EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2013
EMA/CHMP/398765/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kineret

International non-proprietary name: anakinra

Procedure No. EMEA/H/C/000363/X/0042

Note

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

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Product information

Name of the medicinal product:	Kineret
Applicant:	Swedish Orphan Biovitrum AB (publ) SE-112 76 Stockholm Sweden
Active substance:	anakinra
International Nonproprietary Name/Common Name:	anakinra
Pharmaco-therapeutic group (ATC Code):	Interleukin inhibitor (L04AC03)
Therapeutic indication:	Kineret is indicated in adult and paediatric patients for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including: - Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA) - Muckle-Wells Syndrome (MWS) - Familial Cold Autoinflammatory Syndrome (FCAS)
Pharmaceutical form:	Solution for injection
Strength:	100 mg/0.67 ml
Route of administration:	Subcutaneous use
Packaging:	Pre-filled syringe
Package sizes:	1, 7 and 28 pre-filled syringes

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List of abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the curve
BSA	Body surface area
CAPS	Cryopyrin-associated periodic syndromes
CI	Confidence interval
CINCA	Chronic infantile neurologic cutaneous articular syndrome
CL/F	Apparent total body clearance after subcutaneous administration, where F=systemic bioavailability
Cmax	Maximum plasma concentration
CNS	Central nervous system
CRF	Case report form
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DMARDs	Disease modifying antirheumatic drugs
DNA	Deoxyribonucleic acid
DSSS	Diary symptom sum score
E. coli	*Escherichia coli*
ESR	Erythrocyte sedimentation rate
FCAS	Familial cold autoinflammatory syndrome
hsCRP	High sensitivity C-reactive protein
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL-1Ra	Interleukin-1 receptor antagonist
IPC	In-process control
IRB	Institutional Review Board
ITT	Intention to treat
ISR	Injection site reaction

JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
MWS	Muckle-Wells syndrome
MAS	Macrophage activation syndrome
NIH	National Institutes of Health
NOMID	Neonatal-onset multisystem inflammatory disease
NSAIDs	Non-steroidal anti-inflammatory drugs
QoL	Quality of life
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
RA	Rheumatoid arthritis
RMANCOVA	Repeated measures analysis of covariance
SAA	Serum amyloid A
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SEM	Standard error mean
SmPC	Summary of product characteristics
Sobi	Swedish Orphan Biovitrum
SOC	System organ class
US	United States
USP	United States Pharmacopoeia
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Swedish Orphan Biovitrum AB submitted to the European Medicines Agency (EMA) on 30 October 2012 an extension application for the Marketing Authorisation for Kineret, through the centralised procedure falling within Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2 c).

Swedish Orphan Biovitrum AB is the Marketing Authorisation Holder (MAH) for Kineret 100 mg solution for injection in pre-filled syringe for subcutaneous use indicated in the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients with an inadequate response to methotrexate alone.

The MAH applied for a new strength 100mg/0.67 ml solution for injection in a pre-filled syringe (subcutaneous injection) for a new indication in adult and paediatric patients for the treatment of Cryopyrin-Associated PeriodicSyndromes (CAPS), including:

- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological,Cutaneous, Articular Syndrome (CINCA)
- Muckle-Wells Syndrome (MWS)
- Familial Cold Autoinflammatory Syndrome (FCAS)

The prefilled syringe also allows the administration of the 100 mg dosage required in RA patients.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0066/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0066/2012 was not yet completed as some measures were deferred.

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 applicant 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 applicant received scientific advice from the CHMP on 19 May 2011. The scientific advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Kineret has been given a Marketing Authorisation in the European Union on 08 March 2002.

1.2. Manufacturers

Manufacturer of the active substance

Boehringer Ingelheim RCV GmbH & Co KG
Dr.-Boehringer-Gasse 5-11
A-1121 Vienna
Austria

Manufacturer responsible for batch release

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

1.3. Steps taken for the assessment of the product

Rapporteur: Jens Ersbøll

- The application was received by the EMA on 30 October 2012.
- The procedure started on 21 November 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 February 2013 (Annex 1).
- The PRAC RMP Advice and assessment overview, adopted by PRAC on 05 March 2013 (Annex 2).
- During the meeting on 21 March 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 03 July 2013. (Annex 4).
- During the CHMP meeting on 25 July 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 August July 2013 (Annex 6).
- PRAC Rapporteur AR, adopted as PRAC on 05 September 2013 (Annex 7).

- During the meeting on 19 September 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension of the Marketing Authorisation for Kineret.

2. Scientific discussion

2.1. Introduction

Problem Statement

The extension of the Marketing Authorisation concerns a new strength (100 mg/0.67 ml) presented in a graduated single-use pre-filled syringe to allow a new dose regimen required for CAPS (Cryopyrin-Associated Periodic Syndromes) patients. The prefilled syringe also allows the administration of the 100 mg dosage required in RA patients.

Cryopyrin-associated periodic syndromes (CAPS) is a rare monogenetic systemic autoinflammatory disease including the 3 sub-diagnoses neonatal onset multisystem inflammatory disease/chronic infantile neurological cutaneous articular syndrome (NOMID/CINCA), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FCAS). CAPS is a life-long disease, and symptoms appear early in life. The intended treatment population thus includes both paediatric and adult patients. The disease affects all ethnic groups and both sexes equally.

In CAPS, the CAPS-associated mutations in the NLRP3 (also known as CIAS1) gene lead to an uncontrolled release of the proinflammatory cytokine IL-1β, which induces inflammatory disease symptoms. The central role of IL-1 in CAPS has been demonstrated with IL-1 blocking agents (canakinumab and rilonacept) leading to a rapid clinical improvement of the inflammatory disease symptoms.

CAPS, in all 3 subdiagnoses, are characterized by a multitude of inflammatory symptoms, including persistent urticarial-like skin rash, arthralgia, fever, headache and malaise. Laboratory findings reflect the presence of systemic inflammation and include leukocytosis, elevations in serum levels of amyloid A (SAA) and C-reactive protein (CRP), and increased erythrocyte sedimentation rate (ESR). Patients with FCAS and MWS experience frequent, intermittent episodes of incapacitation. FCAS is a chronic disease punctuated by acute flares triggered by exposure to cold, whereas in patients with MWS, the symptoms are more constant, and flares are unpredictable. In addition, patients with MWS often develop progressive neurosensory hearing loss. In the most severe form of CAPS, NOMID/CINCA, arthropathy associated with patellar and epiphyseal osseous overgrowth and neurological manifestations, including chronic aseptic meningitis, papilledema, sensorineural hearing loss, and mental retardation also to a variable degree affect patients. Approximately 20% of patients with NOMID/CINCA die before reaching adulthood if untreated. It is estimated that less than 200 individuals are affected by CAPS in the Western world, but milder and incomplete forms of the disease may be difficult to recognize.

About the Product

Kineret (anakinra) is a recombinant, non-glycosylated form of the human interleukin-1 (IL-1) receptor antagonist (IL-1Ra) produced in *E. coli* using recombinant DNA techniques.

Anakinra is a 153 amino acid protein with an approximate molecular weight of 17.3 kDa. Anakinra belongs to the pharmacological class of IL-1 inhibitors, L04AC03 and is currently approved for the treatment of the signs and symptoms of RA in combination with methotrexate, in adults with an inadequate response to methotrexate alone. The recommended dose of anakinra is 100 mg administered once a day by subcutaneous injection. The dose should be administered at approximately the same time each day.

The use of anakinra in CAPS patients includes a new dosage regimen that requires the allowance of partial use of the Kineret syringe. The proposed doses of anakinra in CAPS patients is as follows: recommended starting dose is 1-2 mg/kg/day by subcutaneous injection, and recommended maintenance dose is 1-2 mg/kg/day for milder cases and 3-4 mg/kg/day for more severe CAPS or patients with inadequate responses. Dose adjustments are to be performed in steps of 0.5-1 mg/kg. Daily life long treatment is expected, as anakinra alleviate the symptoms, but does not remove the underlying cause of CAPS.

Type of application and aspects on development

The applicant has submitted an application for an application for an extension of Marketing Authorisation for Kineret, under Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2 c).

The applicant received scientific advice from the CHMP on 19 May 2011. The scientific advice pertained to quality, non-clinical and clinical aspects of the dossier.

2.2. Quality aspects

2.2.1. Introduction

Kineret is currently approved as 100 mg solution for injection in a non-graduated pre-filled syringe. The extension of the Marketing Authorisation concerns a new strength (100 mg/0.67 ml) presented in a graduated single-use pre-filled syringe to allow a new dose regimen required for CAPS (Cryopyrin-Associated Periodic Syndromes) patients.

The graduation of the syringe with a dosage range of 20-100 mg and scale intervals of 10 mg is obtained by placing a graduated label on the syringe instead of the currently approved non-graduated label.

Kineret active substance and finished product are identical to the product already approved, except for the use of a graduated label. No additional changes have been made to the product.

2.2.2. Active Substance

Anakinra is a recombinant, non-glycosylated form of the human interleukin-1 (IL-1) receptor antagonist (IL-1Ra) produced in *Escherichia coli*. The primary amino acid sequence is identical to

the naturally occurring form of the protein except for the addition of an N-terminal methionine residue, required for production in *E. coli*. Anakinra is a 153 amino acid protein with a mass of approximately 17.3 kDa.

Anakinra used for the manufacture of the new strength of Kineret 100 mg/0.67mL solution for injection presented in graduated pre-filled syringes has the same physicochemical, biological and immunological properties and is of the same quality as that used for the already marketed Kineret 100 mg solution for injection supplied in non-graduated pre-filled syringes.

No further data was provided regarding the active substance for this line extension application as no new information or assessment was required.

2.2.3. Finished Medicinal Product

Kineret is supplied as a sterile solution for injection for subcutaneous use with a deliverable volume of 0.67 mL in pre-filled, single use, colourless borosilicate Type I glass syringes. The syringe is labelled with a transparent label with a printed graduation made of a clear polyester film and an acrylic adhesive.

The primary packaging materials, a pre-filled syringe consisting of a syringe barrel assembly and an elastomeric plunger stopper (bromobutyl rubber) have been adequately described. All components meet Ph. Eur. and USP requirements where applicable.

Studies to monitor physicochemical aspects of the elastomeric stopper, extraction characteristics of the rubber closure and functional suitability indicate that the container system has no adverse impact on the finished product. Based on the results of various physical, chemical, and functional tests of the components the selection of the container closure system is therefore considered appropriate for the storage and delivery of the finished product.

Adventitious agents

No excipients of human or animal derived material are used in the manufacture of this medicinal product. All excipients used comply with the European Pharmacopoeia (Ph. Eur.) requirements.

Manufacture of the product

The finished product manufacturing process is generally well-described. The dossier contains adequate detailed information on the manufacturing steps, operating conditions and in-process controls (IPC).

Aging studies have been performed and demonstrated that storage of the syringes does not affect the position or readability of the graduated label. Results from two aging studies (position and adhesion of the label after storage) have been provided and confirmed that the label will not be dislocated during storage.

Product specification

The proposed specifications for Kineret (100 mg/0.67 mL) and analytical methods are detailed in the dossier and remain the same as for the currently approved Kineret (100 mg).

Stability of the product

Based on the stability data provided the requested shelf-life (36 months when stored at 2°C to 8°C in the original container to protect from light) is considered acceptable.

For the purpose of ambulatory use, Kineret may be removed from the refrigerator for 12 hours at temperature not above 25°C, without exceeding the expiry date. At the end of this period, the product must be disposed of.

Kineret is presented in a pre-filled syringe for single use only, containing no preservative. The sterility of the product over its shelf life is assured by the integrity of the primary packaging components.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on development, manufacture and control of the new strength (100 mg/0.67 ml) of Kineret has been presented in a satisfactory manner.

The manufacturing process is well described. It was demonstrated that the manufacturing process of Kineret is capable, within its specified design parameters, of consistently producing a finished product or required quality.

The in-process control tests are described and deemed suitable for controlling and monitoring the manufacturing process.

The labelling process was validated and an additional in-process control was introduced to verify the position of the graduated label.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

2.3. Non-clinical aspects

2.3.1. Introduction

To support the original marketing authorisation application (MAA), an extensive number pharmacology, pharmacokinetics and toxicities studies were conducted.

No new non-clinical studies have been submitted in support of new application. In support of the pharmacodynamic rationale for the use of anakinra in CAPS, the applicant has made reference to literature references.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacodynamics studies performed with anakinra in support of the original application showed that anakinra inhibits the action of the cytokines IL-1α and IL-1β through its antagonist function at the receptor level. These cytokines are critical mediators of inflammation and joint damage in RA and other IL-1 driven diseases and cryopyrinopathies, e.g. CAPS.

Support for a role of anakinra in CAPS

Under normal conditions, serum and other body fluids do not contain detectable levels of IL-1. However, cellular production of IL-1 is induced in response to inflammation, immunologic reactions, microbial invasion, and tissue injury. The acute and chronic inflammatory diseases involving systemic inflammation associated with increased IL-1 activity are the IL-1-driven auto-inflammatory diseases collectively called CAPS. Clinical efficacy data show that a reduction of the IL-1 activity can prevent the tissue lesions. IL-1β is virtually undetectable in human plasma still increased IL-1β serum concentrations in humans with CAPS syndromes was demonstrated by administering the anti-human IL-1β-antibody canakinumab and measuring the IL-1β-antibody complex (Lachmann et al 2009).

Increased serum concentration of IL-1β has also been demonstrated in mice having mutations in the NLRP3 gene (Brydges et al 2009, Meng et al 2009). Hence, mice carrying mutations in the mouse NLRP3 gene (Nlrp3$^{A350V/+}$CreT, Nlrp3$^{L351P/+}$CreT) reproduce many of the features of CAPS syndromes in humans (scaling erythema, fever, arthralgia and conjunctivitis), although the phenotype appears to be more severe in this species (Brydges et al 2009). While the NLRP3 A350V mutants survived for up to 14 days, the NLRP3 L351P mutants all died within post-natal day one. When the NLRP3 A350V mutant mice were crossed with mice lacking the IL-1 receptor type 1, the resultant offspring showed no symptoms or signs of CAPS, demonstrating that IL-1 and its subsequent downstream signalling lies behind the symptoms associated with the condition in this model. Moreover, a slight increase in survival was observed following dosing with IL-1 blockers (Brydges et al 2009).

Meng et al (2009) studied a different NLPR3 gene mutation (R258W) in transgenic mice and found that following 10 days of treatment with an IL-1-receptor blocking antibody, the skin lesions of inflamed R258W mice were markedly improved compared to mice receiving a control treatment.

Although IL-1 plays a role in inflammation, in the brain, the interleukin is also involved in hippocampal-dependent memory process (Goshen et al 2007), and in brain development (Spulber et al 2007, Yirmiya et al 2002). Goshen et al (2007) state "IL-1β, IL-1Ra and IL-1 receptor genes are present during neonatal development in mouse embryos (Kruessel et al 1997), and their proteins are detectable starting from the 2 cell stage and throughout human embryonic development (De los Santos et al 1996) as well as human newborns (Pillay et al 1993). Specifically, IL-1β was found to increase with time in human forebrain cells during the first trimester." In the rat, IL-1 levels are increased immediately before birth and remain elevated until the end of the first post natal week (Guilian et al 1988) which is a period of neurodevelopment (Kaffman and Meaney 2007).

Goshen et al (2007) found that prenatal IL-1 blockade in mice have developmental consequences that results in memory deficiency in adulthood and state that this is consistent with previous reports on the neurodevelopment role of IL-1. Moreover, transgenic mice overexpressing the human soluble IL-1ra have smaller brains and poorer results in hippocampal-dependent learning tests than wild-type animals, and the difference is consistent in young (1 month old) and adult (12 month old) mice (Spulber et al 2011).

2.3.3. Ecotoxicity / environmental risk assessment (ERA)

No dedicated ecotoxicity/environmental risk assessment was performed for this medicinal product, which is in accordance with the applicable guidance. The active substance is a protein, the use of which is unlikely to result in significant risk to the environment. Therefore, anakinra is not expected to pose a risk to the environment.

2.3.4. Discussion on non-clinical aspects

Pharmacodynamics

No new non-clinical pharmacodynamic studies have been performed with anakinra to support he extension application. In support of the PD rationale for the use of anakinra in CAPS, the applicant has made reference to studies in transgenic mice reported in the literature which substantiated the pivotal role of IL-1 in CAPS. Taking into account also the convincing efficacy observed in the clinical studies, the CHMP considered this acceptable.

The available literature also indicated that IL-1 plays an important role in brain development. Hence, there appears to be a narrow physiological range of IL-1 required for optimal brain development and both too little and too much IL-1 is detrimental to the normal (and optimal) brain development (Spulber et al 2011). Anakinra has been shown to cross the blood-brain barrier and has been detected in the cerebrospinal fluid (CSF) of both rhesus monkeys and humans.

The human brain undergoes major development (brain growth spurt) within the first years after birth and brain development continues until adulthood (EMEA/CHMP/SWP/169215/2005). The possible influence of anakinra treatment on this phase of brain development is of importance. Furthermore, as IL-1 also plays an important role in memory and learning, e.g. hippocampal-dependent memory (Goshen et al 2007), the influence of anakinra in older children diagnosed

with less severe forms of CAPS is also of importance. During the procedure the MAH has discussed thoroughly the possible effects of anakinra treatment on brain development based on literature and elaborated on the clinical relevance of the literature findings of negative effects on brain development after pre-natal IL-1 inhibition. In summary, the pre-clinical findings distinctly demonstrated the absence of adverse effects on the development of hippocampal memory functions in pups exposed prenatally to anakinra by daily injections of the dams. Even though, the literature demonstrated that the development of the hippocampal memory is vulnerable to changes in IL-1 homeostasis, it appeared that hippocampal memory is only detrimentally affected when the foetus is subjected to chronic and complete blockade of IL-1 signalling or pathologically elevated IL-1 levels. The MAH has also highlighted results from Lepore et al (2010) where health-related quality of life was evaluated following anakinra treatment, compared to baseline and healthy controls. The MAH highlighted role/social limitations-emotional/behavioural, behaviour, general behaviour, mental health and parent impact-emotional scores, as considered related to normal brain function. In all five categories, the scores were improved (statistically significantly) compared to baseline. So even though the development of hippocampal memory is vulnerable to changes in IL-1 homeostasis, treatment with anakinra did not appear to have adverse effect on cognitive function or memory.

The safety pharmacology studies were evaluated as part of the original marketing authorisation application, and no anakinra related effects on the CNS, cardiovascular and respiratory systems were observed.

In the original MAA, it was established that anakinra acts on different receptors to both NSAIDs and corticosteroids; hence pharmacodynamic drug interaction with commonly co-administered medicine such as NSAIDs and corticoids is not anticipated. However, it has been shown in the clinical setting that co-administration of anakinra and etanercept (TNFα antagonist) increased the risk for neutropenia and serious infections. Therefore the concurrent use of Kineret with etanercept or any other TNF antagonist is not recommended as already addressed in the SmPC.

Pharmacokinetics

The Applicant has not performed any new PK studies. In the original MAA, PK studies performed in rats, rabbits and cynomolgus monkeys were included.

There are no clinical PK data available for children below 4 years of age. Anakinra is primarily excreted via the kidneys. The kidneys are functionally immature in children younger than one year. During the procedure, the Applicant further discussed the possible influence of the lack of kidney maturation on the PK of anakinra in the paediatric population. The glomerular filtration rate as studied by renal clearance of gentamicin and vancomycin (both evaluated as mL/min/kg) as well as inulin (evaluated as mL/min/1.73m^2, body surface area) was provided. For gentamicin and vancomycin, limited variation in body-weight normalised GFR was observed, whereas, when body-surface normalised data obtained for inulin, showed a much larger variation (decrease) in GFR. Records showed as much as a 6-fold difference from neonate (<24 h) to adult (neonate; approximately 20 ml/min/1.73m^2 and adult: 127 ml/min/1.73m^2). However, as the proposed indication is treatment from 8 months of age, the relevant literature value is the one listed for 3-12 months of age, at 103-110ml/min/1.73m^2. As the proposed SmPC specify mild renal impairment as GFR below 50 mL7min or 29 mL/min/1.73m^2, the reduced GFR observed in infants (3-12 months) is of no concern.

Available PK data in severe CAPS patients 4 years of age and above, support minor influence of age on the exposure to anakinra over 3.5 years of treatment. In study 03-AR-0298, patients between 8 months and 4 years of age (not included in the PK population) started at daily dosage of 1-2 mg/kg and were effectively treated with no reported safety concerns.

Toxicology

No new toxicology studies have been submitted in support of the present application. In support of the original application, single and repeated dose toxicity studies have been performed in both rat and cynomolgus monkey, and repeated dose toxicity studies in rhesus monkey as well. The lack of any new single-dose toxicity studies is acceptable and in line with the Questions & answers on the withdrawal of the "Note for guidance on single dose toxicity" (EMA/CHMP/SWP/81714/2010).

Kidney toxicity in the form of proteinuria, increased kidney weight, renal interstitial mononuclear cell infiltration and chronic progressive nephropathy were observed in rats treated with anakinra for 6 months. Taking these findings into consideration along with the fact that the elimination of anakinra is mainly through the kidneys and the kidney is functionally immature in children younger than one year, an increased risk for development of kidney toxicity in young children cannot be fully excluded. During the procedure, the MAH has discussed whether the administration of anakinra to children below one year of age may be associated with kidney toxicity. The MAH has argued, that the kidney toxicity observed in the 6 month rat repeat dose toxicity study is species specific, and due to the protein nature and human origin of anakinra. Anakinra may have contributed to the development of the chronic nephropathy in rats through immune complex formation and the renal excretion of anakinra protein causing a protein overload. In monkeys, proteinuria was also observed in the 4 week repeat dose study. Urinalysis confirmed that anakinra was found in the urine, and the MAH has drawn the conclusion that the proteinuria was a result of excreted anakinra and a sign of functioning renal clearance rather than a sign of kidney toxicity. This is supported by the CHMP. The MAH reinforced that no safety signals related to kidney toxicity was observed in patients down to 8 months of age (03-AR-0298). Therefore, the CHMP considered that there is no specific concern for the use of anakinra in CAPS patients above the age of 8 months with regards to kidney toxicity.

Since 1) slight effects on the immune system was observed in the toxicity studies conducted with anakinra (slight enhancement of the NK cell activity and a mild increase in eosinophil count in rats), 2) neutropenia is observed in the clinical setting and 3) the immune system undergoes development until adolescence, anakinra treatment might potentially be associated with effects on immune system development when administered chronically to children. During the procedure, the MAH has reviewed in the literature the impact of anakinra treatment on the developing immune system. The MAH has not found any indications that the developing immune system in animals is affected by chronic exposure to exaggerated levels of IL-1Ra (Boggs et al 1995, Doughty et al (1997), Ma et al 1998).

The MAH has also performed an examination of the clinical safety data (03-AR-0298), and showed that anakinra exposure would not affect the development of the immune system in CAPS patients. Of the patients younger than 1 year included in Study 03-AR-0298, 3 of 5 were hospitalized due to an infection once or more. However, all patients continued with anakinra treatment during infections, and the infections resolved without sequelae. Also in this study, 2

patients showed transient neutropenia, but did not discontinue anakinra treatment and the neutropenia resolved. Taken together, the published preclinical data from transgenic animals and the clinical safety data do not indicate that exposure to anakinra would affect the development of the immune system in CAPS patients. In addition, according to the proposed indication, patients younger than 8 months should not be treated with Kineret.

No juvenile studies were performed with anakinra. Juvenile animal studies focusing on the risk for treatment-related effects on CNS, kidney and immune system development could have provided valuable information on this aspect. However, finding an appropriate animal model to further elucidate the complexities of IL-1 homeostasis on brain development would prove to be difficult, as the dose-response relationship of IL-1 and brain development is bi-phasic, and both too little and too much is apparently detrimental to normal brain development. As the MAH pointed out, a CAPS mouse model of would possibly be suitable, however, as early mortality appeared evident (Brydges et al 2009), this model would be difficult to implement. Although there is limited clinical data available, the data previously discussed (Lepore et al 2010), are reassuring with regards to brain development. Overall, as discussed earlier in the present assessment, the concerns identified for adverse effects on CNS, kidney and immune system development mainly in children younger than two years of age have been addressed satisfactorily by the MAH and no further animal studies in juvenile models have been considered necessary by the CHMP.

As the proposed extension application does not introduce any new routes of administration, no additional local tolerance study needed to be conducted.

2.3.5. Conclusion on the non-clinical aspects

No new non-clinical studies have been submitted in support of the current extension application which is acceptable to the CHMP. In combination with the convincing clinical efficacy data, the CHMP also concluded that the literature data provided by the applicant supports the use of anakinra for the treatment of CAPS in the paediatric and adult populations.

2.4. Clinical aspects

2.4.1. Introduction

The clinical data consist of the pivotal clinical trial 03-AR-0298 supported by a meta-analysis of published prospective studies on the efficacy of anakinra in CAPS and published data from investigator sponsored, open-label, prospective and retrospective studies.

GCP

The pivotal clinical trial 03-AR-0298 was performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect this clinical trial conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3 Overview of the pivotal and supportive published prospective efficacy and safety studies

Study	CAPS sub-diagnosis	Design and control	Dose s.c. and duration	Primary assessments
Pivotal study				
03-AR-0298	NOMID/ CINCA*	Open-label Treatment withdrawal	0.9–7.6 mg/kg/d Median duration 4.9 years, open ended	Change in the disease diary score and SAA after 3-4 months SAA levels after drug withdrawal of 7 days
Supportive published, prospective efficacy studies				
Lepore et al 2010	NOMID/ CINCA MWS	Open-label Concurrent untreated controls	1–3 mg/kg/d 37.5 months (range, 12-54 months)	CHQPF50 Long-term efficacy
Kümmerle-Deschner et al 2011	MWS	Single group	100 mg/day in pts >40 kg; 1-2 mg/kg/d (up to 8 mg/kg) in pts <40 kg Median of 11 months, range 5-14 months	Change in MWS-disease activity score (DAS)
Hawkins et al 2004	MWS FCAS	Single group	100 mg/day, later reduced to 50 mg/day 12 weeks	Assessment of rash, conjunctivitis, neutrophilia, SAA and CRP
Ross et al 2008	FCAS	Open-label, cold challenge on/off treatment	100 mg/day 4-16 months	Assessement of signs and symptoms of FCAS Cold challenge Change in hsCRP
Hoffman et al 2004	FCAS	Open-label, cold challenge Single-dose study	100 mg at 24 and 1 hour prior to cold challenge 2 single doses	Assessement of signs and symptoms of FCAS Cold challenge

d=day; CHQPF50; Child Health Questionnaire CINCA= Chronic infantile neurologic cutaneous articular syndrome; CRP= C-reactive protein; FCAS= Familial cold autoinflammatory syndrome; hs=high sensitivity; MWS=Muckle-Wells syndrome; NOMID=neonatal-onset multisystem inflammatory disease; SAA=serum amyloid A; s.c.=subcutaneous; yrs=years
* Including 7 patients with overlapping NOMID/CINCA-MWS

Table 4 Overview of supportive published retrospective efficacy and safety studies

Study	CAPS sub-diagnosis	Design and control	Dose s.c. and duration	Primary efficacy assessments
Neven et al 2010	NOMID/ CINCA	Retrospective, chart review	1–10 mg/kg/d 31 months (range 26-42 months)	Long-term efficacy
Leslie et al 2006	NOMID/ CINCA, MWS FCAS	Retrospective, chart review	100 mg/day later reduced to 20-100 mg/day Treated patients 1-39.1 months	Assessement of disease signs and symptoms

d=day; CINCA= Chronic infantile neurologic cutaneous articular syndrome; FCAS= Familial cold autoinflammatory syndrome; MWS=Muckle-Wells syndrome; NOMID=neonatal-onset multisystem inflammatory disease; s.c.=subcutaneous

2.4.2. Pharmacokinetics

General PK has been investigated in healthy subjects and RA patients and was described in the original MAA for anakinra. The PK data in CAPS patients, especially in the paediatric population, is based on the pivotal study 03-AR-0298. For comparative purposes PK data from juvenile idiopathic arthritis (JIA) patients in study 990758 and its extension, study 990779, (Procedure OTH 017 assessed by the CHMP in 2006) and adult RA patients in study 0502 (original MAA) were reported in this submission. Finally, a population PK report 100788 (included in original MAA) was presented based on 3 studies in RA patients (studies 0501, 0502 and 0560). The study population, design, PK analysis method and evaluated PK evaluated variables are described in the table below.

Table 5 Overview of studies providing PK data

Study number	Study population	Study design	Dosage regimen[a]	PK data analysis	PK variables and factors
03-AR-0298	CAPS (NOMID/CINCA, MWS)	Prospective, long-term, open-label. PK samples: before dose, at 2, 4, 8, and 24 hours after first dose and after approx. 3 months and 3 years. One CSF sample at baseline and after 3 months.	s.c. 0.9-5.2 mg/kg/day	Non-compart-mental	Standard PK variables, Accumulation, Distribution to CSF Dose, Age, Body weight, Gender,
990758[b]	JIA	Multi-center, blinded, placebo controlled with an open-label run-in period PK samples: day 1, weeks 2, 4, 8, 12, 16, 20, 24, 28	s.c. 1.0 mg/kg up to 100 mg once daily	Plasma concentrations normalized to 1 mg/kg or 100 mg	Plasma concentration Body weight
0501[b]	RA	Single-center, double-blind, placebo-controlled, single-rising dose PK samples: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours	Single s.c. dose 0.5, 1.0, 2.0, 4.0, 6.0 mg/kg	Non-compart-mental	CL/F, $t_{1/2}$
0502[b]	RA	Single center, open-label PK samples: predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 h	s.c. 1, 2, 4 mg/kg once daily	Non-compart-mental	C_{max}, $t_{1/2}$, $AUC_{(0-24)}$, $AUC_{(0-\infty)}$, CL/F, Accumulation
0560[b]	RA	Multicenter, double-blind, dose-ranging PK sampes: pre-dose, weeks 1, 4, 12, 24 before dosage	30, 75, 100 mg s.c. once daily	Non-compartmental	[c]
0501[b] 0502[b] 0560[b]	RA RA RA	See above See above See above	See above See above See above	Population PK analysis of studies 0501, 0502, and 0560; Study Report 100788[b]	CL/F, V_d/F, k_a, $t_{1/2}$ Body weight, Height, Age, CL_{cr}, Sex, Race

[a]ITT population, i.e. not specifically the PK population, [b]Previously submitted to EMA, [c]Not referred to in the application; PK data included in NONMEM analysis.
CAPS= Cryopyrin-associated periodic syndromes; CSF=cerebrospinal fluid; ITT=intention to treat; JIA=juvenile idiopathic arthritis; NOMID=neonatal-onset multisystem inflammatory disease; NONMEM=nonlinear mixed-effect modeling software; PK=pharmacokinetics; RA=rheumatoid arthritis; s.c.=subcutaneous cerebrospinal fluid; CL/F= apparent total body clearance after subcutaneous administration; $t_{1/2}$=half-life; C_{max}=maximum concentration; AUC=area under the curve; V_d/F=apparent volume of distribution after subcutaneous administration, F=systemic bioavailability, k_a=absorption rate constant, CL_{cr}=creatinine clerance.

Study 03-AR-0298

Pharmacokinetic methodology

Blood samples for PK evaluation were drawn on 3 occasions: after the first dose, after approximately 3 months, and 3 years of treatment. At each occasion, blood was collected before

dose and at 2, 4, 8, and 24 hours after dose. In addition, one CSF sample per patient was drawn at baseline and after 3 months to evaluate the potential increase in interleukin-1 receptor antagonist (IL-1Ra) levels in the CSF following treatment with anakinra. Anakinra concentrations in serum and CSF samples were determined using the IL-1Ra Cytoscreen assay. The bioanalytical method was shifted from an IL-1Ra standard at baseline and Month 3 to an anakinra standard at 3.5 years. IL-1Ra and anakinra were analysed by an enzyme-linked immunosorbent assay (ELISA) method. The CSF samples were determined against the IL-1Ra standard.

Pharmacokinetic results

The PK population comprised 21 patients; of these, 13 patients were assessed at baseline (first dose), 14 at Month 3, and 16 at approximately 3.5 years. The median (range) age at the time of the first anakinra dose (N=21) was 11.4 (4.2-42.2) years. Of the 21 patients 13 were within the age interval 2-11 years, 4 patients within 12-17 years, and 4 patients above 18 years. The median body weight was 31.3 kg with a range of 13.0-82.2 kg. The gender distribution was 11 males and 10 females, and the race distribution was 17 White, 1 Asian, 1 Black, and 2 Other. The dose range during the PK assessments was 1.0-4.5 mg/kg/day administered subcutaneously. The concentration in CSF was measured before start of treatment in 11 patients and after about 3 months in 12 patients.

The PK population exhibited baseline serum concentrations of IL-1Ra before the first dose that extended above but covered that reported for healthy subjects. Once-daily dosing resulted in a low increase in IL-1Ra in serum after the first dose until Month 3, consistent with the PK of anakinra. The IL-1Ra concentration in CSF increased from 15.7 pg/mL before the first dose of Kineret to 797 pg/mL (median of N=12) at Month 3. This is in line with the previous finding of CSF penetration in non-human primates (Fox et al 2010). At a median s.c. dose of 3 mg/kg once daily and a median treatment time of 3.5 years, the median (range) peak steady-state serum concentration of anakinra was 3628 (655–8511) ng/mL and the trough concentration was 203 (53–1979) ng/mL. The median (range) half-life of anakinra was 5.7 (3.1–28.2) hours. Within the age and body-weight range of the subjects in the PK population, the dose-adjusted area under the curve from time 0 to 24 hours (AUC0-24h) and maximum plasma concentration (Cmax) showed no trend versus age or body weight, and there was no gender difference in the PK.

The exposure of IL-1Ra in terms of dose adjusted Cmax, C24h and AUC0-24h is given in the table below after the first dose of anakinra and at Month 3. The estimated median dose normalized AUC0-24h in all patients increased from 4353 ng·h·mL-1/mg·kg-1 at baseline to 4897 ng·h·mL-1/mg·kg-1 following 3 months of treatment, which corresponds to an increase of about 12%. The observed increases in AUC0-24h in the age classes 2-11, 12-17 and ≥18 years were 14%, 33%, and 24%, respectively. The numbers of patients in the respective age groups were small, ranging between 1 and 9.

Table 6 Median (range) of IL-1Ra exposure (PK population)

Following first dose of anakinra[a]				
Parameter	**2-11 yrs (n=9)**	**12-17 yrs (n=1)**	**≥ 18 yrs (n=3)**	**All (n=13)**
C_{max} / Dose	334 (136-921)	191	272 (212-484)	314 (136-921)
C_{24h} / Dose	17.0 (1.5-51.2)	9.2	55.3 (15.7-118)	17.0 (1.5-118)
AUC_{0-24h} / Dose	4353 (1783-6931)	2778	4605 (3114-5010)	4353 (1783-6931)
At Month 3[b]				
Parameter	**2-11 yrs** (n=9)	**12-17 yrs** (n=2)	**≥ 18 yrs** (n=3)	**All** (n=14)
C_{max} / Dose	415 (286-1015)	253 (182-325)	442 (413-733)	414 (182-1015)
C_{24h} / Dose	23.2 (6.5-73.3)	26.1 (20.3-31.9)	45.2 (22.5-105)	25.8 (6.5-105)
AUC_{0-24h} / Dose	4962 (2424-9172)	3686 (2759-4613)	5688 (4135-10204)	4898 (2424-10204)

[a]The unit for C_{max} and C_{24} is ng/mL, for AUC ng·h/mL and for dose mg/kg. Dose of anakinra was 1.0 mg/kg for all patients.

[b]The unit for C_{max} and C_{24} is ng/mL, for AUC ng·h/mL and for dose mg/kg. Median anakinra dose was 1.5, 1.3, 1.5, and 1.5 mg/kg in the respective age column. Median treatment time is 2.7, 2.8, 2.7, and 2.7 months in the respective age column.

IL-1Ra=interleukin-1 receptor antagonist; C_{max}=maximum concentration; C_{24h}=concentration 24 hours after dose; AUC=area under the curve.

The median CSF concentration increased from a baseline value before the first dose of anakinra of 15.7 pg/mL (N=11) to a Month 3 concentration of 797 pg/mL (N=12).

Table 7 CSF concentrations of IL-1Ra at Month 3 (study 03-AR-0298)

	Baseline (N=11)	**Month 3 (N=12)**
	Pre-dose CSF (pg/mL)	CSF during treatment (pg/mL)
Median	15.7[a]	797
Min	15.7[a]	213
Max	69.4	1172

[a]Values < LLOQ are assigned ½ of LLOQ, i.e. 15.7

CSF=cerebrospinal fluid; LLOQ=lower limit of quantification; max=maximum; min=minimum; PK=pharmacokinetics; IL-1Ra= Interleukin-1 receptor antagonist; N=number of patients.

Comparison of PK parameter in CAPS and RA patients

In the table below PK parameter values are listed from the once-daily treated patients in the pivotal CAPS study 03-AR-0298, the 0502 RA study, and the population PK evaluation in RA patients (100788).

Table 8 Overview of dose-normalized PK parameter estimates (studies 03-AR-0298, 0502 and population PK report 100788)

Parameter	03-AR-0298 median (range) 3.5 year treatment	Study 0502[a] median (range) or mean [SD] 7 days treatment	Report 100788 mean (SD)
C_{max} (ng/mL)	999 (419-2432)	878 (558-1065)	NR
t_{max} (hours)	4.0 (2.0-8.0)	6.0 (2.0-10)	NR
CL/F mL/min·kg	73.5[b] (34.1-207)	86.6 (70.3-155)	86.3[c] 128[d]
$t_{1/2}$ (hours)	5.7 (3.1–28.2)	5.7 [2.7][e] 4.1 [1.2][f] 10.7 [4.3][g]	7.5 (2.7)[h] 8.3 (2.0)[i]
C_{24h} (ng/mL)	60 (29–640)	149 (21.3–374)	NR

[a]The dose-normalized parameter estimates are not included in the study report but have been retrospectively estimated.
[b]Mean (SD) =94.4 (53.5)
[c]Mean (SD) CL/F for study 0501/0502 was reported as 105 (27) mL/min. Non-compartmental mean (SD) estimates for study 0501 and study 0502 are 101 (23) and 121 (31) mL/min, respectively. An adjusted value based on the Bayesian estimate and an average reported body weight of 73 kg (71.7 kg for study 0501 and 74.8 kg for study 0502) resulted in CL/F of 86 mL/min kg.
[d]Mean (SD) CL/F for study 0560 was reported as 149 (24) mL/min. Non-compartmental mean (SD) estimate was 149 (24) mL/min. An adjusted value based on the Bayesian estimate and an average body weight of 69.6 kg resulted in a CL/F of 128 mL/min·kg.
[e]1 mg/kg; [f]2 mg/kg; [g]4 mg/kg
[h]Study 0501 and study 0502. Non-compartmental mean (SD) estimates were 5.9 (3.0) and 6.6 (4.0), respectively.
[i]Study 0560 NR=Not reported; SD=standard deviation; C_{max}=maximum concentration; t_{max}= time at maximum concentration; $t_{1/2}$=half-life; CL/F=apparent clearance after subcutaneous administration, F=systemic bioavailability, C_{24h}=concentration 24 hours after dose

Effect of demographic variables on the pharmacokinetics of anakinra

- Body weight

CAPS patients in study 03-AR-0298 were dosed on a body weight basis and adjusted according to the severity of the disease. No definite trend in exposure *versus* body weight was observed. This indicates that the non-adjusted exposure is dependent on the body weight. In the population PK analysis it was demonstrated that anakinra CL/F value increased with increasing body weight.

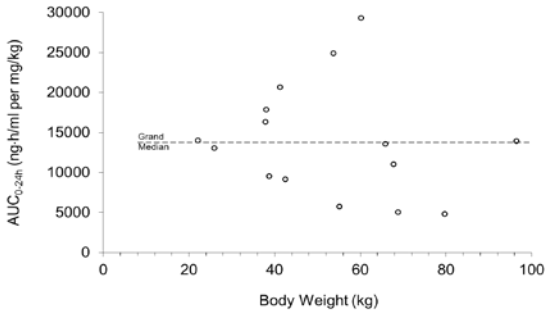


Figure 1 Dose-normalized steady-state AUC0-24h of anakinra versus body weight, 3.5 years of treatment (study 03-AR-0298)

For study 990758, the correlation between body weight and PK parameters in JIA patients has not been directly presented in the report (study 990758). However, plasma concentrations

normalized to a daily fixed s.c. dose of 100 mg anakinra, showed a trend of higher concentrations in the youngest JIA patients compared to JIA patients of higher age and to adult RA patients. Since there is a positive correlation between the JIA patient age groups and the RA patients, the normalized concentrations were inversely related to body weight, with higher ranges of concentrations observed for patients with the lowest body weights. The lower concentration at increasing body weight in in JIA patients (study 990758) is consistent with the results of the population PK modeling performed using data from adult patients with RA, which demonstrated that the anakinra CL/F value increased with increasing body weight (Report 100788). Overall, data on body weight, exposure, and clearance indicate that that dosage of anakinra should be adjusted for body weight, especially in the most severe form of CAPS, i.e. NOMID/CINCA.

- Gender

There was no obvious gender difference in the anakinra serum concentration time profiles in 8 male and 8 female patients in study 03-AR-0298. In the population PK analysis (Report 100788 in original MAA it was concluded that in study 0560 the mean CL/F value was approximately 14% higher in men than in women. However, after adjusting for CLcr and body weight, sex was not a significant factor for CL/F. After adjustment of CLcr and body weight, gender is not significant factor for CL/F.

- Age

PK data is not available for children below 4 years and below 15 kg from study 03-AR-0298. However, patients ≥ 0.7 years and with a body weight ≥ 6.0 kg have been included in the study and have successfully been initiated and maintained on treatment with positive outcome. Thirteen children < 2 years (age median (range) 1.2 (0.7-1.8) years, body weight median (range) 7.7 (6.0-15.2)) were included in the safety/efficacy study and treated successfully. For patients < 2 years of age, the starting dose ranged between 1.0 and 2.4 mg/kg (N=13). It can be estimated that patients at an age of 1 year need a 20% higher dose than a subject of 4 years to adjust for the higher clearance per kg body weight at the lower age. The safe and effective administration of Kineret in patients starting at 0.7 years of age is in line with the theoretically estimated relatively small changes in clearance from 4 years (from which PK data is available for anakinra) and down to about 1 year.

Table 9 Median (range) steady state PK parameters of anakinra per age category from 2 years of age, 3.5 years of treatment (study 03-AR-0298)

Parameter	2-11 yrs (n=5)	12-17 yrs (n=6)	≥ 18 yrs (n=5)	All (n=16)
Dose (mg/kg)	3.0 (2.4-4.4)	3.3 (2.5-4.5)	2.0 (1.5-4.0)	3.0 (1.5-4.5)
Treatment (years)	3.5 (0.7-4.0)	3.4 (2.5-3.8)	3.8 (1.8-4.8)	3.5 (0.7-4.8)
C_{max} / Dose	766 (461-1190)	1114 (684-2432)	1174 (419-2024)	999 (419-2432)
C_{24h} / Dose	34 (32-39)	120 (29-360)	131 (35-640)	60 (28.9-640)
AUC_{0-24h} / Dose	9354 (5759-13061)	15173 (11057-29321)	13933 (4828-24904)	13598 (4828-29321)
CL/F (mL/h·kg)	107 (76.6-173.6)	66.3 (34.1-90.4)	71.8 (40.2-207.1)	73.5 (34.1-207.1)

The unit for C_{max} and C_{24} is ng/mL and for AUC ng·h/mL. PK=pharmacokinetics; C_{max}=maximum concentration; C_{24h}=concentration 24 hours after dose; AUC=area under the curve; CL/F=apparent clearance after subcutaneous administration, F=systemic bioavailability.

A brief overview of general PK is provided for completeness. Distribution to CNS is added.

Absorption

Following subcutaneous injection, anakinra is absorbed with maximal plasma levels obtained within 3 to 9 hours post injection. The relative bioavailability of anakinra following subcutaneous injection is approximately 95%. Following subcutaneous injection, the terminal half-life of anakinra is longer than after intravenous injection (3 to 9.5 hours versus 2 hours), reflecting the effect of the slow absorption rate following subcutaneous injection.

Distribution

Following intravenous injection, anakinra distributes initially into a volume of 3.6 L and subsequently distributes into a steady-state volume of 9 to 15 L. These volumes of distribution data were consistent with initial distribution into the physiological plasma volume (3 L) and subsequent distribution into a steady-state distribution volume that approximates the extracellular volume (18.2 L). In study 03-AR-0298 CSF IL-1Ra concentrations in lumbar puncture samples were measured at baseline and at Month 3 in 11 and 12 patients respectively. The median CSF concentration of CSF IL-1Ra increased from a pre-dose baseline of 15.7 pg/mL to a Month 3 concentration of 797 pg/mL.

Elimination

In the dose-range studied (1 to 10 mg/kg) the pharmacokinetics of anakinra was linear. The clearance is about 150 ml/min and is correlated to renal creatinine clearance. Clearance was modestly higher than the estimated glomerular filtration rate. These data suggest that in humans (like in animals), anakinra is predominantly eliminated via the kidneys. However, the route of

elimination has not been studied directly in humans. Urinary recovery of anakinra in humans was low suggesting that anakinra filtered in the glomeruli is absorbed and metabolised by the renal tubular cells.

Dose proportionality and time dependencies

Dose proportionality

In study 03-AR-0298 the starting dose ranged from 1.0 – 2.4 mg/kg. Dose increments of about 0.5 mg/kg were performed approximately 6 months after initiation of treatment and then after an additional 12 months and thereafter additionally 18-36 months, i.e. after treatment times of about 6, 18, and 36-54 months duration based on clinical response (clinical symptoms and elevated CRP). Due to dose adjustments in order to achieve the treatment objectives, the average dose at the end of the study was higher than the initial dose levelling off to a range of 3.2-3.6 mg/kg after 48-60 months, for all age groups (<2, 2-11, 12-17 and ≥ 18 yrs).

In a retrospective study of 10 patients with CAPS (Neven et al, 2010), the two youngest patients of 3 and 4 months require a dosage of 6 mg/kg/day to achieve relieve of symptoms.

The minimum amount to be delivered directly from the graded syringe is proposed to be 20 mg, and dose adjustments possible in steps of 10 mg. Anakinra PK exhibits approximate dose linearity with a slight tendency to higher than proportional increase with increasing dose.

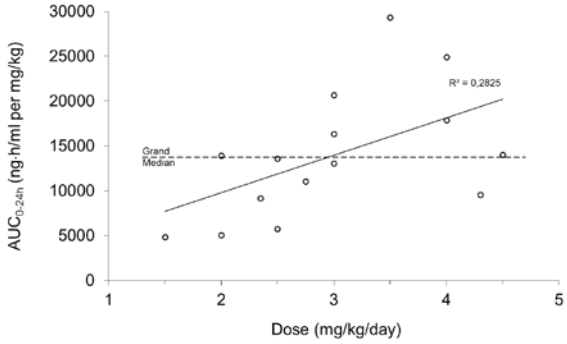


Figure 2 Dose-normalized steady-state AUC0-24h of anakinra versus dose (3.5 years of treatment) (study 03-AR-0298)

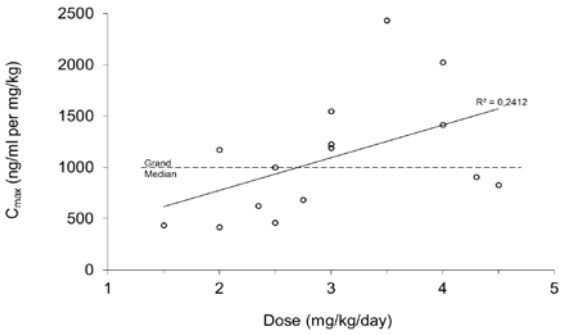


Figure 3 Dose-normalized steady-state Cmax of anakinra versus dose (3.5 years of treatment) (study 03-AR-0298)

No formal dose frequency evaluation was performed. In study 03-AR-0298 95 % of the patient years represented once-daily dosing. During the withdrawal period clinical symptoms appeared after the first day, confirming the necessity of once-daily dosing.

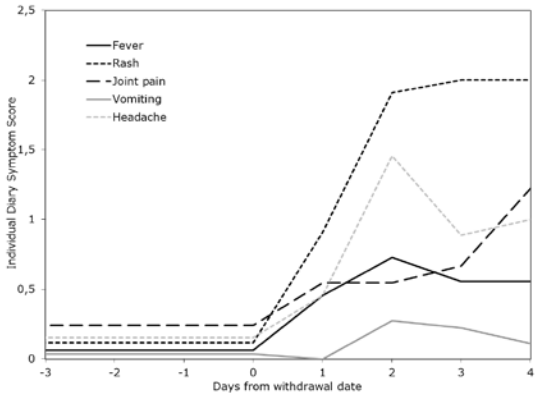


Figure 4 Pre- and post-drug withdrawal diary score for each of the 5 key symptoms of DSSS (study 03-AR-0298)

Time dependency

It was not possible to measure the accumulation of anakinra between 3 months and 3.5 years in study 03-AR-0298 due to change in standard IL-1RA to anakinra in the bioanalytical method. Numerically there is a 3-fold increase in dose-adjusted exposure, but the apparent increase in exposure may be due to the change in standard. Preclinical data have shown significant accumulation that may be the result of decreases in glomerular filtration of anakinra secondary to binding to anti-anakinra antibodies or other proteins. There is no evidence of decreased clearance after 3.5 years of treatment.

Special populations

No new studies have been performed in patients with impaired renal or hepatic functions.

Pharmacokinetic interaction studies

No drug-drug interaction study has been performed.

2.4.3. Pharmacodynamics

Mechanism of action

At the molecular level, CAPS-associated mutations in the NLRP3 (also known as CIAS1) gene leads to an uncontrolled release of the proinflammatory cytokine IL-1β. Kineret blocks the biological activity of IL-1 by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI), which is expressed in a wide variety of tissues and organs. *Ex vivo* CAPS patient cells secrete high levels of cytokine response to inflammatory stimuli, which confirms the importance of IL-1β in the pathogenesis of CAPS. IL-6 is a downstream cytokine of IL-1β and, in contrast to IL-1β, IL-6 is readily measurable in serum from patients with CAPS. Besides the

clinical symptoms of CAPS, IL-1β also mediates the synthesis of the hepatic acute phase reactants CRP and SAA. These are common and sensitive markers for inflammation. CRP, SAA and IL-6 are markers for the pharmacodynamics of anakinra. Together they confirm the antagonism of IL-1β by Kineret and support the treatment effect of Kineret in CAPS.

Primary pharmacology

This section summarizes findings on the selected markers for the PD of Kineret, i.e. CRP, SAA and IL-6. The data on these markers are derived from the pivotal trial supporting this application supported by 7 studies published in the literature. The three selected markers have not consistently been reported in all studies but together they confirm the antagonism of IL-1β by Kineret and support the treatment effect of Kineret in CAPS. The studies are listed below.

Table 10 Overview of studies providing the selected PD data

Study	Study population	Study design	Dosage regimen
03-AR-0298[a]	43[b] CAPS patients (NOMID/CINCA, NOMID/CINCA-MWS)	Open label Treatment withdrawal	0.9–7.6 mg/kg/d[b]
Lepore et al 2010 [d]	14 CAPS patients [b](NOMID/CINCA, MWS)	Open label Concurrent untreated controls	1–3 mg/kg/d
Kümmerle-Deschner et al 2011[e]	12 CAPS patients (MWS)	Single-group	100 mg/day in pts >40 kg; 1-2 mg/kg (up to 8 mg/kg) in pts <40 kg
Hawkins et al 2004	3 CAPS patients (MWS)	Single-group	100 mg/day, later reduced to 50 mg/day
Ross et al 2008	8 CAPS patients (FCAS)	Open-label, cold challenge on/off treatment	100 mg/day
Hoffman et al 2004	4 CAPS patients (FCAS)	Open-label, cold challenge Single-dose study	100 mg at 24 and 1 hour prior to cold challenge 2 single-doses
Neven et al 2010	10 CAPS patients (NOMID/CINCA)	Retrospective, chart review	1–10 mg/kg/d
Leslie et al 2006	15 CAPS patients (NOMID/CINCA)	Retrospective, chart review	100 mg/day later reduced to 20-100 mg/day

[a] Results from a subpopulation are reported in Goldbach-Mansky et al 2006; [b] Safety population; [c] Treated with Kineret; [d] Results from subpopulations are reported in Gattorno et al 2007, Caroli et al 2007, and Lasigliè et al 2011; [e] Results from a subpopulation are reported in Kümmerle-Deschner et al 2011a

Below is the summary of changes of the selected markers (CRP, SAA and IL-6) in the clinical studies:

<u>Study 03-AR-0298</u>

Significant decrease in SAA (149 mg/L to 6 mg/L) and hsCRP (51 mg/L to 4 mg/L) from baseline to 3 Months treatment. IL-6 decreased with treatment and increased in serum when the product was withheld. The median (interquartile range) of IL-6 for cerebrospinal fluid were 43.93 pg/mL (26.19-93.37) at baseline and 21.61 pg/mL (7.76-68.90) at 3 months.

Lepore et al, 2010

A dramatic and persistent normalization of acute phase reactants was reported.

Kümmerke-Deschner et al, 2011

A statistically significant decrease in CRP and SAA from baseline to median follow-up (11 months) was reported. The CRP level normalized in 45% of those who had an elevation at baseline. The SAA levels mirrored the CRP, improving at 2 weeks and significantly decreasing over the long term.

Hawkins et al, 2004

After 7 days, the plasma SAA concentration decreased to <3 mg/L in all 3 subjects and remained below this level on fortnightly follow-up testing for 3 months.

Ross et al, 2008

The reduction in CRP during treatment was significant (mean change -14.38, 95% confidence interval [CI] 7.35 to -21.42, $p \leq 0.0001$) and was followed by a significant increase in CRP (mean change -15.19, 95% CI 4.88 to 25.50, $p = 0.0013$) post-treatment. Similar results were observed for SAA. Overall, the circulating concentration of CRP and SAA closely mirrored the clinical activity of the disease.

Hoffman et al, 2010

There were no significant differences in CRP or SAA between FCAS patients and controls at baseline. Although no change in acute phase reactants were observed the patients pretreated with 2 doses of anakinra 24 h apart before cold challenge did not develop any of the signs or symptoms that they developed during their previous cold challenge.

Neven et al, 2010

Of the 10 patients the two youngest (3 and 4 months old) had baseline CRP of 150 and 305 mg/L, respectively. The median (range) of CRP and SAA for the other 8 patients (6-19.8 years) were 69 (26-110) mg/L and 150 (48-386) mg/L, respectively. CRP and SAA levels in the patients > 6 years of age rapidly decreased 1 month after the initiation of anakinra. Further follow-up revealed dose-dependent benefits in 3 patients. Inflammation marker levels also significantly and persistently improved in the two youngest patients after upward adjustment of the anakinra dosage.

Leslie et al, 2006

Serum CRP and SAA levels normalized (< 10 mg/L) within 1 week in all patients, with median values of 2 mg/L and 5 mg/L, respectively.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

PK has been investigated in healthy subjects and patients with RA in the original MAA for Kineret. PK in CAPS patients and especially in the paediatric population is based on the pivotal CAPS study 03-AR-0298 where 21 of the 43 patients represent the PK population. For comparative

purposes PK data from JIA patients in study 990758 (previously assessed by the CHMP in 2006) and adult RA patients in study 0502 (original MAA) were included. Finally, a population PK evaluation was presented based on 3 studies in RA patients (0501, 0502 and 0560).

PK parameter values were presented from the once-daily treated patients in the pivotal CAPS study 03-AR-0298, the 0502 RA study, and the population PK evaluation in RA patients. The median clearance in study 03-AR-0298 was similar to the estimates from the repeated-dose segment of study 0502 (73.5 versus 86.6 mL/h.kg) whereas the median dose-normalized Cmax was rather higher (999 versus 878 ng/mL). For unknown reasons, a higher estimate was obtained for study 0560 (128 mL/h.kg) compared to study 0501/0502. The median terminal half-life estimates are similar, around 6 hours, for all studies. In study 03-AR-0298 one subject showed a distinctly longer half-life (28.2 hours) than other patients. However, based on the overall PK profile derived from the severe CAPS patients, no markedly different PK characteristics relative to RA patients are observed. Anakinra exhibits approximate dose linearity (Cmax and AUC) with a slight tendency to higher than proportional increase but this raise no clinical concern. The PK in CAPS patients is similar to that of RA patients.

Inter-individual variability from study 03-AR-0298 showed that the coefficient of the maximal concentration (C_{max}) is remarkable stable over time. The $AUC_{(0-24)}$/dose and the clearance range between and 31-51% and 36-59% respectively and thus, shows a greater variability. Intra-individual PK variability could not be estimated due to differences in the bioanalytical methods used during the study period of study 03-AR-0298.

PK results from study 03-AR-0298 have confirmed that anakinra distributes to the central nervous system as anakinra distributes to the cerebrospinal fluid.

The PK profile of anakinra has been evaluated in a subset of the CAPS patients in study 03-AR-0298. The median age of was 11.4 (4.2 to 42.2) years. PK data is thus not available from children below 4 years and below 15 kg. However, patients with an age ≥ 0.7 years and with a body weight ≥ 6.0 kg have been included in the study and have successfully been initiated and maintained on treatment with positive outcome. It was estimated that patients of 1 year need a 20% higher dose than a subject of 4 years to adjust for the higher clearance per kg body weight at the lower age. The safe and effective administration of Kineret in patients starting at 0.7 years of age is in line with the estimated rather small changes in clearance from 4 years and down to about 1 year. It is therefore considered that the PK data presented are representative of the target population.

CAPS patients were dosed on a body weight basis and adjusted according to the clinical response. Patients were started at a body weight adjusted dosage of 1-2 mg/kg/day. In the published studies supporting efficacy of Kineret the starting dose approach has been based on body weight as well as on a fixed dose. In the studies with FCAS patients (Hoffman et al 2009 and Ross et al 2008) only adults were included and they were started at a dosage of 100 mg/day. The same starting dose was used for MWS patients in the study by Hawkins et al 2004 and in the study by Kümmerle-Deschner et al 2011 for patients with body weights > 40 kg. In the study by Leslie et al 2006 NOMID/CINCA patients were also started at a dose of 100 mg. A 100 mg dose corresponds to a 1-2 mg/kg dose in patients within the body weight range 50 to 100 kg. For patients with lower body weights than 50 kg, a 1-2 mg/kg dose would accordingly reduce the starting dose to e.g. 20 mg for a 10 kg child, which in e.g. study 03-AR-0298 has

been demonstrated to be a safe and effective. This provides a rationale for a starting dose recommendation of 1-2 mg/kg for all CAPS patients.

Dose adjustments were performed with the aim to achieve efficacy in severe CAPS patients, i.e. systemic inflammatory remission and absence of organ inflammation. Dose increments of about 0.5 mg/kg were performed approximately 6 months after initiation of treatment and then after an additional 12 months and thereafter additionally 18-36 months, i.e. after treatment times of about 6, 18, and 36-54 months duration. It became clear during the initial years of treatment that, in addition to the basic criteria of preventing disease flares such as rash, fever, and elevated CRP, dose adjustments had to address "smoldering" organ inflammation to prevent progression of organ damage and to preserve organ function (e.g. hearing). Thus, the criteria for dose escalation evolved during the study from dose increases mainly due to clinical symptoms and elevated CRP to focus also on organ inflammation of eyes, inner ear, and CNS. Due to dose adjustments in order to achieve the treatment objectives, the average dose at the end of the study was higher than the initial dose leveling off to a range of 3.2-3.6 mg/kg after 48-60 months, for all age groups (<2, 2-11, 12-17 and ≥ 18 yrs). Information regarding the magnitude of dose adjustments in the supportive published studies are lacking. However, the dose adjustments applied in severe CAPS patients (steps of 0.5-1.0 mg/kg) would also be applicable for less severe CAPS patients. Dose adjustments could be easily managed due to the short half-life of anakinra.

No formal dose frequency response evaluation has been performed. However, the PK profile of anakinra and the data from the drug withdrawal population in study 03-AR-0298 support daily s.c. injection of anakinra. In study 03-AR-0298, 95 % of the patient years represented once-daily dosing and during the withdrawal period clinical symptoms appeared after the first day, confirming the necessity of once-daily dosing.

The accumulation from the first dose until Month 3 was low (using IL-1Ra standard). Concentrations after approximately 3.5 years (using anakinra standard) were similar to those observed in RA studies.

No drug-drug interaction studies have been performed in human subjects. Experimental studies in human hepatocyte culture published in the literature have shown that that interleukin (IL)-1β and IL-6 both suppress cytochrome P450 mRNA and enzyme levels in vitro. The MAH has performed a search in their safety database in order to evaluate the clinical effect of this potential interaction. From a total of 26,000 reports in the safety database, 16 events that could potentially result from an increased activity of the cytochrome P-450 enzyme system were identified. Therefore, the MAH proposed to add in section 4.5 of the SmPC that the formation of CYP450 enzymes is suppressed by increased levels of cytokines, and that treatment with an IL-1 receptor antagonist might normalize/change the formation of CYP450 enzymes. Based on the data presented and analysed the CHMP considered justified to include the information in the SmPC.

Pharmacodynamics

The 8 studies providing efficacy data also reported data on markers for pharmacodynamic responses. SAA and CRP are acute phase reactants that are closely related to IL-1 activity, and thereby reflect treatment efficacy of anakinra. Since CRP and SAA were not measured in all studies, IL-6 was also included as a PD marker to be assessed across studies. Thereby an

outcome was measurable in all studies, including Hoffman et al 2009, where only 2 single-doses were given to FCAS patients. Decreased levels of CRP following anakinra treatment were reported in all CAPS entities at repeated dosages. SAA also decreased in all studies where measurements were performed at repeated dosage. IL-6 decreased in FCAS patients (both at single and repeated dosage), in MWS and in NOMID patients. In study 03-AR-0298 the IL-6 decrease was more marked in CSF than in serum. The combined outcome of CRP, SAA and IL-6 as PD markers confirms that anakinra decreases IL-1 activity in all 3 CAPS entities.

The importance of daily dosing and maintaining adequate anakinra concentrations to achieve a stable PD response in terms of inflammatory biomarkers is obvious from data obtained from the withdrawal period in a subset of the CAPS patients in study 03-AR-0298. In study 03-AR-0298 the median SAA was 7 mg/L during Kineret treatment before the withdrawal period was started. At the end of the drug withdrawal period (duration 2-7 days), SAA had increased to 310 mg/L. A similar rapid response was found for high sensitivity C-reactive protein (hsCRP), which was 4 mg/L before the withdrawal and increased at the end of the withdrawal period to 72 mg/L.

2.4.5. Conclusions on clinical pharmacology

PK in CAPS patients has been shown to be similar to that in RA patients. Gender, race and age are not found to be significant factors for CL/F.

Data from the CAPS studies support a starting dose of 1-2 mg/kg in all 3 CAPS entities and ages. Up- or downward dose adjustments can be performed based on clinical response. Body-weight adjusted dosage is a safe and effective approach for treatment of CAPS, also in children older than one year. Weight adjusted dosage based on clinical and response and measures of CRP in increments of 0.5-1 mg/kg is appropriate. The maintenance dose is in general lowest in FCAS and highest in NOMID/CINCA patients.

No formal dose frequency response evaluation has been performed. However, the PK profile of anakinra and the data from the drug withdrawal population in study 03-AR-0298 support a once daily dosing in patients with severe CAPS or alternatively also on-demand in FCAS patients.

Dose adjustments were performed with the aim to achieve efficacy in severe CAPS patients, i.e. systemic inflammatory remission and absence of organ inflammation. The maximum allowed dose of anakinra was increased over time in the study from 1-2 mg/kg body weight, to 3 mg/kg, 5 mg/kg, and 10 mg/kg. The posology section of the SmPC reflects the clinical study data and current clinical practice.

Untreated CAPS patients are characterized by increased CRP, SAA and IL-6 relative to normal levels. Administration of Kineret resulted in a decrease in the acute phase reactants in all clinical CAPS studies except the study by Hoffman et al 2004, where only two doses of anakinra were given but where nevertheless a marked decrease in IL-6 expression level was observed. Decreased acute phase levels were noted within the first weeks of treatment and sustained throughout the studies. Anakinra treatment often resulted in complete normalization of the acute phase reactants. The combined outcome of CRP, SAA and IL-6 as PD markers confirms that anakinra decreases IL-1 activity in all 3 CAPS entities. The pharmacodynamic action of anakinra as an IL-1 receptor antagonist explains the clinical effect in CAPS patients with elevated IL-1.

2.5. Clinical efficacy

2.5.1. Dose response study

The anakinra dose is adjusted to the clinical response. No formal exposure-response evaluation has been performed.

2.5.2. Main study

Study 03-AR-0298: a long-term outcome study with the IL-1receptor antagonist anakinra in patients with neonatal onset multisystem inflammatory disease (NOMID/CINCA syndrome).

Methods

This was a prospective, long-term, open-label outcome study to investigate the clinical response of Kineret in NOMID/CINCA patients comparing the change in disease diary score from baseline to 3-6 months and every 6 months thereafter while on treatment. Change in SAA levels from before to after treatment was assessed. Long-term effects on neurological parameters, hearing, vision, joint status, and quality of life were studied. The overall study design and sequence of treatment periods are presented in Figure 1.

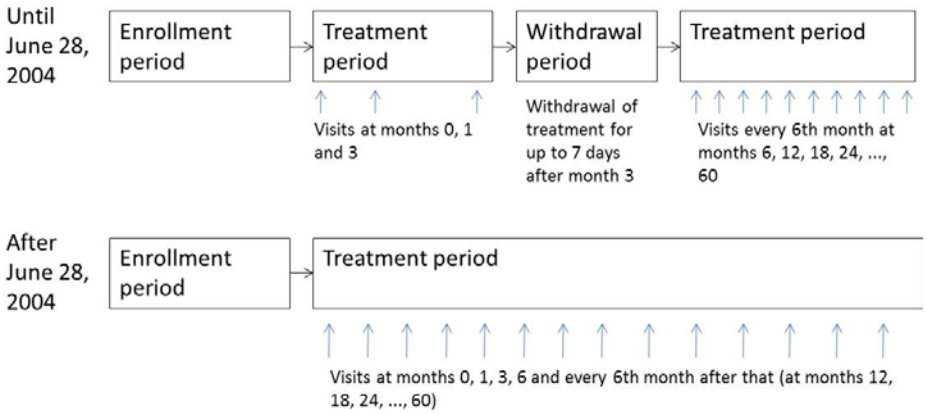


Figure 5 Study 03-AR-0298 design

The study comprised the following phases:

- *Enrolment/observation phase and initial treatment for 1-6 months*

  The enrollment/observation phase lasted for up to 3 weeks to determine main baseline characteristics. If eligible, the patient was started on an open-label administration of Kineret at 1-2 mg/kg/day by s.c. injections.

  Patients were admitted to the NIH for a standardized subspecialty examination before drug initiation and between 3 and 6 months after. The change in clinical diary scores from enrollment/baseline to the 3-6 months appointment was assessed (primary efficacy endpoint).

  Dose escalations between 0.5-1 mg/kg/day were possible in order to elicit positive response, on a case-by-case basis.

The protocol initially included visits after 1 month and after 3-4 months of Kineret treatment; however, for logistic reasons, these visits were no longer mandatory in later versions of the protocol, but instead replaced by a 3-6 month visit. Also, the screening period included 3 occasions for baseline blood draws to determine level of inflammation (1 week apart) for the first 18 patients, but the period was thereafter shortened to 3-7 days and coincided with the first visit to the NIH.

- *Withdrawal phase*

Prior to June 28, 2004, the study included a withdrawal phase, where, during a period of maximum 7 days, Kineret was withdrawn and clinical symptoms were recorded, as well as SAA, hsCRP, and ESR levels determined. However, the withdrawal period was discontinued, because of the significance of the study drug treatment effects seen in the first 11 patients and the severity of their flares upon withdrawal. During the time the withdrawal period was included in the protocol, assessment of change in SAA levels from before to after a maximum of 7 days of drug withdrawal or up to flare was included as a primary endpoint.

- *Month 6 visit and onward (open-ended extension phase)*

Patients received study treatment throughout the study. Patients and parents continued to fill out the NOMID/CINCA daily diaries. At any point during the study, patients could have the dose of Kineret increased by 0.5-1 mg/kg/day increments up to a maximum of 10 mg/kg/day if active disease persisted. They returned to the NIH for an outpatient safety and efficacy evaluation every 6 months. Annually, patients returned to the NIH for a full safety and efficacy assessment visit.

After 5 years of treatment in the study, patients were offered continued treatment and returned only for annual visits.

Study Participants

Individuals with NOMID were eligible for participation in this study. Patients previously evaluated at the NIH who had been clinically diagnosed with NOMID, including patients with and without mutations in CIAS1, were initially approached by telephone or during an NIH visit with an offer of participation. Newly diagnosed individuals could also be recruited.

Inclusion criteria

1. No age limitation (valid from July 2007)
2. Patients fulfilled at least 2 of the following 3 clinical manifestations:
    - Typical NOMID rash
    - CNS involvement (papilledema, cerebrospinal fluid (CSF) pleiocytosis, sensorineural hearing loss)
    - Typical arthropathic changes on radiographs (epiphyseal and/or patellar overgrowth)
3. Onset of manifestations of NOMID/CINCA at ≤6 months of age
4. Stable dose of steroids, NSAIDs, DMARDs for 4 weeks prior to enrolment visit

5. Washout period for biologics: 6 half-lives before Kineret administration for all drugs with anti-TNF properties. For etanercept (6 half-lives=24 days), this calculated to drug discontinuation 3 days before enrolment into the observation period, infliximab and adalimumab (6 half-lives=48 days drug were to be discontinued 27 days before the observation period, and thalidomide (6 half-lives=3 days) were to be discontinued 3 days prior to Kineret administration
6. Patient's or legal guardian's ability and willingness to give informed consent
7. Females of childbearing potential (young women who have had at least one menstrual period regardless of age) had to have a negative urine pregnancy test at baseline prior to performance of any radiologic procedure or administration of study medication. Women of childbearing age and men able to father a child, who were sexually active, were asked to use a form of effective birth control, including abstinence
8. Negative purified protein derivative (PPD) test using 5 T.U. intradermal testing per CDC guidelines with exception of inclusion criteria no. 9 below
9. Patients with latent tuberculosis (TB) (positive PPD test) had to have adequate therapy for TB initiated prior to first dose of study medication as recommended in published guidelines.

Exclusion criteria

1. Having received live virus vaccine during 3 months prior to baseline visit
2. Active infections or a history of pulmonary TB infection with or without documented adequate therapy, patients with current active TB, or recent close exposure to an individual with active TB
3. Positive testing for HIV, Hepatitis B or C known or documented at screening, enrolment or baseline visit
4. A history of, or concomitant diagnosis of, congestive heart failure
5. A history of malignancy
6. Prior use of anti-CD4 antibody
7. Known hypersensitivity to E. coli derived products or any components of Kineret
8. Presence of any other rheumatic disease or major chronic infectious/ inflammatory/ immunologic disease (e.g. inflammatory bowel disease, psoriatic arthritis, spondyloarthropathy, SLE in addition to NOMID/CINCA)
9. Presence of the following at enrolment visit: ALT or AST >2.0 x upper limit of normal (ULN) of the local laboratories values, creatinine >1.5 x ULN, WBC <3.6 x 109/L; platelet count <150,000 mm3
10. Enrolment in any other investigational clinical study or receiving an investigational agent, or had not yet completed at least 4 weeks since ending another investigational device or drug trial
11. Existing concern about compliance with the protocol procedures by patient and/or parent/s and legally acceptable representative/s

12. Lactating females or pregnant females
13. Patients with asthma were only included after evaluation by a pulmonary and infectious disease consultation
14. The use of other anti-IL-1 inhibiting agents or the initiation of a longer acting IL-1 inhibiting agent while on study led to non-enrolment or termination respectively.

Treatments

The initial dose of anakinra given was 1-2 mg/kg body weight per day. First evaluation of the clinical response was done 1-3 months after initiation. At intervals no less than 7 days, a patient who was not in clinical remission could continue to have his/her anakinra dose increased in increments between 0.5 and 1 mg/kg to a maximum dose of 10 mg/kg per day to achieve clinical remission.

Criteria for dose escalation included:

1. A clinically inadequate response (one of the following criteria):
   - improvement on the diary score from baseline by less or equal to 20%
   - SAA level >10mg/mL
   - requirement of additional DMARD therapy (the date and time of initiating additional therapy were to be recorded, for steroid increase.
   - persistently elevated CRP level >0.5mg/dL
   - persistent active (inflammatory) organ disease and/or
2. Development of a flare (as defined below) after having received Kineret for at least 4 weeks.

   A flare was defined as at least 2 of the following parameters:
   - If the typical rash of NOMID worsened (increase in rash diary score by 1 or more) on 4 different days in one week.
   - If fever occurred on 4 or more occasions in one week with a temperature of >98.6°F, (>37°C). Temperature was taken axillary every morning before drug administration, temperature could be taken additionally when clinically suspected.
   - If episodes of vomiting or headache developed on 3 days out of a week, were more frequent than before, and could not be attributed to an infection.
   - If neurosensory symptoms associated with worsening of the disease occurred, including vision or hearing impairment or new onset tinnitus or vertigo (only one criterion required to meet definition of flare). Corneal oedema was retrospectively included as a symptom indicating eye flare because of the seriousness of the condition.

Prior and concomitant therapy

Enbrel, Remicade, Humira, and other anti-TNF inhibitory drugs such as thalidomide were to be discontinued prior to initiation of Kineret therapy because of the increased risk of infection on combination treatment. Concomitant DMARDs other than Enbrel, Remicade, and other anti-TNF

inhibiting agents such as Humira or thalidomide could be continued throughout the study. DMARD use was to remain stable during the initial 3-6 months, but tapering was permitted thereafter. Steroid use could be reduced according to the guidelines.

Objectives

Primary objectives:

- Assess the change in the disease diary score after 3-6 months of open-label administration of anakinra
- Assess the change in serum amyloid A (SAA) levels before and after 3-6 months of treatment
- Assess the change in SAA levels after drug withdrawal of 7 days

Secondary objectives:

Clinical

- Resolution or improvement in CNS disease activity: intracranial pressure, pleiocytosis, number and intensity of recurrent headaches, vomiting, seizures
- Resolution or improvement of eye disease: uveitis, papilledema
- Resolution, improvement or stabilization of hearing impairment: audiogram evaluation
- Resolution or improvement of skin disease: extent and intensity of rash
- Resolution or improvement of joint disease: joint count (numbers of joints with pain and synovitis)
- Improvement and/or resolution of fever
- Change in bone mineral density
- Changes in magnetic resonance imaging (MRI) (ventricular size on brain MRI, degree of bone marrow enhancement on joint MRI)
- Difference in total amount of steroids, NSAIDs, and/or DMARDs used
- Change in aerobic endurance on 9 minute walk test
- Change in questionnaire score (Childhood Health Assessment Questionnaire [CHAQ], Pediatric Quality of Life Inventory [PedsQL], psycho-social evaluation)
- Assessment of long-term improvement in disease diary score
- Pharmacokinetic profiling
- Evaluation of the safety of using anakinra/Kineret in patients with NOMID/CINCA

Laboratory

- Presence of CIAS1 mutations in all patients enrolled
- Change in CRP, ESR before and after treatment

- Degree of change of acute phase reactants including CRP and ESR after drug withdrawal

Outcomes/endpoints

Primary endpoints

- Change in Diary Symptom Sum Score (DSSS) (fever, rash, joint pain, vomiting, and headache), in each individual key symptom, and in secondary symptoms (fatigue, eye redness, sleep problems, difficulties ambulating, seizures, hearing loss, and vision loss) from baseline to Month 3-6. In addition, change from baseline to each visit up to Month 60 and from baseline to each day up to Day 30.
- Change in SAA levels from baseline to Month 3-6, from baseline to each visit up toMonth 60
- Change in SAA levels from Month 3 (before withdrawal) to end of withdrawal.

Secondary endpoints

Clinical

- By organ system – change from baseline to Month 60 in:
  - Intracranial opening pressure, CSF white blood cell (WBC) adjusted cellularity, CSF protein, CSR albumin quotient, CSF albumin, and CSF glucose. Data related to headache, vomiting, and seizure included in diary data endpoints.
  - Papilledema score in best and worst eye, in visual acuity measured as logMAR value in best and worst eye, and visual field measured as mean deviation of Humphrey visual field in best and worst eye. Presence of uveitis up to Month 60.
  - Elevated puretone average (ePTA) score in best and worst ear based on air and bone conduction. Presence and severity of cochlear enhancement base on ear score in best and worst ear up to Month 60.
  - Body surface area of rash and intensity of rash by a visual analog scale (VAS).
  - Total number and rating score of swollen joints, joints with loss of motion, joints with pain on motion, tender joints, and joints with warmth.
- Data related to fever included in diary data endpoints.
- Change from baseline to Month 60 in bone mineral density in L1-L4, L2-L4, femoralneck, Ward's triangle, total hip area, and radius.
- Interpretation (normal/abnormal) of brain MRI to Month 60; ventriculomegaly, leptomeningeal enhancement, dural enhancement, arachnoid adhesions, and white matter lesions.
- Use of steroids and DMARDS (yes/no) at each visit up to Month 60 and prednisoneequivalent steroid dose based on diary data.
- Change from baseline to Month 60 in total distance of 9 minute walk test and in blood pressure and heart rate before, during, and after the walk test.

- Change from baseline to Month 60 in CHAQ, PedsQL, and intelligence quotient (IQ) assessment
- PK parameters (after first dose, Month 3, Month 36-42) and CSF IL-1Ra concentrations (pre-dose, Month 3)
- Adverse events (AEs), serious adverse events (SAEs), deaths, premature discontinuations, clinical safety laboratory variables, and vital signs up to Month 60.

Laboratory

- Presence of CIAS1 mutation and mutation category at baseline.
- Change from baseline to Month 60 in hsCRP and ESR levels and from Month 3 (before withdrawal) to end of withdrawal.

Sample size

Protocol version August 8, 2003, was designed to have a statistical power of 80% with the use of a two-sided test, with a level of significance of 0.05, to detect a mean difference in diary scores before and after treatment equal in magnitude to the standard deviations of the differences. This would have required at least 10 patients.

Randomisation

All patients enrolled received the study drug. Randomisation procedures were not required.

Blinding (masking)

This was an open-label study and blinding procedures were not required.

Statistical methods

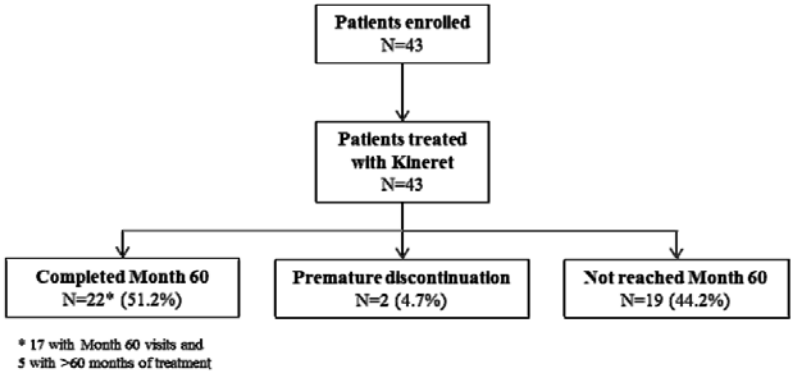
The DSSS (primary endpoint) was the sum of 5 symptoms, and the mean value over the last 30 days before each visit was used as the response variable. The DSSS were primarily analysed using a repeated measures analysis of covariance (RMANCOVA) model. All visits after baseline were used as response in the model. The visit was included as a fixed factor and baseline value as a covariate. Changes from baseline to each visit were estimated based on the RMANCOVA model. In addition to the estimate of change, 95% confidence intervals and p-values comparing the change to zero were calculated. The change from baseline in SAA (primary endpoint) was analysed using similar methods. In addition, the changes from before withdrawal to the withdrawal period were analysed using a RMANCOVA model. The group (drug withdrawal vs. continued treatment), visit, and the interaction between group and visit were included as fixed factors in the model. The value before withdrawal was included as a covariate.

Sensitivity analysis for the primary endpoints was performed by using an analysis of covariance (ANCOVA) model separately for each time point with different data imputation methods and in different subsets. Change from baseline to time points up to 60 months were evaluated for secondary endpoints with the same approach as for the primary endpoints.

Results

Participant flow

The disposition for all patients is illustrated below.



Disposition of patients

Protocol deviations

In all, there were 30 major protocol violations in 26 patients: 1 patient signed the informed consent late, 9 patients were treated before baseline data was obtained, and in 20 patients, the maximum allowed anakinra dose, at that time, was exceeded. One patient started Kineret treatment one day before the informed consent was signed due to administrative delay in getting the IRB approved version uploaded.

Treatment with anakinra had been started in 9 patients before their first visit to NIH and before the official removal of the exclusion criterion forbidding IL-1 antagonist treatment (the question related to the exclusion criterion was erroneously answered by 1 patient). Eight of these patient started treatment because their unstable condition required therapy before travelling to the NIH. Of the 9 patients, 7 were included in the study on their first visit to the NIH, and 2 were later transferred from other studies: one when the diagnosis was confirmed and one when the study focus changed to long-term outcome. None of these 9 patients had baseline data and were therefore not included in the primary efficacy evaluations. For 7 of the 9 patients, demographic and safety data and eligibility criteria were recorded within the first 4 months from treatment start.

Recruitment

In total, 43 patients were enrolled in the study and treated with anakinra. The first patient was enrolled on September 14, 2003, and, for the purpose of this report, the last patient on April 20, 2010. Twenty-two patients completed 60 months of treatment (i.e. either passed the visit Month 60 (N=17) or the duration of the treatment with Kineret was >60 months, although the Month 60 visit is missing), 19 patients had not yet reached 60 months, and 2 patients discontinued the study prematurely due to noncompliance and withdrawal of consent.

Conduct of the study

The focus of the study evolved over time. It was originally intended to determine whether oversecretion of IL-1 was the pivotal pathogenic mechanism in NOMID/CINCA, and whether blocking IL-1 would be an effective treatment strategy. Subsequently, the optimal dosing to control inflammation was to be determined. Through increasing knowledge about the product and disease mechanisms, the long-term objectives of the study changed to determine if Kineret could prevent the progression of pre-existing organ damage and even prevent the development of organ damage in young NOMID/CINCA patients. As a consequence, the study protocol was subject to a number of amendments, most importantly regarding the withdrawal phase, study duration, maximum dose, and age limit for inclusion.

- In protocol version January 30, 2004, the study included a withdrawal phase, where, during a maximum period of 7 days, Kineret was withdrawn and clinical symptoms were recorded, as well as SAA, hsCRP, and ESR levels determined.
- However, because of the significance of the study drug treatment effects seen in the first 11 patients and the severity of their flares upon withdrawal, the IRB at NIH agreed with the investigator's recommendation to discontinue the withdrawal period thereafter.
- The study duration was originally limited to 12 months, but after determination of disease mechanisms involved in NOMID/CINCA and in order to assess the long-term benefits of treatment (as well as assuring availability of treatment for the patients), the study was extended to become open-ended.
- Initially, maintenance doses up to 2 mg/kg were given, but with increasing knowledge of the large safety margin of Kineret treatment and the severity of the disease in some individuals, the study allowed for optimizing dosing, and, consequently, doses up to 10 mg/kg/day could be given.
- The age limit for inclusion in the study was initially 2 years of age. With increasing experience of the safety and efficacy of Kineret treatment, including growing evidence of the potential to prevent irreversible organ damage, the population was extended to include patients of all ages so as to treat patients from the earliest age.

Baseline data

Demographic and other baseline characteristics

Of the 43 patients included in the safety population, 25 (58.1%) were females and 36 (83.7%) were white. Patient ages at treatment start ranged from 0.7 to 46.3 years, with an overall mean (SD) of 10.3 (10.4) years. Most patients were children (36 patients): 13 below 2 years, 18 between 2 and 11 years, and 5 between 12 and 17 years.

The ITT population, ITT diary population, and PK population were overall similar to the safety population with respect to demographic characteristics with the exception of the proportion of patients <2 years being somewhat lower in the ITT populations. In the PK population, there were no patients under the age of 4.

In the Withdrawal population, age was slightly lower in the Treatment group than in the Withdrawal group, because patients <2 years were initially not allowed to enter the study.

All patients fulfilled the inclusion criteria for NOMID/CINCA rash and CNS involvement. No CNS involvement was recorded for patient no. 2009, but there were signs of active CNS inflammation including ventriculomegaly on brain MRI and elevated intracranial pressure, measured as CSF opening pressure on lumbar puncture.

Mutation in exon 3 of CIAS1 was present in 31 patients (72.1%), and the most common type was D303N.

Table 11 Demographic characteristics at baseline (Safety population)

Disease characteristic	Statistic/ category	<2 yrs N=13	2 to 11 yrs N=18	12 to 17 yrs N=5	>=18 yrs N=7	All patients N=43
Diagnosis (n, %)	NOMID	10 (76.9%)	17 (94.4%)	5 (100%)	4 (57.1%)	36 (83.7%)
	NOMID/MWS	3 (23.1%)	1 (5.6%)		3 (42.9%)	7 (16.3%)
Age at diagnosis (years)	Mean	1.1	5.8	11.9	21.7	7.7
	Median	1.0	5.8	12.8	25.8	3.7
	SD	0.5	3.7	4.7	18.7	10.4
	SEM	0.1	0.9	2.1	7.1	1.6
	Min	0.1	0.6	4.1	0.6	0.1
	Max	1.8	11.4	15.9	46.3	46.3
Time since diagnosis (years)	Mean	0.1	2.4	3.7	7.0	2.6
	Median	0.0	0.5	1.3	0.5	0.3
	SD	0.2	3.0	5.8	9.1	4.9
	SEM	0.1	0.7	2.6	3.4	0.7
	Min	0.0	0.0	0.2	0.0	0.0
	Max	0.7	9.0	13.8	20.9	20.9
Mutation in exon 3 of CIAS1 (n, %)	Present	8 (61.5%)	13 (72.2%)	4 (80.0%)	6 (85.7%)	31 (72.1%)
	Not present	4 (30.8%)	4 (22.2%)	1 (20.0%)	1 (14.3%)	10 (23.3%)
	No data	1 (7.7%)	1 (5.6%)	-	-	2 (4.7%)
CIAS1 type (n, %)	D303N	2 (15.4%)	4 (22.2%)	1 (20.0%)	4 (57.1%)	11 (25.6%)
	G569R	1 (7.7%)	2 (11.1%)	-	-	3 (7.0%)
	L264F	1 (7.7%)	1 (5.6%)	-	-	2 (4.7%)
	T348M	1 (7.7%)	1 (5.6%)	1 (20.0%)	-	3 (7.0%)
	Other	3 (23.1%)	5 (27.8%)	2 (40.0%)	2 (28.6%)	12 (27.9%)

Time since diagnosis is the time from diagnosis to the first dose of Kineret. Other CIAS1 types are Q600P, G326E, A374N, V262A, L632F, F443L, G755A, E690K, G307E, F523L, V351L, and I334F.

Disease characteristics at baseline are summarised below.

Table 12 Disease characteristics at baseline (Safety population)

Demographic variable	Statistic/category	<2 yrs N=13	2 to 11 yrs N=18	12 to 17 yrs N=5	>=18 yrs N=7	All patients N=43
Age (years)	Mean	1.2	8.2	15.6	28.7	10.3
	Median	1.1	8.5	16.1	25.8	8.4
	SD	0.4	2.7	1.8	11.2	10.4
	SEM	0.1	0.6	0.8	4.2	1.6
	Min	0.7	3.4	13.2	18.5	0.7
	Max	1.8	11.8	18.0	46.3	46.3
Gender (n, %)	Female	9 (69.2%)	8 (44.4%)	3 (60.0%)	5 (71.4%)	25 (58.1%)
	Male	4 (30.8%)	10 (55.6%)	2 (40.0%)	2 (28.6%)	18 (41.9%)
Race (n, %)	White	11 (84.6%)	13 (72.2%)	5 (100%)	7 (100%)	36 (83.7%)
	Other	2 (15.4%)	3 (16.7%)			5 (11.6%)
	Asian		1 (5.6%)			1 (2.3%)
	Black		1 (5.6%)			1 (2.3%)
Ethnicity (n, %)	Non-Hispanic/ Non-Latino	9 (69.2%)	13 (72.2%)	5 (100%)	7 (100%)	34 (79.1%)
	Hispanic/Latino	4 (30.8%)	5 (27.8%)			9 (20.9%)
Weight (kg)	Mean	8.8	24.4	47.3	53.4	27.1
	Median	7.7	22.8	46.1	51.9	22.0
	SD	2.6	12.5	16.9	19.3	20.4
	SEM	0.7	2.9	7.5	7.3	3.1
	Min	6.0	10.7	31.3	30.8	6.0
	Max	15.2	60.3	69.9	82.2	82.2
Height (cm)	Mean	72.3	109.9	147.9	144.3	108.5
	Median	73.5	104.2	150.0	150.1	103.7
	SD	7.4	21.1	13.3	22.4	33.0
	SEM	2.0	5.0	5.9	8.5	5.0
	Min	61.5	81.5	133.4	112.7	61.5
	Max	82.7	148.6	166.5	169.7	169.7
BMI (kg/m2)	Mean	16.7	19.2	21.4	24.9	19.6
	Median	16.0	19.9	17.6	24.2	19.0
	SD	2.6	3.8	6.4	3.6	4.6
	SEM	0.7	0.9	2.9	1.4	0.7
	Min	12.9	13.9	16.6	20.8	12.9
	Max	23.8	27.3	31.1	29.4	31.1

Age is the age at the first dose of Kineret. Weight, height and BMI are the assessments from the first visit.

Diary symptom sum score (DSSS) at baseline

Symptom severity at baseline was highest for rash followed by joint pain and headache. The proportion of days with at least mild symptom severity was 78.9% for rash, 51.3% for joint pain, and 37.3% for headache. The proportion of days with the highest severity score was below 15% for all key symptoms except rash, which had the highest score on 16.9% of the days. Proportion of days with fever was relatively low, and vomiting was the least common of the individual key symptoms. In addition to the 5 key symptoms, fatigue, hearing loss, eye redness, and difficulties ambulating were present on 40%-60% of the days during the baseline period. Calculations for the distribution of days with each severity (i.e. giving more weight to patients with data available from more days) showed similar results.

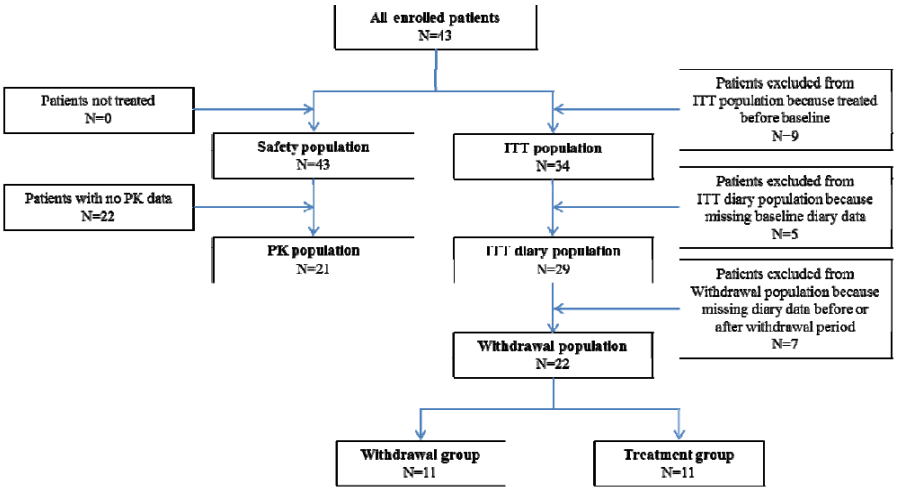
Prior and concomitant therapy

At baseline, 16 of 34 patients (47.1%) in the ITT population were treated with oral steroids, 9 (26.5%) with DMARDs (methotrexate), and 3 (8.8%) with acetazolamide. Use of steroid medication was also obtained from the patient diary. Different types of steroids recorded in the

diary were converted into prednisone-equivalent doses to facilitate comparisons. The mean daily dose of oral steroids before treatment start in the ITT population was 0.35 mg/kg.

Numbers analysed

Five analysis sets were used. The population size for each analysis set was as follows: 43 patients in the Safety population, 34 patients in the ITT population, 29 patients in the ITT diary population, 22 patients in the Withdrawal population, and 21 patients in the PK population.



Analysis data sets

Safety population

All 43 enrolled patients provided data for the evaluation of AEs. Safety laboratory tests and vital signs data were available for 43 patients as well, but only 34 patients were included in the evaluation of change from baseline because of missing baseline values before treatment..

ITT population

The ITT population comprised 34 patients; 9 patients were excluded because they started treatment with Kineret before the first visit in the study, i.e. no baseline data could be obtained. For individual outcome variables, additional patients have been excluded from the ITT analysis of that variable if baseline data was missing. Further, not all patients completed all visits, and because of this, the number of patients may vary at different time points.

ITT diary population

The ITT diary population included 29 patients; 5 patients were excluded from the ITT population because of missing complete baseline diary data for the 5 key symptoms.

Withdrawal population

The Withdrawal population comprised 22 patients, 11 in the Withdrawal group and 11 in the Treatment group. The Withdrawal group consisted of the first 11 patients enrolled in the study, who completed a period of treatment withdrawal for up to 7 days, when disease symptoms were evaluated at the beginning and at the end of the withdrawal period. Data from these patients

were compared with data from 11 patients who were enrolled after the withdrawal period had been removed from the protocol, the Treatment group, by selecting the time period corresponding to the withdrawal period. All patients who did not participate in the withdrawal period and who provided diary data at baseline, Month 3, and during the period corresponding to the withdrawal period (4-10 days after the visit at Month 3) were included in the Treatment group.

PK population

The PK population included 21 patients, in whom serum samples were taken for PK analysis at least once.

Outcomes and estimation

Primary efficacy endpoint

Diary symptom sum score (DSSS)

Analysis of the primary variable, change in DSSS after 3-6 months of administration of Kineret, showed significant improvement. The DSSS included the sum of the 5 key symptoms fever, rash, joint pain, vomiting, and headache. The estimated change in DSSS from baseline to Month 3-6 was -3.5 (95% CI -3.7 to -3.2; p-value <0.0001), and this range of improvement was constant throughout the study. The immediate clinical response to Kineret treatment was reflected in a rapid decrease in DSSS, demonstrated in Figure 5 as change from baseline by day during the first month of treatment. Within 3 days of treatment initiation, the DSSS decreased from a mean (SEM) baseline value of 4.5 (0.6) to 0.8 (0.3).

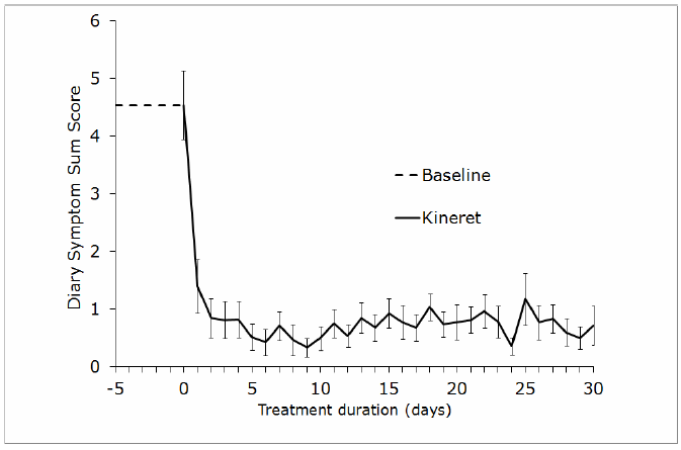
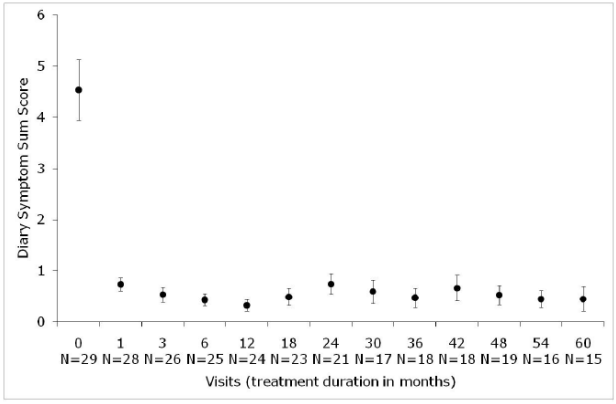


Figure 5 Diary symptom sum score (DSSS) by day during the first month of Kineret treatment (ITT diary population)

The decline in average DSSS was sustained throughout the long-term follow up, with a score equal to 0.7 or lower up to Month 60 (Figure below). The estimated changes from baseline were statistically significant also at all other visits. In addition to the DSSS (i.e. score ranging between 0-20 which can be calculated only if all 5 key symptoms were assessed) the mean symptom score was evaluated (i.e. score ranging between 0-4, which is the average of all available key symptoms and can be calculated regardless of how many of the 5 key symptoms that were assessed). The mean symptom score results were consistent with the DSSS results.



ITT observed cases (N=29). Mean (SEM) for observed cases at all time points.

Figure 6 Diary symptom sum score (DSSS) from baseline to Month 60 after Kineret treatment (ITT diary population)

The estimated changes from baseline were statistically significant also at all other visits (Table 10).

Table 13 Estimated changes in DSSS from baseline (ITT diary population)

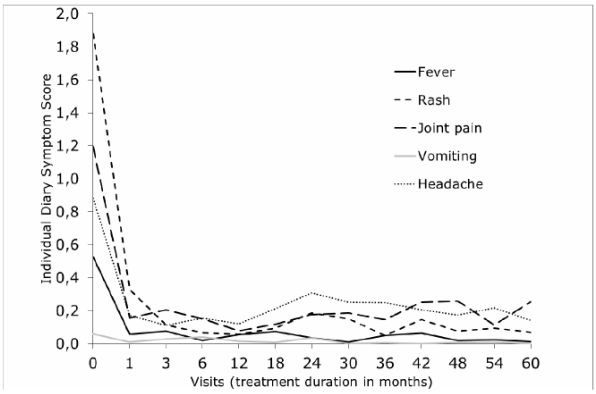
Time point	Estimated change from baseline	SEM	95% CI	p-value vs. baseline
Month 3-6	-3.5	0.1	-3.7 to -3.2	<0.0001
Month 12	-3.6	0.1	-3.9 to -3.3	<0.0001
Month 36	-3.5	0.2	-3.8 to -3.2	<0.0001
Month 60	-3.5	0.2	-3.8 to -3.1	<0.0001

Estimates of change from baseline based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate. ITT observed cases (N=29).

All age groups showed comparable clinical improvement. Further subgroup analyses showed a comparable decrease in DSSS between female and male patients, between patients with and without CIAS1 mutation, and between patients diagnosed with NOMID/CINCA and those with borderline phenotypes between NOMID/CINCA and MWS.

Individual Key and Secondary Symptoms

There was a rapid and sustained decrease in diary symptom score from baseline to Month 60 for each individual key symptom, except for vomiting, which had a very low score already at study initiation.



The figure show mean values for observed cases at all given time points. ITT observed cases (N=29)

Figure 7 Individual diary key symptom scores from baseline to Month 60 after Kineret treatment (ITT diary population)

The estimated changes from baseline were statistically significant for all key symptoms.

Table 14 Estimated change in individual diary key symptoms from baseline to Month 3-6 after Kineret treatment (ITT population)

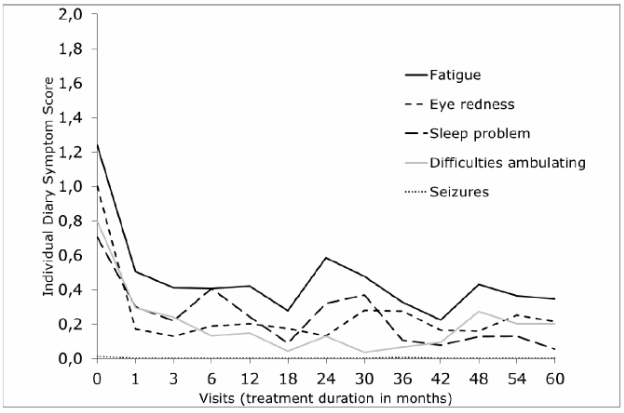
Key symptom	Estimated change from baseline	SEM	95% CI	p-value vs. baseline
Fever	-0.4	0.0	-0.4 to -0.3	<0.0001
Rash	-1.6	0.1	-1.7 to -1.5	<0.0001
Joint pain	-0.9	0.1	-1.0 to -0.8	<0.0001
Vomiting	-0.0	0.0	-0.0 to -0.0	0.0029
Headache	-0.6	0.1	-0.7 to -0.5	<0.0001

Estimates of change from baseline based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate. ITT observed cases (N=29).

There was also a rapid and sustained decrease in diary symptom score from baseline to Month 60 for the secondary symptoms fatigue, eye redness, and sleep problems.

The diary also included 2 fields for reporting hearing and vision loss. There were small changes in hearing that stabilized at Month 12, indicating a subjective improvement in hearing. More than 50% of the patients recorded no symptoms at baseline, and this subgroup showed no worsening with time, but the subgroup with symptoms recorded at baseline improved in hearing from a mean of

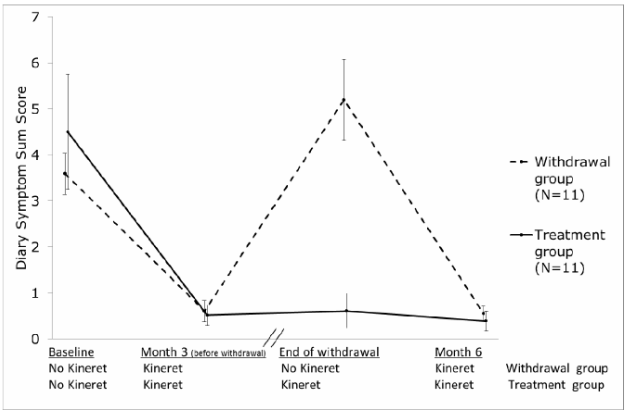
2.3 to 0.9 at Month 12. For vision, there were only very minor changes and no indications of worsening in the subgroup with no vision loss at baseline (21 of 27 patients). In the subgroup with vision loss present at baseline, there was a slight decrease in the self-perceived vision loss score from a mean value of 2.1 at baseline to 1.5 or lower at subsequent visits during the study.



The figure show mean values for observed cases at all given time points. ITT observed cases (N=29)

Figure 8 Individual diary secondary symptom scores from baseline to Month 60 after Kineret treatment (ITT diary population)

Withdrawal period – Diary symptom sum score (DSSS)



The figure shows mean (SEM) for all ITT observed cases (N=22). End of withdrawal was between 4th to 7th day without study medication.
In the Withdrawal group, change from the DSSS value during the 30-day period preceding Month 3 to the DSSS of all days during the withdrawal period was calculated.
In the Treatment group (patients on Kineret throughout the study), data representing the withdrawal period was calculated from the DSSS value during the time period corresponding to the withdrawal period. All patients not participating in the withdrawal period and providing diary data before and after Month 3 were included.

Figure 9 DSSS before and at end of withdrawal period, and after reinstitution of therapy, to Month 6 (Withdrawal population)

Both groups responded after initiation of treatment and had a similar DSSS at Month 3. In the Withdrawal group, the average DSSS increased from 0.6 to 5.2; estimated change 4.6 (95% CI 3.8 to 5.4; p<0.0001) upon withdrawal of treatment, while the average DSSS remained on the same level in the Treatment group (from 0.5 to 0.6). The difference between the Withdrawal and Treatment groups in change from Month 3 (before withdrawal) to end of the withdrawal period was statistically significant, estimated difference between the groups being 4.5 points (95% CI 3.3 to 5.6; p<0.0001) (Table 12).

Treatment was then reinstituted for the Withdrawal group, and 3 months later (at Month 6) both groups had a similar average DSSS again (0.6 in the Withdrawal group and 0.4 in the Treatment group). No significant difference was seen between the groups in estimated change from Month 3 (before withdrawal) to Month 6, i.e. after Kineret treatment had been restarted in the Withdrawal group; 0.0 points (95% CI -1.1 to 1.2; p=0.9422).

Table 15 Estimated changes in DSSS from before to end of withdrawal period, and after reinstitution of therapy, to Month 6 (Withdrawal population)

	Group	Change within the group			Difference between the groups		
		Estim. (SEM)	95% CI	p-value	Estim. (SEM)	95% CI	p-value
Change from before to end of withdrawal period	Withdrawal group (N=11)	4.6 (0.4)	3.8 to 5.4	<0.0001	4.5 (0.6)	3.3 to 5.6	<0.0001
	Treatment group (N=11)	0.1 (0.4)	-0.7 to 0.9	0.7751			
Change from before withdrawal period to Month 6	Withdrawal group (N=11)	-0.1(0.4)	-0.9 to 0.7	0.8609	0.0 (0.6)	-1.1 to 1.2	0.9422
	Treatment group (N=11)	-0.1(0.4)	-0.9 to 0.7	0.7814			

Repeated measures ANCOVA model includes visit, group and the interaction between visit and group as a fixed factors and the before withdrawal period value as a covariate. ITT observed cases (N=22)

Of the 11 patients in the Withdrawal group, 10 reached the criteria for disease flare as recorded by the clinical staff within the specified withdrawal period of maximum 7 days. The patient who did not fulfil the criteria had 6 days of rash, 3 days of joint pain and conjunctivitis, and one episode of fever. The median time until disease flare was 5.0 days (95% CI 2.5 to 6.0). The most frequent fulfilled criteria were rash and headache.

Inflammatory markers: SAA, hsCRP, and ESR

Change in SAA from baseline to 3-6 months was a variable directly related to the primary objective in the study protocol. hsCRP and ESR were secondary variables, but as they all reflect the inflammatory process and closely follow each other.

Levels of SAA, hsCRP, and ESR were elevated before initiation of Kineret therapy. After treatment start, levels for all 3 decreased significantly from baseline. At Month 1, SAA had decreased from a median baseline value of 149 mg/L to 31 mg/L and median hsCRP from 51 mg/L to 9 mg/L. After an additional 2 months (at Month 3) levels were even lower, 6 mg/L and 4 mg/L, respectively, and sustained over time. There was a reduction in median ESR from 52 mm/h at baseline to 13 mm/h at Month 1, a level that changed only slightly at subsequent visits. Very high levels of SAA and hsCRP occurred most frequently at baseline. At subsequent visits, high levels were less frequent and transient. Isolated elevations may have reflected occasional relapses in individual patients over the course of treatment, which can be seen with viral infections and stress.

The estimated changes in SAA, hsCRP, and ESR levels from baseline were statistically significant at all visits ($p<0.0001$).

Table 16 Estimated changes in SAA levels from baseline (ITT population)

Time point	Estimated change from baseline (mg/L)	SEM	95% CI	p-value vs. baseline
Month 3-6	-206	12	-230 to -182	<0.0001
Month 12	-189	17	-222 to -155	<0.0001
Month 36	-220	19	-256 to -183	<0.0001
Month 60	-217	24	-264 to -170	<0.0001

Estimates of change from baseline based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate. ITT observed cases (N=31).

Table 17 Estimated changes in hsCRP levels from baseline (ITT population)

Time point	Estimated change from baseline (mg/L)	SEM	95% CI	p-value vs. baseline
Month 3-6	-53	3	-58 to -48	<0.0001
Month 12	-49	3	-55 to -42	<0.0001
Month 36	-56	4	-64 to -49	<0.0001
Month 60	-57	5	-67 to -48	<0.0001

Estimates of change from baseline based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate. ITT observed cases N=34.

Table 18 Estimated changes in ESR levels from baseline (ITT population)

Time point	Estimated change from baseline (mm/h)	SEM	95% CI	p-value vs. baseline
Month 3-6	-41	2	-45 to -38	<0.0001
Month 12	-39	2	-43 to-35	<0.0001
Month 36	-48	2	-52 to -43	<0.0001
Month 60	-49	3	-54 to -44	<0.0001

Estimates of change from baseline based on a repeated measures analysis of covariance model including visit as a fixed factor and baseline value as a covariate. ITT observed cases (N=34).

Data is shown only for the Withdrawal group, because the SAA, hsCRP, and ESR samples were not taken at a corresponding time at the end of the withdrawal period for the Treatment group. The evidence of disease flare during withdrawal of treatment, as reflected by significant changes in subjective symptom scoring, was also demonstrated as rapid changes in the inflammatory serum markers SAA (primary variable), hsCRP and ESR.

In the 11 patients in the Withdrawal group, the median SAA value was 162 mg/L at baseline and decreased to 7 mg/L before the withdrawal period. At the end of the withdrawal period, SAA had increased to 310 mg/L (compared to before withdrawal $p<0.0001$). Restart of treatment resulted in a decrease at Month 6 to 6 mg/L (compared to before withdrawal $p=0.8932$). Sustained low levels of SAA were evident over time in the ITT population.

There was a reduction in median hsCRP from 50 mg/L at baseline to 4 mg/L before the withdrawal, then an increase at the end of the withdrawal period to 72 mg/L (compared to before withdrawal $p<0.0001$). At Month 6 of treatment, median hsCRP had again decreased to 4 mg/L (compared to before withdrawal $p=0.8519$).

Change in ESR showed a similar pattern with a median value at baseline of 69 mm/h and a decrease to 24 mm/h before withdrawal. At the end of the withdrawal period, ESR had increased to 69 mm/h (compared to before withdrawal $p<0.0001$). Restart of therapy resulted in a decrease at Month 6 to 27 mm/h (compared to before withdrawal $p=0.5601$).

Secondary Efficacy Variables

CNS evaluation

Before Kineret treatment, all patients except 2 in the ITT population with evaluable LP had objective signs of aseptic meningitis. This was evident from results obtained at LP (adjusted cellularity and opening pressure). The patients with normal range values at LP had CNS

involvement in the form of leptomeningeal as well as cochlear enhancement at baseline MRI and papilledema.

The majority of patients had LP done at baseline, Month 3-6, Month 12, and yearly thereafter. However, three patients had no LPs at baseline, and four patients only had limited data throughout the study.

Intracranial pressure

Intracranial opening pressure was measured with a normal value defined as less than 200 mm of water column. At baseline, the mean (SEM) value of 29 patients was 239 (15) mm. The mean value decreased to 212 (17) mm at Month 3 and further to 183 (13) mm at Month 36, and to 179 (18) mm at Month 60.

The estimated change from baseline to Month 3-6 was -52 mm (95% CI -76 to -28; p-value <0.001) and -83 mm (95% CI -123 to -43; p-value <0.001) at Month 60.

CSF cellularity and chemistry

CSF WBC-adjusted cellularity was assessed with a normal value defined as ≤5 cells/µL. Mean (SEM) WBC-adjusted cell count decreased from 27.9 (5.7) cells/µL at baseline to 11.0 (2.8) cells/µL at Month 3. There was an increase in mean at Month 12 compared to Month 6 due to one patient who was affected by a viral meningitis at that time point with an adjusted cellularity of 335/µL. The mean decreased to 5.7 (1.0) cells/µL at Month 36 and further to 3.5 (0.6) cells/µL at Month 60.

The estimated change from baseline to Month 3-6 was -20.6 cells/µL (95% CI -32.9 to -8.3; p-value=0.0013), -6.1 cells/µL (95% CI -19.6 to 7.5; p-value=0.3748) at Month 12, and -27.7 cells/µL (95% CI -47.3 to -8.2; p-value=0.0061) at Month 60.

Total protein, albumin, albumin quotient, and glucose in the CSF were also measured, and levels decreased similarly to adjusted cellularity. CSF glucose was stable over time.

CSF-WBC adjusted cellularity and diary headache score.

The mean (SEM) daily diary headache score (0-4 for increasing severity) rated 0.9 (0.2) at baseline. With initiation of therapy, it decreased rapidly and remained significantly reduced throughout the study with mean scores between 0.1 and 0.3 (p<0.0001 for all time points after baseline compared to baseline). The change in mean CSF WBC over time paralleled the decrease in the diary headache score.

Brain MRI

Ventriculomegaly was present in 10 of 23 patients (43.5%) at baseline, and an additional 2 patients had shunts. As expected in these patients with long-standing disease, treatment had limited effect on this condition; a similar proportion of patients, 7 of 17 (41.2%), had ventriculomegaly at Month 60 as at baseline. One patient with ventriculomegaly present at baseline improved at Month 36. This was a patient who started treatment at the age of 0.8 years (patient no 2042). No patient with normal ventricular appearance at baseline developed ventriculomegaly during treatment.

Leptomeningeal enhancement, which to a higher degree than ventriculomegaly reflects active CNS inflammation, was present in 10 of 25 patients (40.0%) at baseline and in 1 of 19 patients (5.3%) at Month 60. Eight patients with enhancement present at baseline improved at Month 36 and 7 patients at Month 60. One patient worsened at Month 36, but normalized and had no sign of enhancement at Month 60.

Cochlear enhancement

Of the 20 patients (87.0%) with some degree of cochlear enhancement on the initial MRI worst ear, 11 of 20 patients (57.9%) had normalized at Month 3. Four additional patients improved by at least 1 grade, totaling in 15 improved patients (78.9% of those with some degree of cochlear enhancement present at baseline). At Month 36, 10 of 20 patients (50%) were free of cochlear enhancement in both ears and 9 of 19 patients (47.4%) at Month 60 (or last assessment after month 42).

From diary data recording subjective hearing, the subgroup with symptoms at baseline improved in self-perceived hearing from a mean score of 2.3 to 0.9 at Month 12. By objective measures, this is reflected as small improvements in air conduction ePTA score for best ear compared to baseline early in treatment.

Patients ≥12 years had more severe hearing impairment than patients <12 years. The older patients in general stabilized without progressive worsening, but typically did not improve. Patients with normal hearing or limited ePTA abnormalities were younger at baseline and did not deteriorate with treatment over time.

Ophthalmology

Patients underwent full ophthalmologic examinations including visual acuity (presented as logMAR), visual field and dilated eye examinations. Seventeen patients with visual data from both eyes at each visit were included in the analysis; all had baseline data for assessment of visual acuity, papilledema, and uveitis, but only 5 patients performed the visual field examination at baseline.

Inflammatory eye manifestations also included uveitis and papilledema. Uveitis was present (assessed from “trace” to score “3”) at baseline or had occurred historically in 8/17 patients.

During the study, none of these patients experienced any new events. One patient with no previous uveitis reported 2 events as AEs after 8 and 10 months of treatment; the inflammation resolved. Up to Month 60, there had been no other AE reports of uveitis in the study population.

Papilledema score (with 0 as best outcome and 4 as worst) improved significantly during the study with an estimated change from baseline to Month 36 of -0.88 (95% CI -1.06 to -0.70; p-value <0.0001) in the best eye and -1.05 (95% CI -1.20 to -0.89; p-value <0.0001) in the worst eye. The improvement was sustained at the Month 60 visit.

Dermatology

Thirty patients had baseline dermatology data. Mean (SEM) percentage of the body surface area affected with rash was 10.5 (2.3)% at baseline with a decrease to 3.6 (2.4)% at Month 3. At

Month 6 and thereafter, it was 0%. A VAS was used for an overall assessment of skin color, not concentrated to the rash area, but an assessment over the whole body surface, Skin color was scored from zero (normal skin) to 100 (reddest possible skin). Mean (SEM) value at baseline was 37.7 (4.5) with a decrease to 7.6 (3.3) at Month 3 and a further reduction to below 1 at Month 36.

Table 19 Estimated changes in body surface area of rash and VAS from baseline (ITT population)

	Body surface area of rash (%)				VAS for skin color (mm)			
Time point	Estimated change from baseline	SEM	95% CI	p-value vs. baseline	Estimated change from baseline	SEM	95% CI	p-value vs. baseline
Month 3-6	-6.7	0.6	-7.8 to -5.6	<.0001	-28.9	1.6	-32.1 to -25.7	<.0001
Month 12	-8.5	0.8	-10.1 to -6.9	<.0001	-28.6	2.3	-33.0 to -24.1	<.0001
Month 36	-8.4	0.9	-10.1 to -6.7	<.0001	-33.6	2.4	-38.4 to -28.9	<.0001
Month 60	-8.3	1.2	-10.7 to -5.9	<.0001	-34.5	3.4	-41.2 to -27.8	<.0001

ITT observed cases (N=30).
Estimated change from baseline based on repeated measures ANCOVA. Model includes visit (month) as a fixed factor and baseline as a covariate.
Body surface area of rash (%) is the sum of rash proportion on each body region multiplied by the coverage of the region out of the total body surface area. VAS (mm) is an overall assessment of the skin color over the whole body; VAS value 0 indicates normal skin color and value 100 reddest possible skin.

Joint count

Mean (SEM) number of swollen joints decreased from a baseline mean of 7.8 (1.9) to 0 at Month 60, and number of joints with pain on motion decreased from 5.2 (1.6) to 0.4 (0.2) during the same period. The corresponding figures for joints with loss of motion were 8.6 (1.9) to 0.6 (0.3). The decrease in the number of affected joints was seen within the first 12 months of treatment and remained stable up to Month 60.

Table 20 Estimated changes in total number of swollen joints and joints with loss of motion from baseline (ITT population)

	Total number of swollen joints				Total number of joints with loss of motion			
Time point	Estimated change from baseline	SEM	95% CI	p-value vs. baseline	Estimated change from baseline	SEM	95% CI	p-value vs. baseline
Month 3-6	-4.5	0.5	-5.5 to -3.5	<.0001	-4.2	0.7	-5.6 to -2.7	<.0001
Month 12	-8.0	0.7	-9.4 to -6.7	<.0001	-8.0	0.9	-9.8 to -6.2	<.0001
Month 36	-9.0	0.8	-10.5 to -7.4	<.0001	-10.7	1.1	-12.8 to -8.5	<.0001
Month 60	-9.2	0.9	-10.9 to -7.4	<.0001	-11.1	1.2	-13.4 to -8.8	<.0001

ITT observed cases (N=28 for swollen joints and 27 for joints with loss of motion)
Estimated change from baseline based on repeated measures ANCOVA. Model includes visit (month) as a fixed factor and baseline as a covariate.

Concomitant therapy

Use of DMARDs remained on the same level throughout the study, 26.5% (9 of 34 patients) at baseline to 20.0% at Month 60, while use of acetazolamide increased from 8.8% at baseline to 53.3% at Month 60.

Use of steroid medication was also obtained from the patient diary. Among patients with baseline diary data, 13 patients were on glucocorticoid treatment, while 15 patients were steroid free. None of the latter started glucocorticoid treatment during the study. The mean (SEM) prednisone-equivalent dose of these patients were 0.76 (0.31) mg/kg at baseline, but a prompt

tapering of their doses during the first 3 months were seen. At 12 months, 10 of these 13 patients were still on glucocorticoid medication, but at considerably lower doses. At Month 36 and Month 60, there was a further decline in the number of patients with concomitant glucocorticoid treatment, all with lower doses than at baseline.

Table 21 Diary data on glucocorticoid treatment (ITT population)

Patients on glucocorticoids	Patients with continued diary data (N)	Patients with continued glucocorticoid use (N)	Prednisone equivalent dose mg/kg (mean [SEM])	Min	Max
Baseline	13	-	0.76 (0.31)	0.10	4.29
Month 3	10	10	0.52 (0.21)	0.07	2.32
Month 12	12	10	0.15 (0.03)	0.02	0.35
Month 36	9	6	0.12 (0.02)	0.06	0.19
Month 60	8	5	0.07 (0.02)	0.03	0.11

Childhood Health Assessment Questionnaire (CHAQ)

CHAQ scoring ranged from 0 to 3 with 0=no difficulty or not applicable and 3=unable to do, i.e. higher scores indicated more severe impairment. A clinically relevant change was defined as a change in score of 0.125.

Table 22 Estimated changes in CHAQ from baseline in overall pain and parent/patient global rating (ITT population)

	Overall pain (mm)				Parent/Patient global (mm)			
Time point	Estimated change from baseline	SEM	95% CI	p-value vs. baseline	Estimated change from baseline	SEM	95% CI	p-value vs. baseline
Month 3-6	-29.9	2.1	-34.1 to -25.7	<.0001	-26.8	2.0	-30.8 to -22.9	<.0001
Month 12	-32.0	2.8	-37.6 to -26.4	<.0001	-29.8	2.7	-35.1 to -24.5	<.0001
Month 36	-28.9	3.1	-35.0 to -22.9	<.0001	-30.7	2.9	-36.4 to -25.0	<.0001
Month 60	-27.2	3.6	-34.3 to -20.2	<.0001	-28.1	3.4	-34.7 to -21.4	<.0001

Estimated change from baseline based on the repeated measures ANCOVA. Model includes visit (month) as a fixed factor and baseline as a covariate. ITT observed cases (N=28).

Start and maintenance dose

Initially the patients were started on 1 mg/kg. Over time the starting dose was increased and patients enrolled later in the study were started also at higher doses. Throughout the study, the starting dose for treatment ranged from 1.0 to 2.4 mg/kg. The number of patients in the 1 mg/kg dose class (defined as 0.5 to <1.5 mg/kg doses) and in the 2 mg/kg dose class (1.5 to <2.5 mg/kg) were 26 and 17, respectively.

Following initiation of therapy, the clinical response was evaluated intermittently and the dose was either maintained or adjusted. For a patient with inadequate clinical response, the Kineret dose could be increased by 0.5 to 1 mg/kg up to a maximum of 10 mg/kg/day according to the study protocol. The dose range recorded for the safety population at the study visits was 0.9 to 7.6 mg/kg/day. The highest dose was maintained for 15 months. Dosing was performed per mg/kg body weight, and the dose in mg was accordingly adjusted based on changes in body weight. The median dose after 5 years of treatment was similar for those aged <2 years and for those ≥18 years and ranged from 2.8 -3.6 mg/kg/day (overall median 3.1 mg/kg/day).

The median start dose in the study population was 1.4 mg/kg. Due to dose adjustments in order to achieve the specified treatment objectives, the dose for the patients at the end of the study was higher but levelled off to 3.2, 3.6, and 3.2 mg/kg/day after 48, 54, and 60 months, respectively.

Table 23 Dosage (mg/kg/day) of Kineret at selected treatment months in the respective age category (Safety population)

Age at baseline	Visit (month)	Median	Min	Max	N
<2 years	0	1.7	1.0	2.4	13
	6	2.6	1.4	3.7	12
	18	3.4	1.8	4.5	8
	36	3.8	2.0	4.3	5
	60	2.8	2.3	3.4	2
2-11 years	0	1.0	1.0	2.0	18
	6	1.9	1.0	2.7	15
	18	2.4	1.6	7.6	17
	36	2.9	1.8	4.1	13
	60	3.6	2.3	4.7	11
12-17 years	0	1.0	1.0	1.5	5
	6	1.5	1.3	1.7	3
	18	1.6	1.4	1.8	2
	36	2.4	1.9	3.4	3
	60	3.0	2.1	3.3	3
≥18 years	0	1.0	1.0	1.9	7
	6	1.5	1.0	3.0	6
	18	1.5	1.3	2.0	3
	36	2.5	2.0	3.0	3
	60	3.2	2.0	5.0	3

Supportive studies

Lepore et al (J Pediatr 2010)- Follow-up and quality of life of patients with cryopyrin-associated periodic syndromes treated with anakinra.

- Methods

The investigation was a prospective open-label long-term follow-up (12 to 54 months) study of QoL in severely affected CAPS patients (NOMID/CINCA and MWS) treated with Kineret. The study also included a non-randomized parallel cohort with surveillance of untreated patients. Both treated (n = 14) and untreated patients (n = 5) were assessed every 4 to 6 months. One additional patient was enrolled in the registry but never completed the study. Ophthalmologic evaluation and audiometry were performed every 6 months. CNS and/or bone imaging was performed according to patient's clinical needs. Hematological and biochemical profile, C-reactive protein (CRP), ESR, and SAA were obtained at baseline and during control visits. In addition, the Child Health Questionnaire (CHQPF50) was used to assess the QoL in both treated and untreated patients. An international sample of 3315 healthy children (52.2% female), with a mean (standard deviation [SD]) age of 11.2 (3.8) years, constituted the healthy control group

- Patient characteristics

Fifteen of the 20 patients included had a phenotype consistent with NOMID/CINCA, whereas 5 patients had a milder phenotype consistent with MWS. Fourteen of the patients were treated with Kineret, 5 were untreated controls and 1 patient was not evaluated. The mean (SD) age of the 19 prospectively followed patients was 12.4 (10.9) at enrolment. Nine were males and 10 females with 14 patients still in the paediatric age group. The mean age of treated (14 patients) and untreated (5 patients) MWS and NOMID/CINCA patients were 13.9 (12.2) and 8.1 (3.7), respectively. Most of the patients had disease onset during the first weeks of life. Thirteen patients (68%) carried mutations of the CIAS1 gene. At baseline, almost all patients had elevated acute phase reactants and experienced rash, headache and arthralgia.

- Dosage

The starting dose of Kineret was 1 mg/kg/day (maximum 100 mg). In 5 patients, the dose was increased during follow-up, up to 3 mg/kg/day. The major causes for dose increments were the finding of an isolated elevation of acute phase reactants and/or the persistence of papilledema on ophthalmologic evaluation in the absence of other disease-associated clinical manifestations.

- Efficacy results

Treated patients

All treated patients demonstrated an immediate clinical benefit of Kineret, with rash, fever, and joint affection resolving within a few days. A prompt and persistent normalization of inflammatory markers, including SAA, and haematological measures was achieved.

The frequency of headache episodes decreased significantly upon treatment and completely resolved during the follow-up period.

Papilledema was completely resolved in 3 of 7 treated patients who had papilledema present at baseline. In 4 patients partial papilledema still persisted despite an increase in Kineret dosage.

No treated patients had a worsening of their hearing loss during follow-up; 1 patient displayed a slight improvement of the audiogram after treatment with Kineret. None of the treated patients developed new organ manifestations related to the disease during the follow-up period.

There was no difference in the long-term pattern of response to treatment between CIAS1/NALP3-mutated and non-mutated patients observed.

The CHQ-PF50 questionnaire is a self-administered instrument designed to capture the physical, emotional, and social components of health status of children 5-18 years of age and comprises 15 health concepts. In addition, there are 2 summary measures based on US normative standard:
the physical summary score (PhS) and the psychosocial summary score (PsS). These summary measures were used at baseline and at the last follow-up visit. They are standardized to have a mean of 50 and SD of 10. An international sample of 3315 healthy children constituted a healthy control group (Oliveira et al 2007). Patients with both NOMID and MWS showed significantly lower values for both PhS ($p < 0.01$ and $p < 0.05$, respectively) and PsS ($p < 0.01$) compared with healthy control subjects at baseline. Treatment was associated with a dramatic amelioration of negative aspects related to the QoL, with the greatest improvement in the physical (PhS)

summary median score (SD) increasing from a pre-treatment value of 38 (11.8) to 52.2 (4.5) post treatment ($p < 0.001$). Thus, an almost complete normalization of most of the items concerning PhS activities was observed, but with less impact on the psychological domains.

No treatment control patients

Five patients with CAPS who did not receive Kineret therapy were prospectively followed. Of these, 4 patients were diagnosed with NOMID/CINCA with a severe CAPS phenotype, while one was a MWS patient with a milder phenotype. The mean follow-up period of the 5 untreated patients was 45 months (range 19 to 52 months). The patients' ages at enrolment were 3 to 12.1 years (Mean (SD) 8.1 (3.7)). The 4 severly affected no-treatment concurrent control patients had a stable and long-lasting disease course, with daily rash, headaches, and recurrent episodes of arthralgia. All patients displayed chronic elevation of acute phase reactants, including SAA levels, with mild to moderate microcytic anemia. These clinical manifestations were partially controlled by the use of NSAIDs. Three of the patients had persisting papilledema at the last follow-up. One patient developed moderate neurosensory hearing loss, and in 2 patients a worsening of this complication was noted.

Kümmerle-Deschner et al (Arthritis Rheum 2011)- Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome

- Methods

Kümmerle-Deschner et al 2011 studied pediatric and adult MWS patients in a prospective open label single centre trial. The median follow-up was 11 months (range 5-14 months). The aims of the study were to describe a cohort of patients with a severe disease course, and to describe the short-term efficacy of Kineret treatment (after 2 weeks) and the long-term response, as well as the safety of Kineret therapy in MWS patients.

The primary study outcome was the response in MWS-disease activity score (DAS) after 2 weeks of treatment. The MWS-DAS captures active disease in terms of: fever, headache, eye involvement, hearing impairment, oral ulcers, abdominal pain, renal disease, musculoskeletal disease, and rash, and also includes the patient's global assessment score. A good response was defined as controlled MWS disease activity with an MWS-DAS <10 at 2 weeks.

The following efficacy secondary outcomes were also assessed:

- Long-term efficacy in all single domains of the MWS-DAS and the total MWS-DAS score at last follow-up
- Patient- and physician-derived global measures of disease activity and overall health at 2 weeks and last follow-up
- Inflammatory markers at 2 weeks and at last follow-up
- Organ specific disease assessments included renal function and amyloidosis, repeat audiology examinations, CNS and inner ear MRI, and ophtalmological evaluations.

- Patient characteristics

Twelve patients (3 males and 9 females) were included; 5 (42%) were pediatric patients (median age 6.4 years, range 3.0-15.3 years), and 7 were adults (median age 39.0 years, range 20.6-

66.9 years). The majority of patients had elevated levels of markers of inflammation at baseline: ESR elevation was reported for 9 patients (75%), and the CRP was raised in 11 (92%). High serum levels of SAA were seen in 11 of the 12 patients (92%). Severe fatigue was reported for all patients before treatment. The most common organ system features were musculoskeletal and ocular manifestations: Arthralgia were present in all 12 of the patients (100%), arthritis in 8 (67%), and myalgia in 6 patient (50%). Ocular symptoms were seen in 12 patients (100%), with conjunctivitis in 11 (92%) as most common. At baseline, hearing loss was present in 10 patients (83%). Recurrent episodes of headache and oral ulcers were found in 10 patients (83%).

- Dosage

The Kineret doses were 1-2 mg/kg/day in patients with a body weight <40 kg and 100 mg for patients with a body weight ≥40 kg (corresponding to 1-2.5 g/kg/day up to 100 kg body weight). The product was self-administered by s.c. injection once daily. In children with persistent disease activity, the Kineret dose was raised stepwise to a maximum of 8 mg/kg/day. Concurrent NSAID medication was added if required.

- Overall disease activity

Disease activity was significantly lower in all patients at 2 weeks compared to baseline (p=0.0005). MWS organ manifestations improved, as did all patient-derived measures of health and inflammatory markers. In total 92% of the patients had a sustained disease control throughout treatment with a MWS-DAS <10, with a mean score of 3.9. Two children aged 3.0 and 6.4 years required Kineret dose adjustment in order to maintain disease control. The dose had to be stepwise increased to 8 mg/kg/day. Both were carrying the V198M mutation.

- Disease activity in MWS-DAS domains

Musculoskeletal manifestations disappeared in all patients after 2 weeks of treatment, and remained well controlled at last visit in 9 out of 12 patients. Ocular symptoms were present in 4 of 12 individuals at last follow-up. Skin manifestations flared in one patient, who had been previously inactive. Sustained disease control was seen for headache, oral ulcers, and renal disease including proteinuria and hematuria. There was an increase in the number of patients reporting a resolution of abdominal pain. All but one patient remained afebrile at last follow-up.

- Inflammatory markers

SAA levels had normalized in all patients at the primary endpoint visit at 2 weeks while CRP was completely normalized in 5/11 patients with baseline elevations. CRP levels further improved compared to the 2 week endpoint and normalized in the majority of patients. Haematological abnormalities completely resolved in all patients. Mean SAA levels further decreased from 27.5 to 6.6 mg/L.

- Global assessments of health

All global measures of health improved during treatment: The patient global assessment score of overall disease activity decreased from 6.3 at at baseline to 2.5 at last follow-up (0 represents no disease activity and 10 represents maximum disease activity). The patient mood score also decreased from 2.2 to 1.4 (1 represents excellent mood and 3 represents the lowest mood possible). The patient performance score increased from 5.9 at baseline to 8.2 at last follow-up (0 represents inability to perform and 10 represents the best possible performance level). The

physician global assessment score confirmed stable disease control. All patients' measures were statistically significant.

- Long-term effects

MWS sequelae

Amyloidosis, which was confirmed by kidney biopsy in 2 patients at baseline, resolved in one and improved in the other as documented by repeat scans. Delayed puberty, in one patient, had resolved at last follow-up. Sensorineural hearing loss was documented in 10 of 12 patients at baseline and had improved in 2 of the patients at last follow-up, with complete resolution in one. In the second individual, initial hearing impairment was the most severe (grade 4) at baseline, whereas subsequent testing after Kineret treatment revealed only grade 3 impairment. Hearing loss became worse during Kineret treatment in 2 patients: from grade 1 to grade 2 in one and from grade 2 to grade 3 in the other. In the remaining 6 patients reporting hearing loss at baseline, hearing remained stable.

Hawkins et al (Arthritis Rheum 2004) - Spectrum of clinical features in Muckle-Wells Syndrome and response to anakinra

- Methods

This report was the first clinical evidence for the fundamental role of IL-1β in the pathogenesis of inflammation associated with CAPS, and the efficacy of Il-1 inhibition in these patients. The trial was based on the evolving knowledge on the NALP3 (often mutated in CAPS) inflammasome protein complex activation leading to an increased IL-1 production, and the reporting of the spontaneous up-regulation of IL-1 production in unstimulated monocytes obtained from a patient with NOMID/ CINCA syndrome. The clinical features of 3 members of a family, all of whom had MWS associated with a NALP3 mutation, were evaluated at baseline and following initiation of Kineret treatment. The results of three months of treatment were reported. The response of these patients inflammatory disease to treatment were assessed through diaries of symptoms, and clinical and laboratory assessments including measurement of SAA and CRP concentrations.

- Patient characteristics

Three patients diagnosed with MWS with overlapping features of MWS, FCAS and NOMID/CINCA participated in the study. The patients were a 42 years old female (mother), a 15 years old female (daughter) and a 22 years old male (son). During the year prior to treatment, the median SAA (CRP) concentrations in the mother, son, and daughter were 141 mg/l (58 mg/l), 161 mg/l (89 mg/l), and 148 mg/l (42 mg/l), respectively (normal concentration <10 mg/l for both SAA and CRP). The predominant clinical features in the 3 patients were rashes, arthralgia, fever, severe fatigue, and deafness.

- Dosage

An initial dose of 100 mg/day was reduced to 50 mg/day after 2 weeks as a result of the satisfactory treatment response. The patients were treated for 12 weeks.

- Efficacy results

All 3 patients had typical clinical and serologic evidence of active inflammatory disease including rash, conjunctivitis, neutrophilia and intense acute-phase response, SAA and CRP. All overt clinical features associated with active inflammation ceased within 4 hours of first dose of Kineret, including complete resolution of rash, and CRP and SAA had normalized at day 7. After start of therapy, all patients remained free of rash, conjunctivitis, and arthralgia. Furthermore, they tolerated exposure to cold ambient temperature without development of any symptoms.

Hoffman et al (Lancet 2004) - Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist

- Methods

In this study an experimental cold challenge protocol was developed to study the acute inflammatory mechanisms occurring after a general cold exposure in FCAS patients and to investigate the effects of IL-1 inhibition by pretreatment with Kineret. Four participants with FCAS and three healthy controls were exposed for 45 min to a room with an ambient temperature of 4°C. Symptom ratings and physical examinations, blood samples, skin by biopsy and assessments of affected skin surface area, and urine were obtained before cold challenge and repeatedly after the cold challenge. Six to 12 months after the initial non-treated challenge a therapeutic trial with the same protocol was performed, but with Kineret 100 mg administered 24 h and 1 h before the cold challenge.

- Patient characteristics

The study included 4 FCAS patients (3 females and 1 male, aged 49 to74 years) and 3 controls (all males, aged 49 to74 years). During a first phase of the study the patients and controls were exposed to a cold challenge and followed for 18 hours. In the second phase, the FCAS patients returned after 6-12 months for pretreatment with Kineret 100 mg, followed by a cold challenge.

- Dosage

100 mg at 24 and 1 hour prior to cold challenge.

- Efficacy results

After the cold challenge without pre-treatment, the patients developed low-grade fever beginning 2 hours after the challenge, peaking at about 8 hours and abating by the next morning. Evidence of rash began 1 hour after cold challenge and joint pain after 2 hours; both symptoms peaking at 8 hours. There was some evidence of mild general hand swelling and non-articular tenderness in 2 of the FCAS patients about 8 hours after the cold challenge. One patient developed acute painful bilateral conjunctivitis 8 hours after the cold challenge. WBC count and IL-6 levels increased within 1 hour of cold challenge, peaked at 8 and 4 hours, respectively, and returned to baseline by the next morning. After cold challenge with pre-treatment, neither controls nor IL-1Ra treated FCAS patients developed fever. The 3 FCAS patients treated with IL-1Ra before cold challenge did not develop any of the signs or symptoms that developed during the first part despite the same exposure and similar baseline degree of inflammation. Patients developed their usual mild evening rash after the initial dose of IL-1Ra, but had no symptoms at

all after the second dose and remained symptom free for 24-48 hours. After that, the regular cold-induced symptoms and daily rash returned. There was no significant change in total WBC counts or in serum IL-6 induced by the cold challenge in IL-1Ra treated FCAS patients.

Ross et al (J Cutaneous Medicine and Surgery 2008) - Use of anakinra (Kineret) in the treatment of familial cold autoinflammatory syndrome with a 16-month follow-up

- Methods

Eight adult family members with FCAS received Kineret 100 mg daily for 4 weeks. 7 of the patients were severely affected, implicating daily disabling symptoms. Treatment was preceded and followed by 2 weeks of no-treatment control periods. Assessments included repeat laboratory testing of CRP and SAA and physical examinations, and daily diaries capturing cold exposure and symptomatology. Symptoms were graded on a 5- point scale relating to skin, musculoskeletal, and eye symptoms, the presence of fever or chills, and general indicators of well-being. Also in this study an experimental cold challenge protocol was employed, and performed at baseline, during treatment with Kineret, and at a final occasion 2 weeks after the last Kineret administration. A Dermatology Life Quality Investigation (DLQI) assessment was performed, and a long-term assessment of treatment efficacy was done at 4 and 16 months of follow-up in patients continuing treatment.

- Patient characteristics

This study included 8 adult CAPS patients (6 females and 2 males) aged 29-77 years within the more severe spectrum of FCAS in all but one. The patients were seen over an 8-week period, which included 2 weeks pretreatment, 4 weeks of treatment with Kineret and 2 final weeks without medication. In all periods, the patients were exposed to a cold challenge. In addition, a long-term evaluation in continuously treated patients (n=5) was performed by use of a questionnaire at 4 and 16 months after the study.

- Dosage

Four weeks treatment with Kineret, 100 mg SC daily.

- Efficacy results

All patients reported severe signs and symptoms (relating to skin changes, musculoskeletal symptoms, eye problems, fever or chills, and general indicators of well-being) during the initial 2-week non-treatment period, with the exception of the patient aged 77 years. In all patients, signs and symptoms of FCAS resolved within 24 hours of the first injection of Kineret and all remained free of symptoms throughout the 4 weeks of treatment. The symptoms relapsed completely in all patients but one within 36 hours of ceasing Kineret treatment. In the pre- and post-treatment periods, all of the patients developed typical chills and characteristic discomfort within 1 hour of exposure to the cold room. In contrast, all remained completely free of symptoms and signs of FCAS on similar cold challenge during the treatment period.

The reduction in CRP during treatment was significant (mean change -14.38; 95% CI -7.35 to -21.42; $p \leq 0.0001$) and was followed by a significant increase in CRP after treatment (mean change -15.19; 95% CI 4.88 to 25.50; $p=0.0013$). Similar results were observed for SAA.

The subjective experience of skin manifestations was assessed using the Dermatology Life Quality Investigation (DLQI). During treatment, there was a significant improvement in DLQI score, with a mean reduction of -16.75 (95% CI -26.95 to -6.51, p= 0.004), followed by a significant increase when treatment was withdrawn (mean change 20.88, 95% CI 9.43 to 31.32, p=0.0019). At 4 and 16 months after the study, the long-term experience among continuously treated patients was assessed using a questionnaire. All patients remained satisfied with the efficacy of the treatment.

Neven et al (Arthritis Rheum 2010) - Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous articular syndrome.

- Methods

This study retrospectively analyzed the efficacy and safety of Kineret in 10 patients with NOMID/CINCA. This analysis was the first evaluation of the long-term effects of Kineret treatment in severely affected CAPS patients, with a follow-up of 26 to 42 months. The frequency and severity of clinical symptoms (including rash, fever, arthralgia or arthritis, and headache) were recorded before treatment and during follow-up. Inflammatory biologic markers included SAA, CRP and ESR and were measured regularly. In subsets of patients, audiography, vision, CSF examination (protein level, cell counts), and tests of cognitive function (intelligence quotient [IQ], Wechsler Preschool and Primary Scale of Intelligence, or Wechsler Intelligence Scale for Children) were performed. Brain magnetic resonance imaging (MRI), (including fluid-attenuated inversion recovery [FLAIR] imaging and contrast injection) was performed before and after treatment in most patients with the results retrospectively reviewed by the same experienced radiologist.

- Patient characteristics

Eight of the 10 patients were paediatric, including two infants (3 and 4 months, respectively). The mean (SD) age was 10.9 (7.3) years (range 0.25 to 19.8 years) at treatment initiation. All patients exhibited symptoms from the first days of life, and all except the two infants had previous treatment attempts with steroids, NSAIDS, and various DMARDS. 9/10 patients carried mutations of the CIAS1gene. Clinical CNS involvement and aseptic meningitis were present in all patients. Five patients exhibited developmental retardation, with IQ scores between 50 and 70. Brain MRI (with FLAIR imaging and contrast injection) performed before treatment in all except 1 patient showed abnormalities. Median CRP concentration, ESR, and SAA concentration before the start of treatment was 69 mg/L (range 26-110), 62 mm/hour (range 14-120), and 150 mg/L (48-386), respectively. Neutrophilia was also observed in all patients.

- Dosage

In all patients, Kineret treatment was initiated at 1 mg/kg/day, which was gradually increased to 2 to 3 mg/kg/day in 6 of the 8 older patients. In the 2 infant patients, dose increments up to 6 and 10 mg/kg were used.

- Efficacy results

The 8 non-infant patients displayed a rapid clinical response to Kineret, with complete remission of rash, fever, arthralgia, and myalgia within 24 hours of treatment initiation. In the 2 infants, symptoms improved with Kineret at 1 mg/kg/day but with reappearing disease manifestations the dose was increased up to 6 mg/kg/day and 10 mg/kg/day, respectively. Inflammation marker levels also significantly and persistently improved after adjustment of the Kineret dosage.

The high levels of CRP, ESR and SAA observed at baseline were significantly reduced after one month treatment. All of the 8 non-infant patients exhibited CNS involvement at baseline, with headache (7/8), papilledema (7/8) and/or abnormalities found on CSF examination (8/8). After 6 months of treatment, headaches were completely resolved in 3 patients and were decreased in frequency and severity in the remaining 4. Papilledema normalized in 3 patients and improved in the other 4 patients. CSF investigations were repeated in 6 patients; CSF white blood cells significantly decreased in all of these 6 patients compared to baseline. Protein levels decreased but not significantly. One patient exhibited complete normalization of all CSF parameters.

In 5 patients with relapsing headaches and/or papilledema after 1 year of treatment, the Kineret dose was gradually increased to 3 mg/kg/day. These CNS symptoms resolved except for episodic headache in 1 patient. The CSF parameters normalized in 1 patient, improved in 2 patients and remained stable in 2 patients. A re-evaluation of mental retardation at the last follow-up showed no improvement.

Cerebral MRI was reassessed 2 to 3 years after treatment initiation in 4 patients. Small vessel enhancement after contrast injection at baseline improved, as did periventricular white matter anomalies initially present in two of the patients.

Seven of the 8 non-infant patients reported hearing loss at baseline. Six months after start of treatment, 2 of the patients exhibited a 15-dB improvement on audiology assessment that remained stable up to the last follow-up. In 4 patients, hearing remained stable. Visual acuity remained unchanged in all patients. The visual field defects present in 4 patients at baseline normalized in all 4, together with resolution of papilledema. None of the two infants had neurosensory involvement at baseline, or during follow-up.

The two infants displayed irritability at baseline which rapidly improved with treatment. No papilledema developed during follow-up. Both patients exhibited a rapid improvement in CSF parameters within 3 months of treatment and complete normalization after 12 months. One of these younger patients developed a mild developmental retardation.

Two patients had signs of amyloidosis at baseline. Of these, one had an abnormal filtration rate which did not improve during 38 months of Kineret treatment, although the SAA normalized within 6 months, however, no proteinuria developed. In the other patient, proteinuria present at baseline gradually improved and normalized.

Leslie et al (Arch Dermatol 2006) - Phenotype, genotype and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations.

- Methods

This was a retrospective review of medical records in a cohort of 22 patients with CAPS of varying clinical severity, spanning from FCAS to NOMID/CINCA phenotypes, in all cases associated with NALP-3 mutations. Two of the 22 patients were paediatric. Fifteen patients received long-term therapy with Kineret. Besides the characterization of clinical features and routine laboratory parameters, SAA and CRP were measured monthly, and the development of AA amyloidosis was investigated through renal biopsies and SAP scintigraphy in selected cases, which was repeated during long-term treatment follow-up.

- Patient characteristics

Twenty-two patients were included in the review, whereof 15 were treated with Kineret. The phenotype of these patients varied: MWS in 11 patients, NOMID/CINCA in 2 patients and FCAS in 2 patients. Two paediatric patients were included; all others were >18 years of age. Of 7 patients not receiving Kineret treatment, 2 died before therapy was available, 2 had mild disease and declined therapy, and 3 received other (experimental) therapies. Highly elevated inflammatory markers were present at baseline. At baseline almost all (20 out of 22) patients were symptom free in the morning but developed progressive rash, fever, and arthralgia in the late afternoon to evening, accompanied by severe lethargy. Nineteen patients reported frequent diffuse flulike limb aches, which sometimes localized to joints. Knees and ankles were most commonly affected. Twenty-one patients experienced frequent conjunctivitis before treatment. Sensorineural deafness was present in 13/22 patients and was associated with all NALP3 variants except A439V. Hearing impairment was progressive and began in childhood or early adolescence; audiograms generally demonstrated hightone loss, and 8 patients used hearing aids.

- Dosage

All 15 patients treated with Kineret started on 100 mg/day. The dosage was then progressively reduced based on clinical response to 20 to 50 mg/day in all adults. The 2 children maintained the 100 mg/day dosage. The median treatment period was 17.7 months (range 1-39.1 months).

- Efficacy results

All Kineret treated patients had complete remission from rash, fever, conjunctivitis and rheumatic aches within 12 hours after starting Kineret (in 6 patients within 4 hours). The SAA and CRP levels were normalized from 99.5 and 41 mg/L at baseline to 5 mg/L and 2 mg/L, respectively, within 1 week. The treatment effects were sustained throughout the treatment period. Clinical disease recrudesced within 36 to 48 hours of Kineret injections in 5 patients who briefly stopped treatment, demonstrating the necessity of daily maintenance therapy. Nephrotic syndrome remitted within 8 to 33 months in 3 patients who had AA amyloidosis, associated with regression of amyloid on serial SAP scintigraphy. Data on urinary protein leak demonstrated substantial improvement. The fourth treated patient with amyloidosis began taking Kineret 18 months after undergoing renal transplantation; SAP scintigraphy showed regression of amyloid from his spleen and no involvement of the graft.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study 03-AR-0298

The pivotal efficacy study is prospective, open-label, and includes a withdrawal phase, with the objective of determining the effects of anakinra in controlling the inflammatory manifestations in paediatric and adult patients with NOMID/CINCA, the most severe form of CAPS The study is ongoing and has an open ended follow-up period. The data cut-off date is 16 August 2010.

This long-term outcome study investigated the efficacy (PK and safety) of anakinra treatment up to 60 months in paediatric and adult patients with CAPS. The study initially was planned as a "proof of concept" trial to illustrate the effect of IL-1 blockade in NOMID and MWS patients. When anakinra proved efficacious in this patient group the focus changed to results of long-term treatment and prevention of future organ damage. Several amendments were added during the years resulting in a trial with a limited methodological design. No dose finding studies were conducted. The maximum dose per day was increased from 1-2 mg/kg (2003) to 3 mg/kg (2004), 5 mg/kg (2007), and 10 mg/kg (2010). The withdrawal period was reduced from 3 month to 7 days – and there was no blinding of the withdrawal arm. Instead the first 11 patients included comprised the withdrawal group. As the age limit was also changed to include children <2yrs (June 2007) the withdrawal patients are probably not fully representative of the whole studied group. In an amendment in March 2007 patients were included who had participated in other clinical trials at NIH. Nine patients had received anakinra before baseline data was recorded and were thus excluded from the ITT population. Although the principle of "last observation carried forward" was used, the overall quality of the study remains limited and the final conclusions are inevitably impacted. However, the CHMP acknowledged that the study is performed on patients suffering from an extremely rare condition and therefore obvious inherent recruitment problems have impacted the conduct of the trial.

Initial literature reports, e.g. Hawkins et al 2003, of the safe and effective use of anakinra throughout the severity spectrum of all CAPS phenotypes were subsequently followed by successful open label studies and numerous case reports published in the literature. As a result, the CHMP acknowledged the ethical concerns in conducting a randomized placebo controlled trials in CAPS due to the immediate and pronounced clinical response (shown following the withdrawal and subsequent reinstitution of the product) (Ross et al 2008, Goldbach-Mansky et al 2006), and the clear lack of placebo response in trials with other IL-1 inhibitors (Hoffman et al 2009, Lachmann et al 2009). The collection of the three syndromes FCAS, MWS, and NOMID/CINCA under the common syndrome CAPS is justified on the basis of a continuum of increasing severity of inflammatory phenotype with an identical pathogenetic background, and the response to IL-1 blocking therapies.

Validated outcome measures for CAPS do not exist. The endpoints chosen in study 03-AR-0298 correspond well to recently agreed standards for assessment of patients with autoinflammatory disease (Piram et al 2010). In addition to assessment of daily symptoms and acute phase reactants, the importance of assessing long-term disease impact and corresponding therapeutic efficacy, including quality of life and effects on disease-specific organ inflammation in the evaluation is acknowledged by the CHMP.

Supportive studies

In support of the efficacy of anakinra treatment throughout all CAPS subtypes and in adult and pediatric patients, data from published prospective and retrospective studies were provided. These are open-label long-term studies with organ function outcome measures and QoL assessments in severely affected CAPS patients (NOMID/CINCA and MWS). Trials of treatment in FCAS patients, and the prevention of cold-induced disease flares with Kineret, were also included. The selected endpoints in these studies comply with current recognised assessment methods for the indication (Piram et al 2010).

Efficacy data and additional analyses

Study 03-AR-0298

In total, 43 patients were enrolled. Twenty-two patients completed 60 months of treatment, 19 patients had not yet reached 60 months and 2 patients discontinued the study prematurely due to noncompliance and withdrawal of consent. NOMID/CINCA was diagnosed in 36 patients (83.7%). Seven patients (16.3%) were enrolled fulfilling the study inclusion criteria, but had characteristics overlapping between MWS and NOMID/CINCA. Of the 43 patients, 25 (58.1%) were females, and 36 (83.7%) were white. All patients had active disease at baseline. Patient ages at treatment start ranged from 0.7 to 46.3 years, with an overall mean (SD) of 10.3 (10.4) years. Most patients were children (36 patients): 13 below 2 years, 18 between 2 and 11 years, and 5 between 12 and 17 years. The youngest patients were 8 months old. The populations studied are considered representative of the population intended to be treated. CAPS is a life-long disease, and symptoms appear early in life, in NOMID/CINCA even within days or weeks of birth. Both genders are affected equally, and the disease may affect patients of all races.

Out of 43 patients enrolled, 9 were excluded from the ITT group because treatment was started before the baseline visit. Thus, the ITT population was 34 subjects. Five more subjects were excluded due to missing baseline diary data (ITT diary population; n = 29), seven patients were subsequently excluded because of missing diary data before or after the withdrawal period (withdrawal population; n = 22). The first 11 patients constituted the “withdrawal group” and the remaining 11 patients was the “treatment group”.

The primary objectives of the study were to assess the change in DSSS of 5 key symptoms (fever, rash, headache, joint pain, and vomiting) and the change in SAA levels from baseline to 3-6 months of administration of anakinra. Results showed that the key symptoms of NOMID improved rapidly and significantly as assessed by DSSS from baseline to Month 3-6, with an estimated change of -3.5 (95% CI -3.7 to -3.3; p <0.0001) and this range of improvement was constant throughout the study up to Month 60. Within 3 days of treatment initiation, the DSSS decreased from a mean baseline value of 4.5 to 0.8 at Day 3. All age group showed comparable clinical improvement. There was a rapid and sustained decrease in diary symptom score from baseline to Month 60 for each individual key symptom, except for vomiting, which had a very low score already at study initiation. Secondary diary symptom scoring (e.g. fatigue and eye redness) displayed similar changes, decreasing significantly during early treatment up to Month 60.

It was noted that instead of using validated skin and joint scores self-composed scoring systems were used. During the procedure it was clarified that both the dermatology and joint scores, designed for the purpose of the study, were at the time considered to best address the characteristic features of severe CAPS. The most comprehensive way to demonstrate improvement in disease manifestations was to report each component separately. Rash and the individual components of a DAS 28, including joint swelling and pain as well as CRP and ESR have all been reported.

In study 03-AR-0298, the SAA levels decreased significantly over the first 3 months of Kineret treatment (from median 149 mg/L at baseline to 6 mg/L). The decrease in SAA, calculated based on a repeated measures analysis of covariance model, was significant and sustained throughout the study period. The inflammatory serum markers ESR and hsCRP also decreased significantly during the first 3-month treatment period; median ESR from 52 to 16 mm/h and median hsCRP from 51 to 4 mg/L.

An open withdrawal phase after 3 months of treatment served as a treatment control. As evident from symptom scores and inflammatory markers (SAA, hsCRP, and ESR), the withdrawal of anakinra resulted in relapse within a few days. Reinstitution of anakinra led to rapid clinical improvements. The withdrawal phase was discontinued after the first 11 patients due to the dramatic effect of withdrawal and reinstitution.

Long-term results up to 5 years (60 months) showed progression of most of the secondary efficacy variables. Indicators of CNS inflammation (elevated intracranial pressure, laboratory evidence of aseptic meningitis in the CSF, and headache) decreased significantly. Significant improvements were seen in other secondary symptoms, including fatigue, difficulties ambulating, eye redness, and sleep problems, as well as in rash, joint status, endurance test, and QoL scores. Ophthalmology data showed significant reductions in inflammatory eye manifestations including uveitis and papilledema. Visual acuity and peripheral vision did not improve. Hearing loss was not improved by anakinra treatment.

It became clear during the initial years of treatment that, in addition to the basic criteria of preventing disease flares such as rash, fever, and elevated CRP, dose adjustments had to address “smoldering” organ inflammation to prevent progression of organ damage and to preserve organ function (e.g. hearing). Thus, the criteria for dose escalation evolved during the study from dose increases mainly due to clinical symptoms and elevated CRP to focus also on organ inflammation of eyes, inner ear, and CNS. Due to dose adjustments in order to achieve the treatment objectives, the average dose at the end of the study was higher than the initial dose leveling off to a range of 3.2-3.6 mg/kg after 48-60 months, for all age groups (<2, 2-11, 12-17 and ≥ 18 yrs).

Supportive studies

Although the studies were independently designed and conducted, the parameters used when evaluating therapeutic effects in the treatment of CAPS are largely similar allowing descriptive comparisons of the short and long-term effects across studies. The results observed in the pivotal trial were generally consistent with the findings of the supportive studies published in the literature. Throughout these studies, the authors reported that the patients displayed a rapid clinical response to anakinra, with prompt remission of overt symptoms as rash, fever, conjunctivitis, and arthralgia, corresponding to the parameters of the DSSS employed in study

03-AR-0298. A prompt and persistent normalization of inflammatory markers, including SAA, CRP and haematological measures, was achieved in the patients in the two supportive published studies that included patients with the most severe forms of CAPS (Lepore et al 2010, Neven et al 2010), and in MWS patients, a similar decrease in inflammatory marker levels were observed early after treatment initiation (Hawkins et al 2004, Kümmerle-Deschner et al 2011, Leslie et al 2006). This finding is also described in Ross et al 2008 in FCAS patients during 4 weeks of Kineret treatment.

A sustained control of inflammatory disease manifestations was achieved also in the supportive studies, both including long-term data. However, a common finding was the requirement of dose increments in many patients over time to maintain disease control, both in terms of overt symptoms of disease flare and chronic organ inflammation.

2.5.4. Conclusions on the clinical efficacy

The results of study 03-RA-0298 showed that anakinra significantly decreased the primary endpoints NOMID-specific diary scores and biomarkers of inflammation (SAA, CRP, and ESR). Results were consistent across all subgroups including age, gender, presence of CIAS1 mutation, and disease phenotype. Remission was sustained up to 60 months. Following withdrawal, fever, rash, joint pain, and vomiting all appeared after the first day and headache after 2 days. Symptoms promptly responded to reinstitution of anakinra. Indicators of CNS inflammation (elevated intracranial pressure, laboratory evidence of aseptic meningitis in the CSF, and headache) decreased significantly. Significant improvements were seen in other secondary symptoms, including fatigue, difficulties ambulating, eye redness, and sleep problems, as well as in rash, joint status, endurance test, and QoL scores. Ophthalmology data showed significant reductions in inflammatory eye manifestations including uveitis and papilledema. These effects on inflammation are all considered of clinical importance for CAPS patients. Visual acuity and peripheral vision did not improve. Hearing loss was not improved by anakinra treatment.

The results reported in the supportive prospective and retrospective efficacy studies in patients across the whole spectrum of CAPS severity, as well as by published case reports, were in line with the efficacy results observed in the pivotal study 03-AR-0298. In all studies, the onset of response following anakinra treatment was rapid with a clinically relevant effect within a few days. The treatment resulted in a normalization of inflammatory serum markers and overt disease symptoms as shown in the meta-analysis and the descriptive comparison of efficacy. Kineret treatment also reduced or stabilized the progression of neurological manifestations, hearing, vision and QoL in severe CAPS phenotype patients.

The prefilled syringe with a graduated label with a dosage range of 20-100 mg and scale intervals of 10 mg allows the new dose regimen required for CAPS patients as well as the administration of the 100 mg dosage required in RA patients.

2.6. Clinical safety

The safety data of anakinra for the treatment of CAPS originated from the pivotal study 03-AR-0298 supported by published studies and published case reports as well as safety reports from the MAH's safety database. Supportive safety data in JIA patients from study 990758 and its

open label extension, study 990779. These 2 studies were already assessed by the CHMP in 2006 as part of the MAH's obligation to submit paediatric data.

Patient exposure

The safety population included 43 patients, of whom 26 patients (60.5%) had a treatment duration of >4 years. Median duration of exposure expressed as patient years was 4.9 and total exposure 159.8 patient years. Most patients were exposed to dose levels up to 3 mg/kg, with the dose level of 2 mg/kg representing most patient years (76.0).

Table 24 Duration of Kineret treatment as patient years by dose level (Safety population)

Dose level	Number of patients	Mean	Range	Total patient years
1 mg/kg	27	0.8	0.0[1)] - 2.6	20.3
2 mg/kg	40	1.9	0.2 - 5.2	76.0
3 mg/kg	31	1.0	0.0* - 4.0	31.5
4 mg/kg	19	1.4	0.2 - 3.3	27.5
5 mg/kg	7	0.6	0.0* - 1.4	4.0
8 mg/kg	1	0.4	NA	0.4

NA Not applicable
[1)] Exposure duration of 0.0 indicates an exposure shorter than 0.05 years, i.e. less than 9 days.
Duration of treatment is calculated from the date of first dose until date of last dose, date of Month 60 visit, or cut-off date.

There were no major differences in duration between subgroups (baseline age, gender, CIAS1 mutation, and starting dose level), except for a slightly shorter duration of treatment in patients <2 years because this age group was included only during the later years of the study.

An estimation of the total Kineret exposure in CAPS studies, including study 03-AR-0298 and the supporting published studies, is presented below.

Table 25 Estimated extent of exposure in all CAPS studies

Study	Number of patients	Patient years, based on median duration of treatment	Patient years, based on individual data	Patient years, based on individual and calculated individual data
03-AR-0298	43	208.9	159.8	159.8
Kümmerle-Deschner et al 2011	12	11.0	NA	9.6*
Lepore et al 2010	14	43.8	41.8	41.8
Neven et al 2010	10	26.0	NA	22.6*
Ross et al 2008	8	10.7	7.7	7.7
Leslie et al 2006	15	22.1	25.7	25.7
Hawkins et al 2004	3	0.8	0.8	0.8
Hoffman et al 2004	4	0.02	0.02	0.02
TOTAL	**109**	**323.2**	**-**	**267.9**

*calculated by dividing the exposure based on median duration of treatment by 1.15

Adverse events

A summary of treatment-emergent AEs (TEAEs) in each category is presented below.

Table 26 Overview of adverse events in study 03-AR-0298

	Safety population (N=43)			
	No. of patients (N=43)		No. of events (PYRS=159.8)	
	N	%	F	Rate
Any treatment-emergent AE	41	95.3	1233	7.7
- Severe treatment-emergent AE	7	16.3	14	0.1
Significant treatment-emergent AE	15	34.9	32	0.2
- Death	0	0.0	0	0.0
- Other serious AE	14	32.6	24	0.2
- AE leading to permanent discontinuation of study drug	0	0.0	0	0.0
- AE leading to temporary discontinuation of study drug	1	2.3	3	0.0
- AE leading to dose adjustment	5[a]	11.6	11	0.1

[a]All dose adjustments represent dose increases.
Serious AEs which started before the first dose of Kineret, started or worsened after the last dose of Kineret, after Month 60 visit or during the withdrawal period are excluded.

AE=adverse event; F=number of events, N=number of patients, %=proportion of patients, PYRS=patient years, Rate=number of events per patient year.

In total, 1233 TEAEs occurred in 41 patients (95.3%). Thirty-two AEs were classified as significant. None of these events led to permanent discontinuation of study medication, but one patient was temporarily withdrawn from treatment, and dose adjustments (all dose increases) were made for 11 AEs in 5 patients.

The most commonly reported AEs (occurring in >10% of the patients or >10 AEs) are summarised by preferred term in the table below. The most frequent SOCs involved were Infections and infestations (86.0%), General disorders (65.1%), Nervous system disorders (53.5%) and Musculoskeletal and connective tissue disorders (46.5%). The most common AEs were headache (48.8%), arthralgia (41.9%), pyrexia (39.5%), upper respiratory tract infection (39.5%), nasopharyngitis (34.9%), and rash (32.6%). Other frequent AEs were ocular hyperemia, sinusitis, ear infection and otitis media. With the exception of infections, these AEs are also common features of NOMID/CINCA and as such may have been scored in the disease diary as well. Eight patients (18.6%) reported injection site reactions (ISRs).

Most AEs (86.0%) were mild in intensity (1.1% were severe) and classified by the investigator to be unrelated or unlikely related to study treatment (81.3%).

Table 27 Most common (>10 % of patients or >10 adverse events) treatment-emergent adverse events by preferred term (Safety population)

Preferred Term	Safety population (N=43)	
	No. of patients (%)	No. of adverse events (n)
Patients with any treatment-emergent adverse event	41 (95.3%)	1233
Headache	21 (48.8%)	115
Arthralgia	18 (41.9%)	133
Pyrexia	17 (39.5%)	51
Upper respiratory tract infection	17 (39.5%)	48
Nasopharyngitis	15 (34.9%)	40
Rash	14 (32.6%)	51
Ocular hyperemia	12 (27.9%)	35
Sinusitis	12 (27.9%)	28
Ear infection	11 (25.6%)	23
Otitis media	11 (25.6%)	20
Fatigue	10 (23.3%)	27
Diarrhea	10 (23.3%)	16
Oropharyngeal pain	9 (20.9%)	27
Pain in extremity	9 (20.9%)	27
Cough	9 (20.9%)	19
Injection site reaction	8 (18.6%)	12
Neck pain	8 (18.6%)	11
Vomiting	7 (16.3%)	25
Back pain	7 (16.3%)	22
Gastroenteritis	7 (16.3%)	8
Nasal congestion	6 (14.0%)	14
Nausea	6 (14.0%)	14
Abdominal pain	6 (14.0%)	11
Sleep disorder	6 (14.0%)	10
Urinary tract infection	6 (14.0%)	10
Gastrointestinal viral infection	6 (14.0%)	8
Viral infection	6 (14.0%)	8
Condition aggravated	5 (11.6%)	7
Fall	5 (11.6%)	6
Pneumonia	5 (11.6%)	6
Post lumbar puncture syndrome	5 (11.6%)	5
Chest pain	4 (9.3%)	10
Epistaxis	4 (9.3%)	10
Malaise	3 (7.0%)	18
Dizziness	3 (7.0%)	10
Urticaria	1 (2.3%)	15*
Abdominal discomfort	1 (2.3%)	11*

* Urticaria reported 15 times in one patient and abdominal discomfort 11 times in one patient.

Most AEs (427) were recorded during the first year, which also represented most patient years (40.9). The AE reporting rate was 10.4, calculated as number of AEs per patient year. Rates decreased the 2 following years to 6.2 and 4.3, respectively. At year 4, the number of patient years was unchanged, but there was an increase in reported AEs leading to an increase in the reporting rate up to 12.0. At year 5, rates were back to 4.9, the same level as year 3.

There was an increase in AE reporting in 2007 due to reporting of disease symptoms as AEs. The year 2007 was also the fourth treatment year for the first 18 patients, which explains why many AEs related to the disease were recorded year 4, e.g. arthralgia, headache, pyrexia, rash, ocular hyperaemia and fatigue. The number of patient years 2007 was comparable to 2006 and 2008. The frequency of infections (AEs in the SOC Infections and infestations) remained on a stable level. The AE reporting rate was 2.4 the first year of treatment, 1.5 the second year, and

between 1.3 and 1.6 the following years. ISRs were reported during the first year of treatment and thereafter at only one occasion the following year.

Table 28 Treatment-emergent adverse events by organ class and preferred term, classified by age at onset of event (Safety population)

Safety population (N=43)									
	<2 yrs (PYRS: 9.7)		2-11 yrs (PYRS: 71.1)		12-17 yrs (PYRS: 38.2)		≥18 yrs (PYRS: 40.8)		Total
System organ class/ Preferred term	F	rate	F	rate	F	rate	F	rate	F
ANY EVENT	92	9.5	613	8.6	138	3.6	388	9.5	1231
Eye disorders	1	0.1	22	0.3	11	0.3	25	0.6	59
- Ocular hyperemia	1	0.1	12	0.2	5	0.1	17	0.4	35
Gastrointestinal disorders	17	1.8	49	0.7	8	0.2	30	0.7	104
- Vomiting	12	1.2	13	0.2	-	-	-	-	25
- Diarrhea	3	0.3	6	0.1	3	0.1	4	0.1	16
- Nausea	-	-	11	0.2	-	-	3	0.1	14
- Abdominal discomfort	-	-	-	-	-	-	11	0.3	11
- Abdominal pain	-	-	9	0.1	-	-	2	0.0	11
General disorders and administration site conditions	19	2.0	76	1.1	12	0.3	39	1.0	146
- Pyrexia	14	1.4	27	0.4	5	0.1	5	0.1	51
- Fatigue	3	0.3	7	0.1	-	-	17	0.4	27
- Malaise	-	-	17	0.2	-	-	1	0.0	18
- Injection site reaction	-	-	8	0.1	-	-	4	0.1	12
- Chest pain	-	-	3	0.0	1	0.0	6	0.1	10
- Condition aggravated	2	0.2	3	0.0	1	0.0	1	0.0	7
Infections and infestations	33	3.4	156	2.2	20	0.5	64	1.6	273
- Upper respiratory tract infection	3	0.3	29	0.4	3	0.1	13	0.3	48
- Nasopharyngitis	9	0.9	20	0.3	2	0.1	9	0.2	40
- Sinusitis	1	0.1	18	0.3	4	0.1	5	0.1	28
- Ear infection	2	0.2	15	0.2	-	-	6	0.1	23
- Otitis media	2	0.2	12	0.2	-	-	6	0.1	20
- Urinary tract infection	-	-	7	0.1	1	0.0	2	0.0	10
- Gastroenteritis	2	0.2	5	0.1	-	-	1	0.0	8
- Gastrointestinal viral infection	2	0.2	3	0.0	2	0.1	1	0.0	8
- Viral infection	1	0.1	6	0.1	-	-	1	0.0	8
- Pneumonia	3	0.3	3	0.0	-	-	-	-	6
Injury, poisoning and procedural complications	1	0.1	16	0.2	1	0.0	6	0.1	24
- Fall	1	0.1	3	0.0	-	-	2	0.0	6
- Post lumbar puncture syndrome	-	-	4	0.1	-	-	1	0.0	5
Musculoskeletal and connective tissue disorders	1	0.1	73	1.0	35	0.9	97	2.4	206
- Arthralgia	1	0.1	49	0.7	15	0.4	67	1.6	132
- Pain in extremity	-	-	7	0.1	14	0.4	6	0.1	27
- Back pain	-	-	7	0.1	1	0.0	14	0.3	22
- Neck pain	-	-	4	0.1	2	0.1	5	0.1	11
Nervous system disorders	10	1.0	54	0.8	23	0.6	57	1.4	144
- Headache	10	1.0	48	0.7	6	0.2	51	1.3	115
- Dizziness	-	-	1	0.0	8	0.2	1	0.0	10
Psychiatric disorders	1	0.1	5	0.1	2	0.1	6	0.1	14
- Sleep disorder	1	0.1	3	0.0	-	-	6	0.1	10
Respiratory, thoracic and mediastinal disorders	3	0.3	68	1.0	7	0.2	19	0.5	97
- Oropharyngeal pain	-	-	11	0.2	4	0.1	12	0.3	27
- Cough	-	-	16	0.2	2	0.1	1	0.0	19
- Nasal congestion	2	0.2	10	0.1	-	-	2	0.0	14
- Epistaxis	-	-	7	0.1	-	-	3	0.1	10
Skin and subcutaneous tissue disorders	1	0.1	57	0.8	12	0.3	17	0.4	87
- Rash	1	0.1	28	0.4	10	0.3	12	0.3	51
- Urticaria	-	-	15	0.2	-	-	-	-	15

PYRS=patient years, F=Number of events, rate=number of events per patient year. Included in table if >10% of patients or >10 events. Adverse events which started before the first dose of Kineret, started or worsened after the last dose of Kineret, after Month 60 visit, or during the withdrawal period are excluded. NOTE: Two adverse events are excluded due to missing date of onset.

Adverse events by age

The number of AEs per patient year, i.e. the AE reporting rate, by age at AE onset is presented in Table 35. There were similar overall rates in the age groups <2, 2-11, and ≥18 years (9.5, 8.6,

and 9.5, respectively) and a lower rate in the age group 12-17 years (3.6). Individual SOCs indicated that Gastrointestinal disorders, General disorders, and Infections and infestations were more common in patients <2 years and Musculoskeletal disorders in patients ≥18 years.

Adverse events by dose

For AEs classified by dose at AE onset, there were no differences between doses of 1-3 mg/kg/day and ≥4 mg/kg/day in the overall AE reporting rate (7.9 and 6.8) or in rates for individual SOCs and AEs. The dose 3 mg/kg was selected based on the estimated plateau dose level reached during the study.

Adverse events by presence of CIAS1 mutation

There were no major differences between the CIAS1 and non-CIAS1 groups in AE reporting rates (7.4 and 9.2). Thus, CIAS1 mutation was not associated with more or less AEs. Similar rates were obtained for the groups on the SOC level, except for Eye disorders with 55 AEs, whereof 35 ocular hyperemia, in the CIAS1 group and 4 AEs in the non-CIAS1 group.

Serious adverse event / deaths / other significant events

There were no deaths during the study.

There were 24 SAEs reported in 14 patients. Most common were SAEs in the SOC Infections and infestations (13 SAEs), with pneumonia and gastroenteritis occurring in 3 and 2 patients, respectively, and the SOC Injury, poisoning and procedural complications (4 SAEs, all related to lumbar puncture, which was part of the study procedure). Eleven of the SAEs were considered causally related (possible or probable) to drug treatment by the investigator; all were infections, one in combination with an episode of histiocytosis hematophagica. Four SAEs regarding infections were considered not related (unrelated or unlikely). There was one SAE report regarding histiocytosis haematophagica (also known as macrophage activation syndrome [MAS]) in connection with a post-operative infection. The patient, who was mutation negative, had 2 previous episodes of MAS before start of Kineret treatment. She was treated with prednisolone and cyclosporine, and the Kineret dose was maintained at 2 mg/kg/day. The event resolved without sequelae.

Table 29 Treatment-emergent serious adverse events by system-organ class and preferred term (Safety population)

		Safety population (N=43)	
System organ class (SOC)	**Preferred term**	**N (%)**	**F**
ANY EVENT	ANY EVENT	14 (32.6%)	24
Eye disorders	TOTAL FOR SOC	1 (2.3%)	1
	Uveitis	1 (2.3%)	1
General disorders and administration site conditions	TOTAL FOR SOC	2 (4.7%)	2
	Chest pain	1 (2.3%)	1
	Condition aggravated	1 (2.3%)	1
Infections and infestations	TOTAL FOR SOC	7 (16.3%)	13
	Pneumonia	3 (7.0%)	3
	Gastroenteritis	2 (4.7%)	2
	Arthritis bacterial	1 (2.3%)	1
	Cellulitis	1 (2.3%)	1
	Lymphadenitis bacterial	1 (2.3%)	1
	Meningitis enteroviral	1 (2.3%)	1
	Otitis media	1 (2.3%)	1
	Postoperative wound infection	1 (2.3%)	1
	Sinusitis	1 (2.3%)	1
	Wound infection	1 (2.3%)	1
Injury, poisoning and procedural complications	TOTAL FOR SOC	5 (11.6%)	5
	Post lumbar puncture syndrome	4 (9.3%)	4
	Traumatic lumbar puncture	1 (2.3%)	1
Investigations	TOTAL FOR SOC	1 (2.3%)	1
	Catheterization cardiac	1 (2.3%)	1
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	TOTAL FOR SOC	1 (2.3%)	1
	Histiocytosis hematophagica	1 (2.3%)	1
Nervous system disorders	TOTAL FOR SOC	1 (2.3%)	1
	Convulsion	1 (2.3%)	1

F=Number of events, N=Number of patients, %=proportion of patients.
Serious AEs which started before the first dose of Kineret, started or worsened after the last dose of Kineret, after Month 60 visit or during the withdrawal period are excluded.

Injection site reactions

Ten out of 43 (23%) patients reported 17 ISRs (i.e. AEs belonging to MedDRA HLGT Administration site reactions) in study 03-AR-0298. Out of the 17 ISRs, 11 (65%) occurred during the first month and 13 (76%) were reported during the first 6 months. No ISRs were reported after year 2. All ISRs reported during the first 6 months of Kineret treatment occurred in patients who had received a starting dose of 1 mg/kg. With the exception of one event of injection site erythema in a patient 12-17 years, ISRs were only reported in patients 2-11 years and ≥18 years. Most ISRs (13 out of 17) were mild, none was severe and there were no serious ISRs. There was no difference between genders in reporting rates of ISRs. Patients with a *CIAS1* mutation had a similar AE reporting rate of ISRs compared to those without the mutation, 0.1 and 0.2, respectively.

Infections

In total 37 patients out of 43 (86%) reported 273 infections (AE reporting rate 1.7). The most common infections were upper respiratory tract infection (reporting rate 0.3) and nasopharyngitis (reporting rate 0.3). There were no deaths but 7 patients experienced 13 SAEs denoting infections (rate 0.1). Nine were judged as causally related (possible or probable) to drug treatment by the investigator, one in combination with an episode of histiocytosis

hematophagica. Four SAEs denoting infections were considered not related (unrelated or unlikely). In one patient, Kineret was temporarily stopped and in 2 cases the Kineret dose was increased during the infections. All SAEs resolved.

The overall frequency of infections remained stable over time with the exception of a higher reporting rate during the first year of treatment; 2.4 the first year of treatment, 1.5 the second year, and between 1.3 and 1.6 the following years. The reporting rate during the first 6 months was higher (2.9) in patients who had received a starting dose of 1 mg/kg than in those starting on 2 mg/kg (1.3). There was no difference between genders in reporting rates of infections.

The reporting rate for infections was higher in patients <2 years (rate 3.4) and 2-11 years (rate 2.2), than in other age groups. Most infections were classified as mild or moderate. There were no deaths or treatment discontinuations due to infections. Kineret administration was temporarily stopped in 1 patient due to an infection, and doses were increased in 5 patients due to disease flares in connection with the infections. Patients with a *CIAS1* mutation had a similar yearly rate of infections compared to those without the mutation, 1.7 and 2.0, respectively.

Hepatic events

In total there were 6 hepatic events in 5 patients. All events were considered mild, except one episode of Hepatic enzyme increased which was considered to be of moderate severity. All events were non-serious and resolved without sequelae on continued Kineret treatment.

Table 30 Hepatic adverse events in study 03-AR-0298

Event	Number of patients (%)	No of events
Alanine aminotransferase increased	2 (4.7 %)	2
Hepatic enzyme increased	2 (4.7 %)	2
Aspartate aminotransferase increased	1 (2.3 %)	1
Bilirubin conjugated increased	1 (2.3 %)	1

Laboratory findings

At baseline, haemoglobin and haematocrit values were low and WBC, neutrophil, and platelet values were elevated, reflecting active disease in the study population. All values improved rapidly after initiation of Kineret treatment and levels were sustained up to Month 60.

Inflammatory markers (ESR, hsCRP, SAA, haptoglobin, and fibrinogen) were all elevated at baseline. All values improved rapidly after initiation of Kineret treatment and levels were sustained up to Month 60. No clinically relevant changes were found in the urinalysis.

Safety in special populations

A patient became pregnant during the study. Due to the risk of a disease flare, anakinra was continued during the whole pregnancy, and the baby was delivered full-term. After birth, the patient remained on anakinra. The baby was diagnosed with D303N mutation and was started on anakinra treatment before the age of 1 year.

Safety related to drug-drug interactions and other interactions

No interaction studies have been performed for the CAPS indication.

Discontinuation due to adverse events

There were no AEs leading to discontinuation of Kineret treatment. One patient was temporarily withdrawn from treatment due to cellulitis, wound infection and chest pain. These AEs were classified as serious. Treatment was reinstituted after 2 weeks.

Five patients had their doses adjusted due to AEs; all adjustments were dose increases in connection with disease flares. At some of these occasions, CAPS symptoms escalating to flares were induced by infections. Three of the AEs leading to dose adjustment in 2 patients were considered serious.

Safety database report

There were 28 medically confirmed reports with 44 AEs in the MAH safety database in patients with different forms of CAPS (cut-off date 13 May 2012). The majority, 18 reports with 30 AEs, concerns patients with NOMID/CINCA. There are no reports with fatal SAEs. Thirteen out of the 28 medically confirmed reports in CAPS patients were serious, and contain, in total, 20 SAEs.

Table 31 Serious adverse events in CAPS patients

Age group*	Indication** (CAPS)	SOC	PT
Adult	FCAS	General disorders and administration site conditions	Injection site reaction
Adult	NOMID/CINCA	Nervous system disorders	Hypoaesthesia
Paediatric	MWS	Infections and infestations	Herpes simplex
Paediatric	NOMID/CINCA	Psychiatric disorders	Depression
			Suicidal ideation
Adult	NOMID/CINCA	Infections and infestations	Cellulitis
Adult	NOMID/CINCA	Infections and infestations	Lobar pneumonia
Adult	NOMID/CINCA	General disorders and administration site conditions	Therapeutic product ineffective for unapproved indication
Paediatric	NOMID/CINCA	Injury, poisoning and procedural complications	Post lumbar puncture syndrome
Adult	NOMID/CINCA	Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Breast cancer
Adult	NOMID/CINCA	General disorders and administration site conditions	Pain
		Renal and urinary disorders	Calculus urinary
			Hydronephrosis
			Nephrolithiasis
Paediatric	NOMID/CINCA	Infections and infestations	Sepsis
		Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Histiocytosis haematophagic***

Age group*	Indication** (CAPS)	SOC	PT
Adult	NOMID/CINCA	Infections and infestations	Appendicitis
Paediatric	NOMID/CINCA	Ear and labyrinth disorders	Deafness neurosensory
		Infections and infestations	Gastroenteritis
		Renal and urinary disorders	Renal failure acute

* Pediatric patients are patients aged less than 18 years, adult patients are those aged 18 or more.
** During a separate evaluation of hepatic events it was discovered that in one patient with NOMID/CINCA the indication for Kineret treatment was mis-coded. The patient experienced serious events of hepatic steatosis, obesity and dyslipidaemia.
*** This patient has also taken part in study 03-AR-0298, in which she also developed a serious event of MAS.

Safety reported from the literature

There are no fatal AEs, and with the exception of a case report no severe or serious AEs reported in any of the 7 published studies including 66 CAPS patients or in the published case reports comprising 133 CAPS patients. It should be noted that the reported safety information, in many cases, is very limited for published studies and case reports.

Adverse events in published studies with CAPS subdiagnosis NOMID/CINCA

Neven et al. 2012: The most common adverse effects reported were mild local stinging and erythema at the injection sites, which gradually decreased in most patients. All patients gained height and exhibited increased BMI. Two patients became overweight, with BMI more than 2 standard deviation (SD) above normal mean value. No severe infections were reported but it should be noted that all patients had been immunized against Streptococcus pneumonia and Haemophilus influenzae. The 2 youngest patients also received daily antibiotic prophylaxis with penicillin and trimethoprim.

Adverse events in published studies with CAPS subdiagnosis MWS

Kümmerle-Deschner et al. 2011: There were no reports of serious adverse events during the study period. The reported adverse events included mild injection site reactions in 5 patients (42%), mild infections in 5 patients (42%), and hyperactivity and weight gain in 4 patients each (33%). The authors conclude that Kineret was well tolerated.

Hawkins et al. 2004: Mild inflammations at injection sites, decreasing over time, were reported.

Adverse events in published studies with CAPS subdiagnosis FCAS

Hoffman et al. 2004: No adverse events were reported.

Ross et al. 2008: ISRs occurred in 3 of the patients during the 4-week study period. The reactions decreased in severity during the study and had resolved in all patients using the medication in longer-term follow-up. It was specifically reported that neutropenia was not observed, and that there were no infections or other significant adverse reactions.

Adverse events in published studies in mixed CAPS populations

Lepore et al. 2010: Compliance to treatment was good in all patients; there were no cases of treatment withdrawal for AEs. The main AEs observed were local erythematous skin reactions at the injection site, especially at the beginning of the treatment in 4 patients, excessive weight gain in 2 patients; and severe oral aphthosis in 1 patient. Stomatitis improved after Kineret withholding to reappear on re-challenge 1 week later. Treatment with anakinra was, however, ongoing at the time of the last follow-up at 45 months. No severe infections requiring suspension of Kineret for long periods or hospitalizations were observed.

Leslie et al. 2006: Minor local stinging and erythema at the injection sites, gradually diminishing in most patients, were reported. Three adults gained substantial weight, according to the authors presumably reflecting resolution of their former lifelong chronic inflammatory catabolic state.

Adverse events in published case reports

In most published case reports no safety findings were reported or it was only reported that anakinra was well tolerated. There are a few reports describing ISRs and one report describing a need for dose reduction of anakinra due to leukopenia.

Injection site reactions in published studies and case reports

ISRs are the most frequently reported AEs in published studies and case reports in CAPS patients. There are sporadic reports of ISRs that have caused temporary, but not permanent, discontinuations of Kineret treatment. From the limited information available, there are indications that the ISRs occur early during Kineret treatment and decrease over time.

Infections in published studies and case reports

With the exception of a case report described describing an 8-year old boy with the CAPS subdiagnosis NOMID/CINCA who experienced several episodes of gastroenteritis, bronchitis and pharyngo-tonsillitis requiring hospitalization (Rigante et al 2008), no severe or serious AEs denoting infections were reported in published studies and case reports. There were occasional reports of mild, non-serious infections.

Other supportive study

Study 990758/990779

- Study 990758: a randomized, multicenter, blinded placebo-controlled study with an open-label run-in period to evaluate the efficacy, safety and pharmacokinetics of daily, single subcutaneous injections of anakinra in polyarticular-course juvenile rheumatoid arthritis (JRA).
- Study 990779: a companion extension study to evaluate the long-term safety of daily, single subcutaneous injections of anakinra in subjects with JRA who participated in IL-1 ra protocol 990758.

Study 990758 and its extension, study 990779, were initially planned for efficacy evaluation in JIA, but due to insufficient enrolment of patients the primary objective was changed to safety

evaluation. This study was submitted to the CHMP in 2006 (procedure OTH 017). On 22 November 2006, the CHMP concluded that the data cannot support an extension of indication for the treatment of juvenile arthritis.

Eighty-six patients were included in the initial open-label phase, 50 in the placebo-controlled phase (25 on placebo and 25 on Kineret) and 44 in the open-label continuation phase. A total of 29 patients completed study 990758/990779. The total Kineret exposure in the study was 46.8 patient years. The number of patient-years on blinded Kineret and placebo treatment was 8.4 and 6.6, respectively.

Common AEs in study 990758/990779

In study 990758/990779, the overall most commonly reported AE was headache. The reporting rate for headache was higher for Kineret treated patients than for placebo, 1.5 and 0.6 respectively. Most headaches were classified as mild; only one event was classified as severe. There were no SAEs or discontinuations due to headache.

In general, the reporting rate of AEs was highest during the initial 6 weeks of treatment in the open-label phase of study 990758. This pattern was most apparent for ISRs but also headache and infections had a lower reporting rate after week 6. During the blinded phase, headache was the most commonly reported AE and occurred more frequently in Kineret treated patients. Headache was less common during weeks 6 to 12 than during the initial 6 weeks, in both the anakinra and placebo groups. The frequency of ISRs was lower than during the open label 990758 phase, evenly distributed over time and there was no difference in frequency between anakinra and placebo treated patients. Infections had a similar reporting rate over time, both in anakinra and placebo treated patients.

Serious AEs in study 990758/990779

Three patients experienced an SAE (fracture, bacterial infection and papilledema) during the open-label phase of study 990758, giving an overall SAE reporting rate of 0.2. No event was considered to be related to treatment. During the blinded treatment phase, 1 patient on Kineret experienced 1 event of serious herpes zoster (rate 0.1). The event was judged to be related to treatment. One patient reported serious hepatitis in connection with a cytomegalovirus infection during the 990779 open-label phase. The event was judged to be not related to treatment. Two additional SAEs (nephrosis and viral infection) were recorded during this study phase.

Adverse events leading to discontinuation or dose adjustment in study 990758/990779

During the initial open-label phase, 4 patients experienced 7 AEs that led to withdrawal. None of these events were serious. The most common AEs causing withdrawal during the open-label phase were ISRs (rate 0.3), constituting 5 of 7 AEs in 3 patients. During the blinded phase 1 patient on Kineret withdrew due to non-serious arthralgia. During the open-label 990779 phase, 2 patients withdrew due to non-serious AEs defined as RA (rate 0.1).

Injection site reactions in study 990758/990779

During the initial 6 weeks of Kineret treatment, the reporting rate for ISRs was 18.25. The reporting rates thereafter declined rapidly, the reporting rate during weeks >6 to 12, >12-28, >28-40 and >40 was 4.4, 1.4, 0.2 and 0.4, respectively. During the whole study, the reporting rate for ISRs was more than twice as high in females than in males (rate 8.06 vs. 2.79). During the open-label 990758 phase, ISRs were most frequent in the age group 12–18 years, but overall study periods, rates were comparable between age groups. The ISR with the highest reporting rate (3.0) during the open-label 990758 phase, was injection site pain. During the blinded phase the ISR reporting rate in Kineret and placebo treated patients was similar, 1.2 and 1.4, respectively. Most ISRs were mild, none was severe. There were no serious ISRs. ISRs leading to discontinuation only occurred in the open-label phase of study 990758. Five ISRs caused withdrawal of 3 patients.

Infections in study 990758/990779

When calculating the frequency of infections using continuous exposure, 41 patients out of 86 (48%) reported 99 infectious episodes (rate 2.8). The AE reporting rate was relatively constant (2.9 - 3.2) during the first 40 weeks of treatment but decreased to 1.4 thereafter. More females than males experienced infectious episodes (rate 3.4 vs. 1.6), and children 2-11 years old were somewhat more affected than patients 12-18 years old (3.3 vs. 2.1). During the blinded phase the AE reporting rate was slightly higher among Kineret treated patients than placebo treated, 2.5 and 2.1, respectively. The most common AEs in the study judged to be infectious episodes were upper respiratory tract infections and fever. There were no discontinuations due to infectious episodes. Three infectious episodes in 3 patients were classified as serious (impetigo, herpes zoster and hepatitis in connection with a CMV infection), corresponding to a yearly reporting rate of 0.1.

Clinical laboratory evaluations

No clinically relevant patterns of abnormalities in clinical laboratory evaluations were identified in the study populations.

2.6.1. Discussion on clinical safety

The safety population in the pivotal study 03-AR-0298 comprised 43 CAPS patients. The treatment duration was up to 5 years, corresponding to 159.8 patient years of Kineret exposure. Most patients (60.5%) were exposed >4 years, and 91% of the patients were exposed >1 year. The AE reporting frequency was highest during the first year of Kineret treatment and decreased thereafter except for year 4. Headache, arthralgia, pyrexia, upper respiratory tract infection, nasopharyngitis and rash were the most common AEs. All these AEs, apart from infections, are also common features of CAPS. Most AEs were mild in intensity (86.0%) and considered to be unrelated or unlikely related to study treatment (81.3%). Infections seemed to be more prevalent in the younger age groups and occurred with the lowest frequency in the group 12-17 years (0.5), but increased again slightly in the group >18 years (1.6). Analysis of TEAEs classified by presence of CIAS1 mutation showed that there were no major differences between the CIAS1 and non-CIAS1 groups in overall AE reporting rates, 7.4 and 9.2, respectively. Similar

rates were obtained for the groups on the SOC level, except for eye disorders with 55 AEs (rate 0.5), whereof 35 ocular hyperaemia (which could also be a symptom of CAPS) in the CIAS1 group, and 4 AEs in the non-CIAS1 group (rate 0.1). This information was reported in the SmPC.

There were no deaths in the study. Fourteen patients experienced 24 SAEs. SAEs were most common in the SOC Infections and infestations. In total 7 patients (16.3%) developed 13 serious infections (among which 3 pneumonia, 2 gastroenteritis, 1 septic arthritis, 1 otitis media were the most severe). This seemed to be noticeably higher compared to known experience with RA patients. During the procedure the applicant clarified that in the RA safety data, there are a total of 51 serious infections in 923.4 patient years corresponding to 0.06 serious infections/patient year. Among CAPS patients in study 03-AR-0298 there were a total of 13 serious infections in 159.8 patient years, corresponding to 0.08 serious infections/patient year. In conclusion, the CHMP agreed that when time of exposure is taken into account, the frequency of serious infections is similar in patients in the RA safety pool and CAPS patients in study 03-AR-0298. Ten out of 43 (23%) patients reported 17 ISRs. In total 65% occurred during the first month and 76% were reported during the first 6 months. No ISRs were reported after year 2. ISRs were only reported in patients 2-11 years and ≥18 years, with the exception of one event of in a 12-17 years patient. Most ISRs (13) were mild, none was severe and there were no serious ISRs.

There were no permanent discontinuations of study medication due to AEs. Dose adjustments were made for 11 AEs in 5 patients. All dose adjustments were increases in connection with disease flares, in some cases induced by infections.

The lack of control group made difficult to evaluate the spectrum of AEs occurring in the study population. Many of the reported AEs were probably disease manifestation of NOMID/CINCA rather than real reactions to anakinra. At least this was illustrated in year 4 (2007) when the rate of AEs per patients year increased to 12.0 compared to first year (10.4), second year (6.2), third year (4.3) fourth year (12.0), and fifth year (4.9). Therefore, the safety data of anakinra in paediatric patients were supported by safety study 990758 and its long-term extension study 990779 in JIA patients. Eighty-six patients were included in the initial open-label phase, 50 in the placebo-controlled phase (25 on placebo and 25 on anakinra) and 44 in the open-label continuation phase. A total of 29 patients completed study 990758/990779. The total anakinra exposure was 46.8 patient years. The number of patient-years on blinded anakinra and placebo treatment was 8.4 and 6.6, respectively. No patient died during the study. There were 7 SAEs in 6 patients, all during Kineret treatment (fracture, bacterial infection, papilledema, serious herpes zoster, serious hepatitis, nephrosis and viral infection). All SAEs, except for an event of nephrosis resolved without sequelae. Eight patients discontinued study drug permanently due to AEs during Kineret treatment. The most common AEs were ISRs, headache, and upper respiratory tract infections, and the majority was assessed as mild or moderate. During the blinded phase, the most common AEs for patients receiving anakinra were headache.

The pattern of AEs reported in the published studies of different sub-diagnoses of CAPS, appeared similar to that in study 03-AR-0298. No new clinically relevant AEs, either in paediatric or adult patients, were reported in the studies, comprising in total 66 patients with Kineret exposure up to 54 months. No SAEs were reported in the studies. Published case reports comprise 133 CAPS patients. The vast majority of the reports contain very limited safety information and most of the reports have no reported AEs therefore the data must be interpreted with caution. ISRs were the most frequently reported AEs in published studies and case reports

in CAPS patients. The safety data presented in the published studies and case reports do not deviate from the findings in study 03-AR-0298.

In the applicant' safety database there are 28 medically confirmed reports with 44 AEs in patients with different forms of CAPS. In total 18 reports (30 AEs) concerned patients with NOMID/CINCA. There were no reports with fatal SAEs. Thirteen out of the 28 medically confirmed reports were serious, and contain, in total, 20 SAEs. The types and distribution of AEs in CAPS patients compared with the total paediatric and adult patient populations was generally similar. No new clinically relevant AEs have been identified, no AEs occur with a markedly higher frequency among CAPS patients compared to other Kineret-treated paediatric and adult patients.

Overall, no new safety signal was identified and the safety in CAPS patients observed from the pivotal trial and the published literature submitted was generally in line with the known safety profile of anakinra in RA patients.

Kineret is administered from a prefilled syringe. The prefilled syringe contains 100 mg and is intended for single use. When used for treatment of adult patients with RA the whole content of the syringe, 100 mg, is injected. To meet the demands for use in children with CAPS that need smaller and varying doses of Kineret, the syringe is supplied with a graduated label to allow for single-use injections of doses in the interval 20-100 mg in steps of 10 mg. The scale interval has been chosen based on the clinical need to adjust dosing, to achieve an easy-to-communicate dosing versus body weight regimen, and to secure readability and thereby compliance. There remains a potential risk of overdosing or underdosing if the wrong volume of Kineret is injected in a patient requiring a lower dose than 100 mg. The PL, including instructions on the use of the syringe has been designed to further prevent re-use by requiring disposal of the needle cover and discarding the excess solution prior to injection. This addresses the risk of both overdosing and re-use. Usability testing of the graduated syringe confirmed that the instructions for use of the graduated syringe in the PL are both easily understood and easy to adhere to. In addition, as part of the educational programme (as detailed in the RMP), clear instructions on correct injection procedures and disposal of used syringes will be given so that healthcare providers can further instruct patients on the proper use of the graduated syringe.

In order to follow further the long-term safety of Kineret treatment in CAPS patients the MAH will follow (as described in the RMP) the already existing cohort registered in the Eurofever registry via the associated PRINTO network: Paediatric Rheumatology International Trials Organisation (PRINTO)/Eurofever Registry. There are multiple registries across Europe covering autoinflammatory conditions. The EU-supported Eurofever registry is an initiative to collect data from all these registries as well as other previously uncategorized patient groups into one registry. Eurofever is organized and maintained by the PRINTO and the PRINTO network has been utilized to collect data for the Eurofever registry. The PRINTO network will collect data pre-specified by the MAH. PRINTO will compile yearly reports based on the data and supply the reports to the MAH. This non-interventional, post authorization safety study will evaluate the safety of Kineret in the treatment of CAPS in routine clinical care. Focus will be on serious infections, malignancies, injection site reactions, allergic reactions and medication errors. European CAPS patients treated with Kineret at the time of market authorization or starting treatment during the study will be eligible for inclusion in the study. The patients will be enrolled according to the treatment recommendations in the SmPC. The planned duration of the follow-up period for each patient will be 3 years. The duration of the enrolment period will be 1 year and

the study is estimated to enrol 15-20 CAPS patients. Results will be reported annually. The 1st annual submission is expected by July 2015.

2.6.2. Conclusions on the clinical safety

No new safety signal has been observed in the CAPS patients in study 03-AR-0298. The AE and SAE reporting rates were generally low. The most common AEs were headache, arthralgia, pyrexia, upper respiratory tract infection, nasopharyngitis and rash. Apart from infections, all are also common features of CAPS. ISR were common but none were serious. They mainly occurred the first 6 months and tended to ease off with time. No ISRs were reported after year 2. The most common SAEs were reported within the SOC Infections and infestations. The frequency of serious infections was shown as being similar in patients in the RA and CAPS patients in study 03-AR-0298. Infections seemed to be more prevalent in the younger age groups and occurred with the lowest frequency in the group 12-17 years (0.5), but increased again slightly in the group >18 years (1.6). No patients permanently discontinued from the study as a result of an infection.

The pattern of AEs reported in the published literature and the case reports were similar to that in study 03-AR-0298.

Most adverse events in CAPS and JIA patients occurred during the first months of Kineret treatment. Although the reporting rates were generally lower in CAPS patients than in JIA patients, the AE profile was generally similar in the 2 populations. The higher doses of Kineret given to the CAPS patients in study 03-AR-0298 did not seem to affect the safety profile.

The long term safety of anakinra in CAPS treated patients will be further followed-up and characterised with the submissions of annual report of the PRINTO/Eurofever registry results.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 3.1, the PRAC considers by consensus that the risk management system for anakinra (Kineret) for:

- adults for the treatment of the signs and symptoms of Rheumaoid Arthritis (RA) in combination with methotrexate
- adults with an inadequate response to methotrexate alone

- adults, adolescents, children, and infants aged 8 months and older for the treatment of CAPS, including: Neonatal-onset multisystem inflammatory disease (NOMID)/Chronic infantile neurological, cutaneous, articular syndrome (CINCA); Muckle-Wells syndrome (MWS); and familial cold auto-inflammatory syndrome (FCAS))

is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Summary of safety concerns	
Important identified risks	Injection site reactions (ISR)
	Immunogenicity
	Serious infections
	Neutropenia
	Allergic conditions
	Hepatic disorders
	Interaction with TNF-antagonists
Important potential risks	Malignancies
	Macrophage activation syndrome (MAS) (not applicable for RA or CAPS)
	Medication errors including re-use of syringe
	Safety in off-label use
Missing information	Pregnant women
	Lactating women
	Patients with cardiac impairment
	Use in patients with chronic infections
	Use in patients with pre-existing cancers
	Interaction with living vaccines

- **Pharmacovigilance plan**

Table 1: Ongoing and planned studies in the PhV development plan

Study / activity Type, title and category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports**
British Society of Rheumatism Biologics Register (BSRBR) (non-interventional,	Collect and monitor long-term safety data on patients receiving Kineret	Emphasis on malignancies and infections.	Ongoing	Final report planned at the turn of 2013/2014.

Study / activity Type, title and category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports
2)	with all rheumatic conditions biologically naïve at registration.			
German Rheumatism Research Center Berlin Deutsches Rheuma-Forschungszentrum (DRFZ) RABBIT Registry (non-interventional, 2)	Collect information on patients exposed to biologic drugs and assist in follow-up of AEs from health professionals.	Emphasis on malignancies and infections.	Ongoing	Final report Planned December 2012. The report will be appended to PSUR No. 15 with DLP May 1, 2013. Publication planned end of 2012.
Pediatric Rheumatology International Trials Organisation (PRINTO)/Eurofever Registry (non-interventional, 3)	Follow the safety of European CAPS patients treated with Kineret.	Emphasis on Serious infections, malignancies, and medication errors.	Planned	To be decided.
Swedish Biologics Registry (ARTIS) (non-interventional,3)	Provide follow-up data on all biological compounds targeting RA.	Overall safety profile	Ongoing	Reports provided to Sobi every 6 months.

- **Risk minimisation measures**

Table 2: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Injection site reactions (ICRs)	SPC, Sections 4.2 Posology and method Administration and 4.8 Undesirable effects, describes the risk. Section 4.2 describes how to minimize the risk for ISRs.	Educational material for healthcare professionals and patients on how to address the risk of ISRs will be provided together with material regarding correct injection procedures and disposal of used syringes.
Immunogenicity	SPC, Section 4.8 Undesirable effects, describes the risk.	None
Serious infections	SPC, Section 4.8 Undesirable effects, describes the risk.	None
Neutropenia	SPC, Section 4.8 Undesirable effects, describes the risk.	None
Allergic conditions	SPC, Section 4.8 Undesirable effects, describes the risk.	None
Hepatic disorders	SPC, Section 4.8 Undesirable effects, describes the risk	None

Interactions with TNF-antagonists	Concurrent administration of Kineret and etanercept or other TNF-antagonists is not recommended. SPC, Sections 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction describe the risk.	None
Important potential risks		
Malignancies	SPC, Section 4.4 Special warnings and precautions for use, describes the potential risk. Followed as a TME and through the registries	None
Macrophage activation syndrome (MAS) (not applicable for RA or CAPS)	The event is a potential risk, followed as a TME. Currently no further actions planned. N.B. MAS is not applicable for RA or CAPS indications.	None
Medication error/re-use of used syringe	SPC, Section 6.6 Special precautions for disposal and other handling, and package leaflet describes injection procedures.	Healthcare providers will instruct patients and caregivers on correct injection procedures and disposal of used syringes.
Safety in off label use	Promotion only of approved indications. Registration of CAPS and investigation of possible registration of sJIA, thereby reducing off-label use	None
Missing information		
Pregnant women	SPC, Section 4.6 Fertility, pregnancy and lactation, describes the potential risk. Follow up of outcome of pregnancies.	None
Lactating women	SPC, Section 4.6 Fertility, pregnancy and lactation, describes the potential risk.	None
Patients with cardiac impairment	Routine measures sufficient.	None
Safety in off-label use	Outside approved indication. Followed as a TME.	None
Injection site reactions	SPC, Section 4.8 Undesirable effects, describes the risk.	None
Immunogenicity	SPC, Section 4.8 Undesirable effects, describes the risk.	None
Serious infections	SPC, Section 4.8 Undesirable effects, describes the risk.	None
Neutropenia	SPC, Section 4.8 Undesirable effects, describes the risk.	None
Allergic conditions	SPC, Section 4.8 Undesirable effects, describes the risk.	None

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

- **Beneficial effects**

The results of study 03-RA-0298 showed that anakinra significantly decreased the primary endpoints NOMID-specific diary scores and biomarkers of inflammation (SAA, CRP, and ESR). Results were consistent across all subgroups including age, gender, presence of CIAS1 mutation, and disease phenotype. Remission was sustained up to 60 months. Following withdrawal, fever, rash, joint pain, and vomiting all appeared after the first day and headache after 2 days. Symptoms promptly responded to reinstitution of anakinra.

Indicators of CNS inflammation (elevated intracranial pressure, laboratory evidence of aseptic meningitis in the CSF, and headache) decreased significantly. Significant improvements were seen in other secondary symptoms, including fatigue, difficulties ambulating, eye redness, and sleep problems, as well as in rash, joint status, endurance test, and QoL scores.

Ophthalmology data showed significant reductions in inflammatory eye manifestations including uveitis and papilledema.

These effects on inflammation are all considered of clinical importance for CAPS patients. Pre-existing organ damage or failure seems not to be reversed by the treatment.

The prefilled syringe with a graduated label with a dosage range of 20-100 mg and scale intervals of 10 mg allows the new dose regimen required for CAPS patients as well as the administration of the 100 mg dosage required in RA patients.

- **Uncertainty in the knowledge about the beneficial effects**

In the pivotal study, the number of CAPS patients treated with anakinra (n=43) was limited; this is however acknowledged as CAPS is an extremely rare condition limiting the recruitment possibilities. Out of the 43 patients enrolled the ITT diary population was formed of only 29 patients. The withdrawal period included only the first 11 patients. This limited population was probably not representative for the entire study group. However, the dramatic effect observed of withdrawal and reinstitution of anakinra led to the discontinuation of this withdrawal phase.

Even in a setting of a rare disease such as CAPS, a controlled setting is preferable for the evaluation of efficacy to an uncontrolled setting for the conduct of the clinical trial. However because of the high rate of response, the high rate of worsening on withdrawal and the response on re-treatment and the evidence on the beneficial effect of anakinra on signs and symptoms can be considered sufficient as reported by the CHMP in its advice given in 2011. A placebo controlled trial was not feasible given that there were authorised medicinal products for the treatments of

CAPS in the EU and given the severity of the disease. An active comparator study with non-inferiority as the primary goal would have limited results due to the very limited number of CAPS patients.

Clinical data in children <1 year were limited. Especially treatment of infants <8 months of age, premature and newborn lacks clinical (including efficacy and safety) data and PK data. The limited available data is adequately reflected in the SmPC and the indication starts from the age of 8 months with a minimum body weight of 10 kg.

Risks

- **Unfavourable effects**

Anakinra was generally well tolerated during the study 03-RA-0298. The most common AEs were headache, arthralgia, pyrexia, upper respiratory tract infection, nasopharyngitis and rash. Apart from infections, all are also common features of CAPS. The AE pattern in this study did not differ from the known safety profile of anakinra. Most AEs were mild in intensity. The AE rates were similar in the age groups <2, 2-11, and ≥18 years and a lower rate in the age group 12-17 years. No new safety signal has been identified in the results presented. ISR were common but none were serious. They mainly occurred the first 6 months and tended to ease off with time. No ISRs were reported after year 2. The most common SAEs were infections. The frequency of serious infections was shown as being similar in patients in the RA and CAPS patients in study 03-AR-0298. Infections were more common. Infections seemed to be more prevalent in the younger age groups and occurred with the lowest frequency in the group 12-17 years (0.5), but increased again slightly in the group >18 years (1.6). No patients permanently discontinued from the study as a result of an infection. The safety data up to week 60 are considered in line with the known safety profile of anakinra.

The pattern of AEs reported in the published literature and the case reports were similar to that in study 03-AR-0298. No new safety signal, either in paediatric or adult patients, was reported in the studies with a Kineret exposure up to 54 months. With the exception of 1 case no cases of severe infections were reported. Injections site reactions were the most reported AEs, occurred early during treatment and decreased over time in line with the pivotal trial.

To further support the anakinra safety profile in paediatric patient's data from studies 990758/990779 conducted in JIA patients were presented. The most common AE reported was headache. The incidence of IRS was higher than in CAPS but also decreased over time. Infections were common. The most common infections were upper respiratory tract infections. Infections were most common early after start of Kineret treatment and in younger patients as observed within the CAPS patients. The type and frequencies of SAEs were generally similar in JIA and CAPS patients.

The smallest amount the Kineret syringe allows for administration is 20 mg which corresponds to a body weight of minimum 10 kg. The indication starts from the age of 8 months (clinical experience being available from 8 months of age) with a minimum body weight of 10 kg. The MAH has calculated that if the full content of the syringe is injected by mistake, the maximum total dose would amount to 100 mg corresponding to a dose of 10 mg/kg in a 10 kg infant, which is a high dose compared to the recommended starting dose (1-2 mg/kg). This dose only marginally exceeds the recommended therapeutic maintenance dose range for severe CAPS. The

PL includes clear instructions on the use of the syringe to addresses the risk of both overdosing and re-use. Usability testing of the graduated syringe confirmed that the instructions for use of the graduated syringe in the PL are both easily understood and easy to adhere to. In addition, as part of the educational programme (as detailed in the RMP and annex II) clear instructions on correct injection procedures and disposal of used syringes will be given to healthcare providers and patients on the proper use of the graduated syringe.

- **Uncertainty in the knowledge about the unfavourable effects**

Given the limited sample size and the open label design of study 03-RA-0298, the long term effects of anakinra in CAPS patients, especially in children, require further characterisation. The PRINTO/Eurofever registry (described in the RMP) will address this, evaluating the long term safety of Kineret in the treatment of CAPS in routine clinical care. Focus will be on the risks of serious infections, malignancies, injection site reactions, allergic reactions and medication errors. This registry will allow further characterisation of the long term safety of anakinra treatment in CAPS patients. Interim data from the registry will be provided on a yearly basis. The next interim report is expected in July 2015 as detailed in the RMP.

Benefit-risk balance

- **Importance of favourable and unfavourable effects**

Results from study 03-RA-0298 showed that treatment with anakinra dosed at a starting dose of 1-2 mg/kg/day conferred a clinical benefit to the patients reducing the signs and symptoms of the disease. These data are considered valuable and of clinical importance.

The safety profile of anakinra described reported in study 03-RA-0298 and the supporting data was in line with the known safety profile of anakinra. No new safety signal was identified from the data submitted up to week 60. Long term safety of anakinra will be further characterized thought the PRINTO/Eurofever registry.

- ***Discussion on the benefit-risk balance***

The efficacy results presented clearly support a positive effect of anakinra treatment in CAPS. Anakinra significantly decreased the primary endpoints NOMID-specific diary scores i.e. decreased disease manifestations, including reduction in symptoms of fever, rash, joint pain, headache and biomarkers of inflammation (SAA, CRP, and ESR). The onset of response following Kineret treatment was rapid, with a clinically relevant effect within a few days in all patients. Results were consistent across all subgroups including age, gender, and presence of CIAS1 mutations, and the findings were common to all the supportive studies, including patients of all CAPS phenotypes. Following withdrawal, fever, rash, joint pain, and vomiting all appeared after the first day and headache after 2 days. Symptoms promptly responded to reinstitution of anakinra. Indicators of CNS inflammation (elevated intracranial pressure, laboratory evidence of aseptic meningitis in the CSF, and headache) decreased significantly. Significant improvements were seen in other secondary symptoms, including fatigue, difficulties ambulating, eye redness, and sleep problems, as well as in rash, joint status, endurance test and QoL scores. Ophthalmology data showed significant reductions in inflammatory eye manifestations including uveitis and papilledema. Visual acuity and peripheral vision did not improve. Hearing loss was

not improved by anakinra treatment. The evaluation showed that the effects on overt clinical symptoms and inflammatory serum markers were sustained for up to 5 years of anakinra treatment. In all CAPS patients, a starting dose of 1 to 2 mg/kg/day was adequate to achieve the treatment goals. In milder forms of MWS and in FCAS patients, dose adjustments may not be necessary, while in severe forms of CAPS a maintenance dosage of 3 to 4 mg/kg/day may be required.

A sustained control of inflammatory disease manifestations was achieved also in the supportive studies published in the literature. Dose increments in many patients over time to maintain disease control, in terms of symptoms of disease flare and chronic organ inflammation was necessary.

The safety of anakinra treatment has been satisfactorily characterized in the CAPS population. Safety data from the pivotal study were shown to be comparable to the one currently known for anakinra. No new safety signal has been identified in the results presented. The PRINTO/Eurofever registry will further characterize the long term safety anakinra effect in CAPS patients.

In conclusion, based on the available efficacy and safety data presented, the benefit risk balance of Kineret (100 mg/0.67 ml) presented in a graduated single-use pre-filled syringe is considered positive:

- in the treatment of adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including:
  - Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA)
  - Muckle-Wells Syndrome (MWS)
  - Familial Cold Autoinflammatory Syndrome (FCAS).

- in the treatment of the signs and symptoms of Rheumatoid Arthritis (RA) in combination with methotrexate, with an inadequate response to methotrexate alone.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Kineret (100 mg/0.67 ml) presented in a graduated single-use pre-filled syringe for the:

- treatment of adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including:
  - Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA)

- Muckle-Wells Syndrome (MWS)
- Familial Cold Autoinflammatory Syndrome (FCAS).

- treatment of the signs and symptoms of Rheumatoid Arthritis (RA) in combination with methotrexate, with an inadequate response to methotrexate alone.

is favourable and therefore recommends the granting of the extension of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall agree the content and format of the educational materials with the National Competent Authorities in each Member State where Kineret is marketed and prior to marketing in any additional Member State.

The MAH shall ensure that all physicians who intend to prescribe KINERET are provided with the following items:

- Educational material for health care providers
- Educational material for patients and caregivers

The educational material for health care providers shall include the following key elements:

- The importance of explaining the use of the new graduated syringe and correct injection technique to patients and/or caregivers
- The importance of providing patients and/or caregivers with the educational material

The educational material for patients and caregivers will include the following key elements:

- Instructions on use of the graduated syringe
- Instructions on correct injection procedures and disposal of used syringes
- How to manage injection site reactions

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0066/2012 and the results of these studies are reflected in the SmPC and, as appropriate, the Package Leaflet.

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