European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Arcalyst

International Nonproprietary Name: rilonacept

Procedure No. EMEA/H/C/001047

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

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Regeneron UK Limited submitted on 04 July 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Arcalyst, which was designated as an orphan medicinal product EU/3/07/456 on 10 July 2007. Arcalyst was designated as an orphan medicinal product in the following indication: the treatment of cryopyrin-associated periodic syndromes (Familial Cold Urticaria Syndrome (FCUS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA)). The calculated prevalence of these conditions was less than 0.05 in 10,000 persons in the European Union, which, at the time of designation, corresponded to about 2,500 persons.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

The applicant applied for the following indication treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

The approved indication was:

ARCALYST is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) with severe symptoms, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and children aged 12 years and older.

Protocol Assistance

The applicant did not seek Protocol Assistance from the CHMP.

Licensing status:

Arcalyst has been given a Marketing Authorisation in the United States of America on 27th February 2008.

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

Rapporteur: **Ian Hudson** Co-Rapporteur: **Christian K. Schneider**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 04 July 2008.
- The procedure started on 23 July 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 October 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 October 2008. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 17-20 November 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 November 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 April 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 June 2009.

- During the meeting on 22-25 June 2009, the CHMP agreed on the List of Outstanding Issues to be sent to the applicant. The List of Outstanding Issues was sent to the applicant on 25 June 2009.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 30 June 2009.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 09 July 2009.
- During the meeting on 20-23 July 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Arcalyst on 23 July 2009 The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 23 July 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Cryopyrin-associated periodic syndromes (CAPS) are a collection of hereditary periodic fever syndromes; inherited in an autosomal dominant manner, with a sporadic or familial pattern and are associated with mutations in the *CIAS1* gene resulting in an overproduction of IL-1β. They include Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) and Chronic Infantile Neurological, Cutaneous, and Articular Syndrome (CINCA), also known as Neonatal Onset Multisystem Inflammatory Disorder (NOMID).

These conditions are very rare, and Orphan Designation was granted to Arcalyst (EU/3/07/456).

CIAS1 encodes a protein called cryopyrin or NALP3 that is a component of the inflammasome, a protein complex that includes caspase-1 and controls activation of the proinflammatory cytokine, IL-1β (Agostini 2004). CAPS are associated with features of localized and systemic inflammation, including overproduction of serum amyloid A (SAA), a risk factor and pathogenic agent for amyloidosis. Clinical symptoms and signs associated with FCAS, MWS, and CINCA form a spectrum and vary in severity. Common characteristics of these autoinflammatory diseases include chronic inflammation with recurrent fever, cutaneous rash, conjunctivitis, arthralgias, fatigue, and polymorphonuclear leukocytosis with chemotaxis (e.g., migration into skin or CNS). Serious aspects of CAPS include chronic systemic inflammation, pain, impairment of day to day functioning, and chronic elevation of acute phase reactants, including SAA and the associated increased risk of amyloidosis, a severe complication of chronic inflammation in MWS.

About the Product

Arcalyst (rilonacept) is a dimeric fusion protein consisting of the ligand-binding domains of the human cytokine extracellular portions of the human interleukin-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG1. Rilonacept is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.

The pharmaceutical form is powder and solvent for solution for injection (80mg/ml) for subcutaneous use.

ARCALYST is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) with severe symptoms, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and children aged 12 years and older.

2.2 Quality aspects

Introduction

Arcalyst is presented as a lyophilized powder in glass vials and is formulated as a powder and solvent for solution for injection (80mg/ml) for subcutaneous use. The drug product (powder for solution for injection) is supplied in a 20 mL glass vial with a stopper and flip-off aluminium seal, within a thermoformed tray and an outer carton. The drug product is reconstituted before use with solvent for parenteral use (Sterilised Water for Injections), supplied in a 5 ml polyethylene ampoule.

Active Substance

The active substance of Arcalyst, rilonacept, is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP), linked in-line to the Fc portion of human IgG1. Rilonacept is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.

The drug product is presented as a lyophilized powder in glass vials and is formulated as a powder and solvent for solution for injection (80mg/ml). The proposed route of administration is subcutaneous use. The drug product (powder for solution for injection) is supplied in a 20 mL glass vial with a stopper and flip-off aluminium seal, within a thermoformed tray and an outer carton. The drug product

is reconstituted before use with solvent for parenteral use (Sterilised Water for Injections), supplied in a 5 ml polyethylene ampoule.

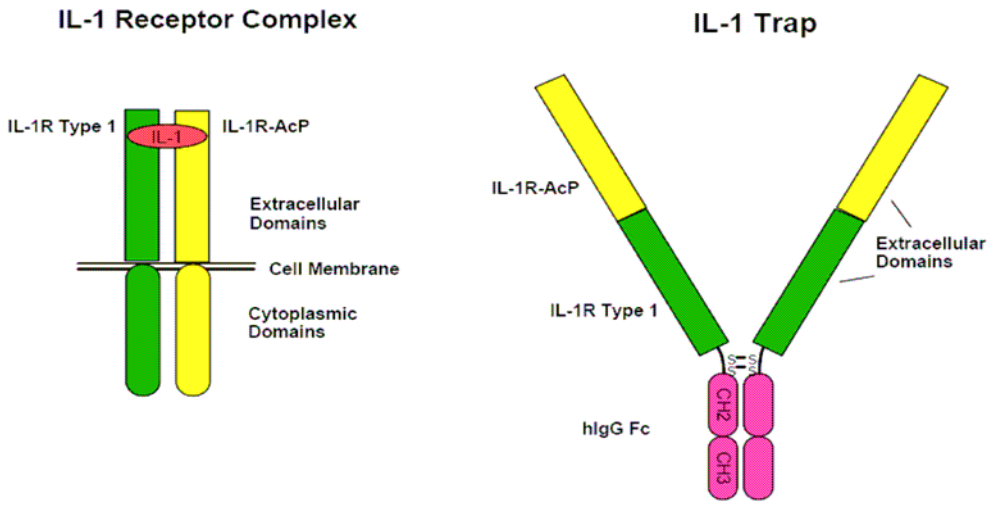
The adult dose consists of 2 ml of reconstituted product containing 160 mg of rilonacept. The pack includes 4 single use vials per carton, 220 mg rilonacept per vial. Cartons also include 4 ampoules of solvent, 8 sterile, disposable 3 mL syringes and 8 sterile, disposable needles.

Drug Substance

Rilonacept is a fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human IgG1. Rilonacept incorporates in a single molecule the extracellular domains of both receptor components required for IL-1 signalling: the IL-1 Type I receptor (IL-1RI) and the IL-1 receptor accessory protein (AcP). Since it contains both receptor components, rilonacept binds IL-1β and IL-1α with picomolar affinity, while the IL-1RI domain alone in the absence of AcP binds to IL-1β with ~1 nM affinity. Rilonacept was created by fusing the sequences encoding the extracellular domains of the IL-1R-AcP, IL-1R Type I, and hIgG Fc in-line without any intervening linker sequences. Rilonacept is a dimeric glycoprotein with a total molecular weight of ~251 kDa, of which 80% is protein (201 kDa) and 20% is carbohydrate (50 kDa).

The dimer is covalently linked by disulphide bonds in the Fc region. It is hypothesized that IL-1β binds between the two chains as shown by the schematic in the below figure. The dimeric rilonacept binds a single molecule of IL-1β with high affinity, which suggests that binding of a second molecule of IL-1 is sterically unfavourable. The schematic drawing of the protein is provided below (Figure 3.2.S.1.2 1-1).

Figure 3.2.S.1.2 1-1 Schematic of the IL-1 Trap



The IL-1 Trap is created by fusing the sequences encoding the extracellular domains of the AcP, IL-1RI, and Fc inline without any intervening linker sequences.

- Manufacture

Rilonacept drug substance is manufactured by Regeneron Pharmaceuticals, (Tarrytown, NY, USA) at the Regeneron facilities located at 81 Columbia Turnpike, Rensselaer, New York 12144-3423, USA, in compliance with Good Manufacturing Practices (GMP). Quality Control testing is also performed at the Regeneron, Rensselaer site.

Chinese Hamster Ovary (CHO) cells are used as the cell substrate for production of drug substance. CHO cells have been engineered to constitutively express rilonacept. Rilonacept is secreted into the culture medium and subsequently isolated and purified using chromatographic and membrane filtration techniques. Adequate information on the starting materials and reagents were provided, including specifications, methods and validations. Specifications have been set for the intermediates,

starting materials and reagents. The impurities are discussed. Methods and where relevant validations have been provided.

- Specification

In general the specification provided for the drug substance and the proposed limits are acceptable. The active substance specifications include tests for appearance, identification, strength, potency, purity and impurities. The specifications reflect all relevant quality attributes of the active substance and are adequately described.

Batch analysis showed consistent production of rilonacept, for the conformance batches and three further full-scale manufacturing batches. The proposed specifications are considered appropriate for rilonacept Drug Substance and the applicant has committed to revise the specification limits after a total of 15 batches are available. Some minor issues related to the specification, which do not have an impact on the positive risk-benefit of the product, remain to be addressed by the Applicant. A corresponding commitment has been provided by the Applicant.

- Stability

The drug substance is not stored before formulation. Stability studies, mainly photostability and forced degradation studies, are described for the drug substance prior to formulation. The drug substance is formulated immediately prior to storage. Data to support the storage of formulated drug substance have been provided.

Medicinal Product

Rilonacept drug product (DP) is supplied as a lyophilized powder in a 20 mL glass vial for reconstitution with 2.3 mL of sterile Water for Injection (WFI). After reconstitution of rilonacept with 2.3 mL of sterile WFI, the solution contains 80 mg/mL rilonacept in an aqueous buffered solution at containing histidine, polyethylene glycol 3350 (PEG 3350), glycine, L-arginine, and sucrose. The total volume of reconstituted rilonacept is 2.7 mL, which allows withdrawal of 2.0 mL (160 mg) for dosage of the patient. The overage allows for losses in the large vials and handling of the viscous product (80mg/mL protein).

- Pharmaceutical Development

Adequate data on the formulation development, including the lyophilisation cycle have been provided by the Applicant. The choice and function of the excipients in the formulation were described.

The container closure systems (1L polycarbonate bottle for formulated drug substance and 20mm glass vial with stoppers and seals for drug product) are demonstrated to be suitable, with respect to compatibility and microbiological safety.

- Manufacture of the Product

Rilonacept drug substance is formulated in an aqueous buffered solution containing histidine, polyethylene glycol 3350, glycine, arginine and sucrose. Rilonacept drug substance is compounded with the formulation buffer to obtain formulated drug substance which is filtered into vials and lyophilized. In-process controls of the production process are considered satisfactory.

Process validation of the rilonacept formulation process at Regeneron included three consecutive full scale batches. Variations between the formulation step described in the validation report and the commercial process have been clarified, with the validation report for the formulation step reflecting the current manufacturing process.

- Product Specification

Specifications for the drug product are satisfactory on the whole, although the specifications should be reviewed and tightened where appropriate. The applicant has committed to revising the DP specifications after a specified number of commercial batches.

Batch analysis for the Drug Product batches have been provided and appear satisfactory.

- Stability of the Product

Stability of the formulated drug substance was adequately demonstrated. The real-time data for 24 months (one supporting lot + three conformance lots) supports the requested shelf-life of 18 months at the storage condition of ≤ -20°C. A commitment to revise the current limits in light of new stability data using commercial batches has been obtained from the Applicant and is considered acceptable.

Stability studies for the lyophilised drug product, with long-term stability at -80°C (6 months) and 5°C (up to 36 months) and accelerated/stress studies at 25°C/60% RH or 45°C/75% RH (up to 6 months), demonstrated acceptable stability under real time conditions of 2 to 8°C for up to 24 months. In-use stability for reconstituted rilonacept drug product was established up to 4 hours at 25°C.

Photostability studies demonstrated significant photosensitivity of the liquid (FDS) as well as the lyophilised product. Storage of the vials with the final drug product in the outer pack was considered to be suitable for light protection for the lyophilized product. Light protection for formulated drug substance storage has also been improved and is considered adequately addressed.

- Adventitious Agents

Except for the CHO cell line, no materials of animal origin are used. No other animal-derived materials are used in the preparation of the active substance or the excipients. Foetal bovine serum (FBS) was used in the preparation of the Research Cell Bank and an initial cell bank established for long-term storage. Certificates of Suitability have been provided for the FBS used in these cell banks. There was no direct use of animal-derived materials in the current Master Cell Bank or Working Cell Banks.

Recombinant insulin is a constituent of the production media used in the rilonacept cell culture. The insulin is produced using materials of animal origin (peptone, pepticase and beef extract). The applicant has confirmed that the two recombinant insulin products are pharmaceutical grade recombinant, human insulin that complies to the EP and USP monographs. Details of the risk assessment and appropriate Certificates of Suitability for insulin have been provided.

All adventitious agents testing for unprocessed bulk, cells at the limit of in vitro cell age, and cell banks is performed according to ICH Q5A, Q5B, and Q5D guidance documents. Test results demonstrated that all test materials were free of detectable adventitious microbial and viral agents. The cells were shown to contain non-infectious, retrovirus-like particles that are a typical feature of the parental CHO-K1 cell line.

The key viral clearing steps from the final manufacturing process were included in detailed viral clearance studies.

The data provided by the applicant provides reassurance that the key viral clearing steps are capable of effectively removing both enveloped and non-enveloped virus species.

In summary the Applicant has provided sufficient information to conclude that the TSE and viral safety of rilonacept has been assured. The risk of TSE transmission through Arcalyst can be excluded and hence the risk of transmitting TSE by Arcalyst is considered very remote.

Water for injection (WFI), syringe and needles for drug product

The manufacturer of the WFI is B. Braun, Melsungen AG, Germany. 5 mL plastic ampoules (MiniPlasco) of sterile water for injection are supplied with the rilonacept Lyophilised Powder.

Manufacture of the WFI is described and appropriate process controls are applied including testing according to Ph. Eur. The containers are transparent plastic ampoules and are made from low density polyethylene without additives, for containers for parenteral and ophthalmic preparations. The terminal sterilisation in polyethylene ampoules has been validated and is satisfactory. The product complies with the Ph Eur monograph for WFI and batch analysis data is provided.

The material necessary for injection of rilonacept (WFI, syringe and needles) are included in the presentations. The pack includes four vials of rilonacept powder and four ampoules of solvent (WFI), with eight sterile disposable 3mL syringes and eight sterile disposable 27-gauge ½ inch needles. The

applicant has provided CE marking details and certificates for the syringe and needles enclosed in the pack.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the Active Substance and Medicinal product have been presented in a satisfactory manner. The results of the tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Risk-benefit balance of the product. The applicant provided a Letter of Undertaking and committed to resolve these as follow-up measures after the opinion, within an agreed timeframe.

2.3 Non-clinical aspects

Introduction

The applicant has conducted an acceptable programme of non-clinical studies for rilonacept, with the exception of the lack of information on placental transfer. The applicant has committed to conduct an additional embryo-fetal developmental toxicity study to investigate this and other aspects of effects during gestation as a follow-up measure (FUM).

GLP

The pivotal non-clinical toxicity studies were all reported to be GLP-compliant. Some minor deviations from GLP have been documented but none is considered to be such as to invalidate the affected studies.

Pharmacology

- Primary pharmacodynamics

The pharmacology of rilonacept was characterised by investigation of target binding interactions, species cross-reactivity and *in vivo* activity supporting an anti-inflammatory indication. Secondary pharmacodynamic studies were limited to investigation of the immunogenicity of rilonacept in rodents and determination of the rate at which antibodies were formed.

Rilonacept was shown to have similar binding to human and cynomolgus macaque IL-1β, IL-1α and the endogenous receptor antagonist of IL-1 receptors, IL-1ra, but a lower affinity for murine IL-1β, IL-1α and IL-1ra. A murine analogue (mIL-1 Trap) was generated and engineered using murine IL-1 receptor genes and Fc domain in a manner mimicking the design of the human version. The binding affinities of mIL-1 Trap for murine IL-1 cytokines were of a similar order to those of rilonacept for the human and monkey ligands.

No specific binding was observed for any of a standard panel of human or monkey tissues upon visualisation with secondary reagents and chromogenic substrate.

- Secondary pharmacodynamics

In a mouse model, rilonacept blocked the production of IL-6 in response to human IL-1β. mIL-1 Trap was active in a mouse model of collagen-induced arthritis, in which it blocked the development of arthritic joints and prevented cartilage erosion in the hind limb joints. Neointimal hyperplasia, induced by ligation of a carotid artery in mice, was also prevented by mIL-1 Trap.

Rilonacept was immunogenic in two strains of mice and one of rats.

There was no evidence that rilonacept activates complement-dependent or antibody-dependent cytotoxicity Fc effector functions.

- Safety pharmacology programme

No adverse effects of rilonacept were observed in safety pharmacology evaluations following repeated dosing of cynomolgus monkeys via intravenous or subcutaneous routes of administration at doses up to 60 mg/kg or 100 mg/kg respectively.

- Pharmacodynamic drug interactions

Not investigated in animal models.

Pharmacokinetics

The pharmacokinetics of rilonacept were investigated in mice, rats and cynomolgus monkeys following single subcutaneous and intravenous administration at doses between 0.3 and 10 mg/kg. Although anti-IL-1 Trap antibodies eventually developed in mice, rats and monkeys, they did not

occur early enough to influence the conclusions from single-dose pharmacokinetic studies. Traditional absorption, distribution, metabolism, and excretion (ADME) studies were not performed, which is acceptable for a glycoprotein.

In rats, C_{max} and AUC increased approximately proportionally with dose after a single SC administration. In monkeys, the AUC increased slightly more than proportionally with dose between 0.3 and 1 mg/kg then proportionally with dose up to 10 mg/kg. The bioavailability of approximately 60 and 70% following SC administration of rilonacept in rats and monkeys, respectively, supported the clinical use of this route of administration. After IV administration, the decline of the rilonacept in serum is biphasic. The terminal half-lives were 61, 38 - 57, and 64 hours in mice, rats and monkeys, respectively, compared with approximately 1 week in humans. The total serum clearance of rilonacept is as follows: mice, 1.6 mL/h/kg rats, 1.4 – 1.8 mL/h/kg and monkeys, 1.9 mL/h/kg. The pharmacokinetic indices of mice, rats and cynomolgus monkeys were similar between males and females within a given species.

A study was conducted to investigate the distribution of radio-labelled rilonacept in rats, but the results were not considered informative because the radio-labelled rilonacept was cleared 12.4 times more rapidly than the unlabelled form. The study indicated that ^{125}I-labelled rilonacept distributes rapidly to highly perfused organs, such as liver, kidney, lung and spleen. No further distribution studies were performed. Clearance through the kidney was not expected or observed. Instead, increased levels of iodinated rilonacept were observed in the liver, which is a known target organ for protein elimination via proteolytic processing.

Rilonacept is a glycoprotein and the level of sialylation affects the pharmacokinetic indices determined after SC administration to rats. The fractional content of sialic acid for a given preparation is called the Z number. A series of independent experiments revealed increased clearance in manufactured batches or purified fractions with low sialic acid content. The results also indicated increased clearance and lower C_{max} and AUC in manufactured batches or purified fractions with low Z number, although there is substantial variability in the pharmacokinetic values observed for either duplicate PK analysis of a single batch, or between different batches with similar Z numbers. Based on a linear regression analysis of the results obtained for Z numbers of between 1.4 and 1.8, the 95% confidence interval variability was 35% for AUCinf. Although the animal data suggest that there is an acceptable range of pharmacokinetic variability in rilonacept batches with Z numbers in the upper range, it is difficult to extrapolate these results to predict pharmacokinetic behaviour quantitatively in humans. It is not established whether pharmacokinetics of rilonacept in rats is a valid predictor of the effect of sialylation in humans, and clearance of rilonacept is much slower in humans than in rodents.

Rilonacept was not found in the amniotic fluid or fetal plasma of monkeys but the samples were collected more than fifty days after the last dose. Antibodies to rilonacept were found in the fetal serum and it is assumed that these were derived from the maternal circulation. It is not known if rilonacept is excreted in the milk. Further investigations will be the subject of a FUM.

Toxicology

The toxicity profile of IL-1 Trap was evaluated in subcutaneous (SC) repeat-dose studies in mice and monkeys, intravenous (IV) repeat-dose studies in monkeys, and developmental and reproductive toxicity studies in mice and monkeys. Because of the potential immunogenicity issues that can develop when using a human recombinant protein in other species, a murine analogue of IL-1 Trap was used for the toxicology studies in mice.

The applicant stated that the material used for the pivotal toxicity studies was representative of that intended for marketing.

- Single-dose toxicity

Specific single-dose toxicology studies were not conducted and the CHMP accepted that they were not likely to contribute to the safety evaluation of rilonacept.

- Repeat-dose toxicity (with toxicokinetics)

The safety studies include repeated-dose toxicity with periods of recovery in cynomolgus monkeys, and developmental and reproductive toxicity studies in cynomolgus monkeys and mice; a number of non-pivotal studies was also conducted. The choice of the cynomolgus monkey was justified on the basis of a tissue cross-reactivity study; there was also no evidence of binding to either monkey or human tissues, indicating a low potential for off-target effects.

The most notable toxicological findings when rilonacept was administered SC in the 6-week and 3 month toxicology studies in cynomolgus monkeys were injection site reactions. These reactions, which are thought to be immune-mediated pathologic sequelae rather than a direct effect of the drug, largely resolved during recovery time off drug. Clinically relevant drug concentrations were not maintained over the course of these studies because of an anti-drug antibody response in over 90% of the monkeys that increased drug clearance. Therefore, higher dose and more frequent administration strategies were used in the 26-week studies to increase exposure.

Large but relatively infrequent IV doses were administered to achieve high C_{max} concentrations with the recognition that drug levels would be low for much of the treatment period because of accelerated clearance. In a second study, the magnitude of SC dose and frequency of administration were increased to override the antibody response, resulting in sustained drug levels throughout the treatment period. Increasing the dose and frequency of administration carried the recognised risk of inducing toxicity from an immune response to the drug, as opposed to any direct effect of IL-1 blockade.

In the 6-month IV study, doses up to 100 mg/kg once every two weeks, which was the highest dose tested, were administered without reaching the NOAEL, although one animal at 100 mg/kg was killed *in extremis* in week 26 following a urinary tract infection and a few animals had sporadic episodes of emesis.

In the 6-month SC study, doses between 15 and 60 mg/kg were administered three times weekly. There was no signal of an increased rate of infections in animals treated with drug. Drug administration in the two high dose groups of 40 and 60 mg/kg resulted in toxicity, which is considered to have resulted at least in part from an anti-drug immune response. The findings in the 15 and 25 mg/kg three times weekly groups did not preclude administration of drug up to these doses in humans. In the 25 mg/kg group of the 6-month SC toxicology study, mean peak plasma rilonacept levels 24 hours after the first and third doses within the first week were approximately 260 µg/mL and 620 µg/mL, respectively. Twenty-four hours after the last dose and in the presence of antibodies, the mean peak plasma level was approximately 200 µg/mL. Although there was a decrease in mean peak plasma level between the third and the last doses because of circulating antibodies, the mean peak plasma level of rilonacept in monkeys exceeds that of the human single-dose PK with a safety factor of around 4 - 8. Also, the dosage of 25 mg/kg three times per week administered SC (75 mg/kg/week), exceeds the currently planned weekly SC dose in humans for CAPS (160 mg/week or 3.2 mg/kg /week for a 50 kg human) with a margin of more than 20.

There was no evidence of an effect on immune function or potential serum complement activation.

The complex of IL-1β and rilonacept was also detected in samples from the six-month SC monkey toxicology study using an optimised, but unvalidated assay in a non-GLP exploratory analysis. These data indicated that rilonacept bound endogenous monkey IL-1β in the toxicology studies, as expected given the similar potency of binding to monkey and human cytokines.

- Genotoxicity

No genotoxicity studies were conducted, and the CHMP considered this acceptable for a product of this nature. A review of the manufacturing process did not suggest the potential presence of any impurities likely to be genotoxic.

- Carcinogenicity

The absence of carcinogenicity studies was considered acceptable for recombinant therapeutic protein. The applicant also noted that there was no reason to suppose that rilonacept is likely to have proliferative or mitogenic properties. IL-1 Trap is not related to any growth hormone or other protein with potential proliferative activity.

The applicant has provided a discussion on IL-1 and tumourigenesis from peer reviewed publications: it was concluded that the data suggest that IL-1 is involved with tumour induction, growth and progression, and that IL-1 blockade via naturally occurring or engineered molecules can suppress tumourigenesis, metastasis, and angiogenesis in a variety of *in vitro* and *in vivo* settings.

- Reproduction Toxicity

A fertility study (Segment I) and pre- and post-natal development study (Segment III) were conducted in mice using mIL-1 Trap. mIL-1 Trap was administered SC at doses of 20 to 200 mg/kg. The low dose was chosen as it gives definitive activity in the CIA mouse model and the high dose was chosen as ten times a definitive pharmacologically active dose (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). There were no effects on the fertility of males or females or on pre- and post-natal development at does up to 200 mg/kg. An embryo-fetal development study (Segment II) conducted in cynomolgus monkeys was performed using rilonacept at doses up to 30 mg/kg administered twice weekly. There were decreases in β-estradiol levels; there are no data to confirm whether this also occurs in humans. The applicant has committed to investigate this further in monkeys in an additional embryo-fetal developmental toxicity study as the FUM noted above. There were no effects on fetal weight, anatomic measurements or soft tissue observations. There was no clear increase in the incidence of skeletal malformations or numerical bone counts.

It is not known whether rilonacept crosses the placenta or is excreted in the milk; the latter point was covered in Section 4.6 of the SPC and the former will be investigated as part of the above-mentioned FUM.

It is accepted that the outcome of the studies conducted using mIL-1 Trap is limited to the identification of potential hazards through blocking IL1 and is not a definitive estimate of risk for rilonacept. Studies in knockout mice where IL-1β or IL-1α were deleted indicated no effect on reproduction (Dinarello, 2003). These strains reproduced normally. Also, mice deficient in the IL-1RI gene exhibited no overt phenotype and reproduced normally (Glaccum, 1997; Labow, 1997). These results suggest that blockade of IL-1 will not have an impact upon reproduction; however, experiments in animals might not be predictive of outcomes in humans.

- Local tolerance

Local tolerance was assessed by evaluation of the injection site responses during the repeat-dose toxicity studies. Inflammatory changes were seen at the injection sites in the repeat-dose toxicity studies; during the recovery period, these changes were almost completely reversed. Additional studies of local tolerance were not considered necessary by the CHMP.

- Other toxicity studies

Immunotoxicity

Since blockade of IL-1 might potentially affect immune function, an assessment of immune function and potential serum complement activation was included as a component of the 6-month SC toxicology study in cynomolgus monkeys: the NK activity of peripheral blood mononuclear cells (PBMC) was examined as a measure for assessing drug-induced immunotoxicity. Rilonacept did not appear to affect adversely or enhance NK activity.

Ecotoxicity/environmental risk assessment

The absence of a formal environmental risk assessment is acceptable as rilonacept is a protein and is therefore exempt from the requirement for an Environmental Risk Assessment. Other components of the drug product are widely used approved excipients in pharmaceutical products and are unlikely to result in any significant risk to the environment.

2.4 Clinical aspects

Introduction

In addition to autoinflammatory diseases such as CAPS, the clinical development programme for rilonacept has included investigations in a number of other inflammatory diseases, which are not the subject of this application.

Protocol Assistance was not requested to CHMP.

Arcalyst is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

The Company applies for a broad indication covering all clinical situations. So far there is no approved treatment for the described indication.

In the pivotal trial Arcalyst has been administered once weekly as a subcutaneous injection at a dose of 160 mg in adults or 2.2 mg/kg in paediatric subjects.

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.

Pharmacokinetics

Six studies have been conducted contributing PK data.

The table below gives a summary of the design and relevant data from these clinical studies

Study Ref. No.	Study Objective	Study Design	Subject No. (M/F) Type Age: Mean (Range)	Treatments (Dose, Dosage Form, Route)	Dose Group	Mean Parameters* (+/- SD) Cmax/Dose (kg/L)	Tmax (hr)	Cl (mL / (day x kg))	Terminal Half-Life (day)	Study Report Location
IL1T-RA-0004, Part A and B	Evaluate efficacy, PK, and safety	Parallel	No. Subjects: 107 (25 in Part A single dose, 82 in Part B multiple dose) Part A: Age Range: 37-72 Age Mean: 53 Gender: F= 18 (72%), M= 7(28%) Part B: Age Range:23-74 Age Mean: 55 Gender: F= 67(82%), M= 15(18%)	Multiple weekly SC injections: Placebo, 50, 100, 200, 400, 800µg/kg	Mean of All Dose Groups	4.11 (1.4)	89 (27)	19.9 (10.3)	7.69 (1.52)	5.3.3.2.1
					50	4.35 (1.3)	90 (36)	18.8 (3.4)	8.15 (1.69)	
					100	3.00 (0.59)	96 (34)	24.1 (4.5)	6.67 (0.40)	
					200	3.73 (0.85)	96 (34)	22.5 (11.2)	8.96 (1.51)	
					400	4.94 (1.3)	78 (12)	12.0 (2.2)	7.28 (0.41)	
					800	4.53 (2.2)	84 (24)	22.1 (2.0)	7.37 (2.23)	
IL1T-RA-0401	Evaluate PK parameters after SC injection and compare two formulations	Parallel	No. Subjects: 103 Age Range: 19-69 Age Mean: 38.2 Gender: F= 55 (53.4%), M= 48 (46.6%)	Single SC injection: Placebo, 50, 80, 104, 120, 160, 240, 320mg	Mean of All Dose Groups†	3.83 (1.1)	84 (36)	22.8 (6.5)	6.31 (1.18)	5.3.3.1.1
					50	2.92 (1.0)	98 (37)	29.8 (14.2)	6.91 (1.54)	
					80	4.54 (0.97)	61 (12)	20.2 (4.2)	6.42 (0.94)	
					104	3.55 (1.06)	92 (34)	22.0 (4.9)	6.85 (0.86)	
					120	3.18 (1.22)	96 (44)	28.1 (8.6)	6.12 (1.53)	
					160	4.11 (0.73)	67 (11)	23.7 (4.4)	5.25 (1.51)	

					240	3.68 (1.21)	120 (48)	21.0 (5.5)	6.13 (0.83)	
					320	4.39 (0.94)	66 (12)	17.7 (4.1)	6.32 (1.03)	
IL1T-RA-0402	Evaluate PK parameters after IV infusion	Parallel	No. Subjects: 28 Age Range: 19-58 Age Mean: 40 Gender: F= 18 (64.3%), M= 10 (35.7%)	Single IV infusion: 100, 300, 1000, 2000mg	Mean of All Dose Groups	14.9 (2.60)	ND	10.3 (1.7)	7.48 (1.07)	5.3.3.1.2
					100	15.1 (2.1)	ND	9.8 (7.4)	7.54 (1.66)	
					300	15.8 (1.5)	ND	9.3 (1.5)	7.60 (1.19)	
					1000	12.1 (0.8)	ND	12.2 (1.6)	7.28 (0.84)	
					2000	16.6 (3.1)	ND	9.7 (1.6)	7.49 (0.74)	

Source: Population Pharmacokinetic Analysis Report, Tables Y.5, Y.6, Y.10, and Y.14
ND Tmax calculations were not performed for this single-dose study.
* Dose- and weight-adjusted PK parameters from the non-compartmental analyses conducted for the Population Pharmacokinetic Analysis Report.
† Calculated values omit the 50 mg dose cohort which utilized P2 DP and analysis was not relevant to the comparison of P1 and P3.

The rilonacept half-life (t1/2), apparent total body clearance (CLTB), and apparent volume of distribution at steady state (Vss) values all appeared to be independent of dose within the 100 mg to 2000 mg rilonacept dose range investigated. The t1/2 was long, at approximately 200 hours (range of means 187.5 hours to 253.7 hours), and both CLTB and Vss, were low, with CLTB at approximately 30 mL/hr (range of means 24.09 mL/hr to 33.28 mL/hr) and Vss, at approximately 6500 mL (range of means 5753.83 mL to 7468.17 mL), indicating that rilonacept is essentially confined to plasma.

PK data on serum levels in CAPS subjects on long-term treatment was provided and showed that following steady state at 5-6 weeks, no further accumulation of rilonacept occurred up to week 88.

One paediatric study and one study in RA patients were conducted using body weight adjusted dosing, in all other studies flat doses were applied. There has been no dose-finding study in CAPS patients, the rationale for the chosen dosing regimen for the intended indication (160 mg SC flat for adults and 2.2 mg/kg for children 5-17y) was based on results from IL1T-RA-0004 and from biopharmaceutics data showing that the binding of rilonacept to IL-1ß was not saturated at the 100mg weekly dose.

Pharmacokinetics after repeated subcutaneous doses was assessed in four multiple dose studies (two in RA patients, one in paediatric patients (ongoing) and in 22 CAPS patients during the Phase III study pertinent to the claimed indication. In all multiple dose studies only sparse samples were collected for determination of Ctrough values.

Mean steady state trough blood levels of total rilonacept following repeated administration of 160 mg weekly in CAPS patients during the relevant periods of drug dosing were calculated to be 23 µg/ml. Variability of measured Ctrough levels were high ranging from 0.68 to 43.4 µg/ml.

Predicted steady-state C_{max}, C_{trough}, and C_{max}/C_{trough} for the CAPS population by population PK model estimation were 31.5 mg/L, 24.8 mg/L, and 1.27 mg/L correspondingly.

Pharmacodynamics

- Mechanism of action

Rilonacept is an *in vivo* inhibitor of IL-1, since binding of IL-1 by Rilonacept blocks the bioactivity of the bound cytokine. Because of its structure, the Fc portion of rilonacept provides the basis for dimerization and a long circulating half-life. Rilonacept has a pharmacokinetic half-life of approximately seven days.

Free cytokine levels have not been measured before or after rilonacept administration. In contrast, cytokine complexes with rilonacept, i.e. Il-1ß bound to rilonacept (IL-1ß complex levels) and total IL-1ra levels (free and captured) were measured in four PD studies as well as in the pivotal CAPS study.

It was considered plausible that, due to the stochiometry of the complexes, total IL-1ra instead of bound IL-1ra was measured. Unfortunately, no baseline values of free cytokines before treatment (neither IL-1ß nor IL-1ra) were measured in the studies.

Complexes with IL-1ra generally comprised less than 15% of the total during active dosing, while IL-1β complexes comprised considerably less than 1% of the total. Thus, the vast majority of the rilonacept in serum is present as free rilonacept.

The IL-1ß complex levels were in the range of 1-4 pM except in CAPS patients where markedly higher levels of 19 pM (up to 66 pM) were measured. This was supposed to reflect the proposed IL-1β overproduction resulting from the cryopyrin mutations underlying CAPS.

Total IL-1ra levels determined in different studies after rilonacept were in the range of 6.6 – 22.5 nM, which exceeds the IL-1β complex levels in RA subjects by 1000-fold or more.

There was no evidence for a relationship between dose (rilonacept concentrations at the respective timepoints) and either IL-1ß complex levels or total IL-1ra levels. This is not surprising since the rilonacept concentrations are at any time very high compared to the affinity to the cytokines so that it has to be assumed that the cytokines are almost completely bound at any time and dose. Therefore, the bound cytokine levels appear to reflect the total amount of cytokine present in serum at the respective time point and do not serve as a biomarker for the response.

- Primary and Secondary pharmacology

Rilonacept tended to normalize the levels of a variety of different acute phase markers and hematological measures in essentially all of the RA studies. In one study, there were statistically significant decreases in CRP, erythrocyte sedimentation rate (ESR), and white blood cells, and there were trends to decrease platelets and rheumatoid factor (RF). Statistically significant decreases in CRP were evident in the 25 mg and 100 mg dose groups; administration of 50 mg also resulted in decreases that were numerically, but not statistically, significant. There was no conclusive evidence that administration of 100 mg rilonacept weekly gave a maximal response across all measured biomarkers.

In part A of the pivotal CAPS study CRP decreased from high baseline values of 20.1 mg/l to normalized mean values of 1.3 mg/l. Similarly, SAA levels decreased from high baseline values of 49.5 mg/l to normalized mean values of 2.5 mg/l.

Immunogenicity (development of anti-rilonacept antibodies) appeared to be very high in the multiple dose studies performed. In two out of 17 pediatric patients treated antibodies were found accompanied by a considerable and (at least in one patient) persistent decrease in rilonacept serum concentrations.

In the pivotal CAPS study, 43% of subjects (20 of 46) dosed with rilonacept for up to 24 weeks in Parts A and B of the study demonstrated a rilonacept-specific response in the anti-rilonacept antibody assay, respectively. The treatment profile (sequence of placebo and drug) of the patients did not determine either frequency or time point of the first appearance of antibodies. Of the 56 samples tested, ten samples from seven subjects were positive for neutralizing antibodies. Interestingly, five of the seven subjects who were positive for neutralizing antibodies tested negative for neutralization at a later timepoint. However, for safety considerations all (binding) antibodies are relevant, whereas the discrimination between binding and neutralising antibodies might be of importance in terms of efficacy reduction. Further investigations of immunogenicity in patients who have a reduction in efficacy are planned.

Two potential pharmacodynamic interactions were identified: Firstly, it is known from experience with another drug that blocks IL-1 (anakinra) that concomitant administration with a TNF-blocking agent has been associated with an increased risk of serious infections and an increased risk of neutropenia. Thus, the concomitant administration of rilonacept with TNF-blocking agents may also result in similar toxicities and should be avoided.

Secondly, the concomitant administration of rilonacept with other drugs that block IL-1 (anakinra) has not been studied. Based upon the potential for pharmacologic interactions between rilonacept and a recombinant IL-1ra, concomitant administration of rilonacept and other drugs that block IL-1 should be avoided.

Pharmacology studies were conducted to establish the in vitro and in vivo efficacy of the IL-1 Trap, including measuring the affinity of IL-1 Trap toward human, monkey, and murine IL-1 cytokines, evaluating the activity of the human and murine versions of the IL-1 Trap in murine models of inflammation, and assessing the immunogenicity of the human IL-1 Trap and murine IL-1 Trap (mIL-

1 Trap) in animals. Binding studies demonstrated that IL-1 Trap potently binds IL-1β and IL-1α from both humans and monkeys. Rilonacept also binds IL-1ra but with a lower affinity than IL-1β or IL-1 α.

Surface plasmon resonance technology (BiaCore) binding experiments were performed to measure the on and off rate constants, allowing calculation of the dissociation constants of IL-1 Trap to IL-1β, IL-1α, and IL-1ra from humans, monkeys, and mice

Clinical efficacy

Rilonacept was subject to clinical investigations in a number of rheumatic related indications and healthy subjects. Only the trials pertinent to this application for CAPS are discussed here.

The clinical development involved one pivotal phase III study consisting of part A and B and one open label exploratory dose-finding pilot study.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	IL1T-AI-0505	5.3.5.1.1	efficacy and long-term safety	Double-Blind, Placebo-Controlled parallel group and randomized withdrawal	PBO rilonacept: 160 mg SC Injection	58	Cryopyrin Associated Periodic Syndromes (CAPS)	48 weeks plus ongoing weekly in extension	Ongoing Full study report for 48 weeks
Pilot	IL1T-AI-0406	5.3.5.2.1	short-term efficacy	Open-Label	rilonacept: 100, 160 and 320 mg SC Injections	10	Auto-inflammatory Diseases	2 yrs	Completed Full

- Dose response studies

There was no formal dose response study for the sought CAPS indication (a dose-response study was conducted in Rheumatoid arthritis). Dose escalation was performed in trial ILIT-AI -0406, a short-term open label efficacy study of rilonacept as treatment for autoinflammatory diseases. Ten (10) subjects were enrolled (5 subjects with FCAS, 1 subject with FMF, and 4 subjects with adult-onset Still's disease (AOSD)).

All subjects received a 300 mg loading dose, and all but one FCAS subject (who escalated to 160 mg/week) and one AOSD subject (who received 300 mg/week) escalated to 320 mg/week of rilonacept. The escalation in dose was based on patient symptoms and clinical decision.

Treatment with a loading dose of 300 mg of rilonacept was associated with a significant reduction in mean subject key symptom score from Baseline to Day 10 for the FCAS subjects (Baseline mean, 1.1; Day 10 mean, 0.2, [0 to 4 scale]; mean percent change, -74% [p = 0.049]).

Active disease symptoms eventually returned during the observation period after the initial rilonacept loading regimen, and all subjects elected to reinstitute dosing of rilonacept in the 1-year extension phase.

Continued dosing at 100, 160, or 320 mg per week of rilonacept resulted in marked decreases in acute phase reactants, CRP, SAA, and ESR over time (all subjects).

In this open-label study, overall, rilonacept was well tolerated. Infections were the most commonly reported adverse events, but most were mild and resolved. One subject with AOSD was reported with a localized atypical mycobacterial infection (severe) for which he was hospitalized (an SAE). The patient was on chronic glucocorticoid treatment. The infection occurred after an intra-articular glucocorticoid injection into the olecranon bursa and subsequent local exposure to a suspected source of mycobacteria. The patient recovered after the administration of the appropriate antimicrobial therapy and debridement. This event was reported as possibly related to rilonacept.

Compatible with a decrease in an overall state of systemic inflammation, mean WBCs, which were high at study start declined with treatment (all subjects) and mean polymorphonuclear leukocytes (neutrophils) and platelets, which were high at study start, declined to within normal range with treatment. There were increases in mean hemoglobin and hematocrit values thought to be compatible with amelioration of bone marrow suppression of chronic inflammatory disease.

The results indicated that the dose of 160mg weekly after a loading dose of 300mg showed prolonged efficacy.

Development of assessment tool for CAPS

ILIT-AI-0507

The pivotal phase 3 study in CAPS was preceded by study ILIT-AI-0507, which was designed to develop a reliable measure of disease activity in CAPS because no measurement instrument had yet been established for the assessment of CAPS symptoms, some of which could only be assessed by patient report (e.g., feeling of fever/chills, joint pain, eye redness/pain, fatigue).

In order to develop a measurable primary efficacy endpoint that assessed clinical disease-related signs and symptoms, the applicant conducted an observational (non-treatment) study (IL1T-AI-0507) which was initiated to define the natural history of CAPS, identify clinical endpoints relevant to treatment of CAPS, and design a Daily Health Assessment Form (DHAF) for assessment of patient-reported outcomes.

DHAFs were used to capture daily patient-reported information regarding specific disease-related symptoms, global assessments (such as overall levels of disease activity), and functional limitations.

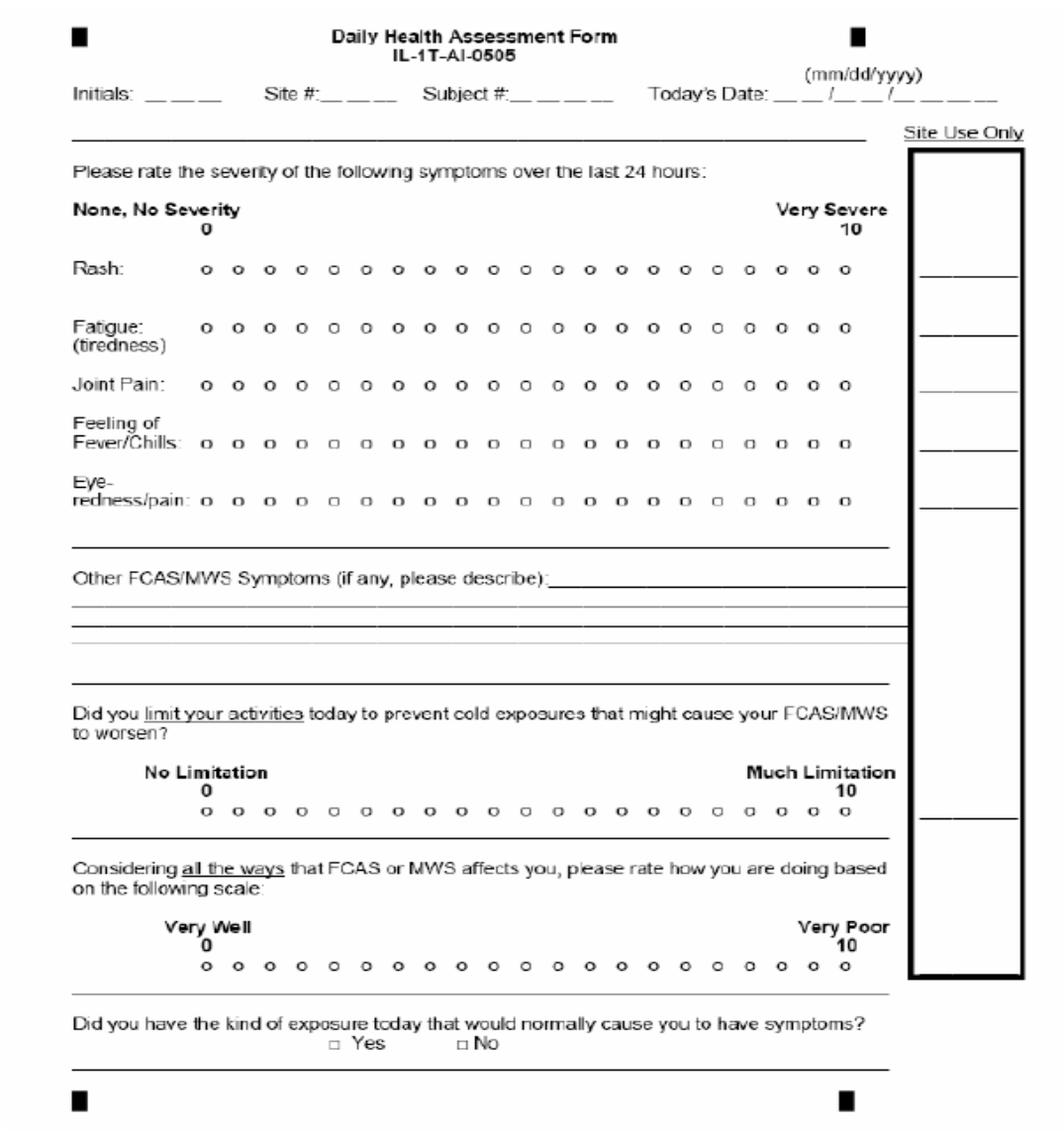
Phase 1 DHAFs asked subjects to report the severity of 11 CAPS related symptoms by using a VAS scale or categorical scale on alternating days. Data analyses from the archetype forms were used to revise the DHAF into a more streamlined form that queried five key symptoms of CAPS (rash, fever, joint pain, eye redness/pain, and fatigue) by using a 10-point VAS scale with half-unit increments. This form was validated for internal consistency (Cronbach alpha reliability measure) and stability of scores over time (test-retest reliability) was demonstrated.

Results

Subjects (n = 48) completed enrolment forms and DHAFs including 21-point VAS (anchored at 0 and 10 with half-unit increments) on a daily basis. There were 38 subjects with FCAS and 4 subjects with MWS enrolled in Phase 1. Median age was 50.8 years of age (range 13 to 82 years); 70% of subjects were female and 100% were white. Aside from CAPS, medical histories were compatible with this general population. The most frequent concomitant medications were nonsteroidal anti-inflammatory drugs (NSAIDs). Five subjects received the biological agent anakinra.

Key symptom scores (KSSs) showed large day-to-day variability highlighting the intermittent nature of these conditions and indicating that multi-week assessment periods would be necessary to create a meaningful endpoint for a therapeutic clinical trial. Three-week average KSS values during Phase 1 and Phase 2) showed means of 1.63 and 2.8, respectively, on a 10-point VAS. The average KSS for the most severe symptom (KSS_{max}) was 6.31 for Phase 1 and 7.59 for Phase 2, but was reported as high as 10 in some subjects. In the optimized DHAF 3a form (Phase 2), KSS correlated strongly with subject daily global assessment ($r = 0.91$, $p < 0.0001$) and limitation of daily activities ($r = 0.68$, $p < 0.0001$). C-reactive protein (CRP) and white blood cell (WBC) values were variable and frequently elevated, particularly in subjects with MWS.

An example of the final DHAF used is given below



Daily Health Assessment Form
IL-1T-AI-0505

Initials: ___ ___ ___ Site #:___ ___ ___ Subject #:___ ___ ___ ___ Today's Date: ___ ___ /___ ___ /___ ___ ___ ___ (mm/dd/yyyy)

Site Use Only

Please rate the severity of the following symptoms over the last 24 hours:

	None, No Severity 0																			Very Severe 10	Site Use Only
Rash:	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	
Fatigue: (tiredness)	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	
Joint Pain:	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	
Feeling of Fever/Chills:	o	o	o	o	□	o	o	o	o	o	□	o	o	o	o	o	□	o	o	o	
Eye-redness/pain:	o	o	o	o	□	o	o	o	o	o	□	o	o	o	o	o	□	o	o	o	

Other FCAS/MWS Symptoms (if any, please describe):

Did you limit your activities today to prevent cold exposures that might cause your FCAS/MWS to worsen?

No Limitation 0 — Much Limitation 10

o o o o o o o o o o o o o o o o o o o o o

Considering all the ways that FCAS or MWS affects you, please rate how you are doing based on the following scale:

Very Well 0 — Very Poor 10

o o o o o o o o o o o o o o o o o o o o o

Did you have the kind of exposure today that would normally cause you to have symptoms?
□ Yes □ No

Conclusions

FCAS and MWS are diseases with significant day-to-day variability. This variability pertains to symptoms as well as laboratory markers of FCAS and MWS and, therefore, disease activity is most effectively measured over multi-week periods. The DHAF form is an appropriate measurement instrument for the clinical evaluation of subjects with CAPS.

- Main studies

Study IL1T-AI-0505

This was the pivotal study in CAPS, a multi-centre, double-blind, placebo-controlled study of the safety, tolerability, and efficacy of rilonacept (weekly subcutaneous (SC) doses of 160 mg of rilonacept in subjects with *CIAS1*-Associated Periodic Syndromes (CAPS) in two parts, A and B, of parallel group and randomized withdrawal design).

METHODS

Study Participants

After written informed consent was obtained, subjects who met the protocol eligibility criteria were enrolled at one of 27 study sites in the United States. The study consisted of

- a 3-week screening period which provided baseline data for the Part A analysis;
- a 6-week randomised double-blind placebo-controlled treatment period (Part A);
- a 9-week single-blind active treatment period which provided baseline data for the Part B analysis;
- a 9-week double-blind randomised withdrawal phase (Part B);
- a 24-week open-label extension phase (OLE);
- a 64-week long-term open-label extension (LTOLE);

Amendments 4 and 6 allowed eligible adult and paediatric subjects to enrol directly into the open-label phases of the trial.

Eligible adult patients with either FCAS or MWS were randomised into the initial 6-week treatment period to receive weekly subcutaneous (sc) injections of either 160mg rilonacept or placebo in approximately equal numbers. Patients were stratified according to disease activity recorded at the Part A baseline in the daily health assessment form (DHAF). Stratum 1 included patients with a score of three or more in at least one key diary symptom during the 21-day baseline period; Stratum 2 included all patients with all scores less than 3. At the end of the 6-week randomised treatment period, all patients received rilonacept weekly for 9 weeks but remained blinded to treatment. Patients were then randomised again to receive either rilonacept or placebo weekly, again in a 1:1 ratio, for a further 9 weeks.

Treatments

There were no formal dose finding studies in CAPS and the dose chosen was based on a small phase II study and PK data in RA.

Patients received subcutaneous (sc) injections of either 160mg rilonacept or placebo.

Objectives

The primary objective was to assess the effect of rilonacept on the clinical signs and symptoms of CAPS when used for chronic therapy.

The secondary objectives were as follows:

- To determine the safety and tolerability of rilonacept in subjects with CAPS
- To assess the effect of rilonacept on laboratory measures of inflammation such as acute phase reactants

Outcomes/endpoints

The primary efficacy variable was the mean change from baseline to endpoint in the mean key symptom score (KSS). This was derived from the assessment of five key symptoms (rash, feeling of fever/chills, joint pain, fatigue and eye redness/pain) recorded daily by patients on the daily health assessment form (DHAF). Each symptom was assessed on a 21-point scale with 0.5-point intervals from 0=none to 10=very severe. For each day the mean of the 5 scores was calculated and the daily means were averaged over the number of days with recorded data in the 21-day observation period to provide a mean key symptom score for that period.

The primary efficacy variable was calculated for each randomised treatment period in Parts A and B. Baseline values for this variable were calculated for the corresponding 21-day period immediately before randomisation for entry into each part of the study.

The specification of the primary efficacy variable as the change from baseline in the mean key symptom score over a period of 21-days was based on the investigation of data recorded in the

observational study (IL1T-AI-0507). The use of the 21-day period was shown to reduce variability and to improve the sensitivity of the measure

A number of secondary and tertiary efficacy variables were investigated. An analysis of the mean change from baseline in the number of disease-flare days was conducted where a disease-flare day was defined as a day where the mean score exceeded 3 points. In addition the mean change in the number of single-symptom disease-flare days was analysed. Patients were also categorised according to the percentage improvement in the mean key symptom score. The analysis of categories of responders was conducted using Fisher's exact test.

No adjustment of the significance level was required as multiplicity of the primary efficacy analyses for each randomised period was controlled by testing a conditional sequence of hypotheses. All tests were two-sided at a significance level of 5%.

No subgroup analyses were planned due to the overall small sample size. No interim analyses were conducted.

Sample size

47 cases with CAPS (3 MWS and 44 with FCAS) were included. In view of the rarity of CAPS this sample size is acceptable.

Only three patients included in the study, one treated with rilonacept and two with placebo, were diagnosed as having MWS with 44 diagnosed with FCAS.

Randomisation

Fifty adult subjects were to be randomized on Day 0 (Visit 2) in a 1:1 ratio to receive a loading dose of 320 mg of rilonacept or placebo, with subsequent weekly SC injections of 160 mg of rilonacept or placebo for a total of 6 doses. Following completion of the double-blind period, subjects were eligible to receive weekly single-blind SC injections of rilonacept for 9 weeks, and were then re-randomized at Week 15 (Visit 7) in a 1:1 ratio to receive weekly SC injections of 160 mg of rilonacept or placebo for a 9-week randomized withdrawal period. Upon completion of this phase of the trial, subjects were eligible to receive weekly SC injections of 160 mg of rilonacept in the 24 week open-label extension phase, and then a 64-week long-term open-label extension; a second informed consent process was required prior to participation in the open-label extension phase of the study. A total of 60 subjects were planned to be screened at approximately 25 study centres in order to obtain 50 evaluable subjects for participation in Parts A & B of the study. Approximately 35 additional subjects, including paediatric subjects aged 7 to 17, are to be screened for entry directly into the open-label extension of the study as a result of protocol Amendments 4 and 6.

Table 8 Disposition of Subjects in Parts A and B

Disposition	Randomization A Part A and Part B Single-Blind		Randomization B Part B Randomized-Withdrawal	
	Rilonacept (n=23)	Placebo (n=24)	Rilonacept (n=22)	Placebo (n=23)
Completed	22	24	21	23
Withdrew for any reason	2 (8%)	0	1 (4%)	0
Reason for Withdrawal				
Adverse Event	0	0	1	0
Noncompliance with protocol	1* (4%)	0	0	0
Decision by Investigator or sponsor	0	0	0	0
Request for withdrawal by the subject	0	0	0	0
Lost to follow-up	0	0	0	0
Other	1† (4%)	0	0	0
Death	0	0	0	0

*This subject was removed from the study in the Part B single-blind phase of the study due to non-compliance with study drug dosing and study visits.
† Subject 018-6891 was removed from the study during Part A while being treated with rilonacept due to hepatitis C that was diagnosed after dosing but determined to have a pre-dose start date based upon Screening liver function test results
Source: Post-text Tables 9.1.3.1, 9.1.3.2

Blinding (masking)

The procedures for blinding were satisfactory.

Statistical methods

Two separate statistical analysis plans were planned for Part A and Part B of the study. In the protocol two populations were defined for the efficacy analysis of Part A. The full analysis set (FAS-A) would have included all randomised patients from Part A who were known to be genotype-positive for CAPS and who received at least one dose of study medication. The per-protocol set (PPS-A) would have included all patients in FAS-A except those with significant protocol violations. Two corresponding populations (FAS-B and PPS-B) were defined for Part B. At the data review meetings held before the blind was broken for any portion of the study it was determined that as protocol violations were minimal no PPS would be specified.

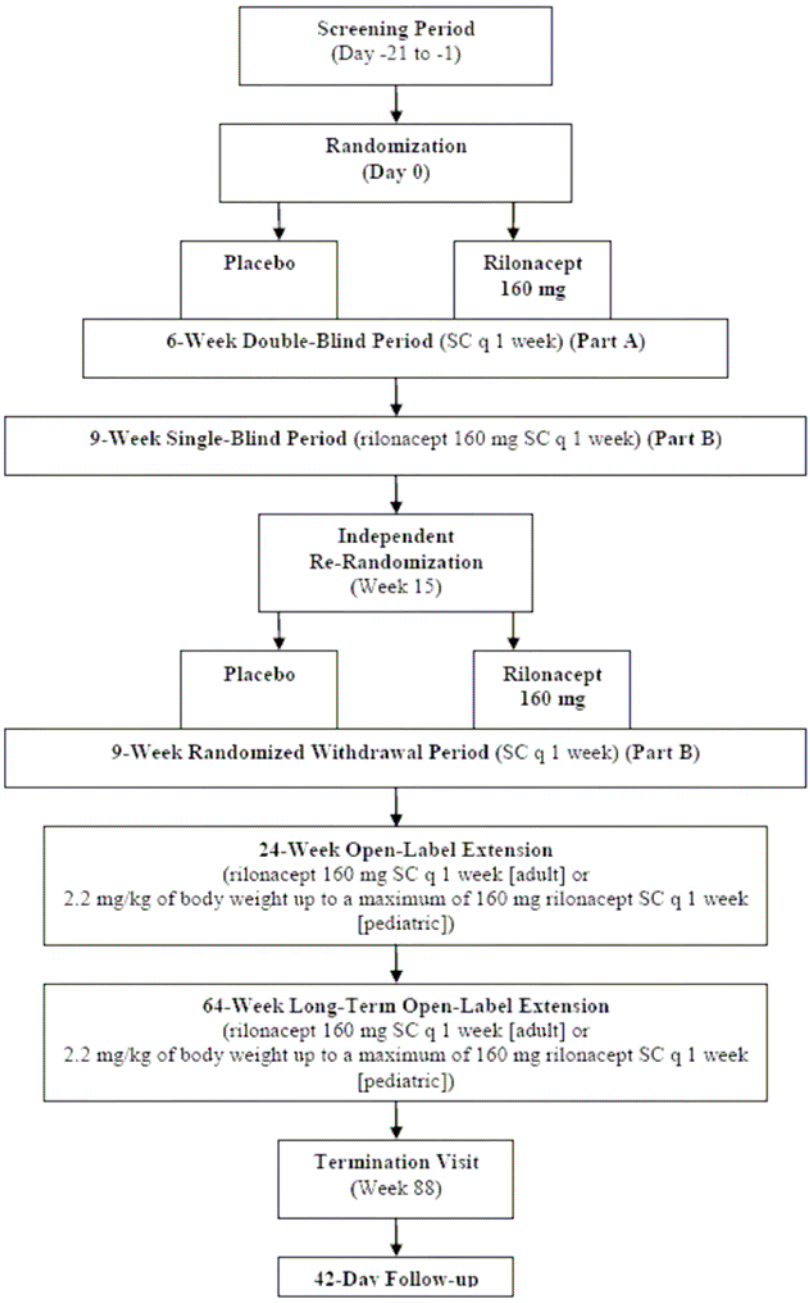
Therefore, as the FAS and PPS populations were almost identical, only one analysis set, FAS, was used for each part of the study. There were no concerns over this decision. The hierarchical testing scheme described is considered sufficient to control the Type I error for the primary analysis without further adjustments for multiplicity. The ANCOVA model including baseline as a covariate is appropriate for the analysis of the primary efficacy variable according to the guideline (CPMP/EWP/2863/99: Points to consider on adjustment for baseline covariates).

It was accepted that the small sample size prevented any meaningful subgroup analyses for patients with two different diagnoses (MWS and FCAS).

RESULTS

Participant flow

Figure 1 **Study Design Schematic**



Conduct of the study

The conduct of the study was deemed satisfactory.

Baseline data

All patients enrolled in Part A, the initial double-blind (DB) portion of the pivotal IL1T-AI-0505 study in CAPS, were white and predominantly female (66%). The racial and ethnic characteristics of study patients lacked diversity, a reflection of the genetic background of those afflicted with these rare genetic syndromes, where exon 3 L353P [L355P according to NM_004895.3 cDNA reference sequence] is the most common *CIAS1* mutation in North America and is associated with a founder family that accounts for up to 90% of cases of FCAS worldwide (Hoffman, 2004). Age ranged from

22 to 78 years. Weight ranged from 50-119 kg. Patients randomized to placebo had similar demographic characteristics to those randomized to rilonacept.

Table 9 Demographic and Baseline Characteristics for Subjects Randomized to Parts A and B – Full Analysis Set

Demographic Trait	Statistic	Randomized Subjects				Total (n=47)
		Randomization A Part A and Part B Single-Blind		Randomization B Part B Randomized-Withdrawal		
		Rilonacept (n=23)	Placebo (n=24)	Rilonacept (n=22)	Placebo (n=23)	
Age (years)	Mean (min-max)	46 (22, 76)	56 (24, 78)	52 (26, 78)	50 (22, 78)	51 (22, 78)
Gender	Number (%) Female	15 (65%)	16 (67%)	14 (64%)	16 (70%)	31 (66%)
	Number Male	8	8	8	7	16
Ethnic Origin	Number (%) White Non-Hispanic	23	24	22	23	47
	Number Black Non-Hispanic	0	0	0	0	0
	Number Hispanic	0	0	0	0	0
	Number Other	0	0	0	0	0
CIAS1 Gene Mutation Positive	Number (%) Yes	23 (100%)	24 (100%)	22 (100%)	23 (100%)	47 (100%)
Height (cm)	Mean (min-max)	168 (155, 190)	169 (158, 183)	170 (155, 190)	167 (158, 179)	168 (155, 190)
Weight (kg)	Mean (min-max)	72 (50, 114)	76 (50, 119)	76 (50, 119)	74 (50, 114)	74 (50, 119)
Baseline Key Symptom Score (KSS)	Mean (min-max)	3.08 (0.73, 8.15)	2.41 (0.64, 5.4)	0.32 (0, 1)	0.23 (0, 2.07)	2.74* (0.64, 8.15)

*Total KSS statistics reflect Part A, but DHAF statistics under Part B reflect Part B Baseline period
Source: Post-text Tables 9.1.3, 9.1.4, and 9.1.6

Numbers analysed

The small numbers and baseline demographics reflect the rarity and genetic background of CAPS. The placebo and rilonacept group were well matched.

Outcomes and estimation

Efficacy results

There was a highly statistically significant difference between the change from baseline for the group randomised to rilonacept compared to that of the group randomised to placebo ($p<0.0001$). This was confirmed in the sensitivity analyses where all models tested resulted in $p<0.0001$. It was concluded that rilonacept was superior to placebo in reducing the mean key symptom score from baseline.

A summary of the primary efficacy analysis for Part A is provided in the table below.

Table 11 **Summary of Mean Change from Baseline to Endpoint in Mean Key Symptom Score (KSS) – Primary Analysis in Part A**

Assessment Period	Statistic	Rilonacept (n=23)	Placebo (n=24)	Comparison p-value*
Baseline Part A	Mean KSS	3.1	2.4	
	Median KSS	2.8	2.0	
	SD	1.9	1.5	
	(min – max)	(0.7, 8.1)	(0.6, 5.4)	
	n	23	24	
Endpoint Part A (Week 6)	Mean KSS	0.5	2.1	
	Median KSS	0.3	1.5	
	SD	0.5	1.6	
	(min – max)	(0.0, 1.7)	(0.4, 6.5)	
	n	23	24	
Change from Baseline Part A to Endpoint Part A	Mean Change	-2.6	-0.3	P<0.0001
	Median Change	-2.3	-0.3	
	SD of Change	1.9	0.7	
	(min – max)	(-8.1, -0.1)	(-1.8, 1.1)	
	n	23	24	
	p-value of significance of change from Baseline†	p<0.0001	NS	

Mean key symptom score derived from the: Daily Health Assessment Form (diary questionnaire); symptom scale is 0=none to 10=very severe.
SD: standard deviation
* comparison p-value is parametric ANCOVA main effects model with Part A Baseline mean KSS as covariate and treatment
† p-value of significance of change from Baseline is 1-sample t-test
NS: not significant

Analysis of change from baseline in the number of disease-flare days and the number of single-symptom disease flare days in Part A of the study confirmed the result of the analysis of the primary variable with a statistically significant improvement in the rilonacept group compared to the placebo group (p<0.0001 in both).

The following table presents the results of the primary analysis for the 45 patients who entered into the Part B randomised-withdrawal portion of the study.

Table 18 Summary of Mean Change from Baseline to Endpoint in Mean Key Symptom Score (KSS): Primary Analysis for Part B

Assessment Period	Statistic	Rilonacept (n=22)	Placebo (n=23)	Comparison p-value*
Baseline Part B (Ending at Week 15)	Mean KSS	0.3	0.2	
	Median KSS	0.2	0.1	
	SD	0.3	0.4	
	(min – max)	(0.0, 1.0)	(0.0, 2.1)	
	n	22	23	
Endpoint Part B (Ending at Week 24)	Mean KSS	0.4	1.2	
	Median KSS	0.2	0.7	
	SD	0.5	1.0	
	(min – max)	(0.0, 2.0)	(0.0, 3.2)	
	n	22	23	
Change from Baseline Part B to Endpoint Part B in Mean KSS	Mean Change	0.1	0.9	P=0.0002
	Median Change	0.0	0.6	
	SD of Change	0.4	0.9	
	(min – max)	(-0.7, 1.5)	(-0.2, 2.7)	
	n	22	23	
	p-value of significance of change from Baseline†	NS	p<0.0001	

Mean Key Symptom Score is derived from the Daily Health Assessment Form (diary questionnaire); symptom scale is 0=no severity to 10=very severe.
SD: standard deviation
*Comparison p-value is parametric ANCOVA main effects model with Part A Baseline mean KSS as covariate and treatment
†p-value of significance of change from Baseline is 1-sample t-test
NS: not significant

As in Part A, comparing the two treatment groups there was a highly statistically significant difference between the change from baseline for the group randomised to rilonacept and that of the group randomised to placebo (p=0.0002). Sensitivity analyses confirmed this result. It was concluded that rilonacept was superior to placebo in maintaining the low levels of disease activity achieved during single-blind administration of study medication.

Analysis of change from baseline in the number of disease-flare days and the number of single-symptom disease-flare days in Part B of the study confirmed the result of the analysis of the primary variable with a statistically significant improvement in the rilonacept group compared to the placebo group (p=0.003 and p=0.01 respectively).

There were also improvements in indices of inflammation (CRP and SAA) as well as global assessments.

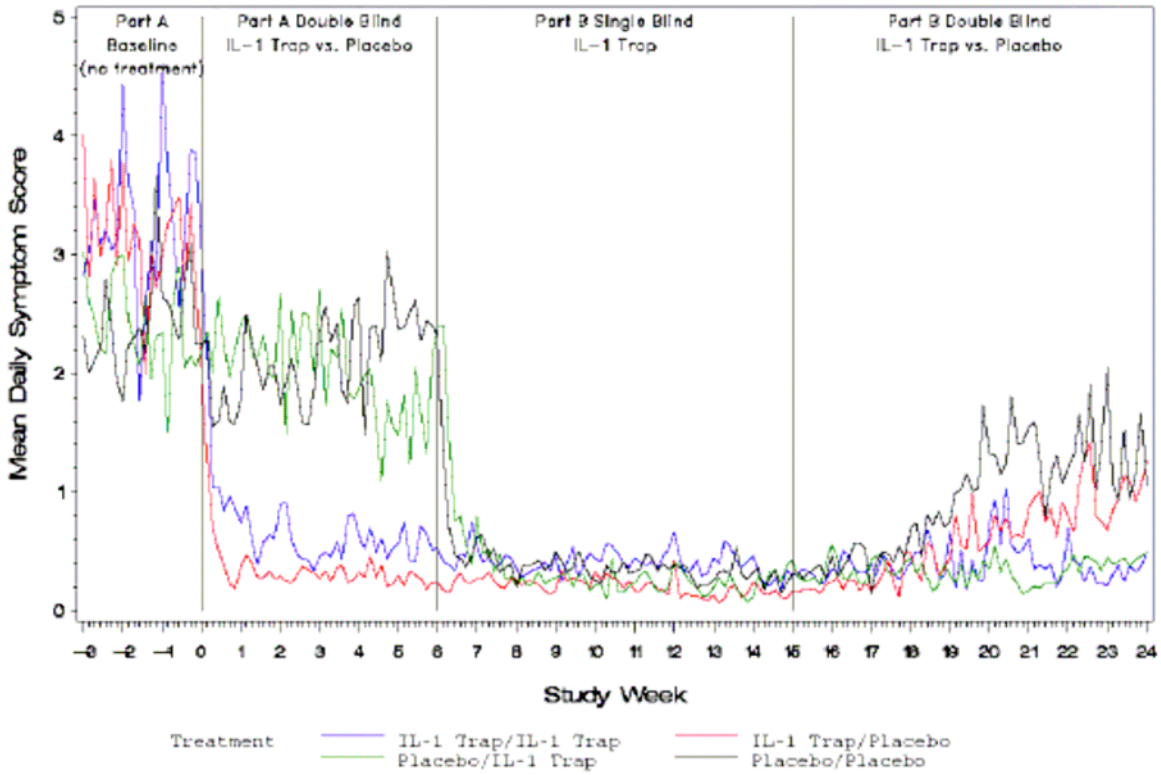
Table 16 Summary of Tertiary and Exploratory Measures of Efficacy for Part A (Physician's Global Assessment, Patient's Global Assessment, Limitation of Activities Assessment, CRP, SAA)

Symptom (Reference Range)	Treatment Group (Part A Randomization)	Baseline Mean	Endpoint Mean	Mean Change from Baseline to Endpoint	Comparison p-value*
Physician's Global	Rilonacept (n=23)	5.6	1.5	-4.2	<0.0001
	Placebo (n=24)	4.7	5.0	0.2	
Patient's Global	Rilonacept (n=23)	3.6	0.9	-2.7	<0.0001
	Placebo (n=24)	3.1	2.7	-0.4	
Limitation of Activities	Rilonacept (n=23)	3.0	0.8	-2.2	0.006
	Placebo (n=24)	2.4	1.6	-0.8	
CRP† (0.0 – 8.4 mg/L)	Rilonacept (n=23)	20.1†	1.3†	-18.4†	<0.0001
	Placebo (n=24)	25.2†	21.8†	-2.1†	
SAA† (0.7 – 6.4 mg/L)	Rilonacept (n=23)	49.5†	2.5†	-48.5†	0.006
	Placebo (n=24)	63.5†	39.7†	-2.8†	

Note: Sample sizes differ due to missing data for laboratory parameters
*Comparison p-value is parametric ANCOVA main effects model with Part A Baseline variable as covariate and treatment. The p-value represents the between-group comparison for placebo vs rilonacept treatment. All comparison p-values are calculated from the mean change from Baseline.
†The values displayed for CRP and SAA change from Baseline are median values.
CRP=C-reactive protein; SAA=serum amyloid A
Source: Post-test Tables 9.2.3.1.1, 9.2.3.2.1, 9.2.4.1.1, 9.2.4.2.1, 9.2.4.3.1, and Analysis Output in Statistical Appendix 11.1.9/T5.2A, T5.4A, T7.2A

Figure 9 below shows the KSS scores of patients throughout the trial up to week 24 and includes the randomised withdrawal period.

Figure 9 **Mean Daily Key Symptom Score by Treatment Group from Week Minus 3 (-3) to Week 24 in Study Part A and Part B**

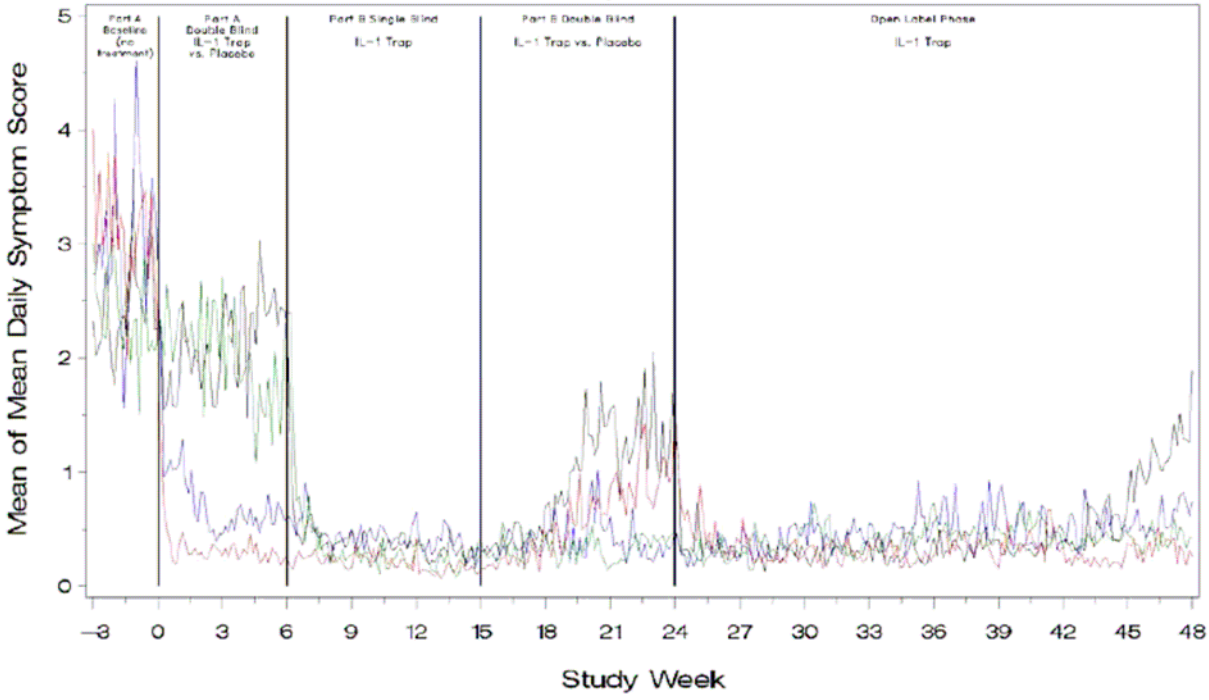


Source: Post-text Figure 9.4.2.3

At 9 weeks after cessation of therapy those on placebo have a lower score than at baseline. This raised the possibility of accumulation of rilonacept. However it was due to the fact that Part B of the study was performed in the summer months and as the majority of patient in the study had FCAS their frequency of flares were less during the randomised withdrawal period of the study.

A separate report was provided for the open label extension period from 24-48 weeks. This period of the trial included additional patients including 4 paediatric subjects. Efficacy was demonstrated in both symptom control and markers of inflammation over this prolonged extension phase.

Figure 3 **Group Mean Daily KSS by Treatment Group from Week -3 to Week 48 for Subjects Enrolled in Part A**



Source:Post-text Figure 9.4.1.1

- Clinical studies in special populations

Paediatric population

The fact that a limited number of paediatric patients were included in the clinical studies combined with the lack of data on the effect of long-term IL-1ß suppression was of concern. The Applicant will need to propose a plan to collect data from the registry on safety and efficacy in children; particularly risk of infection and possible impairment of immune reactions such as response to vaccinations and growth. Additionally, further PK steady state exposure data (AUC, C_{max}, c_{min} during steady state) for paediatric subjects is required.

Clinical safety

The pivotal clinical safety data supporting this application is derived from 1 controlled, double blind, international, Phase III study in adolescent and adult patients with Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

- Patient exposure

The overall extent of exposure for rilonacept was provided for all 17 rilonacept studies through a data cut-off date of 31 Dec 2007. A total of 614 patients were exposed to rilonacept.

Table 2.7.4-3 Number of Person Exposure Years (PEY) in each Dose Group by Study Grouping

Study Grouping	Placebo	Dose of rilonacept			All rilonacept Doses Combined	160 mg rilonacept or more
		< 160 mg	160 mg	> 160 mg		
Pivotal Study, IL1T-AI-0505 Part A	3.01 (n=24)	- (n=0)	3.01 (n=23)	- (n=0)	3.01 (n=23)	3.01 (n=23)
All CAPS patients	7.32 (n=35)	2.32 (n=5)	46.44 (n=64)	4.43 (n=4)	53.19 (n=64)	50.87 (n=64)
All studies	31.00 (n=186)	43.96 (n=257)	51.02 (n=97)	23.21 (n=79)	118.18 (n=417)	74.23 (n=168)
All placebo-controlled studies	26.27 (n=165)	40.91 (n=249)	3.73 (n=32)	7.92 (n=55)	52.55 (n=336)	11.64 (n=87)
Intravenous	4.60 (n=46)	- (n=0)	- (n=0)	11.21 (n=63)	11.21 (n=63)	-
Healthy Volunteers	1.33 (n=40)	1.48 (n=56)	0.52 (n=10)	1.15 (n=25)	3.15 (n=91)	-
Pediatric Population	0.46 (n=6)	- (n=0)	21.94 (n=16)	13.51 (n=12)	35.45 (n=28)	-

Note: Data cutoff: 31 December 2007
Exposure during the Part B of the Pivotal Study, IL1T-AI-0505 is not provided separately, however, it is included in the calculation for "All CAPS patients."
Definition: Year = 48 weeks; Pediatric population = ≤ 17 years of age
Source provided upon request: Exposure Tables 30.1, 30.2, 30.3, 30.4, 30.8, 30.9, 30.11

The 614 patients who received at least 1 dose (from all data sources), include subjects from healthy volunteer studies, patients from intravenous dosing studies, and patients from the ongoing studies of rilonacept. Seventy-seven (77) patients were treated for at least 1 year with rilonacept 160 mg or more. A summary of dose by duration of rilonacept exposure is provided in Table 2.7.4-4.

Table 2.7.4-4 Dose by Duration of Rilonacept from all Sources

Dose	Number of Patients/Subjects, Duration of Treatment with Rilonacept		
	At Least One Dose	At Least 6 Months*	At Least 1 Year**
Any dose	614	114	77
<160 mg	313	1	0
160 mg	150	93	63
>160 mg	167	20	10
160 mg or more	309	114	77

Note: Data cutoff: 31 December 2007
Exposure includes patients/subjects from 0004, 0102, 0111, 0401, 0402, 0404, 0406, 0408, 0409, 0423, 0425, 0503, 0504, 0505, 0608, 0616, and 0619 studies
Every group contains only unique patients/subjects.
Patients/subjects can be in more than one group in case dose is changed during the study.
Each patient/subject was counted for the described dose (or combined dose), as long as the total drug exposure exceeded the time duration as specified above.
Definition: 6 months = 6 * 28 days = 168 days, **1 year = 12 months = 12 * 28 days = 336 days
Source provided upon request: Exposure Table 30.5.1

There were a total of 64 patients with CAPS included in the MAA Dataset.

During the course of the procedure further safety data was provided by the applicant from an additional 45 subjects who entered directly into the OLE phase. For this Update, the cut-off date for data from clinical trials (the Update Dataset) is the date of last patient visit at the completion of the open label extension (OLE) of study IL1T-AI-0505 (approximately 5-May-2008). Four of these were

children aged 12-17 years. As the SAE of bacterial meningitis in the OLE was presented in the initial application there were no further new safety signals from this additional data and infections were the commonest adverse event.

- Adverse events

Seventeen (74%) subjects treated with rilonacept and 13 (54%) subjects treated with placebo reported at least one TEAE during Part A of this study. The most commonly reported TEAE was injection site erythema, reported by 8 subjects (rilonacept: 7; placebo: 1). Upper respiratory tract infection was reported by 7 subjects (rilonacept: 6; placebo: 1). Two TEAEs were reported by 4 subjects each (diarrhoea, nausea).

Table 27 displays a summary of TEAEs reported by at least 2 subjects during Part A.

Table 27 Number (%) of Subjects with Treatment-Emergent Adverse Events (TEAEs) by Preferred Term Reported by at Least 2 Subjects - Part A (Randomization A)

MedDRA Preferred Term v9.0	Rilonacept (n=23)	Placebo (n=24)
Injection site erythema	7 (30%)	1 (4%)
Upper respiratory tract infection	6 (26%)	1 (4%)
Diarrhea	1 (4%)	3 (12%)
Nausea	1 (4%)	3 (12%)
Injection site pruritus	3 (13%)	0 (0%)
Injection site swelling	3 (13%)	0 (0%)
Injection site bruising	2 (8%)	1 (4%)
Sinusitis	2 (8%)	1 (4%)
Cough	2 (8%)	0 (0%)
Hypoaesthesia	2 (8%)	0 (0%)
Injection site inflammation	2 (8%)	0 (0%)
Injection site mass	2 (8%)	0 (0%)
Stomach discomfort	1 (4%)	1 (4%)
Injection site pain	1 (4%)	1 (4%)
Urinary tract infection	1 (4%)	1 (4%)
Abdominal pain upper	0 (0%)	2 (8%)

Source: Post-text Table 9.3.1.1.2.1

No severe adverse events were reported during Part A; all reported TEAEs were assessed by Investigators as mild or moderate in severity. One severe adverse event was reported during the Part B single-blind portion of the study; one subject with a history of migraines since 2004 reported a single incidence of migraine assessed as “severe” by the Investigator. One severe adverse event was reported during the Part B randomized-withdrawal portion of the study; one subject allocated to the rilonacept group reported a single incidence of bronchitis assessed as “severe” by the Investigator. All other reported TEAEs were assessed by Investigators as mild to moderate.

There was one SAE reported during the course of the study; sciatica was reported by a 62-year-old white female treated with rilonacept, with a prior history of osteoarthritis and sciatica, judged not related to study medication by the Investigator. There was one withdrawal from the study due to adverse events; one subject reported worsening of joint pain on left fifth finger and worsening of joint pain on left index finger considered by the Investigator to be moderate, not serious, and not related to study medication.

- Serious adverse event/deaths/other significant events

No SAEs were reported for the pivotal study, IL1T-AI-0505 Part A. No serious infections were reported. Two patients treated with rilonacept reported a total of 4 SAEs (*Hypokalemia, Hyponatremia,* and *Pulmonary embolism* in one patient, and *Sciatica* in another); all of these events were assessed as not related with an outcome of "resolved."

There were no deaths during the Part A and B of the study nor in the 24 week OLE.

There were two deaths reported after the database in the long-term open label extension; one was a 71 year old woman who died of pneumococcal meningitis and the other was a 37 year old man with untreated hypertension and hyperlipidaemia who died of a myocardial infarction with occlusion of the left anterior descending coronary artery.

Immunological events

During the 24 weeks of Parts A and B, subjects were dosed weekly and serum samples for anti-rilonacept antibody assays were collected at six time points (predose; Week 6, the last visit in the Part A double blind phase; Weeks 12 and 15 during the Part B single-blind rilonacept treatment phase; Weeks 21 and 24 during the Part B double blind randomized withdrawal phase). The evaluation for rilonacept-binding antibodies used a sensitive assay with a limit of detection of 300 ng/mL in which drug:antibody complexes are first dissociated with acid treatment before the sample is neutralized and evaluated for binding on a microplate coated with the rilonacept extracellular domain construct

Table 55 Antibody Assay Results by Treatment Profile

Study Drug Allocation Profile*	Subjects anti-rilonacept antibody assay negative n	Subjects anti-rilonacept antibody assay positive	
		Positive prior to dosing with rilonacept n	Positive only after dosing with rilonacept n
D-D-D (n=11)	5	0	6†
D-D-P (n=11)	7	0	4
P-D-D (n=12)	5	0	7
P-D-P (n=12)	9	1‡	3

* D=rilonacept; P=placebo
† Includes subject 002-6965, who discontinued early prior to randomization in Part B, i.e., D-D-x group
‡ Subject 015-6301
Source: Sample Analysis Report/ Appendix 11.2.5

The Applicant stated that there was no evidence of any adverse effect of antibodies on the blood levels of rilonacept, or on clinical and laboratory measures of efficacy or safety. There was no indication that antibody-positive subjects had lower rilonacept levels than subjects that were antibody-negative. Examination of CRP levels for individual subjects also did not indicate a rebound in CRP after development of an antibody positive response. Individual subject key symptom scores did not reveal an exacerbation of CAPS symptoms that correlated with development of binding or neutralizing antibodies.

- Laboratory findings

There were no significant haematology laboratory events reported during Part A. Two cases of abnormal clinical chemistry laboratory events reported during Part A. One subject randomized to placebo, was reported with an AE of hypercholesterolemia. The second subject who was randomized to rilonacept treatment in Part A, was reported with an AE of hyponatremia, with a sodium level of 128 meq/L (reference range 133-145 meq/L) 6 weeks into the 9-week single-blind rilonacept treatment phase, with subsequent assessments within the reference range.

There were two clinical chemistry events assessed by Investigators during the Part B single-blind phase as clinically significant. One subject, randomized to placebo in Part A, had an AE of increased blood uric acid levels from a sample drawn pre-dose on the day of the first Part B single-blind dose of rilonacept. The second subject (who was reported with an AE of hypercholesterolemia during Part A

when randomized to treatment with placebo), was also reported with an AE of hypercholesterolemia during the Part B single-blind rilonacept treatment phase, which was ongoing at the Week 24 visit.

- Safety in special populations

A limited number of paediatric patients were included in the clinical studies and this fact, combined with the lack of data on the effect of long term IL-1ß suppression, is a concern. The Applicant was requested to propose a plan to collect data from the registry on safety and efficacy in children; particularly risk of infection and possible impairment of immune reactions such as response to vaccinations and growth.

Also, further PK steady state exposure data (AUC, C_{max}, C_{min} during steady state) especially for paediatric subjects were required.

- Safety related to drug-drug interactions and other interactions

The known increase in infections following the addition to anti-TNF therapy to anti-IL1 therapy has prompted the warning in the SPC and PL.

No specific drug interaction studies were carried out. However because the formation of CYP450 enzymes is suppressed by increased levels of cytokines during chronic inflammation, it is expected that for a molecule that binds to IL-1, such as rilonacept, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin). Upon initiation of ARCALYST, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or plasma levels should be performed and the individual dose of the medicinal product may need to be adjusted as needed. This warning has been added to the SPC.

- Discontinuation due to adverse events

There were no withdrawals due to TEAEs in IL1T-AI-0505 Part A. In ongoing studies of rilonacept, two additional withdrawals due to adverse events were reported through 31-March-2008. In the open label extension of IL1T-AI- 0505, one patient withdrew due to *Chronic sinusitis* assessed as mild in severity and not related to study medication. The event was noted as ongoing at the time the patient discontinued study participation. In IL1T-GA-0619 (study in gout patients) one patient withdrew due to *Arthralgia* assessed as moderate in severity and related to study medication. The event resolved within 16 days of onset.

Table 8 Disposition of Subjects in Parts A and B

Disposition	Randomization A Part A and Part B Single-Blind		Randomization B Part B Randomized-Withdrawal	
	Rilonacept (n=23)	Placebo (n=24)	Rilonacept (n=22)	Placebo (n=23)
Completed	22	24	21	23
Withdrew for any reason	2 (8%)	0	1 (4%)	0
Reason for Withdrawal				
Adverse Event	0	0	1	0
Noncompliance with protocol	1* (4%)	0	0	0
Decision by Investigator or sponsor	0	0	0	0
Request for withdrawal by the subject	0	0	0	0
Lost to follow-up	0	0	0	0
Other	1† (4%)	0	0	0
Death	0	0	0	0

*This subject was removed from the study in the Part B single-blind phase of the study due to non-compliance with study drug dosing and study visits.
† Subject 018-6891 was removed from the study during Part A while being treated with rilonacept due to hepatitis C that was diagnosed after dosing but determined to have a pre-dose start date based upon Screening liver function test results
Source: Post-text Tables 9.1.3.1, 9.1.3.2

The side effect profile of rilonacept was mainly restricted to injection site reactions and upper respiratory tract infection. No opportunistic infection or development of autoimmunity was seen in CAPS patients. The death from pneumococcal meningitis in the long-term open label extension period may have been related to treatment, but evidence of chronic sinusitis was present which may have been a pre-disposing factor. Overall the safety profile is limited (see below).

From the Integrated analysis of safety performed Table 2.7.4-12 provides a summary of patients with treatment-related TEAEs occurring in greater than or equal to 1% of rilonacept patients with greater frequency than in placebo patients.

Table 2.7.4-12 Number (%) of Patients with Treatment-related TEAEs occurring in greater than or equal to 1% of Rilonacept Patients and with Greater Frequency than in Placebo Patients by SOC, HLT, and PT – Placebo-controlled studies

System Organ Class MedDRA High Level Term MedDRA Preferred Term (V9.0)	Placebo N=165	< 160 mg rilonacept N=249	160 mg rilonacept N=32	> 160 mg rilonacept N=55	All Doses rilonacept N=336
Any TEAE	69 (41.8)	160 (64.3)	18 (56.3)	29 (52.7)	207 (61.6)
General disorders and administration site conditions	**56 (33.9)**	**133 (53.4)**	**14 (43.8)**	**29 (52.7)**	**176 (52.4)**
Injection and infusion site reactions	**54 (32.7)**	**129 (51.8)**	**14 (43.8)**	**28 (50.9)**	**171 (50.9)**
Injection site irritation	36 (21.8)	89 (35.7)	0 (0)	3 (5.5)	92 (27.4)
Injection site erythema	9 (5.5)	34 (13.7)	10 (31.3)	23 (41.8)	67 (19.9)
Injection site pain	14 (8.5)	25 (10.0)	2 (6.3)	16 (29.1)	43 (12.8)
Injection site pruritus	3 (1.8)	20 (8.0)	4 (12.5)	7 (12.7)	31 (9.2)
Injection site swelling	2 (1.2)	15 (6.0)	4 (12.5)	2 (3.6)	21 (6.3)
Injection site oedema	4 (2.4)	1 (0.4)	1 (3.1)	15 (27.3)	17 (5.1)
Injection site bruising	4 (2.4)	7 (2.8)	3 (9.4)	3 (5.5)	13 (3.9)
Injection site nodule	1 (0.6)	6 (2.4)	0 (0)	0 (0)	6 (1.8)
Injection site urticaria	1 (0.6)	4 (1.6)	1 (3.1)	1 (1.8)	6 (1.8)
Injection site reaction	0 (0)	3 (1.2)	0 (0)	1 (1.8)	4 (1.2)
Infections and infestations	**5 (3.0)**	**19 (7.6)**	**3 (9.4)**	**1 (1.8)**	**23 (6.8)**
Upper respiratory tract infections	**3 (1.8)**	**9 (3.6)**	**3 (9.4)**	**1 (1.8)**	**13 (3.9)**
Upper respiratory tract infection	1 (0.6)	4 (1.6)	3 (9.4)	0 (0)	7 (2.1)
Sinusitis	1 (0.6)	3 (1.2)	0 (0)	1 (1.8)	4 (1.2)
Urinary tract infections	**0 (0)**	**4 (1.6)**	**0 (0)**	**0 (0)**	**4 (1.2)**
Urinary tract infection	0 (0)	4 (1.6)	0 (0)	0 (0)	4 (1.2)
Nervous system disorders	**2 (1.2)**	**12 (4.8)**	**1 (3.1)**	**0 (0)**	**13 (3.9)**
Headaches NEC	**2 (1.2)**	**7 (2.8)**	**0 (0)**	**0 (0)**	**7 (2.1)**
Headache	2 (1.2)	7 (2.8)	0 (0)	0 (0)	7 (2.1)
Neurological signs and symptoms NEC	**0 (0)**	**3 (1.2)**	**1 (3.1)**	**0 (0)**	**4 (1.2)**
Dizziness	0 (0)	3 (1.2)	1 (3.1)	0 (0)	4 (1.2)
Respiratory, thoracic and mediastinal disorders	**2 (1.2)**	**3 (1.2)**	**0 (0)**	**1 (1.8)**	**4 (1.2)**
Coughing and associated symptoms	**0 (0)**	**3 (1.2)**	**0 (0)**	**1 (1.8)**	**4 (1.2)**
Cough	0 (0)	3 (1.2)	0 (0)	1 (1.8)	4 (1.2)

Patients were assigned to dose groups according to dose at the start of the adverse event.
Source provided upon request: Statistical Tables 7.2.4, 7.19.4

In the rilonacept development program, no treatment-emergent treatment-related *Dizziness* or *Vertigo* was reported.

- Post marketing experience

Additional safety data was provided from a safety update on the long-term open label extension cut-off April 2008 and PSUR data from 27.2.2008- 26.5.2009.

From the PSUR data provided a "loss of effect" was reported in 13 cases and as a result the clinical specific obligation relating data collection on safety and efficacy in the Global Registry has been expanded to include assessment of patients who develop loss of effect on Arcalyst and to assess the PK/PD and immunogenicity in these cases.

One 15-day alert report was about a case of FCAS who developed iritis (not a features of FCAS) and this has been added to the table in section 4.8 of the SPC.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of the follow up measures, as discussed below.

The Applicant did not provide a statement signed by Regeneron and the qualified person responsible for pharmacovigilance (QPPV), indicating that the Applicant has the services of a QPPV and the means for the notification of any adverse reaction occurring either in the Community or in a third country.

The Applicant clarified that they have the services of a QPPV, who resides in the Community (The Netherlands).

As the QPPV is not medically qualified, the Applicant should describe how they are able to obtain medical input from a trained physician. The Applicant provides a description of the organisation, giving location of the pharmacovigilance database, and the names and addresses of the organisations and locations where global and European Economic Area (EEA) pharmacovigilance activities are undertaken. Information flow of safety reports and main processes are also provided.

The Applicant provided reassurance regarding the overall pharmacovigilance organisation. However, organisational charts were not provided. The Applicant was asked to provide a high level organisation chart of the Regeneron group providing an overview of the global and EEA Pharmacovigilance units and organisations identified by the Applicant as to where pharmacovigilance activities are carried out and, illustrating the relationships between them, with affiliate/parent companies and contractors. The chart(s) should show the main reporting relationships with management and clearly show the position and reporting line of the EEA QPPV, within the organisation. Other departments in the Regeneron group who interface with the Pharmacovigilance system i.e. regulatory affairs, marketing, sales, quality assurance and audit should be shown. The Applicant should state who has access to the Pharmacovigilance data.

The Applicant provided a list of written procedures as specified in Volume 9A for both Regeneron and Vigilex. There does not appear to be a SOP covering "Meeting commitments to Competent Authorities in relation to a marketing authorisation" for either Vigilex or Regeneron. The Applicant was asked to clarify whether a procedure is in place and if not should describe how this topic is dealt with in practice. In the chart detailing the flow of safety information from post-marketing sources to the Competent Authorities, the Applicant states that both Regeneron and Vigilex perform continuous monitoring, risk assessment and signal detection but Regeneron do not have a SOP covering these topics. The Applicant is asked to clarify whether they have a SOP and if not describe how the procedures are carried out in practice.

A copy of the registration of the QPPV with the EudraVigilance system and identification of the process to be used for electronic reporting to the Agency and to the Competent Authorities is provided by the Applicant. The database is capable of electronic reporting but Regeneron Medical safety is not equipped to make such submissions at this time so EvWeb is utilised for electronic reporting. The Applicant should provide a statement regarding the validation status of the system and whether it is E2B compliant.

The information provided by the Applicant is generally satisfactory, however, further information stating whether pharmacovigilance training is provided to medical/sales representatives, and who is responsible is required. The Applicant should describe the ongoing quality assurance procedure in place for day to day Pharmacovigilance activities and detail the persons/groups responsible.

The Applicant should provide information regarding corrective procedures and preventative action as the result of the auditing and quality assurance process and who is responsible for overseeing them-is the QPPV involved in them.

Following assessment of the D121 responses the conclusions on the PhV system are:

Provided that the deficiencies are rectified prior to the Applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The Applicant must ensure that the system of Pharmacovigilance is in place and functioning before the product is placed on the market.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks		
Increased risk of Injection site reaction	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: Severe injection site reactions will be included as an event of special interest in the Global Patient Registry.	Routine: Proposed SPC Section 6.6 contains the following advice: Sites for subcutaneous injection, such as the abdomen, thigh, or upper arm, should be rotated. Injections should never be m Routine: Proposed SPC Section 6.6 contains the following advice: Sites for subcutaneous injection, such as the abdomen, thigh, or upper arm, should be rotated. Injections should never be made at sites that are bruised, red, tender, or hard. ade at sites that are bruised, red, tender, or hard. Additional: Physicians Educational Program
Infection	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: infection, including serious infection, will be included as an event of special interest in the Global Patient Registry.	Routine: Proposed SPC section 4.4 contains the following warning: Interleukin-1 (IL-1) blockade may interfere with immune response to infections. Serious, life threatening infections have been reported in patients taking ARCALYST. There was a greater incidence of infections in patients treated with ARCALYST compared with placebo. In an open-label extension study, one patient developed bacterial meningitis and died. ARCALYST should be discontinued if a patient develops a serious infection. Treatment with ARCALYST should not be initiated in patients with an active or chronic infection. In clinical studies, ARCALYST has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Taking ARCALYST with TNF inhibitors is not recommended because this may increase the risk of serious infections. Drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		latent tuberculosis (TB). It is unknown whether taking drugs such as ARCALYST that block IL-1 increases the risk of TB or other atypical or opportunistic infections. Physicians should consider testing for TB prior to initiation of treatment. Additional: Physicians Educational Program; Patient Alert Card
Changes in lipid profile	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: cardiovascular disorders will be included as an event of special interest in the Global Patient Registry.	Routine: Proposed SPC Section 4.4 contains the following statement: Patients should be monitored for changes in their lipid profiles and provided with medical treatment if warranted (see section 4.8). Proposed SPC Section 4.8 contains the following statement: Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Patients with CAPS treated with ARCALYST experienced mean increases from baseline for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides of 19mg/dl, 2mg/dl, 10mg/dl, and 57mg/dl respectively after 6 weeks of open-label therapy. Physicians should monitor the lipid profiles of their patients (for example after 2-3 months) and consider lipid-lowering therapies as needed based upon cardiovascular risk factors and current guidelines. Additional: Physicians Educational Program
Immunogenicity/ hypersensitivity/ immune reactions	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: anti-rilonacept antibodies will be measured as part of the Global Patient Registry. Hypersensitivity/ immune reactions will be included as an event of special interest in the Global Patient Registry.	Routine: Proposed SPC section 4.4 contains the following warning: Antibodies directed against the receptor domains of rilonacept were detected by an ELISA assay in patients with CAPS after treatment with ARCALYST in clinical studies. There was no correlation of antibody activity with either clinical efficacy or safety. Routine: Proposed SPC section 4.4 contains the following warning: Although hypersensitivity reactions related to treatment with ARCALYST were not seen in the initial clinical

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		program, if a hypersensitivity reaction occurs, administration should be discontinued and appropriate therapy initiated. Additional: Physicians Educational Program
Important potential risks		
Risk of neoplasm	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: neoplasms will be included as an event of special interest in the Global Patient Registry.	Routine: Proposed SPC section 4.4 contains the following warning: The impact of treatment with ARCALYST on the development of malignancies is not known. However, treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies. Additional: Physicians Educational Program
Drug interactions	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: concomitant drug use will be recorded as part of the Global Patient Registry.	Routine: Proposed SPC section 4.5 contains the following warnings: No interaction studies have been performed. The concomitant administration of ARCALYST with any TNF inhibitors is not recommended (see section 4.4). The concomitant administration of rilonacept with other IL-1 inhibitors has not been studied and is therefore not recommended. The formation of CYP450 enzymes is suppressed by increased levels of cytokines during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as rilonacept, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin). Upon initiation of ARCALYST, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or plasma levels should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		In addition section 4.4 includes the following warnings regarding combinations not recommended: The combination of ARCALYST with tumour necrosis factor (TNF) inhibitors has not been evaluated in clinical trials. An increased incidence of serious infections has been associated with administration of another IL-1 inhibitor in combination with a TNF inhibitor. ARCALYST should not be used with TNF inhibitors because of increased risk of serious infections (see section 4.5). The concomitant use of rilonacept with other IL-1 inhibitors is not recommended (see section 4.5).
Long-term efficacy and safety	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: A physician's global assessment of disease activity will be included as part of the Global Patient Registry, which will also monitor long-term safety.	Physicians Educational Program
Neutropenia	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: Details of any reported cases of neutropenia associated with rilonacept use will be collected as part of the Global Patient Registry.	Routine: Proposed SPC section 4.4 contains the following warning: Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) has been observed commonly with another product that inhibits IL-1 used in a patient population (rheumatoid arthritis) other than CAPS. Administration of ARCALYST to patients with CAPS was not associated with neutropenia in the clinical program. Neutropenia was observed commonly in patients with rheumatoid arthritis (not an approved use) who were administered ARCALYST subcutaneously in clinical studies. None of these patients had serious infections associated with the neutropenia. Additional: Physicians Educational

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		Program
Foetal defects	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: Details of any pregnancies and pregnancy outcomes associated with rilonacept use will be collected as part of the Global Patient Registry.	Routine: Proposed SPC section 4.6. contains the following statements regarding use during pregnancy and lactation: There are no adequate data from use of rilonacept in pregnant women. Reproductive toxicity studies have been conducted in animals (see section 5.3). The potenital risk for humans is unknown. ARCALYST should not be used during pregnancy unless clearly necessary. It is unknown whether rilonacept is secreted in human or animal breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with ARCALYST should be made taking into account the benefit of breast-feeding to the child and the benefit of ARCALYST therapy to the woman. Additional: The Alert Card advises patients to talk with their doctor if they become pregnant or plan to become pregnant or if they are nursing and physician training will highlight the need to avoid becoming pregnant while on rilonacept unless clearly necessary. Additional: Physicians Educational Program
Off-label use (including use in NOMID/CINCA)	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: Details of any off-label use of rilonacept will be collected as part of the Global Patient Registry.	Routine: Proposed SPC section 4.1 states that ARCALYST is for use in FCAS and MWS in adults and children from the age of 5 years and older. Additional: Physician training will include the need to prescribe rilonacept within the terms of the Marketing Authorisation. Single-source distribution will allow the tracking of prescription patterns.
Important missing information		
Use in hepatic impairment	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU	Routine: Proposed SPC section 5.2 includes the following statement: No pharmacokinetic data are available

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	approval date and/or International Birth Date). Additional: Details of any use of rilonacept in patients with hepatic impairment will be collected as part of the Global Patient Registry.	in patients with hepatic impairment. As with other large proteins elimination of rilonacept is expected to be via proteolytic catabolism and target mediated clearance. Consequently, impaired liver function is not expected to affect the pharmacokinetics of rilonacept in a clinically significant way.
Confirmation of dosing regimen	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: dosing data will be collected as part of the Global Patient Registry. Clinical effectiveness and safety data will be summarized and described in relationship to administered dose levels and dosing intervals.	Routine: Section 4.2 of the SPC provides clear dosing recommendations for adults and children, respectively. Additional: A physicians training program will be conducted to ensure that doctors are informed of the dosing regimen applicable to rilonacept. Pharmacovigilance activities will include evaluation of dose and dose interval data collected from the Global Patient Registry.
Possible impairment of vaccine efficacy/ Safety risks associated with live vaccines	Routine: post-marketing surveillance (PSURs in accordance with EMEA timetable, based on the EU approval date and/or International Birth Date). Additional: post-vaccination antibody titers will be determined as part of the new interventional Vaccination Study.	Routine: Proposed SPC section 4.4. contains the following warnings: No data are available on the efficacy or risk of vaccination in patients taking ARCALYST. Prior to initiation of ARCALYST therapy adult and paediatric patients should receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. Live vaccines should not be given concurrently with ARCALYST. Additional: The Alert Card informs patients to tell their doctors if they are scheduled to receive any vaccine. In addition, physician training program will emphasize the messages in the SPC.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The submitted dossier for Arcalyst is considered comprehensive and of good quality. A number of deficiencies initially identified in the dossier were resolved by the responses submitted by the Company.

Information on development, manufacture and control of the Active Substance and Medicinal product have been presented in a satisfactory manner. The results of the tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Risk-benefit balance of the product. The applicant provided a Letter of Undertaking and committed to resolve these as follow-up measures after the opinion, within an agreed timeframe.

Non-clinical pharmacology and toxicology

The Applicant has conducted an acceptable programme of non-clinical studies for rilonacept.

The answers to the non-clinical questions raised during the assessment of the product were considered acceptable and there were no unresolved issues. Report of an additional embryo-fetal developmental toxicity study in cynomolgus monkeys to investigate placental transfer, exposure of the conceptus and measurement of hormonal levels in the adults will be provided when available.

Efficacy

CAPS is an orphan disease which is comprised of a spectrum of disorder ranging from FCAS (variable severity and commoner in the USA than in Europe) to a more severe form; MWS which is characterised by daily symptoms, to NOMID – the most severe form complicated by amyloidosis growth abnormalities and limited life expectancy. CAPS has a high unmet medical need. Currently unlicensed medications for this indication are used but require daily injections. This is problematic particularly in view of injection site reactions and this is difficult particularly for children. The development of Arcalyst provides a substantial benefit for these rare patients, who without treatment have a poor quality of life.

Safety

From the safety database all the adverse reactions reported in clinical trials and PSUR data from data from 27.2.2008- 26.5.2009 have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 2.5 adequately addressed these.

Although the safety database is currently limited the development of a Global Registry will increase knowledge about the safety of this product.

- User consultation

The small print size, length and problematic terms in the PL contributed to unsatisfactory results of the user testing. The applicant was required to revise the PL to develop a patient friendly package leaflet. Afterwards, the amended and adopted version should be used for another user consultation.

This further readability testing should reflect more details on recruitment methodology, and a better definition of inclusion and exclusion criteria.

Risk-benefit assessment

Benefits

- Demonstrated benefits

The benefits of treatment with a once weekly SC injection of rilonacept relate to the reduction of inflammation in CAPS. Persistent uncontrolled inflammation in CAPS can lead to a poor quality of life and in the case of ~25% of MWS can result in amyloidosis with end-organ damage. This outcome is difficult to prevent currently as there are no licensed treatment options in this rare patient group. The other treatments used (steroids, colchicine, non-steroidal anti-inflammatory drugs, anti-IL1 therapy) are either not very effective (NSAIDs, colchicine), have an adverse safety profile (steroids) or lack randomised controlled trial evidence of efficacy in CAPS (e.g. daily Kineret). The introduction of a treatment which has been demonstrated in the pivotal trial to reduce the severity and frequency of clinical symptoms of inflammation in this patient group provides a better treatment option than those that are currently available off licence.

Subgroup analyses indicate that clinical efficacy is seen in both genders and in younger and older adults. Although efficacy was also evident in four paediatric patients (13-16 years of age) treated with open label rilonacept the experience in the paediatric population is very limited.

Importantly rilonacept has been shown to reduce biomarkers of systemic inflammation (CRP and SAA) in line with improvement in clinical symptoms. Persistently elevated SAA levels (above 50mg/L) are associated with a high risk of continued amyloid deposition in patients with amyloidosis. Amyloidosis leads to organ damage as a result of deposition of amyloid fibrils and occurs in up to 25% of MWS. With sustained reduction in SAA levels this adverse outcome of prolonged inflammation should be prevented by long-term treatment with rilonacept. The introduction of rilonacept for these cases is a major advance in therapeutic options currently available.

- Uncertain benefits

It is not known if the observed effect on disease symptoms and signs as well as laboratory parameters of inflammation will translate into a substantially different long-term prognosis and the prevention of secondary organ damage, e.g. kidney failure and arthropathy due to amyloidosis. However, given the important role of IL-1beta is appears likely that long-term inhibition will have a beneficial effect.

Risks

- Demonstrated risks

Infections

Treatment-related infections, which were considered by the investigators as treatment-related, were more common in patients treated with rilonacept (9%) than in patients treated with placebo (0%) during Part A of the pivotal CAPS study. In Part B (randomized withdrawal) the incidence of infections was similar between the rilonacept (0%) and placebo-treated (4%) patient groups. This finding may be related to the fact that Part A of the trial was initiated in the winter months, while Part B was predominantly performed in the summer months. There have been instances in which patients taking rilonacept have developed serious infections; one patient in the open label portion of the pivotal study in CAPS died after developing sinusitis and bacterial (streptococcus pneumonia) meningitis.

Local injection site reactions (ISR)

Injection site reactions (Injection and infusion site reactions, MedDRA HLT) were the most commonly reported treatment-related TEAEs and the most commonly reported treatment-related TEAEs that led to study withdrawal in all rilonacept studies. None of the ISRs were reported as an SAE. However, in patients with CAPS all events were assessed as mild to moderate in severity, resolved within 1-2 days, and none resulted in permanent withdrawal from the study.

- Potential risks

Malignancies

Treatment with immunosuppressants may result in an increase in the risk of malignancies. While data collected so far in the rilonacept development program does not indicate an excess risk of neoplasm, the impact of treatment with rilonacept on the development of malignancies is not known.

Interleukin-1 blockade may interfere with immune response to infections and normal immune response to new antigens. No data are available on either the efficacy of live vaccines or on the risks of secondary transmission of infection by live vaccines in patients receiving rilonacept. No data are available on the effectiveness of vaccination with inactivated (killed) antigens in patients receiving rilonacept. The applicant has been requested to conduct an interventional vaccination study that will investigate the influence of Arcalyst on immunogenicity and the potential for generalised infection with live vaccination pathogens.

Immunogenicity

Forty percent of patients during the 48-week course of the CAPS pivotal trial (24-week blinded portion Parts A and B) tested positive on at least one occasion for a treatment-emergent rilonacept-specific binding antibody. 24% tested positive during the 24 week open label extension. The impact on safety and efficacy has not been conclusively demonstrated.

Reproductive Toxicology

Animal studies that were conducted to assess reproductive toxicity are inconclusive with regard to effects on the fetus. There are no adequate data from the use of rilonacept in pregnant women in clinical studies of rilonacept. It is not known whether rilonacept is secreted in human milk or absorbed systemically after ingestion.

Drug Interactions

Formal studies have not been conducted to examine the pharmacokinetics of SC administration of rilonacept in CAPS patients with hepatic impairment.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. By reversing inflammation, it is possible that treatment with rilonacept could normalize CYP450 enzymes, which could be relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin).

There is a limited safety database available to date with rilonacept and no significant experience with long-term (over 2 year) continuous use in the indicated population. Two deaths in the long-term extension phase included one 71 year old woman with pneumococcal meningitis and evidence of chronic sinusitis, and a 37 year old man with multiple risk factors for cardiovascular disease who died suddenly from a myocardial infarct. The risks include injection site reactions and infections (predominantly upper respiratory tract infections) immunogenicity and possibly malignancy and neutropenia (as seen with other IL-1 blocking agents).

However the mechanisms of action are not the same in Kineret and rilonacept-- as rilonacept can bind endogenous IL-1ra- it is theoretically possible that rilonacept could cause inflammation in some disease states where endogenous IL1ra is high. In addition because IL-1 has actions on diverse cells in the body (including bone marrow, uterus, CNS) the effects of long-term treatment are difficult to predict. This includes effects on pregnancy, for which there is insufficient pre-clinical data. The risk in this group can be minimised by prescription being limited to experts in the diagnosis and management of CAPS and treatment of patients who require systemic therapy.

Other risks relate to the unknown effects with long-term use and use in certain patients with CAPS (such as those with co-morbidities such as hepatic impairment, or those on concomitant medication – although the potential danger of concomitant use with anti-TNFs is highlighted in section 4.4 of the SPC).

In addition the potential for off label use in other patient groups exists and the Applicant has been requested to propose measures to asses the extent of this and will develop a Global Registry to address this.

A possible risk for those with FCAS is treatment at a time of year when their symptoms are minimal. In the summer months these milder cases will have the risks of treatment without the benefit. Therefore restricting the indication to patients with severe disease minimises this.

An additional potential risk is blunting of the inflammatory response associated with an acute episode of sepsis. This is a possibility with all immunosuppressive medication and the restriction of prescription of experts in this field and addition of a warning in the SPC addresses this.

Lack of sufficient data in children (efficacy safety and PK data) will also be addressed in the Global Registry (for safety and efficacy) and as an interventional study (for PK). The interventional study constitutes a specific obligation.

Further potential risks such as development of anti-IL-1R antibodies causing immune complexes (by binding soluble IL-1R) or binding to IL-1R on cell surfaces (which could result in blocking or stimulation) exist, but seem unlikely following assessment of the D121 responses.

Balance

Efficacy in both FCAS and MWS with confirmed CASI mutations was clearly demonstrated both by a reduction of the clinical symptoms associated with CAPS and by a reduction in inflammatory markers. The efficacy is maintained on prolonged treatment up to 48 weeks.

The short term safety profile of rilonacept is favourable in this population, supporting an overall positive benefit/risk assessment for its use in the treatment of patients with FCAS and MWS. The longer term safety is unknown. Of note one death considered probably related to therapy has been observed. Because rilonacept blocks IL-1beta, there is an increased risk of infections during treatment. Serious infections, while rare, have occurred. However IL-1 blockade is associated with infections and the requirement for use of the minimally effective dose is important when long-term treatment is planned. The D121 responses have provided sufficient evidence to support the dosing schedule and dose proposed.

Conclusions

The overall benefit/risk balance of Arcalyst is positive as the applicant has undertaken the specific Obligations and FUMs.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required: see as detailed in section 2.5.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Arcalyst in the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) with severe symptoms, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and children aged 12 years and older, was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.