1. NAME OF THE MEDICINAL PRODUCT

Kevzara 150 mg solution for injection in pre-filled syringe
Kevzara 150 mg solution for injection in pre-filled pen
Kevzara 200 mg solution for injection in pre-filled syringe
Kevzara 200 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kevzara 150 mg solution for injection in pre-filled syringe
Each pre-filled syringe contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).
Kevzara 150 mg solution for injection in pre-filled pen
Each pre-filled pen contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).

Kevzara 200 mg solution for injection in pre-filled syringe
Each pre-filled syringe contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).
Kevzara 200 mg solution for injection in pre-filled pen
Each pre-filled pen contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).

Sarilumab is a human monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology.
For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear, colourless to pale yellow sterile solution of approximately pH 6.0.

4. CLINICAL PARTICULARS

The marketing of Kevzara is subject to a risk management plan (RMP) including a 'Patient safety information card'. The Patient safety information card' emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

4.1 Therapeutic indications

Rheumatoid Arthritis (RA)
Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see section 5.1).

Polymyalgia Rheumatica (PMR)
KEVZARA is indicated for treatment of adult patients with polymyalgia rheumatica who cannot tolerate corticosteroid taper.

4.2 Posology and method of administration

Treatment should be initiated and supervised by healthcare professionals experienced in the diagnosis and treatment of rheumatoid arthritis and polymyalgia rheumatica.

Posology
Rheumatoid Arthritis
The recommended dose of sarilumab is 200 mg once every 2 weeks administered as a subcutaneous injection.

Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and liver enzyme elevations.

Polymyalgia Rheumatica
Initiate treatment with Kevzara in patients who had at least one episode of unequivocal PMR flare while attempting to taper prednisone at a dose that is ≥7.5 mg/day or equivalent
The recommended dosage of KEVZARA is 200 mg once every two weeks given as a subcutaneous injection, in combination with a tapering course of systemic corticosteroids. KEVZARA can be used as monotherapy following discontinuation of corticosteroids.

Discontinue KEVZARA if the patient develops neutropenia (using ANC results obtained at the end of the dosing interval), thrombocytopenia, or liver enzyme abnormalities.

Dose modification:
Treatment with sarilumab should be withheld in patients who develop a serious infection or an opportunistic infection until the infection is controlled [see Special warnings and precautions for use (4.4)].

Initiating treatment with sarilumab is not recommended in patients with a low neutrophil count, i.e. absolute neutrophil count (ANC) less than 2×10^9/L.

Initiating treatment with sarilumab is not recommended in patients with a platelet count below 150×10^3/µL.

Table 1: Dosage Modifications due to Neutropenia, Thrombocytopenia, or Elevated Liver Enzymes in Patients with Rheumatoid Arthritis (see sections 4.4 and 4.8):

Low Absolute Neutrophil Count (see section 5.1)	
Lab Value (cells x 10^9/L)	**Recommendation**
ANC greater than 1	Current dose of sarilumab should be maintained.
ANC 0.5-1	Treatment with sarilumab should be withheld until >1 x 10^9/L. sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ANC less than 0.5	Treatment with sarilumab should be discontinued.

Low Platelet Count	
Lab Value (cells x 10^3/µL)	**Recommendation**
50 to 100	Treatment with sarilumab should be withheld until >100 x 10^3/µL. sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
Less than 50	If confirmed by repeat testing, treatment with sarilumab should be discontinued.

Liver Enzyme Abnormalities	
Lab Value	**Recommendation**
ALT > 1 to 3 x Upper Limit of Normal (ULN)	Clinically appropriate dose modification of concomitant DMARDs should be considered.
ALT > 3 to 5 x ULN	Treatment with sarilumab should be withheld until < 3 x ULN. sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ALT > 5 x ULN	Treatment with sarilumab should be discontinued.

Dosage Modifications for Patients with Polymyalgia Rheumatica

- Laboratory Abnormalities: Discontinue KEVZARA in patients with PMR who develop the following laboratory abnormalities [see Special warnings and precautions for use (4.4)]:
  - neutropenia (ANC below 1,000 per mm^3 at the end of the dosing interval)
  - thrombocytopenia (platelet count below 100,000 per mm^3)
  - ALT elevations 3 times above the ULN

Dosage modifications have not been studied in patients with PMR with these conditions. For treatment initiation criteria, refer to the dosage recommendations for PMR [see Posology and method of administration (4.2)].

Missed dose

If a dose of sarilumab is missed and it has been 3 days or less since the missed dose, the next dose should be administered as soon as possible. The subsequent dose should be administered at the regularly scheduled time. If it has been 4 days or more since the missed dose, the subsequent dose should be administered at the next regularly scheduled time, the dose should not be doubled.

Special populations

Renal impairment

No dose adjustment is required in patients with mild to moderate renal impairment. Sarilumab has not been studied in patients with severe renal impairment (see section 5.2).

Hepatic impairment

The safety and efficacy of sarilumab have not been studied in patients with hepatic impairment, including patients with positive hepatitis B virus (HBV) or hepatitis C virus (HCV) serology (see section 4.4).

Elderly

No dose adjustment is required in patients over 65 years of age (see section 4.4).

Paediatric population
The safety and efficacy of sarilumab in children up to 18 years of age have not been established. No data are available.

Method of administration
Subcutaneous use.

The total content (1.14 ml) of the pre-filled syringe/pre-filled pen should be administered as a subcutaneous injection. Injection sites (abdomen, thigh and upper arm) should be rotated with each injection. sarilumab should not be injected into skin that is tender, damaged, or has bruises or scars.

A patient may self-inject sarilumab or the patient's caregiver may administer sarilumab if their healthcare professional determines that it is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of sarilumab prior to use.

Comprehensive instructions for administration of this medicinal product are given in the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Serious infections
Patients should be closely monitored for the development of signs and symptoms of infection during treatment with sarilumab (see sections 4.2 and 4.8). As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Sarilumab should not be administered in patients with an active infection, including localised infections. The risks and benefits should be considered prior to initiating treatment in patients who have:
- chronic or recurrent infection;
- a history of serious or opportunistic infections;
- HIV infection;
- underlying conditions that may predispose them to infection;
- been exposed to tuberculosis; or
- lived in or travelled to areas of endemic tuberculosis or endemic mycoses.

Treatment with sarilumab should be withheld if a patient develops a serious infection or an opportunistic infection.

A patient who develops an infection during treatment should also undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

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 sarilumab. The most frequently observed serious infections with sarilumab included pneumonia and cellulitis (see section 4.8). Among opportunistic infections, tuberculosis, candidiasis, and

pneumocystis were reported with sarilumab. In isolated cases, disseminated rather than localised infections were observed in patients often taking concomitant immunosuppressants such as MTX or corticosteroids.

Tuberculosis
Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating treatment with sarilumab. Patients with latent or active tuberculosis should be treated with standard antimycobacterial therapy before initiating treatment. Anti-tuberculosis therapy should be considered prior to initiation of treatment in patients with a past medical history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. When considering anti-tuberculosis therapy, consultation with a physician with expertise in tuberculosis may be appropriate.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Viral reactivation
Viral reactivation has been reported with immunosuppressive biologic therapies. Cases of herpes zoster were observed in clinical studies with sarilumab (see section 4.8). No cases of Hepatitis B reactivation were reported in the clinical studies; however patients who were at risk for reactivation were excluded.

Laboratory parameters
Neutrophil count
Treatment with sarilumab was associated with a higher incidence of decrease in ANC (see section 4.8). Decrease in ANC was not associated with higher incidence of infections, including serious infections.

- Initiating treatment with sarilumab is not recommended in patients with a low neutrophil count, i.e., ANC less than 2 x 10^9/L. In patients who develop an ANC less than 0.5 x 10^9/L, treatment with sarilumab should be discontinued (see section 4.2).
- Neutrophil count should be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter. For recommended dose modifications based on ANC results, see section 4.2.
- Based on the pharmacodynamics of the changes in ANC, results obtained at the end of the dosing interval should be used when considering dose modification (see section 5.1).

Platelet count
Treatment with sarilumab was associated with a reduction in platelet counts in clinical studies. Reduction in platelets was not associated with bleeding events (see section 4.8).

- Initiating treatment with sarilumabis not recommended in patients with a platelet count below 150 x10^3/μL. In patients who develop a platelet count less than 50 x 10^3/ μL, treatment with sarilumab should be discontinued.
- Platelet count should be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter. For recommended dose modifications based on platelet counts, see section 4.2.

Liver enzymes
Treatment with sarilumab was associated with a higher incidence of transaminase elevations. These elevations were transient and did not result in any clinically evident hepatic injury in clinical studies (see section 4.8). Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic medicinal products (e.g., MTX) were used in combination with sarilumab.

Initiating treatment with sarilumab is not recommended in patients with elevated transaminases, ALT or AST greater than 1.5 x ULN. In patients who develop elevated ALT greater than 5 x ULN, treatment with sarilumab should be discontinued (see section 4.2).

ALT and AST levels should be monitored 4 to 8 weeks after start of therapy and every 3 months thereafter. When clinically indicated, consider other liver function tests such as bilirubin. For recommended dose modifications based on transaminase elevations, see section 4.2.

Lipid abnormalities
Lipid levels may be reduced in patients with chronic inflammation. Treatment with sarilumab was associated with increases in lipid parameters such as LDL cholesterol, HDL cholesterol, and/or triglycerides (see section 4.8).

Lipid parameters should be assessed approximately 4 to 8 weeks following initiation of treatment with sarilumab, then at approximately 6 month intervals.
Patients should be managed according to clinical guidelines for the management of hyperlipidaemia.

Gastrointestinal perforation and diverticulitis
Cases of gastrointestinal perforation and diverticulitis have been reported in association with sarilumab. Gastrointestinal perforation has been reported in patients with and without diverticulitis. Sarilumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with new onset abdominal symptoms such as persistent pain with fever should be evaluated promptly (see section 4.8).

Malignancies
Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with sarilumab on the development of malignancies is not known but malignancies were reported in clinical studies (see section 4.8).

Hypersensitivity reactions
Hypersensitivity reactions have been reported in association with sarilumab (see section 4.8). Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Patients should be advised to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, administration of sarilumab should be stopped immediately (see section 4.3).

Hepatic impairment
Treatment with sarilumab is not recommended in patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8).

Vaccinations
Concurrent use of live vaccines as well as live attenuated vaccines should be avoided during treatment with sarilumab as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving sarilumab. Prior to initiating treatment, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines. The interval between live vaccinations and initiation of therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents (see section 4.5).

Cardiovascular risk
RA patients have an increased risk for cardiovascular disorders and risk factors (e.g. hypertension, hyperlipidaemia) should be managed as part of usual standard of care.

4.5 Interaction with other medicinal products and other forms of interaction

Sarilumab exposure was not affected when coadministered with MTX based on the population pharmacokinetic analyses and across study comparisons. MTX exposure is not expected to be changed by sarilumab coadministration; however, no clinical data was collected. Sarilumab has not been investigated in combination with Janus kinase (JAK) inhibitors or biological DMARDs such as Tumor Necrosis Factor (TNF) antagonists.

Various *in vitro* and limited *in vivo* human studies have shown that cytokines and cytokine modulators can influence the expression and activity of specific cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) and therefore have the potential to alter the pharmacokinetics of concomitantly administered medicinal products that are substrates of these enzymes. Elevated levels of interleukin-6 (IL-6) 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 signalling by IL-6Rα antagonists such as sarilumab might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered medicinal products concentrations.

The modulation of IL-6 effect on CYP enzymes by sarilumab may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of sarilumabin patients being treated with CYP substrate medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., theophylline) should be performed and the individual dose of the medicinal product should be adjusted as needed.

Caution should be exercised in patients who start sarilumab treatment while on therapy with CYP3A4 substrates (e.g., oral contraceptives or statins), as sarilumab may reverse the inhibitory effect of IL-6 and restore CYP3A4 activity, leading to decreased exposure and activity of CYP3A4 substrate (see section 5.2).Interaction of sarilumab with substrates of other CYPs (CYP2C9, CYP 2C19, CYP2D6) has not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective contraception during and up to 3 months after treatment.

Pregnancy
There are no or limited amount of data from the use of sarilumab in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Sarilumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab.

Breast-feeding
It is unknown whether sarilumab is excreted in human milk or absorbed systemically after ingestion. The excretion of sarilumab in milk has not been studied in animals (see section 5.3).
Because IgG1 are excreted in human milk**,** a decision must be made whether to discontinue breast-feeding or to discontinue sarilumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No data are available on the effect of sarilumab on human fertility. Animal studies showed no impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Kevzara has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Rheumatoid Arthritis

Summary of the safety profile

The most frequent adverse reactions are neutropenia (14.2%), upper respiratory infections (7.1%), increased ALT (6.8%), urinary tract infections (5.7%), and injection site erythema (5.3%). The most common serious adverse reactions are infections (2.9%) (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions listed in the table have been reported in controlled clinical studies. The frequency of adverse reactions listed below is defined using the following convention:
very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: Adverse reactions

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infection
		Urinary tract infection
		Nasopharyngitis
		Oral herpes
	Uncommon	Pneumonia
		Cellulitis
		Diverticulitis
Blood and lymphatic system disorders	Very common	Neutropenia
	Common	Thrombocytopenia
		Leukopenia
Metabolism and nutrition disorders	Common	Hypercholesterolemia
		Hypertriglyceridemia
Gastrointestinal disorders	Rare	Gastrointestinal perforation
Hepatobiliary disorders	Common	Transaminases increased
General disorders and administration site conditions	Common	Injection site erythema
		Injection site pruritus

Description of selected adverse reactions

Infections

In the placebo-controlled population, the rates of infections were 84.5, 81.0, and 75.1 events per 100 patient-years, in the 200 mg and 150 mg sarilumab+ DMARDs and placebo + DMARDs groups respectively. The most commonly reported infections (5% to 7% of patients) were upper respiratory tract infections, urinary tract infections, and nasopharyngitis. The rates of serious infections were 4.3, 3.0, and 3.1 events per 100 patient-years, in the 200 mg, 150 mg sarilumab+ DMARDs, and placebo + DMARDs groups, respectively.

In the sarilumab+DMARDs long-term safety population, the rates of infections and serious infection were 57.3 and 3.4 events per 100-patient years, respectively.

The most frequently observed serious infections included pneumonia and cellulitis. Cases of opportunistic infection have been reported (see section 4.4).

The overall rates of infections and serious infections in the sarilumab monotherapy population were consistent with rates in the sarilumab+ DMARDs population.

Gastrointestinal perforation
Gastrointestinal perforation was reported in patients with and without diverticulitis. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medicinal products (NSAIDs), corticosteroids, or methotrexate. The contribution of these concomitant medications relative to sarilumab in the development of gastrointestinal perforations is not known (see section 4.4).

Hypersensitivity reactions
In the placebo-controlled population, the proportion of patients who discontinued treatment due to hypersensitivity reactions was higher among those treated with sarilumab (0.9% in 200 mg group, 0.5% in 150 mg group) than placebo (0.2%). The rates of discontinuations due to hypersensitivity in the sarilumab+ DMARDs long-term safety population and the sarilumab monotherapy population were consistent with the placebo-controlled population. In the placebo-controlled population, 0.2% of the patients treated with sarilumab 200 mg every two weeks (q2w) + DMARD reported serious adverse reactions of hypersensitivity reactions, and none from sarilumab 150 mg q2w + DMARD group.

Injection site reactions
In the placebo-controlled population, injection site reactions were reported in 9.5%, 8%, and 1.4% of patients receiving sarilumab 200 mg, 150 mg, and placebo respectively. These injection site reactions (including erythema and pruritus) were mild to moderate in severity for the majority of patients (99.5%, 100%, and 100%, for sarilumab 200 mg, 150 mg, and placebo respectively). Two patients on sarilumab (0.2%) discontinued treatment due to injection site reactions.

Laboratory abnormalities
To allow for a direct comparison of frequency of laboratory abnormalities between placebo and active treatment, data from weeks 0-12 were used as this was prior to patients being permitted to switch from placebo to sarilumab.

Neutrophil count
Decreases in neutrophil counts below 1 x 10^9/L occurred in 6.4% and 3.6% of patients in the 200 mg and 150 mg sarilumab+ DMARDs group, respectively, compared to no patients in the placebo + DMARDs group. Decreases in neutrophil counts below 0.5 x 10^9/L occurred in 0.8% and 0.6% of patients in the 200 mg and 150 mg sarilumab+ DMARDs groups, respectively. In patients experiencing a decrease in absolute neutrophil count (ANC), modification of treatment regimen such as interruption of sarilumab or reduction in dose resulted in an increase or normalisation of ANC (see section 4.2).

Decrease in ANC was not associated with higher incidence of infections, including serious infections.

In the sarilumab+ DMARDs long-term safety population and the sarilumab monotherapy population, the observations on neutrophil counts were consistent with those seen in the placebo-controlled population (see section 4.4).

Platelet count
Decreases in platelet counts below 100 x 10^3/µL occurred in 1.2% and 0.6% of patients on 200 mg and 150 mg sarilumab+ DMARDs, respectively, compared to no patients on placebo + DMARDs**.**

In the sarilumab+ DMARDs long-term safety population and the sarilumab monotherapy population, the observations on platelet counts were consistent with those seen in the placebo-controlled population.

There were no bleeding events associated with decreases in platelet count.

Liver enzymes
Liver enzyme abnormalities are summarised in Table 3. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as interruption of treatment or reduction in dose, resulted in decrease or normalisation of liver enzymes (see section 4.2). These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency (see section 4.4).

Table 3: Incidence of liver enzyme abnormalities in controlled clinical studies

	Placebo + DMARD N = 661	**Sarilumab 150 mg + DMARD N = 660**	**Sarilumab 200 mg + DMARD N = 661**	**Sarilumab monotherapy any Dose N = 467**
AST				
>3 x ULN – 5 x ULN	0%	1.2%	1.1%	1.1%
>5 x ULN	0%	0.6%	0.2%	0%
ALT				
>3 x ULN – 5 x ULN	0.6%	3.2%	2.4%	1.9%
>5 x ULN	0%	1.1%	0.8%	0.2%

Lipids
Lipid parameters (LDL, HDL, and triglycerides) were first assessed at 4 weeks following initiation of sarilumab+ DMARDs in the placebo-controlled population. At week 4 the mean LDL increased by 14 mg/dL; mean triglycerides increased by 23 mg/dL; and mean HDL increased by 3 mg/dL. After week 4 no additional increases were observed. There were no meaningful differences between doses.

In the sarilumab+ DMARDs long-term safety population and the sarilumab monotherapy population, the observations in lipid parameters were consistent with those seen in the placebo-controlled population.

Malignancies
In the placebo-controlled population, malignancies occurred at the same rate in patients receiving either sarilumab+ DMARDs or placebo + DMARDs (1.0 events per 100 patient-years).

In the sarilumab+ DMARDs long-term safety population and the sarilumab monotherapy population, the rates of malignancies were consistent with the rate observed in the placebo-controlled population (see section 4.4).

Polymyalgia Rheumatica
Safety has been studied in one Phase 3 study (SAPHYR) in 117 PMR patients of whom 59 received subcutaneous KEVZARA 200 mg [Pharmacodynamic properties (5.1)]. Of these, 45 patients received KEVZARA for at least 24 weeks, 44 patients for at least 40 weeks, and 10 patients for at least 52 weeks. The total patient years duration in the KEVZARA PMR population was 47.37 patient years during the 12-month double blind, placebo-controlled study.

The common adverse reactions occurring in ≥5% of patients treated with KEVZARA were neutropenia (15.3%), leukopenia (6.8%), constipation (6.8%), rash pruritic (5.1%), myalgia (6.8%), fatigue (5.1%), and injection site pruritus (5.1%).

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.

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

Overall Infections
In SAPHYR, the proportion of patients with infections was lower in the KEVZARA group (37.3%) compared to the placebo group (50.0%). Two patients (3.2%) in the KEVZARA group and 1 patient (1.7%) in the placebo group had an event of herpes zoster.

Serious infections
In SAPHYR, the proportion of patients with serious infections was similar in the KEVZARA group (5.1%) compared to the placebo group (5.2%).

Injection Site Reactions
In SAPHYR, three patients (5.1%) in the KEVZARA group experienced injection site reactions of pruritus which were mild in severity. No patient in the placebo group experienced injection site reactions.

Laboratory Abnormalities
Decreased neutrophil count
In SAPHYR, decreases in neutrophil counts less than 1,000 per mm^3 occurred in 12% of the KEVZARA treated group and no patient in the placebo treated group. Decreases in neutrophil counts less than 500 per mm^3 occurred in 3.4% of patients in KEVZARA treated group compared to no patient in the placebo treated group.

Decreased platelet count
In SAPHYR, decreases in platelet counts between 75,000 to 100,000 per mm^3 occurred in two patients (3.4%) in the KEVZARA group, compared to no patient in the placebo treated group. These platelet count decreases were transient and not associated with bleeding events.

Elevated liver enzymes
In SAPHYR, no KEVZARA treated patients had an ALT or AST greater than 3 times the upper limit of normal (ULN). In the placebo treated group, 2 patients had ALT elevations greater than 3 times the ULN.

Lipid Abnormalities
In SAPHYR, cholesterol levels ≥299.27 mg/dL were observed in 8/58 (13.8%) patients in the KEVZARA group compared to 4/58 (6.9%) patients in the placebo group. Triglycerides ≥407.4 mg/dL were observed in 3/58 (5.2%) patients in the KEVZARA group compared to 1/58 (1.7%) in the placebo group.

No significant differences in mean HDL between KEVZARA group and placebo group were observed. At Week 52, mean increase from baseline for LDL and triglycerides levels were observed in the KEVZARA group though both remained within the normal range.

Rheumatoid Arthritis and Polymyalgia Rheumatica

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with sarilumab.

In the placebo-controlled population, 4.0%, 5.6%, and 2.0% of RA patients treated with sarilumab 200 mg + DMARDs, sarilumab 150 mg + DMARDs and placebo + DMARDs respectively, exhibited a positive response in the anti-drug antibody (ADA) assay. Positive responses in the neutralising antibody (NAb) assay were detected in 1.0%, 1.6%, and 0.2% of patients on sarilumab 200 mg, sarilumab150 mg, and placebo respectively.

In the RA sarilumab monotherapy population, observations were consistent with the sarilumab + DMARDs population. Anti Drug Antibody (ADA) formation may affect pharmacokinetics of sarilumab. No correlation was observed between ADA development and either loss of efficacy or adverse reactions. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used and testing conditions. For these reasons, comparison of the incidence of antibodies to sarilumab with the incidence of antibodies to other products may be misleading.

In the PMR population, 1 patient (1.8%) in the KEVZARA 200 mg + 14-week corticosteroid taper group exhibited an ADA response. None of the patients in the placebo +52-week corticosteroid taper group exhibited an ADA response. Neutralizing antibodies were detected in the PMR patient with ADA response on KEVZARA 200 mg; the patient did not demonstrate a clinical response. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the safety, and/or effectiveness of sarilumab is unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

There is no specific treatment for Kevzara overdose. In the event of an overdose, the patient should be closely monitored, treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosupressants, Interleukin inhibitors, ATC code: L04AC14

Mechanism of action
Sarilumab is a human monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-bound IL-6 receptors (IL-6Rα), and inhibits IL-6-mediated signalling which involves ubiquitous signal-transducing glycoprotein 130 (gp130) and the Signal Transducer and Activator of Transcription-3 (STAT-3).

In functional human cell-based assays, sarilumab was able to block the IL-6 signalling pathway, measured as STAT-3 inhibition, only in the presence of IL-6.

IL-6 is a pleiotropic cytokine that stimulates diverse cellular responses such as proliferation, differentiation, survival, and apoptosis and can activate hepatocytes to release acute-phase proteins, including C-reactive protein (CRP) and serum amyloid A. Elevated levels of IL-6 are found in the synovial fluid of patients with rheumatoid arthritis and play an important role in both the pathologic inflammation and joint destruction which are hallmarks of RA. IL-6 is involved in diverse physiological processes such as migration and activation of T-cells, B-cells, monocytes, and osteoclasts leading to systemic inflammation, synovial inflammation, and bone erosion in patients with RA.

The activity of sarilumab in reducing inflammation is associated with laboratory changes such as decrease in ANC and elevation in lipids (see section 4.4).

Pharmacodynamic effects
Following single-dose subcutaneous (SC) administration of sarilumab 200 mg and 150 mg in patients with RA rapid reduction of CRP levels was observed. Levels were reduced to normal as early as 4 days after treatment initiation. Following single-dose sarilumab administration, in patients with RA, ANC decreased to the nadir between 3 to 4 days and thereafter recovered towards baseline (see section 4.4). Treatment with sarilumab resulted in decreases in fibrinogen and serum amyloid A, and increases in haemoglobin and serum albumin.

Rheumatoid Arthritis
Clinical efficacy
The efficacy and safety of sarilumab were assessed in three randomised, double-blind, controlled multicentre studies (MOBILITY and TARGET were placebo-controlled studies and MONARCH was an active comparator-controlled study) in patients older than 18 years with moderately to severely active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline.

Placebo-controlled studies
MOBILITY evaluated 1197 patients with RA who had inadequate clinical response to MTX. Patients received sarilumab 200 mg, sarilumab 150 mg, or placebo every 2 weeks with concomitant MTX. The primary endpoints were the proportion of patients who achieved an ACR20 response at week 24, changes from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) score at week 16, and change from baseline in van der Heijde-modified Total Sharp Score (mTSS) at week 52.

TARGET evaluated 546 patients with RA who had an inadequate clinical response or were intolerant to one or more TNF-α antagonists. Patients received sarilumab 200 mg, sarilumab150 mg, or placebo every 2 weeks with concomitant conventional DMARDs (cDMARDs). The primary endpoints were the proportion of patients who achieved an ACR20 response at week 24 and the changes from baseline HAQ-DI score at week 12.

Clinical response
The percentages of sarilumab+ DMARDs-treated patients achieving ACR20, ACR50, and ACR70 responses in MOBILITY and TARGET are shown in Table 4. In both studies, patients treated with either 200 mg or 150 mg of sarilumab+ DMARDs every two weeks had higher ACR20, ACR50, and ACR70 response rates versus placebo-treated patients at week 24. These responses persisted through 3 years of therapy in an open-label extension study.

In MOBILITY, a greater proportion of patients treated with sarilumab 200 mg or 150 mg every two weeks plus MTX achieved remission, defined as Disease Activity Score 28-C-Reactive Protein (DAS28-CRP) < 2.6 compared with placebo + MTX at week 52. Results at 24 weeks in TARGET were similar to the results at 52 weeks in MOBILITY (see Table 4).

Table 4: Clinical response at weeks 12, 24, and 52 in placebo-controlled studies, MOBILITY and TARGET

	Percentage of patients					
	MOBILITY MTX inadequate responders			TARGET TNF inhibitor inadequate responders		
	Placebo + MTX N = 398	Sarilumab 150 mg + MTX N = 400	Sarilumab 200 mg + MTX N = 399	Placebo + cDMARDs* N = 181	Sarilumab 150 mg + cDMARDs* N = 181	Sarilumab 200 mg + cDMARDs* N = 184
Week 12						
DAS28-CRP remission (< 2.6)	4.8%	18.0%†††	23.1%†††	3.9%	17.1%†††	17.9%†††
ACR20	34.7%	54.0%†††	64.9%†††	37.6%	54.1%†	62.5%†††
ACR50	12.3%	26.5%†††	36.3%†††	13.3%	30.4%†††	33.2%†††
ACR70	4.0%	11.0%††	17.5%†††	2.2%	13.8%†††	14.7%†††
Week 24						
DAS28-CRP remission (< 2.6)	10.1%	27.8%†††	34.1%†††	7.2%	24.9%†††	28.8%†††
ACR20‡	33.4%	58.0%†††	66.4%†††	33.7%	55.8%†††	60.9%†††
ACR50	16.6%	37.0%†††	45.6%†††	18.2%	37.0%†††	40.8%†††
ACR70	7.3%	19.8%†††	24.8%†††	7.2%	19.9%††	16.3%†
Week 52						
DAS28-CRP remission (< 2.6)	8.5%	31.0%†††	34.1%†††	NA§	NA§	NA§
ACR20	31.7%	53.5%†††	58.6%†††			
ACR50	18.1%	40.0%†††	42.9%†††			
ACR70	9.0%	24.8%	26.8%			
Major clinical response¶	3.0%	12.8%†††	14.8%†††			

*cDMARDs in TARGET included MTX, sulfasalazine, leflunomide and hydroxychloroquine

† p-value <0.01 for difference from placebo

††p-value <0.001 for difference from placebo

†††p-value <0.0001 for difference from placebo

‡ Primary endpoint

§ NA=Not Applicable as TARGET was a 24-week study

¶ Major clinical response = ACR70 for at least 24 consecutive weeks during the 52-week period

In both MOBILITY and TARGET, higher ACR20 response rates were observed within 2 weeks compared to placebo and were maintained for the duration of the studies (see Figures 1 and 2).

Figure 1: Percent of ACR20 response by visit for MOBILITY

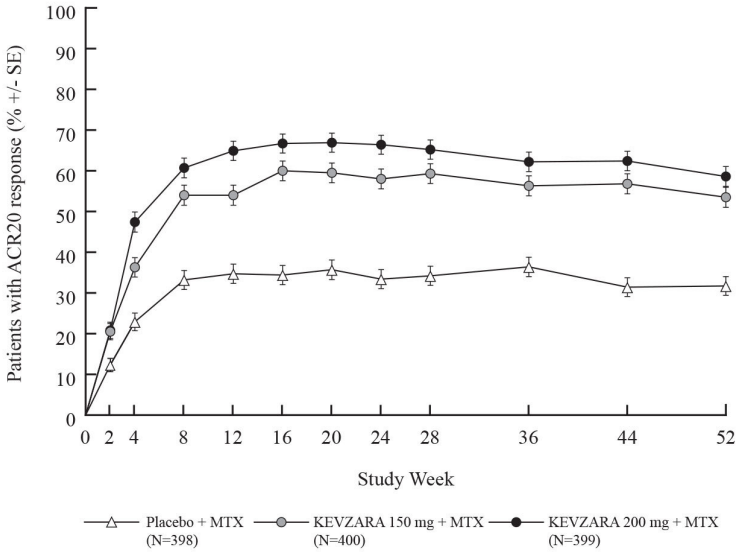
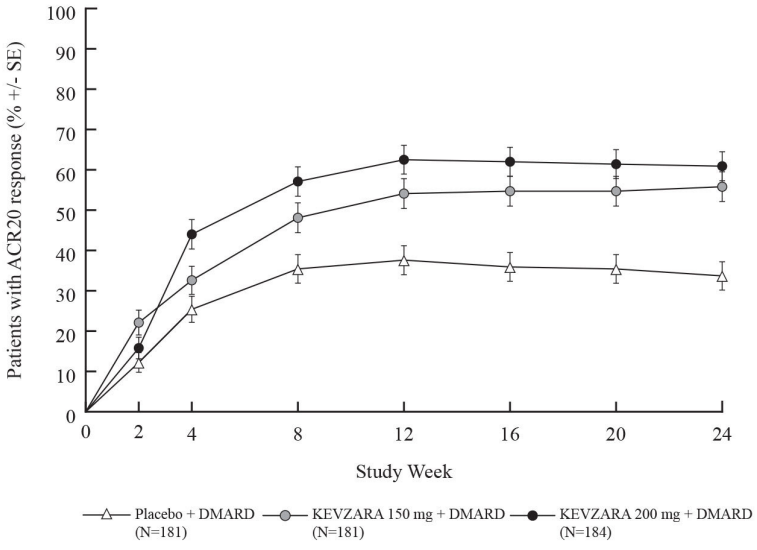


Figure 2: Percent of ACR20 response by visit for TARGET



The results of the components of the ACR response criteria at week 24 for MOBILITY and TARGET are shown in Table 5. Results at 52 weeks in MOBILITY were similar to the results at 24 weeks for TARGET.

Table 5: Mean reductions from baseline to week 24 in components of ACR score

	MOBILITY			TARGET		
Component (range)	**Placebo + MTX (N = 398)**	**Sarilumab 150 mg q2w* + MTX (N = 400)**	**Sarilumab 200 mg q2w* + MTX (N = 399)**	**Placebo + cDMARDs (N = 181)**	**Sarilumab 150 mg q2w* + cDMARDs (N = 181)**	**Sarilumab 200 mg q2w* + cDMARDs (N = 184)**
Tender Joints (0-68)	-14.38	-19.25†††	-19.00†††	-17.18	-17.30†	-20.58†††
Swollen Joints (0-66)	-8.70	-11.84†††	-12.43†††	-12.12	-13.04††	-14.03†††
Pain VAS† (0-100 mm)	-19.43	-30.75†††	-34.35†††	-27.65	-36.28††	-39.60†††
Physician global VAS‡ (0-100 mm)	-32.04	-40.69†††	-42.65†††	-39.44	-45.09†††	-48.08†††
Patient global VAS‡ (0-100 mm)	-19.55	-30.41†††	-35.07†††	-28.06	-33.88††	-37.36†††
HAQ-DI (0-3)	-0.43	-0.62†††	-0.64†††	-0.52	-0.60†	-0.69††
CRP	-0.14	-13.63†††	-18.04†††	-5.21	-13.11†††	-29.06†††

* q2w = every 2 weeks
‡ Visual analogue scale
†p-value <0.01 for difference from placebo
††p-value <0.001 for difference from placebo
†††p-value <0.0001 for difference from placebo

Radiographic response
In MOBILITY, structural joint damage was assessed radiographically and expressed as change in van der Heijde-modified Total Sharp Score (mTSS) and its components, the erosion score, and joint space narrowing score at week 52. Radiographs of hands and feet were obtained at baseline, 24 weeks, and 52 weeks and scored independently by at least two well-trained readers who were blinded to treatment group and visit number.

Both doses of sarilumab+ MTX were superior to placebo + MTX in the change from baseline in mTSS at 24 and 52 weeks (see Table 6). Less progression of both erosion and joint space narrowing scores at 24 and 52 weeks was reported in the sarilumab treatment groups compared to the placebo group.

Treatment with sarilumab+ MTX was associated with significantly less radiographic progression of structural damage as compared with placebo. At week 52, 55.6% of patients receiving sarilumab 200 mg and 47.8% of patients receiving sarilumab 150 mg had no progression of structural damage (as defined by a change in the TSS of zero or less) compared with 38.7% of patients receiving placebo.

Treatment with sarilumab 200 mg and 150 mg + MTX inhibited the progression of structural damage by 91% and 68%, respectively, compared to placebo + MTX at week 52.

The efficacy of sarilumab with concomitant DMARDs on inhibition of radiographic progression that was assessed as part of the primary endpoints at week 52 in MOBILITY was sustained up to three years from the start of treatment.

Table 6: Mean radiographic change from baseline at week 24 and week 52 in MOBILITY

	MOBILITY MTX Inadequate responders		
	Placebo + MTX (N = 398)	**Sarilumab 150 mg q2w* + MTX (N = 400)**	**Sarilumab 200 mg q2w* + MTX (N = 399)**
Mean change at week 24			
Modified Total Sharp Score (mTSS)	1.22	0.54†	0.13††
Erosion score (0-280)	0.68	0.26†	0.02††
Joint space narrowing score	0.54	0.28	0.12†
Mean change at week 52			
Modified Total Sharp Score (mTSS) ‡	2.78	0.90††	0.25††
Erosion score (0-280)	1.46	0.42††	0.05††
Joint space narrowing score	1.32	0.47†	0.20††

* q2w=every two weeks

† p-value <0.001

†† p-value <0.0001

‡ Primary end point

Physical function response

In MOBILITY and TARGET, physical function and disability were assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI). Patients receiving sarilumab 200 mg or 150 mg + DMARDs every two weeks demonstrated greater improvement from baseline in physical function compared to placebo at week 16 and week 12 in MOBILITY and TARGET, respectively.

MOBILITY demonstrated significant improvement in physical function, as measured by the HAQ-DI at week 16 compared to placebo (-0.58, -0.54, and -0.30 for sarilumab 200 mg + MTX, sarilumab 150 mg + MTX, and placebo + MTX, every two weeks, respectively). TARGET demonstrated significant improvement in HAQ-DI scores at week 12 compared to placebo (-0.49, -0.50, and -0.29 for sarilumab 200 mg + DMARDs, sarilumab 150 mg + DMARDs, and placebo + DMARDs, every two weeks, respectively).

In MOBILITY, the improvement in physical functioning as measured by HAQ-DI was maintained up to week 52 (-0.75, -0.71, and -0.46 for sarilumab 200 mg + MTX, sarilumab 150 mg + MTX, and placebo + MTX treatment groups, respectively).

Patients treated with sarilumab+ MTX (47.6% in the 200 mg treatment group and 47.0% in the 150 mg treatment group) achieved a clinically relevant improvement in HAQ-DI (change from baseline of ≥0.3 units) at week 52 compared to 26.1% in the placebo + MTX treatment group.

Patient reported outcomes

General health status was assessed by the Short Form health survey (SF-36). In MOBILITY and TARGET, patients receiving sarilumab 200 mg + DMARDs every two weeks or sarilumab 150 mg + DMARDs every two weeks demonstrated greater improvement from baseline compared to placebo + DMARDs in physical component summary (PCS) and no worsening on the mental component summary (MCS) at week 24. Patients receiving sarilumab 200 mg + DMARDs reported greater improvement relative to placebo in the domains of *Physical Functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning, and Mental Health.*

Fatigue was assessed by the FACIT-Fatigue scale. In MOBILITY and TARGET, patients receiving sarilumab 200 mg + DMARDs every two weeks or sarilumab 150 mg + DMARDs every two weeks demonstrated greater improvement from baseline compared to placebo + DMARDs.

Active Comparator-controlled Study

MONARCH was a 24 –week randomised double-blind, double-dummy study that compared sarilumab 200 mg monotherapy with adalimumab 40 mg monotherapy administered subcutaneously every two weeks in 369 patients with moderately to severely active RA who were inappropriate for treatment with MTX including those who were intolerant of or inadequate responders to MTX.

Sarilumab mg was superior to adalimumab 40 mg in reducing disease activity and improving physical function, with more patients achieving clinical remission over 24 weeks (see Table 7).

Table 7: Efficacy results for MONARCH

	Adalimumab 40 mg q2w* (N=185)	**Sarilumab 200 mg q2w (N=184)**
DAS28-ESR (primary endpoint) p-value versus adalimumab	-2.20 (0.106)	-3.28 (0.105) < 0.0001
DAS28-ESR remission (< 2.6), n (%) p-value versus adalimumab	13 (7.0%)	49 (26.6%) < 0.0001
ACR20 response, n (%) p-value versus adalimumab	108 (58.4%)	132 (71.7%) 0.0074
ACR50 response, n (%) p-value versus adalimumab	55 (29.7%)	84 (45.7%) 0.0017
ACR70 response, n (%) p-value versus adalimumab	22 (11.9%)	43 (23.4%) 0.0036
HAQ-DI p-value versus adalimumab	-0.43(0.045)	-0.61(0.045) 0.0037

*Includes patients who increased the frequency of dosing of adalimumab 40 mg to every week because of an inadequate response

Polymyalgia Rheumatica

The efficacy and safety of KEVZARA in PMR were assessed in a randomized, double-blind, placebo-controlled, 52-week, multicenter study (SAPHYR) (NCT03600818) in adults with PMR diagnosed according to American College of Rheumatology/European Union League against Rheumatism (ACR/EULAR) classification criteria. Patients had at least one episode of unequivocal PMR flare while attempting to taper corticosteroids.

In SAPHYR, patients with active PMR were randomized to receive KEVZARA 200 mg every two weeks with a pre-defined 14-week taper of prednisone (n= 60) or placebo every two weeks with a pre-defined 52-week taper of prednisone (n=58). One participant was randomized but not treated in the KEVZARA 200 mg arm. Patients experiencing a disease flare or unable to adhere to the assigned prednisone tapering schedule could receive corticosteroids as rescue therapy.

The primary endpoint was the proportion of patients with sustained remission at Week 52. Sustained remission was defined as achievement of disease remission no later than Week 12, absence of disease flare from Week 12 through Week 52, sustained reduction of CRP (to <10 mg/L) from Week 12 through Week 52, and successful adherence to prednisone taper from Week 12 through Week 52. An additional endpoint was total cumulative corticosteroid dose over 52 weeks.

Clinical Response

The proportion of participants achieving sustained remission at Week 52 was higher in the KEVZARA arm compared to the placebo arm; this difference was statistically significant. At 52 weeks, a higher proportion of patients in the KEVZARA arm achieved each component of the sustained remission endpoint compared to the placebo An analysis was conducted that removed all acute phase reactants (CRP and ESR) criteria from the definition of the sustained remission, given sarilumab's direct impact on acute phase reactants. The results of this analysis were consistent with the primary analysis (see Table 8).

Table 8 Clinical Response in Placebo-Controlled SAPHYR in Adults with Active PMR

		Placebo (N=58)	KEVZARA (N=60)
Sustained remission at Week 52			
	Number of patients with sustained remission, n (%)	6 (10.3)	17 (28.3)
	Proportion difference (95% CI) vs. placebo		18.0 (4.2, 31.8; p=0.0193)
Components of sustained remission at Week 52			
	Absence of signs and symptoms and CRP < 10 mg/L (disease remission*) no later than Week 12, n (%)	22 (37.9)	28 (46.7)
	Absence of disease flare‡ from Week 12 through Week 52, n (%)	19 (32.8)	33 (55.0)
	Sustained reduction of CRP (<10 mg/L) from Week 12 through Week 52, n (%)	26 (44.8)	40 (66.7)
	Successful adherence to prednisone taper from Week 12 through Week 52, n (%)	14 (24.1)	30 (50.0)
Sensitivity analysis removing acute phase reactants (CRP and ESR) from sustained remission at Week 52			
	Number of patients with sustained remission, n (%)	8 (13.8)	19 (31.7)
	Proportion difference (95% CI) for sarilumab vs. placebo		17.9 (3.1, 32.6)

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

Effect on Concomitant Corticosteroid Use

The total actual cumulative corticosteroid dose included all corticosteroids taken during the study (i.e., prednisone taper regimen per protocol, add-on prednisone prior to Week 12, corticosteroid use due to rescue, or corticosteroid use during the treatment period to manage an adverse reaction not related to PMR). The total actual cumulative prednisone equivalent corticosteroid dose was lower in the KEVZARA arm (mean [SD] 1039.5 [612.2] mg and median 777 mg) relative to the placebo arm (mean [SD] 2235.8 [839.4] mg and median 2044 mg).

5.2 Pharmacokinetic properties

Rheumatoid Arthritis
The pharmacokinetics of sarilumab were characterised in 2186 patients with RA treated with sarilumab which included 751 patients treated with 150 mg and 891 patients treated with 200 mg subcutaneous doses every two weeks for up to 52 weeks.

Absorption
The absolute bioavailability for sarilumab after SC injection was estimated to be 80% by population PK analysis. The median t_{max} after a single subcutaneous dose was observed in 2 to 4 days. After multiple dosing of 150 to 200 mg every two weeks, steady state was reached in 12 to 16 weeks with a 2- to 3-fold accumulation compared to single dose exposure.

For the 150 mg every two weeks dose regimen, the estimated mean (± standard deviation, SD) steady-state area under curve (AUC), C_{min}, and C_{max} of sarilumab were 210 ± 115 mg.day/L, 6.95 ± 7.60 mg/L, and 20.4 ± 8.27 mg/L, respectively.

For the 200 mg every two weeks dose regimen, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 396 ± 194 mg.day/L, 16.7 ± 13.5 mg/L, and 35.4 ± 13.9 mg/L, respectively.

In a usability study sarilumab exposure after 200 mg Q2W was slightly higher (C_{max} + 24-34%, $AUC_{(0-2w)}$ +7-21%) after use of a pre-filled pen compared to the pre-filled syringe.

Distribution
In patients with RA, the apparent volume of distribution at steady state was 8.3 L.

Biotransformation
The metabolic pathway of sarilumab has not been characterised. As a monoclonal antibody sarilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination
Sarilumab is eliminated by parallel linear and non-linear pathways. At higher concentrations, the elimination is predominantly through the linear, non-saturable proteolytic pathway, while at lower concentrations, non-linear saturable target-mediated elimination predominates. These parallel elimination pathways result in an initial half-life of 8 to 10 days, and at steady-state an effective half-life of 21 days is estimated.

After the last steady state dose of 150 mg and 200 mg sarilumab, the median times to non-detectable concentration are 30 and 49 days, respectively.
Monoclonal antibodies are not eliminated via renal or hepatic pathways.

Linearity/non-linearity
A more than dose-proportional increase in pharmacokinetic exposure was observed in patients with RA. At steady state, exposure over the dosing interval measured by AUC increased approximately 2-fold with a 1.33-fold increase in dose from 150 to 200 mg every two weeks.

Interactions with CYP450 substrates
Simvastatin is a CYP3A4 and OATP1B1 substrate. In 17 patients with RA, one week following a single 200-mg subcutaneous administration of sarilumab, exposure of simvastatin and simvastatin acid decreased by 45% and 36%, respectively (see section 4.5).

Polymyalgia Rheumatica
The pharmacokinetic profile of subcutaneous sarilumab in PMR patients was determined using a population pharmacokinetic analysis on a data set including 58 PMR patients treated with repeated subcutaneous administration of sarilumab 200 mg every two weeks. In general, pharmacokinetic exposures were higher in patients with PMR when compared to patients with RA. For this dose regimen, the estimated mean (± SD) steady-state AUC, Cmin and Cmax of sarilumab were 551 ± 321 mg.day/L, 27.0 ± 21.5 mg/L, and 46.5 ± 23.0 mg/L, respectively. The median time to steady state in PMR patients was estimated to be 28 weeks. There was accumulation following subcutaneous administration of sarilumab 200 mg, with an accumulation ratio of approximately 6-fold based on the mean trough concentrations.

Special populations
Age, gender, ethnicity and body weight
Population pharmacokinetic analyses in adult patients with RA (ranging in age from18 to 88 years with 14% over 65 years) showed that age, gender and race did not meaningfully influence the pharmacokinetics of sarilumab.
Body weight influenced the pharmacokinetics of sarilumab. In patients with higher body weight (>100 Kg) both 150 mg and 200 mg doses demonstrated efficacy; however, patients weighing >100 Kg had greater therapeutic benefit with the 200 mg dose.

Renal impairment
No formal study of the effect of renal impairment on the pharmacokinetics of sarilumab was conducted. Mild to moderate renal impairment did not affect the pharmacokinetics of sarilumab. No

dose adjustment is required in patients with mild to moderate renal impairment. Patients with severe renal impairment were not studied.

Hepatic impairment
No formal study of the effect of hepatic impairment on the pharmacokinetics of sarilumab was conducted (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity, carcinogenic risk assessment and toxicity to reproduction and development.

No long-term animal studies have been performed to establish the carcinogenicity potential of sarilumab. The weight of evidence for IL-6Rα inhibition mainly indicates anti-tumour effects mediated by multiple mechanisms predominantly involving STAT-3 inhibition. *In vitro* and *in vivo* studies with sarilumab using human tumour cell lines showed inhibition of STAT-3 activation and inhibition of tumour growth in human tumour xenograft animal models.

Fertility studies conducted in male and female mice using a murine surrogate antibody against mouse IL-6Rα showed no impairment of fertility.

In an enhanced pre-/postnatal developmental toxicity study, pregnant Cynomolgus monkeys were administered sarilumab once-weekly intravenously from early gestation to natural birth (approximately 21 weeks) Maternal exposure up to approximately 83 times the human exposure based on AUC after subcutaneous doses of 200 mg every 2 weeks, did not cause any maternal or embryo-foetal effects. Sarilumab had no effect on maintenance of pregnancy or on the neonates evaluated up to 1 month after birth in body weight measurements, in parameters of functional or morphological development including skeletal evaluations, in immunophenotyping of peripheral blood lymphocytes, and in microscopic evaluations. Sarilumab was detected in the serum of neonates up to 1 month. The excretion of sarilumab in Cynomolgus monkey's milk has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
L - Arginine hydrochloride
L - Histidine
Polysorbate 20
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Once removed from the refrigerator, do not store Kevzara above 25 ºC.

Use the pen/syringe within 14 days after taking it out of the refrigerator and do not put it back into refrigeration.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC). Do not freeze.

Store in the original carton in order to protect from light.

6.5 Nature and contents of container

All presentations contain a 1.14 ml solution in a syringe (type 1 glass) equipped with a stainless steel staked needle and an elastomer plunger stopper.

Pre-filled syringe 150 mg
The single-use pre-filled syringe has a styrene-butadiene elastomer needle cap and is equipped with a white polystyrene plunger rod and a light-orange polypropylene finger flange.

Pre-filled syringe 200 mg
The single-use pre-filled syringe has a styrene-butadiene elastomer needle cap and is equipped with a white polystyrene plunger rod and a dark-orange polypropylene finger flange.

Pre-filled pen 150 mg
The syringe components are pre-assembled into a single-use pre-filled pen with a yellow needle cover and light-orange cap.

Pre-filled pen 200 mg
The syringe components are pre-assembled into a single-use pre-filled pen with a yellow needle cover and dark-orange cap.

Pack sizes:

- 2 pre-filled syringes
- Multipack containing 6 (3 packs of 2) pre-filled syringes
- 2 pre-filled pens
- Multipack containing 6 (3 packs of 2) pre-filled pens

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The pre-filled syringe/pre-filled pen should be inspected before use. The solution should not be used if it is cloudy, discoloured, or contains particles, or if any part of the device appears to be damaged.

After removing the pre-filled syringe/pre-filled pen from the refrigerator, it should be allowed to reach room temperature (<25°C) by waiting 30 minutes for the pre-filled syringe or 60 minutes for the pre-filled pen as applicable, before injecting Kevzara.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. After use, the pre-filled syringe/ pre-filled pen should be placed into a puncture-resistant container and discarded as required by local regulations.

7. MARKETING AUTHORISATION HOLDER

Sanofi-aventis Israel Ltd

8. MANUFACTURER

Sanofi-aventis groupe, France

9. LICENSE NUMBER

Kevzara 150 mg: 160-37-35260 Kevzara 200 mg: 160-38-35261

Revised in 03/2023 according to MoH guidelines.