KEVZARA STUDIES COMPENDIUM

KEVZARA®
(sarilumab) injection
200 mg

OVERVIEW OF THREE PHASE 3 STUDIES ASSESSING EFFICACY AND SAFETY OF KEVZARA IN RHEUMATOID ARTHRITIS

Genovese MC, Fleischmann R, Kivitz AJ, et al. *Arthritis Rheumatol.* 2015;67:1424-1437.
Fleischmann R, van Adelsberg J, Lin Y, et al. *Arthritis Rheumatol.* 2017;69:277-290.
Burmester GR, Lin Y, Patel R, et al. *Ann Rheum Dis.* 2017;76:840-847.

MOBILITY[1,2] (N=1197)	TARGET[1,3] (N=546)	MONARCH[4] (N=369)
MTX-IR: Inadequate clinical response to MTX therapy	TNF-IR: Inadequate clinical response or intolerance to ≥1 TNF-α antagonists	MTX-IR: Inadequate clinical response to, intolerant of, or inappropriate for MTX therapy

OVERVIEW OF STUDIES

The MOBILITY, TARGET, and MONARCH trials were multicenter, randomized, double-blind, Phase 3 studies that evaluated the efficacy and safety of KEVZARA® (sarilumab) in combination with MTX, cDMARD(s), or as monotherapy, respectively, in adult patients with moderately to severely active RA.

MOBILITY and TARGET are the registrational pivotal trials for KEVZARA and data from these studies are included in the US Prescribing Information (USPI). MONARCH data are not included in the KEVZARA USPI. Please see page 6 for additional context on MONARCH.

INDICATION

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

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 additional Important Safety Information throughout and click here for full Prescribing Information, including Boxed WARNING.

To view the full manuscript, please [click here].

MOBILITY STUDY

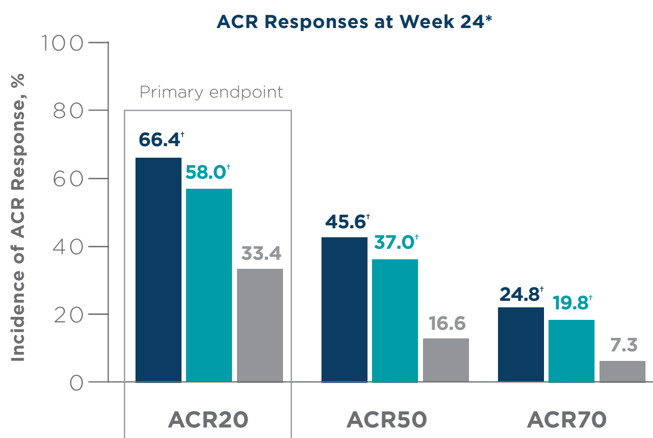
Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study

STUDY DESIGN

The MOBILITY trial evaluated the efficacy and safety of 2 different doses of KEVZARA® (sarilumab) in combination with MTX in patients with moderately to severely active RA who had an inadequate clinical response to MTX. Patients were randomized to receive KEVZARA 200 mg, KEVZARA 150 mg, or placebo, in combination with MTX.[1]

KEVZARA + MTX PROVIDED IMPROVEMENTS IN SIGNS AND SYMPTOMS OF RA[1]

ACR Responses at Week 24*



Patients treated with either 200 mg or 150 mg of KEVZARA every 2 weeks + MTX had higher ACR20, ACR50, and ACR70 response rates versus placebo + MTX-treated patients at Week 24.[1]

After week 16 in MOBILITY, patients with an inadequate response could have been treated with open-label KEVZARA 200 mg every 2 weeks.[2]

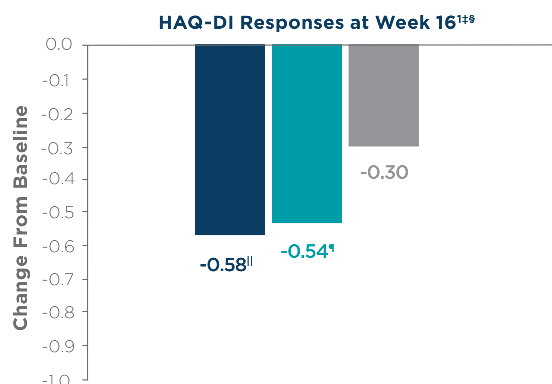
*Adapted from KEVZARA [prescribing information]. Bridgewater, NJ: Sanofi/Regeneron Pharmaceuticals, Inc.

†*P*<0.0001.

ADDITION OF KEVZARA TO MTX SHOWED GREATER IMPROVEMENT IN PHYSICAL FUNCTION THAN PLACEBO + MTX[1]

Change from baseline in the HAQ-DI score at Week 16 was greater among patients who received KEVZARA 200 mg or 150 mg every 2 weeks + MTX versus placebo + MTX.[1]

HAQ-DI Responses at Week 16‡§



‡Adapted from KEVZARA [prescribing information]. Bridgewater, NJ: Sanofi/Regeneron Pharmaceuticals, Inc. §These data are from the USPI and are consistent with the publication.[1,2] ||Difference from placebo: -0.26 (95% CI: -0.34, -0.18). ¶Difference from placebo: -0.24 (95% CI: -0.31, -0.16).

KEVZARA + MTX REDUCED THE PROGRESSION OF STRUCTURAL DAMAGE IN PATIENTS WITH RA[1]

Both doses of KEVZARA + MTX were superior to placebo + MTX in the change from baseline in mTSS over 52 weeks.[1#]

mTSS at Week 52**

	KEVZARA 200 mg + MTX (n=399)	KEVZARA 150 mg + MTX (n=400)	Placebo + MTX (n=398)
Mean change	0.25††	0.90††	2.78
LS mean difference (95% CI)	-2.52 (-3.38, -1.66)	-1.88 (-2.74, -1.01)	

- 91% and 68%‡‡ greater inhibition of joint damage progression with KEVZARA 200 mg + MTX and KEVZARA 150 mg + MTX, respectively, at Week 52 relative to placebo + MTX.[1]
- Week 52 analysis employs a linear extrapolation method to impute missing or post-rescue data.[1]

#Structural joint damage was assessed radiographically and expressed as change in van der Heijde-mTSS and its components, the erosion score and joint space narrowing score at Week 52, in Study 1 (MOBILITY).[1] **These data are from the USPI and are consistent with the publication.[1,2] ††Indicates significant difference favoring KEVZARA + MTX vs placebo + MTX.[1] ‡‡Based on post hoc comparisons of mean change in mTSS per treatment group.

KEVZARA in combination with MTX provided improvements in symptomatic, functional, and radiographic outcomes compared with placebo plus MTX.[1]

SUMMARY OF ADVERSE EVENTS

In the overall long-term safety population from the USPI, the most frequent (incidence ≥3%) adverse reactions observed with KEVZARA® (sarilumab) in clinical studies were neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections. The most common serious adverse reactions were infections. The most common adverse reaction that resulted in discontinuation of therapy with KEVZARA was neutropenia. Decrease in ANC was not associated with the occurrence of infections, including serious infections.[1]

52-week safety data specific to the MOBILITY study are provided in the table below.[2]

Event, n (%)*†‡	KEVZARA 200 mg + MTX (n=424)	KEVZARA 150 mg + MTX (n=431)	Placebo + MTX (n=427)
AEs	331 (78.1)	321 (74.5)	263 (61.6)
SAEs	48 (11.3)	38 (8.8)	23 (5.4)
AEs leading to treatment discontinuation	59 (13.9)	54 (12.5)	20 (4.7)
AEs leading to death	1 (0.2)	2 (0.5)	2 (0.5)
Most frequent AEs by system organ class			
Infections and infestations	168 (39.6)	173 (40.1)	133 (31.1)
Upper respiratory infection	37 (8.7)	36 (8.4)	24 (5.6)
Bronchitis	24 (5.7)	14 (3.2)	17 (4.0)
Urinary tract infection	23 (5.4)	22 (5.1)	16 (3.7)
Blood and lymphatic disorders	80 (18.9)	51 (11.8)	11 (2.6)
Neutropenia	61 (14.4)	40 (9.3)	1 (0.2)
Leukopenia	18 (4.2)	9 (2.1)	0
Anemia	3 (0.7)	1 (0.2)	7 (1.6)
Laboratory investigations	68 (16.0)	65 (15.1)	36 (8.4)
ALT levels increased	32 (7.5)	37 (8.6)	14 (3.3)
Transaminase levels increased	15 (3.5)	10 (2.3)	3 (0.7)
AST levels increased	5 (1.2)	3 (0.7)	3 (0.7)
GI disorders	64 (15.1)	49 (11.4)	46 (10.8)
Diarrhea	17 (4.0)	12 (2.8)	9 (2.1)
Nausea	13 (3.1)	9 (2.1)	9 (2.1)
Dyspepsia	6 (1.4)	4 (0.9)	5 (1.2)

*Adapted from Genovese MC, Fleischmann R, Kivitz AJ, et al. *Arthritis Rheumatol*. 2015;67:1424-1437. †Safety analyses were conducted in all patients in Cohorts 1 and 2§ who received ≥1 dose of study medication and who were randomized to receive KEVZARA 200 mg, KEVZARA 150 mg, or placebo. ‡Summary of AEs during double-blind period. §In Cohort 1, patients were randomized to receive placebo or 1 of 5 doses of KEVZARA (100 mg QW, 150 mg QW, 100 mg Q2W, 150 mg Q2W, or 200 mg Q2W). In Cohort 2, patients were randomized to receive KEVZARA 200 mg Q2W, KEVZARA 150 mg Q2W, or placebo in combination with weekly MTX.

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.
  - 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.

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

The MOBILITY study was sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.

To view the full manuscript, please click here.

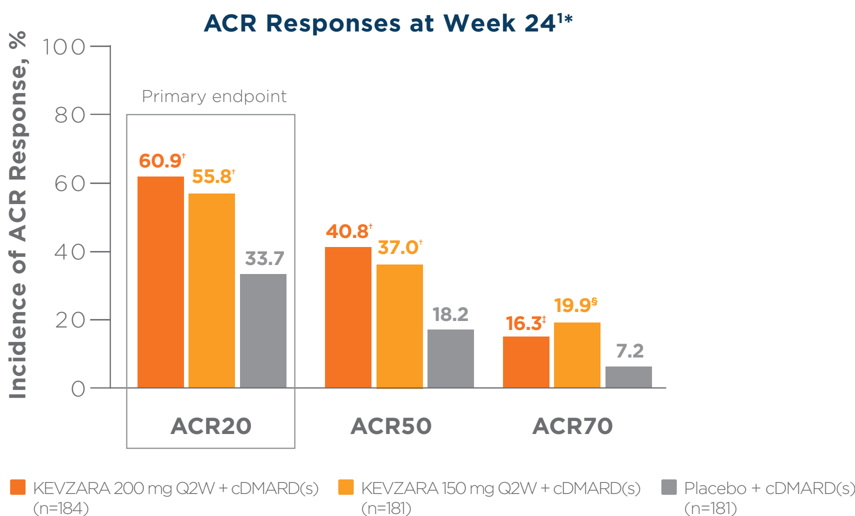
TARGET STUDY

Sarilumab and Nonbiologic Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Tumor Necrosis Factor Inhibitors

STUDY DESIGN

The TARGET trial evaluated the efficacy and safety of 2 different doses of KEVZARA® (sarilumab) in combination with cDMARD(s) in patients with moderately to severely active RA who had an inadequate clinical response or were intolerant to one or more TNF-α antagonists. Patients were randomized to receive KEVZARA 200 mg, KEVZARA 150 mg, or placebo, in combination with cDMARD(s).[1]

KEVZARA + cDMARD(s) PROVIDED IMPROVEMENTS IN SIGNS AND SYMPTOMS OF RA[1]



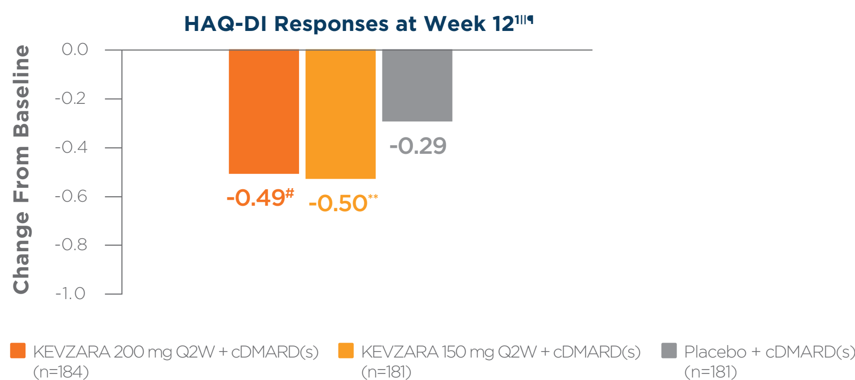
Both doses of KEVZARA + cDMARD(s) provided improved ACR20 responses at Week 24. ACR50 and ACR70 response rates were also improved compared with placebo + cDMARD(s) at Week 24.[1]

After Week 12 in TARGET, patients with inadequate response could have been treated with open-label KEVZARA 200 mg every 2 weeks.[3]

*Adapted from KEVZARA [prescribing information]. Bridgewater, NJ: Sanofi/Regeneron Pharmaceuticals, Inc.

†*P*<0.0001. ‡*P*<0.01. §*P*<0.001.

TREATMENT WITH KEVZARA + cDMARD(s) SHOWED IMPROVEMENT IN PHYSICAL FUNCTION[1]



Patients receiving either 200 mg or 150 mg of KEVZARA + cDMARD(s) had greater improvements in the other coprimary endpoint of HAQ-DI than those in the placebo + cDMARD(s)–treated group. Change from baseline in HAQ-DI score at Week 12 was greater with KEVZARA + cDMARD(s) than with placebo + cDMARD(s).[1]

||Adapted from KEVZARA (sarilumab). US Prescribing Information. Sanofi-Genzyme. Cambridge, MA and Regeneron Pharmaceuticals, Inc. Tarrytown, NY; May 2017.
¶These data are from the USPI and are consistent with the publication.[1,3] #Difference from placebo: -0.21 (95% CI: -0.33, -0.10). **Difference from placebo: -0.20 (95% CI: -0.32, -0.09).

Both doses of KEVZARA in combination with cDMARD(s) provided improvements in the signs and symptoms of RA and physical function compared with placebo.[1]

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.

ACR20, American College of Rheumatology 20% improvement criteria; cDMARD, conventional disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C-reactive protein; TJC, tender joint count; TNF, tumor necrosis factor.

SUMMARY OF ADVERSE EVENTS

In the overall long-term safety population from the USPI, the most frequent (incidence ≥3%) adverse reactions observed with KEVZARA® (sarilumab) in clinical studies were neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections. The most common serious adverse reactions were infections. The most common adverse reaction that resulted in discontinuation of therapy with KEVZARA was neutropenia. Decrease in ANC was not associated with the occurrence of infections, including serious infections.[1]

24-week safety data specific to the TARGET study are provided in the table below.[3]

Event, n (%)[3*]	KEVZARA 200 mg + cDMARD(s) (n=184)	KEVZARA 150 mg + cDMARD(s) (n=181)	Placebo + cDMARD(s) (n=181)
AEs	120 (65.2)	119 (65.7)	90 (49.7)
SAEs	10 (5.4)	6 (3.3)	6 (3.3)
AEs leading to treatment discontinuation	17 (9.2)	14 (7.7)	8 (4.4)
AEs leading to death	0	0	1 (0.6)
Most frequent AEs by system organ class			
Infections and infestations	56 (30.4)	40 (22.1)	48 (26.5)
Urinary tract infection	13 (7.1)	6 (3.3)	12 (6.6)
Nasopharyngitis	7 (3.8)	11 (6.1)	9 (5.0)
Pharyngitis	6 (3.3)	2 (1.1)	3 (1.7)
Upper respiratory tract infection	6 (3.3)	4 (2.2)	6 (3.3)
Blood and lymphatic disorders	29 (15.8)	25 (13.8)	9 (5.0)
Neutropenia	23 (12.5)	23 (12.7)	2 (1.1)
Thrombocytopenia	5 (2.7)	0	0
Leukopenia	3 (1.6)	2 (1.1)	0
Anemia	1 (0.5)	0	5 (2.8)
Laboratory investigations	30 (16.3)	19 (10.5)	8 (4.4)
ALT increased	10 (5.4)	5 (2.8)	2 (1.1)
AST increased	6 (3.3)	2 (1.1)	0
Transaminases increased†	3 (1.6)	2 (1.1)	0
Lipid levels			
TC increased from <240 mg/dL to ≥240 mg/dL	59/161 (36.6)	58/152 (38.2)	22/158 (13.9)
LDL increased from <160 mg/dL to ≥160 mg/dL	42/171 (24.6)	48/169 (28.4)	15/165 (9.1)
HDL increased from <60 mg/dL to ≥60 mg/dL	38/105 (36.2)	42/106 (39.6)	32/108 (29.6)

*Adapted from Fleischmann R et al. *Arthritis Rheumatol*. 2017;69:277-290. †Patients with increases in ALT and AST levels as reported by the investigator.[3]

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- ***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.

AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SAE, serious adverse event; TC, total cholesterol.

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

KEVZARA® (sarilumab) injection 200 mg

The TARGET study was sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.

To view the full manuscript, please click here.

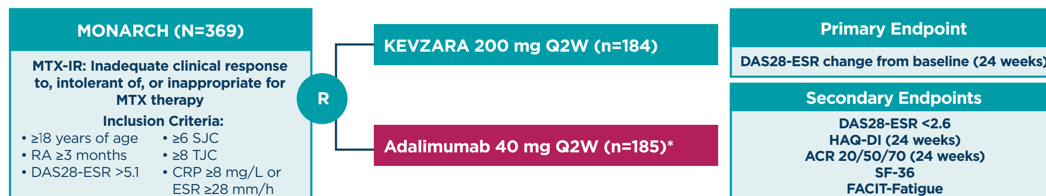
MONARCH STUDY

Efficacy and Safety of Sarilumab Monotherapy Versus Adalimumab Monotherapy for the Treatment of Patients with Active Rheumatoid Arthritis (MONARCH): A Randomised, Double-Blind, Parallel-Group Phase III Trial

STUDY DESIGN

The MONARCH trial was a multicenter, randomized, double-blind, double-dummy, active-controlled Phase 3 superiority study that evaluated the efficacy and safety of KEVZARA® (sarilumab) 200 mg Q2W monotherapy vs adalimumab 40 mg Q2W monotherapy in RA patients who should not continue treatment with MTX due to intolerance or inadequate response.[4]

Efficacy analyses were conducted in the ITT population, which included all randomized patients, including those who increased the dose frequency of adalimumab or matching placebo. Data collected after permanent treatment discontinuation were excluded.[4]



*The recommended dose of adalimumab SC is 40 mg Q2W. Some patients not taking concomitant MTX may derive additional benefit from increasing the SC dosing frequency to 40 mg QW; see adalimumab full Prescribing Information.[5]

ADDITIONAL CONTEXT

The objective of MONARCH was to compare efficacy and safety of KEVZARA monotherapy and adalimumab monotherapy in patients with active RA who should not continue treatment with MTX due to intolerance or inadequate response.[4]

MONARCH data are not included in the KEVZARA full Prescribing Information.[1]

DAS28-ESR and FACIT-Fatigue were endpoints evaluated in MONARCH; however, there are no DAS28-ESR and FACIT-Fatigue data contained in the KEVZARA USPI.[4]

Adalimumab and KEVZARA have different indications and can be used differently in clinical practice.[1,5]

The study design permitted dose escalation from adalimumab 40 mg Q2W to QW after Week 16 in patients who had not achieved at least 20% improvement in TJC and SJC. By Week 24, 8.6% of patients on adalimumab were dose-adjusted.[4]

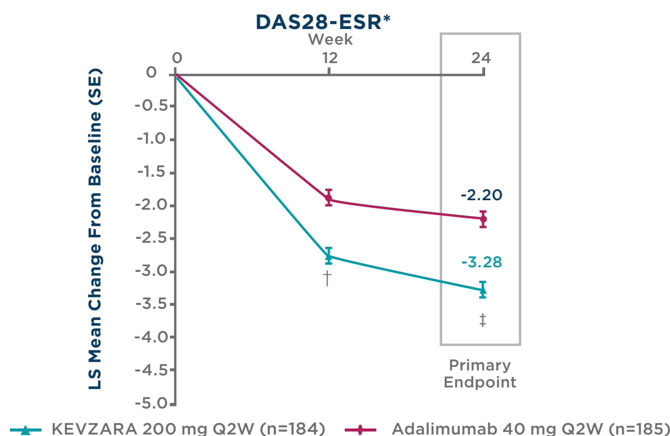
STUDY LIMITATIONS

KEVZARA and adalimumab can be used as monotherapy or in combination with non-biologic DMARDs. In MONARCH, both agents were only used as monotherapy.[1,4,5]

Evaluation of the efficacy of KEVZARA monotherapy compared with KEVZARA + MTX or adalimumab + MTX has not been conducted.[1]

MONARCH did not evaluate radiographic outcomes after treatment with KEVZARA monotherapy compared with adalimumab monotherapy.[4]

KEVZARA PROVIDED SIGNIFICANTLY GREATER IMPROVEMENTS IN DAS28-ESR THAN ADALIMUMAB[4]



KEVZARA provided greater improvements in disease activity and the signs and symptoms of RA than adalimumab, as measured by greater reductions in DAS28-ESR, the primary endpoint (see figure on left), and DAS28-CRP.

A greater proportion of patients who received KEVZARA achieved low disease activity at Week 24, defined as DAS28-ESR <2.6, compared with the adalimumab group (26.6% vs 7.0%; *P*<0.0001).

The mean change in DAS28-CRP at Week 24 was -2.86 in the KEVZARA group and -1.97 in the adalimumab group (difference: -0.88 [95% CI: -1.14 to -0.63; nominal *P*<0.0001).

*Adapted from Burmester GR et al. *Ann Rheum Dis*. 2017;76:840-847.
†Difference: -0.89 (95% CI: -1.18 to -0.59; nominal *P*<0.0001).
‡Difference: -1.08 (95% CI: -1.36 to -0.79; *P*<0.0001).

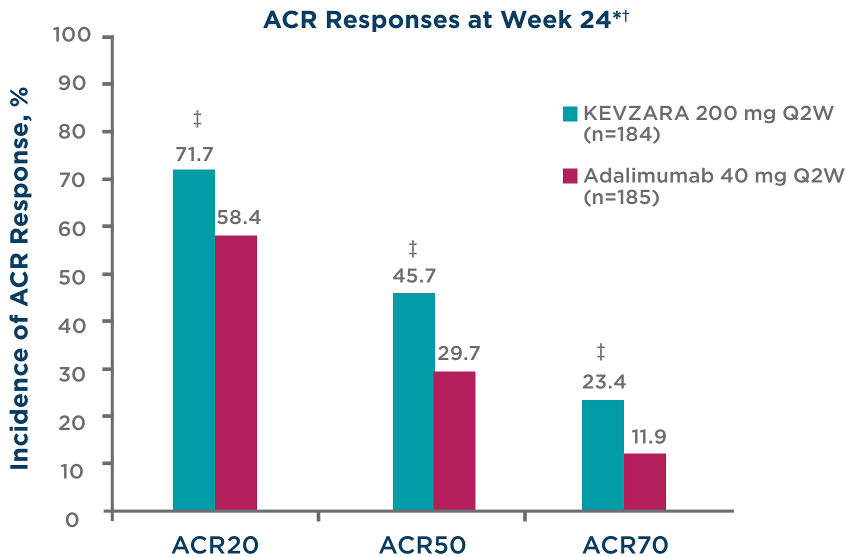
IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS

- **For Rheumatoid Arthritis:** The most common serious adverse reactions were infections. The most frequently observed serious infections included pneumonia and cellulitis. The most common adverse reactions (occurred in at least 3% of patients treated with KEVZARA + DMARDs) are neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections.

ACR20/50/70, American College of Rheumatology 20%, 50%, and 70% improvement criteria; CRP, C-reactive protein; DAS28, disease activity score using 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; IR, inadequate responder; ITT, intention-to-treat; MTX, methotrexate; Q2W, every 2 weeks; QW, once a week; R, randomization; SC, subcutaneous; SJC, swollen joint count; TJC, tender joint count.

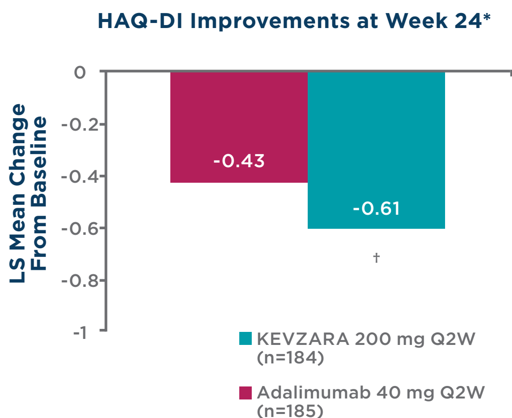
KEVZARA PROVIDED SIGNIFICANTLY GREATER IMPROVEMENTS IN ACR20/50/70 THAN ADALIMUMAB[4]



A significantly greater proportion of patients who received KEVZARA® (sarilumab) achieved ACR20, ACR50, and ACR70 responses by Week 24, compared with patients who took adalimumab.

*Sensitivity analyses and statistical methods are described in the online supplementary appendix. Sensitivity analyses for the primary endpoint were consistent with the primary analysis.
†Adapted from Burmester GR et al. *Ann Rheum Dis*. 2017;76:840-847.
‡*P*<0.01 vs adalimumab.

TREATMENT WITH KEVZARA LED TO A SIGNIFICANTLY GREATER MEAN CHANGE FROM BASELINE IN HAQ-DI VS ADALIMUMAB[4]



Patients who received KEVZARA had greater improvements in HAQ-DI scores at Week 24 compared with those receiving adalimumab. Additionally, the proportion of patients who demonstrated a clinically meaningful improvement of ≥0.3 units was greater in the KEVZARA group than in the adalimumab group (62.0% vs 47.6%; nominal *P*<0.01).

*Adapted from Burmester GR et al. *Ann Rheum Dis*. 2017;76:840-847.
†Difference: -0.18 (95% CI: -0.31 to -0.06; *P*=0.0037).

- At Week 24, patients treated with KEVZARA had significantly greater improvement in SF-36 PCS compared with adalimumab-treated patients (8.7 vs 6.1; *P*=0.0006). Both groups demonstrated similar improvements in SF-36 MCS at Week 24 (7.9 vs 6.8; *P*=0.3319)
- Improvements from baseline to Week 24 in FACIT-Fatigue scores were observed in both groups (10.2 vs 8.4; *P*=0.0689)

Please see summary of MONARCH adverse events on following page.

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.

FACIT, Functional Assessment of Chronic Illness Therapy; LS, least squares; MCS, mental component score; PCS, physical component score; SE, standard error.

MONARCH: SUMMARY OF ADVERSE EVENTS[4]

The most commonly observed adverse reactions were neutropenia and injection site reactions in the KEVZARA group, and headache and worsening RA in the adalimumab group. Neutrophil counts of ≤1.0 Giga/L occurred at a higher rate with KEVZARA than with adalimumab (10.3% vs 1.1%).

n (%)*	KEVZARA 200 mg Q2W (n=184)	Adalimumab 40 mg Q2W (n=184)†
Overall results		
AEs	118 (64.1)	117 (63.6)
SAEs	9 (4.9)	12 (6.5)
AEs leading to treatment discontinuation	11 (6.0)	13 (7.1)
AEs *(≥3% in any treatment group)*		
Infections	53 (28.8)	51 (27.7)
Bronchitis	12 (6.5)	7 (3.8)
Nasopharyngitis	11 (6.0)	14 (7.6)
Upper respiratory infection	3 (1.6)	7 (3.8)
Neutropenia	25 (13.6)	1 (0.5)
Headache	7 (3.8)	12 (6.5)
Rheumatoid arthritis	1 (0.5)	7 (3.8)
Injection site erythema	14 (7.6)	6 (3.3)
Alanine aminotransferase increased	7 (3.8)	7 (3.8)
Accidental overdose‡	6 (3.3)	11 (6.0)
Dyslipidemia§	3 (1.6)	8 (4.3)
Serious infections		
Patients with at least 1 serious infection	2 (1.1)	2 (1.1)
Bursitis, infective	1 (0.5)	0
Mastitis	1 (0.5)	0
Arthritis, bacterial	0	1 (0.5)
Respiratory tract infection	0	1 (0.5)
Deaths‖	1 (0.5)	0

*Adapted from Burmester GR et al. *Ann Rheum Dis*. 2017;76:840-847. †One patient was randomized but not treated in the adalimumab group and was not included in the safety population. ‡Protocol defined as ≥2 doses within 11 calendar days or within 6 days for adalimumab-treated patients who switched to weekly dosing. §Dyslipidemia was defined by standardized MedDRA query. ‖One patient in the KEVZARA group died of acute cardiac failure secondary to aortic dissection and papillary muscle rupture on Day 36.

- 16 patients (8.7%) receiving KEVZARA and two patients (1.1%) receiving adalimumab had an ANC between ≥0.5 and 1 Giga/L, and 3 patients (1.6%) receiving KEVZARA reported an ANC of <0.5 Giga/L. There was no evidence of an association between decreases in neutrophil counts and risk of infections or serious infections.
- The mean increase in ALT at Week 24 was greater in the KEVZARA group (6.1 IU/L) compared with the adalimumab group (2.1 IU/L).
- More patients in the KEVZARA group demonstrated a greater mean increase from baseline in LDL-C compared with patients in the adalimumab group (0.27 mmol/L vs no change).

IMPORTANT SAFETY INFORMATION (CONT'D)

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 additional Important Safety Information throughout and click here for full Prescribing Information, including Boxed WARNING.

REFERENCES

1. KEVZARA [prescribing information]. Bridgewater, NJ: Sanofi/Regeneron Pharmaceuticals, Inc.
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3. Fleischmann R, van Adelsberg J, Lin Y, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. *Arthritis Rheumatol*. 2017;69:277-290.
4. Burmester GR, Lin Y, Patel R, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis*. 2017;76:840-847.
5. Humira (adalimumab). US Prescribing Information. AbbVie Inc. North Chicago, IL 60064.

AE, adverse event; ALT, alanine aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

MONARCH was sponsored by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.[4]

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