22 February 2018
EMA/CHMP/169769/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Kineret

International non-proprietary name: anakinra

Procedure No. EMEA/H/C/000363/II/0056

Note

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

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List of abbreviations

ACR	American College of Rheumatology
ACR30	An improvement of ≥30 % from baseline in at least 3 of any 6 variables listed below. Also, no more than 1 of the 6 variables may worsen by >30 % from baseline. 1. Physician global assessment of disease activity (VAS). 2. Parent/patient assessment of overall well-being (VAS). 3. Functional ability. 4. Number of joints with active arthritis. 5. Number of joints with limited range of motion. 6. ESR/CRP.
ADA	Anti-drug antibody
AE	Adverse event
AJC	Active joint count
AOSD	Adult-onset Still´s disease
AUC	Area under the curve
CAPS	Cryopyrin-associated periodic syndromes
CARRA	Childhood Arthritis & Rheumatology Research Alliance
CI	Confidence interval
CLcr	Creatinine clearance
CL/F	Clearance relative to bioavailability
Cmax	Maximum concentration
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CSR	Clinical study report
DMARD	Disease modifying anti rheumatic drug
ESR	Erythrocyte sedimentation rate
ICSR	Individual case safety report
IFNγ	Interferon-γ
IL-1	Interleukin-1
IL-1R	Interleukin-1 receptor
IL-1RI	Interleukin-1 receptor, type I
IL-1Ra	Interleukin-1 receptor antagonist

ISR	Injection site reaction
i.v.	Intravenous
JIA	Juvenile idiopathic arthritis
MAS	Macrophage activation syndrome
MTX	Methotrexate
Nabs	Neutralizing antibodies
NOMID	Neonatal Onset Multisystem Inflammatory Disease
NSAID	Nonsteroidal anti-inflammatory drug
PASS	Post-authorisation safety study
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic
PGE2	Prostaglandin E2
PIP	Pediatric investigational plan
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
RA	Rheumatoid arthritis
SAA	Serum amyloid A
SAE	Serious adverse event
s.c.	Subcutaneous
SD	Standard deviation
SJIA	Systemic juvenile idiopathic arthritis
SOC	System organ class
TGFβ	Transforming growth factor β
Th	T helper
TNF	Tumor necrosis factor
Treg	Regulatory T cell
WBC	White blood cells

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 3 April 2017 an application for a variation.

The following variation was requested:

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

Extension of indication to include a new indication for Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe for the treatment of active Still's disease, including Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
In addition, the marketing authorisation holder took the opportunity to make some editorial changes in the SmPC and Package leaflet.

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

Information on paediatric requirements

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

At the time of submission of the application, the PIP P/0066/2012 was completed.

The PDCO issued an opinion on compliance for the PIP P/0066/2012.

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 did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Fátima Ventura

Timetable	Actual dates
Submission date	3 April 2017
Start of procedure:	22 April 2017
CHMP Rapporteur Assessment Report	16 June 2017
CHMP Co-Rapporteur Assessment Report	22 June 2017
PRAC Rapporteur Assessment Report	23 June 2017
PRAC members comments	28 June 2017
Updated PRAC Rapporteur Assessment Report	29 June 2017
PRAC Outcome	6 July 2017
CHMP members comments	10 July 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 July 2017
Request for supplementary information (RSI)	20 July 2017
CHMP Rapporteur Assessment Report	9 October 2017
PRAC Rapporteur Assessment Report	13 October 2017
PRAC members comments	18 October 2017
Updated PRAC Rapporteur Assessment Report	19 October 2017
PRAC Outcome	26 October 2017
CHMP members comments	30 October 2017
Updated CHMP Rapporteur Assessment Report	3 November 2017
2nd Request for supplementary information (RSI)	9 November 2017
CHMP Rapporteur Assessment Report	23 January 2018
PRAC Rapporteur Assessment Report	26 January 2018
PRAC members comments	31 January 2018
Updated PRAC Rapporteur Assessment Report	2 February 2018
PRAC Outcome	8 February 2018
CHMP members comments	12 February 2018
Updated CHMP Rapporteur Assessment Report	15 February 2018
CHMP opinion:	22 February 2018

2. Scientific discussion

2.1. Introduction

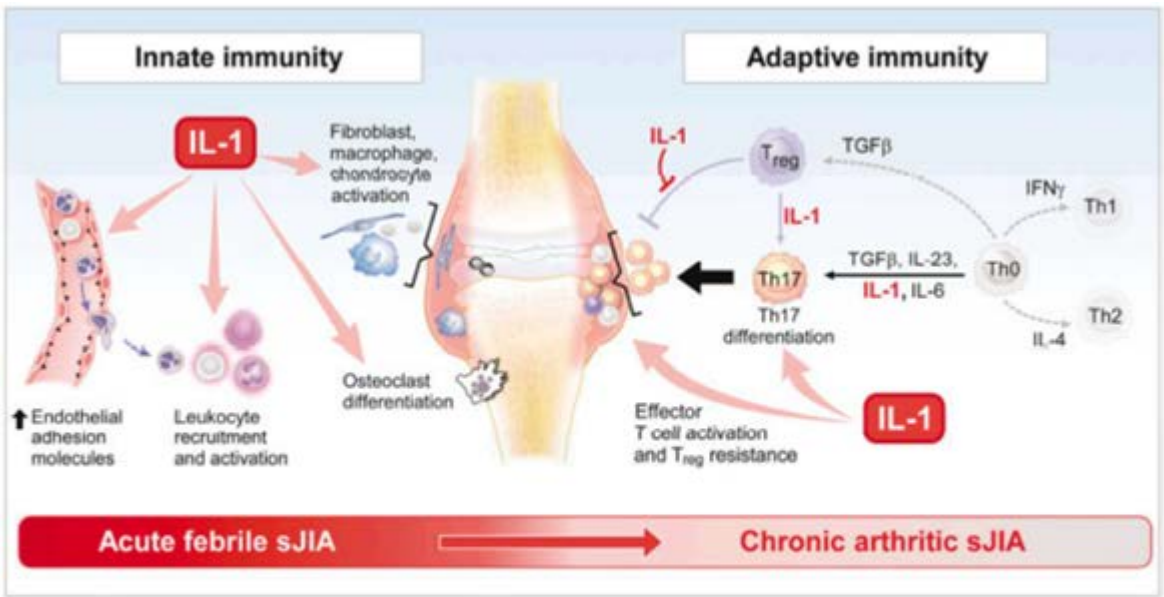
Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult Onset Still's Disease (AOSD) are both rare systemic disorders. The two groups of patients are typically treated by paediatricians (SJIA) and by adult rheumatologists (AOSD) separately as if they are two separate diagnostic entities. Their pathogenesis is still not completely understood, but is believed to be of auto-inflammatory nature. Laboratory and clinical observations suggest an inappropriate activation of the innate immune system, with hypersecretion of the proinflammatory cytokines IL-1 and IL-6 in both SJIA and AOSD. Traditionally, similar treatments have been used.

If symptoms appear during the late teens it appears arbitrary whether a diagnosis of SJIA or AOSD is being used.

The pathogenesis of Still's disease, including all ages of onset, is still not completely understood, but laboratory and clinical observations indicate an inappropriate activation of the innate immune system, with hypersecretion of the proinflammatory cytokines IL-1 and IL-6, as an important mechanism of the disease. The activation of several proinflammatory cytokines, such as TNFα, IL-1, IL-6, IL-8, and IL-18 in disease pathogenesis has led to new targeted therapies for improved disease control. The IL-1 inhibitor anakinra is one such targeted treatment.

Paediatricians describing the molecular mechanisms and cytokines in SJIA, propose that IL-1 promotes inflammation in an antigen-independent manner through activation of endothelium, leukocytes, and tissue lineages. IL-1 also modulates antigen-driven T cell immunity by activating T cells, inhibiting the efficacy of regulatory T cells, and promoting Th17 differentiation. New-onset SJIA, characterized by excess IL-1 production, could thereby give rise to an autoimmune T cell-driven arthritis. Based on this biphasic model, effective blockade of IL-1 (or IL-6) in the early disease process could forestall the development of T cell autoimmunity and alter the long-term course of the disease.

Figure 1 – The biphasic model of SJIA



Source: Nigrovic 2014.

IFNγ=Interferon-γ; IL-1=Interleukin 1; SJIA=Systemic juvenile idiopathic arthritis; TGFβ=Transforming growth factor β; Th=T helper; Treg=Regulatory T cell.

Regardless of age at onset the disease course in Still's disease is often progressive and followed by chronic morbidity. The prognosis in both paediatric and adult patients is poor in 50 % of the patients with severe joint destruction 10 years after disease onset. Despite a variety of treatments some children have a refractory course with significant morbidity and the disease often extends into adulthood. Among SJIA patients treated into adulthood, joint replacement had been required in up to 75 %.

A vast body of evidence points to the pivotal role of IL-1 and IL-6 in the pathogenesis of both SJIA and AOSD, and blockade of the IL-1 or IL-6 have emerged as an important therapeutic strategy in patients of all ages. The long-acting IL-1β inhibitor canakinumab is approved for Still's disease and the long-acting IL-6 inhibitor tocilizumab is approved for treatment of SJIA (Kotter et al. 2007, Raffeiner et al. 2011, Hoshino et al. 1998, Jamilloux et al. 2015).

Anakinra is a recombinant Interleukin-1 receptor antagonist (IL-1Ra) that blocks the biological activity of cytokine IL-1 (IL-1α and IL-1β) by competitively inhibiting its binding to the IL-1RI (Interleukin-1 receptor, type I), thereby controlling active inflammation.

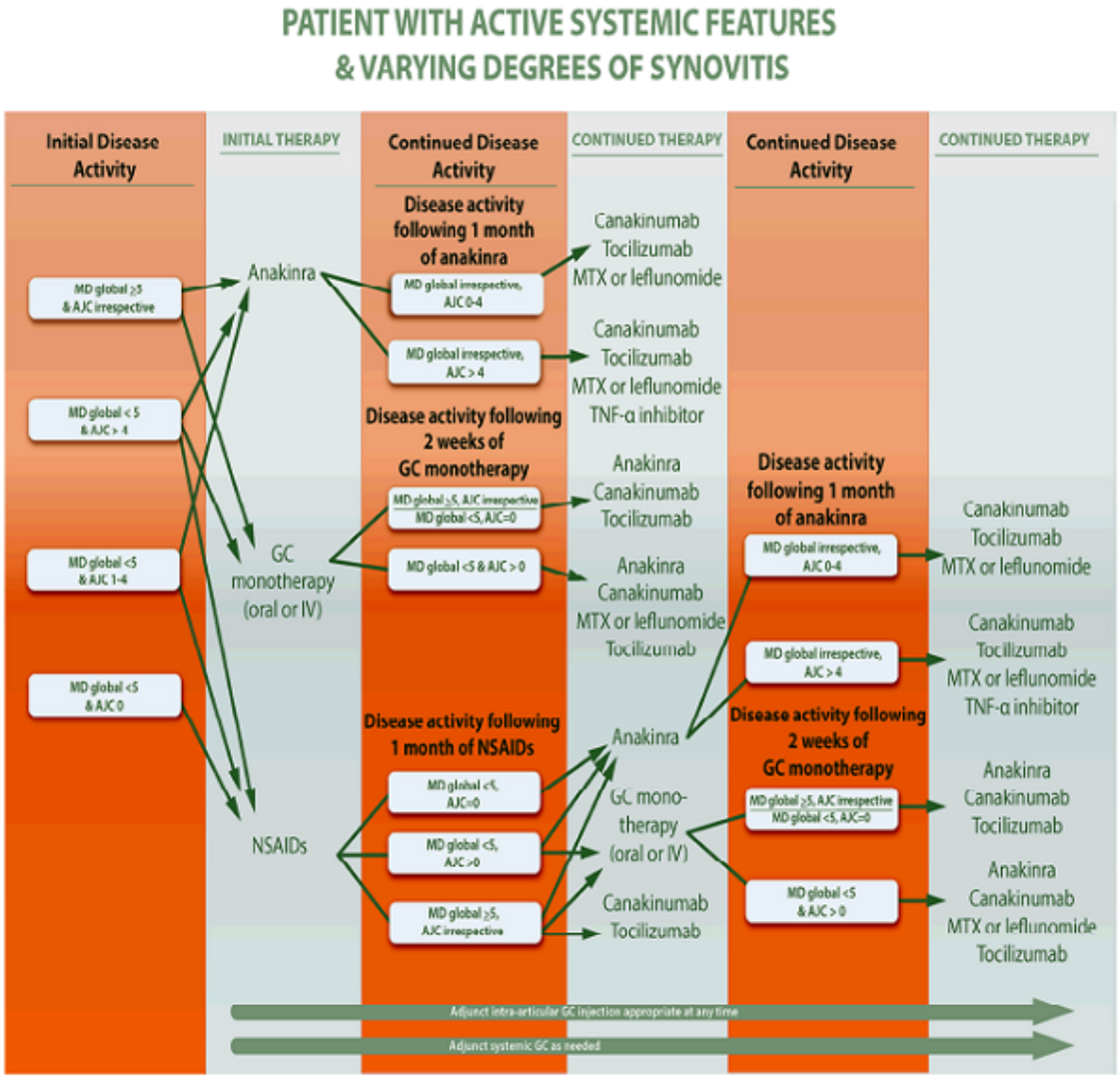
Kineret is currently approved for treatment of Rheumatoid arthritis (RA) and cryopyrin-associated periodic syndromes (CAPS) in the European Union (EU).

Anakinra is in this variation proposed to be indicated for the treatment of active Still's disease, including SJIA and Adult Onset Still's Disease (AOSD).

Although not approved for the treatment of SJIA and AOSD, there are a number of publications and registers supporting the use of anakinra in these conditions. Anakinra is also included in treatment recommendations issued by Childhood Arthritis & Rheumatology Research Alliance (CARRA) (DeWitt et al. 2012, Kimura et al. 2014) and the American College of Rheumatology (ACR) (Ringold et al. 2013). The short half-life of anakinra makes it well suited for treatment of Still's disease if withdrawal of treatment is, of some reason, needed. Since treatment of the early phase of the disease is typically based on high dose glucocorticoids, early IL-1 inhibitor treatment offers a potential for rapid tapering of glucocorticoids to avoid steroid dependency and the associated risks of osteoporosis, hypertension, growth disturbances and diabetes. Some of these are of particular relevance in children (Kim et al. 2012). The long half-life IL-1β inhibitor canakinumab (half-life of 26 days) is approved for treatment of Still´s disease, including SJIA and AOSD. However, there is a reluctance to introduce the treatment early during the disease course because of the prolonged time required to modify exposure to the drug (half-life 26 days). It is important to quickly be able to terminate IL-1 inhibition therapy should untoward effects or other clinical reasons for discontinuation occur. Anakinra that inhibits both IL-1β and IL-1α and has a short half-life (median 5.7 hours) enables flexible dosing and minimizes unnecessary immunosuppression and duration of potential treatment-related AEs.

In the current ACR guideline for the treatment of SJIA (2013 update of the 2011 ACR guidelines) (Ringold et al. 2013), anakinra is recommended for use in SJIA patients with active systemic features and varying degrees of synovitis as an initial therapeutic option for patients with an overall physicians assessment score ('MD global') of ≥5 irrespective of the number of active joints or an 'MD global'<5 and >0 active joints. In these patients anakinra was also recommended for patients with continued disease activity after treatment with glucocorticoid monotherapy or NSAID monotherapy (Figure 2).

Figure 2 – ACR treatment pathways for patients with active systemic features and varying degrees of synovitis



Source:Ringold et al. 2013.
AJC=Active joint count; GC=Glucocorticoid; MTX=Methotrexate; NSAID=Nonsteroidal anti-inflammatory drug; TNF=Tumor necrosis factor.

The proposed new indication was for the treatment of active Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD).

The approved indication is:

Kineret is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids.

Kineret can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs).

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

The evidence to support the benefit of anakinra in Still's disease is mainly based on bibliographical data from real-world clinical studies. The assessment of known and potential risks of anakinra treatment in Still's disease are also based on bibliographical data, but mostly on data from the use of anakinra in company-sponsored clinical studies in multiple indications, and the company post-marketing safety database, including Individual case safety reports (ICSRs) from patients treated for Still's disease as well as other indications.

A PIP was requested by PDCO in connection with the line-extension application for Kineret in Cryopyrin-associated periodic syndromes (CAPS). The PIP, including a waiver granted for children from birth to less than 1 year of age, was approved on March 28, 2012 (P/0066/2012). On December 12, 2014, a compliance check showed that the PIP was fulfilled (EMA/PDCO Compliance Report 12/12/2014).

The PIP (EMEA-001212-PIP01/11) included the following clinical measures related to Systemic Juvenile Idiopathic Arthritis (SJIA):

- A prospective, randomized, double-blind, placebo-controlled, MAH-sponsored study to evaluate the safety, clinical response, and pharmacokinetics of anakinra in polyarticular course of Juvenile Idiopathic Arthritis (JIA), including a subpopulation of SJIA patients (study 990758).
- A prospective, multicenter, randomized, double-blind, placebo-controlled, investigator-sponsored study to evaluate safety and efficacy of anakinra in patients with SJIA (Quartier et al. 2011).
- A meta-analysis of available published data on efficacy and safety of anakinra in patients with SJIA (Meta-analysis SJIA).

No Scientific Advice was requested.

2.2. Non-clinical aspects

2.2.1. Introduction

This submission proposes an extension of the indication for Kineret (anakinra) to include also the treatment of active Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD). The principal biological action of anakinra is to antagonize the effects of interleukin-1 (IL-1) cytokines, which is utilized to mitigate the symptoms of IL-1 driven diseases. No additional non-clinical pharmacodynamic studies relating to the proposed indication have been performed. A number of non-clinical pharmacodynamic studies have been published in the literature and included in the original MAA. In essence, the non-clinical pharmacodynamics studies show that anakinra efficiently inhibits the action of the cytokines IL-1α and IL-1β. These cytokines are critical mediators of inflammation and joint damage in rheumatoid arthritis, cryopyrinopathies and other IL-1 driven diseases, e.g. SJIA, AOSD, and CAPS.

To support the clinical development program of anakinra an extensive number of safety pharmacology and toxicology studies (all included in the original submission) were conducted covering general toxicity, reproductive toxicity, genotoxicity, carcinogenicity (tumour stimulation) and antigenicity/immunotoxicity. All studies were conducted in compliance with Good Laboratory Practice (GLP).

The current submission consists of a new non-clinical safety study in juvenile animals. A developmental toxicity study in juvenile rats (GLP compliant) has been conducted aimed to specifically investigate

memory and learning function in juvenile rats. A series of safety pharmacology studies (all included in original submission) were conducted in an additional number of species: mice, rats, dogs, and ex vivo guinea pig ileum. No anakinra related effects were seen in tests of central/autonomic, analgesic activity, cardiovascular, digestive, or renal functions.

The general toxicity studies were conducted in rats and non-human primates in which anakinra were administered via the subcutaneous (s.c.) and the intravenous (i.v.) routes. Dosing was commonly performed more frequently in the non-clinical studies than in man to ensure sufficient exposure in animals. Plasma exposure measurements were performed including immunogenicity analysis for the detection of anti-anakinra antibodies. In the chronic study in the rat, doses at up to 200 mg/kg/day were administered s.c. twice daily for 6 months.

In the reproductive and embryo-foetal developmental toxicity studies, the rat and the rabbit were selected as the test species.

No regular carcinogenicity studies were performed. Long-term carcinogenicity studies were not regarded as relevant when considering the proteinaceous nature of anakinra. According to the ICH S6 guideline standard carcinogenicity studies are generally inappropriate for biotechnology-derived pharmaceuticals. There are no concerns about a carcinogenic potential inherent to anakinra based on the pharmacological mode of action and observed minimal effects on the host cell resistance studies and slight enhancement of natural killer (NK) cell activity. Thus, no further studies were considered to be needed. A full set of in vitro and in vivo genotoxicity tests were conducted.

Since anakinra is an immunomodulator (antagonizing IL-1 signalling), several studies have investigated potential adverse effects on the immune system, including effects on host resistance, abscess resolution, and overall immune competence (all included in original submission).

2.2.2. Pharmacology

No new studies were submitted.

2.2.3. Pharmacokinetics

No new studies were submitted.

2.2.4. Toxicology

Juvenile toxicity

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

The following parameters and end points were evaluated in all animals: clinical signs, body weights, multiple Y water maze test (function of learning), and gross necropsy. An additional 5 male and 5 female animals were allocated to separate satellite groups in the control group and the 200 mg/kg/day group. In addition to the end points above, these animals were also subjected to sampling and analysis of serum and CFS for the presence of anakinra along with the weighing and collection of the brain and liver.

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

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

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

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

The liver and brain absolute weights and weights relative to body weight in animals dosed at 200 mg/kg/day were comparable to the controls. The liver/brain weight ratios in animals dosed at 200 mg/kg/day were also comparable to the controls.

In conclusion, administration of anakinra by twice daily subcutaneous injection to Sprague Dawley rats from Day 7 postpartum to at least Day 44 postpartum was well tolerated in rats at levels of up to 200 mg/kg/day. Administration at 200 mg/kg/day in males and 60 or 200 mg/kg/day in females was associated with an increase in non-adverse clinical observations (fur staining and wet fur) which were found to recover after the cessation of dosing. The anakinra-treated animals did not show any signs of adverse effects on the hippocampus-dependent memory and learning function test when compared with vehicle treated control animals either on last week of dosing or after a one month recovery period.

2.2.5. Ecotoxicity / environmental risk assessment

The drug substance anakinra is a recombinant protein (Interleukin-1 receptor antagonist) produced in E. coli bacteria containing an expression plasmid in which a synthetic gene coding for human IL-1Ra has been inserted.

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA 2006), proteins are exempted from environmental risk assessment because they are unlikely to result in significant risk to the environment. The product does not contain any other components that would require an environmental risk assessment under the European Medicines Agency guidelines.

2.2.6. Discussion on non-clinical aspects

The performed juvenile study did not show any concerns regarding learning and memory as tested in the study performed (Y-maze learning test). No adverse effects, except wet and red stained fur on the muzzle, were observed at doses of 60 and 200 mg/kg/day. Therefore, it is concluded that anakinra is well tolerated at doses of up to 200 mg/kg/day (100 times the human dose) in rats treated form PND 7 to at least 44 and that anakinra does not have any detrimental effect on learning and memory (in rats) at doses of up to 200 mg/kg/day.

The SmPC has been updated to include the information from the juvenile study.

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

2.2.7. Conclusion on the non-clinical aspects

The extension application is approvable from a non-clinical perspective.

2.3. Clinical aspects

2.3.1. Introduction

The benefit of anakinra in Still's disease is mainly based on bibliographical data from real-world clinical studies. The assessment of known and potential risks of anakinra treatment in Still's disease are also based on bibliographical data, but mostly on data from the use of anakinra in company-sponsored clinical studies in multiple indications, and the company post-marketing safety database, including ICSRs from patients treated for Still's disease as well as other indications.

Kineret is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids.

Kineret can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs).

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

No Scientific Advice was requested.

A PIP was requested by PDCO in connection with the line-extension application for Kineret in CAPS. The PIP, including a waiver granted for children from birth to less than 1 year of age, was approved on March 28, 2012 (P/0066/2012). On December 12, 2014, a compliance check showed that the PIP was fulfilled (EMA/PDCO Compliance Report 12/12/2014).

The PIP (EMEA-001212-PIP01/11) included the following clinical measures related to SJIA:

- A prospective, randomized, double-blind, placebo-controlled, MAH-sponsored study to evaluate the safety, clinical response, and pharmacokinetics of anakinra in polyarticular course JIA, including a subpopulation of SJIA patients (study 990758).
- A prospective, multicenter, randomized, double-blind, placebo-controlled, investigator sponsored study to evaluate safety and efficacy of anakinra in patients with SJIA (Quartier et al. 2011).
- A meta-analysis of available published data on efficacy and safety of anakinra in patients with SJIA (Meta-analysis SJIA).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 – Listing of company-sponsored studies and published studies

Study	Location of study report/publication	Diagnosis	Study design and study duration	Number of patients	Anakinra dose
Company-sponsored study 990758	5.3.5.1	JIA including SJIA	Prospective, multicenter, open-label run-in phase for 12 weeks to select responders. Randomized, double-blind, placebo-controlled phase for 16 weeks.	86 JIA patients, of which 15 SJIA (anakinra) 50 JIA patients, of which 11 SJIA (9 anakinra; 2 placebo)	1 mg/kg/day, maximum 100 mg/day.
Company-sponsored study 990779	5.3.5.1	JIA including SJIA	Open-label extension phase for 12 months.	47 JIA (SJIA: Not reported)	1 mg/kg/day, maximum 100 mg/day.
Ilowite, 2009[a]	5.4	JIA including SJIA	Prospective, multicenter, open-label run-in phase for 12 weeks to select responders. Randomized, double-blind, placebo-controlled phase for 16 weeks. Open-label extension phase for 12 months.	86 JIA patients, of which 15 SJIA (anakinra) 50 JIA patients, of which 11 SJIA (9 anakinra; 2 placebo) 47 JIA (SJIA: Not reported)	1 mg/kg/day, maximum 100 mg/day.
Quartier, 2011	5.4	SJIA	Prospective, multicenter, randomized, double-blind, placebo-controlled phase for 1 month. Open-label extension phase for an additional 11 months.	12 anakinra; 12 placebo 22 anakinra	2 mg/kg/day, maximum 100 mg/day.
Vastert, 2014	5.4	SJIA	Prospective, observational cohort study (first-line treatment). Mean 32 months (12 to 54 months).	20	2 mg/kg/day, maximum 100 mg/day. In 2 patients, the dose was increased to a maximum of 4 mg/kg/day.
Gattorno, 2008	5.4	SJIA	Prospective, open-label study. Mean 1.36 year (0.3 to 2.59 years).	22	Initially 1 mg/kg/day, maximum 100 mg/day; individualized up to 4 mg/kg/day.
Lequerre, 2008	5.4	SJIA	Prospective, multicenter, open-label study. Mean 14.7 months (2 to 27 months).	20	1 to 2 mg/kg/day, maximum 100 mg/day (increased to 100 mg twice daily for one patient).
Pascual, 2005	5.4	SJIA	Prospective open-label study. Mean 6.6 months (2 to 12 months).	9	2 mg/kg/day, maximum 100 mg/day.
Nigrovic, 2011	5.4	SJIA	Retrospective chart review (first-line treatment). Mean 14.5 months (7.5 to 26 months).	46	Median starting dose 1.5 mg/kg/day (IQR 1.1 to 2.0 mg/kg/day). Minimum dose given 0.93 mg/kg/day and maximum 11.2 mg/kg/day (during MAS episode).
Zeft, 2009	5.4	SJIA	Retrospective chart review. Median 6 months (1 to 40 months).	33	Median 1.6 mg/kg/day (0.8 to 9.1 mg/kg/day).
Pardeo, 2015	5.4	SJIA	Retrospective single-center study. At least 6 months.	25	Median starting dose 2.0 mg/kg/day (IQR 1.3 to 2.0 mg/kg/day); dose increase up to 5 mg/kg/day.
Marvillet, 2011[b]	5.4	SJIA	Retrospective chart review (6 of 22 patients received anakinra as first-line treatment). 11 to 56 months.	22	1 to 3 mg/kg/day
Irigoyen, 2006	5.4	SJIA	Retrospective chart review. Mean 12 months (3 to 28 months).	14	Not reported
Ohlsson, 2008	5.4	SJIA	Retrospective, multicenter chart review. Median 1 year (0.75 to 2.3 year).	7	1 to 2 mg/kg/day
Nordstrom, 2012	5.4	AOSD	Multicenter, randomized, open-label phase for 24 weeks. Open-label extension for 28 weeks.	12 anakinra; 10 DMARD 16 anakinra	100 mg/day

Study	Location of study report/publication	Diagnosis	Study design and study duration	Number of patients	Anakinra dose
Laskari, 2011	5.4	AOSD	Prospective open-label study. Median 15 months (1.5 to 71 months).	25	100 mg/day
Lequerre, 2008	5.4	AOSD	Prospective, multicenter, open-label study. Mean 14.3 months (1 to 27 months).	15	100 mg/day
Naumann, 2010	5.4	AOSD	Prospective open-label study. 6 to 48 months.	8	100 mg/day
Ortiz-Sanjuan, 2015	5.4	AOSD	Retrospective, multicenter, open-label study. 12 months.	41	100 mg/day
Giampietro, 2013	5.4	AOSD	Retrospective, multicenter, chart review. Mean 23 months.	28	100 mg/day
Cavalli, 2015	5.4	AOSD	Retrospective chart review. At least 12 months.	20	100 mg/day
Giampietro, 2010	5.4	AOSD	Retrospective, multicenter, chart review. Mean 30.7 months.	19	100 mg/day
Dall'Ara, 2016	5.4	AOSD	Retrospective chart review. Study duration not reported.	13	Not reported
Iliou, 2013	5.4	AOSD	Retrospective, observational study. Study duration not reported.	10	100 mg/day
Gerfaud-Valentin, 2014	5.4	AOSD	Retrospective chart review. Mean 27.8 months (14 to 36 months)	6	Not reported

[a]Publication based on company-sponsored studies 990758 and 990779.
[b]Abstract not received and accepted in a scientific journal, but selected to be included in the Meta-analysis SJIA based on study-specific response criteria.
AOSD=Adult-onset Still´s disease; DMARD=Disease modifying anti rheumatic drug; IQR=Interquartile range; JIA=Juvenile idiopathic arthritis; MAS=Macrophage activation syndrome; SJIA=Systemic juvenile idiopathic arthritis.

In addition to the studies in the approved PIP for SJIA and the PIP-requested meta-analysis, the submission is based on published SJIA studies identified in a literature search.

In order to identify all published studies with relevant information on clinical pharmacology, efficacy and safety, extensive literature searches were performed in collaboration with Still´s disease and methodology experts. The search strategy was disease and treatment specific but sufficiently broad to minimize the risk of missing relevant published studies. The 2 major databases MEDLINE and EMBASE were searched up to a cut-off of September 30, 2016.

For the clinical pharmacology summary all published studies and case reports related to clinical pharmacology were reviewed. Studies and case reports including PK data and anakinra anti-drug antibody (ADA) data, and studies and case reports including PD data related to the basic mechanism of action for anakinra in Still's disease, were summarized and results have been compared across populations and studies.

2.3.2. Pharmacokinetics

The PK of anakinra has been previously described, in the original MAA and line extension application, for anakinra including the potential for interactions with other drugs. This was based on patients with RA, CAPS, and JIA. The main features of these studies together with the new studies including SJIA have been submitted and discussed.

The MAH-sponsored study 990758 and the study by Urien et al. 2013 (which includes the patients in Quartier et al. 2011) provided PK data for patients with SJIA. None of the case reports retrieved in the literature searches for AOSD up to September 30, 2016 presented PK data.

Analyses of data from the clinical pharmacology studies have been performed to evaluate the PK/PD characteristics as well as the dosing regimen of anakinra in patients with Still's disease.

Table 2 – Overview of studies providing PK data

Study number / published study	Study population	Study design	Dosage regimen[a]	PK data analysis	PK variables and factors
Still's disease studies					
990758[b,e] Ilowite et al. 2009	JIA with polyarticular, pauciarticular, or systemic (i.e. SJIA) diagnoses	Multicenter, blinded, placebo-controlled study with an open-label run-in period. PK samples: Day 1, Weeks 2, 4, 8, 12, 16, 20, 24, 28	1.0 mg/kg s.c. (maximum 100 mg/day)	Plasma concentrations normalized to 1 mg/kg/day or 100 mg/day	Plasma concentration Body weight
Quartier et al. 2011	SJIA	Multicentre, randomized, double-blind, placebo. PK samples: Month 2 and Month 6	2 mg/kg/day s.c. (maximum 100 mg/day)	Plasma concentrations	Trough concentrations
Urien et al. 2013	SJIA + patients with other autoinflammatory conditions	Same patients as in Quartier et al. 2011, and an additional number of patients	2 to 10 mg/kg/day s.c.	Population PK/PD with CRP as biomarker	CL/F, C_{50}
Previously submitted to EMA					
0530	HV	Single-center, cross-over study	Single-dose 70 mg i.v. 3-h infusion 70 mg s.c.	Non-compartmental	CL, CL/F, CL_{cr}
0541	HV[c]	Single-center, parallel group study	Single-dose 1, 2, 3, 5, 7, 10 mg/kg i.v. 3-h infusion	Non-compartmental	CL, V_{ss}, $t_{1/2}$, MRT_{iv}, $MRT_{infusion}$
0555	CRF patients	Open-label, single-dose study	Single 1.0-mg/kg i.v. over 1 minute	Compartmental	Cmax, $t_{½}$, AUC, Vc, Vss, CL, CLr, CLd
0501	RA	Single-center, double-blind, placebo-controlled, single-rising dose study. PK samples: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours.	Single dose 0.5, 1.0, 2.0, 4.0, 6.0 mg/kg s.c.	Non-compartmental	CL/F, $t_{1/2}$

Study number / published study	Study population	Study design	Dosage regimen[a]	PK data analysis	PK variables and factors
0502	RA	Single-center, open-label study. PK samples: predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours.	1, 2, 4 mg/kg/day s.c.	Non-compartmental	C_{max}, $t_{1/2}$, AUC_{0-24}, $AUC_{0-\infty}$, CL/F, accumulation
0560	RA	Multicenter, double-blind, dose-ranging study. PK samples: pre-dose, Weeks 1, 4, 8, 20, 24	30, 75, 100 mg/day s.c.	Non-compartmental	[d]
0501 0502 0560	RA RA RA	See above See above See above	See above See above See above	Population PK analysis (NONMEM) of studies 0501, 0502, and 0560; report 100788	CL/F, V_d/F, k_a, $t_{1/2}$ Body weight, height, age, CL_{cr}, gender, race
03-AR-0298	CAPS (NOMID/ CINCA, MWS)	Prospective, long-term, open-label study. PK samples: before dose, at 2, 4, 8, and 24 hours after first dose, and after approximately 3 months and 3 years. One CSF sample at baseline and after 3 months.	0.9 to 5.2 mg/kg/day s.c.	Non-compartmental	Standard PK variables, accumulation, distribution to CSF Dose, age, body weight, gender

[a]Dosage according to the protocol, i.e. not specifically the PK population; [b]Subanalysis of patients with SJIA, Statistical report 990758; [c]Japanese subjects; [d]PK data included in NONMEM analysis. [e]The study has previoulsy been submitted to EMA, but not with respect to the Still's disease post hoc subanalysis

AUC_{0-24h}=Area under the plasma concentration time curve up to 24 hours after dose; $AUC_{0-\infty}$=Area under the plasma concentration time curve from zero hours to infinity; CAPS=Cryopyrin-associated periodic syndromes; CL_{cr}=creatinine clearance; CL/F=Apparent total body clearance after subcutaneous administration; CLd= dialysate clearance, CLr= Renal clearance, CSF=Cerebrospinal fluid; CINCA=Chronic infantile neurological, cutaneous, and articular syndrome; C_{max}=Maximum concentration; CRF=chronic renal failure; C_{50}=pharmacodynamic response at 50% inhibitor concentration; F=systemic bioavailability; HV=healthy volunteers; ITT=Intention to treat; JIA=Juvenile idiopathic arthritis; k_a=Absorption rate constant; MWS=Muckle-Wells syndrome; NOMID=Neonatal-onset multisystem inflammatory disease; NONMEM=Nonlinear mixed-effect modeling software; PK=Pharmacokinetics; RA=Rheumatoid arthritis; s.c.=Subcutaneous; $t_{1/2}$=Half-life; V_d/F=Apparent volume of distribution after subcutaneous administration.

The PK of anakinra in JIA patients (including SJIA) was based on sparse sampling from 86 paediatric patients in the age range of 3 to 17 years and a post-hoc analysis of the 13 SJIA PK patients was performed.

Typical PK parameters of anakinra have been derived from study 03-AR-0298 (CAPS patients) following administration of 1.0 to 4.5 mg/kg/day s.c. At a median s.c. dose of 3.0 mg/kg once daily (N=16) and a median treatment time of 3.5 years, the median (range) steady-state Cmax of anakinra was 3628 ng/mL (655 to 8511 ng/mL) and C24h 203 ng/mL (53 to 1979 ng/mL). The median (range) half-life of anakinra was 5.7 hours (3.1 to 28.2 hours).

Table 3 – Demographics and dosage in studies with PK objectives

Study number	Number of subjects/patients in PK subset	Age interval in PK subset (years)	Body weight (kg)	Dosage regimen in PK subset
0530	12[a]	20 to 30	61.4 to 91.8	Single-dose 70 mg i.v. Single-dose 70 mg s.c.
0541b	24[a]	20 to 28	50.0 to 76.5	Single-dose 1, 2, 3, 5, 7, 10 mg i.v.
0555	HD: 10 CAPD: 10	HD: 44 to 78 CAPD: 55 to 76	HD: 55 to 76 CAPD: 53 to 88	Single-dose 1.0-mg/kg i.v. over 1 minute
0502	15	21 to 60	53.1 to 135	1, 2, or 4 mg/kg/day s.c. (3, 7 and 5 patients, respectively)
990758	23	3 to 17	12.4 to 101	1.0 mg/kg/day s.c. (maximum 100 mg/day)
990758 subanalysis[c]	13	3 to 17	12.4 to 71.4	
Report 100788d 0501 0502 0560	 20 15 342	 21 to 67 21 to 60 19 to 86[c]	 52.0 to 103 53.1 to 135 39.0 to 125	 Single-dose 0.5, 1, 2, 4, or 6 mg/kg s.c. 1, 2, or 4 mg/kg/day s.c. 30, 75, 150 mg/day s.c.
03-AR-0298[e]	21[f]	4.2 to 42.2	13.0 to 82.2	1.0 to 4.5 mg/kg/day s.c.
Quartier et al. 2011	17 to 22[g]	8.5±4.54[h]	No data	2 mg/kg/day s.c. (maximum 100 mg)
Urien et al. 2013	22[i]	2.26 to 16.8	10 to 83	2 to 10 mg/kg/day s.c.

[a]Antril formulation (Appendix 1); [b]Japanese subjects. [c]Post hoc subanalysis, Statistical report 990758, of PK population (N=13) of SJIA patients (N=15); [d]The report lists reasons for excluded concentration data in the NONMEM analysis as reflected in Figure 2.7.2 - 22.[e]Dosage regimen refers to dosage during PK assessments. [f]One subject (Subject 2000) provides limited data due to twice-daily dosage; [g]PK population at Month 2 and 6, respectively; [h]Mean±SD, N=24; [i]In addition 65 patients with various autoinflammatory conditions.
CAPD=Continuous ambulatory peritoneal dialysis patients; HD=Hemodialysis patients; NONMEM=nonlinear mixed-effect modeling software; PK=pharmacokinetics; SD=Standard deviation; SJIA=Systemic juvenile idiopathic arthritis.

PK data in Study 990758

Study 990758 was a company-sponsored 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 patients with JIA or SJIA. The patients received open-label treatment with daily s.c. doses of 1.0 mg/kg/day up to a maximum dose of 100 mg/day. At week 12 responders were randomized 1:1 to daily s.c. doses of placebo or anakinra. The original report described the overall population. One sample was collected from each subject on screening, Day 1, Weeks 2, 4, 8, 12, 16, 20, 24, and 28 or at early termination. Data collected from all patients were pooled to be used to characterize a population profile.

15 patients included in study 990758 had the diagnosis of systemic JIA. For the purpose of the preparation of the present variation regarding the indication in Still's disease, post-hoc analyses on anakinra plasma concentrations, anakinra antibodies, and inflammatory markers were performed based on these patients. Eight female and seven male subjects were included. Median age was 11, range 3 to 17 years, median body weight 32.0 kg, range 12.4 to 71.4 kg. Out of the 15 patients, 13 had at least one anakinra plasma concentration measurement, but two of the 13 had for unknown reasons anakinra concentrations below LLOQ. The 11 patients ranged from 96 to 229 ng/ml per mg/kg and the median steady state dose normalized anakinra concentration over 28 weeks was 157 ng/mL per mg/kg (Table 4).

This is similar to that observed in the total JIA population and also comparable to RA patients, 192 ng/mL per mg/kg (Table 5).

Concentrations in the overall population normalized to a fixed dose of 100 mg s.c. seemed to be inversely related to body weight, with higher ranges of concentrations observed for patients with the lowest body weights. This observation is consistent with the results of the population PK analysis in adult patients with RA, for which the anakinra CL/F value increased with increasing BW after s.c. administration.

The results suggest that 1 mg/kg daily s.c. dosing of anakinra for JIA patients would provide an anakinra exposure comparable to that reported for RA patients.

Table 4 – Dose normalized plasma concentrations (ng/mL per mg/kg) from Day 1 until Week 28 in 11 SJIA patients (study 990758)

	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 2 - 28
n	7	6	8	8	7	3	4	3	6	45
Median	0	187	135	174	151	96	229	179	228	157
Mean	5	205	158	183	240	326	404	293	281	240
SD	14	156	155	126	191	449	429	277	200	222

Source: Statistical report 990758.
2 SJIA patients have been excluded from the PK population due to plasma levels consistently below LLOQ. Including these 2 patients results in a Week 2 to 28 median value = 143 ng/mL per mg/kg. Subanalysis of the SJIA patients with respect to the PD marker CRP is presented in Section 2.2.1.1.
CRP=C-reactive protein; n=Number of samples; PD=Pharmacodynamic; SD=Standard deviation; SJIA=systemic juvenile idiopathic arthritis.

Table 5 – Dose-normalized serum concentrations in children per age category (JIA study 990758) and in adults (RA study 0560)

1 mg/kg s.c. normalized concentration (ng/mL)				
Study (Age)	990758[a] (3 to 6 years)	990758[a] (7 to 12 years)	990758[a] (13 to 17 years)	0560[b] (Adult)
n	21	98[b]	85	1475
Mean (SD)	182 (161)	259 (304)	194 (185)	221 (152)
Median	95.8	167	145	192

Source: Study 990758 (JIA) and study 0560 (adult RA).
[a]The time of blood collection in relation to dose was not recorded; [b]The majority of the samples were collected between 12 and 16 hours postdose.
CV=coefficient of variance; JIA=Juvenile idiopathic arthritis; max=maximum; min=minimum; n=number of serum samples; RA=Rheumatoid arthritis; s.c.=subcutaneous; SD=standard deviation.

PK data in Study by Quartier et al 2011

In this multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial) 24 patients was randomized. Efficacy was evaluated after 1 month of treatment. After Month 1 patients taking placebo were switched to anakinra and all received an anakira dose of 2 mg/kg/day. PK samples (Ctrough) were taken at Month 2 and 6 when 22 and 17 patients, respectively, remained in the study (Amendment 2 of the protocol). PK analyses showed a trend towards lower anakinra concentrations in patients with lower body weight and those who had failed to respond to anakinra after 1 month

(mean±SD trough anakinra concentration 45.5 ± 51 ng/mL, range 20–122) compared to responders (136.5 ± 106 ng/mL, range 20–353), but overall this difference was not statistically significant.

PK data in Study by Urien et al 2013

In this study Anakinra pharmacokinetics in children and adolescents with systemic-onset juvenile idiopathic arthritis and auto-inflammatory syndromes was investigated, including 22 patients with SJIA.

(NB: Anakinra and CRP data from the 22 SJIA patients in Quartier et al. 2011 were included in an analysis describing the population PK of anakinra in Urien et al. 2013).

The PK analysis was based on data from 87 paediatric patients (32 girls and 52 boys) with a total of 148 anakinra concentrations. The 22 SJIA patients had a median age of 7.6 years (range 2.26 to 16.8 years) and a median body weight of 21 kg (range 10 to 83 kg). The remaining 65 patients had a median age of 8 years (range 0.73 to 21 years) and a median body weight of 21 kg (range 4.3 to 60 kg). These were patients with various auto-inflammatory conditions treated with anakinra doses of 2 to 10 mg/kg/day. The population PK of anakinra was described by the following equations with body weight as the sole significant covariate on clearance and volume of distribution:

Absorption rate, ka (h^{-1}) = 0.38

Clearance, CL/F (L/h) = 0.847 x $BW^{0.47}$

Volume of distribution, V/F (L) = 2.581 x $BW^{0.76}$

The model predicted CL/F for a 70 kg subject to be 104 mL/min. The model predicts a higher clearance per kg body weight in children than in adults, e.g., a CL/F of 140 mL/h/kg for a 30-kg subject, and a CL/F of 250 mL/h/kg for a 10-kg subject. Thus, clearance increased with dose in a non-linear manner and lower exposure was to be expected in younger children if given the same dose. From this relationship CL/F can be estimated to be 42 ml/min at 10 kg and 104 ml/min at 70 kg, which indicates that paediatrics need about 2-fold higher doses to achieve the same exposure as in adults.

2.3.3. Pharmacodynamics

Mechanism of action

Anakinra is a recombinant IL-1Ra that blocks the biological activity of cytokine IL-1 (IL-1α and IL-1β) by competitively inhibiting its binding to the IL-1RI, thereby controlling active inflammation. Anakinra has a short half-life (median 5.7 hours) compared to the approved IL-1β inhibitor canakinumab (half-life of 26 days). This enables flexible dosing with anakinra.

Primary and secondary pharmacology

7 studies and 3 case reports including SJIA patients and 6 studies and 10 case reports including AOSD patients provided data on markers for PD responses. C-reactive protein (CRP) and serum amyloid A (SAA) were selected for evaluation since they 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.

In SJIA patients levels of CRP were reported to be reduced in all 7 studies and 3 case reports, and normalized or < 0.5 mg/dL in 3 of the studies and in all case reports. SAA was reduced in 1 study and IL-6 in 1 study and 1 case report.

In AOSD patients levels of CRP were reported to be reduced in all 6 studies and 10 case reports, and normalized or < 0.5 mg/dL in 3 of the studies and in 4 of the case reports. SAA and IL-6 were not measured.

Table 6 – Overview of SJIA studies providing the selected PD data

Study number / published study	Study population	Study design	Dosage regimen
990758/990779	13 SJIA patients[b]	Multicenter, blinded, placebo-controlled study with an open-label run-in period.	1.0 mg/kg/day s.c. (maximum 100 mg/day)
Gattorno et al. 2008	22 SJIA patients	Prospective, open-label study	1 mg/kg/day s.c. (maximum 100 mg/day). Could be increased to 4 mg/kg/day.
Lequerre et al. 2008	20 SJIA patients (and 15 AOSD patients, Table 2.7.2 - 3)	Prospective, multicenter, open-label study.	1 to 2 mg/kg/day s.c. (maximum 100 mg/day)
Nigrovic et al. 2011	46 SJIA patients	Retrospective chart review (first-line treatment)	Median starting dose 1.5 mg/kg/day s.c .(range 0.93 to 11.2 mg/kg/day)
Quartier et al. 2011	22 SJIA patients[c]	Prospective, multicenter, randomized, double-blind, placebo-controlled study (1 month)	2 mg/kg/day s.c. (maximum 100 mg/day)
Urien et al. 2013	22 SJIA patients[d]	Population PK/PD	2 to 10 mg/kg/day s.c.
Vastert et al. 2014	20 SJIA patients[e]	Prospective, uncontrolled, observational cohort study (first-line treatment)	2 mg/kg/day s.c.

Source: Clinical studies presented in Section 2.7.3.1.4.2, Table 2.7.3 - 1 and Table 2.7.3 - 2.
[a]The selected PD data are CRP, SAA, IL-6; [b]Post hoc subanalysis, Statistical report 990758, of PK population (N=13) of SJIA patients (N=15); [c]12 anakinra patiens from blinded phase + 10 from placebo switching to anakinra from Month 1; [d]and in addition 65 patients with various autoinflammatory conditions; [e]10 patients after 3 years. The study population is the total number of patients included in the study.
AOSD=Adult onset Still´s disease; CRP=C-reactive protein; JIA=Juvenile idiopathic arthritis; PD=Pharmacodynamic; SAA=Serum amyloid A; SJIA=Systemic juvenile idiopathic arthritis.

Table 7 – Summary table of the influence of anakinra on the PD marker CRP, SAA, and IL-6 in clinical studies and case reports including patients with Still's disease (SJIA and AOSD)

Study/Author	CRP	SAA	IL-6
SJIA studies			
990758	Decreased	-	-
Gattorno et al. 2008	Decreased, normalized	-	Decreased
Lequerre et al. 2008	Decreased	-	-
Nigrovic et al. 2011	Decreased, normalized	-	-
Quartier et al. 2011	Decreased	Decreased	-
Urien et al. 2013	Decreased	-	-
Vastert et al. 2014	Decreased, Normalized	-	-
SJIA case reports			
Hedrich et al. 2012	Decreased, Normalized	-	Decreased
Topaloglu et al. 2016	Decreased, Normalized	-	-
Verbsky et al. 2004	Decreased, Normalized	-	-
AOSD studies			
Giampietro et al. 2013	Decreased	-	-
Laskari et al. 2011	Decreased	-	-
Lequerre et al. 2008	Decreased	-	-
Ortiz-Sanjuan et al. 2015	Decreased, Normalized	-	-
Naumann et al. 2010	Decreased, Normalized	-	-
Nordstrom et al. 2012	Decreased, Normalized	-	-
AOSD case reports			
Ahmed et al. 2015	Decreased	-	-
Debiais et al. 2008	Decreased	-	-

Study/Author	CRP	SAA	IL-6
Eriksson et al. 2013	Decreased	-	-
Fitzgerald et al. 2005	Decreased	-	-
Hartig et al. 2014	Decreased	-	-
Maier et al. 2008	Decreased, Normalized	-	-
Priori et al. 2008	Decreased, Normalized	-	-
Vercoutere et al. 2011	Decreased, Normalized	-	-
Vordenbaumen et al. 2009	Decreased	-	-
Yilmaz et al. 2014	Decreased, Normalized	-	-

Source: The respective studies and case reports in Section 2.2.
AOSD=Adult-onset Still's disease, CRP=C-reactive protein, IL-6=Interleukin-6, PD=Pharmacodynamic, SAA=Serum amyloid A, SJIA= Systemic juvenile idiopathic arthritis.

A summary of the influence of anakinra on the PD markers CRP, SAA, and IL-6 as presented is given in Table 7. A more detailed summary of findings of selected markers in some of the included studies are presented below.

PD data in study 990758/990779

Post-hoc analysis with respect to patients with SJIA and CRP as PD marker are summarized in table 8 .The CRP levels were consistently decreased during the open-label 12 weeks of the study as well as during the following 16 blinded weeks.

Table 8 – CRP (mg/mL) at baseline Day 1, during open-label phase (12 weeks) and during blinded phase (16 weeks)

Baseline N=13	Week 2 N=13	Week 4 N=13	Week 8 N=12	Week 12 N=12	Week 20 N=8	Week 24 N=8	Week 28 N=8
94.0 (36.0, 147.0)	3.0 (1.0, 26.0)	1.0 (1.0, 22.0)	1.0 (1.0, 37.0)	1.5 (1.0, 96.5)	1.0 (1.0, 14.5)	1.0 (1.0, 24.5)	1.0 (1.0, 5.0)

Source: Statistical report 990758.
Values depict median (Q1, Q3).
CRP=C-reactive protein; N=number of SJIA patients.

Gattorno et al, 2008

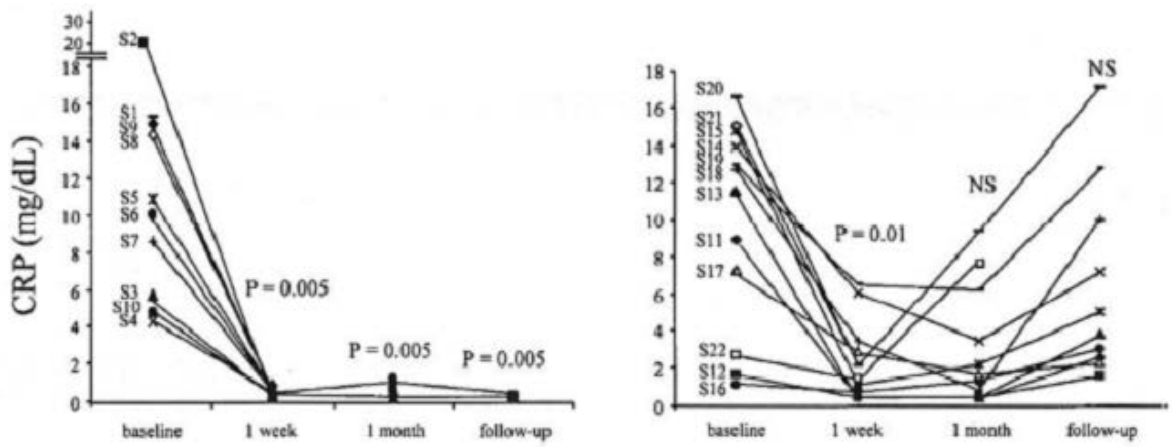
The pattern of response to anti–interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. The dosage regimen was 1 mg/kg/day (maximum 100 mg/day), which could be increased to 4 mg/kg/day. The age at treatment onset ranged between 0.9 and 18.7 years. During the first week of treatment, 2 distinct patterns of response to anakinra in the patients with SJIA were seen. One group of 10 patients (patients S1–S10) showed prompt control of systemic and articular manifestations, with normalization of CRP levels and persistence of complete control of the disease after a mean follow-up of 1.36 years (range 0.3 to 2.59 years). These patients were designated complete responders (Figure 3, left panel). 4 months after the start of therapy, they were able to discontinue all medications except anakinra. A second group of 11 patients [patients S11–S20 and S22

(incomplete responders or non-responders)] exhibited a variable response to anakinra treatment, with general improvement soon after the initiation of the therapy, but with a tendency toward recurrence of the disease manifestations and elevation acute-phase reactant levels, during follow-up, despite increases in the daily dosage to 3 or 4 mg/kg (Figure 3, right panel). Conversely, the systemic features in these patients, such as fever and rash, were generally well controlled over time, which indicates that SJIA is a heterogeneous condition.

No differences were observed in baseline levels of acute phase reactants [CRP, Erythrocyte sedimentation rate (ESR), fibrinogen, ferritin] or haemoglobin between the 2 groups. Conversely, complete responders had a significantly higher number of circulating neutrophils [median 19.3 x 103/mm3 (range 6.1 to 30.9 x 103/mm3)] compared with incomplete responders and non-responders [median 9.1 x 103/mm3 (range 7.3 to 19.7 x 103/mm3)] ($p = 0.02$). No significant differences in the amounts of secreted IL-1β and IL-18 were observed between responders and incomplete responders/non-responders.

A significant down-modulation after 1 week of treatment was observed for IL-6 (mean ± SD serum concentration after treatment 79.9±66.8 pg/mL; $p = 0.009$). When responders and non-responders were analysed separately, significant decreases in the levels of IL-6 ($p = 0.02$) and GM-CSF ($p < 0.05$) were observed in the responder group only.

Figure 3 – CRP response to anakinra in patients with SJIA who were designated complete responders (left) and those designated incomplete responders or nonresponders (right)



Source: Gattorno et al. 2008.
At the time of statistical analysis, the duration of follow-up did not differ between the 2 groups. Numbers preceded by the letter S are individual patient numbers. P values (versus baseline) were determinded by Wilcoxon's nonparametric matched pairs test.
CRP=C-reactive protein; NS=not significant.

Leguerre et al, 2008

The dosage regimen was 1 to 2 mg/kg/day with a maximum of 100 mg/day. The mean (SD) age at treatment onset was 12.4 (5.2) years. CRP decreased and response to anakinra treatment was rapid and sustained in a significant proportion of SJIA patients suggesting that IL-1 is a key cytokine (Table 9). The authors raised the issue whether the anakinra dosage should have been increased in patients that did not respond.

Table 9 – CRP before and at the latest follow-up for SJIA patients (N=20) undergoing anakinra treatment

Parameter	At anakinra onset	Last visit[a] on anakinra	p value[b]
CRP, mg/L	78.9 (42.3)	25.5 (29.9)	0.0006

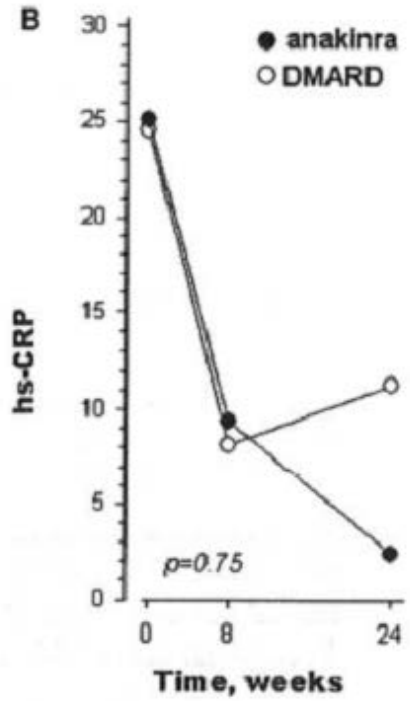
Source: Lequerre et al. 2008.
Values depict Mean (SD).
[a]14.7 (2 to 27) months; [b]Non-parametric Wilcoxon test.
CRP= C-reactive protein; N=Number of SJIA patients; SJIA= Systemic juvenile idiopathic arthritis

Nordstrom et al, 2012. AOSD patients.

The dosage regimen was 100 mg/day. The mean (SD) age at treatment onset was 39 (18) years.

The efficacy of anakinra was studied *versus* DMARD in refractory AOSD. Anakinra induced rapid responses, indicated by significant improvements in physical health. CRP normalized by Week 8, with no difference between the groups (Figure 4).

Figure 4 – CRP levels in anakinra and DMARD treatment groups



Source: Nordstrom et al. 2012.
CRP (C-reactive protein) normalized by week 8 in both groups, with no statistical difference between the anakinra group and the disease-modifying antirheumatic drugs (DMARD) group.
C=C-reactive protein; DMARD=Disease modifying anti rheumatic drug.

Anti-anakinra antibodies

The studies providing data on anakinra antibodies are presented in table 10.

Table 10 – Overview of studies providing anakinra ADA data

Study number	Study population	Study design	Dosage regimen
Still's disease studies			
990758/990779	Subanalysis of patients with SJIA from JIA study 990758 / 990779 N=15[a], 3 to 17 years	Multicenter, blinded, placebo-controlled study with an open-label run-in period.	1.0 mg/kg/day s.c. (maximum 100 mg/day)
Previously submitted to EMA			
990758/990779	JIA (polyarticular, pauciarticular, or SJIA) N=86, 3 to 17 years	Multicenter, blinded, placebo-controlled study with an open-label run-in period.	1.0 mg/kg/day s.c, (maximum 100 mg/day)
960180	RA N=419, 20 to 83 years	Multicenter, randomized, double-blind, placebo-controlled. Anakinra + MTX or Placebo + MTX. 24 weeks treatment	0.04, 0.1, 0,4, 1, 2 mg/kg/day s.c.
990757	RA N=1414, 19 to 85 years	A 6-months randomized, blinded, placebo-controlled phase followed by an open label 30 months phase	100 mg/day s.c.
990145	RA N=906, 20 to 84 years	Placebo + MTX or anakinra + MTX for 1 year[b] followed by open-label treatment with anakinra for 2 years[c]	100 mg/day s.c.
03-AR-0298	CAPS N=43, 0.7 to 46.3 years	Prospective, long-term, open-label study.	0.9 to 5.2 mg/kg/day s.c.

[a]SJIA population = 15 patients (Statistical report 990758). Number of patients with ADAs and NAbs Week 12 was 9 (8) and 7 (5) at Week 28;
[b]Stable dose of MTX; [c]The dose of MTX could be managed as needed.
The study population refers to the total population included in the study.
ADA=Anti-drug antibody; CAPS=Cryopyrin associated periodic syndrome; JIA=Juvenile idiopathic arthritis; MTX=Methotrexate; RA=Rheumatoid arthritis; s.c.=Subcutaneous; SJIA = systemic juvenile idiopathic arthritis.

A high proportion of SJIA patients in study 990758 developed ADA (71 % in the blinded phase) and no neutralizing antibodies (NAbs) were detected. Also in other patient populations the frequency of NAbs was low (0 to 3 %).

Table 11 – Presence of ADAs and Nabs by visit (Study 990758, SJIA Population)

Patient	ADAs	NAbs	ADAs	NAbs
	Week 12	Week 12	Week 28	Week 28
	Positive	Negative		
	Positive	Negative	Positive	Negative
			Positive	Negative
	Positive	Negative	Positive	Negative
	Positive	Negative		
	Positive	Negative		
	Positive	Negative	Positive	Negative
	Positive	Negative	Negative	
	Positive	Negative	Positive	Negative
	Negative		Negative	

Source: Statistical report 990758.
NAbs=neutralizing antibodies

The high incidence of ADA in SJIA patients is consistent with previous experiences in other patient populations. Anti-anakinra antibodies were detected at one or more time-points in 50 % to 82 % in RA and JIA patients. The presence or absence of anti-anakinra antibodies was reported to have either no effect on the safety profile or in a few cases worsening of RA.

In patients with JIA, no correlation between antibody development and adverse events (AEs) was observed. In patients with CAPS (study 03-AR-0298) the development of antibodies over time and their potential influence on outcome measures has also been evaluated. These data may also have applicability for patients with Still's disease, since both conditions are inflammatory and the treatment schedules the same. The proportion of patients with antibodies at least once post-baseline was 82.5 %. During the first 36 months, the proportion of patients with antibodies (ADA+) ranged from 42.9 % (Month 1) to 78.6 % (Month 3). At the end of study (Month 60), 50 % of the patients were ADA+. Anakinra half-life, AUC, as well as peak and trough concentrations did not indicate a consistent influence of ADAs on the elimination of the drug.

No consistent difference between ADA- and ADA+ patients with respect to change in the efficacy measure was observed throughout the study. There was no relevant difference in the overall annual rate of treatment-emergent AEs in ADA- and ADA+ patients.

The sub-analysis of the 15 SJIA patients in study 990758 with respect to ADA was performed by presence of ADAs (immunoassay) and of NAbs (cell based assay) at the 2 visits during treatment, i.e. Week 12 (open label phase) and Week 28 (blinded phase) (Table 11). Of the 9 patients tested for ADA at Week 12 all but 1 were ADA-positive. 8 of these patients were also tested for NAbs and all were found to be negative. Of the 7 patients tested at Week 28, 5 patients (71.4 %) were found to be ADA-positive and 2 (28.6 %) were ADA-negative. Of the 5 ADA-positive patients all were NAbs-negative. No placebo patient tested positive.

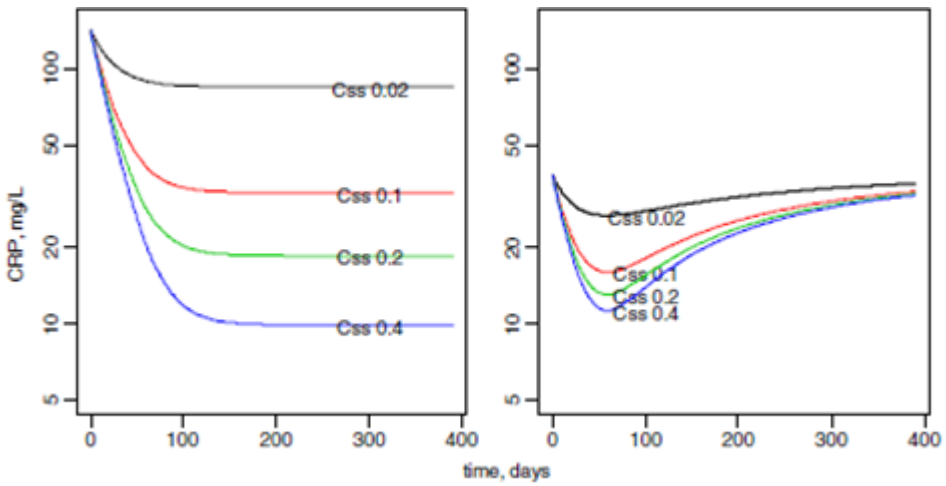
2.3.4. PK/PD modelling

A PK/PD modelling of anakinra and CRP data investigated in children and adolescents treated for SJIA and auto-inflammatory syndromes was published by Urien et al. 2013. The data were fitted to a PK/PD model via a population approach using Monolix.

The combined PK/PD model including CRP data from 22 SJIA patients predicted that an average anakinra steady-state exposure of at least 400 ng/mL, corresponding to an AUC0-24h,ss of 9600 ng*h/mL, is required to produce a decrease in CRP levels to 10 mg/L or below. This exposure is similar to that in an adult RA patient at a daily dose of 1 mg/kg, but lower than the median dose-normalized steady-state AUC0-24h,ss of anakinra in NOMID patients.

According to the model a dosage of 2 mg/kg/day to Still's disease patients was appropriate in the 10 to 50 kg body weight range, but not at body weights < 10 kg, for which the effective mean dose would be 3 mg/kg/day. A fixed dose of 100 mg/day would be effective for patients with a body weight ≥ 50 kg.

Figure 5 – Model-predicted effect of anakinra on the C-reactive concentration-time courses assuming 0.02 to 0.40 mg/L mean steady-state anakinra concentrations in the 2 subgroups of patients. Left, high base level with large CRP decrease, right, moderate base CRP with initial decrease followed by a re-increase in CRP concentrations.



Dosage regimen

A target dose for treatment of patients with Still's disease over a body-weight range of 2 to 200 kg has been derived based on PK/PD modelling and doses reported in clinical studies and case reports.

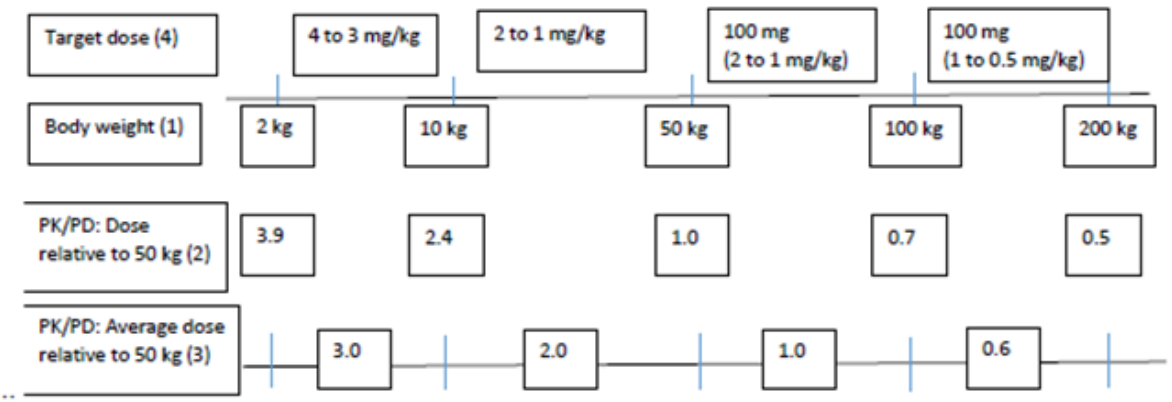
The PK modelling included in total 86 subjects with body weights ranging from 4.3 to 83 kg and an age range of 2.26 to 21 years. The combined PK/PD model included data from 22 SJIA patients ranging in body weight from 10 to 83 kg and in age from 2.26 to 16.8 years.

CL/F was described by the relationship CL/F = 0.847 x BW0.47. This relationship shows that an mg/kg body-weight adjusted clearance is non-linear with a higher clearance at lower body weights. The simulation identified body-weight intervals that could potentially be clinically important: patients with body weights of 2 to 10 kg, 10 to 50 kg, and 50 to 100 kg (Figure 6). To achieve the same anakinra concentration across the body-weight intervals the dose levels relative to the dose given to a patient with a body weight of 50 kg were estimated to be 3.9 at 2 kg, 2.4 at 10 kg, 1 at 50 kg, and 0.7 at 100 kg according the modelling. Tentative average dose levels relative to adults of the body weight range 50 to

100 kg to achieve similar concentrations over the whole body-weight range could be approximated to 3 (2 to 10 kg), 2 (10 to 50 kg) and 1 (50 to 100 kg).

Dosage at body weights > 100 kg was not presented in the publication since underlying weight data did not cover that. If extrapolations would be allowed it can be estimated that for a body weight of 200 kg, clearance would be further reduced and the dose relative to the body-weight interval 100 to 200 kg would be about 0.6.

Figure 6 – PK/PD modelling aiming at a similar anakinra concentration over the body weight range 2 to 200 kg, and dosing in Still's disease patients



Source: Adapted fromUrien et al. 2013.
The following sequence of evaluations is shown. 1) Body-weight intervals identified as potentially clinical important: 2 to 10, 10 to 50, 50 to 100 and 100 to 200 kg. 2) Dose levels relative to a body weight of 50 kg resulting in similar anakinra plasma concentrations estimated by PK/PD modelling. 3) Suggested average relative dose levels based on PK/PD modelling for the respective body-weight interval. 4) Integration of clinically used doses and estimates from PK/PD modelling: body-weight adjusted doses for pediatric patients and fixed dose for adults.

The starting dose in most clinical studies with paediatric patients with Still's disease was 1 to 2 mg/kg/day. These patients can be assumed to belong to either the body-weight interval 10 to 50 kg or 50 to 100 kg (as the 22 SJIA patients in the PK/PD modelling). It is not known how the 2 mg/kg doses were distributed over the 2 body weight intervals. Therefore, the target dose based on the clinical studies is assumed to be 1 to 2 mg/kg for these paediatric patients. These clinically used dose levels are in agreement with the average relative dose levels predicted by Urien et al. 2013. Paediatric patients with a body weight below 10 kg is from the PK/PD modelling expected to require a higher dose (2.4 to 3.9 mg/kg) to achieve similar anakinra concentrations as adults due to the non-linear clearance (Figure 31).

All adult patients described in the studies received anakinra 100 mg/day as a starting dose, and often also as the maintenance dose. Since the adult patients' doses were not body-weight adjusted, the 100 mg dose corresponds to 2 to 1 mg/kg in the range 50 to 100 kg. The average 75 kg patient in this body-weight class administered a 100 mg dose would thus have received 1.3 mg/kg, which is in general agreement with the PK/PD modelling. For patients at the lower end of this interval, i.e. a 50 kg patient, a 100 mg dose would correspond to about 2 mg/kg which is higher than the prediction, but still well within the safety margin of anakinra. A 200 kg patient given a 100 mg dose would receive a dose corresponding to 0.5 mg/kg, which is in agreement with the PK/PD modelling (Figure 6).

Thus, from a clinical pharmacology perspective, and taking doses used in the majority of the clinical studies into account, the following rationale for a dosage recommendation can be formulated. The target dose for treatment of patients with Still's disease would be between 2 to 1 mg/kg to patients with body weights between 10 and 50 kg, between 2 and 1 mg/kg for patients between 50 and 100 kg, and 1 to 0.5 mg/kg for patients between 100 and 200 kg. The target dose for patients with a body weight above 50 kg

can be approximated to a fixed dose of 100 mg as justified by clinical efficacy, safety and clinical pharmacology data. The target dose for patients below a body weight of 10 kg is 3 to 4 mg/kg/day.

Dose adjustments

The starting dose in adults was 100 mg/day in published studies. No clinical information is available on the potential consequences of dose changes and no dose adjustments are therefore proposed for adult patients.

Anakinra exhibits approximate dose linearity regarding Cmax and AUC. Dose adjustments in steps of up to 1 mg/kg to a maximum of 8 mg/kg/day have been shown to be safe and effective in paediatric patients with CAPS. In paediatric patients with Still's disease dose adjustments up to a dose of 9.1 mg/kg/day have been made to control active inflammation. In paediatric patients with Still's disease, the dose has in the great majority of cases ranged from 1 to 4 mg/kg/day. The steps used in the dose adjustments have not been specified. Response to dose adjustments, such as clinical symptoms and laboratory measurements, can be readily managed due to the short half-life of anakinra.

Dosage frequency

Patients with Still's disease have been treated with once daily s.c. injections of anakinra. Less frequent injections with maintained disease remission has been reported (3 times weekly) but only one such reduced dosage frequency has been identified in the literature search (Maier et al. 2008). When the disease is in an active phase immediate onset of effect (within hours) as well as rapid reappearance of symptoms within a few days at discontinuation of drug treatment has been reported. This supports the need for daily injections of patients with Still's disease.

As a consequence of the reduced clearance of anakinra in patients with chronic renal failure on dialysis (Yang et al. 2003, study 0555), a reduced dosage frequency to every other day should be considered for these conditions (creatinine clearance < 30 mL/min, as estimated from serum creatinine levels). This precaution is justified by the substantial elimination of anakinra by the kidney, and that the risk of adverse events may be greater in patients with impaired renal function if the dosage regimen is not adjusted.

Dosage recommendation

Based on the clinical pharmacology evaluations, published studies, and considering the SJIA consensus treatment plan issued by CARRA (Kimura et al. 2014) together with a well characterised safety profile, the proposed labelling text for dosage of anakinra is:

The recommended starting dose for patients weighing 50 kg or more is 100 mg/day by s.c. injection. Patients weighing less than 50 kg should be dosed by body weight with a starting dose of 1 to 2 mg/kg/day.

2.3.5. Discussion on clinical pharmacology

The PK of anakinra has been previously characterized in healthy volunteers and patients with JIA, CAPS and RA. PK data in patients with Still's disease are limited to post analysis of 13 SJIA patients included in the MAH-sponsored study 990758 and 22 SJIA patients, included in the two published studies by Quartier and Urien.

The analysis across populations indicates that PK exposure to anakinra is comparable and that the general and previous description of anakinra PK also applies to the Still's disease population.

The dosing in the CAPS study is comparable to the dosing used in study 990758 and the proposed dose in Still's disease. Anakinra is approved in children with CAPS from 8 months of age and with a body weight > 10 kg, and these age and weight restrictions also apply to the Still's disease indication.

The PK data from the Quartier study used in the PK/PD model suggest that low-weight children could have benefitted from a higher dose (i.e. > 2 mg/kg/day). In the proposed posology, dose escalation up to 4 mg/kg/day is recommended in case of inadequate response.

The starting dose in most clinical studies with paediatric patients with Still's disease was 1 to 2 mg/kg/day and all adult patients in the presented studies received anakinra 100 mg/day as a starting dose. CRP and other inflammatory markers were reduced in all studies and case reports in both SJIA and AOSD patients. This supports the dosage used in the studies.

Anakinra is eliminated by glomerular filtration and subsequent tubular metabolism, and clearance decreases with decreasing creatinine clearance, up to 75 % decrease in clearance in subjects with ESRD. However, Anakinra has successfully been administrated to patients with severe renal impairment and ESRD, without unexpected safety findings (Yang et al. 2003). The current contraindication can therefore be adjusted to a warning in section 4.4 with specific dosage recommendations for patients with severe renal impairment or ESRD.

Dosage in patients with mild and moderate renal impairment has been clarified, including the rational for dosing every other day in patients with ESRD. Simulations have shown that Anakinra trough concentrations will be similar in patients with ESRD dosed every second day compared to patients with normal renal function dose daily. Cmax and AUC will be higher, but no unexpected safety concerns have been identified in patients with ESRD.

Response was often rapid and consistent with the short half-life of anakinra. A group of non/incomplete responders were identified in the only randomized study with AOSD patients. Response of treatment should be evaluated after 1 month. In case of persistent systemic manifestations dose may be adjusted in children or continued treatment with Kineret should be reconsidered by the treating physician. This is adequately reflected in the SmPC for the attention of the prescriber.

Anti-anakinra antibodies were frequent in the SJIA patients in study 990758 and the open label extension 990779. This is consistent with immunogenicity in other studied populations. No patients developed neutralising antibodies and no impact on PK, efficacy or safety was identified.

2.3.6. Conclusions on clinical pharmacology

The PK data of anakinra in SJIA are limited and no data are available in AOSD patients. However, the pharmacokinetics of anakinra in the SJIA population appears to be comparable to PK in other populations (RA; JIA, CAPS) and extrapolation to AOSD is considered acceptable.

The PD data in both clinical studies and case reports all demonstrate rapid and deep response on PD markers of IL-1 blockade, which support the use of anakinra in Still's disease.

The proposed dosage is consistent with the doses used in the studies and case reports and supported by the PK/PD model.

Patients with severe renal impairment and ESRD have successfully been treated with anakinra with no unexpected toxicity, and the current contraindication in severe renal impairment is removed and changed into a warning with dosage recommendations in section 4.4.

2.4. Clinical efficacy

Since the introduction of anakinra in 2002 in the EU for the treatment of RA, a number of inflammatory disorders have been found to benefit from IL-1 inhibition. Although not approved for the treatment of SJIA and AOSD, published studies and registers indicate the use of anakinra for more than 10 years in these conditions.

SJIA and AOSD share common clinical manifestations, and there is a growing understanding that these are different diagnostic names applied to one single inflammatory condition, here referred to as Still´s disease. However, the majority of published studies of treatment results are based on studies conducted by paediatric rheumatologists using the diagnostic label SJIA or by rheumatologists treating adults using the label AOSD. Therefore, the efficacy of anakinra for individual studies is summarized separately for SJIA and AOSD.

2.4.1. Dose response study

No dose response study has been conducted.

A target dose for treatment of patients with Still's disease over a body-weight range of 2 to 200 kg has been derived based on PK/PD modelling and doses reported in clinical studies and case reports (see pharmacology part of this assessment).

2.4.2. Main studies

Still's disease with paediatric onset

The evaluation of efficacy of anakinra in Still´s disease with paediatric onset is based on the studies included in the PIP:

- A prospective, randomized, double-blind, placebo-controlled, MAH-sponsored study to evaluate the safety, clinical response, and pharmacokinetics of anakinra in polyarticular course JIA, including a subpopulation of SJIA patients (study **990758**).
- A prospective, multicentre, randomized, double-blind, placebo-controlled, investigator-sponsored study to evaluate safety and efficacy of anakinra in patients with SJIA (**Quartier et al. 2011**).
- A meta-analysis of available published data on efficacy and safety of anakinra in patients with SJIA **(Meta-analysis SJIA)**.

A literature search identified 2 additional published clinical studies in SJIA.

Still's disease with adult onset

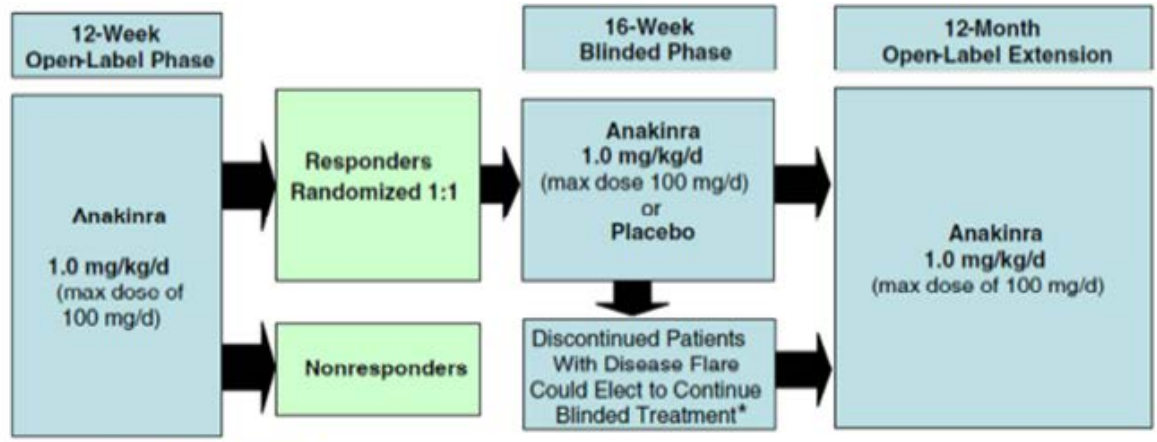
Evidence of efficacy in Still´s disease with adult onset have been demonstrated by a meta-analysis of 8 published studies **(Hong et al, 2014)** including a randomized, active-controlled, open-label study (**Nordstrom et al, 2012**), as well as 3 additional published clinical studies in AOSD.

Prospective randomized studies:

Study 990758 (Ilowite et al 2009) was a prospective, multicentre study of 86 patients with JIA, of which 15 were diagnosed with SJIA. The study consisted of a 12-week open-label run-in phase (anakinra treatment 1 mg/kg/day, maximum 100 mg/day), followed by a randomized, double-blind, placebo controlled phase for 16 weeks for patients responding to anakinra treatment, and a 12-month open-label extension phase. Data for the 15 SJIA patients from the open-label run-in phase were evaluated in a meta-analysis as a PIP requirement. The design of the study is shown in Figure 7. The study was

originally designed to assess the efficacy of anakinra in JIA patients, but insufficient enrolment led to an amendment of the protocol that changed the primary endpoint from efficacy to safety.

Figure 7 – Study design (990758/990779)



Source: Study 990758/990779.
*Patients could switch treatment arm if they chose to continue.
d=Day.

Sample Size

Approximately 90 subjects were enrolled to evaluate the safety of anakinra in the JRA population.

Outcomes/Endpoints

The primary efficacy endpoint was the proportion of subjects with disease flares during the 16-week blinded phase.

Secondary Efficacy Endpoints: Time-to-disease flare from randomization in the 16-week blinded phase. Change from week 12 assessments for each of the JRA core set components at week 28.

Safety Endpoints: Treatment emergent adverse events, Laboratory assessments, Antibody response.

Baseline data

The demographic and baseline characteristics of the SJIA population are presented in the table below:

Table 12 – Demographics and baseline characteristics (990758, SJIA PK Population)

	SJIA PK Population (N = 13)				
	Anakinra dose (mg/kg/day)	Age (years)	Body Weight (kg)	Sex	Race
Patient					
	1.09				
	1.07				
	1.05				
	1.12				
	1.12				
	1.06				
	1.05				
	1.09				
	1.21				
	1.09				
	1.19				
	1.02				
	1.06				
Summary					
n	13	13	13		
Mean (SD)	1.09 (0.06)	10.3 (4.4)	33.6 (17.2)		
Median (Range)	1.09 (1.02 - 1.21)	11.0 (3 - 17)	32.0 (12.4 - 71.4)		
Male				7 (53.8)	
Female				6 (46.2)	
White or Caucasian					6 (46.2)
Black or African American					1 (7.7)
Hispanic or Latino					5 (38.5)
American Indian or Alaska Native					1 (7.7)

Source: DEM_SJIA_PK_T.SAS 2017-01-31T07:51:47 Z9FRBE
The SJIA PK Population consists of all SJIA patients with a PK measurement (including BLQ) at any time.
BLQ= Below limit of quantification; N=Number of patients; PK=Pharmacokinetics; SD=Standard deviation; SJIA=Systemic juvenile idiopathic arthritis.

Outcomes and estimation

Eleven of 15 SJIA patients (73 %) were ACRpedi 30 responders in the 12-week open-label run-in phase. During the 16-week double-blind, placebo-controlled phase, 2 of 9 patients randomized to anakinra had disease flares at Week 28 compared with 1 of 2 patients randomized to placebo.

Post-hoc analyses showed that CRP and ESR decreased over time during the open-label run-in phase when all patients receive anakinra, with a median CRP level of 114.0 mg/L at Baseline versus 1.5 mg/L at Week 12, and a median ESR level of 45.5 mm/hour at Baseline versus 7.5 mm/hour at Week 12. The decreased CRP and ESR levels during anakinra treatment seen during the open-label run-in phase were sustained during the blinded-phase (Table 13).

Table 13 – CRP and ESR over time (study 990758, SJIA ITT Population, anakinra patients during Blinded phase)

Inflammatory marker	Week 12 (Baseline) n=8	Week 20 n=8	Week 24 n=8	Week 28 n=8
CRP (mg/L)	1.5 (1.0, 12.0)	1.0 (1.0, 14.5)	1.0 (1.0, 24.5)	1.0 (1.0, 5.0)
ESR (mm/hour)	7.5 (3.5, 19.5)	9.0 (5.0, 12.0)	5.5 (2.0, 8.5)	5.0 (2.5, 8.0)

Source: Statistical report 990758.
Values depict median (Q1, Q3).
CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; ITT=Intent to treat; n=Number of patients for which inflammatory markers were measured; SJIA=Systemic juvenile idiopathic arthritis.

Quartier et al, 2011

Study participants

Inclusion criteria were age ranging from 2–20 years, a diagnosis of SJIA, more than 6 months' disease duration, active systemic disease (disease-related fever and/or C-reactive protein (CRP) >20mg/L and/or first hour erythrocyte sedimentation rate (ESR) >20) and significant overall disease activity at day 1 (D1) (at least three of the following criteria: (1) physician global assessment of disease activity 20/100; (2) parent/patient assessment of disease effect on overall wellbeing ≥20/100; (3) Childhood Health; Assessment Questionnaire score ≥0.375/3; (4) ≥2 joints with active arthritis; (5) ≥2 joints with non-irreversible limited range of motion and (6) ESR ≥30) despite oral prednisone or prednisolone ≥0.3 mg/kg or 10 mg/day (whichever was lower).

Female subjects entering the study were prepubescent, sexually inactive or required to use effective contraception.

Exclusion criteria included previous treatment with an IL-1 inhibitor or any condition contraindicating immunosuppressive treatment. Intravenous or intra-articular steroids, immunosuppressive drugs and disease-modifying anti-rheumatic drugs (DMARDs) had to be stopped at least 1 month before study onset or for longer periods of time depending on their half-life. Nonsteroidal anti-inflammatory drugs and corticosteroids had to be taken at stable dosage for 1 month before D1 and until month 1 (M1). All patients entering the study, and their parents for patients aged <18, gave written informed consent.

Study design

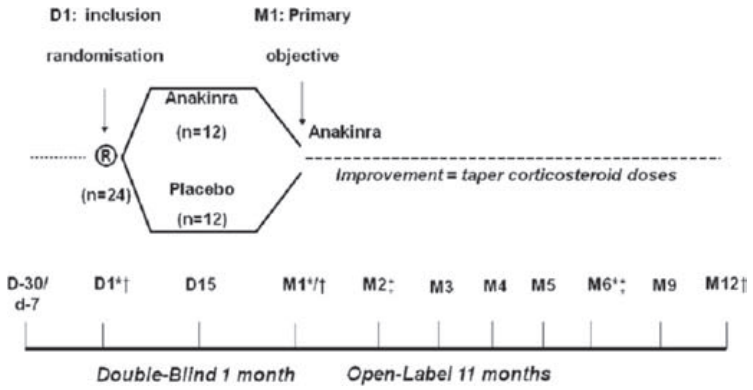
Part 1 was a randomised, double-blind, placebo-controlled phase. At D1, eligible patients were randomised to receive either anakinra or placebo (1:1) from D1 to M1. Patients were stratified by centres and randomisation was balanced across treatments and centres.

Investigators, other caregivers, the patients and their parents remained blinded to the assigned treatment.

The primary objective was to demonstrate a higher proportion of responders in group 1 than group 2. No immunosuppressive drugs or DMARDs were allowed during the trial. Nonsteroidal anti-inflammatory drugs and corticosteroids had to be taken at stable dosage for 1 month before D1 and until M1.

Part 2 was an open-label treatment period: all patients received anakinra after M1. Tapering the dose of corticosteroids was allowed after the M1 visit (reduction of 0.4–0.5 mg/kg monthly for daily doses of ≥1.5 mg/kg, 0.3–0.4 mg/kg for doses between 1.0 and 1.5 mg/kg, 0.2–0.3 mg/kg between 0.6 and 1.0 mg/kg, 0.1–0.2 mg/kg between 0.3 and 0.6 mg/kg, ≤0.10 mg/kg for doses <0.3 mg/kg).

Figure 8 – Study design



*Measurement of serum amyloid A and ferritin levels, assessment of the percentage of glycosylated ferritin, gene expression profi ling analysis and cytokine measurements. †Measurement of the concentration of anakinra in plasma (pharmacokinetic analyses). ‡Measurement of serum antipneumococcal antibodies. D, day; M, month.

Measurement of serum amyloid A (SAA) and ferritin levels and the percentage of glycosylated ferritin were performed at D1, M1 and M6. Pharmacokinetic (PK) analyses were performed on blood taken at M2 and M6.

Concentrations of anakinra in plasma samples were determined using the antibody (Ab) ELISA.

Patients who were naive from anti-pneumococcal immunisation received Pneumo23 immunisation at D1 in order to assess at M1 and M12 the effect of anakinra treatment on anti-pneumococcal Ab response to five capsular polysaccharides.

Objectives

The primary objective was to compare the efficacy of a 1-month treatment with anakinra (2 mg/kg subcutaneous daily, maximum 100 mg) *versus* placebo between two groups each with 12 patients with SJIA. Response was defined by a 30% improvement of the paediatric American College of Rheumatology criteria for JIA, resolution of systemic symptoms and a decrease of at least 50% of both C-reactive protein and erythrocyte sedimentation rate compared with baseline. After M1, patients taking placebo were switched to anakinra. Tapering the dose of corticosteroids was allowed after the M1 visit (reduction of 0.4–0.5 mg/kg monthly for daily doses of ≥1.5 mg/kg, 0.3–0.4 mg/kg for doses between 1.0 and 1.5 mg/kg, 0.2–0.3 mg/kg between 0.6 and 1.0 mg/kg, 0.1–0.2 mg/kg between 0.3 and 0.6 mg/kg, ≤0.10 mg/kg for doses <0.3 mg/kg).

Secondary objectives included tolerance and efficacy assessment for 12 months, and analyses of treatment effect on blood gene expression profiling.

Results

Outcomes and estimation

At M1, 8/12 (67%) responders were receiving anakinra and 1/12 (8%) responder receiving placebo (p=0.003). Ten patients from the placebo group switched to anakinra; nine were responders at M2. Between M1 and M12, six patients stopped treatment owing to an adverse event (n=2), lack of efficacy (n=2) or a disease flare (n=2). In group 2 there were responders at M1 (p=0.003), therefore the primary objective of the trial was met.

Two patients from the control group stopped treatment after 5 and 11 days, respectively, owing to pain from injections and were withdrawn from the trial after the M1 visit; one of them, a child who presented a marked disease flare at D1, was the only responder at M1 in the control group

Blood gene expression profiling at enrolment and at 6 months' follow-up showed one set of dysregulated genes that reverted to normal values in the clinical responders and a different set, including interferon (IFN)-inducible genes, that was induced by anakinra.

The dose of corticosteroids was then either maintained stable or reduced in accordance with the protocol recommendations at each visit.

Seventeen patients continued the trial until M6. Their mean daily dose of predniso(lo)ne was 0.18 mg/kg (median 0.1 mg/kg).

Table 14 – Responses at month 1

Response	Group 1 Anakinra (n = 12) Number of responders (%)	Group 2 Placebo (n = 12)	p Value*
Primary objective (modified ACRpedi 30)†	8 (67)	1 (8)	0.003
Systemic symptoms responders†	8 (67)	1 (8)	0.003
Primary objectives used in other trials			
ACRpedi 30 responders	11 (92)	7 (58)	0.059
ACRpedi 30 and no fever‡	11 (92)	6 (50)	0.025
ACRpedi 30, no fever and CRP <15 mg/l§	10 (83)	3 (25)	0.004
Modified ACRpedi 50, 70 and 100 response†			
Modified ACRpedi 50 responders	7 (58)	0	0.005
Modified ACRpedi 70 responders	5 (42)	0	0.038
Modified ACRpedi 100 responders	0	0	1
Response to individual variables	**Mean variation from D1 to M1 (%)**		**p Value¶**
CRP	−71	−16	0.001
ESR	−64	−18	0.002
SAA	−70	−2	<0.001
Number of active joints	−46	−18	0.040
Number of joints with LOM	−36	−20	0.148
CHAQ	−37	−9	0.236
Physician's disease activity assessment**	−63	−20	0.002
Parent/patient's global assessment**	−36	−23	0.544
Parent/patient's assessment of pain**	−29	−21	0.219

*χ^2 Test.
†Body temperature <38°C for more than 7 days, CRP and ESR normalised or decreased by at least 50% (=systemic symptoms responders) and also, in responders to the trial primary objective, ACRpedi 30, 50, 70 or 100 (whichever level is indicated) response compared with D1.
‡Body temperature <38°C for more than 7 days and ACRpedi 30 response compared with D1.
§Body temperature <38°C for more than 7 days, CRP <15 mg/l and ACRpedi 30 response compared with D1 as in a recent trial with the anti-interleukin 6 receptor antibody tocilizumab.
¶Mann–Whitney test.
**Using a visual analogue scale (0–100 mm).
ACRpedi 30, American College of Rheumatology Pediatric 30 response; CHAQ, Childhood Health Assessment Questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LOM, joints with limitation of passive motion; SAA, serum amyloid A.

Nordstrom et al, 2012 was a 24-week multicenter, randomized, open-label study of 22 patients with corticosteroid-dependent refractory AOSD. This was followed by the option of a 28-week open-label extension if improvement did not occur within the initial 24 weeks. Patients were randomized to anakinra (n=12; 100 mg/day) or DMARD (n=10). The mean (SD) age of the anakinra group was 39 (18) years, and median (range) disease duration was 14 months (2 to 240 months). The mean (SD) age of the DMARD group was 39 (17) years, and median (range) disease duration was 19 months (3 to 204 months).

The primary endpoint was remission according to specific criteria at 8 weeks:

- Afebrile (≤37 ºC body temperature) in the absence of NSAIDs 24 hours prior to measurement.
- Decrease of CRP and ferritin to reference limits and normal swollen and tender joint counts.

HAQ, Medical Outcomes Study Short-Form 36, and global and disease-related assessments of health were also applied.

After 4 weeks, the effect of anakinra therapy was assessed. Enhancement of DMARD dose was allowed, but escalation of corticosteroids implied treatment failure. Efficacy was then assessed at Weeks 8, 12 and 24.

Data for the 12 AOSD patients treated with anakinra were evaluated in a meta-analysis performed by Hong et al. 2014 (discussed below).

Outcomes and estimation

Randomized, open-label phase (24 weeks): More patients receiving anakinra than those on DMARD achieved remission. In remission at Week 4 were 6 of 12 patients versus 3 of 10 patients, and in remission at Week 8 were 7 of 12 patients versus 5 of 10 patients. At Week 24, 6 of 12 on anakinra were in remission versus 2 of 10 on DMARD. In both treatment groups, CRP had normalized by Week 8, and the mean corticosteroid doses had been reduced by Week 24. In addition, anakinra induced greater improvement in physical health as measured by Medical Outcomes Study Short-Form 36.

Open-label extension phase (additional 28 weeks): During the open-label extension phase, switching or add-on treatment with the comparator drug was possible if improvement did not occur within 24 weeks. A total of 17 patients completed the open-label extension phase (Week 52), of which 7 of 14 anakinra-treated patients, and 2 of 3 patients on DMARD, were in remission.

The authors concluded that anakinra induced more beneficial responses than DMARD.

Analysis performed across trials (pooled analyses and meta-analysis)

Study populations

Still's disease with paediatric onset: 245 anakinra-treated patients with Still's disease have been included in the studies. The mean age ranged from 7 to 12.4 years, and the median age ranged from 6 to 8.5 years, across studies, with an age range of 0.75 to 17 years at treatment start or disease onset. The mean disease duration ranged from 0.2 to 7 years, and the median disease duration ranged from 4.9 to 29 months, across studies, with a disease duration range from 1 month to 21 years. Almost all patients received glucocorticoids prior to anakinra treatment. The majority of patients also received MTX or anti-TNF therapy.

The patients in most studies were refractory to treatment pre-anakinra therapy. In one prospective uncontrolled study (Vastert et al. 2014), and in 2 retrospective uncontrolled studies (Nigrovic et al. 2011, Marvillet et al. 2011) anakinra was given as first-line therapy.

Still's disease with adult onset: 197 anakinra-treated patients with Still's disease are overall included in the studies. The mean age ranged from 32.8 to 42 years across studies, with an age range of 17 to 73 years at treatment start. The mean disease duration ranged from 5.7 to 9.4 years, and the median disease duration ranged from 7 months to 3.5 years, across studies, with a disease duration range from 1 month to 22 years. Almost all patients received MTX, anti-TNF or glucocorticoids prior anakinra treatment.

In addition to the 245 patients with paediatric onset and the 197 patients with adult onset, a number of case series and case reports including an approximate number of 154 patients (age range of 5 months to

73 years) were also identified in the literature search.

Meta-analysis in Still's disease with paediatric onset

As part of a PIP commitment, efficacy of anakinra in SJIA has been evaluated by Sobi in a meta-analysis of published studies **(meta-analysis SJIA)**.

The scientific databases used in the literature search included MEDLINE, EMBASE, BIOSIS Previews, SciSearch and PASCAL. In total, the search identified 493 publications where 188 were found to be related to anakinra treatment of SJIA. Out of these, 26 publications were identified to be potentially suitable for inclusion in the meta-analysis. These 26 publications were evaluated against predefined selection criteria to check if they could be included in the meta-analysis.

ACRpedi 30 was used for the meta-analysis of ACR response criteria. The study-specific response was defined as a complete or partial benefit of anakinra treatment, as interpreted by the authors of the study. This typically included assessment of disease activity (e.g. fever, rash, active joints) as well as pain assessed by physician and patient/parent, normalization on laboratory tests (CRP levels, ESR, WBC count, haemoglobin level, albumin levels, platelet count) and need for supplementary medication to maintain clinical remission (prednisone dose).

Based on the selection criteria, 4 studies were included in the meta-analysis using ACRpedi 30 responder criteria, and 5 studies were included in the meta-analysis using study-specific response criteria. One additional study was included in the sensitivity analysis of ACRpedi 30.

A summary table of the included studies is presented below:

Table 15 – Basic characteristics of included studies, patient population, and dosage (patients with Still's disease with paediatric onset)

Study	Study design	Number of patients	Disease duration (SD or range)	Age at start of anakinra (SD or range)	Anakinra dose	Time points of efficacy assessment[a]
Studies selected for the main analysis (studies that used ACRpedi 30 responder criteria)						
Ilowite et al. 2009[b]	Prospective, randomized, double-blind, placebo-controlled study[c]	15[d]	Mean 4.7 years (1 to 16 years)	Mean 12 years (3 to 17 years)	1 mg/kg/day, maximum 100 mg/day	3 months
Quartier et al. 2011	Prospective, randomized, double-blind, placebo-controlled study	12 anakinra 12 placebo	Mean 4.2 (3.33) years Mean 3.2 (1.95) years	Mean 9.5 (5.19) years Mean 7.5 (3.73) years	2 mg/kg/day, maximum 100 mg/day	1 month
Lequerre et al. 2008[e]	Prospective, multicenter, open-label study	20	Mean 7.0 (4) years	Mean 12.4 (5.2) years	1 to 2 mg/kg/day, maximum 100 mg/day (increased to 100 mg twice daily for one patient)	3, 6 months
Pascual et al. 2005	Prospective open-label study	9	Mean 4.6 (3.8) years	Mean 8.4 (4.8) years	2 mg/kg/day, maximum 100 mg/day	2 months
Additional studies selected for the analysis using study-specific response criteria						
Gattorno et al. 2008	Prospective open-label study	22	Mean 3.4 years (0.3 to 10.9 years)	Mean 10.3 (4.6) years	Initially 1 mg/kg/day, maximum 100 mg/day; individualized up to 4 mg/kg/day.	1 month
Nigrovic et al. 2011	Retrospective chart review	46	Mean 0.2 years (0.12 to 0.47 years)	Median 7.6 years (0.75 to 15.7 years)[f]	Median starting dose 1.5 mg/kg/day (IQR 1.1 to 2.0 mg/kg/day). Minimum dose given 0.93 mg/kg/day and maximum 11.2 mg/kg/day (during MAS episode).	1 month
Marvillet et al. 2011	Retrospective chart review	22	Mean 2.4 years (0 to 10.2 years)	Mean 8.6 years (1.8 to 15.6 years)	1 to 3 mg/kg/day	3 months
Irigoyen et al. 2006	Retrospective chart review	14	Not reported	Mean 7 years (1 to 15 years)[f]	Not reported	1.5 months
Ohlsson et al. 2008	Retrospective, multicenter chart review	7	Not reported	Median 8.5 years (5.2 to 15 years)	1 to 2 mg/kg/day	1 month
Study used in the sensitivity analysis						
Vastert et al. 2014[g]	Prospective, observational cohort study	20	Newly diagnosed	Mean 7.9 years (1.1 to 15.3 years)	2 mg/kg/day, maximum 100 mg/day In 2 patients, the dose was increased to a maximum of 4 mg/kg/day	3, 12 months

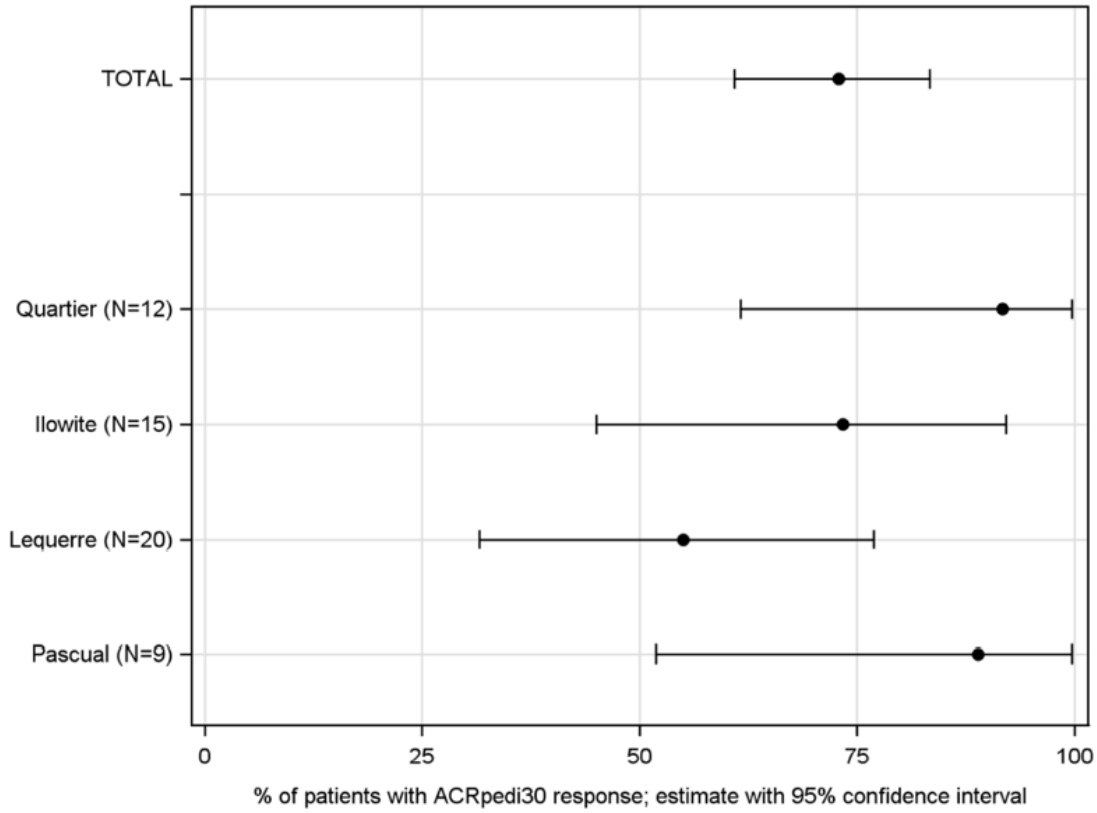
[a]Time points up to 3 months were used in the short-term meta-analysis.
[b]The publication is based on the Company-sponsored study 990758/990779.
[c]Only data from the open-label run-in phase were used in the meta-analysis.
[d]A total of 86 patients in this study included also patients with polyarticular (n=62) and pauciarticular arthritis (n=9).
[e]The study also describe 15 patients with AOSD treated with anakinra (see Table 2.7.3 - 13).
[f]At disease onset.
[g]ACRpedi 70 non-responders were counted as ACRpedi 30 non-responders; data were used in a sensitivity analysis.
ACRpedi 30=30 % improvement of the pediatric American College of Rheumatology criteria for juvenile idiopathic arthritis; AOSD=Adult-onset Still´s disease; IQR=Interquartile range; MAS=Macrophage activation syndrome; n=Number of patients; SD=Standard deviation.

A comparison on long-term responses was not feasible due to different treatment schemes. Most of the selected studies were only evaluating short-term responses.

Meta-analysis efficacy results

ACRpedi 30 responder criteria: In all 4 studies, the majority of patients responded to anakinra treatment according to ACRpedi 30. Short-term ACRpedi 30 response rates ranged from 55 % to 92 %, and the 95 % CIs of all 4 studies were overlapping. In the meta-analysis, the estimated ACRpedi 30 response rate was 73 % (95 % CI: 61 % to 83 %).

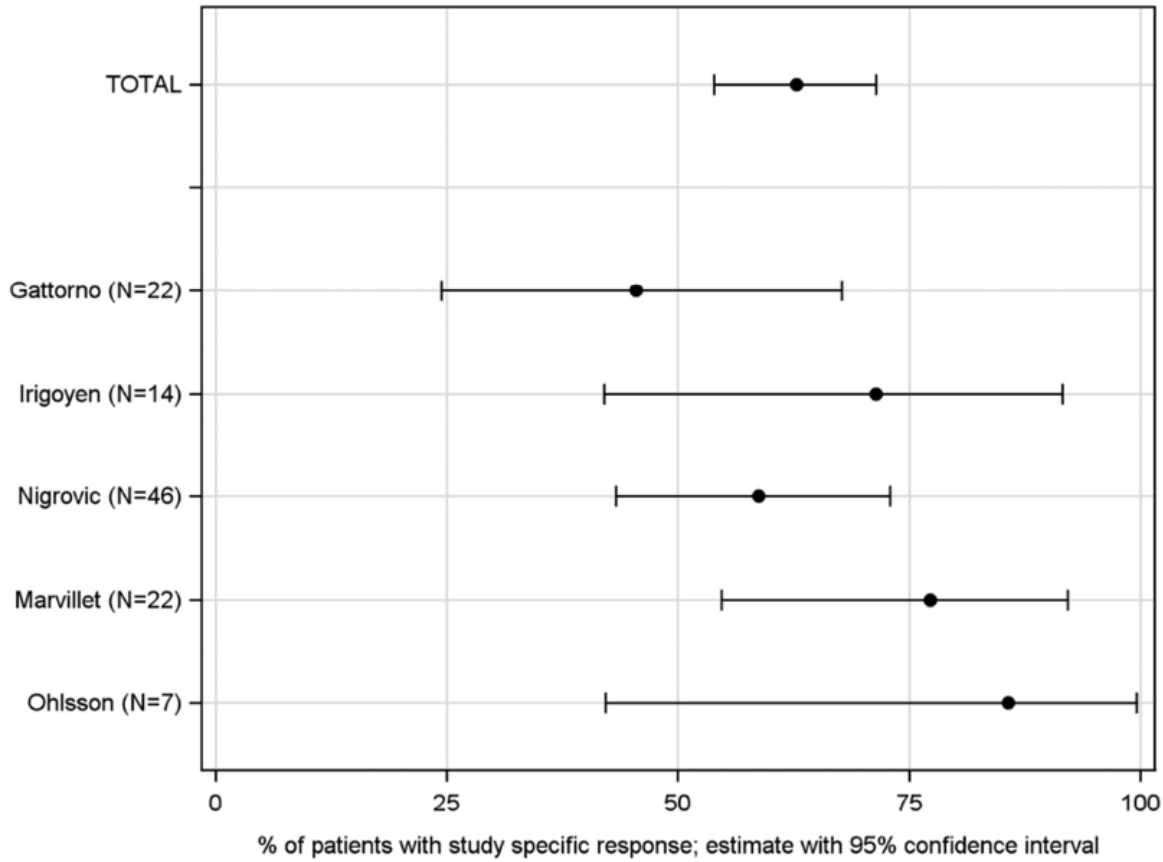
Figure 9 – Short-term (up to 3 months) response in ACR paediatric 30 criteria to anakinra treatment (Meta-analysis SJIA)



Source: Meta-analysis SJIA.
ACRpedi 30=30 % improvement of the pediatric American College of Rheumatology criteria for juvenile idiopathic arthritis; N=Number of patients treated with anakinra; SJIA=Systemic juvenile idiopathic arthritis.

Study specific response criteria: The study-specific response rates in the 5 studies ranged from 45 % to 86 %. In the meta-analysis, the estimated study-specific response rate was 63 % (95 % CI: 54 % to 71 %).

Figure 10 – Short-term (up to 3 months) study-specific response to anakinra treatment (Meta-analysis SJIA)



Source: Meta-analysis SJIA.
N=Number of patients treated with anakinra; SJIA=Systemic juvenile idiopathic arthritis.

Hong et al, 2014, meta-analysis in Still's disease with adult onset

A literature search in EMBASE, PubMed, and the Cochrane Library was performed on August 15, 2014, where a total of 273 published studies were identified. 8 studies, comprising a total number of 134 patients, were selected for the meta-analysis. A summary table of the included studies is presented below:

Table 16 – Basic characteristics of included studies, patient population, and dosage (patients with Still's disease with adult onset)

Study	Study design	Number of patients	Disease duration (SD or range)	Age at start of anakinra (SD or range)	Anakinra dose	Study duration
Nordstrom et al. 2012	Prospective, randomized, active-controlled, open-label study	12 anakinra 10 DMARD	Median 14 months (2 to 240 months) Median 19 months (3 to 204 months)	Mean 39 (18) years[a] Mean 39 (17) years[a]	100 mg/day	24 weeks
Laskari et al. 2011	Prospective, open-label study	25	Median 7 months (1 to 228 months)	Median 32 years (18 to 71 years)	100 mg/day	Median 15 months (1.5 to 71 months)
Lequerre et al. 2008[b]	Prospective, multicenter, open-label study	15	Mean 7.8 (6.4) years	Mean 38.1 (12.8) years	100 mg/day	Mean 14.3 months (1 to 27 months)
Giampietro et al. 2013	Retrospective, multicenter, chart review	28	Mean 9.3 years (1 to 22 years)	Mean 40.3 years (23 to 72 years)	100 mg/day	Mean 23 months
Cavalli et al. 2013	Retrospective chart review	19[c]	Mean 9 years	Mean 41 years	100 mg/day	At least 24 months
Giampietro et al. 2010	Retrospective, multicenter, chart review	19	Mean 9.4 years	Mean 40.6 years (range 23 to 73 years)	100 mg/day	Mean 30.7 months
Ilhou et al. 2013	Retrospective, observational study	10	Not reported	Not reported	100 mg/day	Not reported
Gerfaud-Valentin et al. 2014b	Retrospective chart review	6	Not reported	Not reported	Not reported	Mean 27.8 months (14 to 36 months)

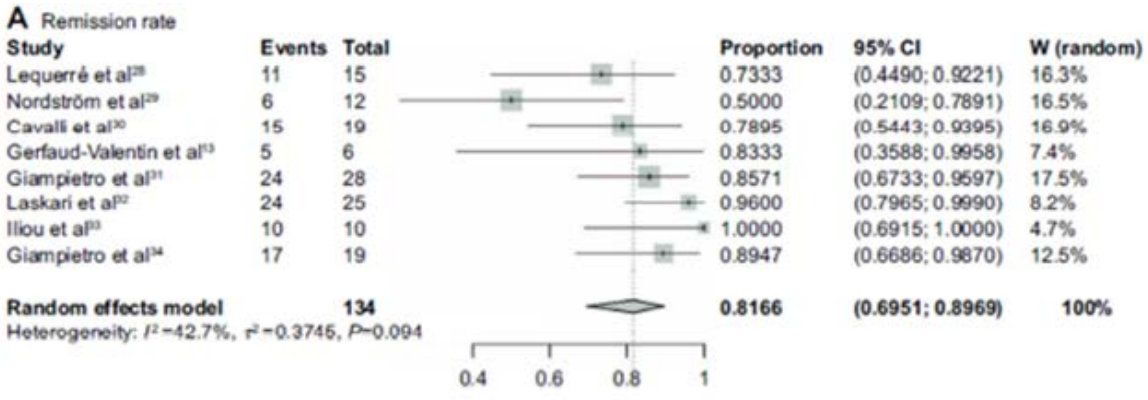
[a]At study entry.
[b]The study also describe 20 patients with SJIA treated with anakinra (see Table 2.7.3 - 12).
[c]Cavalli et al. 2013 was included as an abstract in the meta-analysis; the result from the full publication (Cavalli et al. 2015) is presented in Section 2.2.3.3, Table 2.7.3 - 2, Table 2.7.3 - 11, Table 2.7.3 - 15, Table 2.7.3 - 17, and Table 2.7.3 - 21.
DMARD= Disease modifying anti rheumatic drug; SD=Standard deviation; SJIA=Systemic idiopathic juvenile arthritis.

Meta-analysis efficacy results

Remission rate: For the calculation of remission rate, the number of patients with complete or partial response at the last follow-up in the anakinra group, and the total number of patients receiving anakinra, was used.

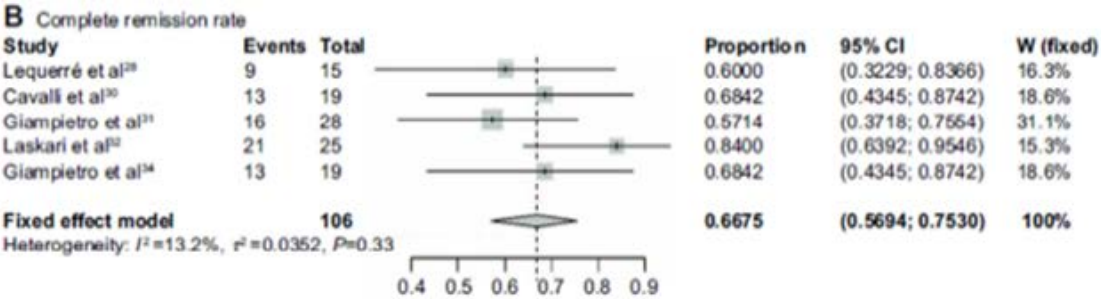
All 8 studies investigated the effect of anakinra in AOSD remission (Figure 11). The remission rate at latest follow-up ranged from 50 % to 100 %, with the remission rate estimated in all studies being 81.66 % (95 % CI: 69.51 % to 89.69 %).

Figure 11 – Remission rate (Hong et al. 2014)



Complete remission rate: For the calculation of complete remission rate, the number of patients with complete response at the last follow-up in the anakinra group, and the total number of patients receiving anakinra, was used. The complete remission rate was estimated in 5 studies (Figure 12). The complete remission rate ranged from 57 % to 84 %, with the complete remission rate estimated in the 5 studies being 66.75 % (95 % CI: 59.94 % to 75.3 %).

Figure 12 – Complete remission rate (Hong et al. 2014)



Responder rate

The effect of anakinra on responder rate in patients with Still´s disease with paediatric onset is summarized in Table 17. Across the other studies, the percentage of responders ranged between 55 % and 100 %, with a responder rate above 75 % in most studies.

Table 17 – Responders and non-responders during treatment in patients with Still's disease with paediatric onset

Study	Number of patients	Responders % (n)	Complete responders % (n)	Partial responders % (n)	Non-responders % (n)
Quartier et al. 2011	12 anakinra	67 % (8)	Not reported	Not reported	33 % (4)
	12 placebo	8 % (1)	Not reported	Not reported	92 % (11)
Vastert et al. 2014	20	80 % (16)	Not reported	Not reported	20 % (4)
Gattorno et al. 2008	22[a]	77 % (17)[b]	45 % (10)	32 % (7)	18 % (4)
Lequerre et al. 2008	20	55 % (11)[b]	30 % (6)	25 % (5)	45 % (9)
Pascual et al. 2005	9	100 % (9)[b]	78 % (7)	22 % (2)	0 % (0)
Nigrovic et al. 2011	46	98 % (45)[b]	59 % (27)	39 % (18)	2 % (1)
Pardeo et al. 2015	25	Not reported	56 % (14)	Not reported	Not reported
Marvillet et al. 2011	22	Not reported	73 % (16)	Not reported	Not reported
Irigoyen et al. 2006	14	Not reported	71 % (10)	Not reported	Not reported
Ohlsson et al. 2008	7	86 % (6)[b]	86 % (6)	0	14 % (1)
Total number of anakinra-treated patients	**197**				

Studies report response or remission. Remission is interpreted as complete response.
[a]One patient could not be classified in terms of response.
[b]Responders were further divided into complete and partial responders.
n=Number of responders or non-responders.

The effect of anakinra on responder rate in patients with Still´s disease with adult onset is summarized in Table 18. Across the other studies, the percentage of responders ranged between 73 % and 100 %, with a responder rate above 80 % in most studies. In 2 studies where only the percentage of complete responders was reported, this was 83 % and 92 %.

Table 18 – Responders and non-responders during treatment in patients with Still's disease with adult onset

Study	Number of patients	Responders % (n)	Complete responders % (n)	Partial responders % (n)	Non-responders % (n)
Nordstrom et al. 2012	12 anakinra	Not reported	50 % (6)	Not reported	Not reported
	10 DMARD	Not reported	30 % (3)	Not reported	Not reported
Laskari et al. 2011	25	96 % (24)[a]	84 % (21)	12 % (3)	4 % (1)
Lequerre et al. 2008	15	73 % (11)[a]	60 % (9)	13 % (2)	27 % (4)
Naumann et al. 2010	8	100 % (8)	100 % (8)	0	0
Giampietro et al. 2013	28	86 % (24)[a]	54 % (15)	32 % (9)	14 % (4)
Cavalli et al. 2015	20	80 % (16)[a]	70 % (14)	10 % (2)	20 % (4)
Giampietro et al. 2010	19	89.5 % (17)[a]	68.4 % (13)	21.1 % (4)	10.5 % (2)
Dall'Ara et al. 2016	13	Not reported	92 % (12)	Not reported	Not reported
Iliou et al. 2013	10	100 % (10)[a]	100 % (10)	0	0
Gerfaud-Valentin et al. 2014b	6	Not reported	83 % (5)	Not reported	Not reported
Total number of anakinra-treated patients	**156**				

Studies report response or remission. Remission is interpreted as complete response.
[a]Responders were further divided into complete and partial responders.
DMARD=Disease modifying anti rheumatic drug; n=Number of responders or non-responders.

Anakinra effect on additional measures of efficacy

Systemic signs and symptoms of inflammation

11 studies, comprising a total number of 230 paediatric anakinra-treated patients, reported the effect of anakinra on systemic signs and symptoms. In paediatric patients, there was a significant difference between anakinra and placebo with regards to normalization of fever and inflammatory markers after 1 month of treatment (67 % versus 8 %, p=0.003). In adult patients, there was a numerical difference between anakinra and DMARDs (50 % versus 30 %) in remission rate, which implies normalization of systemic signs and symptoms as this was a part of the definition of remission. However, no specific details of systemic signs and symptoms were provided in the study.

Table 19 – Normalization of systemic signs and symptoms during treatment in patients with Still's disease with paediatric onset

Study	Number of patients	Fever % (n)	Rash % (n)	Inflammatory markers % (n)
Quartier et al. 2011	12 anakinra 12 placebo	67 % (8) 8 % (1)	Not reported Not reported	67 % (8) 8 % (1) CRP, ESR, SAA
Vastert et al. 2014	20	90 % (18)	Not reported	90 % (18) CRP, ESR, ferritin
Gattorno et al. 2008	22[a]	45 % (10)	45 % (10)	45 % (10) CRP, ESR, ferritin
Lequerre et al. 2008	20	70 % (14)	70 % (14)	Not reported
Pascual et al. 2005	9	100 % (7 of 7)	Not reported	89 % (8) ESR
Nigrovic et al. 2011	46	97 % (35 of 36)	97 % (35 of 36)	84 % of 31 patients (CRP) 63 % of 30 patients (ESR) 83 % of 26 patients (ferritin)
Zeft et al. 2009	33	100 % (7 of 7)	100 % (7 of 7)	Significant decrease in mean ESR at 1 to 2 months, and 3 to 4 months
Pardeo et al. 2015	25	56 % (14)	56 % (14)	56 % (14) CRP, ESR, ferritin, neutrophils
Marvillet et al. 2011	22	82 % (18)	82 % (18)	Not reported
Irigoyen et al. 2006	14	100 % (3 of 3)	100 % (9 of 9)	Not reported
Ohlsson et al. 2008	7	Not specified	Not specified	86 % (6) ESR
Total number of anakinra-treated patients	**230**			

[a]One patient could not be classified in terms of response.
CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; n=Number of patients; SAA=Serum Amyloid A.

Eight studies, comprising a total number of 160 adult anakinra-treated patients, reported the effect of anakinra on systemic signs and symptoms. Across the studies, fever, rash and inflammatory markers normalized in 54 % to 100 % of patients. Normalization of fever and rash was seen within days and of inflammatory markers within weeks of therapy.

In 378 anakinra-treated patients in 18 uncontrolled studies, fever, rash and inflammatory markers normalized in 45 % to 100 % of patients. Normalization of fever and rash was seen within days and of inflammatory markers within weeks of therapy.

Arthritis

For SJIA patients, beneficial effects of anakinra on the arthritis components of the ACR score was specifically reported in four studies. In the MAH-sponsored study 990758 (Ilowite, 2009), the effect on arthritis was not specifically stated, however, 11 of 15 patients (73 %) were ACRpedi 30 responders at Week 12. A marked improvement was seen in tender joint count and swollen joint count in AOSD patients, in the three studies where this was evaluated. Some studies have suggested that non-responders to anakinra were more likely to have persistent disease with chronic long lasting arthritis.

Table 20 – Tender joint count and swollen joint count at anakinra onset and at last follow-up

Study	At start of anakinra	At last follow-up
Tender joint count		
Lequerre et al. 2008	8.5 (5.9)[a]	1.5 (2.7)[a]
Giampietro et al. 2013	3.6 (3.2)[a]	1.4 (2.9)[a]
Laskari et al. 2011	12 (0 to 38)[b]	Not applicable
Swollen joint count		
Lequerre et al. 2008	5.9 (5.8)[a]	0.9 (1.5)[a]
Giampietro et al. 2013	4.2 (4.5)[a]	1.53 (4.1)[a]
Laskari et al. 2011	1 (0 to 15)[b]	Not applicable

Source: Hong et al. 2014.
[a]Values depict mean (SD).
[b]Values depict mean (range).
SD=Standard deviation.

Glucocorticoid-sparing effect

Seven studies with a total of 152 paediatric anakinra-treated patients, reported the use of glucocorticoids at anakinra start and at study end. In paediatric studies reporting discontinuation of glucocorticoids, a total number of 12 of 43 patients (28 %) stopped glucocorticoid treatment completely. In studies reporting reduction in dosage of glucocorticoids, the majority of patients had tapered their dose of glucocorticoids at study end.

Table 21 – Glucocorticoid-sparing effect in patients with Still's disease with paediatric onset

Study	Number of patients	Glucocorticoid use at anakinra start % (n)	Glucocorticoid use during study
Quartier et al. 2011	12 anakinra 12 placebo	100 % (12) 100 % (12)	Glucocorticoid dose reduced in 12 patients. Glucocorticoid dose reduced in 3 patients.
Lequerre et al. 2008	20	100 % (20)	Glucocorticoid treatment stopped in 1 patients. Glucocorticoid dose reduced in 10 patients (by 15 % to 78 %).
Pascual et al. 2005	9	100 % (9)	Glucocorticoid treatment stopped in 1 patient. Glucocorticoid dose reduced in 6 patients.
Nigrovic et al. 2011	46	67 % (31)	Glucocorticoid treatment stopped in the majority of patients at Month 2.
Zeft et al. 2009	33	82 % (27)	Glucocorticoid dose significantly reduced.
Pardeo et al. 2015	25	56 % (14)	Glucocorticoid treatment stopped in 10 patients. Glucocorticoid dose reduced in 4 patients.
Ohlsson et al. 2008	7	100 % (7)	Glucocorticoid dose reduced to a median value of 0 mg/kg/day at 6 months (range 0 to 0.25 mg/kg/day).
Total number of anakinra-treated patients	**152**		

n=Number of patients receiving glucocorticoids.

A total of 191 adult anakinra-treated patients, reported the use of glucocorticoids at anakinra start and at study end. In studies reporting discontinuation of glucocorticoids, a total number of 24 of 65 patients

(37%) stopped glucocorticoid treatment completely. In studies reporting reduction in dosage of glucocorticoids, many patients had tapered their dose of glucocorticoids at study end.

Table 22 – Glucocorticoid-sparing effect in patients with Still's disease with adult onset

Study	Number of patients	Glucocorticoid use at anakinra start % (n)	Glucocorticoid use during study
Nordstrom et al. 2012	12 anakinra	100 % (12)	Glucocorticoid treatment stopped in 3 patients. Mean glucocorticoid dose reduced by Week 24[a].
	10 DMARD	100 % (10)	All patients still on glucocorticoid treatment. Mean glucocorticoid dose reduced by Week 24[b].
Laskari et al. 2011	25	88 % (22)	Glucocorticoid treatment stopped in 12 patients. Median glucocorticoid dose significantly reduced at each visit.
Lequerre et al. 2008	15	80 % (12)	Glucocorticoid treatment stopped in 2 patients. Glucocorticoid dose reduced in 8 patients (by 45 % to 95 %).
Naumann et al. 2010	8	100 % (8)	Glucocorticoid dose reduced in all patients.
Ortiz-Sanjuan et al. 2015	41	97.6 % (40)	Median glucocorticoid dose significantly reduced.
Giampietro et al. 2013	28	100 % (28)	Glucocorticoid dose reduced in 15 patients.
Cavalli et al. 2015	20	95 % (19)	Glucocorticoid treatment stopped in 7 patients. Glucocorticoid dose reduced in 8 patients.
Giampietro et al. 2010	19	100 % (19)	Glucocorticoid dose reduced.
Dall'Ara et al. 2016	13	100 % (13)	Glucocorticoid dose reduced.
Iliou et al. 2013	10	100 % (10)	Glucocorticoid dose reduced in 10 patients.
Total number of anakinra-treated patients	**191**		

[a]Mean glucocorticoid dose reduced by 10.8 prednisolone equivalents.
[b]Mean glucocorticoid dose reduced by 10.5 prednisolone equivalents.
DMARD=Disease modifying anti rheumatic drug; n=Number of patients receiving glucocorticoids.

In total, 17 studies, comprising a total number of 343 anakinra-treated patients, reported the use of glucocorticoids at anakinra start and at study end.

Early treatment with anakinra

It has been hypothesized that new-onset SJIA, characterized by excess IL-1 production, could give rise to an autoimmune T cell-driven arthritis. Based on the biphasic model proposed by Nigrovic 2014, effective blockade of IL-1 (or IL-6) in the early disease process could forestall the development of T cell autoimmunity and alter the long-term course of the disease.

In most published studies, patients generally had long-standing and refractory disease and were receiving systemic glucocorticoids and DMARDs when treatment with anakinra was initiated. Recent studies have investigated the timing of therapy and used anakinra as first-line therapy and in patients with new-onset disease. Early treatment has only been described in paediatric patients in the prospective uncontrolled study by Vastert et al. 2014 and in the retrospective uncontrolled studies by Nigrovic et al. 2011, Pardeo et al. 2015, and Marvillet et al. 2011.

IL-1 inhibition with anakinra early in the disease course was associated with positive outcome and appears to lead to reduction of the use of glucocorticoids (and therefore of the adverse effects associated

with glucocorticoids), as well as affect the natural course of the disease and reducing the risk of developing persistent arthritis.

Persistence of efficacy and/or tolerance effects

The published studies were not specifically design to study long-term treatment, however, 8 studies present efficacy of anakinra over time, with follow-up periods for more than 3 months.

Long-term efficacy of anakinra was shown in a total of 8 prospective and retrospective studies for up to 3 years in paediatric patients, and for up to nearly 6 years in adult patients, thus supporting the conclusion that treatment with anakinra in patients with Still´s disease provides long-term efficacy. Long-term efficacy of anakinra was not confirmed during the open continuation phase over 12 months in the Quartier et al. 2011 study.

There are no reports of the need to increase the dose over time due to development of tolerance.

Clinical studies in special populations

The effect of major demographic factors, including sex or ethnicity, or other intrinsic or extrinsic factors, such as disease severity, prior treatment, concomitant illness or drugs, alcohol, tobacco and body weight, has not systematically been reported in the published studies.

The efficacy of anakinra has been thoroughly described in this submission with regards to paediatric and adult patients with Still´s disease, but there are no specific studies available for the use of anakinra among elderly Still´s disease patients. However, elderly patients were included in the available studies.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The evidence to support an approval of anakinra for Still's disease with paediatric onset are two prospective, randomized, double-blind, placebo-controlled studies- one MAH-sponsored and one investigator-sponsored. Both were part of the approved PIP. Additionally a meta-analysis of available published data on efficacy and safety of anakinra in SJIA patients has been performed by the Applicant and a published meta-analysis including a randomized, active-controlled, open-label study (**Nordstrom et al, 2012**) in patients with adult-onset Still's disease to evaluate the effect and safety of anakinra in the adult population. A literature search has identified additional published studies. Altogether, evaluation of efficacy is based on 442 patients with Still's disease (245 paediatric and 197 adult) overall representative of the Still's disease population. Only a small number of SJIA patients were included in the randomized trials. Most of the data to support efficacy is from prospective and retrospective uncontrolled studies in patients with Still's disease.

The patients enrolled in the RCTs, prospective and retrospective studies are representative of the overall Still's disease population. The limited number of subjects in the randomized studies is supplemented by a substantial number of patients in uncontrolled studies. Though a publication bias is anticipated to some degree, overall the totality of patients evaluated for efficacy is notable.

Efficacy data and additional analyses

The meta-analysis demonstrated a short term (3 months) ACRpedi 30 response rate in the paediatric studies of 73 %, and in the adult studies at latest follow up a remission rate of 82 % and a complete

remission rate of 67%. In both paediatric and adult patients, a high proportion of the patients treated with Kineret markedly improved and complete remission was achieved in many patients. The efficacy results were consistent across the studies compared.

The proportion of non-responders was up to 45 % in one study, and treatment effect should be evaluated after 1 month. This is addressed in the SmPC. In case of persistent systemic manifestations dose may be adjusted in children or continued treatment with Kineret should be reconsidered by the treating physician.

Effect on other measures, including systemic signs of the condition and arthritis was also positive, though data were limited and reported inconsistently in the published studies. A glucocorticoid sparing effect was demonstrated across studies, though use, discontinuation and reduction of glucocorticosteroids were inconsistently reported across studies. Many patients could stop glucocorticoids completely, 28% of paediatric patients and 37 % of adult patients where this was reported, which is clearly beneficial due to the well-known side-effects, especially in chronic and long-term treatment

No patients younger than 2 years of age were included in the clinical studies. The proposed age and weight limit in the indication is in line with the CAPS indication, where PK, efficacy and safety data are available. For Still's disease, no specific efficacy or safety data are available for children younger than 2 years. In the literature, at least three patients younger than 2 years of age have been identified, and nine anakinra treated patients with Still's disease have been identified in the post-marketing safety database. There is a medical need in patients younger than 2 years of age, as the incidence of Still's disease peaks at the age of 2. Extrapolation of efficacy and safety of Kineret treatment in Still's disease from older children to children below the age of 2 is acceptable. PK of Kineret of children >= 8 months and > 10 kg has been established in the CAPS indication and since dosing is comparable in the Still' disease and CAPS indication alignment of the age limits of the other anakinra indications is acceptable.

Studies in adult patients with follow-up of 6 years and studies in paediatric patients with up to 3 year follow-up could demonstrate maintained effect, but in one of the randomized, controlled trials with active comparator (Quartier), the effect weaned over time.

Hypothetically early treatment could be advantageous, prevent development of T-cell autoimmunity and reduce the risk of developing chronic arthritis. Few studies have investigated the effect of anakinra in early treatment, and though the data are promising, they are not conclusive. Given the identified risks of Kineret and the undetermined effect of early treatment, Kineret is not indicated as first line treatment for patients with mild disease.

As such, the Kineret first-line indication is restricted to active Still's disease with moderate to high disease activity and second-line in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids.

Methotrexate was allowed in the company sponsored RCT and DMARDs were used in the clinical studies included to support the application. Kineret can be used as monotherapy or in combination with other anti-inflammatory drugs and DMARDs including methotrexate in accordance with clinical guidelines.

2.4.4. Conclusions on the clinical efficacy

The pathogenesis of Still's disease including hypersecretion of IL-1 and the mechanism of action of anakinra with IL-1 inhibition support the use of Anakinra for the condition.

Only three small randomized, prospective, controlled studies are available to support the efficacy of anakinra in Still's disease. However, an extensive literature search has identified a substantial number of publications adding up to more than 400 patients with Still's disease, which is a rare condition.

Overall, all results point in the same direction of efficacy of anakinra in both paediatric and adult patients with Still's disease. During assessment it was clarified that the majority of subjects included in the studies where patients with active systemic features of moderate to high disease activity, or with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids. The indication was therefore restricted to reflect the available evidence of efficacy. Remission is achieved in the majority of patients and most patients seem to have an effect on the systemic signs and symptoms associated with the condition. Anakinra also appears to have a glucocorticoid-sparing effect. The effect on clinical efficacy endpoints is supported by the effect on markers of IL-1 activity, with a decrease in CRP and other inflammatory markers.

2.5. Clinical safety

Introduction

The safety evaluation of anakinra is based on exposure in patients with Still's disease, as well as in patients with RA, JIA, CAPS, and other indications where anakinra have been used for many years. Although anakinra has not been approved for treatment of SJIA, usage of anakinra is widely documented in the literature. The safety during this real-world usage is captured in the literature search performed for this application.

Safety information about anakinra treatment in Still's disease with paediatric and adult onset comes from the following sources:

- The MAH-sponsored study 990758 with open label extension (990779) in 86 JIA patients, including a subgroup of 15 SJIA patients
- 504 patients with Still's disease with paediatric onset (289 patients) and with adult onset (215 patients) presented in publications identified in a literature search performed September 30, 2016. Studies presenting safety data in patients who had received at least one dose of anakinra was included in the safety analysis. Patients described in the literature on an individual basis are handled as medically confirmed ICSR and included in the Sobi post-marketing safety database. The safety information of these patients are part of the post-marketing evaluation.
- The Sobi post-marketing safety database including more than 566 medically confirmed ICSRs where the indication for anakinra treatment was Still's disease in adult or paediatric patients (data lock point September 30, 2016).

Additional safety data in patients treated for RA, CAPS, and other indications include:

- 8518 patients with various indications since the initiation of anakinra clinical studies in May 1994.
- Pooled safety data from MAH-sponsored studies in 3330 adult RA patients, whereof 2372 received anakinra and 958 placebo. More than 140 patients were treated with anakinra doses of ≥150 mg/day.
- Data from a prospective open-label study of anakinra in 43 patients with NOMID, whereof 36 were younger than 18 years of age.
- Approximately 2300 medically confirmed ICSRs from the Sobi post-marketing safety database where the indication for anakinra treatment was other than Still's disease.

Investigation of the safety of anakinra in the paediatric population is supported by the safety evaluation in study 03-AR-0298 in patients with severe CAPS. The safety in the adult population is supported with the substantial safety information collected in MAH-sponsored studies in RA, as well as during post-

marketing use since the approval 2001.

Publications describing individual patients have been excluded since the safety information in these patients are included in the Sobi post-marketing safety database as medically confirmed Individual Case Safety Reports (ICSR). However, there may still be a risk for overlap i.e. some AEs may be reported twice.

Patient exposure

Exposure in Still's disease

Safety data have been obtained from a total of 504 patients with Still´s disease (289 paediatric and 215 adult patients), exposed to anakinra in the studies identified for this application (table 23 and 24). The ages span from 0.75 to 17 years in the paediatric patients, and the majority of patients with adult onset were between 30 and 40 years of age, ranging up to 73 years of age. The mean disease duration varies greatly across the studies, from 0.06 to 24.1 years.

Table 23 – SJIA reports/publications including safety data

Study	Study design	No. of anakinra treated patients
990758/990779 (Ilowite et al. 2009)	Prospective randomized double-blind, placebo-controlled	15 SJIA/71 JIA
Quartier et al. 2011	Prospective randomized, double-blind placebo-controlled	22
Vastert et al. 2014	Prospective uncontrolled study	20
Gattorno et al. 2008	Prospective uncontrolled study	22
Lequerre et al. 2008	Prospective uncontrolled study	20
Pascual et al. 2005	Prospective uncontrolled study	9
Nigrovic et al. 2011	Retrospective uncontrolled study	46
Zeft et al. 2009	Retrospective uncontrolled study	33
Rossi-Semerano et al. 2015	Retrospective uncontrolled study	27
Pardeo et al. 2015	Retrospective uncontrolled study	25
Marvillet et al. 2011	Retrospective uncontrolled study	22
Irigoyen et al. 2006	Retrospective uncontrolled study	14
Ohlsson et al. 2008	Retrospective uncontrolled study	7
Hedrich et al. 2012	Retrospective uncontrolled study	4
Canna et al. 2009	Case studies	3
Total No. of SJIA patients		289

JIA= juvenile idiopathic arthritis; No.=Number; SJIA=Systemic juvenile idiopathic arthritis.

Table 24 – AOSD publications including safety data

Study	Study Design	No. of anakinra treated patients
Nordstrom et al. 2012	Prospective randomized, active controlled open-label study	16
Laskari et al. 2011	Prospective uncontrolled study	25
Lequerre et al. 2008	Prospective uncontrolled study	15
Ortiz-Sanjuan et al. 2015	Retrospective uncontrolled study	41
Rossi-Semerano et al. 2015	Retrospective uncontrolled study	35
Giampietro et al. 2013	Retrospective uncontrolled study	28
Cavalli et al. 2015	Retrospective uncontrolled study	20
Giampietro et al. 2010	Retrospective uncontrolled study	19
Iliou et al. 2013	Retrospective uncontrolled study	10
Gerfaud-Valentin et al. 2014b	Retrospective uncontrolled study	6
Total No. of AOSD patients		215

AOSD=Adult onset Still´s disease; No.=Number.

Exposure to anakinra in the Still's disease population in MAH-sponsored studies is limited to one study (990758/990779/Ilowite et al, 2009) with 15 paediatric patients where a daily anakinra dose of 1 mg/kg (maximum 100 mg) was used. No dose adjustments were allowed. The exposure was 15.6 patient-years in the 15 SJIA patients. In the total safety population of 86 patients, the exposure was 62.8 patient-years.

The doses in the majority of published studies of paediatric patients were 1 to 2 mg/kg/day s.c. (maximum 100 mg/day). Dose escalations up to 11 mg/kg/day without reported safety problems have been described (Nigrovic et al. 2011). There is insufficient detail of treatment durations in some studies with only median values or ranges being reported.

The dose in all published studies of patients with adult onset was 100 mg/day.

Exposure in other indications

Anakinra has been approved in EU since 2002 for the treatment of the signs and symptoms of RA in combination with methotrexate, in adults with an inadequate response to methotrexate alone. Up to the data lock point for collection of safety data (September 30, 2016), the estimated exposure to anakinra in MAH-sponsored clinical studies is 6404 patient-years, which was generated in 8518 subjects. The majority of study subjects were patients with RA. The post-marketing exposure across all indications has been estimated to be 87,969 patients-years.

In study 03-AR-0298 in patients with severe CAPS, the treatment duration was up to 5 years in 43 patients, corresponding to 159.8 patient-years of anakinra exposure. Most patients (60.5 %) were exposed >4 years, and 91 % of the patients were exposed >1 year.

Adverse events

Analyses of the most common AEs can only be performed for study 990758/990779.

Adverse events in study 990758/990779

AE information was obtained when the patients came for scheduled visits. The information was coded in World Health Organization Adverse Reactions Terminology (WHO-ART).

Table 25 – Overview of adverse events study 990758/990779 (SJIA safety population)

	990758 Open Label (N = 15, TDUR = 3.1)		990758+990779 Blinded anakinra (N = 10, TDUR = 2.8)		990758+990779 Blinded Placebo (N = 3, TDUR = 0.5)		990779 Open Label (N = 10, TDUR = 9.7)	
Category	**n (%)**	**F (R)**	**n (%)**	**F (R)**	**n (%)**	**F (R)**	**n (%)**	**F (R)**
Any treatment-emergent AE	14 (93.3)	66 (21.3)	6 (60.0)	44 (15.9)	2 (66.7)	12 (23.7)	9 (90.0)	69 (7.1)
Severe treatment-emergent AE	0	0	1 (10.0)	1 (0.4)	0	0	1 (10.0)	3 (0.3)
Death	0	0	0	0	0	0	0	0
Other serious AE	0	0	0	0	0	0	1 (10.0)	2 (0.2)
AE leading to permanent discontinuation of study drug	1 (6.7)	1 (0.3)	0	0	0	0	0	0
AE leading to temporary discontinuation of study drug	0	0	0	0	0	0	0	0

T_AE_OVERS.SAS 2013-09-27T12:35:29 Z9FRBE
n=Number of patients; F=Number of adverse events, R=Number of events divided by total duration of treatment across all patients; TDUR=Total duration of follow-up across all patients in years.

Yearly AE reporting rates in the SJIA population decreased over time. Most treatment-emergent AEs were reported during the open-label phase of study 990758 (66 AEs in 14 patients), giving an AE reporting rate of 21.3 events/patient year.

AE reporting rates were higher for placebo than for anakinra treated SJIA patients during the blinded phase; 23.7 vs. 15.9, respectively. However, as there were only 3 patients exposed to placebo no conclusions can be drawn. The reporting rate decreased to 7.1 events/patient year (69 AEs in 9 patients) in patients continuing in the open-label phase of study 990779.

There were 2 SAEs in one patient during the 990779 open-label phase.

One patient discontinued study drug permanently on Day 1 of the 990758 open-label phase due to an AE (ISR). There were no discontinuations due to AEs in patients treated with placebo.

In the total study population of both SJIA and JIA patients, AE reporting rates were similar for anakinra and placebo during the blinded phase, 12.7 and 15.1 events/patient-year, respectively, and decreased to 5.7 (204 AEs in 30 patients) in the patients continuing in the open-label phase in study 990779.

In total there were 7 SAEs, all on anakinra: 3 events in 3 patients during the open-label 990758 phase, 1 event during the blinded phase, and 3 events in 2 patients during the open-label 990779 phase (Table 26).

Table 26 – Overview of adverse events in study 990758/990779, total safety population

Adverse event	990758 Open-label anakinra (N=86 PYRS=18.80)			990758 + 990779 Blinded anakinra (N=33 PYRS=8.42)			990758 + 990779 Blinded Placebo (N=28 PYRS=6.55)			990779 Open-label anakinra (N=44 PYRS=35.54)		
	No. of patients N (%)	No. of events F	Rate	No. of patients N (%)	No. of events F	Rate	No. of patients N (%)	No. of events F	Rate	No. of patients N (%)	No. of events F	Rate
Any treatment-emergent AE	80 (93.0)	541	28.8	21 (63.6)	107	12.7	21 (75.0)	99	15.1	30 (68.2)	204	5.7
- Severe treatment-emergent AE	8 (9.3)	10	0.5	2 (6.1)	2	0.2	1 (3.6)	1	0.2	3 (6.8)	5	0.1
- Death	0	0	0	0	0	0	0	0	0	0	0	0
- Other serious AE	3 (3.5)	3	0.2	1 (3.0)	1	0.1	0	0	0	2 (4.55)	3	0.1
- AE leading to permanent discontinuation of study drug	4 (4.6)	7	0.4	1 (3.0)	1	0.1	0	0	0	3 (6.8)	3	0.1
- AE leading to temporary discontinuation of study drug	0	0	0	1 (3.0)	1	0.1	0	0	0	2 (4.55)	3	0.1

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

Adverse events in published studies in Still's disease

The most common AEs reported in Still's disease with paediatric onset were ISR. The incidence of ISRs appears to decrease as therapy continues. Only in a minority of ISRs caused the patients to stop anakinra treatment *Infections* were also a commonly reported AE, both bacterial and viral. These were generally not serious. No injection site infections were reported. Table 27 14 summarizes AEs reported in the published studies.

Table 27 – Summary of AEs in published safety studies in Still's disease with paediatric onset

Study	No. of pts.	No. of ISRs	No. of infections	No. of MAS	Other AEs	Comments
Randomized double-blind placebo controlled study						
Quartier et al. 2011; controlled phase	12	11	2	No reports	No reports	
Quartier et al. 2011; extension phase	22	21	48	No reports	22	Vomiting, abdominal pain (n=9). ,skin lesions (n=5), hematuria (n=2), back pain (n=2), dental fracture, asthenia, vertigo Sudden elevation of transaminases (1 patient).
Prospective studies						
Gattorno et al. 2008	22	No. not specified	No reports	2	No reports	
Vastert et al. 2014	20	13	Several	No reports	No reports	
Lequerre et al. 2008	20	18	5	No reports	Several	
Pascual et al. 2005	9	9	No reports	No reports	4	Two episodes of hypotension and vomiting with negative viral and bacterial cultures in 1 patient who had underlying myocardial dysfunction occurred during treatment. Therapy was restarted after resolution of the symptoms without complications.
Retrospective studies						
Nigrovic et al. 2011	46	20	6	5	4	45 patients with evaluable data Eosinophilic hepatitis required discontinuation of therapy in an 8-year-old patient receiving anakinra at 1.5 mg/kg/day; this patient is also described by Canna et al. 2009. Elevation of liver enzymes under anakinra treatment was noted in 2 additional patients, but therapy could be continued. A 9-month-old infant developed mild asymptomatic neutropenia (ANC 500 cells/µl) which resolved with alternate-day dosing.
Zeft et al. 2009	33	18	1	1	3	1 neutropenia (neutrophils>0.9x10^3/l). The patient also experienced one episode of MAS Transient hives within weeks of therapy occurred in 2 patients

Study	No. of pts.	No. of ISRs	No. of infections	No. of MAS	Other AEs	Comments
Rossi-Semerano et al. 2015	26	-	-	-	-	In this report, the use of anakinra is described across a variety of off-label indications. The adverse events are not presented per indication. This publication relates to 185 patients where anakinra was used at least once in any indication.
Pardeo et al. 2015	25	2	No reports	0	No reports	
Marvillet et al. 2011	22	0	2	2	1	1 patient stopped treatment due to severe skin reaction. Location not reported.
Irigoyen et al. 2006	14	Frequent	No reports	No reports	No reports	
Ohlsson et al. 2008	7	3	3	No reports	No reports	
Hedrich et al. 2012	4	3	1	1	No reports	
Individual case series						
Canna et al. 2009	3	No reports	No reports	No reports	3	3 patients with hepatitis treated with anakinra were selected for this case study 1 patient is also included in Nigrovic et al. 2011

AE=Adverse event; ISR=Injection site reaction; MAS=Macrophage activation syndrome; No.=Number; pts=Patients.

Few AEs were reported in the studies in Still's disease with adult onset. The majority of reports including ISRs were non-serious and did not lead to discontinuation of anakinra. Infections were also reported, and as with the ISRs the majority of patients reporting infections did not permanently stop anakinra treatment.

Table 28 summarizes AEs reported from 12 AOSD patients in a randomized open-label study and from 164 patients in other published studies identified for this submission.

Table 28 – Summary of AEs in published studies in Still's disease with adult onset

Study	No. of pts.	No. of ISRs	No. of infections	No. of MAS	Other AEs	Comment
Randomized open label study						
Nordstrom et al. 2012	16	8	No reports	No reports	Nos. not reported	Other adverse events during the study included flu-like symptoms, diarrhea, and myalgias.
Prospective studies						
Laskari et al. 2011	25	0	7	No reports	3	3 of the 25 patients were withdrawn due to severe urticarial reactions after 1.5 to 3 months of treatment
Lequerre et al. 2008	15	1	4	1	3	2 withdrawals due to skin rash after 1 month and 3 months, respectively. 1 osteonecrosis of the femoral hip considered related to long-lasting corticosteroid treatment by the investigator.
Retrospective studies						
Ortiz-Sanjuan et al. 2015	41	6	5	No reports	6	In 2 patients, therapy was permanently discontinued due to cutaneous reactions; in 6 patients, the reactions were mild and only localized to the injection site. 1 patient experienced myopathy with elevation of muscle enzymes and had to stop anakinra treatment. 3 mild leukopenia
Giampietro et al. 2013	28	Several	No reports	No reports	No reports	
Cavalli et al. 2015	20	2	2	No reports	No reports	
Giampietro et al. 2010	19	Several	No reports	No reports	No reports	
Iliou et al. 2013	10	No reports	No reports	No reports	No reports	
Gerfaud-Valentin et al. 2014b	6	1	No reports	No reports	No reports	

AE=Adverse event; ISR=Injection site reaction; MAS=Macrophage activation syndrome; No.=Number; pts=Patients.

Common adverse events in study 990758/990779

The most common AEs in SJIA patients during the open-label phase in study 990758 were various types of ISRs, followed by rash and headache, both with an AE reporting rate of 1.3 events/year. Most AEs were of mild or moderate severity. There were no SAEs or discontinuations due to headache.

The yearly AE reporting rates in the open-label 990779 phase were generally lower than in other study phases. The most common AE was fever, 9 episodes occurred in 7 patients (rate 0.9 events/year), followed by arthralgia and abdominal pain, both with a yearly reporting rate of 0.6. All 3 types of events were reported only as being of mild or moderate severity.

The most common AEs in the total JIA population during the open-label phase in study 990758 were various types of ISRs, upper respiratory infections) and headache, all with an AE reporting rate of 1.9 events/patient/year. Other common AEs were fever and arthralgia, both with an AE reporting rate of 1.1. Most AEs were of mild or moderate severity.

Serious adverse event / deaths / other significant events

Deaths

No patient died during study 990758/990779.

In the total Sobi safety data base, 28 patients treated with anakinra for Still's disease suffered a fatal SAE. In the majority of reports there are multiple confounding factors, and no clear causal relationship between anakinra and the events can be established.

Serious adverse event

SAEs in Still´s disease with paediatric onset

SAEs reported in study 990758/990779 and in the published studies are summarized in Table 29 and Table 30, respectively. The most common SAEs were infections and, in published studies, MAS.

Table 29 – Summary of SAEs in the total study population in study 990758/990779

Phase of study	No. of Patients	No. of patients with SAE	Details
Open-label phase 990758	86	3 (3.5 %)	Fracture (1 patient), bacterial infection (1 patient), papilledema (1 patient). None considered treatment-related, all patients continued in the study.
Blinded phase, anakinra treated patients	33	1 (3.0 %)	Herpes zoster.
Open-label phase 990779	44	2 (4.5 %)	Nephrosis (1 patient), considered treatment-related, patient withdrew.
			Hepatitis (due to CMV infection) and viral infection in one patient (SJIA patient), neither SAE considered related to treatment.

CMV=Cytomegalovirus; No.=Number; SAE=Serious adverse event; SJIA=Systemic juvenile idiopathic arthritis.

Table 30 – Summary of SAEs in published studies in Still's disease with paediatric onset

Study	No. of pts treated with anakinra	No. of patients with SAE	Details
Randomized double-blind placebo controlled study			
Quartier et al. 2011; randomized controlled phase	12	0 (0 %)	No SAEs reported
Quartier et al. 2011; extension phase	22	6 (27 %)	Infections: 4 patients (all continued in study), Crohn's Disease: 1 patient (withdrew), vertebral collapse: 1 patient (continued in study)
Prospective studies			
Gattorno et al. 2008	22	2 (9 %)	2 patients with MAS (both discontinued, one re-treated without MAS recurrence)
Vastert et al. 2014	20	0 (0 %)	
Lequerre et al. 2008	20	1 (5 %)	1 patient withdraw due to an SAE; visceral leishmaniasis. This serious adverse event occurred during month 6 of anakinra treatment. Anakinra treatment was stopped, and treatment specific for leishmaniasis was started and resulted in a favorable outcome. SJIA became active again following treatment withdrawal and anakinra was restarted.

Study	No. of pts treated with anakinra	No. of patients with SAE	Details
Pascual et al. 2005	9	0 (0 %)	Two episodes of hypotension and vomiting with negative viral and bacterial cultures in 1 patient who had underlying myocardial dysfunction occurred during treatment. Therapy was restarted after resolution of the symptoms without complications.
Retrospective studies			
Nigrovic et al. 2011	46	7 (15 %)	45 evaluable patients MAS: 5 episodes in 4 patients during treatment, 3 serious infections. (There were also 6 MAS episodes in 6 patients at presentation before anakinra treatment.)
Zeft et al. 2009	33	3 (9.1 %)	1 MAS 1 acute EBV infection. 1 injection site sterile abscesses, which left hyperpigmented scars. .
Rossi-Semerano et al. 2015	26	5 (19 %)	In this report, the use of anakinra is described across a variety of indications. The adverse events are not presented per indication. This publication relates to 185 patients where anakinra was used at least once in any indication. Overall, 9 % of patients presented an SAE, mainly severe infection (5.1 %), with no difference in frequency between pediatric and adult patients. 5 patients with SJIA experienced SAEs. 1 patient treated with anakinra 2 mg/kg/day experienced severe toxidermia associated chronic myocarditis after 156 days of treatment; the patient died 3 days after anakinra withdrawal due to disease flare with acute myocarditis. 3 patients experienced MAS and 1 scarlet fever
Pardeo et al. 2015	25	0 (0 %)	
Marvillet et al. 2011	22	3 (14 %)	1 patient stopped due to severe skin reaction 1 patients stopped due to severe pneumonia 2 patients with MAS
Irigoyen et al. 2006	14	0 (0 %)	
Ohlsson et al. 2008	7	3 (43 %)	1 patient developed gastroenteritis with pre-renal failure requiring inotropic support one month after starting anakinra. 1 patient developed a chronic cough with clubbing one year after starting anakinra. Lung biopsy showed changes secondary to adenovirus infection. The patient also developed varicella pneumonitis requiring hospital admission 2 years after starting anakinra.
Hedrich et al. 2012	4	0 (0 %)	1 patient developed MAS 2 weeks after start of anakinra concomitantly with positive evidence of HHV6 infection. The patient remained on anakinra treatment
Individual case studies			

Study	No. of pts treated with anakinra	No. of patients with SAE	Details
Canna et al. 2009	3	3 (100 %)	3 patients with hepatitis treated with anakinra were selected for this case study Patient 1 had no liver function test elevations prior to treatment with anakinra, while patient 2 had mild transaminitis with MAS just prior to initiation of anakinra, and patient 3 had multiple bouts of transaminitis with flu-like illnesses both before and after her acute hepatitis. After development of abdominal pain in all patients and jaundice in 2 patients, acute hepatitis was diagnosed between 44 and 250 days after initiation of anakinra treatment. Patient 1 also had a prolongation of prothrombin time. Liver biopsies had mixed inflammatory infiltrates with associated hepatocellular injury suggestive of an exogenous trigger. In all patients, hepatitis persisted despite cessation of known hepatotoxic drugs until discontinuation of anakinra. Cessation of anakinra resulted in rapid improvement of liver enzymes, but two patients experienced a SJIA flare. Patients 1 and 2 were restarted on anakinra for refractory disease, without further liver problems. 1 patient is also included in Nigrovic et al. 2011.
TOTAL	**273**	**33 (12 %)**	

No.=Number; MAS=Macrophage activation syndrome; SAE=Serious adverse event; SJIA=Systemic juvenile idiopathic arthritis.

There were 6 patients with JIA that experienced 7 SAEs during study 990758/990779, whereof 1 patient with SJIA experienced 2 of the SAEs. Various serious infections constituted the most common type of SAEs, 4 out of 7 (Table 29). There are no indications of a different SAE risk or profile in SJIA patients compared to the total safety population of the study.

SAEs were reported for 33 out of 273 (12 %) patients in the published studies (Table 30). MAS is identified here as an SAE but has a known association with SJIA (Sawhney et al. 2001). There were 14 reports of MAS in 13 patients. The majority continued or re-started anakinra without recurrence of MAS. There were no reports of MAS in the 2 randomized trials.

The study by Canna et al. 2009 specifically investigated SJIA patients with hepatitis who were taking IL-1 RA and hence the 100 % result for the proportion of patients with this event. One of the Canna et al. 2009 patients was also reported by Nigrovic et al. 2011. 2 patients restarted anakinra without further liver events.

The SAE profile in study 990758/990779 is similar to that seen in published articles included in this application and in studies of adult RA patients. With the exception of MAS, the types of SAEs seen in anakinra treated SJIA patients concur with the known safety profile of anakinra.

SAEs in Still´s disease with adult onset

The most commonly described events leading to anakinra discontinuation are various types of skin reactions.

Infections, bacterial and viral, are described both as SAEs, severe AEs and as cause for temporary or permanent withdrawal of anakinra treatment. Only 2 events of MAS are described, possibly indicating a lower frequency of MAS in adult Still's patients compared to paediatric.

Table 31 – Summary of SAEs in published studies in Still's disease with adult onset

Study	No. of pts treated with anakinra	No. of events reported as SAEs	Details
Randomized open label study			
Nordstrom et al. 2012	16	1	1 patient withdrew during the randomized phase due to a disease flare (reported as SAE), but continued in the open-label extension with combined anakinra and MTX.
Prospective studies			
Laskari et al. 2011	25	0	3 patients withdraw due to severe urticarial reactions
Lequerre et al. 2008	15	0	2 patients withdrew due to skin rash after 1 month and 3 months, respectively. 1 varicella and MAS leading to transient anakinra withdrawal 1 event each of bronchitis 1 uncomplicated hepatitis A 1 cutaneous infection after a piercing 1 osteonecrosis of the femoral hip. The osteonecrosis was considered related to long-lasting corticosteroid treatment by the investigator.
Retrospective studies			
Ortiz-Sanjuan et al. 2015	41	0	2 withdrawn due to cutaneous reactions 1 withdrawn due to phalanx osteomyelitis 1 withdrawn due to respiratory tract infection (pseudomonas aeruginosa) and an abscess in a gluteal muscle. 1 withdrawn due to myopathy with elevation of muscle enzymes
Rossi-Semerano, 2015 #276	35	3	1 pneumonia, 1 VZV infection, and 1 MAS and with a concomitant infection
Giampietro et al. 2013	28	0	2 withdrawn due to rash at the site of injections
Cavalli et al. 2015	20	0	
Giampietro et al. 2010	19	0	1 withdrawn due to rash at the site of injection
Ilicu et al. 2013	10	0	
Gerfaud-Valentin et al. 2014b	6	0	
Total	**211**	**4 (0.2 %)**	

MAS= Macrophage activation syndrome; MTX=Methotrexate; No.=Number; SAE=Serious adverse event.

Significant adverse events

Infections

In the total study population described in study 990758/990779, serious infections were uncommon and there were no indications of an increasing frequency of infectious episodes over time, rather the frequency tended to be lower during the latter part of the study. Younger patients and females seemed to be more affected by infectious episodes, however, the reason for this is not clear.

Upper respiratory tract infections were the most commonly reported infectious events.

There are no indications that the sub-group of SJIA patients has a different safety profile with regard to infectious episodes compared to the full population in study 990758/990779. Infections were reported in

most published studies, both in paediatric and adult patients with Still's disease. Most were non-serious, but a small number were serious and required temporary or permanent withdrawal of anakinra treatment.

An increased risk for serious infections has been associated with anakinra and the current data support that this is true also for patients with Still's disease. Infections are well recognized triggers for MAS in patients with Still's disease. This should be taken into account when deciding on discontinuing anakinra treatment during a severe infection.

In conclusion, there are no indications of relevant differences in the frequency of non-serious and serious infections between Still's patients and other populations treated with anakinra. In addition to routine post-marketing safety surveillance reports, all serious infections are systematically reviewed by Sobi at the individual case level.

Injections site reactions

Different types of ISRs are generally the most commonly reported AEs in the studies included in this submission. In post-marketing safety surveillance reports, ISRs are also the most frequently reported events. In general, ISRs are most frequent in the paediatric population and least frequent in elderly. The vast majority of reported ISRs, both in clinical studies and in reports from post-marketing use, are non-serious and of mild to moderate intensity. ISRs typically appear within 2 weeks of therapy and disappear within 4 to 6 weeks, as reported in RA studies. The early appearance and subsequent disappearance applies also to Still's patients. It is notable that only few patients were described to have discontinued treatment due to ISRs.

It is known that cooling of the injection site, warming the injection liquid, use of cold packs (before and after the injection), and use of topical corticosteroids and antihistamines after the injection can alleviate the signs and symptoms of ISRs. No measures used to alleviate ISRs are described either in published studies or in study 990758/990779, possibly because the effects of such measures were unknown at the time when several of the studies were performed.

MAS (macrophage activation syndrome)

MAS is identified as an SAE although it has a known association with Still's disease, especially SJIA (Ravelli et al. 2015). In the total Still's disease population included in the literature search, consisting of 505 patients, there are 15 reports of MAS in 14 patients treated with anakinra. 13 of the patients with MAS episodes were paediatrics.

Details are provided in Table 32. In the 3 randomized trials there are no reports of MAS either in patients treated with anakinra or control drug.

Table 32 – Reports of MAS in studies in Still's disease with paediatric onset

Study	No of pts.	No. of MAS	Comment:
Gattorno et al. 2008	22	2	On day 13 of treatment, 2 patients (patients S11 and S21) presented with laboratory features consistent with MAS, i.e., marked elevation of liver enzyme, ferritin, and triglyceride levels, and decreased platelet count. Both patients discontinued anakinra and were treated with steroids and cyclosporine A, with rapid control of the MAS. 6 months later, patient S11 was re-treated with anakinra for a relapse of his underlying disease, without any further sign of MAS. The parents of patient S21 did not allow reinstitution of the treatment with anakinra after complete control of MAS was achieved.
Nigrovic et al. 2011	46	5	45 evaluable patients. MAS was observed on 5 occasions in 4 patients after initiation of anakinra: 1 patient on anakinra 1.2 mg/kg/day with abrupt discontinuation of steroids 2 weeks into therapy; 1 patient on anakinra 1.3 mg/kg/day developed Epstein-Barr virus infection 4 months into therapy; 1 patient on anakinra monotherapy 1.6 mg/kg/day had 2 episodes MAS at 5 and 8 months The patient was treated with cyclosporine A and corticosteroids. Anakinra was withheld for 2 days during the 2nd episode but was then restarted; 1 patient presented with MAS had received corticosteroids, cyclosporine, and anakinra 1.6 mg/kg/day. The patient developed a second episode on day 18 that responded to corticosteroids and anakinra at 2.2 mg/kg/day.
Zeft et al. 2009	33	1	One patient developed MAS while receiving anakinra at 1.1 mg/kg.
Rossi-Semerano et al. 2015	26	3	In this report, the use of anakinra is described across a variety of indications. The adverse events are not presented per indication. This publication relates to 185 patients where anakinra was used at least once in any indication. 3 patients with SJIA experienced MAS
Marvillet et al. 2011	22	2	8 episodes were present at the time of SJIA diagnosis, and 2 while receiving anakinra.
Hedrich et al. 2012	7	1	A 2.75-year-old patient initially responded to anakinra (4 mg/kg) within 10 days, but relapsed after 2 weeks and developed MAS when he also presented with positive evidence of HHV6 infection. Prednisolone was added and tapered over the following weeks. The patient remained on anakinra during and after the MAS episode.

MAS=Macrophage activation syndrome; SJIA=Systemic juvenile idiopathic arthritis.

As described in several publications, infections are well recognized triggers for MAS in Still's disease patients. This should be taken into account when deciding on discontinuing anakinra treatment during a severe infection. The majority of Still's patients with MAS episodes described in the literature continued or re-started anakinra treatment without recurrence of MAS.

Anakinra, with or without additional immunosuppressive therapy, has been used for successful treatment of MAS (Minoia et al. 2014, Miettunen et al. 2011) Also in patients already treated with anakinra when developing MAS, an increase of the anakinra dose can help alleviating the MAS, as described by e.g. Nigrovic et al. 2011.

A causal relationship between anakinra and MAS has not been established.

Laboratory findings

Clinical chemistry, haematology, and urinalysis were systematically reported for JIA and SJIA patients in study 990758/990779. A total of 4 SJIA patients experienced laboratory toxicities of grade 3 during anakinra treatment.

Open-label phase Study 990758 and the blinded phase: One SJIA patient experienced a haemoglobin toxicity grade 3 on study Day 1, haemoglobin was 73 g/L. The patient discontinued the study on the same day due to an AE of injection site pain. One SJIA patient experienced a calcium toxicity grade 3 on study Day 200, with calcium of 1.6 mmol/L. The patient continued anakinra treatment and completed the whole study. Another SJIA patient experienced an albumin toxicity grade 3 while receiving anakinra; albumin was 20 g/L. This patient discontinued the study 2 weeks later due to a disease flare. Both patients received anakinra when the toxicities occurred.

Another SJIA patient experienced 2 haemoglobin toxicities grade 3 while on placebo.

One JIA patient experienced transient neutropenia (neutrophils < 1.0 x 109/L) on Day 141 (blinded phase) with a count of 0.79 x 109/L while on anakinra; the count recovered to 1.0 x 109/L by the next study visit. The neutropenia was not associated with an SAE or infection.

Another JIA patient experienced a grade 4 increase in calcium during the open label phase. The subject had been taking a calcium supplement prior to the increase.

A third JIA patient experienced an ALT toxicity grade of 3 while on anakinra. This was reported as a non-serious unrelated AE. In addition this patient had another non-serious adverse event of PT “Hepatic function abnormal” one month later. Both events resolved and were considered mild and not related to anakinra treatment by the investigator. During the blinded phase, while on anakinra, the same patient experienced another ALT toxicity grade of 4 and a concomitant AST toxicity grade of 3. In none of the 3 cases was there a concomitant increase of bilirubin above the upper reference limit. The patient continued anakinra treatment and completed the study after a total of 442 days.

Open-label Study 990779: No clinically relevant trends were observed in laboratory parameters during the open-label study 990779.

Transient neutropenia occurred in one SJIA patient on Day 176 with a count of 0.91 x 109/L; the count recovered to above 1.0 x 109/L by the next study visit and was not associated with any clinical sequelae. The patient completed the whole study.

Another SJIA patient experienced an AST toxicity grade 3 on Day 183 with concomitant increases in ALT, ALP and bilirubin. The increases in liver tests coincided with the patient’s SAE of hepatitis which was considered by the investigator to be due to a CMV infection. The patient completed the whole study.

No patient experienced any associated clinical sequelae with the grade 3 and 4 laboratory abnormalities.

Laboratory findings are very rarely reported in published studies.

Safety in special populations

Intrinsic factors have not explicitly been studied for Still’s disease.

Elderly patients, mainly patients with RA, who have been exposed to anakinra, have shown a safety profile that is comparable to that in other adults.

Safety in elderly patients has previously been evaluated, mainly in RA patients. A total of 752 patients ≥ 65 years of age, including 163 subjects ≥ 75 years of age, have been studied in earlier, company sponsored clinical trials. No differences in the safety profile were observed between elderly and younger subjects, except for ISRs that were less frequent among elderly patients.

Studies in patients with hepatic and renal impairment have shown that anakinra mainly is excreted through the kidneys and that mean plasma clearance of anakinra after s.c. administration in subjects with severe renal insufficiency (creatinine clearance < 30 mL/min) and end stage renal disease was reduced

by 70 % and 75 %, respectively (study 20000268). Anakinra is not eliminated by dialysis, removal of anakinra via HD and CAPD is minimal (< 2.5 % of total clearance).

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

Safety related to drug-drug interactions and other interactions

Interactions between anakinra and other medicinal products have not been investigated in formal studies. In clinical trials, no interactions between anakinra and non-steroidal anti-inflammatory drugs, corticosteroids, and DMARDs have been observed.

Patients treated with anakinra and etanercept were observed to have a higher rate of serious infections (7 %) and neutropenia than patients treated with etanercept alone in study 20000223 and its extension 20010190 in patients with RA receiving background treatment with methotrexate. The rates of serious infections and neutropenia in patients treated with the combination of anakinra and etanercept are also higher than what has been observed in previous trials where anakinra was used alone.

Use of anakinra in combination with TNF blocking agents is therefore not recommended.

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

This potential interaction is valid for patients with Still's disease, as well as for CAPS and RA, and is reflected in Section 4.5, *Interaction with other medicinal products and other forms of interaction*, in the SmPC.

Discontinuation due to adverse events

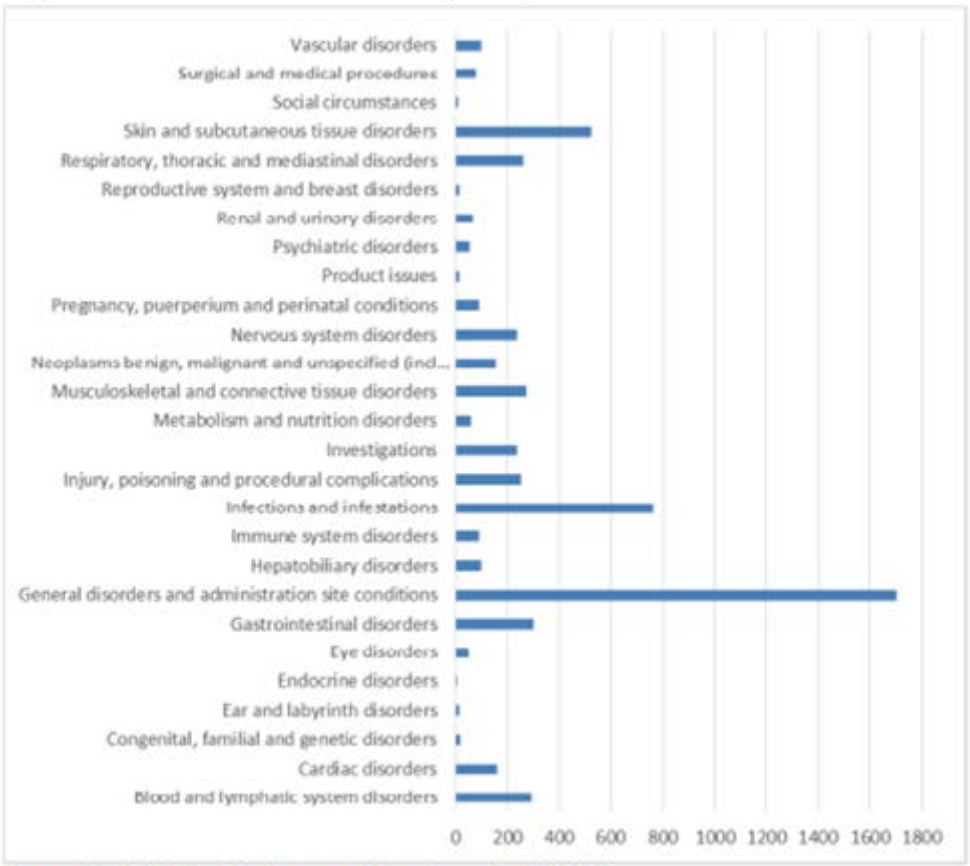
No SAE caused a patient to discontinue the study 990758/990779. However, 1 out of 15 SJIA patients was permanently withdrawn due to an AE during the initial open label phase in study 990758. The patient discontinued on Day 1 of the open-label phase due to ISRs.

Post marketing experience

The AEs associated with anakinra use in adults are well documented since its approval for treatment of RA in 2001. By September 30, 2016, there were 2885 case reports with 5932 medically confirmed post-marketing AEs in the Sobi Safety Database.

Figure 13 provides an overview of the number of AEs by SOC in all indications combined from the Sobi Safety Database. "General disorders and administration site conditions" is the SOC with most reported AEs. This SOC contains AEs indicating various types of injection site reactions, the most common anakinra adverse drug reaction. The distribution of AEs in the Sobi Safety Database corresponds to the known safety profile of anakinra.

Figure 13 – Number of AEs by SOC, all indications



Source: The Sobi Safety Database, cut-off date: September 30, 2016.
AE=Adverse event; SOC=System organ class.

Adverse events in paediatric and adult patients with Still's disease

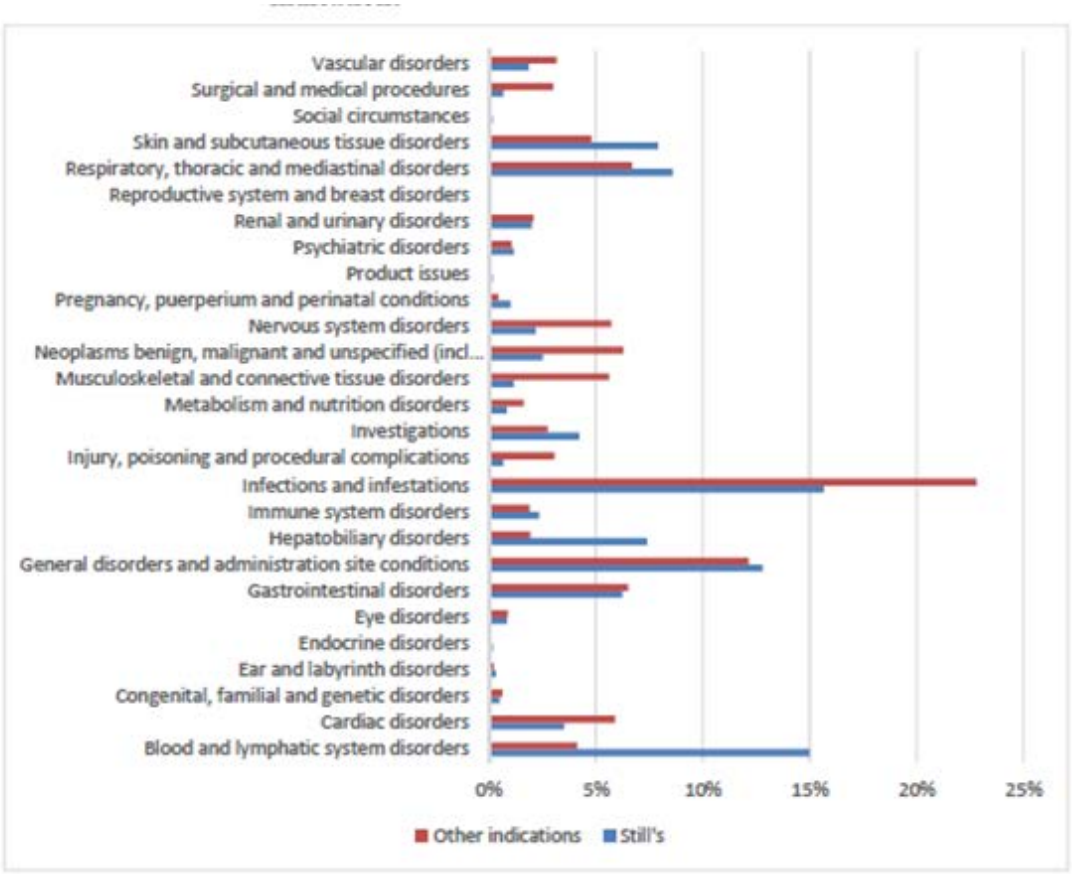
There are 566 medically confirmed post-marketing reports with 1346 AEs in the Safety Database concerning patients where the indication for anakinra treatment is reported to be Still's disease in either paediatric or adult patients. Out of these, 237 reports (42 %) with 570 AEs concern paediatric patients. There are 102 case reports with a total of 193 AEs, whereof 54 serious, where the age or age group is unknown. These reports have been included in the adult population.

There are only minor differences in the distribution of SAEs over MedDRA SOCs in paediatric and adult patients with Still´s disease.

It is notable that events of MAS constitute 74 % of all SAEs seen in paediatric patients with Still's disease but only 38 % in adults. The reason for this difference in frequency is not clear. The frequency of fully developed MAS in SJIA and AOSD is similar, 10 to 15 %. However, the true frequency of MAS in SJIA may be higher since subclinical and mild MAS occurs in another 30 to 40 % of patients with SJIA (Gerfaud-Valentin et al. 2014a,Ravelli et al. 2015).

As when comparing all AEs there are some differences in the distribution of SAEs across indications. The major difference is the higher relative frequency of MAS and hepatobiliary events in patients with Still's disease.

Figure 14 – Distribution of SAEs by SOC, patients with Still's disease and other indications



MAS is a known serious complication to Still's disease. The frequency of fully developed MAS in Still's disease is 10 to 15 % (Gerfaud-Valentin et al. 2014a,Ravelli et al. 2015). Anakinra has not been associated with MAS and it should be noted that there are multiple reports describing anakinra as a successful treatment for MAS.

Anakinra has been associated with signs of liver injury, including non-infectious hepatitis. However, various signs of hepatocellular injury are also common manifestations of Still's disease, both in paediatric and adult patients, and are also common in patients that develop MAS, including subclinical MAS.

2.5.1. Discussion on clinical safety

The presented data in paediatric and adult patients with Still's disease together with substantial safety data from post-marketing in both Still's disease and other indications are overall adequate to evaluate short term safety of anakinra in the proposed indication.

No new adverse events have been identified. The most common adverse events were ISRs, and most were mild and did not necessarily lead to treatment discontinuation. Fever, rash and headache are also common adverse events. The rate of AEs seems to be declining over time. Overall, around 12 % of patients discontinued treatment, mainly due to injection site reactions or infections. The reporting rate for ISRs was slightly higher in females than in males. However, there were no major differences between the AE profiles in male vs. female patients. The infections rate is higher in children of younger age, but this is not considered related to Kineret treatment.

12 % of the paediatric patients in the published studies experienced a SAE compared to 0.4 % in the adult population. Underreporting is expected in the published studies in the adult population. The most commonly reported SAEs were infections and MAS. Infection is a well-known risk of anakinra. A trend for increased rate of infections in children of younger age is reported in Still´s disease patients and CAPS patients. The most commonly reported infectious episodes were upper respiratory tract infections. There were no discontinuations due to infectious events. In CAPS patients an increased rate of infection is documented in patients <2 years (3.4) and 2 to 11 years (2.2), compared with the older age groups.

MAS is more frequent in children, and is probably more related to the underlying condition than to anakinra treatment. No causal relationship between MAS and anakinra has been established. Infections may trigger MAS, Anakinra may alleviate symptoms of MAS and cessation of anakinra treatment may worsen MAS. Recommendations have been included in section 4.4 of the SmPC to guide prescribers in case of infections and/or MAS.

To guide the prescriber it has been stated in the SmPC that "*Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with Still's disease. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of Still's disease, as these are known triggers for MAS.* ***Available data are limited regarding whether Kineret can be continued during serious infections in patients with Still's disease. If Kineret treatment is continued during serious infections to reduce the risk for a disease flare, careful monitoring is required."***

Discontinuation of anakinra treatment in case of infections in Mb Still patients could increase the risk of disease flare, with possible increased risk of MAS. Available data are limited regarding whether Kineret can be continued, but Kineret has been safely administered also during serious infections.

MAS is an important potential risk of Kineret and intensified post marketing safety surveillance is planned. A specific questionnaire will be sent out if a case report describing MAS in a patient with Kineret is received. A post marketing prospective observational study in the Eurofever registry via the associated Pediatric Rheumatology International Trials Organisation (PRINTO) network is ongoing (see Risk Management Plan section). A final report after one year from the start of the study will be provided. The proposed methodology is considered adequate.

The overall safety data in other indications are substantial, and the safety information from patients with Still's disease is sufficient for assessment of short term safety. A non-interventional PASS is planned to collect long-term safety data from existing registries.

Overall, the safety profile of anakinra in Still's disease was comparable to the safety in other conditions besides an increased risk of MAS and hepatobiliary disorders. Data in the submitted studies and post-marketing reports all indicated an increased risk of hepatobiliary disorders in patients with Still's disease. Also, additional case reports of anakinra related liver toxicity has raised concerns. Though the condition Still's disease itself carries a risk of increase in liver values the risk of anakinra induced liver toxicity, especially in patients with Still's disease is still a concern and precautions addressed in the SmPC, especially how to monitor hepatic function and early signs of liver toxicity has been included.

2.5.2. Conclusions on clinical safety

Overall, anakinra used in patients with Still's disease seems to be well tolerated with an acceptable and well-known safety profile. Mild and manageable ISRs are the most common adverse events.

Patients with Still's disease have an increased risk of infections and infections are also a risk of anakinra.

The results of the studies and post-marketing reports suggest a risk of liver toxicity with anakinra, especially in patients with Still's disease. This is adequately reflected in the SmPC. Furthermore, safety data are still lacking for long-term use in Still's disease, but appropriate investigation of long-term safety using registries with data of > 1000 SJIA patients and data going back to 2011 will be conducted.

2.5.3. PSUR cycle

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

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 4.4 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

Safety concerns

Summary of safety concerns	
Important identified risks	• Injection site reactions (ISR) • Immunogenicity • Serious infections • Neutropenia • Allergic conditions • Hepatic disorders • Interactions with TNF-antagonists
Important potential risks	• Malignancies • Macrophage activations syndrome (MAS) (not applicable for RA or CAPS) • Medication errors including reuse of syringe
Missing information	• Use in pregnant women • Use in lactating women • Use in patients with cardiac impairment • Use in patients with chronic infections • Use in patients with pre-existing cancers • Interaction with living vaccines

Pharmacovigilance plan

Study / activity Type, title and category (1-3) *	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports (planned or actual)**
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 • injection site reactions • allergic reactions • medication errors, including reuse of the syringe	Recruitment completed, follow-up ongoing	Updates will be provided in connection with PSURs. Final report planned for 2020.
Pediatric Rheumatology International Trials Organisation (PRINTO)/Pharmachild Registry (non-interventional, 3)	Follow-up of long term safety and MAS in patients with Still's disease	Long-term safety and MAS in patients with Still's disease	Planning phase	Final report expected end 2018 - beginning 2019

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
Injection site reactions (ISRs)	SPC, Sections 4.2 Posology and method of administration and 4.8 Undesirable effects describe the risk. Section 4.2 describes how to minimize the risk for ISRs.	Educational material for healthcare professionals treating patients with CAPS and Still's disease and patients on how to address the risk for 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, Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects describe the risk.	The patients will receive a patient reminder card. The card will be titled "Important Safety Information" and include text regarding serious infections.
Neutropenia	SPC, Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects describe the risk.	None
Allergic conditions	SPC, Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects describe the risk.	None
Hepatic disorders	SPC, Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects describe 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. N.B. MAS is not applicable for RA or CAPS indications. SPC, Section 4.8 Undesirable effects describes the potential risk.	Educational material for healthcare professionals and patients with Still's disease describing the risk of MAS.
Medication errors including reuse of 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.
Missing information		

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Use in pregnant women	SPC, Section 4.6 Fertility, pregnancy and lactation describes the potential risk. Follow-up of pregnancy outcome.	None
Use in lactating women	SPC, Section 4.6 Fertility, pregnancy and lactation describes the potential risk.	None
Use in patients with cardiac impairment	Routine measures sufficient.	None
Use in patients with chronic infections	SPC, Section 4.4 Special warnings and precautions for use describes the potential risk.	None
Use in patients with pre-existing cancers	SPC, Section 4.4 Special warnings and precautions for use describes the potential risk.	None
Interaction with living vaccines	SPC, Section 4.4 Special warnings and precautions for use describes the potential risk.	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

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

The package leaflet included in this submission is identical to the previously readability tested package leaflet for Kineret (indicated for RA and CAPS) with the only difference between the two leaflets being the new indication.

As this information is the only differing aspect between the PILs, the result of the Readability Test for the Kineret (indicated for RA and CAPS) also applies to Kineret (indicated for RA, CAPS and Still's disease).

2.8. Significance of paediatric studies

The CHMP is of the opinion that Study 2: *Open-label study to evaluate safety and clinical response in patients with neonatal onset multisystem inflammatory disease*, and Study 5: *A multicentre randomised double-blind placebo-controlled trial to evaluate safety and efficacy of anakinra in patients with systemic-onset juvenile idiopathic arthritis. (ANAJIS trial)* contained in the agreed Paediatric Investigation Plan *P/0066/2012,* are completed, and have been completed after 26 January 2007, are considered as significant.

In accordance with the criteria foreseen in the 'EC Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on the criteria for assessing significant studies' (2014/C 338/01), Study 5 is considered significant in line with criteria a) being randomised placebo controlled comparative efficacy studies, whilst Study 2 is a prospective clinical study, the results of which contribute to further characterisation of the safety profile of the medicinal product in the paediatric population.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

SJIA and AOSD are terms that identify pathological conditions, characterized by similar laboratory and clinical features, gene expression profiles, pathogenic mechanisms and treatment approaches, indicating that they are reflections of the same disease, Still´s disease, with the differentiating factor being the age at onset (with an arbitrarily age cut-off).

Still´s disease is a debilitating and difficult-to-treat disorder with few approved treatment options. In children it is the most severe form of arthritis. The onset of Still's disease is characterized by prominent systemic features with arthritis ensuing slowly during the first weeks or months of disease. Systemic features tend to subside or become less prominent with persisting arthritis in over half of the patients. The disease course is often progressive and followed by chronic morbidity, regardless of age at onset.

3.1.2. Available therapies and unmet medical need

To date NSAIDs, glucocorticoids, methotrexate, TNFα antagonists and IL-1/IL-6 inhibitors are used in the treatment of Still's disease, but are often only partially effective. The most commonly used treatment has been glucocorticoids which are effective in controlling systemic symptoms, as well as arthritis. However, this is achieved at high doses (often at doses markedly higher than 1 mg/kg/day prednisone equivalent) which are associated, in the long term, with a wide range of adverse events, including osteoporosis, pathological fractures (e.g. vertebral compression), cataracts, growth retardation, diabetes, and susceptibility to infection.

The IL-1β inhibitor canakinumab is approved for treatment of Still's disease, and the IL-6 inhibitor tocilizumab is approved for treatment of SJIA. However, these treatments are to be used in second-line after inadequate response to NSAIDs and systemic corticoids. Both can be given as monotherapy or in combination with methotrexate. Kineret was applied for a first-line indication, but during assessment this was restricted to first-line in patients with moderate to severe disease activity or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids to reflect as this was the main patient population in the clinical studies submitted to support the application.

When a diagnosis of AOSD or SJIA is suspected, it might be appropriate to use a short-acting IL-1 inhibitor such as anakinra to investigate whether the disease process is actually responding to IL-1 blockade.

Anakinra is today being used off-label for treatment of Still's disease. The recommendations issued by the CARRA (DeWitt et al. 2012,Kimura et al. 2014) and the ACR (Ringold et al. 2013) to use anakinra in the treatment of SJIA underpins the importance of a short-acting IL-1 inhibitor for the treatment of the disease.

3.1.3. Main clinical studies

The evidence to support the benefit of anakinra in Still's disease is mainly based on bibliographical data from real-world clinical studies. The paediatric investigational plan included a prospective, randomized, double-blind, placebo-controlled, MAH-sponsored study to evaluate the safety, clinical response, and

pharmacokinetics of anakinra in JIA, including a subpopulation of SJIA patients (study 990758), a prospective, multicentre, randomized, double-blind, placebo-controlled, investigator-sponsored study to evaluate safety and efficacy of anakinra in patients with SJIA (Quartier et al. 2011) and a meta-analysis of available published data on efficacy and safety of anakinra in patients with SJIA (Meta-analysis SJIA).

The assessment of known and potential risks of anakinra treatment in Still's disease are also based on bibliographical data, but mostly on data from the use of anakinra in company-sponsored clinical studies in multiple indications, and the company post-marketing safety database, including Individual case safety reports (ICSRs) from patients treated for Still's disease as well as other indications.

3.2. Favourable effects

The safety and efficacy have been demonstrated in a published randomized controlled study in 24 SJIA patients treated with Kineret for up to 1 year. After a 1-month blinded phase, 8 of 12 patients in the Kineret treated group were identified as modified ACRpedi30 responders compared to 1 of 12 in the placebo group. At the same time point, 7 of 12 in the Kineret treated group were classified as ACRpedi50 and 5 of 12 as ACRpedi70 responders compared to none in the placebo group. 16 patients completed the subsequent open label phase and among 7 responders at month 12, 6 had stopped glucocorticoid treatment and 5 of them had inactive disease.

In a published prospective, uncontrolled, observational cohort study of 20 patients with new-onset SJIA Kineret was used as initial therapy after failure to respond to NSAIDs, but before the use of DMARDs, systemic glucocorticoids, or other biologic agents. Treatment with Kineret resulted in normalization of body temperature in 18 of 20 patients. At 1 year follow-up, 18 of 20 patients showed at least an adapted ACRpedi 70 response, and 17 of 20 patients reached an adapted ACRpedi 90 response as well as inactive disease.

The safety and efficacy of Kineret versus DMARD have been reported in a published 24-week multicentre, randomized, open-label study of 22 patients with glucocorticoid-dependent refractory AOSD. At Week 24, 6 of 12 patients on anakinra were in remission versus 2 of 10 patients on DMARDs. During an open-label extension phase, switching or add-on treatment with the comparator drug was possible if improvement did not occur within 24 weeks. 17 patients completed the open-label extension phase (Week 52), of which 7 of 14 Kineret-treated patients, and 2 of 3 patients on DMARDs, were in remission at that time point.

Additional published data in Still's disease indicate that Kineret induces a rapid resolution of systemic features such as fever, rash, and elevation of acute phase reactants. Glucocorticoid doses can in many cases be reduced after initiation of Kineret therapy.

Furthermore the beneficial effect of anakinra in Still's disease in both paediatric and adult patients has been shown in two meta-analyses of published data on efficacy and safety in patients with SJIA which demonstrated a high response rate, irrespectively of response criteria, in clinically relevant outcomes.

In summary a high rate of normalization of systemic signs of inflammation such as fever, rash and increased CRP has also been demonstrated across studies. Rash and fever disappeared after few days of anakinra treatment, and inflammatory markers in all studies, including CRP and ESR, was normalized within weeks.

Most studies reported use of glucocorticoids and demonstrated that anakinra had a substantial glucocorticoid-sparing effect, which is of significant clinical benefit to the patients due to the well-known side-effects of glucocorticoids, especially in long-term treatment.

The benefits of anakinra have been reported consistently across studies, regardless of study design and concomitant treatment.

3.3. Uncertainties and limitations about favourable effects

Some patients are identified as non-responders, up to 45 % in the submitted studies. Treatment response should be evaluated after 1 month. This is reflected in the SmPC.

The evidence to support the benefit of anakinra comes mainly from uncontrolled studies. Only three small randomized studies are available to support the real-world evidence. Some publication bias is expected. Also, the publication of results, both prospectively and retrospectively collected, are likely to be from dedicated centres and the external validity of the results may be questionable.

No children below the age of 2 have been included in the clinical studies; however, efficacy of Kineret in children below the age of 2 has been shown in few cases identified in the literature. While extrapolation of efficacy and safety to children below the age of 2 is acceptable, no PK data in children below 8 months are available to support dosing. The indication is therefore limited to children > 8 months of age and > 10 kg in line with the other Kineret indications.

A potential disadvantage of anakinra is the short half-life (4-6 h). This could imply that in some patients more than one injection is needed per 24 hours though this was only very rarely effectuated in the clinical studies. Especially in children with a much higher clearance of anakinra a considerable volume has then to be injected.

3.4. Unfavourable effects

Safety data for > 400 patients with Still's disease are available. Supporting safety data from other indications include more than 6000 patient-years of anakinra treatment in the MAH-sponsored clinical studies and more than 80,000 patient years of anakinra treatment as post-marketing experience.

The most common adverse events following anakinra treatment is ISRs, mostly mild to moderate that only rarely lead to discontinuation of treatment. Other common adverse events are fever, rash and headache. Infections are a serious well-known risk of anakinra treatment. The rate of SAEs was generally low, with a higher incidence in the paediatric studies (12 %) and probably underreporting in the adult studies (0.4 %).

Higher incidences of MAS and liver related adverse events were seen in the patients with Still's disease compared to incidences in other indications. A causal relationship between MAS and anakinra has not been established.

3.5. Uncertainties and limitations about unfavourable effects

Recently several case report of anakinra related liver toxicity in Still's disease has been published. A causal relationship has not been established but cannot be ruled out either. Long term safety data in Still's disease are limited but will be evaluated in a PASS study using registry data from > 1000 SJIA patients.

No children below the age of 2 have been included in the clinical studies, but limited evidence from the literature and the few cases from the post-marketing safety database indicate similar safety in children younger than 2 years compared to older children and adults. As mentioned above, while extrapolation of efficacy and safety to children below the age of 2 is acceptable, no PK data in children below 8 months

are available to support dosing. The indication is therefore limited to children > 8 months of age and > 10 kg in line with the other Kineret indications.

3.6. Effects Table

Table 33 - Effects Table for anakinra in Still's disease with paediatric onset

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ACR response criteria	30 % improvement in ACR for JIA	ACRpedi 30	73 % (95 % CI: 61 % to 83 %)	N/A	Meta-analysis. N= 56 4 included studies. No comparator	Meta-analysis SJIA
Study-specific response	Short-term (up to 3 months) study-specific response		63 % (95 % CI: 54 % to 71 %)	N/A	Meta-analysis. N = 111 5 included studies. No comparator.	Meta-analysis SIJA
Responder rate	Study specific definition of responder/complete/ partial responder/non-responder	[Range]	Responders: [55 – 100%] Complete responders: [30 – 86 %] Partial responders: [22 – 39 %] Non-responders: [0 – 45 %]	N/A	10 studies including 197 patients. Only four studies reported all four respond ate subtypes.	
Unfavourable Effects						
MAS	MAS in study 990758/990779	Reports of MAS	Controlled phase: No reports Extension phase: no reports	Placebo	MAH-sponsored RCT.	990758/990779 Ilowite, 2009.
MAS	MAS in published studies	Reports of MAS	15 reports in 14 patients, 13 of the patients were pediatric	N/A	Data from 1 RCT, 4 prospective uncontrolled and 8 retrospective uncontrolled studies, 1 caser report.	
Infections	Infections in Quartier study	Number of infections	Controlled phase: 2 in 12 patients Extension phase: 48 in 22 patients		multicentre, randomised, double-blind, placebo-controlled trial	

Table 34 - Effects Table for anakinra in Still's disease with adult onset

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Remission rate	Patients with partial or complete response at last follow up	events	82 % (95 % CI: 69.5 % to 89.7)	N/A	Meta-analysis. N=134 8 included studies.	Hong et al, 2014)
Complete remission	Complete response at last follow-up	events	66.8 % (95 % CI: 56.9 % to 75.3 %)	N/A	Meta-analysis N= 106 5 included studies	Hong et al, 2014)
Responder rate	Study specific definition of responder/complete/ partial responder/non-responder		Responders: [73 – 100%] Complete responders: [50 - 100 %] Partial responders: [0 - 32 %] Non-responders: [4 - 20 %]	N/A	10 studies including 156 patients.	
Unfavourable Effects						
MAS	MAS in published studies	Reports of MAS	1 MAS case reported in 180 adult patients (0.6 %)	N/A	Safety data reported in 9 studies (1 randomized open-labe, 2 prospective and 6 retrospective studies)	
Infections	Infections reported in published studies	events	18 infections reported in 176 patients (10%)	N/A	Infections reported in 4 out of 9 studies N=176	
Infections	Infections in randomized study	events	No reports	DMARD	N=16 24 week DB + 26 week OLE	Nordstrom et al, 2012

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The benefits of anakinra in Still's disease has been demonstrated in one MAH-sponsored randomized clinical trials, two published randomized controlled trials and otherwise in published uncontrolled prospective and retrospective studies. Anakinra has been used off-label for more than ten years for the treatment of Still's disease. Still's disease is a rare condition, and each individual published study is too small to show significant effect of anakinra in clinically relevant endpoints. As such, the efficacy of anakinra has been investigated in two meta-analyses, one in paediatric patients and one in adult patients with Still's disease, and both meta-analysis show a high response rate of anakinra. Additional clinically relevant endpoints, e.g. glucocorticoid sparing effect and effect on systemic signs and symptoms all point

in the same direction and support the use of anakinra in Still's disease. The safety of anakinra in Still's disease is well-described in the published studies together with the post-marketing experience also from other indications. An increased incidence of MAS is likely related to the underlying condition and anakinra may actually alleviate MAS and not cause MAS. However, data are limited regarding administration of Kineret during a serious infection in patients with Still's disease. Available data is limited regarding whether Kineret can be continued during serious infections. If Kineret treatment is continued during infections, careful monitoring is required. Besides an increase in liver enzymes and a potential increased risk of anakinra-related liver toxicity in Still's disease, the overall safety profile is comparable across indications. The reporting rate of serious adverse events is low, especially in adults, and the most common AEs are mild to moderate ISSR.

However, data for early treatment are yet limited and restricted to uncontrolled studies. Clinical guidelines recommend treatment of sJIA with anakinra as monotherapy only in patients with higher severity or in patients with continued disease activity after treatment with glucocorticoid monotherapy or NSAID monotherapy. Patients included in the clinical controlled studies had also in general moderate to severe disease activity. It should also be noted that canakinumab (Ilaris) has a second line indication in Still's disease, and tocilizumab (RoActemra) a second-line indication in SJIA. Taking into account the known risk of infections with anakinra, and the uncertainties regarding liver toxicity, anakinra as first-line treatment is restricted to patients with moderate to severe active systemic disease or second line in patients with continued disease activity after treatment with NSAIDs or glucocorticoids.

3.7.2. Balance of benefits and risks

The high response rates of anakinra across studies and response criteria for patients with Still's disease are of significant clinical value and clear benefit to the patients. The demonstrated glucocorticoid-sparing effect is considerable. Avoidance or limitation of the well—known side effects of long-term glucocorticoid treatment is important. The identified potential higher incidence of anakinra related liver toxicity events in patients with Still's disease is easily outweighed by the beneficial effects shown in the controlled and uncontrolled studies.

3.8. Conclusions

The overall B/R of Kineret is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include a new indication for Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and the RMP (version 4.4) are updated accordingly. Furthermore, the product information is brought in line with the latest QRD template version 10. In addition, the marketing authorisation holder took the opportunity to make some editorial changes in the SmPC and Package leaflet.

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

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.

In addition, 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.

Additional risk minimisation measures

Prior to launch of the new indication Still's disease for Kineret in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The main objectives of the programme are to provide information on the method of administration, raise awareness on the potential risk of macrophage activation syndrome (MAS) and on the potential risk of serious infections.

The MAH shall ensure that in each Member State where Kineret is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe or use Kineret have access to/are provided with the following educational package:

- Physician educational material

- Patient and caregiver information pack

- **The physician educational material** should contain:
  - The Summary of Product Characteristics
  - Guide for healthcare professionals

- The Guide for healthcare professionals shall contain the following key elements:
  - The importance of explaining the use of the syringe and correct injection technique to patients and/or caregivers
  - That it is not recommended to start treatment with Kineret in patients with an ongoing infection
  - Information on macrophage activation syndrome (MAS) in patients receiving the product for the treatment of Still's disease
  - The importance of providing patients and/or caregivers with the educational material

- **The patient and caregiver information pack** should contain:
  - Patient information leaflet
  - The patient and caregiver guide
  - The patient reminder card

- The patient and caregiver guide shall contain the following key messages:
  - Instructions on use of the syringe
  - Instructions on correct injection procedures and disposal of used syringes
  - How to manage injection site reactions

- The patient reminder card shall contain the following key messages:
  - Patient identification
  - Contact details of their physician
  - The prescribed dose of Kineret
  - The early signs indicative of MAS
  - A description of the signs of serious infections

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 Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/0066/2012 have been completed after the entry into force of that Regulation.

5. EPAR changes

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

Scope

Extension of indication to include a new indication for Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and the RMP (version 4.4) are updated accordingly. Furthermore, the product information is brought in line with the latest QRD template version 10. In addition, the marketing authorisation holder took the opportunity to make some editorial changes in the SmPC and Package leaflet.

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

Summary

Please refer to the scientific discussion Kineret EMEA/H/C/000363/II/0056.

Attachments

1. SmPC, labelling and Package Leaflet (changes highlighted) as adopted by the CHMP on 22 February 2018.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 09 March 2018. The principles to be applied for the deletion of CCI are published on the EMA website at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first. For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.