment scheduled after completion of predefined CS taper at Week 16 in the KEVZARA arm and Week 52 in the comparator arm.[4]

CS=corticosteroid; ITT=intention to treat; PMR=polymyalgia rheumatica.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ***Laboratory Abnormalities.*** Treatment with KEVZARA was associated with decreases in absolute neutrophil counts (including neutropenia), and platelet counts; and increases in transaminase levels and lipid parameters (LDL, HDL cholesterol, and/or triglycerides). Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with KEVZARA. Assess neutrophil count, platelet count, and ALT/AST levels prior to initiation with KEVZARA. Monitor these parameters 4 to 8 weeks after start of therapy and every 3 months thereafter. Assess lipid parameters 4 to 8 weeks after start of therapy, then at 6 month intervals.
- ***Gastrointestinal Perforation.*** GI perforation risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids. Gastrointestinal perforations have been reported in clinical studies, primarily as complications of diverticulitis. Promptly evaluate patients presenting with new onset abdominal symptoms.
- ***Immunosuppression.*** Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with KEVZARA on the development of malignancies is not known but malignancies have been reported in clinical studies.
- ***Hypersensitivity Reactions.*** Hypersensitivity reactions have been reported in association with KEVZARA. Hypersensitivity reactions that required treatment discontinuation were reported in 0.3% of patients in controlled RA trials. Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of KEVZARA immediately. Do not administer KEVZARA to patients with known hypersensitivity to sarilumab.
- ***Active Hepatic Disease and Hepatic Impairment.*** Treatment with KEVZARA is not recommended in patients with active hepatic disease or hepatic impairment, as treatment with KEVZARA was associated with transaminase elevations.
- ***Live Vaccines.*** Avoid concurrent use of live vaccines during treatment with KEVZARA due to potentially increased risk of infections. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving KEVZARA. Prior to initiating treatment, it is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines.

ADVERSE REACTIONS

- **For Polymyalgia Rheumatica:** Serious adverse reactions of neutropenia occurred in 2 patients (3.4%) in the KEVZARA group compared to none in the placebo group. The proportion of patients with serious infections was similar in the KEVZARA group (5.1%) compared to the placebo group (5.2%). The common adverse reactions occurring in ≥5% of patients treated with KEVZARA were neutropenia, leukopenia, constipation, rash pruritic, myalgia, fatigue, and injection site pruritus.

Safety data were generally consistent with the known safety profile of KEVZARA in RA[1,2,5]

In the SAPHYR trial of patients with PMR, the incidence of infections was lower in the KEVZARA group (37.3%) compared to the placebo-controlled group (50.0%).[2]

- The incidence of serious infections was similar in the KEVZARA group (5.1%) compared to the placebo-controlled group (5.2%)[2]

The most common adverse events (≥5%) occurring in patients in the SAPHYR study[2]

Adverse event % (n)	KEVZARA 200 mg Q2W + 14-week CS taper (N=59)	Placebo Q2W + 52-week CS taper (N=58)
Neutropenia	15.3% (9)	0.0%
Leukopenia	6.8% (4)	0.0%
Constipation	6.8% (4)	0.0%
Myalgia	6.8% (4)	0.0%
Rash pruritic	5.1% (3)	0.0%
Fatigue	5.1% (3)	0.0%
Injection site pruritus	5.1% (3)	0.0%
A higher incidence of serious adverse events was observed in the placebo Q2W + 52-week CS taper arm (20.7%) compared to the KEVZARA 200 mg Q2W + 14-week CS taper arm (13.6%).[3]		

Serious Adverse Reactions

Serious adverse reactions of neutropenia occurred in 2 patients (3.4%) in the KEVZARA group compared to none in the placebo group. In both cases of neutropenia, the participants had a neutrophil count less than 500 per mm^3 without any infections and resolved following permanent discontinuation of study drug.[2]

The most common adverse reactions that resulted in permanent discontinuation of therapy with KEVZARA were: neutropenia, which occurred in 3 patients (5.1%); infection (including COVID-19), which occurred in 3 patients (5.1%); intervertebral discitis (n=1), and pneumonia (n=1).[2]

Post-Treatment Adverse Events

Post-treatment AEs were reported in 4/59 (7%) patients in the KEVZARA arm and 7/58 (12%) patients in the comparator arm.[1]

Post-treatment serious AEs were reported in 2/59 (3%) patients in the KEVZARA arm and 1/58 (2%) patients in the comparator arm.[1,2]

AE=adverse event; CS=corticosteroid; PMR=polymyalgia rheumatica; Q2W=once every 2 weeks; SAPHYR=SArilumab in Patients witH polYmyalgia Rheumatica.

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KEVZARA® (sarilumab) injection 200 mg

KEVZARA: The First and Only FDA-Approved Steroid-Sparing* Treatment Indicated for PMR

- KEVZARA demonstrated statistically significant **sustained remission at Week 52**[1,2]
- KEVZARA patients used less corticosteroids in the SAPHYR trial[1]
  - While the comparator arm used a 52-week CS taper consistent with ACR/EULAR guidelines, **the KEVZARA arm used a 14-week CS taper**[1,6]
- **Numerically fewer patients treated with KEVZARA experienced flares** after clinical remission from Week 12 through Week 52[1,2]
- In PMR, the overall safety profile observed in the KEVZARA 200 mg Q2W + 14-week CS taper treatment group was generally **consistent with the known safety profile of KEVZARA in RA**[1,2,5]

***The total actual cumulative prednisone equivalent corticosteroid dose was lower in the KEVZARA arm (KEVZARA 200 mg Q2W + 14-week CS taper) with a mean [SD] of 1039.5 [612.2] mg and a median dose of 777 mg relative to the placebo arm (placebo Q2W + 52-week CS taper) with a mean [SD] of 2235.8 [839.4] mg and a median dose of 2044 mg.[2]**

ACR=American College of Rheumatology; CS=corticosteroid; EULAR=European Alliance of Associations for Rheumatology; PMR=polymyalgia rheumatica; Q2W=once every 2 weeks; RA=rheumatoid arthritis; SAPHYR=Sarilumab in Patients witH polYmyalgia Rheumatica; SD=standard deviation.

Visit KEVZARA.com/hcp/pmr to learn more.

Click here to access the free article, "Sarilumab for Relapse of Polymyalgia Rheumatica during Glucocorticoid Taper," published by *The New England Journal of Medicine*.

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

- Exercise caution when KEVZARA is co-administered with CYP substrates with a narrow therapeutic index (e.g. warfarin or theophylline), or with CYP3A4 substrates (e.g. oral contraceptives or statins) as there may be a reduction in exposure which may reduce the activity of the CYP3A4 substrate.
- Elevated interleukin-6 (IL-6) concentration may down-regulate CYP activity such as in patients with RA and hence increase drug levels compared to subjects without RA. Blockade of IL-6 signaling by IL-6Rα antagonists such as KEVZARA might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered drug concentrations.

USE IN SPECIFIC POPULATIONS

- KEVZARA should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. Because monoclonal antibodies could be excreted in small amounts in human milk, the benefits of breastfeeding and the potential adverse effects on the breastfed child should be considered along with the mother's clinical need for KEVZARA.
- Use caution when treating the elderly.

Advise patients to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Please see Important Safety Information throughout and click here to see full Prescribing Information, including Boxed WARNING.

References: 1. 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. **2.** KEVZARA [prescribing information]. Bridgewater, NJ: Sanofi/Regeneron Pharmaceuticals, Inc. **3.** Data on file. Bridgewater, NJ: Sanofi/Regeneron Pharmaceuticals, Inc. **4.** 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. Supplementary appendix available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa2303452/suppl_file/nejmoa2303452_appendix.pdf. Accessed November 1, 2023. **5.** Fleischmann R, Genovese MC, Lin Y, et al. Long-term safety of sarilumab in rheumatoid arthritis: an integrated analysis with up to 7 years' follow-up. *Rheumatology.* 2020;59(2):292-302. **6.** Dejaco C, Singh YP, Perel P, et al. 2015 recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis*. 2015;74(10):1799-1807.

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