SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Kineret. This scientific discussion has been updated until 1 December 2003. For information on changes after 1 December 2003 please refer to module 8B.

1. Introduction

Anakinra is a competitive antagonist (without agonist activity) at Interleukin 1 (IL-1) cell surface receptors. Thus anakinra inhibits the biological activity of Interleukin 1α and 1β (IL-1αand IL-1β), which are considered critical mediators of inflammation and joint damage in rheumatoid arthritis.
The indication is "Kineret is indicated for the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients with an inadequate response to methotrexate alone."

2. Part II: Chemical, pharmaceutical and biological aspects

Composition
Kineret is a ready to use aqueous formulation of anakinra provided in a pre-filled syringe and vial containing 100 mg of active substance (0.67 ml deliverable/extractable volume respectively). The formulation contains citrate, sodium chloride, EDTA, polysorbate 80, water for injections and sodium hydroxide. The pH, excipients and their concentrations were selected to minimise chemical degradation during storage. When choosing excipients consideration was also given to choice of pharmacopoeial substances, frequency of pharmaceutical use, and minimisation of patient discomfort.

Active substance
Anakinra, the active substance, is a recombinant form of human interleukin-1 receptor antagonist (r-metHu IL-1ra) produced in *E. coli*. It has the amino acid sequence of the naturally occurring form of the protein with the addition of an N-terminal methionine residue, required for production in *E coli*. It is a 153 amino acid protein with a molecular weight of 17.3 kDa.
The applicant provided descriptions of the expression vector, encoding gene construct used for generation of the cell line, and preparation of the master cell bank (MCB). Details of the tests conducted on the MCB have been provided. A working cell bank will be introduced post authorisation.

Fermentation
Anakinra is produced by a fermentation process that is comprised of cell expansion of the master cell bank, inoculation of the fermentor, cell growth in the fermentor, induction of product, and cell harvest. Afterwards, the cells are lysed, and the lysate is collected for further processing.

Purification
Purification of anakinra is accomplished by a sequence of chromatographic and filtration steps for the generation of filtered purified bulk product. In-process controls and specifications are adequate to control product quality and consistency of the purification process. In-process acceptance limits have been set for critical purification parameters. The company has provided information on the removal of host cell derived impurities, process- and product-related impurities. The active substance is produced by Amgen Inc., USA. The fermentation and purification processes have been validated.

Characterisation
Anakinra has been characterised using physico-chemical and biological assays. Anakinra is adequately controlled by a combination of physico-chemical, biological and immunological methods. Appropriate specifications have been set for analysis of the active substance at release and at the end of the shelf life. Methods used for release testing have been described and validated. Batch analysis data demonstrate a consistent production of the active substance.

Other ingredients

All excipients used comply with the European Pharmacopoeia requirements. For polysorbate 80, the only material of ruminant origin, sufficient information has been provided to demonstrate compliance with the TSE guideline. The company has undertaken to implement the use of polysorbate of vegetable origin.
The 3 ml vial container closure system consists of a borosilicate Type 1 glass with rubber stopper and aluminium seal and polymer flip off cap. The 1 ml syringes are made of borosilicate Type I glass with staked needle. All components meet Ph Eur requirements.

Product development and finished product
The manufacturing process for the final product consists of a dilution of the filtered purified bulk (active substance) to the desired concentration with buffer, followed by sterile filtration and sterile filling into vials or syringes. Production of the Finished Product is carried out at Amgen Manufacturing Limited, Puerto Rico. Packaging, labelling, and final release is performed by Amgen Europe B.V., Breda, The Netherlands.
The manufacturing process for the final product has been validated and is controlled by in-process controls and product release specifications. The quality of the final product is ensured by analyses of the product by a combination of physico-chemical, biological, and immunological methods. Methods used for specification testing have been described and validated.

Stability of the Product
Based on real-time stability results after storage at 2-8°C, a shelf life as described in the product information is acceptable for both pharmaceutical forms (vials and syringes).

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics
No formal pharmacodynamic studies relating to proposed indications have been performed by the applicant. However published literature have been listed and provided. The cytokines IL-1α and IL-1β are considered to be critical mediators of inflammation and joint damage in rheumatoid arthritis, and through its antagonist function, anakinra inhibits the action of these IL-1 cytokines. In different animal models of arthritis, systemic administration of anakinra attenuated the inflammatory response, bone destruction and cartilage degeneration.

- **General and safety pharmacology programme**

The effects of anakinra (IL-1ra) were assessed in a series of safety pharmacology studies in mice, rats, dogs and on guinea pig ileum. In mice and rats, no anakinra related effects were seen in tests for central/autonomic, analgesic activity, anti-inflammatory activity, cardiovascular, digestive or renal functions. In guinea pig ileum, there was no influence of anakinra on autonomic nervous system and smooth muscle. No anakinra related effects relating to blood pressure, heart rate, respiration, blood flow or ECG were observed.

- **Pharmacodynamic interactions**

Anakinra acts at different receptors to both NSAIDs and corticosteroids, and an interaction at the receptor systems is therefore not anticipated.

Pharmacokinetics
Pharmacokinetics studies were conducted in rats, rabbits and cynomolgus monkeys.
SC injection resulted in prolongation of measurable plasma levels compared to IV injection in each animal species. $T_{½}$ values were however comparable for IV and SC administration. Bioavailability after SC dosing was 62, 72 and 88%, respectively, in rat, rabbit and cynomolgus monkey. The mean terminal half-life values were 0.89, 1.18 and 3.30 hours for rat, rabbit and cynomolgus monkey. Results from a rat study demonstrated that the kidney was responsible for approximately 80% of the anakinra plasma clearance. Allometric scaling of animal data predicted anakinra plasma clearance in humans reasonably well.
In the rat, a marked accumulation of plasma anakinra concentration of up to 48 times the day 1 values was observed after SC administration for 14 days. The decrease in the systemic clearance of anakinra after multiple doses could be attributed to decreases in renal glomerular filtration due to binding of

anakinra to anti-anakinra antibody or other proteins. In the rhesus monkey, there was no accumulation after daily doses of 100 or 200 mg/kg/day SC for 28 days, whereas there was 74% accumulation after doses of 10 mg/kg/day for the same period.
Since the passive transfer of all drugs with a MW over 1 kd across the human placenta are impeded, the placental passive transfer of a anakinra with MW 17 kd would be minimal. Moreover, anakinra is water-soluble, decreasing the probability of passive transfer.
Concerning active transfer, IL-1ra is naturally present in amniotic fluid, maintaining placental homeostasis, and possibly protecting against IL-1β-induced pre-term parturition. Foetuses will be exposed to IL-1ra by swallowing and respiring amniotic fluid. Infants are also naturally exposed to IL-1ra through breast milk.
Safety margins were calculated by comparing C_{max} and AUC values from rat and human studies. Safety margins ranged from 42 to 190 based on the C_{max} ratio and from 29 to 91 based on the AUC ratio.
Distribution studies showed that steady-state tissue-to-plasma anakinra concentration ratios in the rat were consistent with distribution into the physiologic extracellular fluid volume for all tissues except for the kidney; the kidney had a ratio much larger than the extrcellular volume of the kidney, indicating that the kidney is the major organ to eliminate anakinra from the circulation.

- **Pharmacokinetic drug interactions**

Pharmacokinetic and toxicological interaction studies were done with the anti-rheumatic drugs methotrexate and PEG-sTNF-RI (a PEGylated inhibitor of the TNF receptor). Anakinra given SC to rats up to 100 mg/kg/day for 28 days and methotrexate given orally up to 0.2 mg/kg/day in the same period did not change the kinetics of either drug. However, C_{max} and AUC of anakinra increased over time to the same extent as when anakinra was given without methotrexate co-administration. In another interaction study, rats received anakinra IV and PEG sTNF-RI SC. There were no significant differences in anakinra pharmacokinetics when anakinra was coadministered with PEG-sTNF-RI. Similarly, no alterations of anakinra pharmacokinetics after SC administration in monkeys was seen with concomitant PEG sTNF-R1 SC administration.
As reported in the literature, both IL-1α and IL-1β have been shown to down-regulate the expression and activity of cytochrome P450 monooxygenases in in vitro assay systems. Since anakinra blocks receptor association of IL-1 α and IL-1β, this could result in the inhibition of down-regulation of CYP by these cytokines. However definitive evidence is lacking regarding the in vivo modulation of CYP in humans with RA.
Interactions with NSAIDs or corticosteroids can occur prior to or during absorption, via alteration of a metabolism or excretion mechanism, or by effects at the site of action. No alteration in absorption is expected, as anakinra is not given orally. Anakinra is not metabolised by the liver via phase 1 or 2 mechanisms and is not known to inhibit cytochrome P450 enzymes. Therefore the applicant argues that there is no reason to anticipate altered metabolism of NSAIDs or corticosteroids. It is also argued that no alteration of elimination should be expected, as the mechanisms involved in elimination are thought not to be the same for anakinra as that for NSAIDs and corticosteroids; however no data were provided.

Toxicology

The activity of human IL-1β and of anakinra in rhesus and cynomolgus monkey blood as well as in human blood was shown. Human IL-1β induced production of IL-6 in both monkey species, and concentrations required for a 50% response were similar. Anakinra inhibited the IL-1β response in all three species with similar efficacy. The experiments confirmed that the pharmacological activity of anakinra in monkey whole blood is comparable to its activity in human whole blood. Based on these arguments, it is claimed that the monkey can be considered to be a valid species for the assessment of human safety.

- **Single dose toxicity**

A single dose toxicity study of anakinra was conducted in rats. There were no pharmacotoxic signs, body weight changes, macroscopic or microscopic observations that were attributed to the test article at IV doses up to 720 mg/kg. Anakinra was administered IV to cynomolgus monkeys at doses of up to 150 mg/kg given in an escalating fashion with a 48-hour observation interval between doses. There were no test article-related pharmacotoxic signs observed during the study period, and physical examination revealed no abnormal signs. Although SC is the intended route of administration of anakinra, the IV data support the absence of systemic toxicity, at doses and exposure levels that are higher than those that could be achieved through SC administration.
It was concluded that anakinra lacks acute toxic effects even in very high doses.

- **Repeat dose toxicity**

Rats
Four 2-week IV toxicity tests were conducted in rats at doses up to 30 mg/kg/day. No systemic toxicity was observed in these studies. Histopathologic and clinical findings showed that test article at 30 mg/kg/day induced a reversible perivascular inflammation within intravenous injection sites.
Anakinra was given SC to rats at up to 120 mg/kg/day, for up to 14 days. No treatment-related toxicity was noted. Chronic inflammation was observed only in the test article-treated rats. The NOEL for systemic toxicity was considered to be 120 mg/kg/day after 14 days treatment. The NOEL for local inflammatory reactions was 80 mg/kg/day in the rat.
In a 6-month toxicity study in rats, SC treatment produced local injection site inflammation at all dosages. At 200 mg/kg/day, there was an increase in the weight of the kidneys in male rats and of the liver in both genders. The increased liver weight was claimed not to be associated with any histopathological (gross or microscopic liver lesions) or liver enzyme changes.
At 200 mg/kg/day, systemic toxicity was noted for the kidney after 6 months of dosing. Proteinuria, renal interstitial mononuclear cell infiltration and chronic progressive nephropathy were observed. There were no observed treatment-related changes in haematology or clinical chemistry during the study. Using the Dunnett test, statistical evaluation of CPN incidence showed that there was no significant difference in incidence of CPN in the treated vs. control animals ($p \geq 0.05$). There was however a trend towards increased CPN with dose in male rats.
Two long-term extension studies are ongoing to evaluate the safety of anakinra in over 1300 anakinra treated subjects. In both of these studies, serum chemistry and urinalysis are being conducted on a regular basis during the 3 year study duration. This should provide information on potential long-term toxicity.
Concerning safety concerns on the likelihood of renal toxicity in renal insufficiency: The exclusion of severely renally impaired patients from treatment with anakinra would assure additional mitigation. Such a recommendation has been made in the Summary of Product Characteristics, where, in the absence of clinical data in this patient population, patients with severe renal impairment ($CL_{cr} < 30$ ml/minute) are contraindicated.
It is suggested that drug accumulation seen preclinically after daily treatment for one month or more is not related to nephrotoxic effects but is due to immune complexes. It has been reported by the applicant that immune complexes were observed in 12 out of 12 tested rat samples, supporting the hypothesis that plasma accumulation of anakinra in rats was due to immune complex formation.

Monkeys
In a 2-week SC test in rhesus monkeys, the incidence of slight inflammation at the injection site was higher in the high dose group and was attributed to the test article. Antibody to anakinra was detected in almost all animals by day 15. There were no other observed effects that could be attributed to the test article. The NOEL for systemic toxicity was set at the highest dose tested of 80 mg/kg/day. The NOEL for local inflammatory reactions was 5 mg/kg/day.
In a 4-week SC toxicity study in rhesus monkeys, treatment-related inflammatory skin lesions were observed in 5 of 10 animals receiving 200 mg/kg/day. Alterations in haematology parameters were also observed; elevations in white blood cell counts and decreased red blood cell parameters in a few animals. Proteinuria was more frequent in treated animals than in controls, but not seen in the recovery group. Although the observed proteinuria was treatment-related it was considered to be biologically

irrelevant, because protein in urine appeared to be mainly excreted drug. Urine albumin and globulin levels, indicators of proteinuria, were normal in all animals. Furthermore there were no histopathologic lesions.
A low incidence of antibodies was present for all treated groups. It is argued that the observed lower antibody titer in high dose groups compared to low dose groups could be caused by the high drug levels interfering with the ability of the assay to detect antibody. Circulating drug would decrease the amount of antibody in a serum sample that would be detected. This phenomenon is well known with antibody-detecting assays.
Haemolytic Staphylococcus was cultured from a lesion on one high dose female animal. It is believed that the bacteria were probably introduced into the subcutaneous tissue through the injection procedure and that the observed infection is therefore not an indication of immune suppression. The abscess responded only to topical treatment and did not progress to septicaemia, supporting an intact immune system.
Enlarged peripheral lymph nodes were seen in 3 of 6 high dose animals and were considered to be a secondary response to the injection site lymphohistiocytic inflammation. This is thought to be suggestive of a functional immune cell response to antigenic stimulation. Thymus and spleen weight and histology showed no treatment-related changes.
A one-week IV continuous infusion study was performed in male rhesus monkeys given anakinra 150 mg/kg/day. A 2-week IV study was performed in cynomolgus monkeys at doses up to 30 mg/kg/day. There were no noted toxic effects in the treated animals from both studies. Antibodies against anakinra were detected in all animals from the 2-week study.
The potential for anakinra to induce QT interval prolongation was also assessed in a 4-week repeat dose combination study of anakinra with PEG sTNF-RI administered SC in monkeys. There were no significant changes in QT intervals in animals treated with anakinra alone at 100 mg/kg or in combination with PEG sTNF-RI at doses up to 25 mg/kg.

- **Genotoxicity**

A full set of in vitro and in vivo genotoxicity tests were conducted and there was no evidence of genotoxicity associated with anakinra.

- **Carcinogenicity**

The carcinogenic potential has been evaluated with emphasis on: risk of direct tumour production; risk of tumour stimulation; indirect effects of anakinra on tumour growth.
Risk of direct tumour production: This is considered unlikely, as anakinra is a human recombinant protein and also as anakinra was judged non-mutagenic in mutagenicity assays. Furthermore no treatment-related tumours were found in the 6-month rat study.
Risk of tumour stimulation: Binding of anakinra to IL-1 receptors does not cause signal transduction. The evidence presented indicates that anakinra does not appear to directly stimulate mitogenesis or cell proliferation. Anakinra may interact with tumours; however, any putative interaction will be dependent on IL-1 effects and the relative IL-1 levels. The relevance of these in vitro studies to predict the direct risk of cancer for patients receiving anakinra treatment is difficult to ascertain as it is presently unclear as to the role and extent that IL-1 plays in preventing certain tumours from growing.
Indirect effects of anakinra on tumour growth: There was no evidence of immunosuppression in the rat and monkey toxicity studies. Anakinra also had no effect on specific immune functions such as antibody formation to Keyhole Limplet Hemocyanin or cytotoxic T lymphocyte response in mice. Additionally, IL-1ra stimulates NK cells in mice. NK cells play an important role in tumour surveillance.
A literature search reveals no published data on increased tumorigenicity in transgenic or knockout animals. Seven years of experience with IL-1ra overexpressing mice and IL-1ra mutant knock-out mice have been provided in detail from the Director of the laboratory that produced these animals. There is apparently no increased carcinogenic risk in the knockout mice.

- **Reproduction Toxicity**

Fertility, embryo-foetal development and peri-, post natal development reproduction studies were conducted in rats and rabbits at doses up to 200 mg/kg/day. There was no evidence of anakinra related reproduction toxicity.
Studies with IL-1ra overexpressing mice and with mice deficient for the IL-1 type 1 receptor have also shown normal reproductive capacity. Repeated IP injections of IL-1ra do not affect embryo implantation in either wild type or IL-1 receptor deficient mice.
Safety margins to human exposure were at least 15 fold for rabbits and 100 fold for rats. The highest dose tested in the reproductive studies i.e 200 mg/kg, which is approximately 200-fold the intended clinical dose and 24-fold over the human exposure.
IL-1ra is naturally present in high amounts in amniotic fluid, which is a strong argument that anakinra treatment poses no risk for reproduction toxicity or for impaired reproductive performance.

- **Local Tolerance**

No formal local tolerance studies have been performed. Microscopic examination of the SC or IV injection sites in the repeat dose studies in rats and monkeys revealed subacute to chronic inflammation at the injection site (SC studies) or perivascular inflammation (rat IV studies), with incidence and severity tending to increase with dose.
It has been shown in a study comparing mast cell degranulation, and inflammatory cell infiltration in rats given intradermal injection of IL-1ra or its vehicle, that skin reactions were due mostly to the vehicle (CSEP) intradermal activity. There was no immunological component to the skin reactions; therefore they were characterised as pesudoallergic.
The presentation of injection site reactions is very different between patients and rats or monkeys.
The leukocyte and lymphocyte infiltration seen in rats represents an expected antigenic response to the human protein. The strong local recruitment of inflammatory cells at injection sites in the 6-months rats suggested that there was no immunosuppression.

- **Other toxicity (antigenicity, immunotoxicity and dependence) studies**

A relative increase in AUC was seen in rats and monkeys the longer-term repeat-dose studies and is thought to be connected to the antibody production by formation of anakinra-antibody complexes.
The applicant has developed an *in vitro* neutralising antibody assay (bioassay) and a biosensor (BIAcore) assay that offers improved sensitivity to low affinity antibodies. Neutralising potential was investigated and it was concluded that the antibody response in rats and monkeys is not neutralising. It has been shown that the anakinra antibodies had lower affinity than the positive control antibody in both monkeys and rats.
In the few existing animal disease models, anakinra retained its biological activity during the treatment period (4 weeks in a rat model, 14 days in another rat model).
Immunotoxicity studies and repeat-dose studies do not provide evidence for anakinra-induced immunosuppression.
The best and most used assay for evaluation of immunosuppression is the antibody forming cell assay to sheep red blood cells. This assay requires functional T- lymphocytes, B-lymphocytes and APC macrophages. Anakinra treatment did not result in immunosuppression in this assay. In addition plaque forming and NK cell activity assays did not provide evidence of anakinra mediated immunotoxicity.

- **Ecotoxicity/Environmental Risk Assessment**

No significant impact to the environment is expected from the release of anakinra because of the small amounts potentially discharged, the high rate of biodegradation of the product, and the lack of toxicity at the low concentrations that is expected to be discharged.
Anakinra is considered a non-hazardous biodegradable product. The environmental impact in terms of use and disposal of anakinra is expected to be negligible.

4. Part IV: Clinical aspects

Clinical pharmacology

Pharmacodynamics
Studies specifically investigating the pharmacodynamic action of anakinra in humans have not been performed. As pre-clinical studies have adequately described the pharmacodynamics of anakinra, the lack of such data is considered acceptable.

Pharmacokinetics

- **General**

Following subcutaneous injection, anakinra is absorbed with maximal plasma levels obtained within 3 to 9 hours post injection. The relative bioavailability of anakinra following subcutaneous injection is approximately 95%.
Following intravenous injection, anakinra distributes initially into a volume of 3.6 L and subsequently distributes into a steady-state volume of 9 to 15 L. These volume-of distribution data were consistent with the initial distribution into the physiological plasma volume (3 L) and subsequent distribution into a steady-state distribution volume that approximates the extracellular volume (18.2 L).
The effect of choice of injection site was not investigated. The recommendation in the SPC and patient information leaflet is therefore that; patients should rotate the injection site, which includes thigh, arm, and abdomen and is based on the anakinra clinical studies, where subjects were instructed to rotate the site of injection.
Following intravenous infusion, anakinra is eliminated fairly rapidly with a half-life of approximately 3 hours. The clearance is about 150 ml/min and is correlated to renal creatinine clearance. Clearance was modestly higher than the estimated glomerular filtration rate. These data suggest that in humans (like in animals), anakinra is predominantly eliminated via the kidneys. However, the route of elimination has not been studied directly in humans. Urinary recovery of anakinra in humans was low suggesting that anakinra filtered in the glomeruli is absorbed and metabolised by the renal tubular cells.
Following subcutaneous injection, the terminal half-life of anakinra is longer than after intravenous injection (3 to 9.5 hours versus 2 hours), reflecting the effect of the slower absorption rate following subcutaneous injection.
In the dose-range studied (1 to 10 mg/kg) the pharmacokinetics of anakinra was linear. No accumulation was observed after repeated subcutaneous administration of up to 2.0 mg/kg/day of anakinra. Repeated administration of higher doses (4.0 mg/kg/day) resulted in the accumulation of anakinra.
The clearance of anakinra is slightly reduced (10 to 15%) in the elderly above 65 years of age and in females compared to healthy younger males (age below 65 years). However, when correcting for differences in creatinine clearance and body weight, there was no effect of gender and age on the clearance of anakinra.
Clearance of anakinra is only moderately reduced in patients with moderate hepatic impairment. Thus, no dosage adjustment is considered necessary for this population.
Patients with mild to moderate renal insufficiency were included in the pivotal clinical trials. The safety profile of anakinra in patients with mild renal insufficiency was similar to the safety profile in patients with normal renal function. The safety profile of anakinra in a limited number of patients with moderate renal insufficiency did not indicate any safety concerns.

As to be expected clearance of anakinra was significantly impaired in patients with severe renal insufficiency. This results in a higher exposure after single dose administration. The magnitude of the difference of exposure following repeated administration between patients with normal renal function and patients with severe renal impairment is unknown. As no studies have been performed in patients with severe renal insufficiency and as clinically important increases in exposure cannot be ruled out in this population, anakinra should not be used in patients with severe renal insufficiency. A warning statement has been included in the SPC.

- **Interaction studies**

There is no evidence that any important PK interaction with NSAIDs or corticosteroids or other concomitant drugs used by rheumatoid arthritis patients, could reasonably be anticipated when anakinra is given to patients with RA. Based on the current evidence available it is believed that the interaction potential of anakinra is low. Therefore no pharmacokinetic or pharmacodynamic interaction studies were performed. Considering the nature of the product and its pharmacokinetics, this is considered acceptable.
Overall the pharmacokinetic and pharmacodynamic documentation for anakinra is acceptable.

Clinical efficacy
Clinical studies presented were performed complying with Good Clinical Practice principals according to the Note for Guidance on Good Clinical practice for trails on Medicinal Products from the European Committee for Proprietary Medicinal Products.

Dose response studies
The phase II studies conducted by the applicant provided evidence for the choice of administration frequency but does not justify any selection of dose. Dose selection is based on the results of the pivotal trials.

Main Studies

Description of the studies
The trials 0560 (with its extension study 0564 and following open-label extension studies 0564E1, E2, E3) and 960180 (with its extension study 960181), involving 891 patients with RA, were designed to provide evidence of safety and efficacy of anakinra in RA. To support the claim for combination treatment with other DMARDs, the applicant has submitted a confirmatory efficacy analysis from study 990145 and an interim analysis of safety data from study 990757.

- Study 0560

This study was a randomised, double-blind, placebo-controlled, multicentre, dose-ranging study designed to determine the efficacy and safety of anakinra (30, 75 or 150 mg) administered subcutaneously once daily for 24 weeks in patients with RA.
Study 0564 was an extension of study 0560. This study was a randomised, double-blind, multicentre, non-placebo controlled, parallel-group study of anakinra in subjects with RA, to determine the long-term efficacy and safety of anakinra (30, 75 or 150 mg) administered subcutaneously once daily in patients with RA. Subjects completing study 0560 and who received placebo were randomised in a blinded fashion to receive one of three doses of anakinra. Subjects completing study 0560 and who received anakinra, continued to receive the same dose of anakinra in a blinded fashion.

- Study 960180

This study was a randomised, double-blind, placebo-controlled (add-on to MTX), multicentre, dose-ranging study designed to determine the efficacy and safety of anakinra administered subcutaneously once daily in patients with RA who are receiving concomitant treatment with stable doses of methotrexate (MTX) and folic acid.

- Study 990145

Study 990145 was a multi-centre, double-blind, randomised, placebo-controlled trial to study the ability of anakinra to retard joint destruction, and to evaluate the long term safety of anakinra in

subjects with RA. A confirmatory efficacy analysis from study 990145, which included 501 patients on a fixed dose of 100 mg/day, compared clinical outcome in patients already receiving MTX treated with either anakinra or placebo. While the study was designed primarily to assess the effects of anakinra on joint destruction, the analysis provided in support of this application also examined the 6-month effects of anakinra in combination with MTX (N = 250) versus MTX alone (N = 251) on signs and symptoms using the ACR composite score.

Primary endpoints/assays

The primary endpoint was the proportion of patients exhibiting at least a 20% improvement from baseline in the ACR score (ACR_{20}). A patient is defined as having at least a 20% improvement in ACR_{20} score if all of the following criteria are fulfilled:

- At least a 20% decrease from baseline in the number of tender/painful joints and the number of swollen joints,
- 20% improvement in at least 3 out of the following 5 assessments: subjects assessment of disease activity, investigator's assessment of disease activity, subjects assessment of pain, health assessment questionnaire (HAQ) disability score, acute phase reactant (CRP).

For study 0560 and study 960180, the primary endpoint was the proportion of subjects who achieved an ACR_{20} response at week 24 and week 12 respectively.

In the anakinra pivotal trials, which pre-dated the issued EU guidance (CPMP "Points to Consider on slow-acting anti-rheumatic medicinal products in rheumatoid arthritis" (CPMP/EWP/556/95)), the pre-specified primary efficacy endpoints used the American College of Rheumatology (ACR) definition of improvement in RA. This endpoint utilises an aggregate, validated composite of the patient's clinical status from both the physician's and the patient's perspective, and includes all of the measures noted in the guidance document.

Improvement criteria such as the ACR and EULAR (European League Against Rheumatism) criteria are becoming increasingly accepted in rheumatology practice as an appropriate, validated primary measure of efficacy. Study 0560 was the only study designed to investigate structural damage from data on radiological progression. In the protocol, the Larsen score was the method chosen to evaluate the effect of anakinra in retarding structural damage. Radiographs were also evaluated using the Modified Sharp Score (TMSS).

Statistical analysis

- Study 0560

The primary efficacy population was a modified intention-to-treat (M-ITT) population defined as all subjects receiving at least one dose of study drug and having at least one post baseline measurement for the endpoint being evaluated. For missing data the last observation carried forward principle (LOCF) was used. Analysis of the primary efficacy parameter (fraction of patients experiencing a 20% or greater improvement in ACR_{20} at week 24) was performed by 3 Cochran-Mantel-Haenszel (CMH) tests pair wise comparing each dose of anakinra against placebo. An Agresti-Coull test for dose-response was also performed.

Furthermore in order to account for the missing radiographs for 77 subjects, the 0560 clinical study report incorporated numerous sensitivity analyses to assess the effect of missing radiographs on study outcome. These consisted of:

- simulated worst-case analyses
- an ITT analysis that included all subjects randomised and assumed subjects with missing data had radiographic progression
- evaluation of baseline characteristics among subjects included/excluded from the analysis
- relationship between the ACR_{20} response and Larsen scores.

- Study 960180

The primary efficacy population was the ITT population defined as all subjects who were randomised to treatment irrespective of whether or not they received treatment. The primary safety population consisted of all patients receiving at least one dose of study medication. Analysis of the primary efficacy parameter (proportion of patients experiencing a 20% or greater improvement in ACR_{20} response criteria at week 12) was performed by an initial test for trend using a Likelihood Ratio Test with adjustment for centre. If a statistically significant dose-response relationship was observed, pair-wise comparison of each anakinra dose against placebo were performed. For the pair-wise

comparisons, a logit model including centre and treatment effect was used. Exploratory analyses investigating the effect of various baseline covariates were also performed. These analyses singularly introduced each covariate into the previously described logit model to assess the impact of these covariates.

- Study 990145

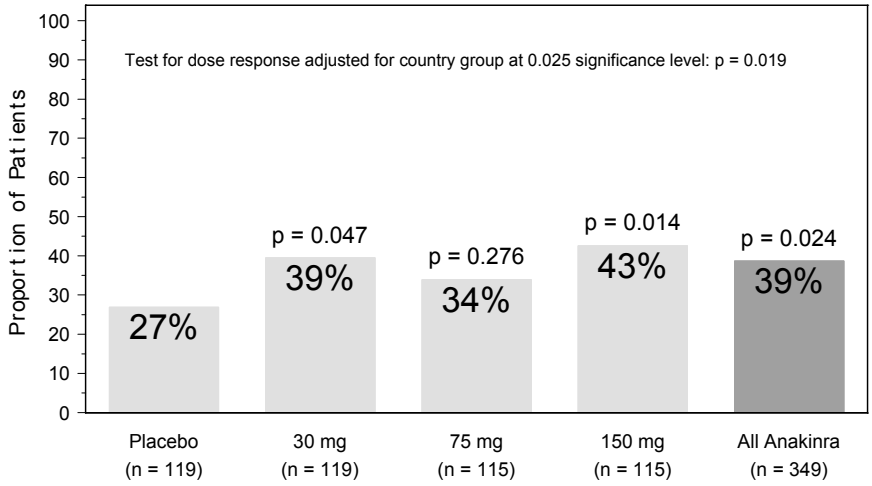
The primary analysis for the ACR_{20} response rate at week 24 was a logistic regression model adjusted for centre. Efficacy analyses for dichotomous secondary endpoints ($ACR_{50,}$ $ACR_{70,}$ and sustained ACR_{20}) used a similar logistic regression model. Continuous secondary endpoints (ACR components and duration of morning stiffness) were analysed with a repeated measures mixed model. All efficacy analyses were performed at a 2-tailed alpha level of 0.05.
Safety analysis consisted of the crude and exposure-adjusted subject incidence rates of adverse events and serious adverse events, including serious infectious episodes.

Results

- Study 0560

Study 0560 provided evidence that in a mixed RA population including both DMARD naïve and DMARD experienced patients, 24 weeks of treatment with anakinra 150 mg once daily is superior to placebo as regards reduction of disease activity.

Study 0560: Proportion of Subjects Achieving an ACR_{20} Response at Week 24 by Treatment Group LOCF Imputation (M-ITT)



n = Number of evaluable patients
p-values correspond to pairwise comparisons between each anakinra dose group and placebo adjusted for country group

Study 0560: ACR Components and ESR Mean Change From Baseline at Week 24

	Study 0560 Modified ITT Population/LOCF		
	Placebo	Anakinra 75 mg/d	Anakinra 150 mg/d
Number Evaluable	**119**	**115**	**115**
Swollen Joints[a]	-5.64	-6.08	-9.39**
Tender Joints[b]	-5.16	-8.99*	-11.95**
HAQ[c]	-0.03	-0.19*	-0.28**
Physician Global[d]	-0.62	-0.87*	-1.04**
Patient Global[d]	-0.51	-0.79*	-0.96**
Pain[e]	-0.04	-0.11	-0.18**
CRP (mg/dL)[f]	-0.36	-1.04*	-0.98*
ESR (mm/hr)	0.78	-7.86*	-10.36**

* p-value < 0.05; ** p-value < 0.01
Least squares means and p-values obtained from ANOVA model adjusted for country group and treatment-by-country interaction.

[a] Scale: 0 to 66

[b] Scale: 0 to 68

[c] Health Assessment Questionnaire: Scale 0 best to 3 worst, mean score over eight categories

[d] Study 0560, Ordinal Scale: 0 to 4; study 960180, Visual Analogue Scale: 0 to 100

[e] Study 0560, Visual Analogue Scale: 0 to 1; study 960180, Visual Analogue Scale: 0 to 100

[f] Study 0560, p-values result from an ANOVA model of log change CRP; data presented in the table are untransformed values.

The proportion of subjects achieving an ACR_{20} response was greater for all anakinra groups compared to placebo. Using Dunnett's adjustment for multiple comparisons, only the 150 mg dose had a significant effect on the ACR_{20} response.

A significantly higher proportion of subjects receiving anakinra 150 mg achieved Good or Moderate EULAR response at week 24 compared to subjects receiving placebo ($p = 0.005$). In addition a significantly higher proportion of subjects receiving any dose of anakinra also achieved Good or Moderate EULAR response at week 24 compared to subjects receiving placebo ($p = 0.046$).

The extension study 0564 provided some evidence that the efficacy of anakinra was maintained for at least 48 weeks.

The efficacy of anakinra monotherapy was not compared to that of other DMARDS. Thus, the data presented are considered insufficient to support a claim for a first line indication for anakinra in the treatment in RA.

Some subjects included in study 0560 were intolerant to/have failed previous DMARD treatment. Although a higher proportion of subjects who received anakinra achieved an ACR_{20} response compared to subjects receiving placebo, due to small sample sizes, efficacy was not clearly demonstrated in these subjects with prior DMARD experience. Therefore the study is considered insufficient to support a claim for a second line indication for anakinra in the treatment in RA patients who have failed other therapies.

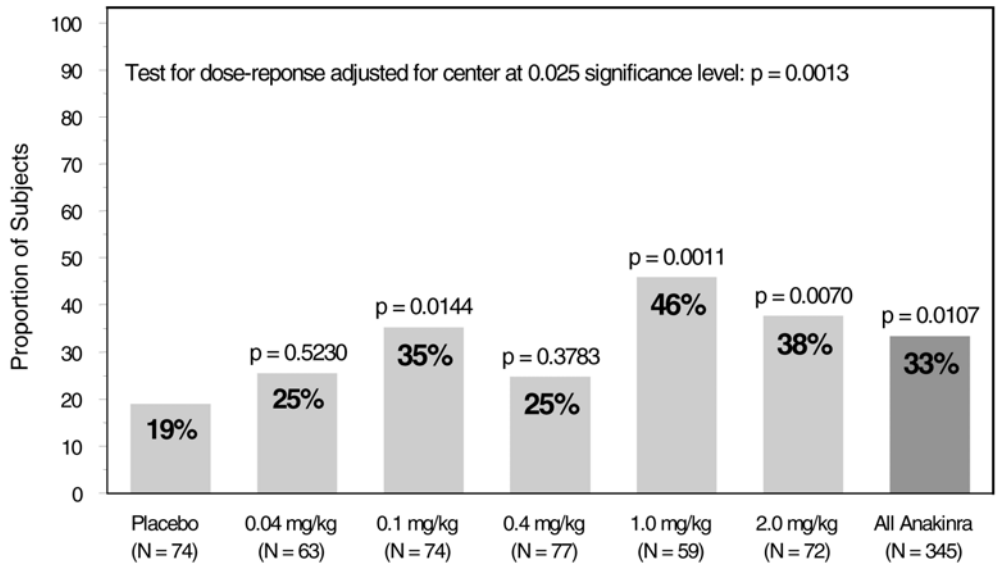
As only patients who completed study 0560 were eligible for inclusion in study 0564, the risk of "self-selection" favouring inclusion of patients who have some benefit from treatment without experiencing significant side effects was discussed. Although it has been demonstrated that the group of patients continuing in study 0564 did not differ from the group of patients included in study 0560 as regards demographic and disease characteristics, the risk of "self-selection" was taken into account when interpreting the results. A sensitivity analysis presented for ACR_{20} at week 24 based on the intention to treat population, indicated that self-selection did not appear to have had any major impact on the results.

In study 0560 and 0564, the potential effect on study outcome with respect to concomitant medication (27 - 58% of the patients receiving steroids) was examined. The analyses provided by the applicant demonstrates that the concomitant medication had no impact on the results.
In study 0560, protocol violations involving concomitant medication were relatively frequent. To investigate the effect of these protocol violations, supplementary analyses where subjects with protocol violations were considered as non-responders, were also performed.
Study 0560 provided evidence that anakinra significantly decreases the rate of radiographic progression of disease over a period of 48 weeks. Subjects treated with anakinra for 48 weeks demonstrated a significant slowing of radiographic progression seen as early as 24 weeks after initiating treatment. This reduction of radiographic progression was shown to be sustained for a further 24 weeks of anakinra treatment. At least 50% of subjects showed no further erosions and no further joint space narrowing after 24 and 48 weeks of treatment. However, because the radiographic data does not fully conform with the CPMP "Points to consider on slow-acting anti-rheumatic medicinal products in rheumatoid arthritis" (CPMP/EWP/556/95), a formal DCART claim cannot be granted.

- Study 960180

A total of 419 subjects were randomised and included in the ITT dataset.
This study demonstrated that in RA patients who are inadequately controlled on MTX, the addition of anakinra is superior to placebo as regards reduction of disease activity.
The result is clearly in favour of anakinra at 1.0 mg/kg, where a significantly higher proportion of patients (27%) achieved an ACR_{20} response over the placebo group at the primary efficacy endpoint.

Study 960180: Proportion of Subjects Achieving an ACR_{20} Response at Week 12 Intent-to-treat Population Using Nonresponder Imputation



N = Number of subjects randomized
p-values correspond to pairwise comparisons between each anakinra dose group and placebo adjusted for center

Study 960180: ACR Components and ESR Mean Change From Baseline at Week 24

	Study ITT Population		960180
	Placebo	Anakinra 1 mg/kg/d	Anakinra 2 mg/kg/d
Number Evaluable	**48**	**59**	**46**
Swollen Joints[a]	-4.17	-6.30	-7.61
Tender Joints[b]	-8.28	-8.83	-11.18
HAQ[c]	-0.15	-0.37*	-0.51**
Physician Global[d]	-14.08	-22.34*	-24.46*
Patient Global[d]	-3.61	-13.83*	-20.44**
Pain[e]	-2.58	-12.90*	-22.78**
CRP (mg/dL)	-0.19	-0.77	-0.77
ESR (mm/hr)	-4.15	-12.36**	-14.45**

* p-value < 0.05; ** p-value < 0.01
Least squares means and p-values obtained from ANOVA model adjusted for country group and treatment-by-country interaction. For study 960180 a Mixed Model was employed.

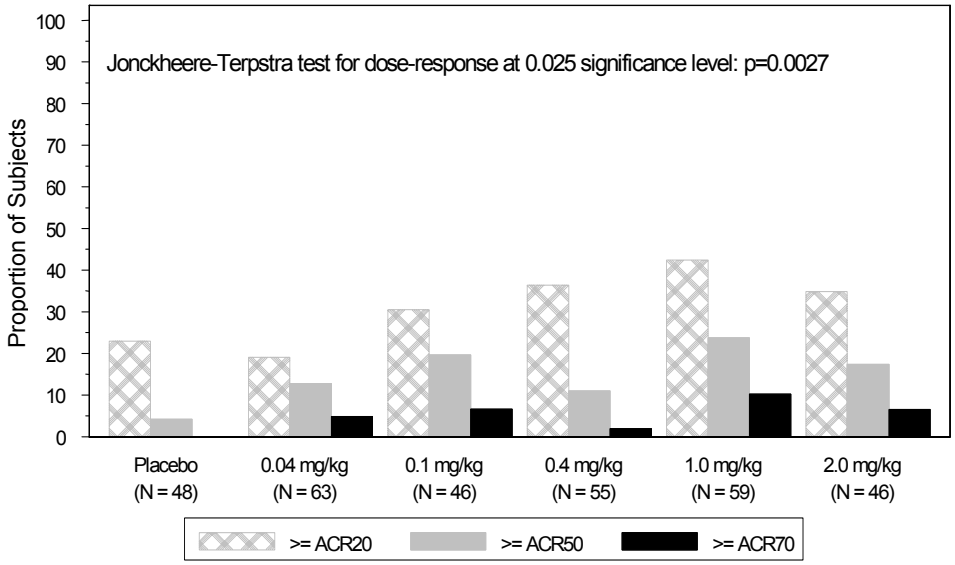
[a] Scale: 0 to 66
[b] Scale: 0 to 68
[c] Health Assessment Questionnaire: Scale 0 best to 3 worst, mean score over eight categories
[d] Visual Analogue Scale: 0 to 100
[e] Visual Analogue Scale: 0 to 100

Despite the relative low number of patients in this group (n = 59), the results for the 1.0 mg/kg anakinra group appear to be robust to possible bias caused by discontinuation, and potential unblinding due to injection site reactions (ISR). The effect of anakinra appears to be present across the population irrespectively of factors such as sex, age, duration of disease, previous DMARD use etc.

For study 960180, a higher proportion of subjects receiving anakinra 1.0 mg/kg achieved Good or Moderate EULAR response at week 24 compared to subjects receiving placebo. Although the results trended towards an effect, the result was not statistically significant (p = 0.059).

Furthermore, the magnitude of clinical response increased significantly across the doses explored. The proportion of subjects achieving an ACR_{50} response or ACR_{70} response was higher in subjects in most anakinra dose groups compared with subjects in the placebo group at 24 weeks and most pronounced in 2 highest anakinra dose groups.

Study 960180: Proportion of Subjects Responding by ACR Magnitude at Week 24 Intent-to-treat Population Using Nonresponder Imputation

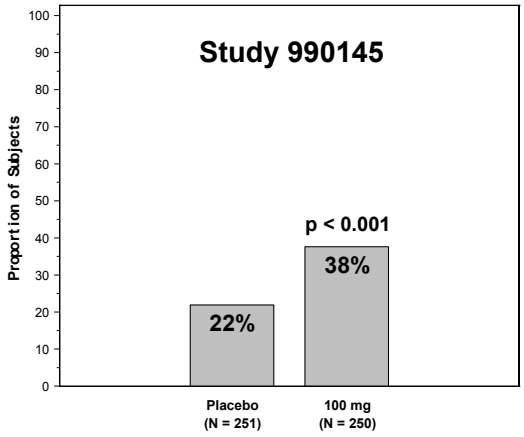


N = Number of evaluable subjects

- Study 990145

This prospectively designed confirmatory analysis of the signs and symptoms data, demonstrated that the ACR_{20} response rate is statistically significantly higher with anakinra (plus MTX) than with placebo (plus MTX). The proportion of subjects achieving at least an ACR_{20} response at week 24 was 38% (94/250) for anakinra plus MTX subjects versus 22% (55/251) for placebo plus MTX subjects ($p < 0.001$).

Study 990145: Proportion of Subjects Achieving an ACR20 Response at Week 24 Using Nonresponder Imputation



Study 990145: Summary of Changes from Baseline in Endpoints of Signs and Symptoms at Week 24

	Placebo (N = 251)	Anakinra (N = 250)
Tender/painful joint count (0 - 68)		
N	168	183
Adjusted mean	-8.65	-12.00
SE	0.90	0.88
p-value		0.006
Swollen joint count (0 - 66)		
N	168	183
Adjusted mean	-6.45	-6.78
SE	0.61	0.59
p-value		0.686
Physician's assessment of disease activity (0 - 100)		
N	169	181
Adjusted mean	-20.08	-25.16
SE	1.49	1.45
p-value		0.012
Subject's assessment of disease activity (0 - 100)		
N	169	181
Adjusted mean	-8.92	-17.73
SE	1.66	1.60
p-value		< 0.001
Subject's assessment of pain activity (0 – 100)		
N	169	181
Adjusted mean	-11.71	-19.00
SE	1.79	1.73
p-value		0.003
Health assessment questionnaire (0 - 3)		
N	169	183
Adjusted mean	-0.18	-0.29
SE	0.03	0.03
p-value		0.017
C-reactive protein (mg/dL)[a]		
N	170	184
Adjusted mean	-0.10	-0.51
SE	0.04	0.03
p-value		< 0.001
Erythrocyte sedimentation rate (mm/hr)		
N	170	182
Adjusted mean	-5.98	-16.19
SE	1.25	1.22
p-value		< 0.001
Duration of morning stiffness (min/day)		
N	169	183
Adjusted mean	-35.66	-48.17
SE	5.81	5.62
p-value		0.112

N Number of subjects who were randomised as of 18 May 2000 and who received at least 1 dose of study drug

n Number of subjects included in analysis at week 24

SE Standard error of the adjusted mean

The adjusted mean and SE are estimated based on a repeated measures mixed model adjusted for study week, treatment by study week interaction, centre and baseline value.

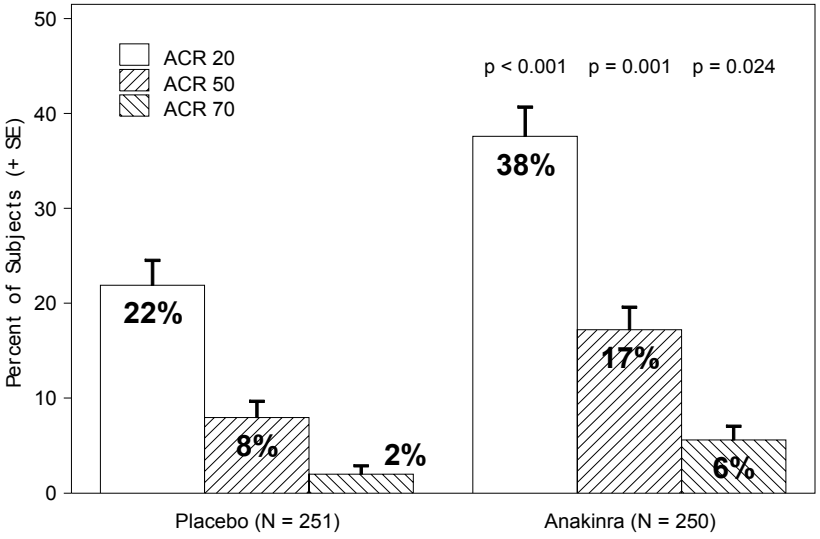
p-value corresponds to the comparison between anakinra and placebo.

[a] Based on log transformed values

The breakdown of the data into the percentage of responders by treatment groups indicates that like for the ACR_{20} response criteria, anakinra also increases the number of patients fulfilling the more stringent response criteria ACR_{50} and ACR_{70}. In study 990145, improvements of 50% and 70% in the

symptoms of RA were significantly more common for subjects receiving anakinra than for those receiving placebo.

Study 990145: Percent of Subjects by ACR Level of Improvement at Week 24 Using Non-responder Imputation



N = Number of subjects who were randomized as of 18 May 2000 and who received at least 1 dose of study drug
p-value corresponds to comparison between anakinra and placebo using a logistic regression adjusted for center

The data presented supports that anakinra 100 mg/day is superior to placebo in reducing signs and symptoms of disease activity in RA patients inadequately controlled on MTX alone.
The original dose proposal was "at least 1.0 mg/kg" based upon an integrated weight-normalised analysis of the 0560 and 960180 data. Although study 990180 used a somewhat different dosing regimen to that of study 990145 (0.04 mg/kg to 2.0 mg/kg once daily in study 990180 compared to a fixed dose of 100 mg/day in study 990145), the two studies taken together supports the efficacy of anakinra 100 mg/day.
The efficacy of anakinra in combination with other DMARDs other than MTX has not been studied. The efficacy of anakinra has been demonstrated in combination with MTX only and this is the only indication for which approval is sought.

Clinical studies in special populations
Data available do not indicate that the efficacy of anakinra differs between elderly (age > 65 years) and non-elderly (age < 65 years) patients. Based on population pharmacokinetics, age does not appear to have a significant independent effect on anakinra elimination. However, there are no data on exposure levels in elderly. As elderly patients have lower body weight and different body composition than younger subjects, exposure levels will be higher than expected based solely on the difference in renal clearance. Safety data from study 990145 suggests that anakinra is not markedly different in patient below and above 65 years. As the risk of infections is increased in the elderly population, an appropriate warning has been included in the SPC.
Studies have not been carried out in children.

Exploratory analysis performed across trials (subset analyses)

In study 0560, a series of subset analyses were performed to examine if the positive effects observed for anakinra were mediated by baseline covariates. The applicant has demonstrated that the effect of anakinra is distributed uniformly across the study population. The evidence presented does not indicate that the effect of anakinra decreases in patients with more severe disease. However the analyses presented are not considered sufficient to support a second-line indication.

Data summaries on the percentage of responders by treatment groups have been provided for studies 960180 and 0560. As regards the individual components of the ACR composite, anakinra improves all components except for tender joint count. The proportion of patients achieving 20% improvement of the individual components was generally higher in the anakinra group than in the placebo group, supporting the conclusions of the primary analysis.

Also as regards the EULAR response criteria, anakinra appears superior to placebo. As requested by the CPMP, a statistical analysis of the differences between the EULAR response rates for anakinra and placebo was performed for studies 0560 and 960180. In the individual pivotal studies 0560 and 960180, higher proportions of subjects either receiving anakinra 150 mg or 1.0 mg/kg achieved a Good or Moderate EULAR response at week 24 compared to subjects receiving placebo.

Clinical safety

Summary of Exposure to Anakinra

	Patients Exposed		**Patient-years Exposure**	
	Placebo	**Anakinra**	**Placebo**	**Anakinra**
Pivotal RA studies and extensions[a]	195	829	69.6	1034.0
Other RA studies[b]	48	411	7.0	275.74
Totals	243	1240	76.6	1309.74

[a] Studies 0560, 0564, 0564E1, 0564E2, 0564E3, 960180, and 960181

[b] Studies 0501, 0502, 0502E, 0505, 0512, 960182, 970102, 970189, and 980220

Duration of Exposure to Anakinra

Dose Level	**< 75 mg/day or < 1.0 mg/kg/day**	**≥ 75 mg/day or ≥ 1.0 mg/kg/day**
Total patients exposed	270	559
Total patients exposed for ≥ 6 months	172	318
Total patients exposed for ≥ 1 year	108	175

Adverse events and serious adverse event/deaths

Generally the safety profile of anakinra appears acceptable. Apart from injection sites reactions (ISR), anakinra is generally well tolerated. ISR are common but usually mild to moderate and not requiring discontinuation. In addition to ISR, headache, abdominal pain and rash occurred more frequently in patients treated with anakinra compared to patients who received placebo.

Anakinra was associated with a small risk of hypersensitivity reactions. None of these involved true anaphylactic shock. However, the SPC includes an appropriate warning about this risk and instructions about necessary measures in case of hypersensitivity. Compared to placebo, anakinra was not associated with an overall increased risk of serious adverse events.

The data suggest that anakinra may also be associated with an increased incidence of serious infections. The incidence of serious infections in the placebo- controlled trials was 1.8% for anakinra subjects and 0.7% in the placebo subjects. It must be concluded that the results of study 990757 in combination with the previously reported studies demonstrate that anakinra is associated with an increased risk of serious infections. The type of infections associated with anakinra treatment does not appear substantially different from what can be observed in a heavily treated RA population. Provided that adequate measures are taken, this problem is considered to be manageable. It should be stressed that all immunosuppression is associated with an increased risk of infection. The importance of this

risk must always be weighed against the risks of the disease itself and the efficacy of the drug. The SPC warns about this and provides adequate recommendations as regards special precautions.
The available data does not suggest that anakinra has any negative effect on renal function in humans. The incidence of serious and non-serious adverse events related to the renal system did not differ significantly between placebo and anakinra treated patients. Proteinuria was present at baseline in a substantial number of patients in both the anakinra and the placebo group. The fraction of patients experiencing deterioration of proteinuria or proteinuria "de novo" was similar in anakinra and placebo treated patients. This was also true for haematuria. Patients with significant proteinuria were identified. None of the cases were associated with abnormal serum creatinin. Significant proteinuria was not constant and in most cases patients entered the study with proteinuria.
Anakinra was not associated with any clinically relevant effect on vital signs or with any significant adverse effect on renal function.
Exposure adjusted death and malignancy rates during anakinra exposure were not significantly different from what is expected in a similar untreated population. However, the duration of exposure and hence the number of cases in the safety database is relative small. Thus the estimates of the number of malignancies are relatively imprecise. While the data seem to rule out that anakinra is associated with a major increase in the risk of malignancies, a smaller increase cannot be ruled out. Such effects can only be estimated after larger scale exposure. Consequently, the applicant has proposed a post-marketing surveillance program designed to address this issue.
Study 990145 provided supportive evidence that the safety profile of anakinra and MTX is similar to the safety profile of anakinra monotherapy. Compared to placebo, anakinra treatment (with or without MTX) is associated with significantly higher risk of injection site reactions although the majority (95%) were mild to moderate in severity. Furthermore, infections appear more common in the anakinra group than in the placebo group.
Study 990757 was designed to provide additional supportive data evaluating the safety of anakinra in a controlled clinical trial setting with a large number of subjects (N = 1414) who were representative of a broad rheumatoid arthritis (RA) population. These subjects were receiving a broad range of DMARDs and in some cases, multiple DMARDs.
This study confirmed previous safety experience and is considered supportive for the general safety of anakinra. Anakinra is associated with increased risk of ISR, but these are generally mild to moderate and rarely leading to discontinuation of treatment. As to be expected due to its pharmacodynamic effect, anakinra was also associated with an increased risk of serious infections (1.8% in the anakinra group compared to 0.7% in the placebo group). The spectrum of infections was generally unremarkable and infections resolved upon discontinuation of anakinra treatment and initiation of appropriate antibiotic treatment. The present data does not indicate that anakinra treatment is associated with an increased incidence of malignancies.
Combination treatment with anakinra and TNF-alpha blockers cannot be recommended at the present time, as clinical evidence of the safety and efficacy of the combination has not been established.
There were no deaths related to adverse events.

Laboratory findings

Apart from decreases in WBC and ANC count, anakinra was not associated with any clinically relevant changes in laboratory parameters. In a minority of patients the decrease in WBC and ANC count appears excessive and at least potentially harmful. Although no clinical sequelae were reported and the leucopenia appears reversible, anakinra should not be used in patients with leucopenia and/or neutropenia. Furthermore during anakinra treatment, WBC and ANC counts should be monitored and appropriate warnings and recommendations are stated in section 4.4 of the SPC.
The data on antibody response to anakinra indicates that the risk of development of antibodies against anakinra is low and that presence of antibodies is not associated with adverse effects or lack of efficacy. The adverse event profile of the subjects who provided a positive response in neutralising antibody tests to anakinra was unremarkable. It is concluded that neutralising antibodies are rare and even if they do occur, the limited data does not indicate that they are of clinical relevance.

Safety in special populations

Detailed examination of the anakinra safety database confirms that RA patients with a history of asthma can be safely treated with anakinra. With respect to worsening of asthma, no recommendation for caution in the use of anakinra in patients with a history of asthma is required.

The available data does not suggest that the safety profile of anakinra differs between patients with normal renal function and patients with mild to moderate renal impairment. This conclusion is based on a relatively large population of patients with mild renal impairment (400 patients) and a smaller population of patients with moderate renal impairment. Based on these numbers it is appropriate to allow use in mild renal impairment without any restrictions.
Anakinra can be used in patients with moderate renal impairment. However caution should be exercised due to the limited experience in these patients. Because of the documented higher exposure and lack of safety data in patients with severe renal impairment, anakinra should be contraindicated in these patients.

Post Marketing surveillance:
Patients treated with Kineret and etanercept were observed to have a higher rate of serious infection when compared with historical controls that were treated with Kineret. In addition, in a double-blind placebo-controlled trial in patients receiving background methotrexate, patients treated with Kineret and etanercept were observed to have a higher rate of serious infections and neutropenia than patients treated with etanercept (see section 4.4).

The MAH has submitted data from the Amgen clinical trials (20000125 and 20000223) an updated draft SmPC and Clinical Expert report and copies of the CIOMS forms relating to the reports of serious infections

The study 20000223 was a multicentre, double-blind, randomised, and active-controlled study with a duration of 24 weeks. RA patients on a stable MTX dose of 10-25 mg/week with active disease were randomised to one of 3 treatment arms:

Group 1: Etanercept 25 mg twice weekly
Group 2: Etanercept 25 mg once weekly + anakinra 100mg daily
Group 3: Etanercept 25 mg twice weekly + anakinra 100 mg daily

Therapy was initiated in 242 patients, with 80 patients in Group 1, and 81 patients each in Groups 2 and 3.
The primary efficacy endpoint was the proportion of subjects achieving improvements of 50% according to the American College of Rheumatology (ACR) response criteria at 24 weeks (ACR-50). The secondary efficacy endpoints included the proportion of subjects with improvements of 20% (ACR-20) and 70% (ACR-70) at 12 weeks and 24 weeks.

Efficacy results
The efficacy results showed that there was no beneficit in patients receiving combination treatment with etanercept and anakinra when compared to patients receiving etanercept alone. Comparisons of the ACR-50 response at week 24 demonstrated no significant differences between the 3 treatment groups, the result were 41%, 39% and 31% in group 1,2 and 3 respectively.

Safety results
Overall, 204 of the 242 patients enrolled in the study completed the study. 75 in group 1, 63 in group 2 and 66 in Group 3. The differences in withdrawal rates in the combined-therapy groups were attributed to occurrence of adverse effects. A total of 13 subjects in the combination groups withdrew due to adverse events, compared to no subjects in the etanercept alone group. Injection site reactions were reported in 69% of patients receiving combination therapy compared to 40% in the etanercept alone group. Other frequently reported adverse reactions were upper respiratory tract infections (15%) and nausea (10%).
A total of 26 patients reported serious adverse events. The proportion of patients in the combination treatment groups who reported serious adverse events (21/162, 13%) was twice the number seen in the etanercept alone group (5/80, 6%). The most commonly reported serious adverse event were injection site pain (3), pneumonia (3) and cellulitis (3). These were reported in patients taking combination therapy.

Serious infections
Serious infections were experienced by 9/162 (6%) of patients receiving combination therapy. No patients in the etanercept alone group (Group 1) experienced any serious infections. The reported infections were: Pneumonia (3), Cellulitis(3),Herpes zoster,Pyelonephritis,Pneumonitis (1 each). In 2 cases, one of cellulitis and one of pneumonitis, the investigator considered the infection to be unrelated to the study drugs. Of the 3 patients with cellulitis, one had diabetes requiring insulin therapy, one had an antecedent wound, and all three patients were also being treated with prednisone. Of the three patients with pneumonia, one had asthma and the diagnosis of pneumonia was not supported by laboratory investigations in another patient

One patient had a fatal outcome. This was a 70 year old female who was on concomitant treatment with MTX (15mg/week) and rofecoxib (25mg twice daily). The patient developed a wound infection after seven weeks of therapy. She was subsequently hospitalised with antibiotic associated gastroenteritis. The patient died of acute respiratory failure which was attributed to pulmonary fibrosis.

5. Overall conclusions and benefit/risk assessment

Quality
The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
Viral Safety and Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications.

Preclinical pharmacology and toxicology
Overall, the primary pharmacodynamic studies provided adequate evidence that through its antagonist function, anakinra inhibits the action of the IL-1 cytokines IL-1α and IL-1β which are considered to be critical mediators of inflammation and joint damage in RA. The general pharmacology studies indicated that the safety pharmacology profile was acceptable, concerning central/autonomic, analgesic activity, anti-inflammatory activity, cardiovascular, digestive or renal functions.
Overall, the toxicology programme revealed low toxicity of anakinra even at high single or repeated doses. Some indications of kidney toxicity seen in rats were concluded to be related to anti-anakinra antibody formation which is anticipated not to pose a problem in the clinical situation.

Efficacy
Studies 0560 and 990180 indicated that anakinra given as monotherapy or in combination with MTX, respectively, is superior to placebo as concerns reduction of signs and symptoms of disease activity in patients with RA.
However since the efficacy of anakinra was not compared to that of established therapy (e.g. MTX), a first line monotherapy indication was not considered acceptable. Furthermore, as the placebo controlled study included a mixed population of both DMARD naïve and DMARD experienced patients, it was not clearly demonstrated that anakinra (as monotherapy) would be effective in patients unresponsive to previous DMARDs. Based on these objections, only the indication for "treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients inadequately controlled on methotrexate alone" was considered acceptable.
Although this indication was supported by the originally submitted study 960180, the CPMP considered that the sample size of this study was insufficient to provide robust evidence of the efficacy of anakinra. In order to respond to the concerns of the CPMP, the applicant provided confirmatory efficacy data on signs and symptoms of disease activity from the ongoing study 990145, primarily designed to investigate the effect of 100 mg/day anakinra plus MTX on the progression of structural damage in patients with RA.
After initiating the study, but before breaking the blind, the applicant prospectively designed a confirmatory analysis of the signs and symptoms data of all subjects who received ≥ 1 dose of study drug. This analysis, which included 501 patients demonstrated that the ACR_{20} response rate is statistically significantly higher with anakinra (plus MTX) than with placebo (plus MTX): 38% versus 22%, $p = 0.00005$. Although study 960180 used a somewhat different dosing regimen than study

990145 (0.04 mg/kg to 2.0 mg/kg s.c. once daily in study 990180 compared to a fixed dose of 100 mg/day in study 990145), the two studies taken together supports the efficacy of anakinra 100 mg/day.
The validity of this analysis as an appropriate basis for the approval of a drug was debated by the CPMP and was defended by the applicant at an oral explanation held on 17 October 2001. The applicant's claim that the analysis presented is the final analysis of signs and symptoms and that no other analysis will be performed on the signs and symptoms endpoint was accepted on the basis that that the signs and symptoms analysis was prospectively defined and documented prior to the blind break i.e.:

- Clearly stated objective and hypothesis (confirmation of signs and symptoms)
- Specified primary endpoint of ACR_{20} at 6 months
- Prospectively determined sample size (n = 500)
- Tested at 0.05 alpha level which excludes the opportunity for any further confirmatory analysis of signs and symptoms.

Safety
The size of the safety database of anakinra fulfils the requirement of the relevant ICH Guideline. Furthermore the size of the safety database compares favourably with the size of safety databases of anti-TNF products recently approved for similar indications. The safety profile of anakinra is acceptable for this type of product. Injection site reactions (ISR) are common but rarely severe or require discontinuation. Neutropenia occurs in approximately 2.5% of treated patients. In most cases, neutropenia is mild and reversible even during continued treatment. However, more severe cases have been reported and a few of these patients had infections, although none of these infections were serious. Provided that adequate precautions are taken, this risk is considered manageable. As concerns serious infections, anakinra is associated with a small but increased risk. This is to be expected and has required warnings in the SPC and adequate precautions during use. The present data does not indicate that anakinra is associated with an increased risk of malignancies. However, the limited duration of exposure does not allow any firm conclusions on this question. Finally, a few cases of positive results from neutralising antibody tests with anakinra have been reported. The presence of these antibodies was, however, not associated with any clinically relevant adverse events. Overall, the safety of anakinra has been adequately demonstrated.
Post-marketing surveillance is necessary. The applicant proposes to address the issue of long term safety (especially cancer and infections) by setting up a case-control study in collaboration with British Society of Rheumatology (BSR). Currently the BSR have set up a prospectively defined case-control study involving patients with RA who are treated with anti-TNF medication. The aim of the study is to investigate the potential effect of anti-TNF therapy on risk of malignancies. The applicant is planning to make an agreement with BSR to include patients treated with anakinra in the above-mentioned study.

Concurrent administration of etanercept and Kineret has been associated with an increased risk of serious infections and neutropenia. This combination has not demonstrated increased clinical benefit; such use is not recommended .

Benefit/risk assessment
Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Kineret was favourable in the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients with an inadequate response to methotrexate alone.