EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2020
EMA/236936/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kineret

International non-proprietary name: anakinra

Procedure No. EMEA/H/C/000363/II/0070

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
AA	Amyloid A
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AOSD	Adult-Onset Still's Disease
CAPS	Cryopyrin-associated periodic syndromes
CINCA	Chronic infantile neurological, cutaneous and articular syndrome
CL_{cr}	Creatinine clearance
CL/F	Clearance relative to bioavailability
CRP	C-reactive protein
EEA	European Economic Area
ESR	Erythrocyte sedimentation rate
ESRD	End stage renal disesase
EU	European Union
EULAR	European League Against Rheumatism
FMF	Familial Mediterranean fever
GI	Gastrointestinal
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL-1β	Interleukin-1 beta
ISR	Injection site reaction
i.v.	Intravenous
JIA	Juvenile idiopathic arthritis
LRR	C-terminal ligand binding leucine-rich repeat domain
MedDRA	Medical Dictionary for Regulatory Activities
MEFV	Mutated Mediterranean fever-associated gene
NAb	Neutralising antibody
NOMID	Neonatal onset multisystem inflammatory disease
PD	Pharmacodynamic
PK	Pharmacokinetics
QoL	Quality of life
RA	Rheumatoid arthritis
SAA	Serum amyloid A
SAE	Serious adverse event
s.c.	Subcutaneous
SD	Standard deviation
SJIA	Systemic juvenile idiopathic arthritis
SOC	System organ class
t_{max}	Time to reach maximum plasma concentration
TNF	Tumor necrosis factor
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 14 October 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of Familial Mediterranean Fever (FMF) for Kineret, to be given in combination with colchicine, if appropriate; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 5.0 has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Mark Ainsworth Co-Rapporteur: Fátima Ventura

Timetable	Actual dates
Submission date	14 October 2019
Start of procedure:	2 November 2019
CHMP Rapporteur Assessment Report	19 December 2019
CHMP Co-Rapporteur Assessment Report	20 December 2019
PRAC Rapporteur Assessment Report	19 December 2019
PRAC members comments	8 January 2020
Updated PRAC Rapporteur Assessment Report	13 January 2020
PRAC Outcome	16 January 2020
CHMP members comments	20 January 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	25 January 2020
Request for supplementary information (RSI)	30 January 2020
PRAC Rapporteur Assessment Report	02 March 2020
PRAC members comments	04 March 2020
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Joint Rapporteurs Assessment Report	10 March 2020
PRAC Outcome	13 March 2020
CHMP members comments	16 March 2020
Updated CHMP Joint Rapporteurs Assessment Report	19 March 2020
Opinion	26 March 2020

2. Scientific discussion

2.1. Introduction

Anakinra (trade name Kineret) is a recombinant form of the naturally occurring IL-1 receptor antagonist, which binds to the interleukin-1 receptor and prevents the activity of the cytokines IL-1α and IL-1β by competitively inhibiting their binding to interleukin-1 receptor type 1, thereby controlling active inflammation.

Anakinra was first approved in EU/EEA in 2002 for the treatment of rheumatoid arthritis (RA) in adults. Anakinra was approved for Cryopyrin-Associated Periodic Syndromes (CAPS) in 2013 and Still's disease in 2018 in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above.

This type-II variation application includes the proposed new indication:

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

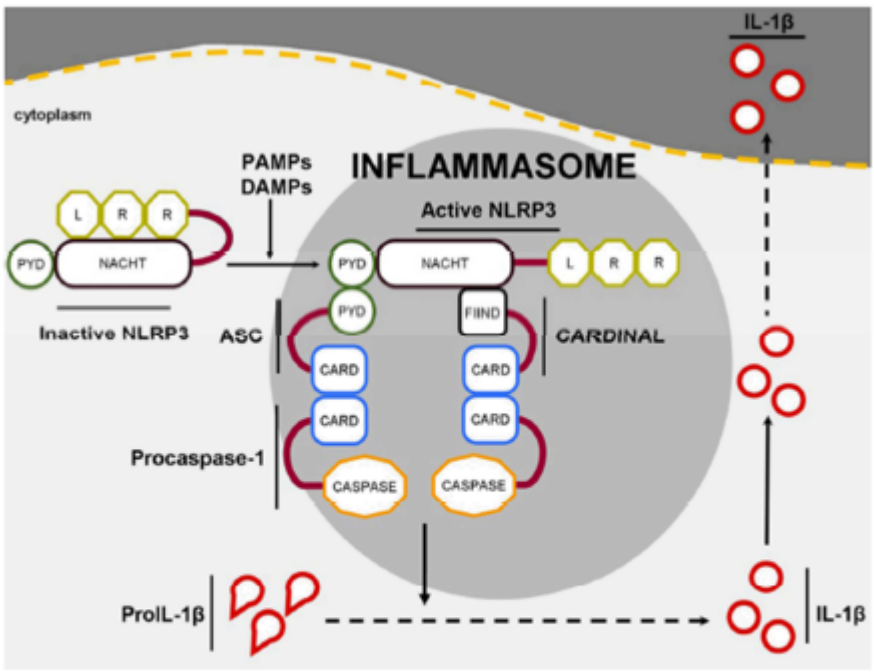
The recommended dose for both adults and children weighing 50 kg or more is 100 mg/day by subcutaneous injection. Patients weighing less than 50 kg should be dosed by body weight with a recommended dose of 1-2 mg/kg/day.

2.1.1. Problem statement

Disease or condition

Familial Mediterranean Fever (FMF) is a rare monogenic inherited condition that shares the same pathophysiological feature resulting from the activation of the inflammasome with several other hereditary periodic fever syndromes, e.g., CAPS. FMF is caused by mutations in the Mutated Mediterranean fever-associated gene (MEFV) gene coding for pyrin, which is a component of the inflammasome functioning in inflammatory response and production of Il-1β (Figure 1).

FMF manifests with a typical clinical picture with recurrent febrile episodes with abdominal, chest and joint pain.



Source: Rigante et al. 2018 (21).
Abbreviations: ASC, apoptosis-associated speck-like protein containing a C-terminal CARD; CARD, caspase activation/recruitment domain; DAMPs, damage-associated molecular pattern molecules; FIIND, function-to-find domain; IL-1β, interleukin-1beta; LRR, C-terminal ligand binding leucine-rich repeat domain; NACHT, nucleotide-binding and oligomerization domain; NLRP3, NACHT, LRR, and PYD domains-containing protein 3; PAMPs, pathogen-associated molecular patterns; ProIL-1β, IL-1 precursor; PYD, pyrin domain.

Figure 1 The activation of the inflammasome in hereditary periodic fever syndromes

Epidemiology

FMF has traditionally been considered an autosomal recessive disease. FMF was originally restricted to populations living around the Mediterranean basin. For example, there is an estimated total of 100 000 FMF patients in Turkey[1]. The prevalence rate in France in 2013 was estimated at 1 in 5000 individuals, i.e. 5000 to a maximum of 10 000 patients[2]. Significant number of patients are also found in Germany, Greece, Cyprus, and Italy [1,3,4]. 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[1]. Because of ongoing migration, the future incidence is likely to increase in the EU

Clinical presentation, diagnosis and stage/prognosis

FMF is typically presented with recurrent febrile attacks, accompanied by signs of peritonitis, pleuritis or acute synovitis, lasting 1 to 3 days, and resolving spontaneously. The skin may be affected by erysipelas-like erythema. Attacks occur randomly, from once per week to once in several months, and

[1] Ben-Chetrit E, Touitou I. Familial mediterranean Fever in the world. Arthritis Rheum. 2009;61(10):1447-53.
[2] PNDS. Fièvre Méditerranéenne Familiale (FMF). Centre de référence des maladies auto-inflammatoires de l' enfant. ; 2013.
[3] La Regina M, Nucera G, Diaco M, Procopio A, Gasbarrini G, Notarnicola C, et al. Familial Mediterranean fever is no longer a rare disease in Italy. Eur J Hum Genet. 2003;11(1):50-6.
[4] Deltas CC, Mean R, Rossou E, Costi C, Koupepidou P, Hadjiyanni I, et al. Familial Mediterranean fever (FMF) mutations occur frequently in the Greek-Cypriot population of Cyprus. Genet Test. 2002;6(1):15-21.

patients are free of symptoms between the attacks. Emotional stress, fatigue, surgery, menstruation, vigorous exercise, and cold exposure may trigger an attack, but no definite precipitant is known.

Typical laboratory manifestations of an FMF attack are elevated acute-phase reactants including erythrocyte sedimentation (ESR), C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin, C3, and C4. The most severe and potentially life-threatening complication of FMF is secondary amyloid A amyloidosis being the primary cause of premature death in FMF patients.

The median age of disease onset in children was in one study 2.6 (IQR 1.2 to 4.9) years with 16 % having onset below 2 years of age. The lowest age of onset described is 4 months. Early onset may cause more severe disease.

FMF is diagnosed by the clinical picture and the diagnoses can be supported, but not necessarily excluded, by genetic testing. Various diagnostic criteria have been suggested, including the Tel Hashomer criteria.

Management

According to a recent (European League Against Rheumatism) EULAR guideline[5] there are 2 main goals in the treatment of FMF:

- To prevent the clinical attacks.
- To suppress chronic subclinical inflammation and elevation of acute phase reactants, in particular SAA protein, and its consequences, including secondary AA amyloidosis and other long-term complications.

Colchicine, an alkaloid with inhibitory effects on multiple cellular functions, including microtubule assembly, cell adhesion, and inflammasome activation is in the EULAR guideline recommended to be given as soon as the clinical diagnosis is established. The colchicine dose ranges between 1 and 3 mg daily and is determined clinically on the basis of its effect on the prevention of attacks. Continuous therapy with colchicine prevents FMF attacks in 60 to 65 % of patients and induces partial remission in a further 30 to 35 %. In addition, regular use of colchicine reduces the long-term risk of amyloidosis.

In patients who fail to respond to colchicine or who cannot tolerate it, biological drugs, especially IL-1 treatment, should be considered according to the recent EULAR guideline. The long-acting IL-1β antibody canakinumab was approved for treatment of FMF in the EU/EEA on 23 October 2009.

2.1.2. The development programme/compliance with CHMP guidance/scientific advice

Kineret was first approved in EU on 8 March 2002 for the treatment of rheumatoid arthritis (RA) in adults. It was then approved for Cryopyrin-Associated Periodic Syndromes (CAPS) in 2013 and Still's disease in 2018 in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above.

Since the introduction of anakinra in 2002 in the EU for the treatment of RA, a number of inflammatory disorders have been found to benefit from IL-1 inhibition. Although not approved for the treatment of FMF, there are numerous publications since more than a decade from several countries, reporting the usefulness of anakinra in FMF.

[5] Ozen S, Demirkaya E, Erer B, Livneh A, Ben-Chetrit E, Giancane G, et al. EULAR recommendations for the management of familial Mediterranean fever. Ann Rheum Dis. 2016;75(4):644-51.

On October 2019, the MAH applied for an extension of indication for Kineret, under Article 16 of Commission Regulation (EC) No 1234/2008 and Annex II (point 2a).

This proposed indication is for the treatment of Familial Mediterranean Fever (FMF). Kineret should be given in combination with colchicine, if appropriate. The proposed target population is adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or aboveThis application is primarily based on bibliographical data from a randomised, double-blind, placebo-controlled study in patients with FMF (Ben-Zvi et al. 2017)[6].

In addition, the following studies and analysis have been submitted as supportive data:

- Bibliographic data from 12 retrospective uncontrolled clinical studies of anakinra in patients with FMF (Table 1);
- Recent data from an ongoing real-world study conducted at the Tel Hashomer hospital in Israel (interim report);
- Efficacy and safety data in the paediatric population from anakinra treatment of a related hereditary periodic fever syndrome sharing the same pathophysiological features as FMF: CAPS (MAH study report 03-AR-0298 from the pivotal study submitted in support of the CAPS indication);
- MAH´s data from company-sponsored studies of anakinra in other indications;
- Data from MAH's post-marketing safety database in various indications, including FMF.

Studies and case reports describing anakinra treatment of FMF were identified through literature search to further support the application.

The MAH did not receive scientific advice for this application.

2.2. Non-clinical aspects

2.2.1. Introduction

The principal biological action of anakinra is to antagonise the effects of IL-1 cytokines, which is utilised to mitigate the symptoms of IL-1 driven diseases such as FMF. No additional pharmacodynamic studies relating to the proposed indication have been performed. In essence, the pharmacodynamic studies performed show that anakinra efficiently inhibits the action of the cytokines IL-1α and IL-1β. These cytokines are proinflammatory and mediates local and systemic inflammation in rheumatoid arthritis, cryopyrinopathies and other IL-1 driven diseases, e.g. FMF and Still's disease.

An extensive number of safety pharmacology and toxicology studies have been conducted (all included in the original MAA) covering general toxicity, reproductive toxicity, genotoxicity, carcinogenicity (tumour stimulation) and antigenicity/immunotoxicity. All studies were conducted in compliance with GLP.

The application also refers to two studies in juvenile animals also submitted with the procedure (II-0056) for the indications of active Still's disease, Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD) in 2017. One study (GLP compliant) was specifically aimed to

[6] Ben-Zvi I, Kukuy O, Giat E et al. Anakinra for Colchicine-Resistant Familial Mediterranean Fever: A Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis Rheumatol. 2017 Apr;69(4):854-862.

investigate memory and learning function in developing juvenile rats treated with anakinra to support paediatric indications.

2.2.2. Pharmacology

Anakinra is a recombinant protein consisting of 153 amino acids with a molecular mass of 17.3 kDa and almost identical to the naturally occurring nonglycosylated form of human IL-1Ra except for the addition of an N-terminal methionine residue. IL-1Ra is a member of the IL-1 cytokine family. The IL-1 signalling pathway consists of two agonists (IL-1α and IL-1β), two classes of receptors (IL-1RI and IL-1RII), which exist in both membrane bound and soluble forms, and one soluble antagonist (IL-1Ra). The membrane bound IL-1RI present in various types of cells is responsible for the initial signalling action of IL-1α and IL-1β. The circulating receptor antagonist IL-1Ra binds to the type I receptor and antagonises the actions of IL-1α and β by a competitive binding to the receptor without possessing any intrinsic agonist activity. In this way it can suppress the inflammatory processes mediated by IL-1α and IL-1β. The endogenous IL-1 receptor antagonist (IL-1Ra) binds with approximately a 100-fold higher affinity to IL-1RI than to IL-1RII (Dripps et al. 1991)[7].

Anakinra has been demonstrated to be active in animal models of inflammatory diseases, such as rat and guinea pig experimental autoimmune encephalomyelitis models of multiple sclerosis; rat models of stroke and head trauma; mouse models of graft-versus-host disease, corneal allograft survival; and several animal models of arthritis. A more detailed description of the pharmacological and pharmacodynamics properties of anakinra was provided in the original MAA.

IL-1 cytokines are major drivers of many autoinflammatory diseases and the most powerful endogenous pyrogens and potent recruiters and activators of neutrophils and macrophages. Dysregulation of the IL-1 cytokines has been demonstrated to result in the so-called monogenic autoinflammatory disorders such as cryopyrinopathies (CAPS/ Neonatal Onset Multisystem Inflammatory Disease (NOMID)) and FMF.

FMF is an autosomal recessive inherited autoinflammatory disease with mutations in a gene designated MEFV. The MEFV gene encodes a 781 amino acid protein known as pyrin. The majority of the mutations are localised in exon 10, which encodes the B30.2/SPYR domain of the molecule where most recessive mutations associated with FMF are found. Disease-associated mutations produce less of the pyrin protein, i.e. a negative regulator of caspase1, leading to a net increase in mature IL-1β. Indeed, the mutant form of pyrin encoded by the MEFV gene has been shown to enhance inflammation through IL-1β secretion and production. Monocytes from FMF patients with MEFV-mutation stimulated with lipopolysaccharide (LPS) displayed an increased secretion of IL-1β (Omenetti, et al. 2014 - NEW)[8]. Likewise, in a mouse model of FMF (FMF-KI), aberrant caspase-1 activation mediated the maturation and release of IL-1β (Sharma et al. 2017 - NEW)[9]. Mice deficient in pyrin, demonstrate increased maturation and secretion of IL-1β (Chae et al. 2003 - NEW)[10]. In contrast to its biologic homolog IL-1α, IL-1β requires proteolytic cleavage by caspase-1 to become activated.

[7] Dripps, D. J., B. J. Brandhuber, R. C. Thompson and S. P. Eisenberg. "Interleukin-1 (IL-1) receptor antagonist binds to the 80-kDa IL-1 receptor but does not initiate IL-1 signal transduction." J Biol Chem (1991) 266(16): 10331-10336.
[8] Omenetti, A., S. Carta, L. Delfino, A. Martini, M. Gattorno and A. Rubartelli. "Increased NLRP3-dependent interleukin 1beta secretion in patients with familial Mediterranean fever: correlation with MEFV genotype." Ann Rheum Dis (2014) 73(2): 462-469.
[9] Sharma, D., B. R. Sharma, P. Vogel and T.-D. Kanneganti. "IL-1β and Caspase-1 Drive Autoinflammatory Disease Independently of IL-1α or Caspase-8 in a Mouse Model of Familial Mediterranean Fever." The American Journal of Pathology (2017) 187(2): 236-244.
[10] Chae, J. J., H. D. Komarow, J. Cheng, G. Wood. Et al. Kastner."Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and defect in macrophage apoptosis." Mol Cell (2003) 11(3): 591-604.

2.2.3. Pharmacokinetics

No new non-clinical data have been submitted in relation to non-clinical pharmacokinetics which was considered acceptable to the CHMP.

2.2.4. Toxicology

No new toxicology studies were submitted. However, the studies in juvenile animals are summarised here as background information.

Juvenile toxicity study: a feasibility study in the neonatal rat

Study title: Anakinra: A Feasibility Study by Subcutaneous Injection in Rats to Determine the Tolerability of the Proposed High Dose Level and Confirm Feasibility of Once and Twice Daily Dosing (Charles River Study no. 497888).

The objective of this study was to determine the tolerability of the proposed high dose level and confirm feasibility of once and twice daily dosing of anakinra, when administered by s.c. injection to juvenile rats. This study was not conducted in compliance with GLP.

Anakinra was administered to two groups of 4 male and 4 female Sprague-Dawley rat pups in each group, each received anakinra by subcutaneous (SC) injections of 2 mL/kg. The doses of anakinra were 100 mg/kg/day (Group 1) and 200 mg/kg/day (100 mg/kg/bid) (Group 2), respectively. The formulation was used as received, i.e. anakinra drug substance containing 50 mg anakinra/mL. The pups were treated every day from day 4 until day 10 postpartum (Group 1) or until day 19 postpartum (Group 2).

All the animals were observed twice daily for mortality/moribundity and examined for reaction to treatment regularly throughout the day on dosing days. Following completion of dosing, all animals were sacrificed.

There were no clinical signs or effects on body weight in any of the animals administered with anakinra.

The administration of anakinra was well tolerated at dose levels of 100 mg/kg after administration either once or twice daily to juvenile animals.

Juvenile toxicity study: a 6-week neonatal/juvenile study in the rat

Study title: Anakinra: A 6 week neonatal / juvenile study to determine the adverse effects on memory and learning functions in rats after subcutaneous injection followed by a one-month recovery period (Charles River Study no. 498001).

The objective of this study was to determine any adverse effects of anakinra on the learning and memory function when administered by twice daily subcutaneous injections to juvenile rats and after a one moth recovery period. In addition, exposure to anakinra was determined in serum and cerebrospinal fluid (CSF). The study was conducted in compliance with GLP (serum and CSF analysis were performed as non-GLP).

Anakinra was administered to three groups of 20 male and 20 female Sprague-Dawley rat pups, each received anakinra twice daily from Day 7 postpartum until at least Day 44 postpartum (where Day 0 was the day of birth) by SC injections of 2 mL/kg. The daily doses of anakinra were 20, 60 and 200 mg/kg (10, 30 and 100 mg/kg/bid). Control animals received vehicle (10 mM citrate buffer, 140 mM sodium chloride, 0.5 mM EDTA and 0.1% Polysorbate 80, pH 6.5).

The following parameters and endpoints were evaluated in all animals: clinical signs, body weights, multiple Y water maze test (function of learning), and gross necropsy. Two groups of one control and one of high dose animals, 5 males and 5 females in each group, were designated satellite animals, used for collecting brain and liver, serum and CSF samples for later weight measurements and bioanalysis.

The serum levels of anakinra showed that all Group 4 high dose animals treated at 200 mg/kg/day were exposed to anakinra and there was low variability between animals. The anakinra levels in the high dose animals treated at 200 mg/kg/day ranged between 15 and 33 µg/mL with a mean of 22 µg/mL, 2 hours post-dosing. The anakinra levels in CSF from high dose animals ranged between 0.13 and 0.22 µg/mL with a mean of 0.18 µg/mL, i.e. approximately 1 % of the serum levels. There was no anakinra detected in the serum samples or CSF samples of control animals.

Signs of reaction to treatment with anakinra were confined to an increase in the incidence of animals with red staining of the muzzle and a wet muzzle at 60 and 200 mg/kg/day when compared to the controls.

There was no effect of dose administration on body weight gains.

In all anakinra dosed groups, the performance in the Y-maze learning test was similar, both during the treatment period and in the recovery period.

Liver and brain absolute weights in all anakinra dosed animals were comparable to the controls. Brain/body weight ratios in all anakinra dosed animals were also comparable to the controls.

Administration at 200 mg/kg/day in males and 60 or 200 mg/kg/day in females was associated with an increase in non-adverse clinical observations (fur staining and wet fur) which were found to recover after the cessation of dosing. The anakinra-treated animals did not show any signs of adverse effects on the hippocampus-dependent memory and learning function test when compared with vehicle-treated control animals, either on last week of dosing or after a one-month recovery period.

Overall, the administration of anakinra by twice daily SC injection to Sprague-Dawley rats from Day 7 postpartum to at least Day 44 postpartum was in general well tolerated in rats at levels of up to 200 mg/kg/day.

2.2.5. Ecotoxicity/environmental risk assessment

Anakinra is the recombinant form of the human interleukin-1 receptor antagonist (IL-1ra) produced in E coli K12 using recombinant DNA techniques. E coli K12 is non-pathogenic, non-toxigenic, and has an extended history of safe large-scale use. It has also been shown to survive poorly in the environment and is not known to have adverse effects on humans, plants or other microorganisms.

Approval of the application for the addition of a therapeutic indication does not increase the use of the active moiety and does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

Considering the protein nature of anakinra, it is not expected to be stable or remain biologically active in the environment and it is unlikely to pose a risk to the environment even if adding a new therapeutic indication. The absence of an updated ERA is therefore acceptable.

2.2.6. Discussion on non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological characteristics of anakinra have been defined and documented by non-clinical studies in accordance to current practice and regulatory guidelines presented and assessed by CHMP at the time of the MA.

No anakinra related effects were seen in safety pharmacology studies investigating analgesic activity, central/autonomic, cardiovascular, gastrointestinal, or renal functions at that time.

In the present application, no additional pharmacodynamic, pharmacokinetics or toxicology studies relating to the proposed indication have been performed. However, the results of two toxicology studies in juvenile rats were summarised in the non-clinical overview.

The results of the juvenile toxicity study (Study 497888) showed that the administration of anakinra was well tolerated at dose levels of 100 mg/kg after administration either once or twice daily to juvenile animals.

The results of the juvenile toxicity study (Study 498001) showed that the administration of anakinra by twice daily subcutaneous injection was in general well tolerated in rats at levels of up to 200 mg/kg/day. The cognitive performance of the anakinra treated adolescent animals was tested in a multiple Y water maze test. The anakinra-treated animals did not show any signs of adverse effects on the hippocampus-dependent memory and learning function test when compared with vehicle-treated control animals, either on last week of dosing or after a one-month recovery period. The pre-clinical safety data section of the SmPC is considered up to date and no further changes are proposed in this application. This is acceptable to CHMP.

The MAH has provided a justification for not performing any additional ERA studies, due to the active substance being a protein. This is considered acceptable by CHMP.

2.2.7. Conclusion on the non-clinical aspects

No new non-clinical studies have been submitted in this application, which was considered acceptable by the CHMP. The subcutaneous use of anakinra in both the paediatric and the adult population is supported from a non-clinical perspective as per details assessed in previous applications. There were no relevant findings from the non-clinical safety evaluation that indicated any risk of undesired effects in juvenile patients at the proposed dosing regimen.

No environmental studies have been conducted to support the request for the extension of the indication. This is acceptable considering that anakinra is a protein and it is therefore unlikely to be stable or remain biologically active in the environment and pose a risk to the environment even when adding a new therapeutic indication.

The pre-clinical safety data section of the SmPC (section 5.3) remains unchanged.

2.3. Clinical aspects

2.3.1. Introduction

GCP

Not applicable. This application was only supported by literature and therefore no GCP documentation

was required.

- **Tabular overview of clinical studies**

Efficacy data have been collected in a minimum of 200 colchicine-resistant, colchicine-intolerant or amyloidosis patients in 13 published studies, all including at least 5 patients, and in an ongoing interim retrospective real-world study of a cohort of 44 patients treated with anakinra at the Tel Hashomer hospital during the last decade (Table 1).

The assessment of known and potential risks of anakinra treatment in FMF is mainly based on data from the use of anakinra in company sponsored clinical studies in multiple indications and the MAH post-marketing safety database, which includes ICSRs from patients treated for FMF as well as other indications in addition to bibliographic data from studies presented in Table 1.

Table 1 Published efficacy studies in patients with FMF selected according to predefined criteria

Study	Trial location	Study design Study duration	Number of anakinra patients	Colchicine dose	Anakinra dose	Anakinra duration
Prospective randomized double-blind placebo-controlled study						
Ben-Zvi et al. 2017 [6]	Israel	Randomized double-blind placebo-controlled. 4 m.	Anakinra 12 adults Placebo 13 adults	Mean±SD 2.2±0.8 mg/day Mean±SD 2.1±0.5 mg/day	100 mg/day placebo	4 m
Retrospective uncontrolled studies						
Akar et al. 2018[11]	Turkey	Multicenter retrospective chart review Duration > 6 months treatment	151 adults	Mean dosage 1.7 mg/day	100 mg/day in 96.4 % of patients 50 to 300 mg/day in 3.6 % of patients	Mean 19.6 m, (range 6 to 98)
Vitale et al. 2016[12]	Italy	Multicenter retrospective chart review Duration not reported	29 adults 3 children	Not reported	Not reported	Mean±SD 24.34± 27.03 m
Kucuksahin et al. 2017[13]	Turkey	Multicenter retrospective chart review Duration not reported	24 adults	1 to 2 mg/day	100 mg/day	Varies between 2.5 and 36 m
Ozen et al. 2017[14]	International	Multicenter retrospective chart review in patients with ≥1 year of follow-up	20 Age not reported	Not reported	Not reported	Median Anti-IL-1 3.0 m (range 1.0 to 96.0)

[11] Akar S, Cetin P, Kalyoncu U et al. Nationwide Experience With Off-Label Use of Interleukin-1 Targeting Treatment in Familial Mediterranean Fever Patients. Arthritis Care Res (Hoboken). 2018 Jul;70(7):1090-1094.
[12] Vitale A, Insalaco A, Sfriso P, Lopalco G, Emmi G, Cattalini M, et al. A Snapshot on the On-Label and Off-Label Use of the Interleukin-1 Inhibitors in Italy among Rheumatologists and Pediatric Rheumatologists: A Nationwide Multi-Center Retrospective Observational Study. Frontiers in pharmacology. 2016;7:380.
[13] Kucuksahin O, Yildizgoren MT, Ilgen U. Anti-interleukin-1 treatment in 26 patients with refractory familial mediterranean fever. Mod Rheumatol. 2017 Mar;27(2):350-355.
[14] Ozen S, Kuemmerle-Deschner JB, Cimaz R, Livneh A, Quartier P, Kone-Paut I, et al. International Retrospective Chart Review of Treatment Patterns in Severe Familial Mediterranean Fever, Tumor Necrosis Factor Receptor-Associated Periodic Syndrome, and Mevalonate Kinase Deficiency/Hyperimmunoglobulinemia D Syndrome. Arthritis Care & Research. 2017;69(4):578-86.

Study	Trial location	Study design Study duration	Number of anakinra patients	Colchicine dose	Anakinra dose	Anakinra duration
Pecher et al. 2017[15]	German	Single center retrospective chart review Duration not reported	13 adults	2 mg/day	100 mg/day	Median 36 m (range 8 to 64)
Rossi-Semerano et al. 2015[16]	France	Multicenter retrospective chart review between January 2011 to January 2013	13 adults and pediatrics	Not reported	Adults 100 mg/day Pediatrics 1 to 6 mg/kg/day	Median 13 m (IQR 27)
Cetin et al. 2015[17]	Turkey	Multicenter retrospective chart review Duration not reported	12 10 adults 2 pediatrics	Max tolerated dose; median 1.5 mg/day, range 1–3	100 mg/day	Median 14 m (range 4 to 36)
Eroglu et al. 2015[18]	Turkey	Single center retrospective chart review between 2006 and 2013.	11 pediatrics and adults	Median dosage 0.035 mg/kg/day, range 0.03–0.06	1 to 5 mg/kg/day	Median 8 m (range 4 to 60)
Özcakar et al. 2016[19]	Turkey	Single center retrospective chart review Duration not reported	10 2 adults 8 pediatrics	Patients ≥11 years; 2–3 mg/day Patients <11 years; 1.5 mg/day	1 mg/kg/day, max 100 mg/day, reduced to 3 times per week in chronic kidney disease patients.	Median 15 m (range 9 to 40)
Basaran et al. 2015[20]	Turkey	Multicenter retrospective chart review Duration not reported	8 1 adult 7 pediatrics	2 mg/day	1 mg/kg/day, increased to 3 mg/kg/day if needed	Mean 16.1 m[1] (range 3 to 28)
Meinzer at al 2011[21]	France	Multicenter retrospective chart review Duration not reported	6 2 adults 4 pediatrics	1 to 2 mg/day	Adults 100 mg/day Pediatrics 1 mg/kg/day	Median 8 m (range 2 to 18)
Özen et al. 2011[22]	Turkey	Single center retrospective chart review Duration not reported	5 pediatrics and adults	1.5 mg/day	1 to 2 mg/kg/day	Median 9 m (range 2 to 30)

[15] Pecher AC, Igney-Oertel A, Kanz L, Henes J. Treatment of familial Mediterranean fever with anakinra in patients unresponsive to colchicine. Scand J Rheumatol. 2017;46(5):407-9.
[16] Rossi-Semerano L, Fautrel B, Wendling D, Hachulla E, Galeotti C, Semerano L, et al. Tolerance and efficacy of off-label anti-interleukin-1 treatments in France: a nationwide survey. Orphanet Journal of Rare Diseases. 2015;10(1).
[17] Cetin P, Sari I, Sozeri B, Cam O, Birlik M, Akkoc N, et al. Efficacy of interleukin-1 targeting treatments in patients with familial mediterranean Fever. Inflammation. 2015;38(1):27-31.
[18] Eroglu FK, Beşbaş N, Topaloglu R, Ozen S. Treatment of colchicine-resistant Familial Mediterranean fever in children and adolescents. Rheumatology International. 2015;35(10):1733-7.
[19] Özçakar ZB, Özdel S, Yılmaz S. Anti-IL-1 treatment in familial Mediterranean fever and related amyloidosis. Clin Rheumatol. 2016 Feb;35(2):441-6.
[20] Başaran Ö, Uncu N, Çelikel BA, Taktak A, Gür G, Cakar N. Interleukin-1 targeting treatment in familial Mediterranean fever: an experience of pediatric patients. Modern rheumatology. 2015;25(4):621-4.
[21] Meinzer U, Quartier P, Alexandra JF, Hentgen V, Retornaz F, Kone-Paut I. Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. Semin Arthritis Rheum. 2011;41(2):265-71.
[22] Özen S, Bilginer Y, Aktay Ayaz N, Calguneri M. Anti-Interleukin 1 Treatment for Patients with Familial Mediterranean Fever Resistant to Colchicine. The Journal of Rheumatology. 2011;38(3):516-8.

[1] duration for all IL-1 treated patients SD, standard deviation; IQR, interquartile range; m, months; y, years

2.3.2. Pharmacokinetics

All published studies from the literature search related to clinical pharmacology were reviewed. No published studies reporting PK data in FMF patients were identified in the literature search. The MAH has not conducted any PK studies in patients with FMF.

For the evaluation of the immunogenicity data (anti-drug antibody (ADA) formation) in this application, 7 studies in different indications were evaluated.

The PK of anakinra has previously been extensively described in healthy volunteers and in patients (RA, CAPS: Neonatal onset multisystem inflammatory disease (NOMID)/ Chronic infantile neurological, cutaneous and articular syndrome (CINCA), JIA and SJIA) in the original MAA and the application for CAPS including the potential for interactions with other drugs.

The effects of *age* (in adult and paediatric patients), *body weight*, *renal function* (a major potential issue in FMF as a result of amyloidosis in non-adequately treated patients) have also been addressed across indications.

Anakinra PK data summarised in this submission were from healthy subjects and patients who were given anakinra s.c. doses of 1 to 10 mg/kg/day, fixed doses of 30 to 100 mg, or i.v. doses of 1 mg/kg or 70 mg. The age range was 2.26 to 86 years and the body weight 10 to 135 kg.

Absorption

Following s.c. administration of anakinra the bioavailability was complete (95.4 %), the median t_{max} was 4 to 6 hours and the terminal half-life was 5.7 to 8.26 hours, reflecting absorption rate-limited elimination.

Distribution

No new study has been submitted regarding anakinra distribution.

Several publications indicate that anakinra in therapeutic concentrations penetrates the blood-brain-barrier.

Distribution into the CSF was demonstrated in the study submitted in support of the CAPS indication (study 03-AR-0298). The median CSF concentration increased from a baseline value before the first dose of anakinra of 15.7 pg/mL to a Month 3 concentration of 797 pg/mL. Relative to the concentration in serum, the exposure in CSF was low and the median CSF/serum ratio can be calculated to <0.2 %.

Elimination

Renal filtration and proximal tubular cell metabolism account for the majority of the elimination of anakinra. After adjusting for creatinine clearance (CL_{cr}) and body weight, gender and age were not significant factors for the mean plasma clearance.

Dose proportionality and time dependencies

The PK of anakinra was linear within the studied dose range.

The PK of anakinra have been described in other indications and other populations, including CAPS which is a hereditary periodic fever syndrome in many ways comparable to FMF.

It diseases such as RA, CAPS, JIA, and Still's disease (SJIA) may be assumed to be similar in FMF patients is acceptable that the PK results obtained in healthy volunteers and in patients with other inflammatory.

The conclusions and recommendations related to pediatric patients and renal impaired patients with FMF are similar to those in patients with other inflammatory diseases such as RA, CAPS, JIA, and Still's disease (SJIA) and are acceptable.

Special populations

Children

An increased dose-adjusted CL/F (clearance relative to bioavailability) and a decreased exposure have been indicated in paediatric patients. To achieve similar anakinra plasma concentrations, paediatric patients should be dosed by body weight, while paediatric patients with a body weight above 50 kg and adults may be given a fixed dose.

Impaired renal function

A study in chronic renal failure patients undergoing dialysis showed that the mean plasma clearance in subjects with chronic renal failure was reduced to 13 % of the value reported in healthy subjects, suggesting that the kidney is the major organ responsible for the elimination of anakinra. For patients with severe renal impairment (Cl_{cr}<30 mL/min) or end stage renal disease including dialysis the prescribed anakinra dose is recommended to be administered every other day. This recommendation is based on PK data and simulations in subjects with severe renal impairment and end stage renal disease (ESRD).

In another study where anakinra PK was compared in subjects with various degrees of renal impairment, systemic anakinra exposure increased with decreasing renal function following a single s.c. dose of 100 mg anakinra. CL/F reduction was 16 %, 50 %, 70 % and 75 % in subjects with mild, moderate, and severe renal impairment, and subjects with ESRD, respectively, as compared to subjects with normal renal function. With appropriate adjustment of dosage anakinra can be given to patients with severe renal impairment or ESRD.

Ethnicity

FMF is restricted to people of Mediterranean descent. Thus, a comparison of PK across ethnic groups is not relevant for this application and not specifically discussed here.

Pharmacokinetic interaction studies

No new studies to assess drug metabolism and drug interactions in FMF have been performed in addition to those included in the MAA, conducted in healthy volunteers and patients with other diseases.

The formation of cytochrome P450 (CYP450) enzymes is suppressed by increased levels of cytokines (*e.g.*, IL-1) during chronic inflammation. Thus, it may be expected that for an IL-1 receptor antagonist, such as anakinra, the formation of CYP450 enzymes could be increased, *i.e.*, normalised, during treatment. This would be clinically relevant for CYP450 substrates with a narrow therapeutic index. In patients receiving such drugs concomitantly with anakinra, therapeutic monitoring of the effect or drug concentration is recommended, with subsequent adjustment of the individual dose of medical product if necessary.

Anakinra is expected to be used as add-on therapy to colchicine in many cases of FMF. Since colchicine is a CYP3A4 substrate, initiation of anakinra treatment may reduce the blood concentration of colchicine and thereby its clinical effect. However, in the published clinical studies in which anakinra was used as add-on therapy to colchicine, the overall anti-inflammatory effect of anakinra and colchicine increased upon initiating anakinra therapy, as documented by the reduced and normalized levels of inflammatory PD biomarkers SAA, CRP, and Erythrocyte sedimentation rate (ESR).

2.3.3. Pharmacodynamics

Pharmacology data for anakinra originate from the following sources:

- PK studies in healthy volunteers and in patients with inflammatory diseases (RA, CAPS, JIA, and SJIA), including paediatric patients and patients with chronic renal failure.
- Published pharmacodynamics (PD) data in patients with FMF.
- Immunogenicity data (formation of anakinra-ADAs and NAbs) in patients with RA, CAPS, JIA, and SJIA.

Mechanism of action

FMF is caused by mutations in the MEFV gene coding for pyrin, which is a component of the inflammasome functioning in inflammatory response and production of Il-1β. Experimental studies showed that pyrin plays a pivotal role in the regulation of both inflammation and apoptosis, and mutated pyrin leads to full-blown inflammation characterized by excessive IL-1 secretion in FMF. Anakinra is a recombinant form of the naturally occurring IL-1 receptor antagonist, which binds to the interleukin-1 receptor and prevents the activity of the cytokines IL-1α and IL-1β by competitively inhibiting their binding to interleukin-1 receptor type 1, thereby controlling active inflammation.

Primary and secondary pharmacology

PD data were derived from at least 220 adult FMF patients given 100 mg daily s.c. administration of anakinra and at least 12 paediatric FMF patients given 1 to 2 mg/kg daily of anakinra. Duration of anakinra treatment was a few months in most studies ranging from a few days up to 98 months.

The inflammatory biomarkers and the biomarkers reflecting renal function in individual studies are summarised in Table 2.

Table 2 Summary table of the publications with including inflammatory and renal biomarker data in patients with Familial Mediterranean fever following treatment with anakinra or anti-interleukin-1 treatment

Study/Author	Population	Inflammatory biomarkers			Renal biomarkers		
	Number of patients[1)]	CRP	ESR	SAA	Total protein	Serum albumin	24h urinary protein excretion
Prospective, randomized, double-blind, placebo-controlled studies							
Ben-Zvi et al. 2017 [6]	Adult patients n=12	√		√			
Retrospective uncontrolled studies							
Akar et al. 2018[11]	Adult patients n=151 (172)	√	√				√
Alpay N et al. 2012[23]	Adult patient n=1	√					
Basaran et al. 2015[20]	Adult and pediatric patients, n=4	√	√				
Cetin P et al. 2015[17]	Adult and pediatric patients, n=12	√	√				
Eroglu FK et al. 2015[18]	Adult and pediatric patients, n=5	√		√			
Kucuksahin et al. 2017[13]	Adult patient n=24 (26)	√	√	√			
Pecher A-C et al. 2017 [15]	Adult patients n=13	√		√			
Roldan R et al. 2008[24]	Pediatric patients n=1	√	√				
Stojanovic KS et al. 2012[25]	Adult patients n=3	√					

[23] Alpay N, Sumnu A, Caliskan Y, Yazici H, Turkmen A, Gul A. Efficacy of anakinra treatment in a patient with colchicine-resistant familial Mediterranean fever. Rheumatol Int. 2012;32(10):3277-9.
[24] Roldan R, Ruiz AM, Miranda MD, Collantes E. Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine. Joint Bone Spine. 2008;75(4):504-5.
[25] Stankovic Stojanovic K, Delmas Y, Torres PU, Peltier J, Pelle G, Jeru I, et al. Dramatic beneficial effect of interleukin-1 inhibitor treatment in patients with familial Mediterranean fever complicated with amyloidosis and renal failure. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2012;27(5):1898-901.

Varan Ö et al. 2018[26]	Adult patients n=9 (16)	√	√	√		√	√
Özçakar ZB et al. 2014[27]	Adult and pediatric patients, n=4	√	√	√	√	√	√

[1)] In studies where anti-interleukin-1 treatment were administered including both anakinra and canakinumab, the number of anakinra treated patients are presented as well as the total number of patients in the study. Results in these studies are presented for the total population (anakinra and canakinumab treated patients), since anakinra results are not presented separately in these publications. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SAA, Serum amyloid A.

Inflammatory biomarkers were used as PD parameters in all 12 studies evaluating PD and renal biomarkers in 3 of these studies evaluating PD. A total of 239 patients received anakinra in the 12 published studies with PD data in patients with FMF. In three studies, 30 out of 214 patients received another IL-1-blocker (canakinumab); the results do not distinguish between treatment with canakinumab or with anakinra, however the vast majority of patients (184 of 214) received anakinra treatment, so the results can generally be attributed to anakinra.

In the randomised, double-blind, placebo-controlled study (Ben-Zvi et al. 2017) in patients with colchicine-resistant FMF defined as experiencing at least 1 attack per month in any of the FMF sites despite having received a maximal tolerated dose of colchicine. The inflammatory biomarkers CRP and SAA were measured before and at the end of treatment with study drugs. Daily administration of anakinra 100 mg for 4 months in 12 adult patients with colchicine-resistant FMF reduced inflammation as seen by lowering of CRP and SAA levels.

Table 3 Inflammatory biomarkers CRP and SAA. Results presented as mean ± SD

	Anakinra 100 mg/kg (n=12)		**Placebo (n=13)**		**p-value [1)]**
	Baseline	**4 months**	**Baseline**	**4 months**	
CRP (mg/L)	23.3 ± 38.2	3.9 ± 3.6 (n=10)	43.5 ± 54.2	19.9 ±18 (n=10)	0.069
SAA (mg/L)	104.1 ± 186 (n=11)	11.1 ± 19.1 (n=10)	218.5 ± 368.2	110.3 ± 131 (n=6)	0.069

Source: Ben-Zvi et al. 2017

Abbreviations: CRP, C-reactive protein; SAA, serum amyloid A

[1)] Comparison of mean values at study termination (4 months)

In the retrospective study with review of 172 FMF patients (Akar et al. 2018) the majority (88%) of patients received anakinra and 12 % received canakinumab. Following at least 6 months anti-IL-1 treatment, the inflammatory biomarkers CRP and ESR were statistically significantly reduced. The urinary protein excretion was statistically significantly reduced with a reduced number of patients with proteinuria.

[26] Varan O, Kucuk H, Tufan A. Anakinra for the treatment of familial Mediterranean feverassociated spondyloarthritis. Scandinavian Journal of Rheumatology. 2016;45(3):252-3.
[27] Ozcakar ZB, Ozdel S, Yilmaz S, Kurt-Sukur ED, Ekim M, Yalcinkaya F. Anti-IL-1 treatment in familial Mediterranean fever and related amyloidosis. Clinical rheumatology. 2016;35(2):441-6.

Table 4 Change of biomarkers CRP, ESR and 24-hour urinary protein before and after anti-interleukin-1 treatment

	Before anti-interleukin-1 treatment	After anti-interleukin-1 treatment	p-value
CRP levels (mg/L)	49.4 (0.0-220)	9.3 (0-110)	<0.001
ESR (mm/h)	43.2 (2-129)	18.7 (0-154)	<0.001
24-hour urinary protein (mg)	5458.7 (550-19 610)	3557.3 (0-18 500)	<0.001

Source: Akar et al. 2018

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

A total of 44 colchicine-resistant FMF patients were included in the interim report from the ongoing retrospective study at the Tel Hashomer hospital, Israel. Median CRP decreased from 14.8 mg/dL (IQR 2.5 to 71.2) before treatment to 2.3 mg/dL (IQR 0.5 to 13) during treatment, and median ESR decreased from 37 mm/hr (IQR 10.75 to 53.75) to 17 mm/hr. (IQR 10.5 to 13.9).

The effect of anakinra in FMF patients on PD biomarkers has been summarised in Table 5 and Table 6.

Table 5 Summary table of inflammatory biomarker data in patients with Familial Mediterranean fever before and after treatment with anakinra or anti-interleukin-1 treatment

Publication Population	No of patients[1] on anakinra (anti-IL-1)1) Treatment duration (m)	Age (y) Mean/ median[2] (SD/range)	Inflammatory biomarkers[2]					
			Before anakinra treatment			After anakinra treatment		
			CRP levels (mg/L)	ESR (mm/h)	SAA (mg/L)	CRP levels (mg/L)	ESR (mm/h)	SAA (mg/L)
Ben-Zvi et al. Adults	n=12 4 m	38.4 (10)	23.3 (38.2)		104.1 (186)	3.9 (3.6)		11.1 (19.1)
Akar et al. Adults	n=151(172)1) 6-98 m	Mean 36.2 (18-68)	49.4 (0.0-220)	43.2 (2-129)		9.3 (0-110)	18.7 (0-154)	
Alpay et al. Adults	n=1 ≈1.5 m	52	102			≈ 5		

Publication Population	No of patients[1)] on anakinra (anti-IL-1)1) Treatment duration (m)	Age (y) Mean/ median[2)] (SD/range)	Inflammatory biomarkers[2)]					
			Before anakinra treatment			After anakinra treatment		
			CRP levels (mg/L)	ESR (mm/h)	SAA (mg/L)	CRP levels (mg/L)	ESR (mm/h)	SAA (mg/L)
Basaran et al. Pediatrics	n=4 4-14 m	(16-18)	(1.47-9.72)	(27-44)		(0.14-0.7)	(5-14)	
Cetin et al. Adults n=10 pediatrics n=2	n=12 6-98 m	31 (14-50)	43.3 (5-195)	42 (8-110)		5 (0.7-53)	14 (5-100)	
Eroglu et al. Adults and pediatrics	n=5 4-60 m	13.2 (2-24)	n=4 (1-12)		n=1 43	n=4 (0.1-1.2)		n=1 6
Kucuksahin et al. Adults	n=24 (26) 1) 3-36 m	(20-57)	89.6 (42.1)	80.1 (21.3)	9.0 (4.7)	6.8 (5.2)	17.2 (0.3)	0.9 (0.8)
Pecher et al. Adults	n=13 6 m	31 (19-49)	4.1 (0.7-25.8) [3)]		138 (6-1460)	0.3 (0.0-2.2) [3)]		4.3 (1-177)
Roldan et al. Pediatrics	n=1 1w	9	168	95		1.5	3	
Stojanovic et al. Adults	n=3 5 d to 3 m	(27-61)	(45-189)			(1-6)		
Varan et al. Adults	n=9 (16) 1) 3-58 m	39 (25-59)	15.85 (2.11-82)	52 (9-92)		3.63 (1-37)	21 (8-51)	
Özçakar et al. Pediatrics	n=4 9-23 m	(6.5-18)	(11-120)	(53-69)		(0.6-8.0)	(15-28)	

[1)] In studies where anti-interleukin-1 treatment were administered including both anakinra and canakinumab, the number of anakinra treated patients are presented as well as the total number of patients in the study. Results in these studies are presented for the total population (anakinra and canakinumab treated patients), since anakinra results are not presented separately in these publications.

[2)] Results are presented as median (min-max), (min-max), mean (SD), except for Akar et al. presented as mean

(min-max) and except for studies with only one individual value

[3)] mg/dl. Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SAA, serum amyloid A.

Table 6 Summary table of renal function biomarker data in patients with Familial Mediterranean fever before and after treatment with anakinra or anti-interleukin-1 treatment

Publication Population	No of patients on anakinra[1)] (anti-IL-1) Treatment duration (m)	Age (y) Mean/ median (SD/range)	Renal function biomarkers					
			Total protein (g/dl)	Serum albumin (g/dl)	24-h urinary protein excretion (mg/m²/h)	Total protein (g/dl)	Serum albumin (g/dl)	24-h urinary protein excretion (mg/m²/h)
Akar et al.[2)] Adults	n=47 6-98m	36.2 (18-68)			5458.7 (550-19 610)			3557.3 (0-18 500)
Varan et al. [2)] Adults	n=6(10) [1)] 3-58 m	39 (25-59)		3.85 (2.8-4.6)	1606 (244-7822)		4.1 (3.0-4.12)	519 (93-4293)
Özçakar et al. Paediatrics	n=1 12 m	14	3.4	0.8	190	5.8	3.4	12

[1)] In studies where anti-interleukin-1 treatment were administered including both anakinra and canakinumab, the number of anakinra treated patients are presented as well as the total number of patients in the study. Results in these studies are presented for the total population (anakinra and canakinumab treated patients), since anakinra results are not presented separately in these publications.

Biomarker results are presented as mean (min-max) in Akar et al. and as median (min-max) in Varan et al.
Abbreviations: Anti-IL-1, anti-interleukin-1.

The studies and case reports included in the submission showed that the inflammatory PD biomarkers CRP, ESR and SAA were decreased and normalised following anakinra treatment in FMF patients, supporting the mechanism of action of anakinra in FMF.

The effect of anakinra treatment in FMF patients with amyloidosis on the renal biomarkers serum albumin and 24-h urine protein excretion support the renal preservative effect of anakinra in these patients.

Immunogenicity

The immunogenicity of anakinra was not evaluated in patients with FMF in any published studies identified in the literature search, or in any internal study.

ADA and NAb data were derived from company-sponsored clinical studies, including patients with JIA, SJIA, RA, and CAPS (CAPS patients not tested for NAb) who were given anakinra s.c. daily doses of 0.04 mg/kg to 5.2 mg/kg.

During the blinded phase of a study in patients with JIA including SJIA patients (following a 12-week open-label treatment with anakinra), 72 % of patients in the anakinra group and 44 % patients of

patients in the placebo group were ADA-positive. No patient treated with anakinra tested positive for NAbs. No ADA-related trends were observed in the rate and occurrence of AEs. Among the patients with SJIA, 71.4 % of the patients in the anakinra group (and no patients in the placebo group) were ADA-positive. No patient tested positive for NAbs.

Anakinra-ADAs were reported in 3 studies in patients with RA, for 2.5 %, 51.1 %, and 60.5 % of patients in each study. Among these, 0.3 %, 1.9 % and 3.3 % of patients in each study tested positive for NAbs.

In study 03-AR-0298 (submitted in support of the CAPS indication), ADA occurrence as well as the impact on various outcome measures, were estimated in patients with severe CAPS.

Anakinra ADA assessments were made at Month 1, 3, 6 and then every 6 months until Month 60. No patient had anakinra ADAs at baseline. The proportion of patients with antibodies at least once post-baseline was 82.5 %. During the first 36 months, the proportion of patients with antibodies (ADA+) ranged from 42.9 % (Month 1) to 78.6 % (Month 3). The number and proportion of patients with anakinra ADA at baseline, at the time point when the highest proportion of ADA+ patients was observed (Month 3), and the end of the study (Month 60) is shown in Table 7. At the end of study, 50 % of the patients were ADA+.

Table 7 Number and proportion of patients with anakinra ADA by visit (Safety population)

Parameter	Baseline	Month 3	Month 54	Month 60
n/N	0/32	22/28	3/9	3/6
ADA+ (%)	0	78.6	33.3	50.0

Source: Report ADA 03-AR-0298 synopsis and Table 2. ADA, anti-drug antibodies; ADA+, anakinra anti-drug antibodies present; N=total number of patients, n=number of ADA-positive patients.

During the CAPS study there was no consistent trend for dose modifications, change in DSSS (Disease Diary Symptom Sum Score) or treatment-emergent AEs for ADA- and ADA+ patients. Thus, the majority of the patients with CAPS on anakinra treatment for up to 5 years developed transient or persistent anakinra ADAs. Anakinra ADA was not associated with clinical adverse reactions, diminished efficacy or changed PK. All patients with CAPS responded favorably to treatment.

Dose recommendations in FMF

Adult patients

The anakinra dose recommended for adults is 100 mg/day and is based on published data in patients with FMF, including the recently published double-blind, placebo-controlled, randomized study in FMF (Ben-Zvi et al. 2017).

In these publications, including > 220 adult patients with FMF, anakinra at a daily dose of 100 mg resulted in clinically relevant response, reduced and normalized levels of inflammatory biomarkers CRP, ESR and SAA and was well tolerated. 100 mg/day is also the approved dose for the RA indication and for Still´s disease in the EU.

The 100 mg/day was also the dose given to 41 of the 44 patients at the Tel Hashomer hospital (Kivity 2018, Interim report) which resulted in a clinically relevant response, reduced and normalised levels of inflammatory biomarkers CRP and ESR and was well tolerated in the majority of patients.

Paediatric patients

In paediatric patients with FMF (body weight < 50 kg) anakinra 1 to 2 mg/kg once daily is recommended. This dose level is based on 9 publications including a total of > 40 children, where 1 to 2 mg/kg/day has been shown to provide a clinically relevant response, to reduce and normalise levels of inflammatory biomarkers CRP and ESR and to be well tolerated. Anakinra 1 to 2 mg/kg/day is also the approved starting dose in CAPS, with a maximum daily dose of 8 mg/kg. Once daily dosing of 1 to 2 mg/kg with a maximum dose of 4 mg/kg is approved in EU for Still´s disease.

Patients with renal impairment

For patients with severe renal impairment (defined as Cl_{cr} < 30 mL/min, as estimated from serum creatinine levels) or end stage renal disease including dialysis the prescribed anakinra dose is recommended to be administered every other day. This recommendation is based on PK data and simulations in subjects with severe renal impairment and end stage renal disease.

The maximum tolerated dose of anakinra has not been established. No dose limiting toxicities were observed during clinical trials in patients with RA and CAPS. The highest doses reported have been given in an investigator sponsored clinical study of anakinra in subarachnoidal haemorrhage. In total 6 patients were given anakinra as an i.v. bolus of 500 mg over 1 minute, immediately followed by a 10 mg/kg/hr infusion over 24 hours. There were no new or unexpected AEs, and no SAEs considered related to anakinra treatment by either the investigator or the MAH.

2.3.4. Discussion on clinical pharmacology

This submission is based on bibliographic data only.

No new PK data have been submitted and no PK data are available in patients with FMF. However, the PK of anakinra has been investigated in both adults and children down to 8 months of age and >10 kg in other inflammatory indications, including CAPS - a related hereditary periodic fever syndrome - sharing the same pathophysiological features as FMF.

The PK of anakinra is linear and age, body weight and sex are not significant factors for clearance relative to bioavailability (CL/F). A previously assessed Pop PK model has predicted a higher clearance in paediatric subjects and a higher dose compared to adults is needed to reach similar exposure. Renal clearance is a significant factor for CL/F and adjusted dosing is appropriate in subjects with severe renal impairment or ESRD.

It is agreed that no differences in PK is expected across indications, and absence of PK data in FMF is therefore in this case acceptable. PK of anakinra is comparable across indications/populations and extrapolation to FMF is considered acceptable.

Anakinra is approved in children with CAPS from 8 months of age and with a body weight > 10 kg. No additional data in paediatric patients have been submitted but it can be accepted that these age and weight restrictions also apply to the FMF disease indication.

In patients with FMF, mutation of the MEFV gene encoding for pyrin is leading to malfunctioning and overproduction of interleukin-1β (IL-1β) in the FMF inflammasome. Untreated FMF is characterised by increased CRP and SAA. Administration of Kineret results in a decrease in acute phase reactants (e.g. CRP and SAA).

Immunogenicity and formation of ADAs and NAbs have not been investigated in FMF. The incidence of ADAs is high in CAPS, but does not appear to have an impact on efficacy, safety or PK. However, since anti-anakinra antibodies and NAbs were not evaluated in the FMF population the impact of NAbs on

efficacy and safety, is therefore unknown. Even so, as it is not expected that patients with FMF will react differently than CAPS patients or patients with JIA, SJIA, RA, especially in terms of immunogenicity, and as there is also no indication that ADAs against anakinra cross-react with endogenous IL-1Ra in patients it is agreed that this concern is only reflected in RMP. RMP section SVII.3.1 Presentation of important identified risks and important potential risks is updated accordingly with the information that no immunogenicity studies have been performed in FMF patients but due to similarities of FMF with other periodic fever syndromes, there are no indications that FMF patients react differently than patients with the approved indications.

No dose finding study has been conducted in FMF. In most of the published studies included to support the submission, a dose of 100 mg/day anakinra in adult and 1 to 2 mg/kg/day in paediatric subjects (children weighing less than 50 kg) had been administered. In children with inadequate response the dose can be escalated up to 4 mg/kg/day.

In previous anakinra submissions, dosing every other day has been approved in subjects with severe renal impairment or ESRD. This also applies to FMF

2.3.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology has been adequately described, mainly by data previously submitted in other inflammatory indications, to support the use of anakinra in FMF including the proposed dose.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response studies are included in this application. The proposed dose is discussed in the clinical pharmacology sections.

2.4.2. Main study

Anakinra for Colchicine-Resistant Familial Mediterranean Fever (Ben-Zvi et al 2017)

Methods

Design

The main study was single-centre, randomised, double-blind, and placebo-controlled over a treatment period of 4 months.

Study participants

Patients enrolled in the study were adults with FMF (age range ≥18 years to ≤65 years) who were diagnosed according to the Tel Hashomer criteria. They were carriers of at least 2 MEFV mutations and had experienced at least 1 attack per month in any of the 4 FMF sites (abdomen, chest, joints, skin) despite having received a maximal tolerated dose of colchicine (dosage ≥2 to ≤3 mg/day). The FMF

was thereby defined as colchicine-resistant. Patients intolerant to these dose levels of colchicine (with intolerance mainly manifested as symptoms of diarrhoea or abdominal upset or both) were included if their dosage was at least 1.5 mg/day. The patients continued colchicine treatment during the study.

Treatments

The study duration was 4 months. The patients received either anakinra or placebo as a daily self-administered subcutaneous injection of 100 mg/day from prefilled syringes. Concomitant colchicine treatment was 2.1-2.2 mg/day. In both placebo and anakinra group, 92 % took other (unspecified) concomitant mediations during the trial.

Objectives

Primary efficacy outcomes were number of attacks per month, and number of patients with a mean of <1 attack per month.

Febrile manifestations reported by patients were considered to be attacks only if they met the criteria defining attacks, and were confirmed by one of the study team members. The criteria defining an attack included all of the following symptoms: fever of ≥38°C lasting 6 hours to 7 days accompanied by painful manifestations in either the abdomen (with features consistent with a diagnosis of peritonitis), the chest (with features consistent with a diagnosis of pleuritis), the joints (with features consistent with a diagnosis of lower extremity large joint monoarthritis), or the skin (with features consistent with a diagnosis of erysipeloid rash).

The secondary efficacy outcomes included the number of attacks per FMF site, levels of acute phase reactants, quality of life (QoL) as assessed using a 10-cm VAS, and the use of analgesic agents.

Two post hoc analyses were also performed:

- Survival analysis with an endpoint of 4 attacks. The 4-attack target was based on the main inclusion criterion: at least 1 attack per month multiplied by 4 months (study duration).
- Proportion of patients who achieved improvement with anakinra or placebo treatment, according to the modified familial FMF50 score. The calculation was based on the percentages of patients with ≥3 of the 4 following items change of at least 50 %; 1) the total number of attacks, 2) number of joint attacks, 3) CRP and SAA levels (or reaching normal values, defined as ≤5 mg/L for CRP and ≤10 mg/L for SAA), 4) and quality of life rating.

Outcomes/endpoints

Sample size

From the published paper: *Originally, based on the assumption of a mean of 2.5 attacks per patient per month at baseline and a rate of 50% improvement with anakinra treatment, a sample size of 20 patients per group was calculated to allow for detection of the differences between the anakinra and placebo groups with a power of 90% (using nQuery Advisor, version 2.1). However, due to slow enrolment and based on actual data, an interim analysis with re-evaluation of the sample size was performed. At this point, the evaluation was based on the actual mean of 5 attacks per patient per month at baseline, with a group mean of 1.66 attacks per patient per month in the anakinra group and 3.49 attacks per patient per month in the placebo group, and a common standard deviation of 1.55,*

which led to a calculated sample size requirement of 12 patients per group, to allow for detection of differences between the anakinra and placebo groups with a power of 80%

Randomisation and blinding

From the published paper: *Patients were recruited consecutively (by order of arrival) from our FMF-dedicated clinic, and were randomly assigned, in a blinded manner, to receive treatment with either anakinra or placebo. Assignment to either the anakinra group or the placebo group was based on a predetermined key, unknown to both the investigators and the patients, that was established by an external company (TFS Trial Form Support, Lund, Sweden). The randomization was stratified by sex. During the study, patients continued to receive the treatments they had been taking prior to the study, particularly colchicine. Analgesic drugs used prior to recruitment were allowed as needed, but their use was monitored.*

Statistical methods

From the published paper: *Primary and secondary study outcomes were determined by comparing the mean values between the groups at study termination. Due to the small sample size, statistical analysis was based on the nonparametric Wilcoxon–Mann-Whitney rank sum test and the median test for quantitative parameters. The chi-square test was used for data classified as categorical. A Kaplan-Meier survival function curve analysis was performed using the log-rank test. Analyses were performed using 2-tailed tests. P values less than or equal to 0.05 were considered statistically significant. Because of dropouts, differences in the total number of attacks, number of attacks per site, number of AEs, and use of analgesics between the anakinra and placebo groups over the study period were adjusted for the actual time of patient participation in the study, and differences in levels of acute-phase reactants and QoL between the groups were based on the last value available.*

Results

Participant flow

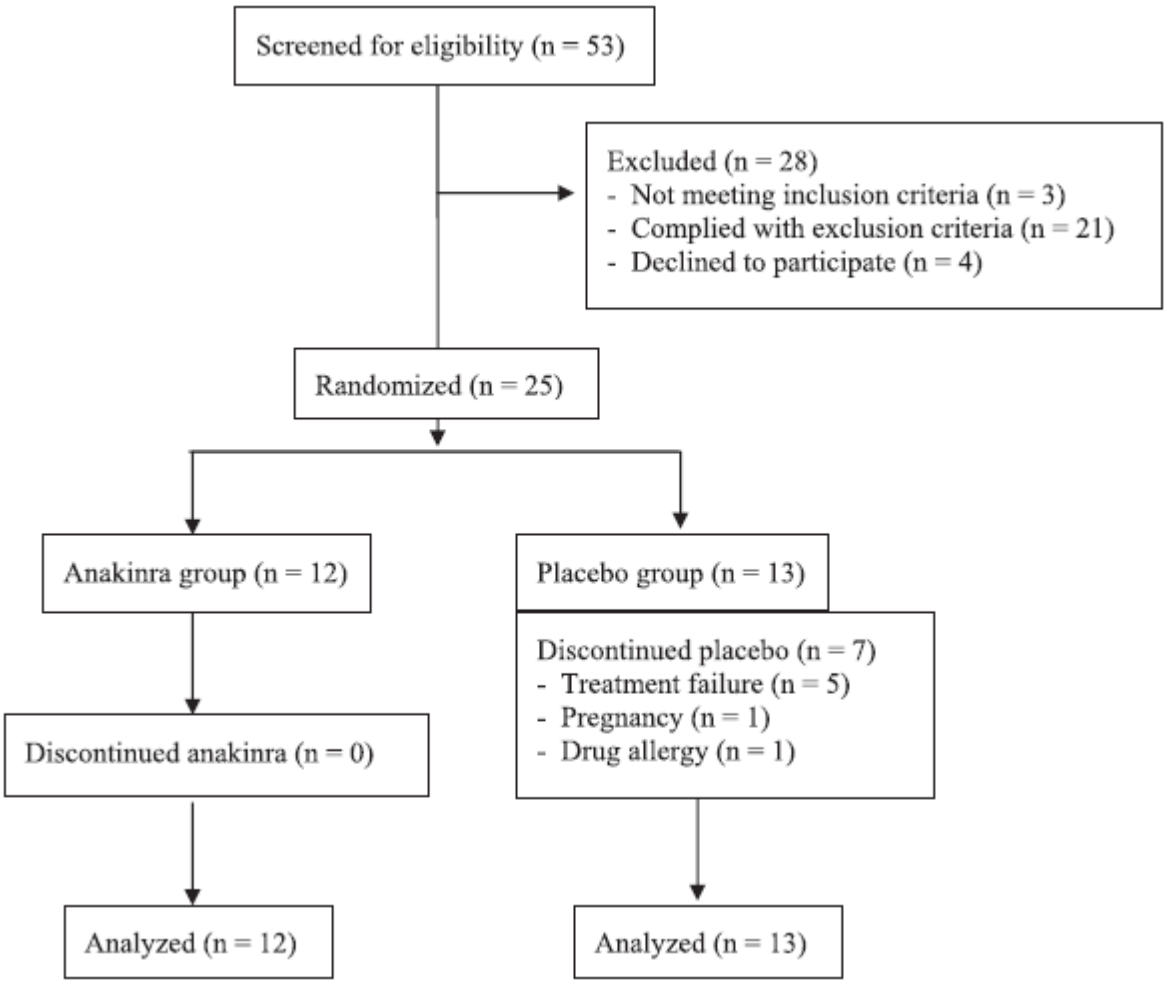


Figure 2 Participant flow

Recruitment

Patients were recruited consecutively (by order of arrival) from the FMF-dedicated clinic.

Conduct of the study

From the published paper: *Physician examination was performed at the time of randomization, at the termination visit (mandatory), and during other study site visits, if required. Baseline parameters, including the physical examination findings, detailed medical history, mean number of attacks and body sites involved, and QoL evaluation, were obtained by the physician during the initial visit. QoL was also assessed at study termination. The study nurse communicated weekly with the patients by telephone, and patients visited the study site clinic twice (on days 30 and 60) for close monitoring of patient compliance, assistance with the interpretation of symptoms as attacks, and for guidance and care for AEs, including injection site reaction. Patients were encouraged to call the nurse and visit the study site, as necessary. Laboratory tests (blood and urine) and pregnancy tests were performed at each study site visit (on days 0, 30, 60, and 120). Two poststudy telephone calls by the study nurse were scheduled for days 150 and 180, to assess the development of long-term AEs. All study data were recorded in case report forms, including data transferred from patient diaries.*

Baseline data

In total, 25 patients with colchicine-resistant FMF (14 women) were enrolled; 12 randomised to receive anakinra and 13 to receive placebo. At randomisation, the patient groups were generally comparable in aspects relevant to evaluation of treatment effects (Table 8).

Table 8 Baseline characteristics of the patients

Parameter	Anakinra (n=12)	Placebo (n=13)
Sex, % female	58	54
Age, years	38.4 ±10	36.1 ±12.4
Colchicine dosage, mg/day	2.2 ±0.8	2.1 ±0.5
Attacks prior to intervention, total no. per patient per month	4.6 ±4.3	5 ±2.5
Abdominal attacks, no. per patient per month	2.1 ±1.6 (n=11)	1.7 ±1.8 (n=12)
Chest attacks, no. per patient per month	1.5 ±1.6 (n=10)	1.4 ±1.5 (n=12)
Joint attacks, no. per patient per month	3 ±3.7 (n=11)	2.7 ±2.4 (n=11)
Skin attacks, no. per patient per month	5.1 ±6.9 (n=2)	1.1 ±1.3 (n=4)
ESR, mm/hour	27.1 ±15 (n=12)	33.8 ±15.4 (n=10)
CRP, mg/L	23.3 ±38.2 (n=12)	43.5 ±54.2 (n=13)
SAA, mg/L	104.1 ±186 (n=11)	218.5 ±368.2 (n=13)
Homozygous M694V MEFV genotype, % of patients	83	70
QoL score on 10-cm VAS	4 ±2.3	3.9 ±1.5
Serious comorbidities, no.	4 (n=3)[1]	3 (n=2)[2]
Concomitant medications other than colchicine, % of patients	92	92

Source: Ben-Zvi et al. 2017
Numbers in parentheses denote patients included in the analysis if different from the original number. Analysis for the specific attacks was performed only for patients experiencing attacks in the indicated sites.
Except where indicated otherwise, values are the mean ±SD. ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SAA, serum amyloid A; QoL, quality of life; VAS, visual analog scale.
[1] Tachycardia, paroxysmal atrial fibrillation, transient ischemic attack.
[2] Status post bacterial endocarditis and aortic regurgitation, episodic vertigo, panic attacks.

Numbers analysed

All randomised patients were included in the analysis.

Outcomes and estimation

The mean number of attacks per patient per month was statistically significantly lower (p=0.037) in those receiving anakinra (1.7) compared to placebo (3.5). The number of patients with <1 attack per month was significantly higher in the anakinra group; 6 patients, compared to none in the placebo group (p=0.005) (Table 9). In the anakinra group, 7 patients had a >90 % reduction in their stated attack frequency, while the frequency of attacks improved to a lesser degree in 5 patients. The difference between the anakinra and placebo groups in the individual sites reached statistical significance only for attacks in the joints (mean 0.8 and 2.1 respectively; p=0.019) indicating that the difference in mean total number of attacks was mainly driven by the lower number of attacks in the joints.

A beneficial effect of anakinra was also noted in QoL (mean VAS score 7.7 in the anakinra group versus 4.2 in the placebo group; p=0.045) (Table 9).

Numerically lower CRP (3.9 versus 19.9 mg/L) and SAA (11.1 versus 110.3 mg/L) were noted for the anakinra treated patients at the last measurement compared to placebo (Table 9).

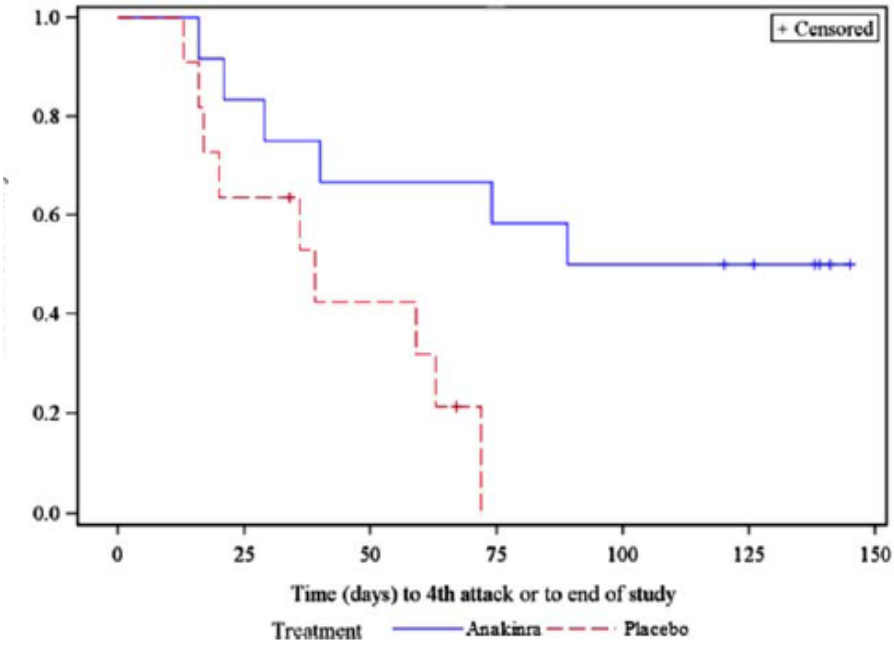
Table 9 Primary and secondary efficacy outcomes

Parameter	Anakinra (n=12)	Placebo (n=13)	p
Primary outcomes			
Attacks in any site per month	1.7 ±1.7 (n=12)	3.5 ±1.9 (n=11)	0.037
No. of patients with <1 attack per month	6	0	0.005
Secondary outcomes			
Abdominal attacks per month	1 ±1.2 (n=11)	1.4 ±1.1 (n=10)	0.38
Chest attacks per month	0.7 ±0.8 (n=10)	1.6 ±1.4 (n=9)	0.3
Joint attacks per month	0.8 ±1.6 (n=11)	2.1 ±1.1 (n=9)	0.019
Skin attacks per month	0 (n=2)	0.3 ±0.6 (n=3)	–
CRP, last measurement, mg/L	3.9 ±3.6 (n=10)	19.9 ±18 (n=10)	0.069
SAA, last measurement, mg/L	11.1 ±19.1 (n=10)	110.3 ±131 (n=6)	0.069
QoL score, 10-cm VAS	7.7 ±2.3 (n=12)	4.2 ±2.9 (n=6)	0.045

Source: Ben-Zvi et al. 2017
Numbers in parentheses denote patients included in the analysis if different from the original number. Analysis for the specific attacks was performed only for patients experiencing attacks in the indicated sites.
Except where indicated otherwise, values are the mean ±SD. CRP, C-reactive protein; SAA, serum amyloid A; QoL, quality of life; VAS, visual analog scale.

Ancillary analyses

The post hoc survival analysis showed that the placebo-treated patients reached the target of 4 attacks significantly faster than the anakinra-treated patients (p=0.015 for difference in survival probability between groups, mean ±SD 39.6 ±22.2 days vs. 89.8 ±51.6 days) (Figure 3).

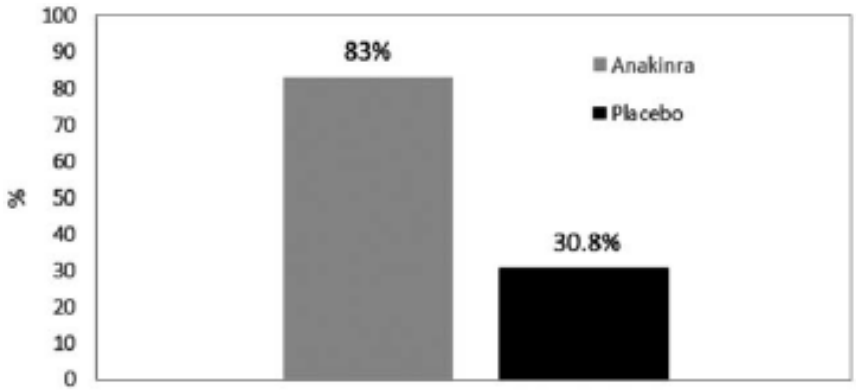


Source: Ben-Zvi et al. 2017

Figure 3 Survival analysis with an endpoint of 4 attacks

The 4-attack target is based on the main inclusion criterion: at least 1 attack per month multiplied by 4 months (study duration).

The second post hoc analysis using the modified FMF50 tool showed that 10 of 12 patients in the anakinra group and 4 of 13 patients in the placebo group achieved the modified FMF50 criteria defining improvement (P<0.008) (Figure 4).



Source: Ben-Zvi et al. 2017

Figure 4 Proportion of patients who achieved improvement with anakinra or placebo treatment, according to modified FMF50 score

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10 Summary of Efficacy for trial Anakinra for Colchicine-Resistant Familial Mediterranean Fever (Ben-Zvi et al. 2017)

Title: Anakinra for Colchicine-Resistant Familial Mediterranean Fever (Ben-Zvi et al. 2017)			
Study identifier	Ben-Zvi et al. 2017		
Design	Double blind placebo-controlled trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		4 months not applicable not applicable
Hypothesis	Exploratory: co-administration in patient resistant to Colchicine		
Treatments groups	Anakinra		Anakinra 100 mg/day s.c. injection self-administered, 12 patients
	Placebo		Placebo, daily self-administered s.c. injection, 13 patients
Endpoints and definitions	Primary endpoint	number of attacks per month number of patients with a mean of <1 attack per month	Criteria defining an attack included all of the following symptoms: fever of ⩾38°C lasting 6 hours to 7 days accompanied by painful manifestations in either the abdomen (with features consistent with a diagnosis of peritonitis), the chest (with features consistent with a diagnosis of pleuritis), the joints (with features consistent with a diagnosis of lower extremity large joint monoarthritis), or the skin (with features consistent with a diagnosis of erysipeloid rash).
	Secondary endpoint	number of attacks per FMF site levels of acute phase reactants QoL use of analgesic agents	Two post hoc analyses were also performed: - Survival analysis with an endpoint of 4 attacks. The 4-attack target was based on the main inclusion criterion: at least 1 attack per month multiplied by 4 months (study duration). - Proportion of patients who achieved improvement with anakinra or placebo treatment, according to the modified familial FMF50 score. The calculation was based on the percentages of patients with ⩾3 of the 4 following items change of at least 50 %; 1) the total number of attacks, 2) number of joint attacks, 3) CRP and SAA levels (or reaching normal values, defined as ⩽5 mg/L for CRP and ⩽10 mg/L for SAA), 4) and quality of life rating QoL assessed using a 10-cm Visual analog scale (VAS),
Database lock	unknown		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Anakinra	Placebo <group descriptor>
	Number of subject	12 (58% female)	13 (54% female) <n>

	Attacks per months	1.7±1.7 (n=12) P = 0.037	3.5±1.9 (n=11)
	No. patients with < 1 attack per month	6 P= 0.005	0
	Abdominal attacks per month	1.0±1.2 (n=11) P=0.38	1.4±1.1 (n=10)
	Chest attacks per month	0.7±0.8 (n=10) P=0.3	1.6±1.4 (n=9)
	Joint attacks per month	0.8±1.6 (n=11) P=0.019	2.1±1.1 (n=9)
	Skin attacks per month	0 (n=2)	0.3±0.6 (n=3)
	CRP, last measurement (mg/L)	3.9±3.6 (n=10) P=0.069	19.9±18 (n=10)
	SAA, last measurement (mg/L)	11.1±19.1 (n=10) P=0.069	110.3±131 (n=6)
	QoL score, 10-cm VAS	7.7±2.3 (n=12) P=0.045	4.2±2.9 (n=6)
Notes	Patients enrolled were adults with FMF (age range ⩾18 years to ⩽65 years); were carriers of at least 2 MEFV mutations and had experienced at least 1 attack per month in any of the 4 FMF sites (abdomen, chest, joints, skin) despite having received a maximal tolerated dose of colchicine (dosage ⩾2 to ⩽3 mg/day)		

Supportive studies

Retrospective uncontrolled studies

Interim report of an ongoing study with anakinra at the Tel Hashomer hospital in Israel (Kivity 2018)

Methods

The present submission includes an interim report describing 44 patients with FMF who have been treated in a real word data (RWD) study. The study is an ongoing single-centre, retrospective, interview and database study. The primary aim of the study is to investigate the efficiency and safety of Anakinra treatment in colchicine resistant patients in a cohort sample size that has not yet been described in literature.

Each patient was his own control: comparing FMF-related symptoms before and during treatment with anakinra.

Primary outcome

Attacks (fever, abdominal, pleuritic, arthritis, leg exertion) duration and severity, patient assessment global score sum which is defined as: (Attacks per month+ attack duration+ number of attack sites)/3*2

Secondary outcome

Inflammatory markers if tested (Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP)). Side effects (serious and non-serious, related and not-related).

Inclusion criteria

Included patients were diagnosed according to Tel Hashomer criteria for FMF and treated with Anakinra al least >2 months.

Exclusion criteria

- Not treated with anakinra
- Treated with anakinra for another indication
- Patients who are unwilling to participate
- Patients with insufficient data

Results

In total, 44 patients with colchicine-resistant FMF treated with anakinra were identified. The age of the patients at time of the study was 44.02±13.3 years. Thirteen of the 44 patients had proteinuria prior to anakinra treatment initiation, seven with amyloidosis. Colchicine treatment were continued during anakinra treatment. Forty-one patients were treated with Anakinra 100mg daily, and 3 patients were treated with Anakinra 50mg daily.

The duration of Anakinra treatment in the study was 18 months (interquartile range (IQR) 9-24).

The median attacks per months before treatment was 4 (IQR 2-5) and after treatment 1 (IQR 0-2) p <0.001. The median attack duration before treatment was 3 days (IQR 3-3) and after treatment 1 day (IQR 0-2.7), p <0.001. Number of attack sites decreased, also median CRP and ESR values decreased during treatment.

Published retrospective uncontrolled studies

Study design and number of included subjects in the retrospective uncontrolled studies are listed in Table 1. As a rare disease, the FMF patient population is small in an individual country, and it should be noted that the patients in the large Turkish study by Akar et al. 2018 may overlap with some patients in the smaller Turkish studies.

The Akar study is summarised below.

Akar et al. 2018: A nationwide experience with the off-label use of interleukin-1 targeting treatment in familial mediterranean fever patients[11]

Methods

This is the largest of the retrospective studies including 172 patients who received at least 6 months of treatment with an IL-1 receptor antagonist at 21 Turkish centres. A total of 151 patients (88 %) were treated with anakinra and 21 with canakinumab (12 %).

The reason for starting anti–IL-1 treatment was reported in 171 patients; 117 patients (68 %) started due to colchicine-resistant disease, 28 (16 %) due to the development/progression of amyloidosis in addition to colchicine-resistant disease, and 20 patients (12 %) started due the presence or progression of amyloidosis. Only 5 % had colchicine intolerance.

Anakinra was administered as a subcutaneous injection of 100 mg/day in 96.4 % of patients; the remaining patients received 50 to 300 mg/day. The mean dosage of colchicine received was 1.7 mg/day.

Results

Among the 145 patients with colchicine-resistant disease and available efficacy information, the attack frequency was significantly reduced (P < 0.001) from 16.8 attacks/year (range 1 to 60) to 2.4 attacks/year (range 0 to 36). Of the 145 patients, 61 (42.1%) were attack free, and 71 (49.7%) were reported to have attack frequencies of <6 per year during data collection. In 11 patients (8%), the attack rate did not change during anti–IL-1 therapy. In the remaining 2 patients, data for attack frequency after treatment were missing. Univariate analyses showed no significant associations between nonresponse to anti–IL-1 treatment and any of the demographic, disease-related clinical, and laboratory data or the presence of comorbidities other than the baseline attack frequency (r = -0.224, P = 0.003).

Baseline data showed that 47 patients had urinary protein excretion of >500 mg/24 hours before the anti–IL-1 treatment. Anti–IL-1 treatment caused a significant reduction of urinary protein levels among those patients (from baseline 5458.7 mg/24 h [range 550–19 610] to 3557.3 mg/24 hours [range 0 to 18 500]) after treatment. At the end of the observation period, 24-h urinary protein excretion had decreased in 36 of 47 patients (77 %), and 10 patients (21 %) had no significant proteinuria at all.

The authors conclude that the results of their large observational study showed that anti–IL-1 treatment (151 patients treated with anakinra and 21 treated with canakinumab) is an effective alternative treatment in patients resistant to colchicine or in patients with progressing amyloidosis, not only for controlling the attacks, but also in decreasing the proteinuria in colchicine-resistant patients with FMF in routine clinical practice.

During the mean treatment period of 19.6 months (range 6 to 98), yearly attack frequency, serum levels of CRP, ESR, and 24-h urinary protein excretion were significantly reduced (p < 0.001) following anti–IL-1 treatment (Table 11).

Table 11 Change of disease-related clinical and laboratory parameters during anti–IL-1

Parameters	Before treatment[1]	After treatment[1]	p
Attacks/year	16.2 (0–96)	2.3 (0–36)	< 0.001†
CRP level, mg/L	49.4 (0.0–220)	9.3 (0–110)	< 0.001†
ESR, mm/hour	43.2 (2–129)	18.7 (0–154)	< 0.001†
24-hour urinary protein, mg	5458.7 (550–19610)	3557.3 (0–18 500)	< 0.001†
Serum creatinine, mg/dL	1.2 (0.3–10.2)	1.1 (0.4–7.7)	0.907

Source: Akar et al. 2018
[1] Values are the mean (range) unless indicated otherwise. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. † Significant.

Comparison and analyses of results across studies

Study population

Both paediatric and adult patients of both sexes intolerant to colchicine or with colchicine-resistant FMF have been treated with anakinra and evaluated in published studies. The age of the anakinra treated

patients included in the published studies varies between 2 and 57 years. In the paediatric population, the majority of patients were older than 6 years old when they started anakinra treatment.

Amyloidosis was the reason for initiation of anakinra in at least 48 patients in the published studies. Disease duration was not consistently reported, but ranged from three to 46 years. In most patients, colchicine was continued during anakinra treatment. The total number of unique patients is estimated to be at least 261 patients, including the patients in the ongoing study.

Characteristics of the anakinra-treated patients with FMF presented in the selected published studies are described in Table 12.

Table 12 Patient characteristics

Study	**Number of patients**	**Age [1] years**	**Disease duration years**	**Resistant/ intolerant to colchicine** (n)	**Resistant to colchicine** (n)	**Intolerant to colchicine** (n)	**Mono- or add on therapy to colchicine** (n)
Prospective randomized double-blind placebo-controlled study							
Ben-Zvi et al. 2017	Anakinra 12 Placebo 13	Mean±SD 38.4±10 Mean±SD 36.1±12.4	Not reported	12 13	Not specified Not specified	Not specified Not specified	12 add on 13 add on
Retrospective uncontrolled studies							
Akar et al. 2018	Total 172 Anakinra 151	Mean age 36.2 (range 18–68)	~.23	171	117 (68 %) 28 (16 %) with amyloidosis in addition to resistance 20 (12 %) amyloidosis 3 other reason	3	Not reported
Vitale et al. 2016	32	29 adults 3 children	Not reported	Not reported	Not specified	Not specified	Not reported
Kucuksahin et al. 2017 (Section 5.3.5.2)	24	Range 20 to 57	Not reported	29[2]	20	7	24 monotherapy
Ozen et al. 2017	20 treated 14 with	Not reported	Not reported	20	Not specified	Not specified	Not reported

Study	Number of patients	Age [1] years	Disease duration years	Resistant/ intolerant to colchicine (n)	Resistant to colchicine (n)	Intolerant to colchicine (n)	Mono- or add on therapy to colchicine (n)
	efficacy data						
Pecher et al. 2017	13	Median 31 (range 19 to 49)	Not reported	13	Not specified	Not specified	Not reported
Rossi-Semerano et al. 2015	13	Median 21.1 (range 5.9 to 60.8)	Median 13.1 (range5.3 to 42.9)	13	Not specified	Not specified	8 add on 5 monotherapy
Cetin et al. 2015	12	Median 31 (range 14 to 50) 2 pediatrics 10 adults	Median 18.5 (range 9 to 46)	12	Not specified	Not specified	12 add on
Eroglu et al. 2015	11	Median 13.2 (range 2 to 24)[3]	Not reported	11	Not specified	Not specified	11 add on
Özcakar et al. 2016	10	Colchicine resistant range 6.5 to 18 Amyloidosis onset range 6 to 13 8 pediatrics 2 adults	Not resported	10	4	Not specified	10 add on
Basaran et al. 2015	8	Range 10.6 to 19 6 pediatrics 2 adults	Not reported	8	Not specified	Not specified	8 add on
Meinzer at al 2011	6	Range 7 to 51 4 pediatrics 2 adults	3 to 6 in children ~20 in adults.	6	4	2	5 add on 1 monotherapy
Özen et al. 2011	5	Median 2 (range 11 to 25)	6 to 10	5	5	0	5 add on

[1] Not specified if this is age at diagnose, included in study, at start of colchicine or anakinra treatment,

[2] There may be more than 1 reason in an individual patient,
[3] Median for 14 IL-1 inhibitor-treated patients

Efficacy results

The efficacy results are summarised in Table 13.

Table 13 Summary of efficacy results

Responders and non-responders during anakinra treatment				**Effect on inflammatory markers**		
Study	**Number of patients[a]**	**Responders[b] % (number)**	**Non-responders % (number)**	**CRP (mg/L)[c]**	**SAA (mg/L)**	**ESR (mm/h)**
Prospective randomized double-blind placebo-controlled study						
Ben-Zvi et al. 2017	12 anakinra/13 placebo	Not reported Mean ± SD attacks per patient per month: anakinra: 1.7 ± 1.7 (n=12); placebo: 3.5 ± 1.9 (n=11); p=0.037[d] No. of patients with <1 attack per month: anakinra: 6; placebo: 0; p=0.005[d]	Not reported	Anakinra: BL: Mean ± SD 23.3 ± 38.2 (n=12) LM: Mean ± SD 3.9 ± 3.6 (n=10); p=0.069[d] Placebo: BL: Mean ± SD 43.5 ± 54.2 (n=13) LM: Mean ± SD 19.9 ± 18 (n=10)	Anakinra: BL: Mean ± SD 104.1 ± 186 (n=11) LM: Mean ± SD 11.1 ± 19.1 (n=10); p=0.069[d] Placebo: BL: Mean ± SD 218.5 ± 368.2 (n=13) LM: Mean ± SD 110.3 ± 131 (n=6)	Not reported
Retrospective uncontrolled studies						
Akar et al. 2018	172 (anakinra 151, canakinumab 21)	91 (132) (n=145 colchicine resistant[e])	8 (11) (n=145 colchicine resistant[e])	BL[f]: Mean (range) 49.4 (0.0 to 220) AT: Mean (range) 9.3 (0 to 110); p<0.001[g]	Not reported	BL: Mean (range) 43.2 (2 to 129) AT: Mean (range) 18.7 (0 to 154);

Responders and non-responders during anakinra treatment				Effect on inflammatory markers		
Study	**Number of patients[a]**	**Responders[b] % (number)**	**Non-responders % (number)**	**CRP (mg/L)[c]**	**SAA (mg/L)**	**ESR (mm/h)**
						p<0.001 [g]
Vitale et al. 2016	32	78 (25)	22 (7)	Not reported	Not reported	Not reported
Kucuksahin et al. 2017	24	i) 100 (20) (n=20 colchicine resistant) ii) 100 (7) (n=7 colchicine intolerant) iii) 100 (2) (n=2 prolonged arthritis)	0 0 0	BL: 89.6 ± 42.1 AT: 6.8 ± 5.2; p<0.05[g]	BL: 9.0 ± 4.7 mg/dL AT: 0.9 ± 0.8 mg/dL; p<0.05[g]	BL: 80.1 ± 21.3 AT: 17.2 ± 0.3 ; p<0.05[g]
Ozen et al. 2017	14	50 (7)	Not reported	Normalization (defined as median <10 mg/L) in 6 patients (43 %)	Normalization (defined as median <10 mg/L) in 6 patients (43 %)	Not reported
Pecher et al. 2017	13	100 (13)	0	BL: Median 4 mg/dL (range 0.7 to 25.8) 6 months: Median 0.3 mg/dL (range 0.0 to 2.2); p<0.05[g]	BL: Median 138 (range 6 to 1460) 6 months: Median 4 (range 1 to 177); p<0.05[g]	Not reported
Rossi-Semerano et al. 2015	13	92 (12)	8 (1)	Not reported	Not reported	Not reported

Responders and non-responders during anakinra treatment				Effect on inflammatory markers		
Study	**Number of patients[a]**	**Responders[b] % (number)**	**Non-responders % (number)**	**CRP (mg/L)[c]**	**SAA (mg/L)**	**ESR (mm/h)**
Cetin et al. 2015	12	Significant decrease in: i) Monthly attacks: BT median 2.5 (range 1 to 4) AT 0 (range 0-3): p=0.003 ii) Yearly attacks: BT median 30 (range 12 to 50) AT 2 (range 0 to 24): p=0.018	8 (1)	BT: Median 43.3 (range 5 to 195) AT: Median 5 (range 0.7 to 53); p = 0.003[g]	Not reported	BT: Median 42 (range 8 to 110) AT: Median 14 (range 5 to 100); p = 0.004[g]
Eroglu et al. 2015	11	64 (7)	36 (4)	BL: 1 to 12 mg/dL (n=8)[h] AT: 0.1 to 4.4 mg/dL (n=8)	BL: 43 to 360 (n=3) AT: 3.7 to 316 (n=3)	Not reported
Özcakar et al. 2016	4 colchicine-resistant patients	Attack frequency decreased with anakinra BT: 12 to 168/year AT: 0 to 3/year		BL: 11 to 120[i] AT: 0.4 to 8	Not reported	BL: 53 to 82 AT: 15 to 40
	6 patients with amyloidosis	All patients attack-free		Not reported	Not reported	Not reported
Basaran et al. 2015	8	100 (8)	0	Decreased in all patients	Not reported	Decreased in all patients
Meinzer et al. 2011	6	100 (6)	0	Not reported	Not reported	Not reported
Özen et al. 2011	5	100 (5)	0	Not reported	Not reported	Not reported

Comparison of efficacy results across studies

None of the efficacy measures are analysed across all studies. However, various important aspects of the evaluation of the efficacy of anakinra in colchicine-resistant FMF patient are similar in a number of publications. Those are presented in the following sections:

- responder rate
- effects on inflammatory markers
- amyloidosis and renal function
- efficacy in colchicine-resistant or intolerant patients
- anakinra as monotherapy and in combination with colchicine
- Efficacy in paediatric versus adult patients
- Persistence of efficacy and/or tolerance effects

Responder rate

Assessment of response to treatment varies among studies, however "complete response" is often reported and defined as the patient being attack-free and "partial response" as a reduced frequency and severity of attacks. Some studies also include normalisation of inflammatory markers in the evaluation of response.

In the randomised double-blind placebo-controlled study responder rate was not presented, but if patients with fewer attacks than 1 per month is regarded as a responder, 6 out of 12 patients (50 %) in the anakinra group responded to treatment compared to 0 out of 13 patients in the placebo group.

In Akar et al. 2018, the largest retrospective real-world study, 91.8 % of the 145 colchicine-resistant patients responded to IL-1 blocking treatment (42.1 % complete responders and 49.7 % partial responders).

Across 9 other retrospective real-world studies where response rate was reported, the percentage of responders varied between 64 and 100 % in the study populations of colchicine-resistant or intolerant patients. Complete response was seen in 42 to 100 % of the patients.

Effects on inflammatory markers

Levels of the 3 inflammatory markers CRP, SAA and ESR are commonly evaluated during treatment of FMF. The effect on the markers are frequently used as a part of the judgement of complete response, partial response and treatment failure.

The effect of anakinra on CRP, SAA and ESR is presented in Table 13 above. Across studies, anakinra given in combination with colchicine significantly reduce inflammation as measured by CRP, SAA and/or ESR levels compared to the preceding study period when colchicine was given alone.

Across studies, inflammatory markers are reduced during treatment.

Amyloidosis and renal function

There is limited information about the effect of anakinra on amyloidosis. However, results are reported in the randomised study by Ben-Zvi and in three retrospective studies. Individual cases are presented from the studies, e.g. a patient with NS (Patient 1) had no attacks during anakinra treatment and partial remission of NS was observed after 1 year of anakinra therapy. Among 47 patients with urinary

protein excretion of >500 mg/24 hours at BL, 24-hour urinary protein excretion had decreased in 77 % patients and 21 % patients had no significant proteinuria after anti-IL-1 treatment

The authors summarise that anakinra induced remission of attacks, normalised acute phase reactants, suppressed amyloidosis-related GIS findings, and was life saving, giving chance for transplantation, and increased life quality of the patients.

Sparse data, mostly from uncontrolled trials indicate that anakinra in colchicine-resistant patients may halt ongoing amyloidosis and decrease proteinuria. The expected mechanism of action is the suppression of SAA.

Regular use of colchicine reduces the long-term risk of amyloidosis and is a well-established first line treatment recommended by EULAR (level of evidence 1b/grade A recommendation).

There are insufficient data to support that anakinra monotherapy or anakinra in combination with colchicine reduce the risk of amyloidosis or improve renal function. Anakinra should be given in combination with colchicine if appropriate.

Efficacy in colchicine-resistant or intolerant patients

The medical need for treatment with anakinra in addition to, or as an alternative to colchicine, is in almost all publications described in general terms of treatment resistance or intolerance, including patients with amyloidosis. It may therefore be assumed that the FMF populations in the evaluated published studies include both patients resistant and intolerant to colchicine treatment. In three of the publications the two subpopulations are specified, resistance to colchicine appears to be the more common reason for the need of anakinra treatment. Efficacy results have in most publications not been presented separately for colchicine-resistant and colchicine-intolerant patients, except in one study of anakinra monotherapy (Kucuksahin et al. 2017) and the study by Meinzer et al. 2011. The evidence of efficacy of anakinra is thus based on populations of mixed resistant patients, and intolerant patients, including patients with amyloidosis.

Therefore, in most of the studies included in the submission (randomized study, published retrospective studies and the interim report) a colchicine dose is stated. It appears that the majority of patients including in the studies to support the submission are colchicine resistant and has continued colchicine treatment concomitantly with anakinra.

Anakinra as monotherapy and in combination with colchicine

In 6 publications colchicine was reported to be concomitantly used during anakinra treatment, in 1 study by Kucuksahin et al. 2017 anakinra monotherapy was given, and in 2 publications anakinra was used alone in some patients, and in combination with colchicine in other patients. In 5 publications it was not reported whether anakinra was used alone or in combination with colchicine during the study periods.

In the Kucuksashin study, 26 patients with FMF were treated with anakinra monotherapy 100 mg/day, and 2 with canakinumab 150 mg/month. The treatment was switched from colchicine to anakinra in 24 patients for several reasons; 20 patients were resistant to colchicine, 7 were intolerant to colchicine, and 2 had prolonged arthritis during colchicine treatment.

The following results were observed:

- 16 of the 20 colchicine-resistant patients had no attacks during anakinra monotherapy, and 4 had decreased frequency and severity of attacks.
- 6 of the 7 patients intolerant to colchicine were attack-free during anakinra monotherapy, while 1 had decreased frequency and severity of attacks.

- 2 patients with prolonged arthritis were attack-free during anakinra monotherapy.
- Overall, anakinra monotherapy was effective in eliminating or reducing the number of attacks in 100 % of patients in this study.

From the Kucuksahin publication: In this study, anti-IL-1 treatments were used for patients with incomplete control of FMF disease activity despite colchicine treatment in 20 patients. Anakinra was used in these patients with excellent responses. It has not been stated why patients with incomplete response to colchicine were switched from colchicine and not instead offered an IL-1 blocking agent as add-on. The publication support that a clinical response is seen in both populations (colchicine resistant and colchicine intolerant), but if the response had been even better as add-on treatment remains unknown.

Although these results are not obtained from controlled studies, the above mentioned cases support efficacy of anakinra use in monotherapy.

Colchicine treatment is recommended by EULAR and the level of evidence is high. First-line treatment of FMF should be colchicine, and an IL-1 blocker added in case of inadequate response or as monotherapy in case of intolerance to colchicine.

Efficacy in paediatric versus adult patients

The majority of patients in the patient population were adults. The MAH provided an overview of data in paediatric FMF patients from published studies, including at least 52 paediatric patients (Table 14).

Table 14 Overview of paediatric patients with FMF treated with anakinra

Study	Number of pediatric patients treated with anakinra	Age at start of anakinra	Gender	Duration of treatment
Vitale et al. 2016	3	Not specified	Not specified	Not specified
Cetin et al. 2015	2	14 and 15 years	2 F	7 and 12 months
Eroglu et al. 2015	11	Median 13.2 years (range 2-24) [a]	Not specified	Median 8 months (range 4 to 60)
Özcakar et al. 2016	8	Range 6-17 years	Not specified	Range 9-40 months
Basaran et al. 2015	6	10.6, 11, 14, 16, 16, 16 years	2 F/ 4 M	Range 3-28 months
Meinzer et al. 2011	4	7 (3 patients) and 12 years	2 F/ 2 M	Range 2-16 months
Özen et al. 2011	5	≥11 years	3 F/ 2 M	Range 2-30 months
Aktay Ayaz et al. 2016	19	Median 11.5 years (range 8.7–16) [b]	Not specified	Not specified
Özen et al. 2017	20 adult and pediatric [d]	Not specified	Not specified	Not specified
Rossi- Semerano et al. 2015	13 adult and pediatric	Median 21.1 years (range 5.9 to 60.8) [c]	Not specified	Median 13 m (IQR 27)[c]
Hacihamdioglu et al. 2012	1	14 years	1 F	9 months
Calligaris et al. 2008	1	15 years	1 F	18 months
Parvaneh et al. 2015	1	15 years	1 F	12 months
Roldan et al. 2008	1	9 year	1 M	6 months
Fernández García et al. 2009	1	11 years	M	6 months
Total at least 52 [e]				

[a] Based on all 14 patients included in the study.

[b] Based on all 26 patients included in the study.

[c] Based on all 14 patients with FMF included the study.

[d] Study included pedriatic patients, but number is not known. 36 out of 46 patients in total were children, and a total of 20 patients received anakinra treatment.

[e] Total number of pediatric patients without consideration for potential overlap between studies, and excluding published studies by Eroglu et al.2015, Özen et al. 2011 and Rossi-Semerano et al. 2015 since these studies included both children and adults but did not report individual patient data.

In the publication by Özcakar et al. 2016 the age of the 10 included patients ranged between 6.5 to 18 years, with most patients in their early teens. An attack frequency of 12 to 168 per year before anakinra treatment decreased to 0 to 3 per year after treatment. An anakinra pretreatment ESR level range of 53 to 82 mm/h decreased to a posttreatment range of 15 to 40 mm/h during attack free periods, and an anakinra pretreatment CRP level range of 11 to 120 mg/L decreased to a posttreatment range of 0.4 to 8 mg/L during attack free periods.

Basaran et al. 2015 describes 8 patients aged 10 to 19 years, most in their late teens, on a per patient basis. All patients were reported to be in remission or complete remission during treatment.

In the publication by Meinzer at al 2011, 2 of the patients were adults when starting treatment with anakinra (51 and 45 years of age), and 4 were paediatrics (12, and 3 patients were 7 years). Complete remission was observed in 5 of the 6 anakinra treated patients and rare moderate episodes were reported for 1 patient.

Patients included in the submitted studies are mostly above 6 years old, although at least one patient aged 2 seems to be included (Eraglu et al. 2015). Doses used ranged from 1mg/kg/day up to 5mg/kg/day. In the Eroglu et al. study, nine patients responded to treatment at the third month, but four of them were switched to canakinumab due to noncompliance, local side effects and active arthritis.

The proposed indication includes children from the age of 8 months, but data in children are very limited. According to the literature included to support the present application, symptoms related to FMF are often noted only when children become more verbal, usually after 2 years of age. However, the onset of disease appears to be before 2 years of age in approximately 24 % of subjects[28,29,30]. As treatment is not initiated until the disease is diagnosed, the actual medical need < 2 years of age could be questioned. This is supported by the low number of subjects < 2 years of age with FMF identified and included in the submission.

In previous submissions for other indications, the PK/PD relationship and a suitable posology have been established in children from 8 months of age. A weight-based dose is required in subjects < 50 kg to ensure comparable exposure. It is considered reasonable to extrapolate efficacy of Kineret treatment of FMF from children 2-18 years to children < 2 years of age. FMF is of the same family of hereditary periodic fever syndromes as CAPS and share the same clinical features. In CAPS, Kineret is indicated in children from 8 months of age.

Persistence of efficacy and/or tolerance effects

The published studies were not specifically designed to study long-term treatment, however almost all real-world studies present efficacy data in patients with FMF during extended anakinra treatment periods. None of the studies report a change in response to treatment over time or a need to increase dose due to development of tolerance.

The mean anakinra treatment duration in Akar et al. 2018, the largest real-world study, was 1.6 years with a range 0.5 to 8.2 years. The median anakinra treatment periods in the other published studies varied between 8 and 36 months. The median duration of anakinra treatment in the interim report was 18 months.

The long-term efficacy of anakinra in diminishing symptoms caused by increased secretion of interleukin 1- β is supported by results from a prospective, open-label study (study report 03-AR-0298). Study objectives included determining the effects in controlling the inflammatory manifestations in paediatric and adult patients with NOMID. CAPS belong to the autoinflammatory syndromes and includes subtypes out of which the most severe phenotype is NOMID. CAPS is a disorder caused by genetic mutations leading to an overproduction of IL-1β. This leads to a generalised, often chronic systemic inflammation clinically characterized by fever, fatigue, myalgia and joint pain, elevations of acute-phase reactants, and inflammatory haematological changes including anaemia. The results in the efficacy population (median age 8.6 years) showed clinical response was consistent across subgroups, including age and gender, and was sustained up to 5 years (study report 03-AR-0298).

[28] Rawashdeh MO, Majeed HA. Familial Mediterranean fever in Arab children: the high prevalence and gene frequency. Eur J Pediatr. 1996;155(7):540-4.
[29] Padeh S, Livneh A, Pras E, Shinar Y, Lidar M, Feld O, et al. Familial Mediterranean Fever in the first two years of life: a unique phenotype of disease in evolution. J Pediatr. 2010;156(6):985-9.
[30] Demirkaya E, Saglam C, Turker T, Kone-Paut I, Woo P, Doglio M, et al. Performance of Different Diagnostic Criteria for Familial Mediterranean Fever in Children with Periodic Fevers: Results from a Multicenter International Registry. J Rheumatol. 2016;43(1):154-60.

Anakinra has been used in FMF up to 8 years. None of the presented studies discuss development of tolerance or change in response over time. Some publication bias is anticipated, but yet the results are acknowledged.

Long-term anakinra efficacy treatment is supported by data from the CAPS study where patients were treated up to 5 years without signs of tolerance.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of anakinra in the treatment of FMF is primarily based on a small randomised placebo-controlled, double-blind, investigator-initiated study including 25 adults subjects (Ben-Zvi et al. 2017). In this study, 12 subjects received anakinra and 13 received placebo. The population included was defined as colchicine-resistant, maintaining colchicine treatment at the tolerated dose. Follow up of these patients is only 4 months.

In support of this application, a number of retrospective studies describing the outcome of anakinra treatment were also reviewed (Akar et al 2018 and others; see Table 1).

In addition, the interim study report from a retrospective cohort of patients treated with anakinra for FMF refractory to colchicine at Tel Hashomer hospital was submitted. A total of 44 patients were treated with anakinra. The duration of anakinra treatment was 18 months.

The total population consisted of at least 277 anakinra treated patients, including 12 patients in the Ben-Zvi study, at least 221 patients in retrospective real-world studies, and 44 patients in the interim report from the ongoing retrospective real-world study.

Efficacy data and additional analyses

It is generally accepted that overproduction of IL-1β plays a major role in the development of FMF.

A positive efficacy response of anakinra is seen both in terms of reducing the number of attacks, as well as in the decreased levels of inflammatory markers (SAA, CRP, and ESR) in FMF resistant to colchicine and also to some extent in patients intolerant to colchicine, though numbers of each study in general are small. The results are consistent across the prospective randomised placebo-controlled study and the retrospective real-world studies with apparently higher response rates in the retrospective studies. Though only publications from English language journals were included in the initial submission, the literature search was deemed accepted by CHMP.

Although significant treatment effect was obtained for number of attacks, a decrease in abdominal and thoracic attacks was not significant. Also, a numerical decrease in CRP and SAA was obtained but not statistically significant. No information on long term data was provided for these patients. The applicant justified the absence of data by the fact that the study was an investigator-sponsored study and not a study sponsored by the MAH. Nonetheless, supportive real-world studies, such as the reported by Akar et al.2018, provided some long-term data obtained from the use of anakinra to treat FMF which support the long-term use for Kineret.

Colchicine reduces the risk of amyloidosis and anakinra should be given in combination with colchicine, if appropriate. Data are insufficient to support that anakinra reduces the risk of amyloidosis or improve renal function.

The responder rate is overall high and of clinical significance in the studies included in the submission. The clinical effect of anakinra is presented in both clinical symptoms of attacks as well as in reduced levels of inflammatory markers such as SAA, CRP and ESR. In the randomised study, the response rate is 50 %. Overall, data from the published studies, consistently demonstrate that anakinra is efficacious in the treatment of FMF, across age groups, though some publication bias is expected with a potential overestimation of the treatment effect.

Most publications do not distinguish between efficacy results in patients with colchicine-resistant FMF and efficacy results in colchicine-intolerant patients with FMF. In one study that separately reports efficacy of anakinra monotherapy in patients intolerant to colchicine, and in patients resistant to colchicine, anakinra decrease attack rate and improve efficacy outcomes in both groups. Colchicine treatment is recommended by EULAR and the level of evidence is high. Colchicine has been found to reduce the long-term risk of amyloidosis. Therefore, first-line treatment of FMF should be colchicine, and an IL-1 blocker added in case of inadequate response or as monotherapy in case of intolerance to colchicine. In line with this guidance, the SmPC recommends the use of Kineret in combination with colchicine, if appropriate.

Assessment of paediatric data on clinical efficacy

The proposed indication includes children from the age of 8 months, although data in children are very limited. It is nevertheless considered reasonable to extrapolate the efficacy of Kineret treatment of FMF from children 2-18 years to children < 2 years of age. FMF is of the same family of hereditary periodic fever syndromes as CAPS and share the same clinical features. The safety profile appears similar across indications, also when Kineret is administered with colchicine. However, data to support safety in children < 2 years of age are limited and rely on extrapolation from children > 2 years of age. To support this, the use of Kineret in children < 2 years in other indications is reassuring. Regarding long-term treatment, the published studies –uncontrolled studies and case reports - include treatment of paediatric subjects for up to 40 months. In the recently submitted PASS study Sobi.ANAKIN-302, the most frequent reason (43.1 %) for Kineret discontinuation is disease remission questioning long-term efficacy, whereas the long-term safety profile in other indications is reassuring. There are no identified safety concerns in FMF compared to other indications and it is considered that efficacy in children < 2 years of age is comparable to efficacy in children > 2 years of age. Though the medical need in children < 2 years of age is limited due to delay in diagnosis, treatment could be appropriate and there are data to support a safe and efficacious posology from other indications.

In conclusion, it is agreed to align the indication in FMF in line with the other following autoinflammatory periodic fever syndromes i.e. in children and infants aged 8 months and older with a body weight of 10 kg or above. The SmPC states that efficacy data in children < 2 years of age with FMF are limited.

2.4.4. Conclusions on the clinical efficacy

Clinical efficacy data of anakinra in FMF based on bibliographic data has been presented to support the submission. Overall, data from the published studies, consistently demonstrate that anakinra is efficacious in the treatment of FMF, across age groups, though some publication bias is expected with a potential overestimation of the treatment effect. The CHMP agreed that anakinra should be given with colchicine if appropriate in children and infants aged 8 months and older with a body weight of 10 kg or above.

2.5. Clinical safety

Introduction

The safety evaluation of anakinra in FMF is based on the following sources:

- A published single centre, double-blind, randomised, placebo-controlled prospective study (Ben-Zvi et al. 2017).
- A review of other relevant publications including safety data in patients diagnosed with FMF, who have received at least 1 dose of anakinra, and have any reported safety data, the largest study comprising 155 patients (Akar et al. 2018).
- Data from an interim report of an ongoing retrospective study in Israeli patients with FMF, treated with anakinra.
- Company-sponsored clinical studies comprising 6404 subject-years in 8518 subjects.
- Post-marketing anakinra exposure data of approximately 102 600 patient-years in various indications since the first approval of anakinra for RA in 2001. The post marketing safety data from the MAH safety database includes 3576 case reports with 7377 medically confirmed post-marketing AEs, whereof 114 medically confirmed case reports with 223 events that concern patients where the indication for anakinra treatment is stated to be FMF.

There are no company sponsored studies in patients with FMF.
Safety data have been obtained from 20 publications. From these it is estimated that between 278 and 438 patients with FMF have been treated with anakinra. This estimation is calculated using a conservative approach for the lower limit (where all possible duplicated patients are excluded) and a liberal approach for the higher limit (where no patients are excluded).

Patient exposure

Since May 1994 and up to May 1, 2018, the estimated exposure to anakinra in completed company sponsored clinical studies is 6404 subject-years, in 8518 subjects. In addition, up to May 1, 2018, it was estimated that 2 patients have been exposed to anakinra in one ongoing double-blind clinical study in Still's disease (Sobi.ANAKIN-301) and 96 patients are estimated to have been exposed to anakinra in one ongoing double-blind clinical study in acute gouty arthritis (Sobi.ANAKIN-401). The estimation is based on the randomisation scheme for the respective studies.

Since the MAH has no access to the data reported in the published studies included in this application, it cannot be excluded that some patients are included in two or more studies, resulting in a risk for data overlap. Taking the risk for overlap into account, it is estimated that between 278 and 438 patients with FMF have been treated with anakinra and reported in the >15 published studies included in this application. This estimation is calculated using a conservative approach for the lower limit (where all possible duplicated patients are excluded) and a liberal approach for the higher limit (where no patients are excluded).

The administered anakinra doses in the published studies and poster abstracts were:

- 100 mg/ day (with a minimum dose of 50 mg/day s.c. (or 100 mg every other day), and a maximum dose of 300 mg/day s.c.) in adult patients (including patients with a history of kidney transplant).
- 1 to 2 mg/kg/day s.c., with a maximum dose of 100 mg/day s.c. in paediatric patients.

In addition to the published studies, an interim report is available from the ongoing retrospective study in Israeli patients with FMF, conducted at the Tel Hashomer hospital (Kivity 2018). In this study, 44 patients with colchicine-resistant FMF were treated with anakinra 100 mg daily for more than 2 months.

Adverse events

Overall the most commonly reported AEs were injection site reactions (ISRs), constituting almost half of the reported AEs, followed by infections, both serious and non-serious.

Less frequently reported AEs (n>5) include known AEs such as allergic reactions, and headache. Gastrointestinal AEs have also been reported.

Table 15 presents the secondary outcomes with regard to safety from the randomised placebo-controlled, double-blind study (Ben-Zvi, 2017). The safety outcomes were, in general, similar between the 2 patient groups, including the number of AEs, the rate of AEs, associations of AEs with specific organ systems, and associations of AEs with the study drug and severity. No SAEs were recorded, and none of the AEs were graded as severe.

Table 15 Secondary safety outcomes*

Parameter	Anakinra (n = 12)	Placebo (n = 13)
Total no. of AEs	94	104
Patients with AEs of any type	83.3	84
Any AEs, mean ± SD no. per patient per month	2.03 ± 1.75	3.34 ± 2.5
Patients with GI AEs (abdominal pain, diarrhea, vomiting)	66	53.8
Patients with infectious AEs (gastroenteritis, URI, viral infection)	33.3	23.1
Patients with musculoskeletal AEs (LBP, arthralgia, extremity pain)	41.7	61.5
Patients with nervous system AEs (headache)	50	38.5
Patients with skin AEs	25	15.4
Patients with local ISR	41.7	46.2
Drug-related AEs		
Patients with drug-related AEs (ISR, headache, presyncope, dyspnea, itching)	16.7	30.8
% of total AEs	4.2	7.7
No. per patient per month, mean ± SD	0.1 ± 0.2	0.2 ± 0.5
Moderate AEs†		
Patients with moderate AEs	33.3	38.5
% of total AEs	4.3	6.7
No. per patient per month, mean ± SD	0.1 ± 1.8	0.1 ± 0.3
No. of analgesic medications per patient per month, mean ± SD	2.8 ± 2.5	3.99 ± 2.5

* Systems with >2 patients with an adverse event (AE) at the given site are shown. The differences between the anakinra and placebo groups were nonsignificant for all parameters. Except where indicated otherwise, values are the percentage of patients. GI = gastrointestinal; URI = upper respiratory tract infection; LBP = low back pain; ISR = injection site reaction.
† All other AEs were considered mild.

Injection site reactions

In other indications than FMF ISRs are usually the most frequently reported AEs during anakinra treatment. In the prospective controlled study (Ben-Zvi et al. 2017) approximately 45 % of patients experienced ISRs and the frequencies of ISRs in the anakinra and placebo groups were comparable.

In the published studies the frequency of ISRs is lower than what would be expected compared to company sponsored studies in RA where approximately 70 % of patients experienced ISRs. In the interim report, there were 11 (25 %) patients with ISRs, whereof 5 stopped anakinra treatment.

ISR are frequent during anakinra treatment, in some cases this may lead to anakinra discontinuation. In the SmPC the frequency is "Very common" for injections site reaction. The types and frequencies of ISRs are similar in FMF to those seen in RA and SJIA. Discontinuation of Kineret due to ISR have occurred in FMF.

Infections

In the prospective controlled study there were no serious infections and the frequency of non-serious infections was similar in anakinra treated patients and patients receiving placebo. In total 4 out of 12 patients receiving anakinra experienced non-serious infections, compared to 3 out of 13 patients receiving placebo.

There are several infections reported in the published literature, both serious and non-serious. The frequencies vary from 3 in 151 patients (Akar et al. 2018) to 1 in 12 patients.

In the interim report, there were 3 serious infections requiring hospitalisation, all 3 were considered related to anakinra. No non-serious infections were reported.

Anakinra has been associated with an increased risk for serious infections, and in patients with RA it is recommended that anakinra is temporary stopped during infections. However, anakinra has been used also during infections without complications.

The use of anakinra during infections has also been documented in the literature including continued use of anakinra during 3 serious infections and continued use of anakinra during an episode of MAS with evidence of an human herpesvirus 6 (HHV6) infection. Furthermore, anakinra has been administered to 1015 patients with sepsis in placebo-controlled company sponsored studies. It was concluded that anakinra did not negatively affect the sepsis treatment outcome, and was well tolerated, with no difference in frequency of deaths, discontinuations due to AEs or SAEs compared to patients receiving placebo. To stop anakinra treatment during infections could trigger disease flares. There are no indications, either from the pivotal registration study in severe CAPS, from case reports in the literature, or clinical studies in sepsis that treatment of infections becomes more difficult by continued anakinra treatment. Also, dose increases of anakinra in connection with infections have been well tolerated.

Serious adverse event/deaths/other significant events

In the prospective controlled study there were no serious or severe AEs, however, one patient stopped anakinra due to an allergic reaction.

Also, in the published literature, e.g., allergic reactions and ISRs sometimes cause discontinuation of anakinra treatment.

In the interim study report from Tel Hashomer hospital, 5 patients reported local site reactions severe enough to cause treatment cessation.

No specific narratives of SAEs are described in the publications included in the application.

In the prospective controlled study there were no deaths.

In the published retrospective real world studies, there was 1 report of death. This was an unidentifiable FMF patient with kidney transplantation on anakinra treatment and concomitant immunosuppressives who developed pneumonia and died due to septic shock. No other deaths were reported in the published literature included in this application.

Laboratory findings

Clinical laboratory values related to the safety profile of anakinra in patients with FMF are available in 2 published studies:

In Akar et al. 2018, baseline data showed that 47 patients had a mean urinary protein excretion of 5458,7 mg/24h (range 550 to19 610), which was significantly reduced to 3557 mg/24h (range 0 to 18 500) after anakinra treatment. Although non-significant, there was also a reduction in serum levels of creatinine, baseline 1.2 mg/dl (0.3 to 10.2) to 1.1 mg/dl (0.4 to 7.7).

In all remaining published studies, no safety laboratory evaluation was presented.

No new safety concerns with impact on laboratory values have been identified in FMF.

Safety in special populations

Information on safety in special groups and situations is limited in the published studies.

Paediatric subjects

Based on the published data, and using the conservative approach, a total of 181 cases reports in patients with FMF were identified in the literature. The studies included both paediatric and adult patients. There were 24 patients under 18 years of age and only one subject under 2 years of age, with most of paediatric patients being older than 6 years old.

Numbers are small, but there are no indications of differences in the safety profile in paediatric subjects compared to adults in FMF. Additionally, the safety profile appears similar across indications, also when Kineret is administered with colchicine. However, data to support safety in children < 2 years of age are limited and would rely on extrapolation from children > 2 years of age. The use of Kineret in children < 2 years in other indications including long-term use is reassuring.

Regarding long-term treatment, the published studies include treatment of paediatric subjects for up to 40 months. However, these are uncontrolled studies, mainly case reports and the level of evidence is limited. In the recently submitted PASS study Sobi.ANAKIN-302, the most frequent reason (43.1 %) for Kineret discontinuation was disease remission. The long-term safety profile in other indications is on the other hand reassuring.

In FMF, data on safety, as well as in efficacy, are limited in children < 2 years of age.

However, there are no identified safety concerns in FMF compared to other indications and it is considered likely that efficacy in children < 2 years of age is comparable to efficacy in children > 2 years of age. Though the medical need in children < 2 years of age is limited due to delay in diagnosis, treatment could be appropriate and there are data to support a safe and efficacious posology from other indications.

Extrapolation of safety of anakinra treatment of FMF from older children to children below the age of 2 is reasonable, and is further supported by safety data in children 8 months and older with the related hereditary periodic fever CAPS/NOMID.

Therefore, it can be agreed to restrict the indication in FMF in line with the restrictions in the other approved autoinflammatory periodic fever syndromes i.e. in children and infants aged 8 months and older with a body weight of 10 kg or above. The product information should state that efficacy data in children < 2 years of age with FMF are limited.

Elderly population

No elderly patients (> 65 years old) with FMF on anakinra treatment were reported in the published studies and abstracts included in this application. Safety in elderly patients has previously been evaluated, mainly in RA patients. A total of 752 patients ≥ 65 years of age, including 163 subjects ≥ 75 years of age, have been studied in earlier, company sponsored clinical studies. No differences in the safety profiles were observed between elderly and younger subjects, except for ISRs that were less frequent among elderly patients.

Data in the elderly are also limited in CAPS and Still's disease.

Hepatic impairment

No patients with FMF and hepatic impairment were described in the published literature included in this application. In total 14 patients with hepatic impairment have been included in a company sponsored study 0502, in the original MAA application.

For patients with hepatic insufficiency, no dosage adjustment is warranted.

Renal impairment

In the published literature and abstracts included in this application, between 39 and 70 patients with FMF and renal impairment were identified.

In company sponsored studies of anakinra in other indications there have been no relevant differences in the safety profile between subjects with normal renal function and those with different degrees of renal impairment.

From the published literature and abstracts included in this application, there are no indications that renal impairment, including renal impairment due to amyloidosis, alters the safety profile of anakinra, or that treatment with anakinra is harmful to patients with proteinuria or increased creatinine levels.

Safety related to drug-drug interactions and other interactions

No drug interactions have been reported in the published literature included for this application.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1). In conditions with increased IL-1 levels it may be expected that for an IL-1 receptor antagonist, such as anakinra, the formation of CYP450 enzymes could be normalised during treatment. This would be clinically relevant for CYP450 substrates with a narrow therapeutic index (e.g., warfarin). Upon start or end of anakinra treatment in patients on these types of medicinal products, it may be relevant to consider therapeutic monitoring of the effect or drug concentration of these products and the individual dose of the medicinal product may need to be adjusted.

In company sponsored clinical studies, no interactions between anakinra and non-steroidal anti-inflammatory drugs, corticosteroids, and DMARDs have been observed.

Initiation of anakinra and colchicine treatment in parallel may reduce the clinical effect of colchicine. However, in the published literature when using anakinra as add-on therapy, the overall anti-inflammatory effect of anakinra and colchicine have been shown to increase upon initiation of anakinra treatment reflected by a reduced and normalized CRP and ESR levels.

There are no indications from the literature that combined administration of colchicine and anakinra would change the safety profile of anakinra.

Discontinuation due to adverse events

In the published literature, e.g, allergic reactions and ISRs sometimes cause discontinuation of anakinra treatment.

In the interim report, there were 11 (25 %) patients with ISRs, whereof 5 stopped anakinra treatment.

According to the SmPC, discontinuation due to AEs in CAPS and SJIA is uncommon. The data in FMF indicate a higher rate of discontinuation, but the frequency is unclear due to limited data.

In 12 FMF patients treated 4 months with Kineret in the published randomised controlled study no allergic event was reported as serious and no event required discontinuation of Kineret.

Post marketing experience

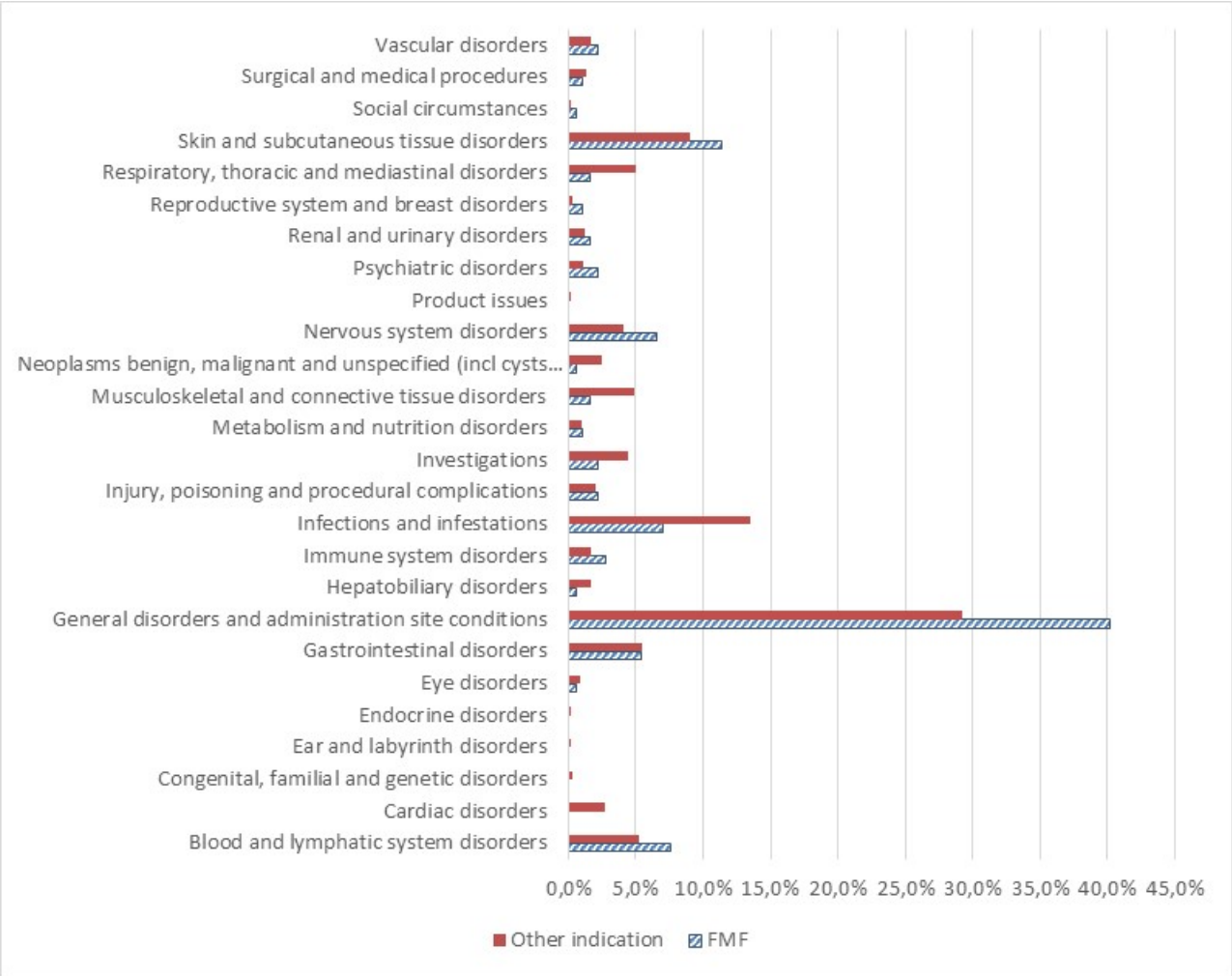
The estimated total commercial patient exposure to anakinra, including use in Named Patient Programs and Compassionate Use Programs, since the initiation of anakinra clinical studies in May 1994 up to May 1, 2018, is 102,625 patient-years. The presented patient exposure has been estimated based on the amount of product distributed.

Despite limited licensed indications, anti-IL1 agents are often used in real-life practice for an increasing number of diseases.

The case reports in the MAH Safety Database represent spontaneous ICSRs reports received by the current MAH Sobi and the previous MAH Amgen, and includes reports from healthcare professionals, consumers, scientific literature, worldwide regulatory authorities, and solicited ICSRs from non-interventional studies. Case reports from company sponsored clinical studies have been filtered and therefore do not appear among the post marketing AEs.

Figure 5 shows the relative distribution of all AEs by SOC in patients with FMF compared to all other indications for anakinra treatment.

In both groups the SOC "General disorders and administration site conditions" is the SOC with most AEs; this SOC contains all PTs related to ISRs, the most common anakinra ADRs. Various ISRs are more common in patients with FMF making the relative number of events in the "General disorders and administration site conditions" SOC higher. Events of infection are relatively less common in patients with FMF. The reasons for these differences are unknown, however, the number of patients with FMF is relatively low and data should therefore be interpreted with caution. With these exceptions the distribution of AEs is similar in the 2 groups.



Source: The Sobi Safety Database, cut-off date: May 1, 2018. % based on total number of events.
AE=Adverse event; FMF, Familial Mediterranean fever; PT, preferred term; SOC=System organ class.

Figure 5 Distribution of AEs by SOC, patients with FMF compared to patients treated with anakinra for other indications (SOC Pregnancy, puerperium and perinatal conditions, PTs indicating Maternal, paternal and fetal exposure, and off-label use excluded)

The overall distribution of AEs from spontaneous reports appears similar in FMF compared to other indications, but various ISRs appear more common in patients with FMF – this is in contrast to the published studies, where ISRs were less frequently reported, likely due to underreporting. A higher incidence of ISRs could explain the higher incidence of drug discontinuation.

2.5.1. Discussion on clinical safety

Safety data from at least 278 anakinra-treated patients with FMF in studies including a published randomised, placebo-controlled study, published retrospective real-world studies, and an interim report of an ongoing study in 44 Israeli patients on anakinra have been presented. Between 39 and 70 patients with renal impairment (whereof between 22 and 39 patients with a kidney transplantation before starting anakinra treatment) were included in the studied population.

No new clinically relevant AEs were seen in patients with FMF treated with anakinra and the safety profile of anakinra in patients with FMF was generally similar to that in other indications. In addition, in

patients with FMF the types and frequencies of ISRs are similar to those seen in RA and SJIA. Also, compared to CAPS and Still's disease, more patients appear to discontinue treatment, nevertheless this may be biased due to limited in FMF. The product information is updated to reflect that discontinuations due to ISRs have occurred also in patients with FMF.

The frequency of certain AEs reported in patients with FMF appears to be lower than that seen in other approved indications. This is likely due to underreporting in the published studies, which mainly focus on efficacy. In addition, there are no indications of a higher frequency of serious infections or other serious AEs in FMF than in other indications.

From the published literature and abstracts included in this application, there are no indications that renal impairment, including renal impairment due to amyloidosis, alters the safety profile of anakinra, or that treatment with anakinra is harmful to patients with proteinuria or increased creatinine levels.

In 12 FMF patients treated 4 months with Kineret in the published randomised controlled study no allergic event was reported as serious and no event required discontinuation of Kineret. The SmPC is updated to reflect this statement.

There were no data in elderly patients with FMF.

Based on the available data, the safety profile of Kineret in the FMF indication is acceptable.

Assessment of paediatric data on clinical safety

Although the numbers are small, there are no indication of differences in the safety profile in paediatric subjects compared to adults in FMF. Furthermore, the safety profile appears similar across indications, also when Kineret is administered with colchicine.

However, data to support safety in children < 2 years of age are limited and would rely on extrapolation from children > 2 years of age. The use of Kineret in children < 2 years in other indications including long-term use is reassuring. In addition, there are no identified safety concerns in FMF compared to other indications and it is considered likely that efficacy in children < 2 years of age is comparable to efficacy in children > 2 years of age. Though the medical need in children < 2 years of age is limited due to delay in diagnosis, treatment could be appropriate and there are data to support a safe and efficacious posology from other indications.

2.5.2. Conclusions on clinical safety

Based on the available data, the overall safety profile of anakinra in FMF appear to be comparable to the safety profile in other indications. Anakinra exposure in FMF from published studies and the included interim report is supported by safety data of anakinra as treatment in several other indications.

No new safety issues have been identified, the CHMP agreed that the and safety in children from 8 months of age can be extrapolated from the data obtained for children with < 2 years in the context of the other approved indications, namely CAPS/NOMID.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 5.2 with the following content:

Safety concerns

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.	Additional pharmacovigilance activities: Sobi.ANAKIN-201 in CAPS Patients (PRINTO/Eurofever Registry)
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 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.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Followed as TME Additional pharmacovigilance activities: Sobi.ANAKIN-201 in CAPS Patients (PRINTO/Eurofever Registry)

Safety concern	Routine risk minimization measure	Pharmacovigilance activities
	Additional Risk Minimization Measure: Guides describing the risk of serious infections for healthcare professionals treating patients with CAPS, FMF and Still's disease, and a reminder card for patients with Still's disease describing serious infections.	
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 $<1.5 \times 10^9$/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 $< 1.5 \times 10^9$/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 conditions	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 Additional pharmacovigilance activities: Sobi.ANAKIN-201 in CAPS Patients (PRINTO/Eurofever Registry)
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 Additional pharmacovigilance activities: Sobi.ANAKIN-201 in CAPS Patients (PRINTO/Eurofever Registry)

Safety concern	Routine risk minimization measure	Pharmacovigilance activities
Macrophage activation syndrome (not applicable for RA, CAPS or FMF)	Routine risk communication: SmPC section 4.4 states that if MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of Still's disease, as these are known triggers for MAS. Additional Risk Minimization Measures: Guides for healthcare professionals and a reminder card for patients with Still's disease describing the risk of MAS.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Followed as a TME Additional pharmacovigilance activities: Sobi.ANAKIN-302 (PRINTO/Pharmachild Registry) in pediatric Still's patients
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 Additional pharmacovigilance activities: Sobi.ANAKIN-201 in CAPS Patients (PRINTO/Eurofever Registry)
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
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	Routine risk communication:	None

Safety concern	Routine risk minimization measure	Pharmacovigilance activities
infections	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.	None
Interaction with living vaccines	Routine risk communication: SmPC section 4.4 states that live vaccines should not be given concurrently with Kineret.	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet has been updated accordingly.

In addition, in section 4.1 of the SmPC the wording of the indication CAPS has been modified to regroup the CAPS and FMF indications under the term "Periodic fever syndromes" for the treatments of adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above.

Furthermore, the PI is brought in line with the latest QRD template version 10.1.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

A user consultation has not been performed for this Type-II variation application as the package leaflet included in this submission is identical to the previously readability tested package leaflet for Kineret (indicated for RA, CAPS and Still´s disease) with the only difference between the two leaflets being the new indication. As this information is the only differing aspect between the PILs, the result of the Readability Test for the Kineret (indicated for RA, CAPS and Still´s disease) also applies to Kineret (indicated for RA, CAPS, Still's disease and FMF).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

FMF is a rare, but the most common, hereditary periodic fever syndrome and is driven by inflammasome activation, which leads to the overproduction of IL-1β. FMF is a rare disorder, but the most common of the autoinflammatory syndrome (AIS), traditionally more common in the Mediterranean region, although an increase in incidence has been seen in other European countries

with high Turkish or Algerian immigration, such as Germany and France. An increase in incidence has been seen in Italy as well.

FMF is typically presented with recurrent febrile attacks, accompanied by signs of peritonitis, pleuritis or acute synovitis, lasting 1 to 3 days, and resolving spontaneously. The most severe and potentially life-threatening complication of FMF is secondary amyloid A amyloidosis, characterized by deposition of misfolded insoluble proteins in various organs and tissues. Amyloidosis results from excessive production of SAA, an acute phase protein released from hepatocytes via stimulation of proinflammatory cytokines (IL-1, IL-6 and TNF-α). Disease onset are seen frequently below the age of 2.

3.1.2. Available therapies and unmet medical need

Colchicine treatment should according to EULAR recommendations be initiated as soon as the clinical diagnosis has been established. Continuous therapy with colchicine prevents FMF attacks in 60 to 65 % of patients and induces partial remission in a further 30 to 35 %, and regular use of colchicine reduces the long-term risk of amyloidosis. However, as documented in a large number of studies, colchicine may be unsuitable or insufficient in a subset of patients with FMF who are non-respondent, partially respondent, or intolerant to colchicine. There is an unmet need if colchicine is inadequate– either because of insufficient response to treatment, or due to safety concerns or intolerance, such as renal impairment, hepatic impairment, gastrointestinal AEs, or potential drug-drug interactions.

Symptoms related to FMF are often noted only when children become more verbal, usually after 2 years of age. However, the onset of disease appears to be before 2 years of age in approximately 24 % of subjects. As treatment is not initiated until the disease is diagnosed, the actual medical need < 2 years of age could be questioned. This is supported by the low number of subjects < 2 years of age with FMF identified and included in the studies.

The IL-1 inhibitor canakinumab is also approved the treatment of FMF in adults, adolescents and children aged 2 years and older. It should be given in combination with colchicine, if appropriate.

3.1.3. Main clinical studies

This application is primarily based on:

- Bibliographical data from 1 randomised, double-blind, placebo-controlled study of anakinra in patients with FMF (Ben-Zvi et al. 2017).

The following studies and analysis have been submitted as supportive data:

- Multiple real-world clinical studies of anakinra in patients with FMF (List of studies can be found in Table 1)
- Recent data from an ongoing real-world study conducted at the Tel Hashomer hospital in Israel (interim report).
- Efficacy and safety data in the paediatric population from anakinra treatment of a related hereditary periodic fever syndrome sharing the same pathophysiological features as FMF: CAPS (study report 03-AR-0298).
- MAH's data from company-sponsored studies of anakinra in other indications.
- Data from the MAH's post-marketing safety database in various indications, including FMF.

3.2. Favourable effects

The safety and efficacy of Kineret in the treatment of patients with colchicine resistant FMF has been demonstrated in a randomised, double-blind, and placebo-controlled published study with a treatment period of 4 months. The mean number of attacks per patient per month was significantly lower in those receiving Kineret (1.7) compared to placebo (3.5). The number of patients with <1 attack per month was significantly higher in the Kineret group; 6 patients, compared to none in the placebo group.

Additional published data in patients with FMF, intolerant to colchicine or with colchicine resistant FMF, demonstrate that the clinical effect of Kineret is evident in both clinical symptoms of attacks as well as in reduced levels of inflammatory markers, such as CRP and SAA. In the published studies the safety profile of anakinra in patients with FMF was generally similar to that in other indications.

Most publications do not distinguish between efficacy results in patients with colchicine-resistant FMF and efficacy results in colchicine-intolerant patients with FMF. In one study that separately reports efficacy of anakinra monotherapy in patients intolerant to colchicine, and in patients resistant to colchicine, anakinra decrease attack rate and improve efficacy outcomes in both groups. Colchicine treatment is recommended by EULAR and the level of evidence is high. Colchicine has been found to reduce the long-term risk of amyloidosis. Therefore, Kineret should be given in combination with colchicine, if appropriate.

Data from the published studies also demonstrate that anakinra is efficacious and safe in the treatment of FMF for the paediatric population. Extrapolation of efficacy and safety from children 2-18 years to children below 2 years of age is considered acceptable by CHMP since FMF is of the same family of hereditary periodic fever syndromes as CAPS which is indicated from 8 months of age and share the same clinical features.

Overall, the benefits of anakinra have been reported consistently across age groups.

3.3. Uncertainties and limitations about favourable effects

Efficacy of anakinra in FMF is mainly based on retrospective studies published in English and publications bias is expected with a potential overestimation of the treatment effect. A small randomised placebo-controlled, double blinded trial (Ben-Zi et al) with 25 FMF patients is the only controlled data to support efficacy. A large retrospective analysis of 172 FMF patients (Akar et al) further support the application and the additional small retrospective uncontrolled studies are not considered of high relevance. In addition, the recent data from the ongoing real-world study conducted at the Tel Hashomer hospital in Israel has been submitted as supportive, although final results are still pending.

It has been shown that anakinra is effective in normalising elevated SAA levels and reverse proteinuria and this may contribute to preventing amyloidosis and preserving renal function. However, clinical data are yet insufficient to support this assumption.

The majority of FMF patients in the studies were also treated with colchicine. Data to support anakinra as monotherapy in FMF are limited. Data are insufficient to support that anakinra reduces the risk of amyloidosis or improve renal function.

Efficacy data in children, especially the very young (under 2 years of age), are limited. This can be explained by the fact that symptoms related to FMF are often noted only when children become more verbal, usually after 2 years of age. The onset of disease appears to be before 2 years of age in approximately 24 % of subjects. Although the medical need in children under 2 years of age is limited

due to delay in diagnosis, treatment could be appropriate and there are data to support a safe and efficacious posology from other indications.

In addition, while extrapolation of efficacy and safety to children below the age of 2 is acceptable, no PK data in children below 8 months are available to support dosing. The indication is therefore limited to children above 8 months of age and above 10 kg in line with the other Kineret indications. In children with inadequate response the dose can be escalated up to 4 mg/kg/day.

3.4. Unfavourable effects

Adverse events data in patients with FMF are based on post-marketing AE reports and published studies. The safety profile of anakinra is also well-established in other indications, including CAPS a periodic fever condition related to FMF. The most common known AEs with anakinra treatment are non-serious and mostly mild or moderate ISRs that usually transiently occur early during treatment across indications. This is true also for patients with FMF. In addition, there are no indications of a higher frequency of serious infections or other serious AEs in FMF than in other indications. No new ADRs have been identified. Discontinuations due to ISRs have occurred also in patients with FMF.

In 12 FMF patients treated 4 months with Kineret in the published randomised controlled study no allergic event was reported as serious and no event required discontinuation of Kineret.

Based on available data, the safety profile of anakinra is considered similar between paediatric and adult's patients in FMF.

3.5. Uncertainties and limitations about unfavourable effects

The safety data in FMF in the retrospective published studies, where the main focus was often only efficacy, are limited. However, given the well-known safety profile of anakinra – also in another fever indication (CAPS) - the safety data are considered sufficient for making an adequate evaluation of the safety of anakinra in adult FMF.

ISR are frequent during anakinra treatment, in some cases this may lead to anakinra discontinuation. In order to minimise this risk, physicians and patients (or caregivers) should receive educational material or information pack which give instructions on how to use the syringe and manage injection site reactions.

Long term safety data in FMF are also limited but some supportive real-world studies provided some long-term data and also supported by the CAPS study where patient where treated up to 5 years.

Safety data in children are also limited, but there are no indications of differences in the safety profile in paediatrics subjects compared to adults in FMF. No children below the age of 2 have been included in the clinical studies for the other indications (CAPS), but limited evidence from the literature and the few cases from the post-marketing safety database indicate similar safety in children younger than 2 years compared to older children and adults.

3.6. Effects Table

Table 16 Effects table for Kineret in the treatment of Familial Mediterranean Fever

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Attack rate	Attack in any site per month	Number	Anakinra (n=12) 1.7 ± 1.7	Placebo (n=11) 3.5 1.9	RCT, DB, investigator-initiated study	Ben-Zvi et al. 2017
Attack rate	No. of patients with <1 attack per month	number	Anakinra: 6	Placebo: 0	-	-
CRP	CRP, last measurement,	mg/L	3.9 ±3.6 (n=10)	19.9 ±18 (n=10)	-	-
SAA	SAA, last measurement,	mg/L	11.1 ±19.1 (n=10)	110.3 ±131 (n=6)	-	-
QoL	QoL score,	10-cm VAS	7.7 ±2.3 (n=12)	4.2 ±2.9 (n=6)	-	-
Attack	Attack/year	number	After treatment: 2.3 (0–36)	Before treatment: 16.2 (0–96)	Retrospective study including 172 patients who received at least 6 months of treatment with an IL-1 receptor antagonist	Akar et al. 2018
CRP	CRP level	mg/L	After treatment: 9.3 (0–110)	Before treatment: 49.4 (0.0–220)	-	-
ESR	ESR	mm/hour	After treatment: 18.7 (0–154)	Before treatment: 43.2 (2–129)	-	-
Unfavourable Effects						
AEs	Total no of AEs	Number	Anakinra: 94	Placebo: 104	RCT, DB, investigator-initiated study	Ben-Zvi et al. 2017
ISR	Patients with local ISR	%	Anakinra: 41.7	Placebo: 46.2	-	-
Drug-related AEs	(ISR, headache, presyncope, dyspnea, itching)	% of total AEs	Anakinra: 4.2	Placebo: 7.7	-	-

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

FMF is a serious condition with risk of amyloidosis with general devastating organ involvement including renal impairment. Amyloidosis is the primary cause of premature death in FMF patients. It is generally accepted that overproduction of IL-1β plays a major role in the development of FMF and IL-1

blocking treatment is recommended by EULAR in in the rare patients who fail to respond to colchicine or who cannot tolerate it.

Canakinumab, a monoclonal antibody targeting IL-1β, is approved for periodic fever syndromes including FMF. Anakinra is a recombinant form of the naturally occurring IL-1 receptor antagonist, which prevents the activity of the cytokines IL-1α and IL-1β.

The efficacy of anakinra in terms of reducing the number of attacks, as well as in the decreased level of inflammatory markers (SAA, CRP and ESR) has been shown in patients with colchicine-resistant FMF and in colchicine-intolerant patients, patient populations with limited therapeutic alternatives in both the controlled study and in the retrospective published studies included to support the application. Moreover, anakinra treatment may contribute to the prevention of amyloidosis by lowering of SAA levels and reversal of proteinuria. However, clinical data are yet insufficient to support this assumption.

The proposed therapeutic indication includes children older than 8 months, but data for children younger than 6 years are scarce. Dosage used in children ranges from the proposed doses up to 5mg/kg. Long term data are not included.

Although the medical need in children under 2 years of age is questioned due to delay in diagnosis, treatment could be appropriate and there are data to support a safe and efficacious posology from other indications. Efficacy extrapolation for children 2-18 years to children under 2 years of age is acceptable by CHMP. In children with inadequate response the dose can be escalated up to 4 mg/kg/day.

The safety profile of anakinra is well-known and no new safety concerns have been identified in the FMF indication. The most common AEs were non-serious and mostly mild or moderate ISRs, followed by infections, that usually transiently occur early during treatment across indications. Although safety data in children are limited there are no indications of differences in the safety profile in paediatrics subjects compared to adults in FMF.

The benefit-risk of anakinra treatment in children with FMF is considered positive in children 8 months and older with a body weight of 10 kg or above in line with the other autoinflammatory periodic fever syndromes as the posology is established, and both efficacy and safety are expected to be comparable in children under 2 years and children above 2 years of age.

3.7.2. Balance of benefits and risks

Based on the efficacy of anakinra demonstrated in the randomised clinical study in patients colchicine-resistant FMF, supportive data from retrospective uncontrolled studies and the know safety profile in other autoinflammatory period fever syndromes, the benefit-risk balance of Kineret is considered positive in the treatment of familial Mediterranean fever.

3.8. Conclusions

The overall B/R of Kineret is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include the treatment of Familial Mediterranean Fever (FMF) for Kineret, to be given in combination with colchicine, if appropriate; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 5.2 has also been updated.

Furthermore, the PI is brought in line with the latest QRD template version 10.1.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Kineret-H-C-000363-II-70'.