EU Risk Management Plan for Kineret (anakinra)

RMP version to be assessed as part of this application:

RMP version number:	6.2
Data lock point for this RMP:	May 1, 2022
Date of final sign off:	April 3, 2023

Rationale for submitting an updated RMP:
Information on serious infections removed from the Healthcare Professional Guide and the Patient Reminder Card, since this information is available in the SmPC. Patient Reminder Card deleted.

Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) added as an Important potential risk.

Summary of significant changes in this RMP:
Information on serious infections removed from the Healthcare Professional Guide and the Patient Reminder Card, since this information is available in the SmPC. Patient Reminder Card deleted.

Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) added as an Important potential risk. In Annex 4 a Questionnaire for DRESS has been added. Changes connected to the updated data lock point (May 1, 2022). Update of clinical exposure tables. Update of data based on the final SAVE-MORE CSR.

Details of the currently approved RMP:

RMP version number:	6.1
Approved with procedure:	PSUSA/209/202205
Date of approval (opinion date):	January 26, 2023

QPPV name: Martin Bowling
QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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Part I: Product overview

Table 1 Product overview

Active substance(s) (INN or common name)	Anakinra (INN), Human interleukin-1 receptor antagonist (r-metHuIL-1ra)
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, Interleukin inhibitors ATC code: L04AC03
Marketing Authorisation Holder	Swedish Orphan Biovitrum AB (publ), (hereafter referred to as Sobi)
Medicinal products to which this RMP refers	Kineret®
Invented name(s) in the European Economic Area (EEA)	Kineret®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Biologic
	Summary of mode of action: Immunosuppressant
	Important information about its composition: Anakinra is a human interleukin-1 receptor antagonist (r-metHuIL-1Ra) produced in Escherichia coli cells by recombinant DNA technology. Anakinra neutralizes the biologic activity of interleukin 1α (IL-1α) and interleukin 1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.
Hyperlink to the Product Information	SmPC

Indication(s) in the EEA	Current: **Rheumatoid Arthritis (RA)** Kineret is indicated in adults for the treatment of the signs and symptoms of Rheumatoid Arthritis (RA) in combination with methotrexate, in adults with an inadequate response to methotrexate alone. **Periodic fever syndromes** Kineret is indicated for the treatment of the following autoinflammatory periodic fever syndromes in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above: *Cryopyrin-Associated Periodic Syndromes (CAPS)* Kineret is indicated for the treatment of CAPS, including: • Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA) • Muckle-Wells syndrome (MWS) • Familial Cold Autoinflammatory Syndrome (FCAS) *Familial Mediterranean Fever (FMF)* Kineret is indicated for the treatment of Familial Mediterranean Fever. Kineret should be given in combination with colchicine, if appropriate. **Still's disease** Kineret is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids. Kineret can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs). **COVID-19** Kineret is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR) ≥ 6ng/ml (see SmPC sections 4.2, 4.4 and 5.1).

Dosage in the EEA	Current: **RA** The recommended dose of Kineret in adults and the elderly is 100 mg administered once a day by SC injection. The dose should be administered at approximately the same time each day. **CAPS** Adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above: *Starting dose:* The recommended starting dose in all CAPS subtypes is 1-2 mg/kg/day by subcutaneous injection. The therapeutic response is primarily reflected by reduction in clinical symptoms such as fever, rash, joint pain, and headache, but also in inflammatory serum markers (CRP/SAA levels), or occurrence of flares. *Maintenance dose in mild CAPS (FCAS, mild MWS):* Patients are usually well-controlled by maintaining the recommended starting dose (1-2 mg/kg/day). *Maintenance dose in severe CAPS (MWS and NOMID/CINCA):* Dose increases may become necessary within 1-2 months based on therapeutic response. The usual maintenance dose in severe CAPS is 3-4 mg/kg/day, which can be adjusted to a maximum of 8 mg/kg/day. In addition to the evaluation of clinical symptoms and inflammatory markers in severe CAPS, assessments of inflammation of the CNS, including the inner ear (MRI or CT, lumbar puncture, and audiology) and eyes (ophthalmological assessments) are recommended after an initial 3 months of treatment, and thereafter every 6 months, until effective treatment doses have been identified. When patients are clinically well-controlled, CNS and ophthalmological monitoring may be conducted yearly. **FMF** The recommended dose for patients weighing 50 kg or more is 100 mg/day by subcutaneous injection. Patients weighing less than 50 kg should be dosed by body weight with a recommended dose of 1-2 mg/kg/day. In children with inadequate response the dose can be escalated up to 4 mg/kg/day. **Still's disease** The recommended dose for patients weighing 50 kg or more is 100 mg/day by subcutaneous injection. Patients weighing less than 50 kg should be dosed by body weight with a starting dose of 1-2 mg/kg/day. In children with inadequate response the dose can be escalated up to 4 mg/kg/day. Response to treatment should be evaluated after 1 month: In case of persistent systemic manifestations dose may be adjusted in children or continued treatment with Kineret should be reconsidered by the treating physician. **COVID-19** The recommended dose of Kineret is 100 mg administered once a day by subcutaneous injection for 10 days.
Pharmaceutical form(s) and strengths	Current: Solution for injection in a prefilled syringe containing 100 mg of anakinra per 0.67 ml (150 mg/ml).
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Anakinra (Kineret®) is a human interleukin-1 receptor antagonist that has been on the market for more than 20 years for treatment of rheumatoid arthritis (RA) in patients older than 18 years. It is considered a safe and well-established treatment based on experience from clinical trials and commercial use. Kineret is also indicated for 2 periodic fever syndromes including Familial Mediterranean Fever (FMF) and Cryopyrin-Associated Periodic Syndrome (CAPS), a disease which includes 3 disease subtypes ranging from the milder manifestations of Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells syndrome (MWS) to the clinically most severe form, Chronic Infantile Neurologic, Cutaneous, and Arthritis (CINCA) syndrome, in the USA also called Neonatal-Onset Multisystem Inflammatory Disease (NOMID). In addition, Kineret is indicated for Still's disease in pediatric and adult patients, i.e., Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD). Lastly, Kineret is indicated for the treatment of adult patients with COVID-19 pneumonia in the EU/EEA.

The data evaluated in the risk management plan (RMP) are safety data from clinical studies in RA, CAPS, juvenile idiopathic arthritis (JIA), and Still's disease including patients with SJIA and AOSD. Safety data from a published clinical study in patients with FMF is also included. Postmarketing experience after Kineret launch in 2001 is also evaluated.

The objective of this RMP is to present identified and potential risks associated with the use of Kineret in RA, CAPS, Still's disease FMF and COVID-19, and to provide a framework for the pharmacovigilance plan and subsequent risk minimization activities.

Still's disease covers SJIA and AOSD. Although often treated as separate diagnostic entities, there is a growing understanding that SJIA and AOSD are one single autoinflammatory disease, representing a continuum of a disease entity with onset at different ages. Clinical study data in this RMP come from the MAH-sponsored safety study in JIA including 15 patients with SJIA (study 990758/990779) and data from the MAH-sponsored anaSTILLs clinical study in patients with Still's disease (Sobi.ANAKIN-301). The information is summarized under the diagnostic label Still's disease.

In the safety specification, the indications RA, CAPS, Still's disease and FMF are accounted for separately, with respect to clinical data. This is to clearly show the similarities of the safety profile between the 4 indications.

For COVID-19 in adult patients with pneumonia, clinical study data in this RMP come from one Investigator Sponsored Study, SAVE-MORE. Post-marketing data of anakinra off label use in COVID-19 is also evaluated.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication Rheumatoid Arthritis (RA)

Kineret is indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age and older. Kineret may be used alone or in combination with other DMARDs.

Incidence and prevalence:

In some geographic areas, the prevalence and incidence of RA vary across ethnic groups. Within ethnic groups, the incidence and prevalence of RA vary according to the geographic area of residence.

Table 2 Rheumatoid arthritis (RA population)

Indication/target population	Rheumatoid arthritis
Incidence of target indication	
North America and Northern Europe	20-50/100 000/year
Southern Europe	9-24/100 000/year
Developing countries	Unknown
Prevalence of target indication	
North America and Northern Europe	0.5 %-1.1 %
Southern Europe	0.3 %-0.7 %

From Tobon et al. 2010 (1).

Demographics of the RA population, ethnic origin, and risk factors for the disease:

Studies conducted at various time points within the same geographic regions suggest that the incidence of RA is declining over time and that this decline is greatest among women (2). One hypothesis for the decline in women may be the exposure to oral contraceptives, which has been suggested to decrease the incidence of RA. Other studies suggest a shift over time in RA onset toward older age groups.

The prevalence is higher in females than in males (Table 3).

Table 3 Prevalence of RA by sex in various countries

Country	Females (%)	Males (%)
United States	1.4	0.74
United Kingdom	1.16	0.44
Spain	0.8	0.20
Italy	0.51	0.13
France	0.51	0.09
Greece	0.45	0.19

From Tobon et al. 2010 (1).

RA is a multifactorial disease that results from interactions between genetic, epigenetic and environmental factors. Personal and lifestyle factors influence the course of the disease. Genetic factors (and gene-environment interactions) is calculated to contribute to 50 % to 60 % of the risk of developing RA. Further cofactors for risk of developing RA involve smoking, hormonal factors, ethnicity, pollutants, diet, urbanization, and infectious agents.

The main existing treatment options:

Disease-modifying antirheumatic drugs (DMARDs) commonly used in RA patients in general are methotrexate, glucocorticoid agents, cyclophosphamide, azathioprine, hydroxychloroquine, leflunomide, sulfasalazine, injectable gold, penicillamine, and non-steroidal anti-inflammatory drugs (NSAIDs). In RA, Kineret has its therapeutic indication in combination with methotrexate in adults with an inadequate response to methotrexate alone. The most commonly used group of biologicals for treatment of RA are anti-tumor necrosis factor (TNF) agents. The concurrent use of anti-TNF agents and etanercept with Kineret is not recommended due to an increased risk of infections. As RA is prevalent in elderly, and as RA patients has an increased prevalence of cardiovascular disease, concomitant use of drugs for the treatment of these disorders is common (anti-hypertensive and lipid-lowering therapy). Interleukin-6 (IL-6) and Janus Kinase inhibitors are also considered for the treatment of RA in case of absence of response to other DMARDs. According to the EULAR recommendations updated in 2022, JAK inhibitors can be used if there are no risk factors for cardiovascular and malignant diseases.

In a large cohort of RA patients, the current drug exposures on risk of serious infection was evaluated (3). The cohort did not include any patients using Kineret, and thus characterizes a background pattern of serious infections with DMARDs in general. The highest risk estimates were associated with the agents that had the greatest immunosuppressant effects, including cyclophosphamide (cases/controls adjusted relative risk, RR 3.26) and glucocorticoids (RR 2.56). An increase in pneumonia related to glucocorticoids, similar to what has been reported by Wolfe et al. 2006 (4), was noted. A moderate increase in the relative risk of infections with azathioprine exposure (1.52), and a mildly increased risk with methotrexate exposure, was noted (1.10).

Natural history of RA, including mortality and morbidity:

RA patients have about 50 % increased risk of premature mortality with a life expectancy decreased by 3-10 years compared to the general population. The inflammatory condition independently increases the incidence of cardiovascular disease in RA.

Epidemiology data are presented below for relevant identified and potential risks.

<u>Infections</u>

There are indications that infections are more frequent among RA patients than non-RA patients. In a cohort study, 609 RA patients and 609 non-RA study subjects were followed up for a mean of 12.7 years and 15.0 years, respectively (5). Hazards ratios for objectively confirmed infections, infections requiring hospitalization, and any documented infection in patients with RA were 1.70 (95 % CI 1.42–2.03), 1.83 (95 % CI 1.52–2.21), and 1.45 (95 % CI 1.29–1.64),

respectively, after adjustment for age, sex, smoking status, leukopenia, corticosteroid use, and diabetes mellitus.

Malignancies

RA patients appear to have an increased incidence of certain cancer types, including lung cancer and lymphoma. Lymphoma has the strongest association with RA compared with the general population, particularly non-Hodgkin lymphoma (NHL). In the general population, the incidence of NHL is approximately 10–45 per 100 000, depending on age group (6). This lymphoma incidence is increased 2-fold in patients with RA in most studies, and a large meta-analysis of 26 studies confirmed a 2–3-fold incidence of lymphoma in RA (7), (8). An increased relative risk of multiple myeloma in RA patients has been found in some studies, but not in others (9).

The risk of lung cancer is increased with an overall standardized incidence ratio (SIR) of 1.63 (95 % CI 1.43 to 1.87). In contrast, a reduced risk was observed for both colorectal and breast cancer (8).

The incidence of cancer in relation to treatment with the most commonly used group of biologicals, anti-tumor necrosis factor (TNF) agents, was reported in a large Swedish cohort, in which the prevalence of anti-TNF therapy was 15 % (10). It was concluded that the overall occurrence of cancer during the first years following anti-TNF therapy in RA is not higher than that in biologics-naive patients with RA, nor does it increase with time. Several other studies have reached the same conclusions (11-13).

Important co-morbidities:

Cardiovascular disease such as myocardial infarction, stroke and cardiac failure are important co-morbidities in RA (14, 15). A meta-analysis calculated the standardized mortality ratios of CV disease to 1.6 (95 % CI 1.5, 1.8) (16). Epidemiological data suggest that the inflammatory condition independently increases CV disease in RA even after adjustment for traditional CV risk factors (15).

RA has been associated with Interstitial Lung Disease (ILD) with a lifetime risk of developing ILD of 7.7% for RA patients vs. 0.9% for subjects without RA (17).

Indication CAPS

Kineret is indicated in adult and pediatric patients for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) including Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA), Muckle-Wells Syndrome (MWS), and Familial Cold Autoinflammatory Syndrome (FCAS).

Incidence and Prevalence:

The estimated incidence of CAPS in the US and in Europe is 1:1 million (18).

Internationally, the prevalence of FCAS and MWS is similar, while the large majority (>80 %) of the estimated 400-500 CAPS patients in the USA have FCAS, the mildest phenotype, due to a

founder effect. In the US, there is a small number of patients with MWS and even fewer with NOMID, while in Europe, MWS is diagnosed more commonly.

Cuisset et al. 2011 (19) conducted a retrospective review (2001–2009) of genetic analysis data and request forms of patients with an *NLRP3* mutation living in France. Over 800 analyses of this gene have been conducted, identifying 135 cases with an *NLRP3* mutation (55 probands; 33 multiplex families); the estimated prevalence in France was equal to 1/360 000.

Table 4 Prevalence of CAPS population

Indication/target population	FCAS (number of patients)	MWS (number of patients)	NOMID/CINCA (number of patients)
Prevalence[a]: North America Europe Developing countries	 400+ Unknown Unknown	 <50 Unknown, <100 Unknown	 <40 <60 Unknown

[a] Based on Hoffman 2009 (18).

Demographics of the CAPS population, ethnic origin, and risk factors for the disease:

CAPS is an ultra-rare, monogenic disease, caused by an autosomal dominant mutation in the *NLRP3* gene, which generates a life-long autoinflammatory syndrome. CAPS includes 3 subdiagnoses ranging from the milder manifestations of FCAS and MWS to the clinically most severe form, CINCA syndrome, also called NOMID in the US. NOMID/CINCA is less common than FCAS/MWS worldwide and typically occurs sporadically without a family history due to de novo mutations (20).

The patients currently identified are predominantly of Caucasian background with an equal sex distribution.

The main existing treatment options:

Before anti-IL-1-directed therapy was introduced in CAPS, a broad variety of anti-inflammatory treatments of CAPS were tried. None of these have been consistently beneficial, and today IL-1-inhibitors are recognized to be the only effective treatment alternative. In mild CAPS (FCAS, mild MWS) patients, additive treatment with NSAIDs during flares in some patients ameliorates joint pain.

In severe CAPS patients, at baseline in study 03-AR-0298 before initiation of Kineret treatment, 16 of 34 patients (47.1 %) in the ITT population were treated with oral steroids with a mean daily dose of 0.76 mg/kg (prednisone-equivalents). Nine patients (26.5 %) were using DMARDs (methotrexate). Methotrexate did not prevent flares during the withdrawal phase in study 03-AR-0298.

Natural history of the indicated condition in the CAPS population, including mortality and morbidity:

The consequences of the chronic and/or relapsing systemic inflammation induced by an uncontrolled release of interleukin-1β in affected subjects, and the resulting progression of organ

damage caused by chronic inflammation, are consequences of the disease. This includes functional organ damage affecting vision, hearing ambulating, and quality of life (QoL). High levels of serum amyloid A may induce the risk of complications to amyloidosis in some patients. Apart from an estimated risk of systemic amyloidosis and renal failure in 10 % to 50 % of MWS patients, due to the rarity of the disease, the epidemiology of other comorbidities in CAPS are largely unknown.

Table 5 Morbidity and mortality of CAPS population

Indication/target population	FCAS	MWS	NOMID/CINCA
Morbidity	A few with amyloidosis	Amyloidosis in up to 20 %, renal failure. Hearing impairment in 25 %.	Chronic aseptic meningitis, high intracranial pressure with risk of ventriculo-megaly, mental retardation, hearing and vision impairment, deafness, growth impairment, osteoporosis
Mortality in target indication	Unknown	Unknown	If untreated, a mortality rate of approximately 20 % before the age of 20 reported

Important co-morbidities:

No specific comorbidities in the CAPS population have been described

Indication Still's disease

Kineret is indicated for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids. Kineret can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs).

Incidence and Prevalence:

Robust epidemiologic data on Still's disease in pediatric and adult patients are lacking since most observations have been reported in small series.

Among the various JIA subtypes, SJIA accounts for 5 % to 15 % of children with JIA seen in North America and Europe. Some population-based studies are available from Europe showing an annual incidence for SJIA between 0.3–0.8 cases per 100 000 persons for children under 16 years of age. The incidence appears to be higher in northern compared to southern European countries. In Asia, SJIA may account for a greater proportion of all childhood arthritis. In India and in Japan 25 % and 50 %, respectively, of JIA appears to be SJIA (21). In SJIA, there is no distinct sex predilection.

AOSD occurs worldwide and among all ethnic groups. The disease affects usually young adults, the median age at diagnosis is approximately 36 years (22), though onsets have been described up to 83 years (23). The incidence has been estimated at 0.16 (per 100 000 persons) in France (24), 0.22 in Japan (25), and 0.4 in Norway (26). The reported prevalence rates range from 0.1 to 1 per 100 000 depending on the region studied (27).

Demographics of the Still's disease population and ethnic origin and risk factors for the disease:

Because of the similar systemic clinical features of SJIA and AOSD, there is a growing understanding that these clinical phenotypes represent the same disease continuum with different ages of onset, i.e., Still's disease in pediatric and adult patients (28). In addition, evidence suggests that SJIA and AOSD are also comparable on a molecular level. Both conditions are characterized by activation of the innate immune system, including elevations of inflammatory cytokines and proteins such as IL-1, IL-6, IL-18, and S100 proteins (29) and both are highly responsive to IL-1 inhibition (30).

The hormonal influences are poorly understood. However, the risk for disease recurrence is increased during the second trimester of pregnancy and the postpartum period (31).

The main existing treatment options:

There are multiple currently available therapies for the treatment of active Still's disease. These therapies can be broadly grouped as NSAIDs, glucocorticoids, classical DMARDs, and biologic DMARDs that inhibit IL-1, IL-6, or TNF-α. The anti-IL-1 agent canakinumab and the anti-IL-6 agent tocilizumab are both approved by the EMA and the FDA for treatment of SJIA. Canakinumab was approved in 2016 by the EMA for treatment of Still's disease including AOSD and SJIA.

NSAIDs such as ibuprofen, naproxen, and indomethacin have traditionally been the first therapies in suspected or newly diagnosed Still's disease. NSAIDs have certain risks: nephrotoxicity, pseudoporphyria/other skin manifestations, and gastrointestinal adverse reactions such as gastritis and duodenitis are common (32). In elderly and other predisposed patients, NSAIDs can cause severe and sometimes fatal gastrointestinal bleedings.

Systemic glucocorticoids are also used in the initial treatment of Still´s disease, especially for patients with active systemic features (32). Glucocorticoids can control the clinical manifestations in approximately 60 % of the patients (33). However, glucocorticoids easily induce dependence; steroid dependence occurred in 42 % of the cases in one study (28). Glucocorticoids have a significant side effect profile, especially when used chronically or at high doses. Long-term glucocorticoid exposure in patients carries the potential for serious adverse events, such as infections, osteoporosis, diabetes, and growth disturbances in children (28, 32).

If NSAID and/or glucocorticoid treatment are insufficient, DMARDs such as methotrexate are frequently added (22). DMARDs are considered early when patients present predictive factors for steroid-dependence, or at the first signs of steroid-dependence. However, DMARDs may cause rash, stomach disturbances, and may be toxic to the liver or bone marrow (28).

The current treatments of Still's disease are also source of many severe complications (22). In a cohort of 57 subjects, 21 % of NSAIDs-treated patients experienced gastrointestinal side effects despite proton pump inhibitor administration, 75 % of corticosteroid-treated patients suffered from adverse events (Cushing syndrome, osteoporosis, aseptic osteonecrosis, diabetes, hypertension, cataract, psychiatric disorders), whereas one third of methotrexate-treated patients experienced complications, such as elevated liver enzymes (15 %), low blood cell counts (10 %), and cough (6 %). Furthermore, the treatments used in Still's disease increases the risk for infectious complications (28).

For the management of systemic features of the disease, anti-IL-1 agents such as anakinra, canakinumab, rilonacept and the anti-IL-6 agent, tocilizumab, have been demonstrated to be effective in clinical trials (29). Several uncontrolled studies and reports demonstrate variable effectiveness of TNF-α blockers in refractory chronic polyarticular Still's disease (29).

Natural history of Still's disease, including mortality and morbidity:

Patients with either SJIA or AOSD exhibit classical clinical and laboratory features, including daily spiking fever, arthralgia or arthritis, evanescent (not fixed) rash, and increased white blood cell count (mainly neutrophils).

Macrophage activation syndrome (MAS) is a severe and potentially fatal complication of Still's disease. MAS (also known as secondary or reactive hemophagocytic lymphohistiocytosis [HLH]) is a process of rapid expansion and activation of macrophages and T lymphocytes leading to a "cytokine storm". Patients with MAS usually have laboratory evidence of cytopenias (thrombocytopenia, leukopenia), elevated serum hepatic enzymes, coagulopathy (elevated D-dimer, prolonged prothrombin time, and decreasing fibrinogen), decreasing erythrocyte sedimentation rate (owing to consumption of fibrinogen), elevated triglycerides, elevated lactate dehydrogenase, and hyperferritinemia (34).

The frequency of fully developed MAS is 12 to 15 % in both pediatric and adult patients but subclinical and mild MAS is described in up to >50 % of patients with SJIA (28), (35), (36). MAS remains a significant cause of mortality in patients with SJIA with an overall mortality rate of 8 % (37). Its high mortality rate may be influenced by an early diagnosis with consequent aggressive treatments, which have been shown to improve the survival of these patients. Infections are well recognized triggers for MAS in patients with Still's disease.

Other morbidity in the Still´s population include bone and cartilage erosion with functional handicap, pulmonary hypertension, pericarditis, peritonitis, disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, diffuse alveolar hemorrhage, and fulminant hepatic failure (28). As in other autoinflammatory syndromes, amyloidosis has been reported in a few cases of chronic uncontrolled inflammation (28).

Important co-morbidities:

Important comorbidities in Still's disease include disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, diffuse alveolar hemorrhage, and pulmonary arterial hypertension (38). Some children have pulmonary involvement, including the later development of pulmonary hypertension or interstitial lung disease (39).

Athreya et al. 1980 (40), before the introduction of IL-1 blocking agents, reported 8/191 children with JRA who had involvement of the lung or pleura for more than 6 weeks, whereof 6 with SJIA. 4 patients had persisting lung disease, in 2 cases described as interstitial. The article's literature review found 3 case reports on patients with JRA that died due to their lung disease, and autopsy showed interstitial fibrosis in 2/3.

Indication Familial Mediterranean fever

Kineret is indicated for the treatment of adult and pediatric patients with Familial Mediterranean Fever (FMF). Kineret should be given in combination with colchicine, if appropriate.

Incidence and prevalence:

FMF is a rare genetic disease originally restricted to populations living around the Mediterranean basin. For example, there is an estimated total of 100 000 FMF patients in Turkey (41). The prevalence rate in France in 2013 was estimated at 1 in 5000 individuals, i.e. 5000 to a maximum of 10 000 patients (42). Significant number of patients are also found in Germany, Greece, Cyprus, and Italy (41, 43, 44). An epidemiological study in Cyprus concluded that 1:25 Greek-Cypriots is a carrier of one of the three most common genetic mutations associated with FMF (43). The outcome of a similar genetic study among Italian patients with relapsing fever of unknown origin resulted in the investigators concluding that "familial Mediterranean fever is no longer a rare disease in Italy" (44). Most FMF patients in France are of North African origin, and most of those who live in Germany are of Turkish origin. Most FMF patients in Italy are located in the central and southern parts of the country, probably originating from Phoenicians and other ascendants who came by way of the sea (41). Because of ongoing migration, the future incidence is likely to increase in the EU.

Demographics of the FMF population ethnic origin, and risk factors for the disease:

Regarding ethnic origin see Incidence and prevalence, above. The onset of FMF occurs before the age of 20 years in approximately 90% of patients (42). In one study, of 814 patients with FMF, in 254 patients (31.2 %) the first FMF attack occurred at ≤2 years of age, with a mean (SD) age at onset of 1.1 (0.8) years (45). The lowest age at onset, 4 months, was described (46) among 194 children with 24% having onset below 2 years. FMF is a monogenic inherited condition that shares the same pathophysiological features resulting from the activation of the inflammasome with several other hereditary periodic fever syndromes, e.g., CAPS. The inflammasome constituent that underlies this derangement is a malfunctioning pyrin, encoded by a mutated MEFV, the FMF-associated gene. Mutation of the MEFV gene encoding for pyrin is leading to malfunctioning and overproduction of interleukin-1 β (IL-1 β) (47, 48).

The frequency of heterozygous carriers of an MEFV (for MEditerranean FeVer) gene mutation, responsible for FMF, is higher than 1 in 5 in Sephardic Jews and Armenians (42), although some patients diagnosed with FMF according to clinical criteria have no mutation (49). The specific mutation sequence alterations named p.H478Y and p.E163A are mainly found among Spanish patients (41). The evidence based clinical criteria for diagnosis of FMF (see below Table 6) does not require an identified mutation.

The main existing treatment options:

Colchicine, an alkaloid with inhibitory effects on multiple cellular functions, including microtubule assembly, cell adhesion, and inflammasome activation (50) is first-line treatment of FMF, according to the EULAR guideline. Colchicine, however, is approved for the treatment of FMF in a limited number of EU/EAA countries only. Colchicine dose ranges between 1 and 3 mg per day and is determined clinically on the basis of its effect on the prevention of attacks. During attacks, the EULAR guideline recommends to continue the usual dose of colchicine and use non steroidal anti inflammatory drugs (NSAIDs) (51).

Although colchicine is safe and efficacious in most patients, 10–45% of patients are either resistant to, partially responsive, or intolerant to treatment with colchicine despite good adherence to therapy (51-53).

Suggested therapeutic alternatives for patients in whom oral colchicine treatment is ineffective include thalidomide, interferon alpha, intravenous colchicine, and tumor necrosis factor blockers (54-56). All of these treatments are limited by insufficient effect, safety concerns, unavailability, and high price, and none has been approved by a regulatory body.

In patients not responding to the maximum tolerated dosage of colchicine and thus regarded as non-responders or resistant to colchicine (51, 52, 57), an alternative biological treatment such as IL-1 blockade is indicated according to the EULAR guideline (51). The long-acting IL-1β monoclonal antibody canakinumab (ILARIS^{TM}) is approved in the EU, US, and in Israel for the treatment of FMF.

Colchicine should be co-administered with alternative biological therapies given that it may reduce the risk of amyloidosis despite persistence of attacks (EULAR recommendations, (51).

Natural history of the FMF population, including mortality and morbidity:

FMF shares the same pathophysiological features resulting from the activation of the inflammasome with several other hereditary periodic fever syndromes (e.g. CAPS, among others), belonging to a family of rare disorders characterized by seemingly unprovoked and self-limited bouts of inflammation.

Patients with FMF experience a marked decrease in quality of life (58). FMF typically presents with recurrent febrile attacks, accompanied by signs of peritonitis, pleuritis or acute synovitis, lasting 1–3 days, and resolving spontaneously. Attacks occur randomly, from once per week to once in several months, and patients are free of symptoms between the attacks. Emotional stress, fatigue, surgery, menstruation, vigorous exercise and cold exposure may trigger an attack. Abdominal attacks are the most frequent manifestations (90–93% in patients). Monoarthritis, mostly of the large joints of the legs (ankle, knee or hip), is the second most common form of attack occurring in 25–30% of the cases (59, 60). The joint is warm, tender and often red, resembling septic arthritis precipitated by minor trauma or effort. Approximately 5% of patients with FMF develop chronic joint damage, the majority resembling spondyloarthritis with sacoileitis and peripheral monoarthritis or oligarthritis (51).

The symptomatic episodes are accompanied by an increase in inflammatory markers: white blood cells, C-reactive protein (CRP), erythrocytes sedimentation rate (ESR), serum amyloid A (SAA), fibrinogen, haptoglobin, C3, and C4 (61).

FMF is diagnosed by the clinical picture that can be supported, but not necessarily excluded, by genetic testing. Various diagnostic criteria have been suggested (60), including the Tel Hashomer criteria (62, 63). In a recent study (59) using a large international registry of autoinflammatory diseases (Eurofever), valid, evidence based, clinical classification criteria were suggested to differentiate between 4 major autoinflammatory diseases (FMF, CAPS, MKD, TRAPS). A diagnosis of FMF is considered if a patient scores a total of at least 60 among the criteria (Table 6). With this scoring, the overall sensitivity and specificity were 68 and 87%, respectively, in a group of patients referred to as a "gold standard" – those carrying two MEFV mutations. The percentage of patients positively diagnosed according to the criteria for different genotypes (less than the "gold standard") was between 50 and 75%.

Table 6 The Eurofever clinical diagnostic/classification criteria* for Familial Mediterranean fever

	Criteria	**Score**
Presence	Duration of episodes < 2 days	9
	Chest pain	13
	Abdominal pain	9
	Eastern Mediterranean‡ ethnicity	22
	North Mediterranean‡ ethnicity	7
Absence	Aphthous stomatitis	9
	Urticarial rash	15
	Enlarged cervical lymph nodes	10
	Duration of episodes >6 days	13
Cut-off		≥60

*The clinical features should be related to the typical fever episodes (i.e., exclusion of intercurrent infection or other comorbidities).
‡Eastern Mediterranean: Turkish, Armenian, non-Ashkenazi Jewish, Arab. North Mediterranean: Italian, Spanish, Greek

Amyloidosis is the most devastating complication in untreated FMF, a progressive condition characterized by deposition of misfolded insoluble proteins in various organs ultimately leading to organ damage. Amyloidosis results from excessive production of serum amyloid A (SAA), an acute phase reactant protein released from hepatocytes via stimulation of pro-inflammatory cytokines e.g. IL-1, and involves primarily kidneys followed by intestines and heart. Amyloidosis may also occur in adrenal glands, spleen, lung, and testes.

In the past, amyloidosis was a common complication in untreated FMF patients, beginning with asymptomatic proteinuria and gradually developing to end-stage renal disease within 2–13 years. Currently however, the prevalence of amyloidosis has dropped significantly as a result of colchicine treatment, environmental factors or epigenetic phenomenon (64). According to the EULAR guideline FMF treatment needs to be intensified in patients with amyloidosis using the maximal tolerated dose of colchicine and supplemented with biologics as required (51).

Patients with colchicine-resistant FMF continue to have serositis attacks and are at increased risk of dying from amyloidosis or developing other conditions related to chronic inflammation. Resistance to colchicine as defined by the EULAR guideline is characterised by ≥1 attack per month in patients treated with the maximum tolerated dosage for ≥6 months.

Abdominal pain during attacks might pose challenges with differential diagnosis, and patients may undergo unnecessary abdominal surgeries; although after diagnosis, the rate decreases (58). Repeated peritonitis attacks with exudative fluid and inflammation might cause adhesions in peritoneal lining over time, leading to obstruction, volvulus, and strangulation (58). Cryptogenic hepatic cirrhosis and non-alcoholic steatohepatitis (NASH) has been reported in FMF (65, 66). In female untreated patients infertilility is common, but has also been reported in females who have had long-term treatment with colchicine (67). Spontaneous abortions or premature birth are more common in FMF compared to healthy women (68, 69) both in untreated and colchicine treated patients. Male infertility has also been reported (58, 67).

Important co-morbidities:

Vasculitises are a group of diseases characterized by inflammation of blood vessels. Several retrospective studies have reported an increased incidence of vasculitis in FMF patients, namely IgA vasculitis and polyarteritis nodosa (70). IgA vasculitis (formerly known as Henoch-Schönlein purpura) occurs in 3 to 11 % of patients (71). Behçet's disease has been reported to occur in combination with FMF (58).

Indication COVID-19

Coronavirus disease 2019 (COVID-19) is an illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 11 March, 2020, the WHO declared COVID-19 a global pandemic. Kineret is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR) ≥ 6ng/ml (see SmPC sections 4.2, 4.4 and 5.1).

Incidence and prevalence:

As of February 10, 2022, more than 394 million cases of COVID-19 have been reported globally, including more than 5.7 million deaths. In the EU/EEA, more than 151 million cases have been reported, including 1.8 million deaths (72).

Demographics of the COVID-19 population, ethnic origin, and risk factors for the disease:

COVID-19 disease has spread all over the world, leading to an ongoing pandemic, and there is an urgent need for effective treatments. Individuals of Black and Asian ethnicity seems to be

more vulnerable to COVID-19 infection, most likely due to socioeconomic factors (73, 74). Advanced age and comorbidities, e.g. hypertension, coronary heart disease, diabetes mellitus, obesity are the main risk factors for severe infection (75).

The main existing treatment options:

Early during the infection, the disease is primarily driven by replication of SARS-CoV-2. Later, the disease is predominantly driven by a hyperinflammatory response that leads to tissue damage and organ failure. It is anticipated that antiviral therapies would have a favorable effect during the early phase of the infection, while anti-inflammatory and immunomodulatory therapies are likely to be more beneficial in the later stages of COVID-19 Apart from preventive measures like keeping a physical distance and vaccination programs, medical treatment of COVID-19 include antiviral therapy, oxygen supplementation, supportive therapy, and corticosteroids (76, 77).

Since the beginning of the COVID-19 pandemic, immunomodulators were suggested as one of the main strategies to attenuate the exaggerated immune response of the host. The most commonly administered drugs are anakinra and tocilizumab targeting the IL-1 and the IL-6 pathways, respectively. Tocilizumab is authorized for use for the treatment of COVID-19 in the EU. As of February 15, 2022, there are 5 antiviral medications and 1 immunomodulator authorized for treatment of COVID-19 in the EU apart from Kineret (78).

Natural history of COVID-19 infection, including mortality and morbidity:

COVID-19 can be classified into 3 clinical stages. In stage 1, an estimated 80 to 84 % of infected patients are slightly symptomatic. In stage 2a, patients have a nonhypoxemic pneumonia but can advance to a hypoxemic pneumonia in stage 2b or ARDS in stage 3. After ~9 to 10 days, 17 to 20 % of patients can evolve toward more severe stages 2b or 3, with increasing requirement for oxygen necessitating admission into an ICU with noninvasive or invasive mechanical ventilation (76, 79).

At the more severe stages of COVID-19, mortality is reaching 60 % (80, 81) and SRF from ARDS is the leading cause of death (82). By preventing the progression from LRTI and pneumonia to ARDS and SRF, the prognosis for patients with moderate to severe COVID-19 would be improved, lives would be saved, and the burden on global healthcare systems during the pandemic would be reduced.

The most important symptoms in adults are fever, cough, fatigue, difficulty breathing, and myalgia (83). Elevated liver enzymes are also relatively common indicating that the SARS-CoV-2 virus has propensity for the liver which may also limit later therapeutic choices. Lymphocytopenia occurs in 87 % of the cases. Chest radiographs are often benign initially or may show signs of interstitial pneumonia with a ground glass appearance (84).

Important co-morbidities:

The risk of severe COVID-19 increases as the number of underlying medical conditions increases in an individual (85). The most frequently reported comorbidities associated with

severity and fatal outcome of COVID-19 are hypertension, heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), diabetes mellitus, obesity, chronic kidney disease, and respiratory diseases (including interstitial lung disease, pulmonary fibrosis and pulmonary hypertension). A systematic review and meta-analysis to evaluate comorbidities associated with severe and fatal cases of COVID-19 were conducted by Spencer Gold et al. Hypertension and diabetes were found to be more frequent among the deceased patients compared to total cases. Respiratory diseases were more common among fatal versus total cases (75).

Part II: Module SII - Non-clinical part of the safety specification

SII.1 Repeated dose toxicity

The subchronic and chronic effects of anakinra have been evaluated for up to 6 months in rats and up to 28 days in monkeys after intravenous (IV) or subcutaneous (SC) administration. Signs of perivascular inflammation were detected in rats after IV administration at the site of injection and at the SC injection sites as local reactions with trace of inflammation. Similar to the findings in rats, chronic inflammation at the injection sites (chronic lymphohistiocytic inflammation) were observed in monkeys.

Moreover, renal interstitial mononuclear cell infiltration and chronic progressive nephropathy were observed in rats administered 200 mg/kg anakinra SC for 6 months. The nature of the lesions indicated that they were aging-related changes specific for the rat and not directly mediated by anakinra. The rats also showed proteinuria, as did rhesus monkeys treated SC with anakinra for 4 weeks. The monkey urine was ELISA-positive for anakinra protein, indicating that the proteinuria observed was a consequence of the treatment causing a high protein load to the kidneys related to the renal excretion of anakinra.

SII.2 Reproductive/Developmental toxicity

The reproduction and developmental toxicity of anakinra has been evaluated in 2 species. Fertility, embryo-fetal development, and peri- and postnatal development reproduction studies were conducted in rats and an embryo-fetal development study in rabbits at doses up to 200 mg/kg/day. These studies did not reveal any evidence of reproduction toxicity or developmental toxicity related to anakinra.

The effect of anakinra treatment on the juvenile development of the hippocampus-dependent learning and memory function has been evaluated in rats at doses up to 200 mg/kg/day. No signs of adverse effects were detected on the performance in a multiple Y water maze test when compared to controls.

SII.3 Genotoxicity and carcinogenicity

The genotoxicity properties of anakinra were evaluated in a complete set of in vitro and in vivo genotoxicity tests. Anakinra did not induce gene mutations in either bacteria or mammalian cells in vitro. In vivo, there was no evidence of chromosomal aberrations or micronuclei in bone marrow cells in mice treated with anakinra. The carcinogenic potential of anakinra has not been evaluated in a formal long-term carcinogenicity study in a rodent species. However, a long-term carcinogenicity study is generally inappropriate for biologics such as anakinra.

Key safety findings from non-clinical studies and relevance to human usage are presented in Table 7.

Table 7 Key safety findings and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Repeat dose toxicity • Injection site reactions • Proteinuria	• Potential risk for injection site reactions. • Proteinuria is not relevant in humans dosed at therapeutic dose levels, estimated safety margin is 5 to 10-fold.
Reproductive and developmental toxicity	Anakinra is not predicted to cause any harm to the fetus or the mother when used during pregnancy.
Carcinogenic potential; long-term data missing. (A two-year carcinogenicity study in a rodent species has not been performed.)	Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. There are no concerns about a carcinogenic potential inherent to anakinra based on the pharmacological mode of action and observed minimal effects on the host cell resistance studies and slight enhancement of natural killer (NK) cell activity.

SII.4 Conclusions on non-clinical data

Injection site reactions have been identified as an important potential risk in humans. No other important potential risks have been identified in the non-clinical studies.

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

Following an extensive clinical trial development program, Kineret was authorized in the US in 2001, in the EU/EEA and Canada in 2002, Australia (2003), Israel (2011), Great Britain (2021), and in Russia in 2022 for the treatment of RA in combination with methotrexate in adults with an inadequate response to methotrexate alone. Since then, Kineret has also been authorized in the US and Canada for the treatment of NOMID (2012 and 2017 respectively), in EU/EEA, Great Britain, Israel, Russia and Australia for the treatment of CAPS (2013-2021), in Australia for the treatment of SJIA (2015), and in the EU/EEA, Great Britain and Russia for the treatment of Still's disease including SJIA and AOSD (2018, 2021). In 2020, Kineret was authorized for FMF in EU/EEA and Israel, and in 2021 in Great Britain and Russia, and for Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in the US in 2020. In 2021, Kineret was authorized for the treatment of adult patients with COVID-19 pneumonia in the EU/EEA.

SIII.2 Clinical trial exposure

Clinical trial safety data in RA

In RA, the clinical safety data in this RMP are from the major placebo-controlled, randomized, blinded clinical trials in patients older than 18 years with RA. When other data are used, this is

specifically stated. The trials included in the RA safety pool are presented in Table 8 and are hereafter referred to as the safety pool.

Open label safety trials, trials in healthy volunteers, indications other than RA, and trials where Kineret treatment was used in combination with other treatments (except methotrexate) are not included in the RA safety pool.

Table 8 Clinical trials included in the RA safety pool

Protocol no./ Study no.	Trial design	No. of patients Kineret	Placebo	Trial duration
0560	A randomized, double-blind, placebo-controlled, multicenter, dose-ranging study of the efficacy and safety of recombinant methionyl human interleukin-1 receptor antagonist (anakinra) in patients with active rheumatoid arthritis.	351	121	6 months (Full study in safety pool)
960180	A 24-week study to evaluate the safety and efficacy of anakinra therapy in the presence of background methotrexate in subjects with active rheumatoid arthritis.	345	74	6 months (Full study in safety pool)
960182	A pilot, dose-ranging study of anakinra in patients with active rheumatoid arthritis.	111	30	3 months (Full study in safety pool)
990145	A multicenter, blinded, randomized, placebo-controlled trial to study the ability of IL-1ra (anakinra) to retard joint destruction, and evaluate the long-term safety of IL-1ra, in subjects with rheumatoid arthritis.	449 (part A) 589 (part B)	450 (part A) 0 (part B)	Part A:12 months Part B: Up to 36 months (6 months part A included in safety pool)
990757	A multicenter, randomized, blinded, placebo-controlled study to describe long-term safety of daily subcutaneous injections of anakinra (r-metHuIL-1ra) in patients with rheumatoid arthritis.	1116 (part A) 1103 (part B)	283 (part A) 0 (part B)	Part A:6 months Part B:Up to 36 months (Full part A included in safety pool)
Total		**2372**	**958**	

Clinical trial safety data in CAPS

Clinical safety data in CAPS in this RMP are derived from study 03-AR-0298, which is presented in Table 9. This trial is an investigator-sponsored trial, conducted at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, USA. A trial report was compiled by Sobi. The trial included 43 patients. NOMID/CINCA was diagnosed in 36 patients (83.7 %), and 7 patients (16.3 %) were enrolled fulfilling the trial inclusion criteria, but had characteristics overlapping between MWS and NOMID/CINCA.

Table 9 Trial 03-AR-0298

Protocol no./ Study no.	Trial name	Trial design	No. of patients (patient years)	Trial duration
03-AR-0298	A long-term outcome study with the IL-1 receptor antagonist anakinra/Kineret® in patients with neonatal onset multisystem inflammatory disease (NOMID/CINCA syndrome)	Therapeutic confirmatory, prospective, open-label	43 (159.8)	Up to 60 months

Clinical trial safety data in Still's disease

There are 2 MAH-sponsored clinical trials that have included patients with Still's disease, see Table 10.

The trial 990758/990779 (published by Ilowite et al. 2009 (86)) was performed by the former MAH Amgen and data have been re-evaluated by Sobi.

This was a safety trial in 86 pediatric patients with JIA, whereof 15 with SJIA. The trial consisted of 3 phases: an initial 12-week open-label phase of trial 990758, a 16-week blinded placebo-controlled phase and a 12-month open-label phase of trial 990779.

The trial Sobi.ANAKIN-301 (anaSTILLs) was performed by Sobi and was a randomized, double-blind, placebo-controlled multicenter phase 3 efficacy and safety study in pediatric and adult patients with Still's disease (SJIA and AOSD). Totally 12 patients received study treatment, 6 patients received anakinra and 6 patients received placebo. One of the patients in the placebo group was diagnosed with lymphoma rather than Still's disease. The study duration was 16 weeks which included a 12-week treatment period and a 4-week follow-up period.

Table 10 Clinical trials in patients with Still's disease

Protocol no./ Study no.	Trial name	Trial design	No. of Still's patients on anakinra (patient years)	Trial duration
990758/990779	990758: A randomized, multi-center, blinded, placebo-controlled study with an open-label run-in period, to evaluate the efficacy, safety, and pharmacokinetics of daily, single, subcutaneous injections of r-metHuIL-1ra (anakinra) in polyarticular-course juvenile rheumatoid arthritis 990779: A companion extension study to evaluate the long-term safety of daily, single, subcutaneous injections of r-metHuIL-1ra (anakinra) in subjects with polyarticular-course juvenile rheumatoid arthritis	Open-label run in (12 weeks) + randomized, double blind placebo controlled (16 weeks) + open label extension (12 months)	15 (15.6)	70 weeks
Sobi.ANAKIN-301 (the anaSTILLs study)	A randomized, double-blind, placebo-controlled, multicenter, phase 3 efficacy and safety study of 2 dose levels of subcutaneous anakinra (Kineret®) in patients with Still's disease (SJIA and AOSD)	Randomized, double-blind, placebo-controlled	6 SJIA/AOSD (1.4)	16 weeks

Clinical trial safety data in FMF

There are no MAH-sponsored clinical studies in FMF, and this indication is therefore not included in the Clinical trial exposure tables below. However, there is an external study, a published double-blind placebo controlled study in 25 patients with FMF whereof 12 patients were treated with anakinra (87).

Clinical trial safety data in COVID-19

Safety and efficacy have been evaluated in the investigator sponsored study SAVE-MORE, a pivotal, multicenter, double-blind, randomized, SoC-controlled study sponsored and performed by the Hellenic Institute for the Study of Sepsis (HISS). In the SAVE-MORE multicenter trial, 594 hospitalized patients with moderate and severe COVID-19 pneumonia and plasma suPAR of 6 ng/mL or more and receiving SoC were 1:2 randomized to subcutaneous treatment with placebo or 100 mg anakinra once daily for 10◦days; 189 patients were allocated to the placebo and SoC arm and 405 patients were allocated to the anakinra and SoC arm.

There is 1 MAH-sponsored clinical trial that has included patients with COVID-19. A Phase 2/3, randomized, open-label, parallel group, 3-arm, multicenter study (Sobi.IMMUNO-101; EudraCT Number: 2020-001167-93) was initiated to investigate the efficacy and safety of anakinra and emapalumab versus standard of care (SoC) in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection. However, recruitment in the study was prematurely closed due to the evolvement of SoC treatment during the timeframe of the study

and its effect on recruitment. As a result, only 16 patients were enrolled. Anakinra was administered as 4-times daily intravenous infusions for 15 days (400 mg/day in total, divided into 4 doses given every 6 hours). A total of 16 patients completed screening and were enrolled in the study. Five patients received treatment with emapalumab, 5 patients received treatment with anakinra, and 6 patients received SoC.

SIII.2.1 Clinical trial exposure

Exposure to Kineret in clinical trials by duration, dose, age and sex, and ethnic origin in patients with RA within the safety pool, CAPS, Still's disease, acute gouty arthritis and COVID-19 are presented in Table 11 to Table 19. Table 20 shows exposure in special populations; the trials included are not part of the RA safety pool and are specified in the table.

Table 11 Cumulative exposure by duration (by indication)

	Number (%) of patients exposed to Kineret	Patient years
Indication: RA		
Duration of exposure		
<0-1 months	2372 (100.0)	189.3
>1-3 months	2168 (91.4)	342.2
>3-6 months	1836 (77.4)	390.4
>6-12 months	176 (7.4)	1.7
Total patient years		923.5
Indication: CAPS		
Duration of exposure[a]		
>0-1 year	43 (100.0)	40.9
>1-2 years	39 (90.7)	36.4
>2-3 years	34 (79.1)	29.0
>3-4 years	28 (65.1)	27.1
>4 years	26 (60.5)	26.5
Total patient years		159.8
Indication: Still's disease		
Duration of exposure		
0-12 weeks	21 (100.0)	4.5
>12-28 weeks	16 (76.2)	2.4
>28-56 weeks	10 (47.6)	5.3
>56 weeks	9 (42.9)	4.0
Total patient years		17.0
Indication: Acute Gouty Arthritis		
Duration of exposure		
<0-5 days	107 (100.0)	1.4
>5-10 days	48 (44.9)	0.6
>10-15 days	29 (27.1)	0.6
>15-20 days	19 (17.8)	0.6
>20 days	12 (11.2)	0.3
Total patient years		3.0
Indication: COVID-19		
Duration of exposure		
<0-5 days	5 (100.0)	0.1
>5-10 days	5 (100.0)	0.1
>10-15 days	5 (100.0)	0.1
>15-20 days	4 (80.0)	0.0
Total patient years		0.2

EXP_DUR_IND_T.SAS 2022-06-21T09:09:22 Z9FRBE
Data from completed trials (the RA safety pool, the CAPS study 03-AR-0298, 15 SJIA patients from the JIA study (990758/990779), the Still's disease study Sobi.ANAKIN-301, the acute gouty arthritis study Sobi.ANAKIN-401 and the COVID-19 study with i.v. administration, Sobi.IMMUNO-101) as of 01-May-2022

a Duration of treatment is calculated from the date of first dose until date of last dose, date of Month 60 visit or cut-off date. Exposure has been calculated as actual duration of treatment and can be >5 years due to variability in the visit window of the Month 60 visit.

In the COVID-19 study SAVE-MORE, 405 patients were treated with anakinra 100 mg SC QD for a median of 10 days (min 1, max 10), resulting in a total exposure of 9.6 patient years.

Table 12 Cumulative exposure by duration (totals)

	Number (%) of patients exposed to Kineret	Patient years
Duration of exposure		
>0-1 year	2548 (100.0)	979.8
>1-2 years	49 (1.9)	41.1
>2-3 years	34 (1.3)	29.0
>3-4 years	28 (1.1)	27.1
>4 years	26 (1.0)	26.5
Total patient years		1103.5

EXP_DUR_SUM_T.SAS 2022-06-21T09:09:24 Z9FRBE
Data from completed trials (the RA safety pool, the CAPS study 03-AR-0298, 15 SJIA patients from the JIA study (990758/990779), the Still's disease study Sobi.ANAKIN-301, the acute gouty arthritis study Sobi.ANAKIN-401 and the COVID-19 study with i.v. administration, Sobi.IMMUNO-101) as of 01-May-2022
Note: For Still's disease patients from the JIA study (990758/990779) 1 year corresponds to 56 weeks

Table 13 Cumulative exposure by dose (by indication)

	Number of patients exposed to Kineret	Patient years
Indication: RA[a]		
Dose of exposure		
<100 mg/day	610	214.7
100 mg/day	1566	637.8
>100 mg/day	196	70.9
Total	2372	923.5
Indication: CAPS[b]		
Dose of exposure[c]		
1 mg/kg	27	16.4
2 mg/kg	40	62.5
3 mg/kg	31	40.2
4 mg/kg	23	28.8
5 mg/kg	11	10.8
6 mg/kg	1	0.3
8 mg/kg	2	0.7
Total	43	159.8
Indication: Still's disease[a]		
Dose of exposure		
1 mg/kg/day (maximum 100 mg)	15	15.6
2 mg/kg/day (maximum 100 mg)	2	0.5
4 mg/kg/day (maximum 200 mg)	4	0.9
Total	21	17.0
Indication: Acute Gouty Arthritis[a]		
Dose of exposure		
100 mg/day	55	1.5
200 mg/day	52	1.5
Total	107	3.0
Indication: COVID-19[a]		
Dose of exposure		
400 mg/day	5	0.2
Total	5	0.2

EXP_DOS_IND_T.SAS 2022-06-21T09:09:27 Z9FRBE

Data from completed trials (the RA safety pool, the CAPS study 03-AR-0298, 15 SJIA patients from the JIA study (990758/990779), the Still's disease study Sobi.ANAKIN-301, the acute gouty arthritis study Sobi.ANAKIN-401 and the COVID-19 study with i.v. administration, Sobi.IMMUNO-101) as of 01-May-2022

a Fixed doses

b Titrated doses

c Duration of treatment is calculated from the date of first dose until date of last dose, date of Month 60 visit or cut-off date. Exposure has been calculated as actual duration of treatment and can be >5 years due to variability in the visit window of the Month 60 visit

Table 14 Exposure by age group and sex (by indication)

	No. of patients exposed to Kineret		Patient years	
	Male	**Female**	**Male**	**Female**
Indication: RA				
Age group				
18-64 years	416	1443	164.1	563.7
≥65 years	141	372	58.6	137.1
Total	557	1815	222.7	700.8
Indication: CAPS[a]				
Age group				
<2 years	4	9	12.5	21.3
2-11 years	10	8	44.7	32.2
12-17 years	2	3	9.4	10.6
18-65 years	2	5	9.9	19.2
Total	18	25	76.5	83.3
Indication: Still's disease				
Age group				
1-11 years	8	6	5.4	5.4
12-18 years	4	2	4.3	1.6
≥18 years	0	1	0	0.2
Total	12	9	9.7	7.3
Indication: Acute Gouty Arthritis				
Age group				
18-64 years	75	9	1.9	0.4
≥65 years	17	6	0.6	0.1
Total	92	15	2.5	0.5
Indication: COVID-19				
Age group				
18-64 years	2	0	0.1	0
≥65 years	2	1	0.1	0.0
Total	4	1	0.2	0.0

EXP_DEM_IND_T.SAS 2022-06-21T09:09:29 Z9FRBE
Data from completed trials (the RA safety pool, the CAPS study 03-AR-0298, 15 SJIA patients from the JIA study (990758/990779), the Still's disease study Sobi.ANAKIN-301, the acute gouty arthritis study Sobi.ANAKIN-401 and the COVID-19 study with i.v. administration, Sobi.IMMUNO-101) as of 01-May-2022
a Duration of treatment is calculated from the date of first dose until date of last dose, date of Month 60 visit or cut-off date. Exposure has been calculated as actual duration of treatment and can be >5 years due to variability in the visit window of the Month 60 visit

Table 15 Exposure by age and sex (SAVE-MORE study)

	No. of patients exposed to Kineret		Patient years	
	Male	**Female**	**Male**	**Female**
Indication: COVID-19				
Age group				
18-64 years	146	86	5.0	3.1
≥65 years	93	80	2.1	1.9
Total	239	166	5.6	4.0

Table 16 Exposure by age group and sex (totals)

	No. of patients exposed to Kineret		Patient years	
	Male	**Female**	**Male**	**Female**
Age group				
<2 years	4	10	12.5	21.6
2-11 years	18	13	50.1	37.4
12-17 years	6	5	13.7	12.2
18-64 years	495	1458	175.9	583.6
≥65 years	160	379	59.3	137.2
Total	683	1865	311.6	791.9

EXP_DEM_TOT_T.SAS 2022-06-21T09:09:33 Z9FRBE
Data from completed trials (the RA safety pool, the CAPS study 03-AR-0298, 15 SJIA patients from the JIA study (990758/990779), the Still's disease study Sobi.ANAKIN-301, the acute gouty arthritis study Sobi.ANAKIN-401 and the COVID-19 study with i.v. administration, Sobi.IMMUNO-101) as of 01-May-2022

Table 17 Exposure by ethnic origin (by indication)

	No. of patients exposed to Kineret	Patient years
Indication: RA		
Ethnic/racial origin		
White/Caucasian	2115	824.7
Hispanic	122	47.1
Black	94	35.7
Asian	20	8.0
Other	21	8.0
Total	2372	923.5
Indication: CAPS[a]		
Ethnic/racial origin		
White	36	135.5
Black	1	5.0
Asian	1	5.1
Other	5	14.3
Total	43	159.8
Indication: Still's disease		
Ethnic/racial origin		
White or Caucasian	13	8.9
Black or African American	2	1.8
Hispanic or Latino	5	6.0
American Indian or Alaska Native	1	0.2
Total	21	17.0
Indication: Acute Gouty Arthritis		
Ethnic/racial origin		
White	78	2.3
Black or African American	26	0.6
Asian	3	0.1
Total	107	3.0
Indication: COVID-19		
Ethnic/racial origin		
White	4	0.2
Asian	1	0.0
Total	5	0.2

EXP_RAC_IND_T.SAS 2022-06-21T09:09:36 Z9FRBE
Data from completed trials (the RA safety pool, the CAPS study 03-AR-0298, 15 SJIA patients from the JIA study (990758/990779), the Still's disease study Sobi.ANAKIN-301, the acute gouty arthritis study Sobi.ANAKIN-401 and the COVID-19 study with i.v. administration, Sobi.IMMUNO-101) as of 01-May-2022
a Duration of treatment is calculated from the date of first dose until date of last dose, date of Month 60 visit or cut-off date. Exposure has been calculated as actual duration of treatment and can be >5 years due to variability in the visit window of the Month 60 visit.

Table 18 Exposure by ethnic origin (SAVE-MORE)

	No. of patients exposed to Kineret	Patient years
Indication: Covid- 19		
Ethnic/racial origin		
White	405	9.6
Black or African American	0	0
Asian	0	0
Total	405	9.6

Table 19 Exposure by ethnic origin (totals)

	No. of patients exposed to Kineret	Patient years
Ethnic/racial origin		
White/Caucasian/Hispanic	2368	1018.7
Black	123	43.1
Asian	25	13.2
Other	32	28.5
Total	2548	1103.5

EXP_RAC_TOT_T.SAS 2022-06-21T09:09:38 Z9FRBE
Data from completed trials (the RA safety pool, the CAPS study 03-AR-0298, 15 SJIA patients from the JIA study (990758/990779), the Still's disease study Sobi.ANAKIN-301, the acute gouty arthritis study Sobi.ANAKIN-401 and the COVID-19 study with i.v. administration, Sobi.IMMUNO-101) as of 01-May-2022

Table 20 Special populations (totals)

Total population		
	No. of patients exposed to Kineret	**Patient years**
Pregnant women	0	
Lactating women	0	
Renal impairment (specify or categorize) Renal failure[a] Hemodialysis (10 patients) Peritoneal dialysis (10 patients) Various degrees of renal function[b]	 20 24	 0.06 0.07
Hepatic impairment[c]	12	0.03
Cardiac impairment	- [d]	
Sub populations with genetic polymorphism	CAPS (study 03-AR-0298): 31 patients (72.1 %) with *NLRP3* mutation[e]	121.6
Immunocompromised	- [f]	

[a] Study 0555 [b] Study 20000268 [c] Study 0563 (all 3 single-dose studies)
[d] No studies on cardiac impairment, but patients with cardiac impairment have been included in several RA studies.
[e] The most common type was D303N (Source: EXP_GEN_IND_T.SAS 2016-11-25T14:51:16 Z9FRBE)
[f] The vast majority of RA patients are immunocompromised due to treatment with DMARDs and cortisone.

SIII.2.2 Exposure to Kineret in clinical trials and post-marketing use combined

Since the initiation of Kineret clinical trials in May 1994 until 1 May 2022, the estimated exposure to Kineret in completed marketing authorization holder (MAH)-sponsored clinical trials and post-marketing use combined is approximately 170 028 person years (Table 21). Further details on post-marketing exposure are included in Section SV.1.2 Exposure.

Table 21 Estimated exposure to Kineret from completed MAH-sponsored clinical trials and market experience in patient years

	Cumulative patient years
Completed MAH-sponsored clinical trials	6 408
Commercial Kineret worldwide	163 620
Total	**170 028**

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Exclusion criteria which remain as contraindications			
Criteria	**Reason for being an exclusion criterion**	**Missing information**	**Rationale**
Sensitivity/allergy to *E. coli*-derived drug preparations.	Anakinra is produced in Escherichia coli cells by recombinant DNA technology.	No	The condition is very rare.
Neutrophil granulocyte count of <1.5 x 10^9/L	An increased susceptibility to infections is a potential safety issue with all agents that alter cytokine response.	No	Neutropenia is considered to be an important identified risk. The current SmPC states that Kineret treatment should not be initiated in patients with neutropenia.

Exclusion criteria which are NOT remaining as contraindications			
Criteria	**Reason for being an exclusion criterion**	**Missing information**	**Rational**
Pregnancy or lactation	Standard exclusion criteria	Yes	
The patient is known to be HBsAg, HCV, HIV positive.	Risk for transmission of infections at blood tests. Suspicion of possible risk for activation of chronic infection.	Yes, use in patients with chronic infections will be followed as missing information.	
Serious infection	To allow unconfounded assessment of efficacy and safety	Yes	
Pre-existing malignancies	To allow unconfounded assessment of efficacy and safety	Yes	
Patients with ALT/AST ≥1.5 ULN or severe hepatic failure defined as Child-Pugh stage of 3	To allow unconfounded assessment of efficacy and safety	No	Single i.v. doses of Kineret were well tolerated by 12 patients with hepatic dysfunction (study 0563). Hepatic enzyme increase and hepatitis are identified risks.
Severe renal impairment (creatinine clearance <30 ml/minute)	Kineret is eliminated by glomerular filtration and subsequent tubular metabolism	No	Posology for patients with renal impairment is defined in the SmPC: Single doses of Kineret were well tolerated by 32 patients with severe renal impairment including dialysis. Doses up to 2 mg/kg/h i.v. in patients with sepsis have been well tolerated.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse drug reactions (ADRs) because of the limited number of patients exposed to Kineret in the CAPS and Still's disease clinical trial programs.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 22 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pediatric patients	Kineret is currently indicated for pediatric use in CAPS, FMF and Still's disease. One study has been performed in CAPS patients (study 03-AR-0298) and 1 study has been performed in children with juvenile RA, a condition that has been renamed JIA (990758/990779). In addition, 1 study has been performed in Still's disease (AOSD and SJIA, Sobi.ANAKIN-301). 36 patients, aged <18 years, with the most severe form of CAPS, NOMID/CINCA, have been exposed to Kineret for up to 5 years (open-label study 03-AR-0298, total exposure 131 patient years). Age at start of treatment influences the individual functional outcome of treatment in severely affected patients. The results from study 03-AR-0298 and the supportive published efficacy studies indicate that Kineret treatment prevented hearing loss in the youngest patients without further damage to the cochlea. In older patients with long-standing, untreated disease, treatment may avert the progression of further impairment, but does not normalize hearing in severe cases. 86 patients with JIA aged 2 to 17 years, including 15 patients with SJIA (Study 990758). Long-term safety in the same patients evaluated in an open-labeled extension (Study 990779). 5 patients with SJIA were exposed to Kineret in the 12-week double-blind, placebo-controlled study Sobi.ANAKIN-301. The patients were younger than 12 years old.. FMF: No experience Covid-19: No experience
Elderly	513 elderly aged ≥65 years (RA safety pool) 112 elderly aged ≥75 years (RA safety pool) In the Sobi.IMMUNO-101 study in patients with COVID-19, 3 of the 5 patients in the anakinra treatment arm were >65 years old and none were >75 years old. In the SAVE-MORE study, 173 patients > 65 years old with COVID-19 were treated with anakinra. No elderly patients with CAPS or Still's disease have been exposed to Kineret in study 03-AR-0298, 990758/990779 and Sobi.ANAKIN-301.

Type of special population	Exposure
Pregnant and breastfeeding women	Not included in the clinical development program. Sobi has information about 381 reports of pregnancy during Kineret exposure, up to 1 May 2022. The outcome of pregnancies was 99 normal infants, 13 children inherited/affected by CAPS or TRAPS 82 pregnancies had abnormal outcomes (spontaneous abortion, stillbirth, adverse events in child). The outcome is unknown in 187 of the reports.
Patients with: hepatic impairment	12 patients (Study 0563)
Renal impairment	20 patients with renal failure; 10 patients with hemodialysis and 10 patients with continuous ambulatory peritoneal dialysis (Study 0555). 24 patients with various degrees of renal impairment (Study 20000268). 9 patients with various degrees of renal impairment (SAVE-MORE study). The supportive published efficacy studies included further patients with renal functional impairment, A subgroup of patients with amyloidotic manifestations (affecting approximately 1/4 of MWS patients) and renal functional impairment at baseline were included in the studies by Kuemmerle-Deschner et al. 2011 (88), Hawkins et al. 2004 (89), and Leslie et al. 2006 (90). Amyloidosis was halted or improved, and a gradual resolution of amyloid-related nephrotic syndrome manifestations was detected.
Cardiac impairment	Patients with cardiac impairment have been included in several studies of RA and in one study of COVID-19 (SAVE-MORE study).
Disease severity different from the inclusion criteria in the clinical trial population	In one study of patients with the most severe form of CAPS (NOMID/CINCA, Study 03-AR-0298), 7 patients had characteristics overlapping between MWS and NOMID/CINCA.
Sub-populations carrying known and relevant polymorphisms	RA: No experience CAPS: The safety profile of Kineret in CAPS patients in study 03-AR-0298 is not clinically relevantly influenced by the absence or presence of a detectable, somatic *NLRP3* mutation, or by the type of *NLRP3* mutation, when detectable. In the supportive published efficacy studies in CAPS, the majority of studies included patients of all ages and all patients reportedly did respond to both short- and long-term treatment, irrespective of NLRP3 gene mutation, age, and sex. Still's disease: No experience FMF: No experience COVID-19: No experience

Type of special population	Exposure
Different racial and/or ethnic origin	In 24 Japanese healthy volunteers aged 20 to 28 years, exposed to single ascending IV doses of anakinra, no apparent difference compared to Caucasians regarding safety and pharmacokinetics was observed (study 0541). RA: In 15 Chinese patients with RA the exposure and apparent clearance of anakinra in Chinese patients were comparable with those for non-Chinese subjects with RA (Study 20000152). In the RA safety pool there were no apparent differences between non-Caucasians (n=257) and Caucasians (n=2115) regarding safety parameters. CAPS patients: Among 43 patients (study 03-AR.0298) 36 were white. The other 7 patients were of Asian (1), black (1) or mixed (5) origin. All patients responded to treatment irrespective of ethnicity. Still's disease patients: 13 Caucasian, 5 Hispanic/Latino, 2 Black/African American, 1 American Indian/Alaska Native (studies 990758/990779 and Sobi.ANAKIN-301). COVID-19: all 405 patients treated with anakinra were white (SAVE-MORE study).

Part II: Module SV - Post-authorisation experience

Kineret was authorized in the US in 2001 and in the EU in 2002, so there is more than 20 years of post-marketing experience, which has been taken into consideration when preparing this RMP.

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Commercial use of Kineret was estimated by determining the number of patients and patient years of exposure from monthly product distribution by region and includes all preparations (i.e., both the previous non-graduated and the current graduated syringe).

The MAH used market research to track US patients over 12 months and monitored their purchasing patterns to determine their compliance. The compliance rate of 5.95 vials per week (85 % of the recommended dose) is used for calculation of exposure for US and Canada. A compliance rate of 5.6 vials per week (80 % of the recommended dose) is used for the calculation of exposure for all other countries.

Exposure is calculated based on the approved dose for patients with RA, i.e., 100 mg/day. During the first years after approval Kineret was almost exclusively used for RA in the approved dose. Kineret is approved for the treatment of RA in the US, EU/EEA, Great Britain, Canada, Israel, Australia and Russia. In the US and Canada Kineret is also approved for NOMID. Kineret is approved for the whole spectrum of CAPS in the EU/EEA, Great Britain, Israel, Russia and Australia. In addition, Kineret is approved for the treatment of SJIA (Australia), Still's disease including SJIA and AOSD (EU/EEA, Great Britain and Russia), FMF (EU/EEA, Great Britain, Israel and Russia), COVID-19 (EU/EEA), and DIRA (US). In addition Sobi is aware of off-label

use in other indications. In some of the indications where Kineret is used the dose can be both higher and lower than the approved dose in RA. This means that the estimated exposure should be interpreted with caution, especially during later years.

SV.1.2 Exposure

Total worldwide commercial exposure on 1 May 2022, was estimated to be 163,620 patient years, including use in named patient programs and compassionate use programs. Estimated exposure to commercial Kineret broken down into geographic areas is shown in Table 23.

Table 23 Estimated exposure to commercial Kineret by geographic area in patient years up to 1 May 2022

Geographic area	Cumulative patient years
EU/EEA[a]	85 463
Rest of world[b]	17 220
North America	60 937
Total	**163 620**

Note: Patient years = number of syringes / (recommended dosage * compliance rate * 52).
[a] Includes EU/EEA, Switzerland, and Great Britain.
[b] Includes also compassionate use or named patient programs.

SV1.2.1 Post-authorization exposure by indication

Besides being used for the on-label indications through literature articles and individual case safety reports (ICSRs), Sobi is aware that Kineret is used off-label in both adults and children.

Despite limited licensed indications, anti-IL-1 agents are often used in real-life practice for an increasing number of diseases. A national survey to record the off-label use in France was started in January 2011. The survey was coordinated by the French National Reference Centre for Auto-inflammatory Diseases under the sponsorship of the “Club Rhumatisme et Inflammation” (CRI). The survey included 189 patients (100 males) from 38 centres. At the time of anti-IL-1 therapy introduction, 139 patients were adults, and 50 were children or adolescents (<18 years old). The mean age at treatment onset for children and adolescents was 8.3 years and for adults 46.6 years. The main off-label used agent was anakinra, used at least once for 185 patients, with canakinumab used for 25 patients. The main off-label diseases treated with anakinra were AOSD (35 patients), gout (28 patients), SJIA (26 patients), CAPS (21 patients), familial Mediterranean fever (FMF) (13 patients), mevalonate kinase deficiency (MKD) (10 patients), synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome (9 patients), and Schnitzler’s syndrome (7 patients). It should be noted that at the time of the survey CAPS, FMF and Still’s disease including SJIA and AOSD were not yet approved indications, and were therefore included in the survey. The survey was published by Rossi-Semerano et al. 2015 (91).

<u>Swedish Rheumatology Quality Registers</u>

Sobi has access to the Swedish Rheumatology Quality Registers (SRQ). SRQ comprises a cooperation between clinical registers in Swedish rheumatology participating in a national

program for continuous follow up of patients for drug surveillance, clinical trials, health economics, clinical research, and health care quality improvement. SRQ works together with research-driven pharmaceutical companies to improve patient health. The register includes only adult patients. Table 24 shows the number of ongoing Kineret treatments outside of the approved label in Sweden by indication from 2016 up to February 2021. Indications with fewer than 2 ongoing treatments during 2021 are not included in the table. Overall, there is a slight increased use of anakinra over time. The most common indication is gout, systemic inflammatory disease NUD and polyarthritis..

Table 24 Number of ongoing treatments with Kineret in the Swedish Rheumatology Quality Registers (SRQ) (status February 2021)

Indication	2016	2017	2018	2019	2020	2021
AOSD[a]	32	34	37	37	39	38
Arthritis NUD[b]	3	3	3	3	4	4
Chronic rheumatic pericarditis	0	0	0	1	2	2
FMF[a]	7	9	11	13	13	13
Gout	13	13	17	18	18	19
Inclusion body myositis	7	5	4	4	4	4
Juvenile Arthritis NUD[b]	3	2	3	4	5	5
Juvenile Mono/Oligoarthritis	1	1	1	1	2	2
Oligoarthritis NUD[b]	2	2	2	2	2	2
Other specified necrotizing vascular conditions	2	2	2	2	2	2
Polyarthritis	8	9	8	10	12	12
Polymyositis	2	2	4	2	2	2
Psoriatic arthritis	3	3	2	2	2	2
Pyrexia NUD[b]	8	7	7	7	6	7
Rheumatoid arthritis[a]	23	20	20	22	29	26
Schnitzler's syndrome	9	9	9	9	9	9
SJIA[a]	5	4	4	7	8	8
Spondylarthritis	6	4	6	5	5	5
Systemic Inflammatory disease NUD[b]	14	12	13	14	16	16

[a] AOSD and SJIA are approved indications in EU/EEA and Great Britain. SJIA is also approved in Australia. FMF is an approved indication in EU/EEA, Great Britain and Israel. Rheumatoid arthritis is an approved indication in the US, EU/EEA, Canada, Australia, Great Britain and Israel.
[b] NUD=Unspecified (non ultra descripta).

Postauthorization off-label pediatric use

It is known from scientific journals and ICSRs that Kineret is prescribed as treatment for rare systemic autoinflammatory diseases affecting children.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Potential for misuse of Kineret for illegal purposes is considered low.

Potential for transmission of infectious agents

Anakinra is produced in *E. coli* cells. Therefore there is no significant risk of contamination with adventitious agents such as mammalian viruses or mycoplasma. Potential nonviral adventitious agents such as contaminating bacteria, fungi and TSE are controlled at several levels. The introduction of such agents is prevented or minimized by controls on starting materials, including raw materials, excipients and cell source.

There are no animal derived materials used in the fermentation or purification of the active substance anakinra.

The manufacturing process and facility are designed to prevent contamination during production of anakinra drug substance. Manufacturing takes place on a campaign basis in suites which are, during production, dedicated to the production of anakinra. Validation of the cleaning procedures confirms that cleaning is effective.

In-process controls ensure that purity requirements are met. Release testing of drug substance and drug product assures purity and quality of the product.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

At the time of the initial RMP, there were no risks considered non-important. Off-label pediatric use was considered an additional safety concern. This is no longer a concern as the pediatric population is now part of the approved indications.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

At the time of the initial RMP, the following risks were included as important:

Table 25 Summary of safety concerns at the time of the initial RMP

Summary of safety concerns	
Important identified risks	Injection site reactions (ISRs)
	Immunogenicity
	Serious infections
	Neutropenia
	Allergic conditions
Important potential risks	Malignancies
	Hepatic disorders
	Macrophage activation syndrome (MAS)
Missing information	Pregnant women
	Lactating women
	Patients with cardiac impairment
Additional safety concern	Off- label pediatric use

See Section SVII.3 Details of important identified risks, important potential risks, and missing information for further details.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The following event classified as important potential risk are to be added to the list of safety concerns:

- Drug reaction with eosinophilia and systemic symptoms (DRESS)

Based on a request from PRAC in July 2020, an investigation of DRESS as an adverse event was performed during the interval. The request was triggered by a publication by Dr Saper et al. (92). The investigation included review of the Sobi global safety database, mechanistic studies, clinical studies and the literature, as well as contacts with Dr Saper. Sobi considers that a causal relationship has not been established between anakinra and DRESS. However, a warning was added under Section 4.4 in the SmPC and in the Core Data Sheet, describing that DRESS has been reported in patients treated with IL-1 inhibitors, predominantly in pediatric patients with Still's disease. In addition, DRESS is proposed to be added as an important potential risk in the RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

No clinically relevant differences have been identified regarding important identified and potential risks between RA, CAPS, FMF, Still's disease and COVID-19 patients in pediatric and adult patients, with the exception of the potential risks of Pulmonary events and DRESS, which are relevant predominantly for Still's disease. Patients with DIRA may have an increased risk of allergic reactions compared to other indications, especially in the first few weeks after commencing treatment.

All risks are presented separately for RA and CAPS patients. If not stated otherwise, the data presented for RA and CAPS are relevant also for Still's disease, FMF and COVID-19 disease, both in pediatric and adult patients. Sobi sponsored studies in unapproved indications have not indicated additional risks or changed the assessment of the identified and potential risks with anakinra.

Patients with RA

Unless stated otherwise, all analyses in the tables below regarding seriousness/outcomes and frequency of the identified and potential risks have been performed on the major placebo-controlled, randomized studies in the RA safety pool i.e., as the percentage of the total number of patients in the RA safety pool.

Outcome of adverse events have in all studies in the RA safety pool been collected as 'AE continuing or not continuing at final visit/end of study'. AEs in the RA safety pool are coded in the WHO-ART system.

Severity and nature of risk have been presented as the percentage of the total number of events in the RA safety pool. The studies included in the safety pool are described in Section SIII.2.

Post-marketing data have also been taken into consideration when evaluating the risks.

Patients with CAPS

Unless stated otherwise, all analyses in the tables below regarding seriousness/outcomes and frequency of the identified and potential risks are based on study 03-AR-0298. It should be noted that the duration of study 03-AR-0298 was up to 5 years, meaning that the time of exposure for

each CAPS patient is longer than for each RA patient in the safety pool, and therefore it is expected that each CAPS patient should have a higher number of AEs per patient.

Post-marketing data have also been taken into consideration when evaluating the risks.

Patients with Still's disease

There are 21 patients with Still's disease treated with anakinra in 2 MAH-sponsored clinical studies (15 patients in study 990758/990779 and 6 patients in study Sobi.ANAKIN-301). Unless stated otherwise, the safety data presented for RA and CAPS are relevant also for patients with Still's disease.

Published studies and case reports as well as other post-marketing data have also been taken into consideration when evaluating the risks.

Patients with FMF

There is no MAH-sponsored clinical study in FMF patients. In a published double-blind placebo controlled study (87) in 25 patients with FMF there are 12 patients treated with anakinra. Therefore, it is not appropriate to calculate separate specific frequencies for the majority of important identified and potential risks for patients with FMF. Unless stated otherwise, the safety data presented for RA and CAPS are relevant also for patients with FMF.

Patients with COVID-19

There is one MAH sponsored clinical study in COVID-19 patients which was stopped early due to inability to enroll patients with evolving clinical treatment regimen for COVID-19 disease. This study had very limited exposure. The Investigator Sponsored Study SAVE-MORE is a double blind placebo controlled study in patients with COVID-19, 405 of which were treated with anakinra. Safety data review did not identify any new risks for anakinra with the use in COVID-19 patients.

Unless stated otherwise, the safety data presented for RA and CAPS are relevant also for patients with COVID-19.

SVII.3.1. Presentation of important identified risks and important potential risks

Identified risk: Injection site reactions (ISRs)

Identified risk: Injection site reactions (ISRs)	
Potential mechanisms	The combination of vehicle constituents and a high protein concentration in the syringe may give rise to mast cell reaction degranulation, causing acute ISRs. Delayed ISRs may be caused by an immune-mediated local reaction (93). Placebo solutions in clinical studies have contained all excipients but no anakinra.

Identified risk: Injection site reactions (ISRs)	
Evidence source(s) and strength of evidence:	Completed clinical studies, literature review, and post-marketing surveillance. Due to the low number of patients, Still's disease , FMF and COVID-19 are not included in the frequency tabulation below. In double-blind, placebo-controlled studies in RA patients, ISRs were the most common and consistently treatment-related reported adverse reactions to Kineret. ISRs are common in post-marketing reports in RA patients. The frequency of ISRs in CAPS patients in study 03-AR-0298 was similar to placebo patients in RA studies and there were no permanent or temporary withdrawals of Kineret due to ISRs in CAPS patients. In 15 patients with SJIA, included in study 990758/990779, ISRs were the most common AEs. One patient discontinued on day 1 of the study 990758 open-label phase due to ISRs. In 12 patients with Still's disease included in study Sobi.ANAKIN-301, ISRs were reported in both the anakinra (4 ISRs in 6 patients) and the placebo (3 ISRs in 6 patients) groups. In COVID-19 patients in the investigator-sponsored study SAVE-MORE there were no ISRs in the placebo group and 2 ISRs in the anakinra group. ISRs were reported in lower frequency compared to RA studies.
Characterization of the risk: Frequency with 95 % confidence interval (CI)	**RA patients (blinded placebo-controlled, randomized studies)** Kineret: 1534/2372 subjects (65 %, 95 % CI [63 %, 67 %]). Placebo: 261/958 patients (27 %, 95 % CI [24 %, 30 %]). **CAPS patients** Kineret: 10/43 patients (23 %, 95 % CI [10.6 %, 35.9 %]). **COVID-19 patients (SAVE-MORE study)** Kineret: 2/405 patients, (0.5%, 95% CI [0.1%, 1.8%]). Placebo: 0/189 patients (0%, 95% CI [0.0%, 1.9%]).

Identified risk: Injection site reactions (ISRs)

Seriousness/outcomes

	RA patients	Placebo patients	CAPS patients
Total number of AEs	3799	423	17
Number of patients (%) with any AE	1534 (64.7 %)	261 (27.2 %)	10 (23.3 %)
Number of SAEs	6	0	0
Number of patients (%) with SAEs	3 (0.1 %)	0	0
Outcome	679 events in 417 (17.6 %) patients continued at end of study.	102 events in 83 (8.7 %) patients continued at end of study	All events resolved without sequelae

COVID-19 (SAVE-MORE study)

	anakinra patients	placebo patients
Total number of AEs	2	0
Number of patients (%) with any AE	2 (0.5)	0 (0)
Number of SAEs	0	0
Number of patients (%) with SAEs	0 (0)	0 (0)
Outcome	2 recovered	N/A

Postmarketing data
Post marketing data are consistent with clinical study data.

<table>
<tr><th colspan="2">Identified risk: Injection site reactions (ISRs)</th></tr>
<tr><td>Severity and nature of risk</td><td>
<table>
<tr><th>Severity</th><th colspan="3">Number of events (%)</th></tr>
<tr><td></td><td>RA patients</td><td>Placebo patients</td><td>CAPS patients</td></tr>
<tr><td>Mild</td><td>2771 (72.9)</td><td>368 (87)</td><td>13 (76.5)</td></tr>
<tr><td>Moderate</td><td>898 (23.6)</td><td>46 (10.9)</td><td>4 (23.5)</td></tr>
<tr><td>Severe</td><td>130 (3.4)</td><td>9 (2.1)</td><td>0 (0)</td></tr>
</table>
COVID-19 patients (SAVE-MORE study)
<table>
<tr><th>Severity</th><th colspan="2">Number of events (%)</th></tr>
<tr><td></td><td>anakinra patient</td><td>placebo patient</td></tr>
<tr><td>Mild</td><td>2 (100)</td><td>0</td></tr>
<tr><td>Moderate</td><td>0</td><td>0</td></tr>
<tr><td>Severe</td><td>0</td><td>0</td></tr>
</table>
Note: only non-serious events were classified according to severity in the SAVE-MORE study.

Severity is not captured in post-marketing safety reports.
</td></tr>
<tr><td>Background incidence/prevalence</td><td>Placebo data as quoted above are indicative of the background risk for ISRs in product containing all excipients but no anakinra.</td></tr>
<tr><td>Risk groups or risk factors</td><td>No risk groups have been identified.</td></tr>
<tr><td>Preventability</td><td>Alternating the injection site is recommended to avoid discomfort at the site of injection. Cooling of the injection site, warming the injection liquid, use of cold packs (before and after the injection), and use of topical corticosteroids and/or antihistamines before or after the injection can alleviate the signs and symptoms of injection site reactions (93).</td></tr>
<tr><td>Impact on the risk-benefit balance of the product</td><td>ISRs typically appear within 2 weeks’ therapy and disappear within 4-6 weeks. ISRs cause pain to the patient, which in a small proportion of patients may lead to discontinuation of treatment. Further characterization of ISRs in the post-marketing setting is not expected to change the positive benefit-risk balance of Kineret.</td></tr>
<tr><td>Potential public health impact of safety concern</td><td>ISRs can potentially affect 63% to 67% of patients exposed to Kineret except in patients with CAPS where the impact is estimated to be less (23 %, 95 % CI [10.6 %, 35.9 %]).</td></tr>
</table>

Identified risk: Immunogenicity

Identified risk: Immunogenicity	
Potential mechanisms	Immunological reaction to exogenous protein. Antibodies are known to occur during treatment with biological therapeutics, including anakinra.
Evidence sources and strength of evidence	Completed clinical studies, literature review, and post-marketing surveillance. The immunogenicity of anakinra has been evaluated in all studies in the safety pool. Many factors influence immunogenicity and antibody detection, i.e., dosing, detection method, duration of treatment, and co-administration of immunosuppressives. These are all factors that vary between studies in the RA safety pool, and, consequently, immunogenicity between the studies varies significantly. The highest incidence of antibodies was found in studies 990757 and 990145. Frequency data for this risk are based on the 1901 Kineret-treated and 680 placebo-treated patients in studies 990757 and 990145, who were tested for

Identified risk: Immunogenicity	
	anti-anakinra antibodies during the full study periods (including open label follow up for up to 3 years). The frequency of antibodies found describes patients positive for anti-anakinra antibodies on at least one time point during the studies. Data for patients with CAPS (study 03-AR-0298), patients with SJIA (study 990758/990779) and patients with Still's disease (SJIA and AOSD, study Sobi.ANAKIN-301) are also presented. There are no studies evaluating immunogenicity in FMF patients, however, due to the similarities of the characteristics of the disease to the other periodic fever syndromes, there are no indications that patients with FMF would react differently than patients with above mentioned indications. In COVID-19 in the SAVE-MORE study anti-drug antibodies were not investigated.
Characterization of the risk: Frequency with 95 % CI	**RA patients (blinded placebo-controlled, randomized studies)** Anakinra anti-drug antibodies 1113/1901 patients (58 %, 95 % CI [56 %, 61 %]). Placebo 2/680 patients (0 %, 95 % CI [0 %, 1 %]). Neutralizing antibodies: Kineret 49/1901 patients (3 %, 95 % CI [2 %, 3 %]). No neutralizing antibodies were detected with placebo. **CAPS patients** In Study 03-AR-0298, 33 out of 40 patients (82.5 %, 95 % CI [71 %, 94 %]) developed anakinra anti-drug antibodies at least once during the study. No test for neutralizing antibodies was performed. **Still's disease patients** In 11 SJIA patients, tested for anti-anakinra antibodies in study 990758/990779, 9 (82 %) tested positive for non-neutralizing antibodies. No SJIA patient tested positive for neutralizing antibodies. All 6 anakinra patients in study Sobi.ANAKIN-301 developed anti-anakinra antibodies during the study. No neutralizing antibodies were detected in any of these patients.
Seriousness/outcomes	No serious reactions have occurred. **Post marketing data** Post marketing data are limited but consistent with clinical study data.
Severity and nature of risk	Possible risk for all protein therapeutics. Serum samples were analyzed for anti-anakinra antibodies. The highest number of positive anti-anakinra antibody tests in RA patients was found in the 2 long-term safety studies 990145 and 990757. No correlation between antibody development and clinical response or AE frequency and severity was observed. One patient on placebo in each study was positive for anti-anakinra antibodies. In the CAPS study, development of anti-anakinra antibodies was not associated with any clinically significant effects on pharmacokinetics, efficacy, or safety.
Background incidence/prevalence	Placebo data as quoted above are indicative of the background risk.
Risk groups or risk factors	Risk groups or risk factors have not been identified.
Preventability	Not applicable
Impact on the risk-benefit balance of the product	May potentially cause decreased efficacy, allergic/anaphylactic reactions or ISRs without effecting the positive benefit-risk balance for Kineret. Further characterization of immunogenicity in the post-marketing setting is not expected to significantly change the positive benefit-risk balance. An analysis concluded that while antibodies are likely to occur in CAPS patients treated with anakinra, evidence shows that chronic daily subcutaneous treatment with anakinra is safe and effective regardless of the development and presence of ADA (94).
Potential public health impact of safety concern	The occurrence of neutralizing antibodies at least once in every three-year treatment period may occur in 2% to 3% of patients exposed to Kineret. Antibodies may also cause

Identified risk: Immunogenicity	
	induction of allergic reactions. No safety issues have been identified to date and the public health impact is low.

Identified risk: Serious infections

Identified risk: Serious infections	
Potential mechanisms	Interference with immune system. An increased susceptibility to infections is a potential safety issue with all agents that alter cytokine response.
Evidence sources and strength of evidence	Completed clinical studies, literature review, and post-marketing surveillance. Due to the low number of patients, Still's disease and FMF are not included in the frequency tabulation below. In study 990758/990779, there were 2 serious infections in 1 SJIA patient: hepatitis due to a cytomegalovirus infection and viral infection. There were no serious infections reported in study Sobi.ANAKIN-301 in Still's disease. Due to the low number of patients, Still's disease is not included in the table. In the published double-blind study in patients with FMF (87) there was no serious infection in either Kineret- or placebo-treated patients. COVID-19 patients in the investigator sponsored study SAVE-MORE had reports of serious infections, the reported rate was lower in the anakinra group than in the placebo group.
Characterization of the risk: Frequency with 95 % CI	**RA patients (blinded placebo-controlled, randomized studies)** Kineret 41/2372 patients (2 %, 95 % CI [1 %, 2 %]). Placebo 9/958 patients (1 %, 95 % CI [0 %, 2 %]. There are 51 serious infections in 923.4 patient years corresponding to 0.06 serious infections/patient year. **CAPS patients** Kineret 7/43 patients (16 %, 95 % CI [5.2 %, 27.3 %]). There are 13 serious infections in 159.8 patient years corresponding to 0.08 serious infections/patient year. **COVID-19 patients (SAVE-MORE study)** Kineret: 37/405 patients, (9.1%, 95% CI [6.3%, 11.9%]). Placebo: 31/189 patients (16.4%, 95% CI [11.1%, 21.7%]).

Identified risk: Serious infections

Seriousness/outcomes

All serious infections are per definition serious.

	RA patients	Placebo patients	CAPS patients
Number of SAEs	51	9	13
Number of patients (%) with SAEs	41 (1.7 %)	9 (0.9 %)	7 (16.3 %)
Outcome	6 events in 4 (0.2 %) patients continued at end of study.	No event continued at end of study	All events resolved without sequelae

COVID-19 (SAVE-MORE study)

	anakinra patients	placebo patients
Total number of AEs	50	44
Number of patients (%) with any AE	37 (9.1)	31 (16.4)
Number of SAEs	50	44
Number of patients (%) with SAEs	37 (9.1)	31 (16.4)
Outcome	19 fatal	18 fatal

Post-marketing data
Post marketing data is consistent with clinical study data.

<table>
<tr><td colspan="2">Identified risk: Serious infections</td></tr>
<tr><td>Severity and nature of risk</td><td>
<table>
<tr><td>Severity</td><td colspan="3">Number of events (%)</td></tr>
<tr><td></td><td>RA patients</td><td>Placebo patients</td><td>CAPS patients</td></tr>
<tr><td>Mild</td><td>1 (2.0)</td><td>0 (0)</td><td>0 (0)</td></tr>
<tr><td>Moderate</td><td>11 (21.6)</td><td>5 (55.6)</td><td>7 (53.8)</td></tr>
<tr><td>Severe</td><td>39 (76.5)</td><td>4 (44.4)</td><td>5 (38.5)</td></tr>
<tr><td>Unknown</td><td>0 (0)</td><td>0 (0)</td><td>1 (7.6)</td></tr>
</table>
COVID-19 patients (SAVE-MORE study)
<table>
<tr><td>Severity</td><td colspan="2">Number of non-serious events (%)</td></tr>
<tr><td></td><td>anakinra patients</td><td>placebo patients</td></tr>
<tr><td>Mild</td><td>0</td><td>0</td></tr>
<tr><td>Moderate</td><td>0</td><td>0</td></tr>
<tr><td>Severe</td><td>0</td><td>0</td></tr>
</table>
Note: there were 50 serious infections in anakinra patients and 44 serious infections in placebo. Only non-serious events were classified according to severity in the SAVE-MORE study.
</td></tr>
<tr><td>Background incidence/prevalence</td><td>Placebo data as quoted above are indicative of the background risk.</td></tr>
<tr><td>Risk groups or risk factors</td><td>For a small number of patients with asthma included in RA studies, the incidence of serious infections was higher in Kineret-treated patients.
In studies, concurrent administration of Kineret and etanercept in RA patients has been associated with an increased risk of serious infections. It is reasonable to assume that this interaction is valid not just for etanercept but for the whole class of TNFα-antagonists.
No specific risk group or risk factor among patients with CAPS, FMF or Still’s disease has been identified. It is reasonable to assume that the results in RA studies presented above apply also to CAPS, FMF and Still’s patients.</td></tr>
<tr><td>Preventability</td><td>The SmPC states that physicians should exercise caution when administering Kineret to patients with a history of recurring infections or with underlying conditions which may predispose for infections.
In the Section 4.4 Special warnings and precautions for use, it is stated that for a small number of patients with asthma the incidence of serious infections was higher in Kineret-treated patients. It is also stated that concurrent administration of Kineret and etanercept has been associated with an increased risk of serious infections and that the concurrent administration of etanercept or other TNFα-antagonists is not recommended.
Recognition of symptoms associated with infections.</td></tr>
<tr><td>Impact on the risk-benefit balance of the product</td><td>May contribute to increased morbidity and hospital stays. Further characterization of serious infections in the post-marketing setting is not expected to change the positive benefit-risk balance.</td></tr>
<tr><td>Potential public health impact of safety concern</td><td>In double-blind placebo-controlled studies in RA patients the confidence interval for the estimated mean incidence of serious infections of 2 % (95 % CI [1 %, 2 %]) is overlapping the confidence interval for the incidence in placebo-treated patients, 1 % (95 % CI [0 %, 2 %] and correspond to 0.06 to 0.08 serious infections per patient year exposed to Kineret.</td></tr>
</table>

Identified risk: Neutropenia

Identified risk: Neutropenia	
Potential mechanisms	IL-1 acts on the bone marrow to increase mobilization of granulocyte progenitors and mature neutrophils, resulting in peripheral neutrophilia. These effects are Il-1 receptor mediated and thus counteracted by IL-1Ra and anakinra. This, in combination with other mechanisms resulting in an inhibitory effect of IL-1 induced inflammatory pathways by anakinra, may in part explain a decrease in neutrophil count seen in some patients.
Evidence sources and strength of evidence	Completed clinical studies, literature review, and post-marketing surveillance. Due to the low number of patients, Still's disease and FMF are not included in the frequency tabulation below. In study 990758/990779, transient neutropenia occurred in one SJIA patient (absolute neutrophil count 0.91 x 10^9/L); the count recovered to above 1.0 x 10^9/L by the next study visit during continued Kineret treatment and was not associated with any clinical sequelae. No patients developed neutropenia (<1.5x10^9/L) in study Sobi.ANAKIN-301. In the published double-blind randomized, placebo-controlled study in patients with FMF (87) there were no events of neutropenia reported. In COVID-19 patients in the SAVE-MORE study neutropenia was reported at a higher rate in patients treated with anakinra compared to the subjects treated with placebo, however at a similar rate as in RA studies.
Characterization of the risk: Frequency with 95 % CI	**RA patients (blinded placebo-controlled, randomized studies)** Kineret 32/2372 patients (1 %, 95 % CI [1 %, 2 %]). Placebo 0/958 patients (0 %, 95 % CI [0 %, 0 %]). **CAPS patients** Kineret 2/43 patients (2 %, 95 % CI [-2.2 %, 7 %]). **COVID-19 patients (SAVE-MORE study)** Kineret: 12/405 patients, (3.0%, 95% CI [1.5%, 5.1%]). Placebo: 1/189 patients (0.5%, 95% CI [0.0%, 2.9%]).

Identified risk: Neutropenia

Seriousness/outcomes

	RA patients	Placebo patients	CAPS patients
Total number of AEs	38	0	2*
Number of patients (%) with any AE	32 (1.3 %)	0	2 (4.7 %)*
Number of SAEs	4	0	0
Number of patients (%) with SAEs	4 (0.2 %)	0	0
Outcome	7 events in 6 (0.3 %) patients continued at end of study.		All events resolved without sequelae

* One of the 2 patients had a neutrophil count of 0.8 x 10^9/L, which was not reported as an AE.

COVID-19 (SAVE-MORE study)

	anakinra patients	placebo patients
Total number of AEs	12	1
Number of patients (%) with any AE	12 (3.0)	1 (0.5)
Number of SAEs	1	0
Number of patients (%) with SAEs	1 (0.2)	0
Outcome	8 recovered/recovering 0 not recovered/ongoing 4 unknown 0 fatal	1 recovered/recovering 0 not recovered/ongoing 0 unknown 0 fatal

Post-marketing data
Post marketing data is consistent with clinical study data.

<table>
<tr><td colspan="2">Identified risk: Neutropenia</td></tr>
<tr><td>Severity and nature of risk</td><td>
<table>
<tr><td>Severity</td><td colspan="3">Number of events (%)</td></tr>
<tr><td></td><td>RA patients</td><td>Placebo patients</td><td>CAPS patients</td></tr>
<tr><td>Mild</td><td>21 (55.3)</td><td>0</td><td>1 (2.3)</td></tr>
<tr><td>Moderate</td><td>14 (36.8)</td><td>0</td><td>0</td></tr>
<tr><td>Severe</td><td>3 (7.9)</td><td>0</td><td>1 (2.3)*</td></tr>
</table>
* The laboratory value was not reported as an AE, therefore Sobi has assigned the severity.

COVID-19 patients (SAVE-MORE study)
<table>
<tr><td>Severity</td><td colspan="2">Number of non-serious events (%)</td></tr>
<tr><td></td><td>anakinra patients</td><td>placebo patients</td></tr>
<tr><td>Mild</td><td>8 (73)</td><td>1 (100)</td></tr>
<tr><td>Moderate</td><td>3 (27)</td><td>0 (0)</td></tr>
<tr><td>Severe</td><td>0 (0)</td><td>0 (0)</td></tr>
</table>
Note: There was one serious neutropenia in anakinra patients only non-serious events were classified according to severity in SAVE-MORE study.
</td></tr>
<tr><td>Background incidence/prevalence</td><td>Placebo data as quoted above are indicative of the background risk.</td></tr>
<tr><td>Risk groups or risk factors</td><td>In RA patients, concurrent administration of Kineret and etanercept has been associated with an increased risk of decreases in neutrophil count. It is reasonable to assume that this interaction is valid not just for etanercept but for the whole class of TNFα-antagonists.
No other specific factors or groups of RA patients have been identified.
In Felty’s syndrome, a severe variant of RA developing in less than 1 % of RA patients, neutropenia is the most common and important feature.
No specific risk group or risk factor among patients with CAPS or Still’s disease has been identified. It is reasonable to assume that the results in RA studies presented above apply also to CAPS and Still’s patients.</td></tr>
<tr><td>Preventability</td><td>In the SmPC in Section 4.4 Special warnings and precautions for use, it is stated that Kineret treatment should not be initiated in patients with neutropenia, and that neutrophil count is recommended to be assessed prior to initiating Kineret treatment and regularly monitored during treatment.
It is also stated in Section 4.4 that concomitant treatment with Kineret and etanercept or other TNFα-antagonists is not recommended.</td></tr>
<tr><td>Impact on the risk-benefit balance of the product</td><td>May contribute to increased susceptibility to infections. Further characterization of neutropenia in the post-marketing setting is not expected to change the positive benefit-risk balance of Kineret.</td></tr>
<tr><td>Potential public health impact of safety concern</td><td>The estimated incidence of neutropenia is 1 % with the 95 % CI [1 %, 2 %]</td></tr>
</table>

Identified risk: Allergic reactions

<table>
<tr><th colspan="2">Identified risk: Allergic reactions</th></tr>
<tr><td>Potential mechanisms</td><td>Drug-induced allergic hypersensitivity.</td></tr>
<tr><td>Evidence sources and strength of evidence</td><td>Completed clinical studies, literature review, and post-marketing surveillance. Due to the low number of patients, Still’s disease and FMF are not included in the frequency tabulation below. In study 990758/990779, 3 patients (20.0 %) with SJIA, experienced AEs indicating allergic reactions. One event was, however, specifically attributed to amethocaine gel. In study Sobi.ANAKIN-301 no allergic reactions were reported however there was one case of urticaria, which was mild and assessed as not related to anakinra treatment by the investigator.

In the published double-blind study in patients with FMF (87) there was no allergic reaction reported.

In a signal evaluation performed 2020 that included both a long-term natural history study 17-I-0016 and post marketing reports, 4 out of 19 Kineret-treated patients with Deficiency of Interleukin-1 Receptor Antagonist (DIRA) had allergic reactions. 3 of the 4 case reports were serious.

In COVID-19 patients in the SAVE-MORE study no hypersensitivity reaction were considered related to anakinra</td></tr>
<tr><td>Characterization of the risk: Frequency with 95 % CI</td><td>RA patients (blinded placebo-controlled, randomized studies)
Kineret 470/2372 patients (20 %, 95 % CI [18 %, 21 %]). Placebo patients 165/958 (17 %, 95 % CI [15 %, 20 %]). The difference in frequency between Kineret-treated and placebo-treated patients was approximately 3 %; included are all kinds of allergic conditions, e.g., seasonal allergy and hay fever.
CAPS patients
Kineret: 23/43 patients (53 %, 95 % CI [39 %, 68 %]).</td></tr>
<tr><td>Seriousness/outcomes</td><td>
<table>
<tr><th></th><th>RA patients</th><th>Placebo patients</th><th>CAPS patients</th></tr>
<tr><td>Total number of AEs</td><td>666</td><td>227</td><td>135*</td></tr>
<tr><td>Number of patients (%) with any AE</td><td>470 (19.8)</td><td>165 (17.2)</td><td>23 (53.5)*</td></tr>
<tr><td>Number of SAEs</td><td>12</td><td>2</td><td>0</td></tr>
<tr><td>Number of patients (%) with SAEs</td><td>11 (0.5)</td><td>2 (0.2)</td><td>0</td></tr>
<tr><td>Outcome</td><td>182 events in 151 (6.4 %) patients continued at end of study.</td><td>37 events in 33 patients (3.4 %) continued at end of study.</td><td>One event of cough in 1 patient (2.3 %) continued at end of study.</td></tr>
</table>
* Rash, ocular hyperemia and urticaria, all representing common symptoms of NOMID/CINCA, accounted for 101 (75 %) of all 135 events. No event required discontinuation of Kineret.

Post-marketing data
Allergic reactions have been identified as an adverse drug reaction (ADR) during post-marketing surveillance.</td></tr>
</table>

<table>
<tr><th colspan="2">Identified risk: Allergic reactions</th></tr>
<tr><td>Severity and nature of risk</td><td>
<table>
<tr><th>Severity</th><th colspan="3">Number of events (%)</th></tr>
<tr><td></td><td>RA patients</td><td>Placebo patients</td><td>CAPS patients</td></tr>
<tr><td>Mild</td><td>471 (70.7)</td><td>156 (68.7)</td><td>131 (90.3)</td></tr>
<tr><td>Moderate</td><td>169 (25.4)</td><td>66 (29.1)</td><td>12 (9.0)</td></tr>
<tr><td>Severe</td><td>26 (3.9)</td><td>5 (2.2)</td><td>1 (0.7)</td></tr>
</table>
</td></tr>
<tr><td>Background incidence/prevalence</td><td>Placebo data as quoted above are indicative of the background risk.</td></tr>
<tr><td>Risk groups or risk factors</td><td>Patients with a history of allergic reactions to any of the excipients of Kineret.
DIRA patients may have an increased risk of allergic reactions, particularly in the first few weeks due to lack of pre-existing immune tolerance to the protein.</td></tr>
<tr><td>Preventability</td><td>Recognition of patients with a history of allergic reactions to any of the excipients of Kineret, including E. coli derived proteins.
Hypersensitivity to the active substance, any of the excipients or to E. coli-derived proteins is a contraindication for Kineret treatment.
DIRA patients should be closely monitored in the first few weeks after starting Kineret treatment.
Testing for anti-anakinra antibodies is not required. Allergic reactions are uncommon and the vast majority are non-serious.</td></tr>
<tr><td>Impact on the risk-benefit balance of the product</td><td>Kineret may contribute to development of allergic reactions. Further characterization in the post-marketing setting is not expected to change the positive benefit-risk balance of Kineret.
DIRA is an ultra-rare, mostly fatal disease and the possibility of an increased risk of hypersensitivity reactions compared to other indications does not change the positive benefit-risk balance in this indication.</td></tr>
<tr><td>Potential public health impact of safety concern</td><td>The difference between Kineret-treated and placebo-treated patients is approximately 3 % in the frequency of all types of allergic conditions (including e.g. seasonal allergy and hay fever).
DIRA is an ultra-rare disease and therefore the possibility of increased risk of hypersensitivity reactions in this indication has no potential impact on public health.</td></tr>
</table>

Identified risk: Hepatic disorders

<table>
<tr><th colspan="2">Identified risk: Hepatic disorders</th></tr>
<tr><td>Potential mechanisms</td><td>No potential mechanism identified.</td></tr>
<tr><td>Evidence sources and strength of evidence</td><td>Completed clinical studies, literature review, and post-marketing surveillance.
Due to the low number of patients, Still’s disease and FMF are not included in the frequency tabulation below. In the SJIA/Still’s study 990758/990779 there was one serious hepatitis due to cytomegalovirus infection. In addition, there were 3 increases of liver tests in one patient. The tests normalized during continued Kineret treatment. No elevations of liver enzymes were observed during the Sobi.ANAKIN-301 study in Still’s disease and no hepatic events were reported.
In the published double-blind study in patients with FMF (87) there was no hepatic event</td></tr>
</table>

Identified risk: Hepatic disorders	
	reported. In COVID-19 patients events of liver function test (LFT) elevations were more frequently reported in the anakinra treated group than the placebo group in the SAVE-MORE study. Majority of the events of LFT elevation were mild to moderate; the rate of severe LFT elevation was comparable between the anakinra group and placebo.
Characterization of the risk: Frequency with 95 % CI	**RA patients (blinded placebo-controlled, randomized studies)** Kineret 14/2372 patients (1 %, 95 % CI [0 %, 1 %]). Placebo 13/958 patients (1 %, 95 % CI [1 %, 2 %]. **CAPS patients** Kineret 5/43 patients (12 %, 95 % CI [2 %, 21 %]). **COVID-19 patients (SAVE-MORE study)** Kineret (Transaminases increased): 125/405 patients, (30.9%, 95% CI [26.4%, 35.4%]). Placebo (Transaminases increased): 52/189 patients (27.5%, 95% CI [21.1%, 33.9%]).

Identified risk: Hepatic disorders

Seriousness/ outcomes

	RA patients	Placebo patients	CAPS patients
Total number of AEs	19	18	6
Number of patients (%) with any AE	14 (0.6 %)	13 (1.4 %)	5 (11.6 %)
Number of SAEs	1	0	0
Number of patients (%) with SAEs	1 (0.0 %)	0	0
Outcome	9 events in 7 (0.3 %) patients continued at end of study.	3 events in 3 (0.3 %) patients continued at end of study.	All events resolved without sequelae

COVID-19 (SAVE-MORE study)

	PT	anakinra patients	placebo patients
Number of patients (%) with any AE	Transaminases increased	125 (30.9)	52 (27.5)
	GGT increased	56 (13)	22 (11.7)
	ALP increased	10 (2.5)	6 (3.2)
Number of SAEs	Transaminases increased	3	2
	GGT increased	1	0
	ALP increased	0	0
Number of patients (%) with SAEs	Transaminases increased	3 (0.7)	2 (1.1)
	GGT increased	1 (0.2)	0
	ALP increased	0	0
Outcome	Transaminases increased	0 fatal	1 fatal
	GGT increased	0 fatal	0 fatal
	ALP increased	0 fatal	0 fatal

Post-marketing data
Hepatic disorders have been identified as an adverse drug reaction (ADR) during post-marketing surveillance.

Severity and nature of risk

RA patients
The majority of reactions reported were mild to moderate in severity.

	Placebo			Kineret		
Preferred term	Mild	Moderate	Severe	Mild	Moderate	Severe
Alkaline Phosphatase	2	1	0	2	0	0

Identified risk: Hepatic disorders

Increased						
Hepatic Enzymes Increased	2	0	0	1	1	0
Hepatic Function Abnormal	3	1	1	6	1	0
Hepatic Neoplasm Benign	0	0	0	0	1	0
Hepatomegaly	1	0	0	0	0	0
SGOT Increased	2	1	0	1	1	0
SGPT Increased	3	1	0	4	1	0
Sum (% of total no. of hepatic events)	13 (72.2)	4 (22.2)	1 (5.6)	14 (73.7)	5 (26.3)	0 (0)

CAPS patients

One event (16.7 %) was of moderate severity, the remaining 5 (83.3 %) were mild.

	Kineret		
Preferred term	Mild	Moderate	Severe
Hepatic enzyme increased	1	1	0
Alanine aminotransferase increased	2	0	0
Aspartate aminotransferase increased	1	0	0
Bilirubin conjugated increased	1	0	0
Sum (% of total no. of hepatic events)	5 (83.3)	1 (16.7)	0 (0)

COVID-19 patients (SAVE-MORE study)

	Number of non-serious events (%)					
	placebo patients			**anakinra patients**		
Preferred term	Mild	Moderate	Severe	Mild	Moderate	Severe
Gamma-glutamyltransferase increased	16	4	1	40	8	7
Alkaline Phosphatase increased	5	1	0	10	0	0
Transaminases increased	41	7	3	92	25	5
Sum (% of total no. of hepatic events)	62 (79)	12 (15)	4 (5)	142 (75)	33 (18)	12 (6)

Note, there were also 3 serious events of transaminases increased and 1 serious event of gamma glutamyl transferase increase in the anakinra group and 2 serious events of transaminases increased in the placebo group. Serious events were not classified according to severity in the SAVE-MORE study.

Background incidence/prevalence	Placebo data as quoted above are indicative of the background risk for RA and CAPS. In Still's disease, increases in liver enzymes are common during disease flares. In addition, patients with Still's disease can have subclinical MAS, which can cause increases in liver tests.
Risk groups or risk	Patients with history of liver disease or of transaminase elevations before start of Kineret

Identified risk: Hepatic disorders	
factors	treatment. No other specific factors or groups of patients within the RA and CAPS populations have been identified. As stated above, patients with Still's disease have an increased risk for hepatic events.
Preventability	Thorough medical history and early recognition of symptoms helps minimize morbidity and mortality. Information about the occurrence of hepatic events, mainly in patients with Still's disease or in patients with predisposing factors, e.g., history of transaminase elevations before start of Kineret treatment, is included in the SmPC.
Impact on the risk-benefit balance of the product	May contribute to development of hepatic disorders. Further characterization in the post-marketing setting is not expected to change the positive benefit-risk balance of Kineret.
Potential public health impact of safety concern	There is no difference in the incidence of hepatic events in Kineret vs. placebo-treated patients, 1 %, 95 % CI [0 %, 1 %] vs. 1 %, 95 % CI [1 %, 2 %], respectively. Patients with Still's disease, however, have an increased intrinsic risk for hepatic events.

Potential risk: Malignancies

<table>
<tr><th colspan="2">Potential risk: Malignancies</th></tr>
<tr><td>Potential mechanisms</td><td>Interference with immune system</td></tr>
<tr><td>Evidence sources and strength of evidence</td><td>Completed clinical studies, literature review, post-marketing surveillance reports, and registries: Rheumatism Biologics register in the UK (BSRBR), in Germany (RABBIT), and in Sweden (ARTIS).
No overall increased frequency of malignancies in Kineret-treated patients has been observed in clinical studies in RA, neither in short-term studies nor in studies with extended patient exposure to Kineret. In CAPS study 03-AR-0298, there were no adverse reactions denoting malignancies.
This is true also for the patients with SJIA included in study 990758/990779 and the patients with FMF included in the published double-blind study (87). In the Sobi.ANAKIN-301 study in patients with Still’s disease, there were no malignancies reported in the anakinra group.
In the SAVE-MORE study COVID-19 patients were treated for a duration ≤ 10 days, one case of unspecified lung tumor was reported during study follow up.
Due to the immunosuppressive properties of Kineret there is, however, a theoretical risk that Kineret could increase the frequency of malignancies.
For the potential risk Malignancies an extended version of the safety pool has been used to compare the incidence of malignancies in Kineret-treated RA patients to placebo over 12 months. In addition, long time follow-up (LTFU) data of up to 36 months of Kineret exposure has been obtained from the extended safety pool. The extended safety pool contains all studies in the safety pool and their respective follow up studies. Studies 990145 (Part A and B), 990757 (Part A and B), 960182, 960180 with LTFU 960181, 0560 with LTFU 564 and 564E1 are included.</td></tr>
<tr><td>Characterization of the risk:
Frequency</td><td>The analysis of the extended safety pool shows that short-term exposure (up to 12 months) to Kineret does not appear to result in an increased risk of developing malignancies compared to placebo.
Long-term exposure (up to 36 months) does not appear to increase the frequency of malignancies expressed as events/100 patient years.
<table>
<tr><th>Group *</th><th>Events/100 patient-years</th><th>Events</th><th>Patient-years</th><th>No of Patients</th></tr>
<tr><td>0-12 M placebo</td><td>5,4</td><td>29</td><td>539</td><td>958</td></tr>
<tr><td>0-12 M Kineret</td><td>4,2</td><td>72</td><td>1711</td><td>2372</td></tr>
<tr><td>0-36 M Kineret</td><td>4,8</td><td>225</td><td>4661</td><td>3066</td></tr>
</table>
* The 0-12 months (M) groups includes the blinded placebo-controlled parts of the studies. The 0-36 M Kineret group includes all patients exposed to anakinra both in the blinded and open label phases of the studies. The median exposure time in the 0-36 M Kineret group is 18 months.
Post-marketing data
Postmarketing data are consistent with clinical study data.</td></tr>
<tr><td>Seriousness/outcomes</td><td>Development of a malignancy is always a serious event.</td></tr>
<tr><td>Severity and nature of risk</td><td>Not applicable as all malignancies are serious events.</td></tr>
<tr><td>Background incidence/prevalence</td><td>Placebo data as quoted above are indicative of the background risk, for RA patients, during short term treatment. Epidemiological data suggest that the RA population has an increased risk of developing malignancies.</td></tr>
</table>

Risk groups or risk factors	No specific factors or groups of patients within the RA or CAPS populations have been identified.
Preventability	No data available.
Impact on the risk-benefit balance of the product	Further characterization in the post-marketing setting is not expected to change the positive benefit-risk balance of Kineret.
Potential public health impact of safety concern	Neither short-term exposure (up to 12 months) nor long-term exposure (up to 36 months) to Kineret appear to increase the frequency of malignancies as compared to placebo-treatment. There is no public health impact.

Potential risk: Medication errors including reuse of syringe

Potential risk: Medication error/reuse of used syringe	
Potential mechanisms	Inaccurate Kineret dosing with graduated syringe. Reuse of a syringe involves a risk of infections that increases with the number of reuses.
Evidence sources and strength of evidence	Completed clinical studies, literature search and post-marketing surveillance. In the published double-blind study in patients with FMF (87) there were no medication errors reported. No medication error events has been reported in COVID-19 patients in the SAVE-MORE study
Characterization of the risk: Frequency with 95 % CI	Not applicable as there are no reports on medication error/reuse of used syringe in either RA, CAPS, JIA or Still's disease studies.

Potential risk: Medication error/reuse of used syringe	
Seriousness/outcomes	There are sporadic case reports in the post-marketing safety database describing medication errors including reuse of syringe.
Severity and nature of risk	Severity is not captured in post-marketing surveillance reports.
Background incidence/prevalence	Kineret is administered from a graduated prefilled syringe that contains 100 mg and are intended for single use. The graduated syringe has a label to allow for single-use injections of smaller and varying doses (20–100 mg) in patients with CAPS, FMF, and Still's disease. In post-marketing experience there are very few reports describing medication errors.
Risk groups or risk factors	Patients with CAPS, FMF and Still's disease who use Kineret doses other than 100 mg.
Preventability	Careful design of product presentation and instructions for use. A usability study has been conducted to verify the users' ability to correctly and safely use the graduated Kineret syringe. The study demonstrated that the Kineret graduated syringe can be handled safely and effectively with the help of the instructions for use. Healthcare providers will instruct patients on correct injection procedures and disposal of syringes.
Impact on the risk-benefit balance of the product	Reuse of a syringe may cause infections. Most infections will likely be mild and local at the injection site. There is a potential risk for serious infections, mainly bacteremia and sepsis. Further characterization in the post-marketing setting is not expected to change the positive benefit-risk balance of Kineret.
Potential public health impact of safety concern	The public health impact is low.

Potential risk: Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)

Events of interstitial lung disease, pulmonary alveolar proteinosis and pulmonary hypertension (including pulmonary arterial hypertension) have been reported, mainly in pediatric patients with Still's disease treated with IL-6 and IL-1 inhibitors, including anakinra. A causal relationship between anakinra and pulmonary events has not been established.

Pulmonary events are not considered a potential risk in either the RA, CAPS FMF or COVID-19 populations.

Potential risk: Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)	
Potential mechanisms	No mechanism has been established.
Evidence source	Post-marketing surveillance case reports and published reports of patients with Still's disease treated with IL-6 and IL-1 inhibitors, including anakinra, who have had complications with interstitial lung disease, pulmonary hypertension and alveolar proteinosis. There were no events of interstitial lung disease, pulmonary alveolar proteinosis or pulmonary hypertension in SJIA patients in study 990758/990779 or in patients with Still's disease in study Sobi.ANAKIN-301.

Characterization of the risk: Frequency with 95 % CI	Not applicable
Seriousness/outcomes	Fatal cases have been reported.
Severity and nature of risk	Initial symptoms may be mild however progressively become worse. In a published cohort of 25 patients 17 (68%) died at a mean of 10.2 months from the diagnosis of pulmonary complications (39). These events have mainly been seen in patients with Still's disease, suggesting important relationship to components of the underlying disease. More information is needed to understand the nature of the risk.
Background incidence/prevalence	Events of interstitial lung disease, pulmonary alveolar proteinosis and pulmonary hypertension have been reported mainly in pediatric patients with Still's disease treated with IL-6 and IL-1 inhibitors, including anakinra. Patients with trisomy 21 seem to be overrepresented: in a cohort of 61 pediatric patients with Still's disease and lung complications 6 patients (10%) had trisomy 21 (92, 95-97). There have been reports of pulmonary complications in SJIA patients before the introduction of IL-1-blocking agents. Athreya et al. 1980 (40) presented 8/191 children with JRA who had involvement of the lung or pleura for more than 6 weeks, whereof 6 with SJIA. 4 patients had persisting lung disease, in 2 cases described as interstitial. The article's literature review found 3 case reports on patients with JRA that died due to their lung disease, autopsy showed interstitial fibrosis in 2/3. **Post-marketing data** There have been published and spontaneous case reports of pulmonary complications, mainly in pediatric patients with Still's disease.
Risk groups or risk factors	Pediatric patients, especially with trisomy 21, with Still's disease treated with IL-6 and IL-1 inhibitors, including anakinra. In one published case series the cohort of Still's disease patients that developed pulmonary events were more likely to have been exposed to IL-1 inhibitors, tocilizumab, corticosteroids, intravenous immunoglobin, cyclosporine, or cyclophosphamide. 15/25 patients (60%) had MAS at pulmonary diagnosis (39). In a different case series (92, 95) 18 of 61 patients (30%) had overt or subclinical MAS at onset of pulmonary events. RA has also been associated with Interstitial Lung Disease (ILD) with a lifetime risk of developing ILD of 7.7% for RA patients vs. 0.9% for subjects without RA (17).
Preventability	Unknown. Respiratory symptoms should trigger a pulmonary workup. Prophylaxis for pneumocystis conferred a distinct survival benefit, despite absence of pneumocystis by direct visualization (92, 95).
Impact on the risk-benefit balance of the product	Further characterization subsequent to data searches and during post-marketing surveillance may inform the benefit-risk balance for treatment of Still's disease.
Potential public health impact of safety concern	The public health impact cannot currently be quantified.

Potential risk: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients treated with IL-1 inhibitors, predominantly in pediatric patients with Still's disease. A causal relationship between Kineret and DRESS has not been established.

Potential risk: Drug reaction with eosinophilia and systemic symptoms (DRESS)	
Potential mechanisms	No mechanism has been established.
Evidence sources and strength of evidence	Post-marketing surveillance case reports and published reports describe DRESS in patients treated with IL-1 inhibitors, predominantly in pediatric patients with Still's disease (92). However, there are significant confounders including failure to fully investigate for and exclude the most common causes of eosinophilia in children, such as helminth infections. Additionally, in the main publication the diagnosis of DRESS in cases was made retrospectively (92, 98). It has also been suggested that certain HLA types are of higher risk of developing DRESS (99)). There have been no cases of DRESS in the clinical studies in RA, CAPS (study 03-AR-0298), JIA/SJIA study (990758/990779), in the study in Still's disease (Sobi.ANAKIN-301) or in the published double-blind study in patients with FMF (87).
Characterization of the risk: Frequency with 95 % CI	Not applicable
Seriousness/outcomes	Fatal cases have been reported.
Severity and nature of risk	Severity is not captured in post-marketing surveillance reports.
Background incidence/prevalence	DRESS is a very rare event, most frequently reported in e.g. patients treated with carbamazepine. Events of DRESS have been reported in pediatric patients with SJIA and SJIA like-disease treated with IL-6 and IL-1 inhibitors, including anakinra. Saper et al. 2019 described 14 cases of DRESS retrospectively classified as "definite" (10 cases) and "probable" (4 cases) according to the terminology in the RegiSCAR Scoring system, out of 61 patients with 'highly fatal lung disease' in patients treated with IL-1 and IL-6 inhibitors (92).
Risk groups or risk factors	Pediatric patients with Still's disease.
Preventability	Other causes of eosinophilia, such as infections should be considered.
Impact on the risk-benefit balance of the product	Further characterization subsequent to data searches and during post-marketing surveillance may inform the benefit-risk balance for treatment of Still's disease.
Potential public health impact of safety concern	The public health impact cannot currently be quantified but is considered low.

SVII.3.2. Presentation of the missing information

Use in pregnant women:

Evidence source:

Pregnant women have not been included in clinical studies.

Population in need of further characterisation:

Pregnancy outcome and safety in pregnant patients.

Use in lactating women:

Evidence source:

It is not known whether Kineret is discharged in human milk. Breast-feeding women were not included in clinical studies.

Population in need of further characterisation:

Lactation influence on child's health.

Use in patients with chronic infections:

Evidence source:

The effect of Kineret treatment in patients with persistent infections has not been studied.

Population in need of further characterisation:

Outcome for patients with chronic infections.

Use in patients with pre-existing cancers:

Evidence source:

The effect of Kineret treatment on already existing cancer has not been studied. Kineret is not recommended in patients with this condition.

Population in need of further characterisation:

Outcome for patients with pre-existing cancer.

Interaction with living vaccines:

Evidence source:

There is no information about the effects of live vaccination on patients receiving Kineret. Live vaccines should not be given during Kineret treatment.

Population in need of further characterisation:

Outcome for patients receiving living vaccine and effectiveness of vaccine.

Part II: Module SVIII - Summary of the safety concerns

Table 26 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Injection site reactions (ISRs)
	Immunogenicity
	Serious infections
	Neutropenia
	Allergic reactions
	Hepatic disorders
Important potential risks	Malignancies
	Medication errors including reuse of syringe
	Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)
	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Missing information	Pregnant women
	Lactating women
	Use in patients with chronic infections
	Use in patients with pre-existing cancers
	Interaction with living vaccines

Part III: Pharmacovigilance Plan

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the following important risks:

- Important identified risks:
  - Hepatic disorders
  - Neutropenia
  - Serious infections
- Important potential risks:
  - Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)
  - Drug reaction with eosinophilia and systemic symptoms (DRESS)

Gathering of specific adverse event report information, including batch numbers, pertaining to a safety concern of special interest is pertinent. The targeted questionnaire is a method of follow-up used to collect structured data on a safety concern. Cumulative review of reports collected in this manner allows for further characterization of the nature of the risk and is used during the review process when considering the relationship between the drug and a safety concern. Examples of questionnaires are available in Annex 4 (Part VII: Annexes).

Other forms of routine pharmacovigilance activities

The following important risks are monitored as Target medical events (TMEs):

- Important identified risks:
  - Serious infections
  - Neutropenia
  - Allergic reactions
  - Hepatic disorders
- Important potential risks:
  - Malignancies
  - Medication error/reuse of used syringe
  - Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)
  - Drug reaction with eosinophilia and systemic symptoms (DRESS)

Target medical events are certain AEs that are closely monitored for evidence of a possible association between Kineret and the events, regardless of the indication for Kineret treatment. TMEs are established as a result of Sobi's own identification of potential safety signals for which a reasonable causal association has not yet been established, and also for post-marketing commitments or regulatory agency requests. Periodic assessment of these events and emerging

safety observations, through synthesis of individual cases, aggregate analysis, and clinical study data, will be described in the PSURs.

III.2 Additional pharmacovigilance activities

There are no ongoing additional pharmacovigilance studies/activities.

A tabulated summary of completed PASSs is presented in Annex 2 (Part VII: Annexes).

III.3 Summary Table of additional Pharmacovigilance activities

There are no ongoing additional pharmacovigilance studies/activities.

Part IV: Plans for post-authorisation efficacy studies

Not applicable. No imposed post-authorization efficacy studies are planned or ongoing.

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

Risk minimization activities proposed in this RMP are risk communications through routine risk minimization measures in the post-marketing setting. These measures are considered sufficient for handling safety concerns in all indications. For some of the risks, there are additional activities (educational materials).

V.1. Routine Risk Minimization Measures

Table 27 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Injection site reactions (ISRs)	Routine risk communication: Information in SmPC section 4.8, and the following recommendations in section 4.2: Alternating the injection site, cooling of the injection site, warming the injection liquid to room temperature, use of cold packs (before and after the injection), and use of topical glucocorticoids and antihistamines after the injection.
Immunogenicity	Routine risk communication: SmPC section 5.1 refers to section 4.8 where the risk is described.
Serious infections	Routine risk communication: Information in SmPC section 4.8 and the following information in section 4.4: Kineret treatment should not be initiated in patients with active infections. Kineret treatment should be discontinued in RA patients if a serious infection develops. In Kineret treated CAPS or FMF patients, there is a risk for disease flares when discontinuing Kineret treatment. With careful monitoring, Kineret treatment can be continued also during a serious infection. Available data is limited regarding whether Kineret can be continued during serious infections in patients with Still's disease. If Kineret treatment is continued during serious infections to reduce the risk for a disease flare, careful monitoring is required. Physicians should exercise caution when administering Kineret to patients with a history of recurring infections or with underlying conditions which may predispose them to infections. Patients should be screened for latent tuberculosis prior to initiating Kineret. The available medical guidelines should be taken into account. Screening for viral hepatitis should also be performed in accordance with published guidelines before starting therapy with Kineret. Kineret treatment can be continued during a serious infection in patients with COVID-19.

Safety concern	Routine risk minimization activities
Neutropenia	Routine risk communication: Information in SmPC section 4.8 and the following information in sections 4.3 and 4.4: Kineret treatment must not be initiated in patients with neutropenia (ANC <1.5 x 10^9/l). It is recommended that neutrophil counts be assessed prior to initiating Kineret treatment, and while receiving Kineret, monthly during the first 6 months of treatment and quarterly hereafter. In patients who become neutropenic (ANC < 1.5 x 10^9/l) the ANC should be monitored closely and Kineret treatment should be discontinued. The safety and efficacy of Kineret in patients with neutropenia have not been evaluated.
Allergic reactions	Routine risk communication: Information in SmPC section 4.8 and the following information in sections 4.3 and 4.4: Kineret is contraindicated in patients with hypersensitivity to the active substance, to any of the excipients or to E. coli derived proteins. If a severe allergic reaction occurs, administration of Kineret should be discontinued and appropriate treatment initiated.
Hepatic disorders	Routine risk communication: Information in SmPC section 4.8 and the following information in section 4.4: Routine testing of hepatic enzymes during the first month should be considered, especially if the patient has pre-disposing factors or develops symptoms indicating liver dysfunction. The efficacy and safety of Kineret in patients with AST/ALT ≥ 1.5 x upper level of normal have not been evaluated.
Malignancies	Routine risk communication: Information regarding this potential risk is presented in SmPC section 4.4.
Medication errors including reuse of syringe	Routine risk communication: SmPC section 6.6 states that the pre-filled syringe is for single use only and any unused medicinal product should be discarded. The syringe should not be shaken and should be allowed to reach room temperature before injecting. Before administration, the solution should be visually inspected for particulate matter and discolouration. Only clear, colourless to white solutions that may contain some product-related translucent-to-white amorphous particles, should be injected.
Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)	Routine risk communication: SmPC section 4.4 describes the potential risk.
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Routine risk communication: SmPC section 4.4 describes the potential risk.
Use in pregnant women	Routine risk communication: SmPC section 4.6 states that as a precautionary measure, it is preferable to avoid the use of anakinra during pregnancy and in women of childbearing potential not using contraception.

Safety concern	Routine risk minimization activities
Use in lactating women	Routine risk communication: SmPC section 4.6 states that breast-feeding should be discontinued during treatment with Kineret.
Use in patients with chronic infections	Routine risk communication: SmPC section 4.4 states that the safety and efficacy of Kineret treatment in patients with chronic and serious infections have not been evaluated.
Use in patients with pre-existing cancers	Routine risk communication: SmPC section 4.4 states that the use of Kineret in patients with pre-existing malignancy is not recommended.
Interaction with living vaccines	Routine risk communication: SmPC section 4.4 states that live vaccines should not be given concurrently with Kineret.

V.2. Additional Risk Minimization Measures

Additional risk minimization - Healthcare Professional and Patient/Carer Guide

Guides are employed to inform healthcare providers of their obligation to instruct patients with CAPS, FMF and Still's disease on correct injection procedures and disposal of used syringes and supplies, along with information material to patients.

The guides for healthcare professionals and patients also include a description of the risk for injection site reactions.

V.3 Summary of risk minimization measures

Table 28 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Routine risk minimization measure	Pharmacovigilance activities
Injection site reactions	Routine risk communication: Information in SmPC section 4.8, and the following recommendations in section 4.2: Alternating the injection site, cooling of the injection site, warming the injection liquid to room temperature, use of cold packs (before and after the injection), and use of topical glucocorticoids and antihistamines after the injection. Additional Risk Minimization Measure: Guides describing how to prevent and manage ISRs for healthcare professionals treating patients with CAPS, FMF and Still's disease, and for patients. The guides describe ISRs and give tips on how to alleviate them.	None
Immunogenicity	Routine risk communication: SmPC section 5.1 refers to section 4.8 where the risk is described.	Evaluation of individual case safety reports (ICSRs) concerning suspected lack of effect.
Serious infections	Routine risk communication: Information in SmPC section 4.8 and the following information in section 4.4: Kineret treatment should not be initiated in patients with active infections. Kineret treatment should be discontinued in RA patients if a serious infection develops. In Kineret treated CAPS of FMF patients, there is a risk for disease flares when discontinuing Kineret treatment. With careful monitoring, Kineret treatment can be continued also during a serious infection. Available data is limited regarding whether Kineret can be continued during serious infections in patients with Still's disease. If Kineret treatment is continued during serious infections to reduce the risk for a disease flare, careful monitoring is required. Physicians should exercise caution when administering Kineret to patients with a history of recurring infections or with underlying conditions which may predispose them to infections. Patients should be screened for latent tuberculosis prior to initiating Kineret. The available medical guidelines should be taken into account. Screening for viral hepatitis should also be performed in accordance with published guidelines before starting therapy with Kineret.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Followed as TME

Safety concern	Routine risk minimization measure	Pharmacovigilance activities
Neutropenia	Routine risk communication: Information in SmPC section 4.8 and the following information in sections 4.3 and 4.4: Kineret treatment must not be initiated in patients with neutropenia (ANC <1.5 x 10^9/l). It is recommended that neutrophil counts be assessed prior to initiating Kineret treatment, and while receiving Kineret, monthly during the first 6 months of treatment and quarterly hereafter. In patients who become neutropenic (ANC < 1.5 x 10^9/l) the ANC should be monitored closely and Kineret treatment should be discontinued. The safety and efficacy of Kineret in patients with neutropenia have not been evaluated.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Followed as a TME
Allergic reactions	Routine risk communication: Information in SmPC section 4.8 and the following information in sections 4.3 and 4.4: Kineret is contraindicated in patients with hypersensitivity to the active substance, to any of the excipients or to E. coli derived proteins. If a severe allergic reaction occurs, administration of Kineret should be discontinued and appropriate treatment initiated.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Followed as a TME
Hepatic disorders	Routine risk communication: Information in SmPC section 4.8 and the following information in section 4.4: Routine testing of hepatic enzymes during the first month should be considered, especially if the patient has pre-disposing factors or develops symptoms indicating liver dysfunction. The efficacy and safety of Kineret in patients with AST/ALT ≥ 1.5 x upper level of normal have not been evaluated.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Followed as a TME
Malignancies	Routine risk communication: Information regarding this potential risk is presented in SmPC section 4.4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Followed as a TME

Safety concern	Routine risk minimization measure	Pharmacovigilance activities
Medication errors including reuse of syringe	Routine risk communication: SmPC section 6.6 states that the pre-filled syringe is for single use only and any unused medicinal product should be discarded. The syringe should not be shaken and should be allowed to reach room temperature before injecting. Before administration, the solution should be visually inspected for particulate matter and discolouration. Only clear, colourless to white solutions that may contain some product-related translucent-to-white amorphous particles, should be injected. Additional Risk Minimization Measure: Guides are employed to inform healthcare providers of their obligation to instruct patients with CAPS, FMF and Still's disease on correct injection procedures and disposal of used syringes and supplies, along with information material to patients.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Followed as a TME
Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)	Routine risk communication: SmPC section 4.4 describes the potential risk.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Followed as a TME
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Routine risk communication: SmPC section 4.4 describes the potential risk.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Followed as a TME
Use in pregnant women	Routine risk communication: SmPC section 4.6 states that as a precautionary measure, it is preferable to avoid the use of anakinra during pregnancy and in women of childbearing potential not using contraception.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pregnancy follow-up questionnaire including questionnaire for neonatal, infant outcome and father information
Use in lactating women	Routine risk communication: SmPC section 4.6 states that breast-feeding should be discontinued during treatment with Kineret.	None
Use in patients with chronic infections	Routine risk communication: SmPC section 4.4 states that the safety and efficacy of Kineret treatment in patients with chronic and serious infections have not been evaluated.	None

Safety concern	Routine risk minimization measure	Pharmacovigilance activities
Use in patients with pre-existing cancers	Routine risk communication: SmPC section 4.4 states that the use of Kineret in patients with pre-existing malignancy is not recommended.	None
Interaction with living vaccines	Routine risk communication: SmPC section 4.4 states that live vaccines should not be given concurrently with Kineret.	None

Part VI: Summary of activities in the risk management plan by product

Summary of risk management plan for Kineret

This is a summary of the risk management plan (RMP) for Kineret. The RMP details important risks of Kineret, how these risks can be minimised, and how more information will be obtained about Kineret's risks and uncertainties (missing information).

Kineret's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Kineret should be used.

This summary of the RMP for Kineret should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Kineret's RMP.

I. The medicine and what it is used for

Kineret is a medicine that is used to treat:

- Rheumatoid Arthritis: Signs and symptoms of rheumatoid arthritis (an immune system disease causing inflammation of the joints) in adults. It is used in combination with methotrexate (a medicine used to reduce inflammation) in patients who have not responded adequately to methotrexate alone
- Cryopyrin-associated periodic syndromes (CAPS). CAPS are a group of diseases where patients have a defect in the gene that produces a protein called cryopyrin. This leads to inflammation in many parts of the body, with symptoms such as fever, rash, joint pain and tiredness. Severe disabilities such as deafness and loss of vision may also occur;
- Still’s disease, a rare disease causing inflammation of joints as well as rash and fever.
- Familial Mediterranean fever (FMF), a hereditary periodic fever. Kineret should be given in combination with colchicine, if appropriate.
- COVID-19, Kineret is used to treat the hyperinflammation (stronger than the usual inflammation) associated with the disease in adults (age 18 years and over) who have pneumonia, need extra oxygen and are at risk of lung failure.

For CAPS, Still’s disease and FMF, Kineret is used in patients from 8 months of age and weighing at least 10 kg (see SmPC for the full indication).

Further information about the evaluation of Kineret’s benefits can be found in Kineret’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kineret, together with measures to minimise such risks and the proposed studies for learning more about Kineret's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Kineret is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Kineret are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kineret. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Summary of safety concerns	
Important identified risks	Injection site reactions
	Immunogenicity
	Serious infections
	Neutropenia
	Allergic reactions
	Hepatic disorders
Important potential risks	Malignancies
	Medication errors including reuse of syringe

Summary of safety concerns	
	Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)
	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Missing information	Pregnant women
	Lactating women
	Use in patients with chronic infections
	Use in patients with pre-existing cancers
	Interaction with living vaccines

II.B Summary of important risks

Important identified risk: Injection site reactions	
Evidence for linking the risk to the medicine	Double-blind, placebo-controlled clinical studies in patients with rheumatoid arthritis (RA) indicate that ISRs can potentially affect 63% to 67% of patients exposed to Kineret except in patients with CAPS where the impact is estimated to be less (23 %, 95 % CI [10.6 %, 35.9 %]).
Risk factors and risk groups	No risk groups have been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 Additional Risk Minimization Measure: Guides describing how to prevent ISRs, for healthcare professionals treating patients with CAPS, FMF and Still's disease, and for patients.

Important identified risk: Immunogenicity	
Evidence for linking the risk to the medicine	In double-blind, placebo-controlled clinical studies anti-drug antibodies to Kineret have been detected however no serious reactions have occurred.
Risk factors and risk groups	Risk groups or risk factors have not been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 5.1

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	In double-blind placebo-controlled studies in RA patients the confidence interval for the estimated mean incidence of serious infections of 2 % (95 % CI [1 %, 2 %]) is overlapping the confidence interval for the incidence in placebo-treated patients, 1 % (95 % CI [0 %, 2 %] and correspond to 0.06 to 0.08 serious infections per patient year exposed to Kineret.
Risk factors and risk groups	For a small number of patients with asthma included in RA studies, the incidence of serious infections was higher in Kineret-treated patients. In studies, concurrent administration of Kineret and etanercept in RA patients has been associated with an increased risk of serious infections. It is reasonable to assume that this interaction is valid not just for etanercept but for the whole class of TNFα-antagonists. No specific risk group or risk factor among patients with CAPS or Still's disease has been identified. It is reasonable to assume that the results in RA studies presented above apply also to CAPS, FMF and Still's patients.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8

Important identified risk: Neutropenia	
Evidence for linking the risk to the medicine	In double-blind placebo-controlled studies the estimated incidence of neutropenia is 1 % with the 95 % CI [1 %, 2 %]
Risk factors and risk groups	In RA patients, concurrent administration of Kineret and etanercept has been associated with an increased risk of decreases in neutrophil count. It is reasonable to assume that this interaction is valid not just for etanercept but for the whole class of TNFα-antagonists. No other specific factors or groups of RA patients have been identified. In Felty's syndrome, a severe variant of RA developing in less than 1 % of RA patients, neutropenia is the most common and important feature. No specific risk group or risk factor among patients with CAPS, FMF or Still's disease has been identified. It is reasonable to assume that the results in RA studies presented above apply also to CAPS, FMF and Still's patients.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8

Important identified risk: Allergic reactions	
Evidence for linking the risk to the medicine	In double-blind placebo-controlled studies in RA patients Kineret-treated patients had an approximately 3 % higher incidence of all types of allergic conditions (including e.g. seasonal allergy and hay fever).
Risk factors and risk groups	Patients with a history of allergic reactions to any of the excipients of Kineret. Patients with DIRA may have an increased risk of allergic reactions, particularly in the first few weeks after starting Kineret treatment.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3, 4.4 and 4.8

Important identified risk: Hepatic disorders	
Evidence for linking the risk to the medicine	The frequency in RA patients for both Kineret and placebo was similar (1%). In CAPS patients the frequency for Kineret was 12% (5 out of 43 patients during up to 5 years of exposure). During postmarketing use hepatic events, considered related to Kineret treatment, have been seen, mainly in patients with a history of liver events and in patients with Still's disease.
Risk factors and risk groups	Patients with history of liver disease or of transaminase elevations before start of Kineret treatment. No other specific factors or groups of patients within the RA, CAPS and FMF populations have been identified. Patients with Still’s disease have an increased risk for hepatic events.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 and 4.8

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	No overall increased frequency of malignancies in Kineret-treated patients has been observed in clinical studies in RA, neither in short-term studies nor in studies with extended patient exposure to Kineret. In CAPS study 03-AR-0298, there were no adverse reactions denoting malignancies. This is true also for the patients with SJIA included in study 990758/990779 and the patients with FMF included in the published double-blind study (87). In the Sobi.ANAKIN-301 study in patients with Still’s disease, there were no malignancies reported in the anakinra group.Due to the immunosuppressive properties of Kineret there is, however, a theoretical risk that Kineret could increase the frequency of malignancies.
Risk factors and risk groups	No specific factors or groups of patients within the RA or CAPS populations have been identified.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4

Important potential risk: Medication errors including reuse of syringe	
Evidence for linking the risk to the medicine	There are sporadic case reports in the post-marketing safety database describing medication errors including reuse of syringe
Risk factors and risk groups	Patients with CAPS, FMF and Still’s disease who use Kineret doses other than 100 mg.
Risk minimisation measures	Routine risk minimisation measures SmPC section 6.6 Additional risk minimization measures Guides are employed to inform healthcare providers of their obligation to instruct patients with CAPS, FMF and Still’s disease on correct injection procedures and disposal of used syringes and supplies, along with information material to patients.

Important potential risk: Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)	
Evidence for linking the risk to the medicine	Post-marketing surveillance case reports and published reports of patients with Still's disease treated with IL-6 and IL-1 inhibitors, including anakinra, who have had complications with interstitial lung disease, pulmonary hypertension and alveolar proteinosis. There were no events of interstitial lung disease, pulmonary alveolar proteinosis or pulmonary hypertension in SJIA patients in study 990758/990779 or in patients with Still's disease in study Sobi.ANAKIN-301.
Risk factors and risk groups	Pediatric patients, especially with trisomy 21, with Still's disease treated with IL-6 and IL-1 inhibitors, including anakinra. In one published case series the cohort of Still's disease patients that developed pulmonary events were more likely to have been exposed to IL-1 inhibitors, tocilizumab, corticosteroids, intravenous immunoglobin, cyclosporine, or cyclophosphamide. 15/25 patients (60%) had MAS at pulmonary diagnosis (39). In a different case series (92, 95) 18 of 61 patients (30%) had overt or subclinical MAS at onset of pulmonary events. RA has also been associated with Interstitial Lung Disease (ILD) with a lifetime risk of developing ILD of 7.7% for RA patients vs. 0.9% for subjects without RA (17).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4

Important potential risk: Drug reaction with eosinophilia and systemic symptoms (DRESS)	
Evidence for linking the risk to the medicine	Post-marketing surveillance case reports and published reports describe DRESS in patients treated with IL-1 inhibitors, predominantly in pediatric patients with Still's disease (92). There have been no cases of DRESS in the clinical studies in RA, CAPS (study 03-AR-0298), JIA/SJIA study (990758/990779), in the study in Still's disease (Sobi.ANAKIN-301) or in the published double-blind study in patients with FMF (87).
Risk factors and risk groups	Pediatric patients with Still's disease.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4

Missing information: Pregnant women	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6

Missing information: Lactating women	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6

Missing information: Use in patients with chronic infections	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4

Missing information: Use in patients with pre-existing cancers	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4

Missing information: Interaction with living vaccines	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Kineret.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Kineret.

Part VII: Annexes

Table of contents

Annex 4 Specific adverse drug reaction follow-up forms

Table of contents

Questionnaire for liver-related events

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Questionnaire for Liver Related Events – Kineret

03Apr2020

Sobi ref no:

Patient details		
Patient's Initials:	☐ Male ☐ Female ☐ Pregnant	Age at onset of event:

Indication for Kineret treatment		
Indication:	Method of diagnosis:	Date of diagnosis: dd/Mmm/yyyy

Current Adverse Event(s)
Term/Diagnosis of the current liver related event:
Did the patient experience any associated symptoms in connection with the event? Yes ☐ No ☐ If Yes, please specify:

Patient history
Does the patient have any predisposing factors for liver related events? Yes ☐ No ☐ If Yes, please specify:
Has the patient had liver related events **prior to Kineret** treatment or **during other treatment**? Yes ☐ No ☐ If Yes, please specify below:
Please specify (Liver function, drug, when):
Has the patient **previously** had any episodes of liver related events in relation to **Kineret** treatment? Yes ☐ No ☐ If Yes, please specify (Liver function, drug, when):
Does the patient consume alcohol? Yes ☐ No ☐ If Yes, please specify:
In your opinion, may the patient's alcohol consumption have contributed to the liver event(s)?

Concomitant disease(s)		
Does the patient have any concomitant disease(s) that potentially could affect the liver? (Infection/other diseases?	Yes ☐ No ☐	If Yes, please specify:

Suspect drug(s)				
Drug name: **Kineret** **Batch number:**	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date: dd/Mmm/yyyy			

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Questionnaire for Liver Related Events – Kineret

03Apr2020

Concomitant drug(s)				
Did the patient receive any **concomitant** drugs at the time of the event or any drugs which were **stopped during the last 2 weeks before** the event? Yes ☐ No ☐ If Yes, please specify below:				
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date:		dd/Mmm/yyyy	
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date:		dd/Mmm/yyyy	
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date:		dd/Mmm/yyyy	

Investigations	
Has an evaluation of possible infectious causes been made? Yes ☐ No ☐ Please specify:	If Yes, date: dd/Mmm/yyyy
Has an evaluation of possible non-infectious causes been made? Yes ☐ No ☐ Please specify:	If Yes, date: dd/Mmm/yyyy
Has any imaging of the liver (e.g. ultrasound, CT, MRI) been performed? Yes ☐ No ☐ Please specify:	If Yes, date: dd/Mmm/yyyy
Has a liver biopsy been made? Yes ☐ No ☐ Please specify:	If Yes, date: dd/Mmm/yyyy

Event description / other relevant patient information

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Questionnaire for Liver Related Events – Kineret

03Apr2020

Laboratory data- Blood tests							
Please, provide results of liver enzyme testing **before exposure to Kineret**.					Date for the testing: dd/Mmm/yyyy		
ALT	AST	ALP	LDH	Bilirubin	PK/INR		
Please, provide liver enzymes **during the event**:							
Date:	dd/Mmm/yyyy	dd/Mmm/yyyy	dd/Mmm/yyyy	dd/Mmm/yyyy	dd/Mmm/yyyy	dd/Mmm/yyyy	**Reference Limits**
ALT							
AST							
ALP							
LDH							
Bilirubin							
PK/INR							
Please, provide results of liver enzyme testing **at follow-up:**					Date for **follow-up**: dd/Mmm/yyyy		
ALT	AST	ALP	LDH	Bilirubin	PK/INR		
Were any other relevant blood tests performed? Yes ☐ No ☐ If Yes, please specify tests and results below:							
Test	**Date** (dd/Mmm/yyyy)	**Result**	**Date** (dd/Mmm/yyyy)	**Result**	**Date** (dd/Mmm/yyyy)	**Result**	**Reference Limits**

Supplementary data has been attached	Yes ☐	No. of pages:	No ☐

Reporter	
Name of reporter:	Specialty:
Signature:	Date: dd/Mmm/yyyy

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Questionnaire for drug exposure during pregnancy

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DRUG EXPOSURE DURING PREGNANCY FORM – PART 1

Version effective 07Jan2021

Sobi ref no:

Please complete the following sections 1-4, including as much info as possible

1. Mother information

Demographics

Age (years):	Date of Birth (dd-Mmm-yyyy):	Weight: kg	Height: cm

Pregnancy

First day of Last Menstrual Period (dd-Mmm-yyyy):

Estimated Date of Conception (dd-Mmm-yyyy):

Estimated Delivery Date (dd-Mmm-yyyy):

Gestational period at time of initial exposure if applicable: Months Trimester

2. Subject exposure to Sobi Drug(s) ☐ Not applicable - *if pregnancy of partner to a male subject participant*

Sobi product	Indication	Dose, units	Frequency	Route	Start date dd-Mmm-yyyy	Stop date dd-Mmm-yyyy	Reson for stopping	Batch number, expiration date

3. Current pregnancy

Results of serology tests (e.g. rubella, toxoplasmosis):

Specific tests, e.g. amniocentesis, ultrasound, maternal serum Alpha Fetoprotein, performed during the pregnancy so far. If any of these tests were performed, please provide any relevant results

4. Pregnancy outcome

Is outcome of pregnancy known? ☐ No ☐ Yes - *If yes, please complete Drug exposure during Pregnancy Form Part 2.*

5. Reporter Contact Details

Name of person completing this form (reporter): **Phone #:**

Email address:

Hospital and adress: **Country:**

Reporter's Qualification

☐ Physician ☐ Nurse ☐ Pharmacist ☐ Other HCP – specify: ☐ Non HCP – specify:

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DRUG EXPOSURE DURING PREGNANCY FORM – PART 1

Version effective 07Jan2021

Name of treating physician (if not the same as reporter):	**Phone #:**
	Email address:
Hospital and adress:	**Country:**

If the reporter of the information is **a health care professional**: Does the reporter agree to be contacted for follow-up? ☐ Yes ☐ No	If the reporter of the information is **a patient or consumer**: Does the reporter allow Sobi to contact the responsible health care professional for follow-up? ☐ Yes ☐ No
Signature:	**Date (dd-Mmm-yyyy):**

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DRUG EXPOSURE DURING PREGNANCY FORM – PART 2

Version effective 07Jan2021

Sobi ref no:

Please complete section 1-2 including as much info as possible

1. Outcome of pregnancy

Neonatal information

☐ Full term live birth ☐ Premature live birth ☐ Stillbirth

Gestational age at birth (if known): weeks

☐ Spontaneous abortion/miscarriage ☐ Elective/therapeutic termination ☐ Unknown *Specify reason for why information is unknown*

Date of Outcome of Pregnancy (dd-Mmm-yyyy):

Foetal information (complete section in the event of an elective termination, spontaneous abortion or late foetal death – *provide details if available*)

Reason for termination:

Gestational age at termination:

Is there any abnormality of the embryo/foetus? ☐ No ☐ Yes .

If yes, please provide results of physical examination (external anomalies) and pathology:

2. Outcome of infant – *check only one box*

☐ Normal newborn

☐ Unknown *Specify reason for why information is unknown*

☐ Congenital malformation/anomaly – *specify:*

☐ Other neonatal problem/abnormality (incl. dysmaturity, neonatal illness, hospitalization, drug therapies – *specify:*

☐ Neonatal/Fetal death

The following sections are only to be completed in case of adverse outcome.

Please complete the section 3-8 ONLY in case of adverse outcome. If no adverse outcome, proceed to 9

3. Delivery

Any problems before delivery? ☐ No ☐ Yes – *If yes, please specify*

Any problems during delivery (incl. delivery complications, foetal distress, amniotic fluid abnormal, abnormal placenta)?

☐ No ☐ Yes – *If yes, please specify*

Any problems after delivery? ☐ No ☐ Yes – *If yes, please specify*

Mode of delivery (e.g. natural birth, i.e. vaginal delivery without medication or anaesthesia, forceps or caesarean section):

4. Infant details

Apgar score 1 min: 5 min:

Gender (sex): ☐ Male ☐ Female

Weight (at birth): grams Length (at birth): cm Head circumference (at birth): cm

Breast Feeding: ☐ Yes ☐ No

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DRUG EXPOSURE DURING PREGNANCY FORM – PART 2

Version effective 07Jan2021

5. Mother obstetrical history

☐ Not applicable (no previous pregnancy) Number of previous pregnancies: Number of other children:

Outcome of previous pregnancies (live birth, miscarriage, elective termination, late fetal death, ectopic pregnancy, molar pregnancy)

Previous maternal pregnancy complications

Previous fetal/neonatal abnormalities and type

6. Relevant maternal medical history

Risk factors for adverse pregnancy outcomes (e.g. hypertension, diabetes) including environmental or occupational exposures (e.g. smoking, acohol use):

Family history of congenital abnormality/genetic diseases, consanguinity or any family relation or lineage between parents – *specify degree*:

7. Mother exposure to other Drugs

Were any other drugs taken during pregnancy (e.g. prescription, over-the-counter)? ☐ Yes – *specify below* ☐ No

Product	Indication	Dose, Units	Frequency	Route	Start Date dd-Mmm-yyyy	Stop Date dd-Mmm-yyyy	Reason for stopping

8. Relevant paternal medical history

Risk factors for adverse pregnancy outcomes including environmental or occupational exposures (e.g. smoking, acohol use):

Family history of congenital abnormality/genetic diseases, consanguinity or any family relation or lineage between parents – *specify degree*:

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Questionnaire for events of neutropenia

Questionnaire for Events of Neutropenia – Kineret

12Mar2020

Sobi ref no:

Patient details		
Patient's Initials:	☐ Male ☐ Female ☐ Pregnant	Age at onset of event:

Indication for Kineret treatment		
Indication:	Date for diagnosis: dd/Mmm/yyyy	Date for start of Kineret treatment: dd/Mmm/yyyy

Current Event of Neutropenia

Were any other hematopoietic cell lines affected? Yes ☐ No ☐ If Yes, please specify:

Has a bone marrow aspiration been performed? Yes ☐ No ☐ If Yes, date: dd/Mmm/yyyy

Results have been appended ☐

Please specify result here if not appended:

Did the patient experience any infections or other associated symptoms during the neutropenia? Yes ☐ No ☐ If Yes, please specify:

Patient history

Does the patient have any predisposing factors for development of neutropenia? Yes ☐ No ☐ If Yes, please specify:

Has the patient had neutropenia **prior to Kineret** treatment? Yes ☐ No ☐ If Yes, please specify:

Has the patient **previously** had any episodes of neutropenia **during Kineret** treatment? Yes ☐ No ☐ If Yes, please specify:

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Questionnaire for Events of Neutropenia – Kineret

12Mar2020

Concomitant disease(s)

Does the patient have any concomitant disease(s) that potentially could affect the neutrophil count?

Yes ☐ No ☐ If Yes, please specify:

Please list all drugs you suspect could have caused the neutropenia

Drug name: Kineret Batch number:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was Kineret stopped? Yes ☐ No ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date: dd/Mmm/yyyy			

Please add additional records if needed

Concomitant drug(s)

Did the patient receive any **other concomitant** drugs at the time of the event or any drugs which were **stopped during the last 2 weeks before** the event? Yes ☐ No ☐ If Yes, please specify below:

Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date: dd/Mmm/yyyy			

Please add additional records if needed

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Questionnaire for Events of Neutropenia – Kineret

12Mar2020

Investigations

Has an evaluation of other possible causes for the neutropenia been made? Yes ☐ No ☐ If Yes, date: dd/Mmm/yyyy

Please specify, incl. results:

Are hematology and clinical chemistry test results appended?	Yes ☐ No ☐ If Yes, please do **not** fill in laboratory data sheet below.

Laboratory data- Hematology

	Before Kineret	During event	During event	During event	During event	At follow-up	
Date:	dd/Mmm/yyyy	dd/Mmm/yyyy	dd/Mmm/yyyy	dd/Mmm/yyyy	dd/Mmm/yyyy	dd/Mmm/yyyy	**Reference Limits**
Total WBC count							
Neutrophil count							
Eosinophil count							
Basophil count							
Monocyte count							
Lymphocyte count							
Hemoglobin							
Thrombocyte count							
Additional hematologic tests							

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Questionnaire for Events of Neutropenia – Kineret

12Mar2020

Laboratory data- Clinical chemistry/other

Were any other relevant blood tests performed? Yes ☐ No ☐ If Yes, please specify tests and results below:

Test	Date (dd/Mmm/yyyy)	Result	Date (dd/Mmm/yyyy)	Result	Date (dd/Mmm/yyyy)	Result	Reference Limits

Event description / other relevant information

Supplementary data has been attached Yes ☐ No ☐ No. of pages:

Reporter

Name of reporter: Specialty:

Signature: Date: dd/Mmm/yyyy

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Questionnaire for events of serious infections

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Questionnaire for Events of Serious Infections – Kineret

12Mar2020

Sobi ref no:

Patient details		
Patient's Initials:	☐ Male ☐ Female ☐ Pregnant	Age at onset of event:

Kineret treatment			
Indication:		Date of diagnosis: dd/Mmm/yyyy	
Start date of Kineret: (dd/Mmm/yyyy) Batch number:	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
Was Kineret stopped? Yes ☐ No ☐	If Yes, please specify date: dd/Mmm/yyyy		
Was Kineret re-started? Yes ☐ No ☐	If Yes, please specify date: dd/Mmm/yyyy		

Current Event
Event:
Body temperature (preferably in °C): Before event: During event (max temperature): After event:
How was the diagnosis established?
Type of infectious agent and main result of resistance testing:

Result of diagnostic test(s)
Results of radiologic investigations:

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Questionnaire for Events of Serious Infections – Kineret

12Mar2020

Supporting lab results (e.g. CRP, WBC incl differential count) including reference limits.
Are hematology and clinical chemistry test results appended? Yes ☐ No ☐ If Yes, please do not fill in laboratory data sheet below.

Test	Date dd/Mmm/yyyy	Result	Date dd/Mmm/yyyy	Result	Date dd/Mmm/yyyy	Result	Reference Limits

Patient history	
Did the patient have any predisposing factors for infections? (E.g. Compromised immune system, indwelling catheter, recent surgery)	Yes ☐ No ☐ If Yes, please specify:
Does the patient have a history of serious infections before Kineret treatment?	Yes ☐ No ☐ If Yes, please specify:

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Questionnaire for Events of Serious Infections – Kineret

12Mar2020

Concomitant disease(s)

Did the patient have any concomitant disease(s) at the time of onset of the infection? Yes ☐ No ☐ If Yes, please specify:

Prophylactic treatment

Was prophylactic antibiotic, antifungal or antiviral treatment given?

Yes ☐ No ☐ If Yes, please specify:

Concomitant treatment

Did the patient receive any **concomitant** drugs at the time of the event or any drugs which were **stopped during the last 2 weeks before** the event? Yes ☐ No ☐ If Yes, please specify below:

Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date:		dd/Mmm/yyyy	
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date:		dd/Mmm/yyyy	
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date:		dd/Mmm/yyyy	
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? Yes ☐ No ☐ If Yes, please specify date:		dd/Mmm/yyyy	

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Questionnaire for Events of Serious Infections – Kineret

12Mar2020

Event description / other relevant information

Supplementary data have been attached	Yes ☐	No. of pages:	No ☐

Reporter	
Name of reporter:	Specialty:
Signature:	Date: dd/Mmm/yyyy

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Questionnaire for Pulmonary events

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Questionnaire Pulmonary Events (PE) (including pulmonary hypertension) in connection with Kineret treatment

03Apr2020

Sobi ref no:

Patient details		
Patient's Initials:	☐ Male ☐ Female ☐ Pregnant	Age at onset of event:

Current Kineret treatment		
Indication:	Age at diagnosis:	Date for onset of Kineret treatment: dd/Mmm/yyyy

Pulmonary event(s)		
Event:	Start date: dd/Mmm/yyyy	Age at onset of event:
Event:	Start date: dd/Mmm/yyyy	Age at onset of event:
Event:	Start date: dd/Mmm/yyyy	Age at onset of event:
Event:	Start date: dd/Mmm/yyyy	Age at onset of event:

Patient history
Does the patient have any predisposing factors for PE? No ☐ Yes ☐ If Yes, please specify:
Has the patient had episodes of PE **prior to Kineret** treatment? No ☐ Yes ☐ If Yes, please specify (type, when, possible triggers):
Has the patient **previously** had any resolved PE **during Kineret** treatment? Yes ☐ No ☐ If Yes, please specify (type, when):

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Questionnaire Pulmonary Events (PE) (including pulmonary hypertension) in connection with Kineret treatment

03Apr2020

Concomitant disease(s)		
Does the patient have any concomitant disease(s) that potentially could increase the risk for PE?	Yes ☐ No ☐	If Yes, please specify:
Has the patient had an allergic reaction to IL-1 or IL-6 inhibitors prior to the PE?	Yes ☐ No ☐	If Yes, please specify type, and when in relation to current PE:
Does the patient have Trisomy 21 (Down's syndrome)?	Yes ☐ No ☐	
Has the patient had clubbing prior to or during the PE?	Yes ☐ No ☐	If Yes, please specify when in relation to current PE:
Did the clubbing occur after administration of Kineret?	Yes ☐ No ☐	If Yes, please specify when in relation to treatment with Kineret:

Drug(s) suspected to have contributed to the current PE				
Drug name: **Kineret** **Batch number:**	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment before PE: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐	If Yes, please specify date: dd/Mmm/yyyy		
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐	If Yes, please specify date: dd/Mmm/yyyy		
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐	If Yes, please specify date: dd/Mmm/yyyy		

Concomitant drug(s) not suspected to have contributed to the current episode of PE				
Did the patient receive any **concomitant** drugs at the time of the event, or any drugs which were **stopped during the last 2 weeks before** the event? No ☐ Yes ☐ If Yes, please specify on next page:				
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐	If Yes, please specify date: dd/Mmm/yyyy		

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Questionnaire Pulmonary Events (PE) (including pulmonary hypertension) in connection with Kineret treatment

03Apr2020

Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			

Event description / other relevant patient information

Investigations			
Has a spirometry been made?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	If Yes, please specify type of evaluation and result:
Has an evaluation SpO2 been made (e.g. by pulse oximetry)?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	If Yes, please specify type of evaluation and result:
Has a BAL been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	If Yes, please specify results: Neutrophil count in BAL: Please specify other findings:
Has a lung biopsy been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify result:

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Questionnaire Pulmonary Events (PE) (including pulmonary hypertension) in connection with Kineret treatment

03Apr2020

Has a chest x-ray been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify result:
Has a CT of thorax been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify result:
Has a MRI of thorax been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify result:
Have any other pulmonary evaluations been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify type(s) and result(s):
Has an echocardiography been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify result:
Has a cardiac catheterization been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify result:

Laboratory data - Blood test dates and results

Date:	Before event dd/Mmm/yyyy	During event dd/Mmm/yyyy	During event dd/Mmm/yyyy	During event dd/Mmm/yyyy	During event dd/Mmm/yyyy	At follow-up dd/Mmm/yyyy	Reference Limits including unit
Hemoglobin							
EVF							
MCV							
White blood cell count							

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Questionnaire Pulmonary Events (PE) (including pulmonary hypertension) in connection with Kineret treatment

03Apr2020

Neutrophil count							
Eosinophils							
CRP							
Ferritin							
Brain natriuretic peptide (BNP)							

Were any other relevant blood tests performed? No Yes If Yes, please specify dates and results:							
Test	Before event dd/Mmm/yyyy	During event dd/Mmm/yyyy	During event dd/Mmm/yyyy	During event dd/Mmm/yyyy	During event dd/Mmm/yyyy	At follow-up dd/Mmm/yyyy	Reference Limits including unit

Supplementary data has been attached	Yes / No	If Yes, no. of pages:

Reporter	
Name of reporter:	Specialty:
Signature:	Date: dd/Mmm/yyyy

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Questionnaire for DRESS

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SWEDISH ORPHAN BIOVITRUM

Questionnaire Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in connection with Kineret treatment

4 July 2022

Sobi ref no:

Patient details				
Patient's Initials:	☐ Male ☐ Female ☐ Pregnant		Date of birth:	dd/Mmm/yyyy

Current Kineret treatment		
Indication:	Age at diagnosis:	Date for onset of Kineret treatment: dd/Mmm/yyyy

Kineret treatment doses (most recent first)				
Batch number:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			
Batch number:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			
Batch number:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			

Other drug(s) suspected to have contributed to the current episode of DRESS				
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			

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Questionnaire Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in connection with Kineret treatment

4 July 2022

Concomitant drug(s) not suspected to have contributed to the current episode of DRESS

Did the patient receive any **concomitant** drugs at the time of the event, or any drugs which were **stopped during the last 2 weeks before** the event? No ☐ Yes ☐ If Yes, please specify on next page:

Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			
Drug name:	Start date: dd/Mmm/yyyy	Dose:	Date for dose adjustment: dd/Mmm/yyyy	New dose:
	Was the drug stopped? No ☐ Yes ☐ If Yes, please specify date: dd/Mmm/yyyy			

Patient medical history

Has the patient had episodes of drug reactions or eosinophilia **prior to Kineret** treatment?

No ☐ Yes ☐ If Yes, please specify (type, when, possible triggers):

Has the patient had an allergic reaction to IL-1 or IL-6 inhibitors prior to the DRESS?

No ☐ Yes ☐ If Yes, please specify (type, when, possible triggers):

Please provide significant past medical history (please attach further pages if required):

Details of the current episode of DRESS

Fever	> 38.5°C ☐ Yes ☐ No	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
Tender Enlarged Lymph Nodes	☐ Yes ☐ No Number of sites:	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
Eosinophilia	☐ Yes ☐ No	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy

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Questionnaire Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in connection with Kineret treatment

4 July 2022

	Maximum Eosinophil count: Units Reference Range: to Units	
Peripheral blood atypical lymphocytes	☐ Yes ☐ No	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
Skin reaction		
Morphology	Scaling / desquamation ☐ Yes ☐ No	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
	Oedema (excluding lower leg oedema) ☐ Yes ☐ No	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
	Purpura (excluding lower leg) ☐ Yes ☐ No	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
	Infiltration ☐ Yes ☐ No Other - please describe:	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
Rash greater than 50% surface area	☐ Yes ☐ No	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
Was a skin biopsy taken?	☐ Yes ☐ No If so, please describe result and also attach report if available:	Date of skin biopsy: dd/Mmm/yyyy

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Questionnaire Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in connection with Kineret treatment

4 July 2022

Involvement of other organs

☐ Yes ☐ No

PLEASE REVIEW THE DEFINITION OF ORGAN DAMAGE ON THE ATTACHED SHEET AND PROVIDE FURTHER DETAILS

End Organ Damage	Liver	☐ Yes ☐ No Please specify:	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
	Kidney	☐ Yes ☐ No Please specify:	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
	Lung	☐ Yes ☐ No Please specify:	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
	Muscle / heart	☐ Yes ☐ No Please specify:	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
	Pancreas	☐ Yes ☐ No Please specify:	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
Other organs		☐ Yes ☐ No If so, please specify:	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy
DRESS symptoms		Did the symptoms take more than 15 days to resolve? ☐ Yes ☐ No	

Alternative causes of eosinophilia excluded

Allergic disease	Chronic urticaria	☐ Yes, excluded	☐ No
	Asthma	☐ Yes, excluded	☐ No
	Allergic rhinitis	☐ Yes, excluded	☐ No
	Gastrointestinal / food allergies	☐ Yes, excluded	☐ No
	Please provide further details, and attach source documents if relevant:		
Infectious causes of eosinophilia	Have the following been excluded?		
	• Helminths, including soil transmitted helminths and strongyloides	☐ Yes, excluded	☐ No
	• Fungal infections, including aspergillus	☐ Yes, excluded	☐ No
	• Protozoa	☐ Yes, excluded	☐ No

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Questionnaire Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in connection with Kineret treatment

4 July 2022

	Has the patient relevant travel or immigration history? ☐ Yes ☐ No If so, please provide further details: Has the patient received a prophylactic dose of ivermectin or albendazole? ☐ Yes ☐ No If so, please provide further details:
Neoplasms	Has the patient hematological neoplasms with clonal eosinophilia? ☐ Yes ☐ No Has a bone marrow biopsy been performed? ☐ Yes ☐ No If so, please provide further details:
Other investigations to rule out symptoms as per RegiSCAR score	Hepatitis A/B/C Mycoplasma/Chlamydia pneumoniae Blood cultures ≤ 3 days of index date Other (infections): serology, PCR, microbiological cultures ANA If so, please provide further details:

Event description / other relevant patient information

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Questionnaire Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in connection with Kineret treatment

4 July 2022

Lung disease			
Does the patient have concurrent lung disease?	Yes ☐ No ☐	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy	Please specify type(s) and result(s):
If so, has the lung disease commenced since starting Kineret?	Yes ☐ No ☐	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy	Please specify type(s) and result(s):
Has the lung disease occurred since starting other IL-1 or IL-6 inhibitors?	Yes ☐ No ☐	Start date: dd/Mmm/yyyy Stop date: dd/Mmm/yyyy	Please specify type(s) and result(s):
Has a lung biopsy been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify result:
Has a chest x-ray been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify result:
Has a CT of thorax been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify result:
Has an MRI of thorax been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify result:
Have any other pulmonary evaluations been performed?	Yes ☐ No ☐	If Yes, date: dd/Mmm/yyyy	Please specify type(s) and result(s):

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Questionnaire Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in connection with Kineret treatment

4 July 2022

Outcome
If fatal, was an autopsy performed? ☐ Yes ☐ No
If so, is an autopsy report available? ☐ Yes ☐ No
If so, please attach.

Supplementary data has been attached	Yes ☐ No ☐	If Yes, no. of pages:

Reporter	
Name of reporter:	Specialty:
Signature:	Date: dd/Mmm/yyyy

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Questionnaire Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in connection with Kineret treatment

4 July 2022

End Organ Involvement Definitions

Involvement internal organs: (0, 1, 2) For acute involvement of each organ, 1 point is given, with a maximum of 2 points. Organ involvement is based on history, clinical investigation, medical imaging, biopsy or other tissue/fluid investigation. Organ involvement is also calculated at presence of the following abnormal laboratory values:

Liver (0, 1)
- ALAT >2 times upper normal limit (*UNL) on at least 2 successive dates or
- conjugated bilirubin >2* UNL on at least 2 successive dates or
- ASAT, total bilirubin, alkaline phosphatase (AP) all >2*UNL at least

Kidney (0, 1)
- Serum creatinine more than 1.5 times above the base value for the patient on at least 2 successive dates, and/or
- proteinuria above 1 g/day,
- haematuria,
- decreased creatinine clearance,
- decreased GFR

Lungs (0, 1)
- Cough and/or dyspnoea in conjunction with
- evidence of interstitial involvement on imaging and/or
- abnormal broncho-alveolar lavage fluid, or biopsy and/or
- abnormal blood gasses

Muscle, heart (0, 1)
- Muscle pain and/or – weakness, myocarditis (often nonspecific symptoms: hypotension, fatigue, chest pain, dyspnoea, malaise, palpitations, tachycardia, cardiac dysfunction, cardiomegaly, sudden cardiac death), with
- raised serum creatine phosphokinase (CPK) > 2*UNL
- raised isoenzymes: CPK-3/CPK-MM (indicative for skeletal muscle), raised CPK-2/MB fraction (indicative for heart muscle involvement)
- serum troponin T > 0.01 µg per liter
- abnormal imaging: chest X-ray/ECHO/CT/MRI/EMG including ECG: ST-T electrocardiogram abnormalities or conduction defects (ST-segment depression, T-wave inversions or non-diagnostic ECG changes (paced or bundle branch block))
- endomyocardial biopsy

Pancreas (0, 1):
- Amylase and/or lipase ≥ 2*UNL

Other organs: spleen, thyroid gland, central nervous system, gastrointestinal tract
- Clinical symptoms and additional investigations: enlargement/imaging, including EEG
- Abnormal lab values: TSH, FT4, FT3
- Biopsy

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Annex 6 Details of proposed additional risk minimisation activities

KINERET INJECTION GUIDES FOR CAPS, FMF AND STILL's DISEASE

Description

- Printed guides for patients and health care professionals (HCPs) to demonstrate the steps required to safely administer Kineret.
- The guides will be distributed to all centers treating patients with CAPS, FMF and Still's disease that Sobi has identified.
- The patient guides are used by the patients when injecting Kineret. They will also be used by health care professionals when instructing the patients on the safe and proper use of Kineret.
- The guides emphasize that patients or caregivers should not be allowed to administer Kineret until the patient or caregiver has demonstrated a thorough understanding of procedures and an ability to inject the product correctly with the graduated prefilled syringe.

Outline of Patient guides content

- Basic disease information
- Kineret, and how it works
- Dosing and administration
    - Risks associated with re-use of the graduated pre-filled syringe
    - Necessary supplies
        - Required supplies
        - Kineret graduated pre-filled syringe package contents
    - Setting up for injection
        - Sterile technique
        - Finding a good work surface
        - Inspecting the syringe & expiration date
        - Warming Kineret to room temperature
    - Preparing the dose of Kineret
        - Proper handling
        - Preparing the correct prescribed dose (20-90 mg)
        - Proper disposal of excess solution
        - Administering the full dose 100 mg
    - Selecting and preparing the injection site
        - Recommended sites
        - Choosing a site
        - Cleaning the site
    - Administering the injection
        - Correct angle, motion, injection speed and depth
        - Withdrawing the needle
        - Cleaning and covering the site
    - Proper disposal of syringe and supplies

- Injection site reactions and their management
  - Overview of injection site reactions (types, when they can occur, duration)
  - Recommendations for the management of injection site reactions based on the information in the SmPC.

Outline of guide for HCPs

- Short description of patient materials: instructions for training patients to self-inject, and specific instructions on the graduated syringe.
- Instructions of dosing and dose calculation for Still's disease, FMF and CAPS.
- Recommendations for the management of injection site reactions based on the information in the SmPC.
- Abbreviated prescribing information from the SmPC.