European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

ILARIS

International Nonproprietary Name: canakinumab

Procedure No. EMEA/H/C/001109

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd. submitted on 04 December 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for ILARIS, which was designated as an orphan medicinal product EU/3/07/439 on 20 March 2007. ILARIS was designated as an orphan medicinal product in the following indication: treatment of cryopirin-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 this condition was 0.05 per 10,000 EU population.

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) in adults, adolescents and children aged 4 years and older with body weight above 15 kg, including:

- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
- Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMEA Decision P/27/2008 for the following condition(s):

- Cryopyrin Associated Periodic Syndromes (CAPS), including:
  - Familial Cold induced Autoinflammatory Syndrome (FCAS) also known as Familial Cold induced Urticaria Syndrome (FCUS)
  - Muckle-Wells Syndrome (MWS)
  - Chronic Infantile Neurologic, Cutaneous, Articular Syndrome (CINCA), also known as Neonatal-onset Multisystem Inflammatory Disease (NOMID)

on the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

Protocol Assistance:

The applicant received Protocol Assistance from the CHMP on 24 February 2006, 2 June 2006 and 24 July 2008. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status:

ILARIS has been given a Marketing Authorisation in the United States of America on 18 June 2009.

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

Rapporteur: **Christian K. Schneider** Co-Rapporteur: **Jaana Kallio**

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 04 December 2008.
- The procedure started on 24 December 2008
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 March 2009. 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 20-23 April 2009 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 28 April 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 04 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 to ILARIS 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

The condition now known as CAPS consists of several disorders once considered to be 3 distinct conditions, but almost all associated with mutations in the NLRP3/CIAS1 gene on chromosome 1q44 that encodes the protein known as NLRP3 (formerly NALP3) or cryopyrin.

The NLRP3 gain-of-function mutations in CAPS are associated with an uncontrolled caspase 1 activity resulting in increased production of IL-1β.

The individual disorders are known as Familial Cold Autoinflammatory syndrome (FCAS), also known as Familial Cold Urticaria (FCU), Muckle-Wells syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic, Infantile, Neurologic, Cutaneous, Articular (CINCA) syndrome.

These conditions may occur singly or as overlapping syndromes (i.e. MWS/FCAS or MWS/NOMID). The world-wide incidence is unknown (often under-diagnosed) but only a few hundred cases are currently diagnosed.

FCAS was described in the dermatological literature in 1940 as recurrent episodes of cold induced fever, arthralgia, conjunctivitis and rash, with intermittent symptom-free periods.

MWS was described in 1962 as a hereditary rheumatological syndrome of urticaria-like rash, sensorineural deafness and amyloidosis, associated with conjunctivitis, arthralgia and fever.

CINCA (NOMID) was described in the early 1980's in the paediatric literature as a sporadic, severe inflammatory disorder starting soon after birth and affecting mainly the skin, skeletal and central nervous systems.

Although the majority of patients with CAPS carry mutations in the NLRP3 gene, about 50% of NOMID and 25% of MWS patients do not show such mutations but do respond to IL-1 blockade just as mutation-positive patients. Furthermore, there seems to be no clear genotype/phenotype relationship, so that the same mutation in NLRP3 may give rise to a severe phenotype in one patient and a milder phenotype in another. These findings suggest that additional so far uncharacterized genetic or environmental factors contribute to IL-1β production and initiate or modulate clinical severity.

Thus, differences in genotypes or response to treatment do not permit FCAS, MWS and NOMID to be classed as distinct clinical entities. The earlier distinction between them is historical, and the consideration of this continuous spectrum of severities as one single disease is scientifically and medically valid. The medical literature still refers to distinct phenotypes and, consistent with a continuum of disease severity, describes overlap syndromes. Thus, a patient with symptoms of both MWS and NOMID, by the classical description, is mostly now categorized as MWS/NOMID overlap.

Canakinumab (ACZ885), the drug substance of Ilaris, is a human monoclonal anti-human interleukin-1β (IL-1β) antibody of the IgG1/k isotype that was designed to bind selectively to and neutralize the activity of IL-1β, a pro-inflammatory cytokine, which is produced mainly by mononuclear phagocytes in response to injury and infection.

A paediatric investigation plan was agreed for canakinumab for the use in Cryopyrin Associated Periodic Syndromes (CAPS). The plan required nonclinical and clinical studies. It is partially completed: within the application, the data from the juvenile toxicity study and a clinical study (ACZ885 A2102) were available.

2.2. Quality aspects

Introduction

Canakinumab (ACZ885) is a recombinant human monoclonal anti-human interleukin-1β (IL-1β) antibody that was designed to bind selectively to and neutralize the activity of IL-1β, a pro-inflammatory cytokine, which is produced mainly by mononuclear phagocytes in response to injury and infection. Canakinumab prevents the binding of endogenous human IL-1β to its cognate receptor on the surface of its target cells, thus functionally neutralizing its pro-inflammatory bioactivity. It does not bind to human IL-lα or the endogenous antagonist IL-lRa. Canakinumab is expressed in a murine Sp2/0-Ag14 cell line.

Drug Substance

General information

Canakinumab is a fully human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass.

Nomenclature

The INN name for the drug substance (DS) is canakinumab. Chemically the drug substance is defined as immunoglobulin G1, anti-(human interleukin-1beta (IL-1β)) human monoclonal; (1Glu>Glp)-γ1 heavy chain (221-214')-disulfide with kappa light chain, dimmer (227-227":230-230")-bisdisulfide.

Structure

The molecular formula for canakinumab is based on the amino acid composition without posttranslational glycosylation, but including N-terminal pyroglutamate formation and lysine residues at the C-terminals of the heavy chains.

General properties

The Canakinumab drug substance is a clear to opalescent aqueous solution.

- Manufacture

Manufacturer

The manufacture of canakinimab drug substance is performed by Novartis Pharma S.A.S., Huningue, France.

Description of manufacturing process and process controls

The manufacturing process for the Canakinumab drug substance has been described in sufficient detail. Batches and scale are defined. Flow charts have been provided.

Briefly, Canakinumab is produced from murine Sp2/0 cells. The murine cell line secretes the monoclonal antibody into a serum-free cell culture medium and subsequently the monoclonal antibody is purified and formulated to produce bulk drug substance (BDS).

A cell banking system consisting of master cell bank (MCB) and working cell bank (WCB) has been established. The fermentation process is performed as standard fed-batch culture and individual steps including inoculum preparation and harvest are adequately described.

The drug substance is purified from the harvested cell culture fluid by centrifugation and clarification, and is then subjected to a sequence of chromatographic steps, virus inactivation treatment and filtrations. The drug substance bulk is frozen for long term storage.

Control of materials

Raw materials

Information on compendial and non-compendial raw materials is presented. For the non-compendial raw materials, tests are performed according to internal specifications. The internal acceptance criteria for non-compendial raw materials are provided.

Raw materials of animal, human or recombinant origin

Materials of human and recombinant origin were used in the culture media for cell banks. Relevant certificates and supplier statements are provided.

Source, history and generation of the cell substrate

The choice of the gene of interest, the origin of the human IL-1β gene and the verification of its identity as well as the construction of the expression vectors for use in Sp2/0-Ag14 cells, and the generation of the production cell line were described.

Cell banking system, characterisation and testing

The generation of the producer cell line, the master cell bank (MCB) and the master working cell banks (WCB) is adequately described. Data on genetic stability of cell banks as well as data on characterisation of the producer cell line and the cell banks used in production are considered satisfactory in general. Consistency of the coding region between MCB, WCB and end of production cells (EPC) has been demonstrated.

Control of critical steps and intermediates

Upon request the applicant provided more information on process parameters and in-process controls (IPCs) for the cell culture and purification process of Canakinumab. The definition of IPCs follows a risk based approach. Based on process experience throughout development, experience with similar processes and process characterization at small scale, operational and performance parameters were classified into critical, key and non-key in a risk assessment prior to process validation at full scale.

The parameter ranges defined during small scale process characterization were confirmed during process validation of three consecutive full scale batches of Canakinumab drug substance. The provided data suggest that the manufacturing process is well controlled. The Applicant committed to submit the results of acceptance criteria for yield when available.

Validation

The full scale drug substance manufacturing process has been adequately validated demonstrating that the fermentation and purification process consistently produce drug substance of reproducible quality that complies with specifications and in-process tests. In addition, holding times of intermediates and chromatography column performances are sufficiently validated.

Manufacturing process development

The development of Canakinumab has encompassed several manufacturing changes to the production which are adequately described.

Comparability of Canakinumab manufactured with the different processes was demonstrated.

Characterisation

The Canakinumab drug substance has been sufficiently characterised by physicochemical state-of-the-art methods revealing that the drug substance has the expected structure of a human IgG1-type antibody. The analytical results are consistent with the proposed structure. Further more, heterogeneity

of the drug substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities.

Overall, the biological characterisation is considered sufficient. Canakinumab drug substance was biologically characterized by its ability to neutralize human IL-1β in cell-based assays as well as by a binding assay. All these different assays delivered comparable results with respect to their relative biological activity.

- Specification

Specifications

Overall, drug substance specifications are adequately set and justified. The specification for the drug substance at release and shelf life includes tests for appearance, identification, potency, pH, impurities, degradation products, bacterial endotoxins and quantity.

Analytical methods

Analytical methods for release testing of drug substance are adequately described and validated. An overview on the sites involved in quality control testing for drug substance has been provided. In case of change in testing site, adequate reports on method transfers and requalification data, respectively, have been provided.

The Applicant has developed a cell-based potency assay as a routine batch release test in which potency is determined by the dose-dependent inhibitory effect on the binding of human IL-1β to its receptor on the surface of a human cell line.

Reference standard

The reference material is adequately characterised. In summary, the results of analysis confirm the identity, content, high purity and biological activity of the new reference material ACZ885.04REF, and demonstrate its suitability as a reference standard. Comparability with previous reference preparations was demonstrated.

Batch data

In general, batch release data revealed a consistent batch to batch production of drug substance; the observed drug substance heterogeneity is consistent from batch to batch.

- Stability

The provided stability data are sufficient to support a defined drug substance shelf life under defined storage conditions.

Drug Product

Description and Composition

Canakinumab 150 mg Powder for solution for injection is a lyophilisate to be reconstituted with water for injection (WFI) for subcutaneous injection.

The reconstituted drug product contains 150 mg/mL canakinumab, histidine, histidine hydrochloride monohydrate, sucrose, and polysorbate 80 and is reconstituted with 1.0 ml WFI prior to subcutaneous injection

There is an overfill which was sufficiently justified.

Container closure system

Canakinumab 150 mg Powder for solution for injection is filled in colorless 6 mL type I glass vials and closed with a coated stopper. The stopper is sealed with an aluminium cap with plastic flip-off component. The cap does not come into contact with the drug product. The container closure system complies with PhEur requirements.

- Pharmaceutical Development

The formulation development has been adequately described. The rationale for the selection of the formulation and container configuration has been adequately addressed and justified.

- Manufacture of the Product

Manufacturer

Canakinumab 150 mg Powder for solution for injection is manufactured by Novartis Pharma Stein AG, Switzerland.

Description of manufacturing process, process controls and process validation

The drug product manufacturing process and the in-process controls are described in sufficient detail. Briefly, Canakinumab 150 mg Powder for solution for injection is produced according to a standard aseptic manufacturing process including thawing of drug substance, bulk compounding, sterile filtration, filling and lyophilization. Critical steps are defined. Flow diagrams have been presented.

The excipients of the drug product formulation comply with the quality requirements of the applicable compendial monograph. No excipients which are not described in a pharmacopoeia are used.

The validation of the drug product manufacturing process has been performed adequately to show consistent batch to batch production. The results of the analysis of the validation batches are all within the predefined specifications. The data suggest a robust manufacturing process.

- Product Specification

Product Specification

The selected parameters to control the drug product have been adequately set. The proposed drug product specifications are consistent with the corresponding drug substance specifications, with ICH guidelines and Ph. Eur. monographs. Specifications are based on the results of release and stability testing of clinical batches during development.

Analytical methods

Adequate information has been provided on analytical methods for control of drug product.

Batch data

Analytical results of drug product batches which were used in clinical trials, stability studies as well as in process validation studies, have been presented. The batch data reveal a consistent and robust production of Canakinumab drug product.

- Stability of the Product

The provided stability data support a defined drug product shelf life at the long term storage condition of 2-8°C.. The Applicant committed to continue the stability study with commercial scale batches and to notify the EMEA immediately in case of confirmed out-of-specification results. The post-approval stability protocol is acceptable.

- Adventitious Agents

TSE safety

Compliance with Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 rev 02) has been sufficiently demonstrated. The materials of human and recombinant origin used in the establishment of the cell bank system as well as the source of those materials and information on compliance with EU requirements on minimizing the risk associated with transmissible spongiform encephalopathies (TSE) are provided. No animal or human materials are used in the commercial manufacturing process of the drug substance.

Viral safety

The fermentation process of the monoclonal antibody Canakinumab is in a culture medium without addition of human or animal derived components. This minimises a possible contamination for adventitious viruses. The cells used for production of Canakinumab have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the cells used for production of Canakinumab with the exception of intracellular A-type and C-type retroviral particles. Such particles are well known to be present in murine Sp2/0 cells. This is acceptable since there is sufficient capacity within the manufacturing process of Canakinumab for reduction of this type of viral particles. Therefore, there are no concerns for the use in the production process of Canakinumab. The purification process of Canakinumab includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps, has been sufficiently demonstrated. The removal capacity of small non-enveloped viruses is based on the chromatography and the nanofiltration. This can be accepted as screening for viruses including a rodent parvovirus test is routinely performed at the end of the fermentation runs. In summary, virus safety of Canakinumab has been sufficiently demonstrated.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The documentation provided with the application demonstrates consistent batch-to-batch production of Canakinumab achieving a consistent quality for the drug substance and the drug product. The fermentation and purification of the drug substance are adequately controlled and validated. The drug substance has been adequately characterised with regard to its physicochemical and biological characteristics using state-of the-art methods. The manufacturing process of the drug product has been described and validated in sufficient detail. In addition, the viral safety and the safety concerning other adventitious agents (including TSE) have been sufficiently assured. In general, appropriate drug substance and drug product specifications have been set. The Applicant committed to resolve some outstanding minor concerns as follow-up measures postauthorisation.

2.3. Non-clinical aspects

Introduction

IL-1 is a pro-inflammatory cytokine and its expression is inducible by a variety of stimuli (e.g. microbial products, cytokines, stress factors). IL-1β is produced via a non-classical pathway of protein secretion, i.e. IL-1β is produced as an inactive precursor molecule which has to be activated by proteolytic cleavage by caspase-1 in the IL-1β inflammasome. Dysregulation of this process may lead to increased secretion of IL-1β and IL-1-mediated disease.

In CAPS patients, mutations in the *CIAS1* gene which control the activation of caspase-1 are observed. Such mutations cause the loss of tight control of IL-1β processing. As a result, relatively minor stresses (e.g. exposure to cold) lead to an increased secretion of IL-1β with consequent systemic disease. In addition, there are chronic inflammatory syndromes without mutations in the *CIAS1* gene but nevertheless elevated IL-1β release *in vitro*.

Canakinumab is a fully human anti-human IL-1β IgG1/k monoclonal antibody. It was generated by hybridoma technology from B cells of HuMab mice immunized with human IL-1β. Subsequently, canakinumab was recombinantly expressed in murine NS0 and Sp2/0 cells. It was shown that the binding properties and neutralizing capacity of the different preparations remained unchanged (refer also to the discussion in the quality section).

The Applicant has conducted several *in vitro* and *in vivo* studies to address the affinity, sensitivity, specificity and biological activity of Canakinumab. Due to the lack of crossreactivity to IL-1β from rodent species, the *in vivo* activity of Canakinumab could not be demonstrated in classical animal disease models. Instead, other models, as described below, were utilised to demonstrate the *in vivo* activity of the antibody (e.g. marmoset, human dermal fibroblasts).

Pharmacology

- Primary pharmacodynamics

In vitro

By surface plasmon resonance, canakinumab was found to bind specifically to human IL-1β with a KaD of 30-60 pM, depending on the assay. As this variability seems to be due to poor quality of the surface plasmon resonance sensograms, the applicant was asked to commit to improve the method to gain reliable results relating to receptor-binding, KD determination, and comparability and to thereby ensure validity of the non-clinical comparability data.

Canakinumab did not cross-react with IL-1a, IL-1Ra, or any other member of the IL-1 family, including IL-18 and IL-33. Using site-directed mutagenesis of recombinant human IL-1β the epitope of canakinumab was mapped precisely. By x-ray crystallography of IL-1β bound to the canakinumab Fab fragment it was found that the epitope partially overlaps with the binding site of IL-1β to the IL-1 receptor. Consequently, soluble IL-1 receptor (both type I and type II) dose-dependently inhibited binding to IL-1β to canakinumab in BIAcore analyses.

In a cell-based *in vitro* assay, canakinumab was found to inhibit the activity of natural and recombinant human IL-1β with IC_{50} of approximately 50 pM. Importantly, in this assay the inhibitory effect of canakinumab and IL-1Ra was found to be additive. Thus, canakinumab does not compromise the biological activity of IL-1Ra, an important endogenous inhibitor of IL-1 activity *in vivo*.

Canakinumab does not bind to IL-1β from mouse, rat, rabbit, or cynomolgus monkey. The only non-human species specifically recognized by canakinumab is the marmoset monkey. This limited species cross-reactivity can be explained with one amino acid in the IL-1β sequence that is crucial for canakinumab binding. At position 64, Glu is present in human and marmoset IL-1β but changed to Ala or Gly in all other species analyzed.

In vivo

With an equilibrium binding constant K_D of ca. 23 pM the binding affinity of canakinumab for marmoset IL-1β was slightly higher than that for human IL-1β. In an *in vitro* assay, canakinumab potently inhibited the expression of a reporter gene induced by marmoset IL-1β. Of note, the potency for marmoset IL-1β was found to be approximately two-fold lower than that for human IL-1β.

Since canakinumab does not react with rodent IL-1β, the *in vivo* activity of canakinumab was demonstrated in models of inflammation induced by human IL-1β in rodents (i.e. mouse joint inflammation, rat fever, neutrophil infiltration into mouse air pouch). In all three models, canakinumab inhibited the IL-1β -induced effects.

- Secondary pharmacodynamics

With regard to secondary pharmacodynamics, it was shown that canakinumab does not block T cell proliferation in a human mixed leukocyte reaction *in vitro*, indicating that canakinumab is not acutely immunosuppressive *in vivo*.

Binding of canakinumab to Fcγ receptors was determined by surface plasmon resonance and was as expected for a human IgG1 antibody. However, canakinumab did not bind to the surface of IL-1β-producing cells in an antigen-dependent manner and did not recruit the complement component C1q. Thus, canakinumab is not expected to mediate antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

To enable further toxicological studies a surrogate antibody (01BSUR) with a murine IgG2a/k isotype was developed. 01BSUR is specific for mouse IL-1β (K_D 302 pM) and does not bind to IL-1α and IL-1Ra. *In vitro*, 01BSUR was able to inhibit IL-1-induced effects in a NIH3T3 fibroblast model with a potency similar to that of canakinumab. *In vivo* bioactivity of 01BSUR was shown in mouse model of collagen-induced arthritis. When given in a semi-prophylactic treatment mode, 01BSUR almost completely inhibited the development of joint inflammation. Using this surrogate antibody in mice, it was further shown that neutralization of IL-1β does not inhibit the development of a T cell-dependent antibody response induced by immunization in the presence of aluminium hydroxide as adjuvant.

- Safety pharmacology programme

Stand-alone safety pharmacology studies were not conducted with canakinumab. However, the cardiovascular system was analyzed as part of the toxicology studies. No treatment-related effects on electrocardiography data were observed throughout treatment and recovery periods.

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted.

Overall, the pharmacological studies have adequately characterized the profile of the product. The specific binding of canakinumab to IL-1β and have demonstrated its capacity to inhibit IL-1-induced effects *in vitro* and *in vivo*. Because it is generally accepted that over-expression of IL-1 plays a major role in the development of CAPS, these studies support the clinical development of canakinumab in the current indication.

Pharmacokinetics

Pharmacokinetics of canakinumab was determined following single IV administration in marmosets, rhesus monkeys and mice and after single SC administrations in marmosets. Pharmacokinetics after multiple dosing was determined as part of the toxicology studies.

Levels of canakinumab in marmoset serum were detected by a competitive ELISA, which was initially developed for the human system and subsequently validated for marmoset matrix. For detection of the surrogate 01BSUR in murine system a comparable competitive ELISA was used. Antibodies against canakinumab and 01BSUR were measured with a BiaCore-based assay qualified to use in marmoset and murine matrix.

Taken together, the pharmacokinetics of canakinumab was as expected for a human IgG antibody characterized by a small volume of distribution, similar to the plasma volume, low systemic clearance and a long terminal half-life. Of note, with 4-7 days the elimination half-life of canakinumab in marmosets was shorter than in rhesus monkeys (17.4 days), mice (14.5 days) and humans (26 days). Shorter half-life for human IgG in marmosets has been observed previously.

Pharmacokinetic parameters were similar in male and female marmosets. A dose-proportional increase in C_{max} was observed between 5 and 50 mg/kg and slightly less than dose-proportional between 50 and 150 mg/kg. On average, Cmax was reached 2-3 days after SC administration. After repeated dosing, a 2-3-fold accumulation occurred. Bioavailability after SC administration was determined to be 60 % based on a cross-study comparison to a single-dose IV study.

Two PK bridging studies were performed to support changes in the canakinumab manufacturing process. Using a cross-over design following single SC injection in marmosets, canakinumab from process A vs. B and from process B vs. C was found to be comparable with regard to its pharmacokinetic characteristics. In addition, the effect of glycosylation of canakinumab on the pharmacokinetics was investigated. These analyses were performed in mice with canakinumab containing primarily biantennary G0, G1 and G2 oligosaccharides vs. high mannose oligosaccharides. It was shown that the pharmacokinetics was not influenced by the type of oligosaccharides attached to the IgG heavy chain.

In addition, pharmacokinetics of 01BSUR was determined in mice after single and repeated SC administration. A dose-dependent increase in C_{max} and AUC was observed. T_{max} was approximately 24 h after dosing and the elimination half-life was ranged between 1 and 17 days.

Toxicology

An extensive program of toxicology studies was performed. Toxicity of canakinumab was analysed in marmoset monkeys. Additional toxicity studies were conducted with the murine surrogate mAb 01BSUR in mice. Regarding toxicokinetics, exposure to canakinumab or 01BSUR was demonstrated in each study. With the analysis method used, no anti-drug antibodies were detected.

- Single dose toxicity

No single-dose toxicity studies were performed with canakinumab, which is acceptable in view of the data provided by the repeated dose toxicity studies.

- Repeat dose toxicity (with toxicokinetics)

In two IV repeat-dose studies canakinumab was given twice a week at doses of 0, 10, 30 and 100 mg/kg. In the first study, a 4-week treatment period was followed by 8 weeks of recovery. In the second study 26 weeks of treatment were followed by 6 weeks of recovery. In both studies, no deaths occurred. There were no test-item related changes with regard to clinical signs, body weight food consumption, ophthalmology, ECG, hematology, clinical biochemistry, urinalysis, organ weights and histopathology. In both studies, the NOEL was 100 mg/kg given IV twice weekly.

A total of three SC repeat-dose studies with canakinumab were performed.

In the first study female marmosets were treated with 0, 5, 50 and 150 mg/kg on day 1 and day 43, terminal necropsy was on day 44. In the second study, marmosets were treated at 0, 15, 50 and 150 mg/kg twice a week for a period of 13 weeks followed by a recovery period of 8 weeks. No test-item related deaths occurred during these studies. No test-item-related changes were observed with regard to clinical signs, body weight, food consumption, ophthalmology, ECG, macroscopic and microscopic evaluation and clinical chemistry. There were not alterations in hematology, immunophenotyping of blood and spleen. In both studies the NOEL was 150 mg/kg given SC.

A third SC repeat-dose study was performed. In this study, marmosets were treated twice weekly for 13 weeks with vehicle or with 150 mg/kg canakinumab from process A or from process C in a pre-filled syringed. In this study, microscopic lesions and clinical pathology changes were observed in all groups, including controls. One male marmoset was sacrificed moribund due to septicemia. Fifteen days later, the cagemate was found dead without significant clinical signs. Other pathological changes

included renal and intestinal lesions in both treated and control animals. Given the poor health already in the control animals, the study was not considered valid by the applicant.

In all other toxicity studies performed with canakinumab in marmosets, such changes have not been observed. Thus, the results of this SC repeat-dose study do not raise concerns regarding the toxicity of canakinumab.

- Genotoxicity

No genotoxicity studies were performed with canakinumab, as it is a protein. This is acceptable according to guideline ICH S6.

- Carcinogenicity

No carcinogenicity studies were performed with canakinumab. According to guideline ICH S6 carcinogenicity studies are generally not required for monoclonal antibodies. Also, the pharmacodynamics of canakinumab does not warrant carcinogenicity studies. Since pro-inflammatory cytokines such as IL-1 are implicated in tumor development, neutralization of IL-1 is not expected to promote tumour development.

- Reproduction Toxicity

Reproductive toxicity studies in marmosets were limited to evaluation of male fertility (part of the 26 weeks repeat-dose toxicity study) and an embryo-fetal development study.

No canakinumab-related effects were observed on the male reproductive system.

In the embryo-fetal development study, pregnant marmosets were treated SC, twice a week, with 0, 15, 50 or 150 mg/kg from GD 25 to GD109. Caesarean section was performed on GD112-114. There were no signs for maternal toxicity. The only finding associated with canakinumab treatment was a slight reduction in the number of fetuses in the 150 mg/kg group, which correlated with a slight trend to decreased placental weight. Both findings were statistically not significant. There were no treatment-related effects regarding fetal development. At GD112-114, placental transfer of IgG was confirmed. However, given that transfer of IgG across the placenta starts late during gestation, it is unlikely that the fetus was exposed to canakinumab during the period of organogenesis.

In addition a full panel of reproductive toxicity studies was performed with the surrogate mAb 01BSUR in mice. In these studies, 01BSUR was administered once weekly by the SC route at doses of 0, 15, 50 or 150 mg/kg.

Male and female fertility was not affected by treatment with 01BSUR.

In the embryo-fetal development study, maternal functions were unaffected by treatment with 01BSUR. Regarding the fetus, 01BSUR had no effect on fetal weights and the overall incidence of fetal malformations or anomalies. However, in the high dose groups there was an increased incidence of litters and fetuses with incomplete ossification of the parietal and the frontal bone that was statistically significant. These findings were considered a transitory delay in ossification and to be of no teratological significance, as there were no changes on any other bones.

In the pre-/post-natal development study, mice were exposed to 01BSUR throughout gestation and lactation. Such treatment resulted in no evidence of maternal toxicity. Furthermore, there were no toxic effects on the development of the pubs, and their survival, physical development, behaviour and reproductive performance.

Taken together the reproductive toxicity studies in marmosets and in mice did not identify a signal for reproductive toxicity by neutralization of IL-1b.

A juvenile animal study was conducted with the surrogate mAb 01BSUR. Mice were treated once weekly with 01BSUR from day 7 to day 70 post partum. There were no treatment-related effects on the development pre- and post-weaning. In the 150 mg/kg group, the mean day to development of the vaginal opening was later than in controls. There was no effect of treatment on fertility.

Regarding the immune system, there were no differences in counts for total lymphocytes and lymphocyte subsets in blood, spleen and thymus. However, functional studies on the immune system

were not included in this study. To exclude possible effects of neutralization of IL-1β on the developing immune system, the applicant committed to perform a juvenile immunotoxicity study, assessing the effect of the canakinumab surrogate on immune function in juvenile animals.

Treatment of mouse pups with 01BSUR by once weekly SC injection for 9 weeks resulted in generally minimal, inflammatory reactions at the injection sites. These were reversible over a 4 week recovery period.

- Toxicokinetic data

Please refer to the section on repeated dose toxicity studies.

- Local tolerance

The local tolerance to canakinumab at the SC and IV injection sites were assessed in the course of the repeat-dose toxicity studies in marmoset. Occasionally mild reactions were observed which were similar in the in the control animals and therefore not test article-related. In a dedicated local tolerance study, a single intra-articular injection of canakinumab (10 mg/kg) to marmosets was well tolerated.

- Other toxicity studies

Three tissue-cross-reactivity studies were performed with canakinumab, each with canakinumab produced by a different process (A, B, C). Together the results indicate that canakinumab drug substance produced with the different manufacturing processes have similar tissue cross-reactivity profiles. In each study, full panels of human tissues (3 donors) and marmoset tissues (2 donors) were used. In general, the staining observed was consistent with the known expression of IL-1b in human tissues. Reactivity of canakinumab with marmoset tissue was qualitatively similar but quantitatively reduced compared with the reactivity for human tissues. The most notable difference in tissue reactivity is that follicular and germinal cells in the ovary and Leydig, Sertoli, and gametogenic precursors in testis were recognized in marmoset but not in human tissues. However, in the absence of effects on the marmoset reproductive system (refer to repeat-dose toxicity studies) and in the absence of staining of human reproductive tissues, the staining of marmoset reproductive tissues is not considered toxicologically relevant.

In conclusion, treatment of marmosets with canakinumab and of mice with the surrogate mAb 01BSUR was well tolerated. In all the studies, NOEL or NOAEL was the highest dose administered (100 mg/kg/dose IV or 150 mg/kg/dose SC). No signals were identified for general toxicity and for reproductive toxicity. Regarding the effects of IL-1β neutralization on the immune system, treatment of juvenile animals for 9 weeks and of adult animals for 4 weeks revealed no negative effects. There was no indication that susceptibility to infection is increased.

Ecotoxicity/environmental risk assessment

In accordance with the current guidelines, as this product is a protein, ecotoxicity and environmental risk assessment are not applicable.

2.4. Clinical aspects

Introduction

Canakinumab is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 4 years and older with body weight equal to and above 15 kg, including:

- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
- Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

For this application, a single pivotal trial (D2304) has been performed in patients with MWS, additional open-label uncontrolled trials have included patients with FCAS, NOMID and NOMID/MWS overlap disease.

There are currently no approved therapies for CAPS: anakinra and various other anti-inflammatory substances are used off-label.

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 clinical studies were conducted contributing PK and PD data. An overview of the main features of all PK studies is given in the following summary table.

Study No.	Objective(s) of the Study	Dose and route of Administration; Dosage Regimen	Number of Subjects treated	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Product type
CACZ885 A1101	Safety, tolerability, PK/PD	IV: 1 mg/kg, 3 mg/kg, 600 mg SC: 150, 300 mg	48	Healthy subjects (Japanese)	Single dose	A (NS0 cell line)
CACZ885 A2102	Efficacy, safety, PK/PD	IV: 10 mg/kg SC: 150 mg (or 2 mg/kg < 40 kg) upon relapse	34	CAPS patients (NALP-3 mutations)	Single dose	A (NS0 cell line)
CACZ885 A2202	Safety, tolerability, immunogenicity, PK/PD	SC: 150 mg (SD or 4 doses weekly)	23	Psoriasis Patients	Single dose Multiple dose (4 doses, weekly interval)	A (NS0 cell line)
CACZ885 B2101	Safety, tolerability, PK	IV: 1, 3 and 10 mg/kg on day 1 and 15	50	Healthy subjects (mild asthmatics)	Two doses (2 weeks interval)	A (NS0 cell line)
CACZ885 A2101	Safety, tolerability, PK/PD	IV: 0.3, 1, 3, and 10 mg/kg on day 1 and 15	53	RA patients	Two doses (2 weeks interval)	A (NS0 cell line)
CACZ885 D2304	Efficacy, Safety, tolerability, PK/PD	SC: 150 mg (or 2 mg/kg < 40 kg) 8-weekly	48 (15 completed part II canakinumab treatment)	CAPS patients (NALP-3 mutations)	Multiple dose (8 weeks interval)	B (Sp2/0 cell line)

The studies examined doses up to 600 mg i.v. and 300 mg s.c. in healthy subjects (studies A1101 and B2101, with a cohort of mild asthmatics), in RA patients (study A2101), in psoriasis patients (study A2202), and in CAPS patients (Studies A2102 and D2304). Canakinumab was administered as an i.v. infusion in B2101, A2101, in a subset of healthy volunteers in A1101, and in stage 1 of A2102. In a subset of volunteers in A1101, in A2202, in stage 2 of A2102, and in D2304 the drug was given as a s.c. injection.

Single-dose pharmacokinetics of canakinumab has been evaluated in Japanese healthy volunteers (A1101), in a subset of psoriasis patients (A2202) and in the adult target population (CAPS patients) after both IV and SC administration. Pharmacokinetics of two doses at intervals of 15 days was analyzed in 2 studies with healthy volunteers/asthma patients and with RA patients (B2101, A2101). Multidose pharmacokinetics was analyzed in A2202, A2102, and D2304 studies (in psoriasis patients and CAPS patients).

There is no classical therapeutic exploratory Phase II study in CAPS patients. Data from the first part of study A2102 was combined with modelling and simulation to predict the dose and the dosing regimen used in the subsequent CAPS studies. A dose of 150 mg s.c. when > 40kg and 2 mg/kg s.c. when ≤ 40kg, both every 8 weeks was applied.

PK data were analyzed in serum using a non-compartmental analysis. A compartmental analysis was done with a population based PK-binding model using pooled data from all 6 studies (233 subjects). The PK-binding model is described by a dynamic drug-ligand binding and turnover model developed based on the following schematic: canakinumab + IL-1β↔canakinumab-IL-1β complex. Using a mixed effects modelling approach, the PK (canakinumab) and PD (total IL-1β) data were analyzed.

A summary of model-based compartmental and non-compartmental pharmacokinetic parameters is found in the following table.

Table: Pharmacokinetic parameters (arithmetic mean) of canakinumab

	Compartmental (model based)								Non-compartmental					
Study	CL_D (L/d)	V_D (L)	V_P (L)	$t_{1/2}$ (d)	PS_D (L/d)	k_a (1/d)	F1	Dose	C_{max} (µg/mL)	T_{max} (d)	$t_{1/2}$ (d)	CL or CL/F[⇔] (L/d)	F	V_z or V_z/F[⇔] (L)
CACZ885 D2304	0.177	3.149	2.469	23.9	0.428	0.305	0.705	150 mg s.c.						
CACZ885 A2102	0.154	2.829	2.262	24.9	0.376	0.371	0.633	10 mg/kg i.v.	149	1.24	31.2	0.182	0.665	8.19
								150 mg s.c.	15.9		26.1	0.228[⇔]		8.33[⇔]
CACZ885 A2101	0.218	3.377	2.703	21.4	0.449	0.238	0.633	0.3 mg/kg i.v.	8.8	14.1	19.6	0.283		7.69
								1.0 mg/kg i.v.	32.2	13.6	23.7	0.203		6.35
								3.0 mg/kg i.v.	81.9	14.1	21.7	0.199		6.16
								10.0 mg/kg i.v.	329	14.2	21.2	0.200		5.87
CACZ885 B2101 Healthy	0.136	3.127	2.462	30.7	0.382	0.307	0.633	1.0 mg/kg i.v.	36.8		30.9	0.125		5.55
								3.0 mg/kg i.v.	111		31.2	0.120		5.26
								10.0 mg/kg i.v.	336		26.4	0.137		5.07
CACZ885 B2101 Asthma	0.177	3.250	2.828	26.0	0.468	0.316	0.633	10.0 mg/kg i.v.	395		25.7	0.156		5.64
CACZ885 A1101	0.155	3.143	2.435	26.9	0.404	0.333	0.633	1.0 mg/kg i.v.	21.0		22.6	0.174		5.44[†]
								3.0 mg/kg i.v.	57.5		27.4	0.160		5.65[†]
								600 mg i.v.	191		27.2	0.168		5.77[†]
								150 mg s.c.	16.9		26.3	0.229[⇔]		8.70[⇔]
								300 mg s.c.	34.1		26.9	0.238[⇔]		8.92[⇔]
								600 mg i.v. + 300 mg s.c.	209		25.2	-		-

The PK characteristics of canakinumab derived from noncompartmental analysis of the serum concentrations were typical for a human IgG1 molecule:

Following the initial s.c. injection of 150 mg canakinumab in 22 CAPS patients, peak serum levels were reached by approximately 7 days (median value) in adult patients and between 2 to 7 days in pediatric patients receiving 2 mg/kg (N=3). Maximum serum concentrations were on average 15.9 (± 3.5) µg/mL in adults and with 7.7-12.4 µg/mL (range) markedly lower in the children. Apparent half-life following the single s.c. dose administration was 26.1 (± 7.31) days. Terminal half-life appeared to be quite constant throughout the administration routes, the doses and populations studied, and is in good agreement with the value expected for an IgG1 antibody (around 23 days). The values obtained from three pediatric patients receiving the BW-adjusted dose (23.7-25.7 days) were in the same range.

Moderate inter-subject variability with a coefficient of variation of approximately 22.2% and 29.1% was observed in C_{max} and AUCo-∞ values.

Absolute bioavailability was properly calculated from parallel IV and SC groups in studies in Japanese healthy subjects as well as in (n=4) CAPS patients. Similar values in the range of 63-70 % has been found for different populations and using different formulations. However, a high variability (± 22% estimated in one study) has to be kept in mind leading to variations in C_{max} and C_{trough} during steady state.

Bioavailability in children or other special populations has not been studied.

From non-compartmental analysis of two studies (after IV administration of different doses in healthy subjects and in CAPS patients) as well as from population PK analysis consistent values of 0.16-0.18 L/d for the total clearance were obtained. This corresponds to about 7 ml/h and is low compared to other monoclonal antibodies.

Clearance of canakinumab appeared to be independent of dose, age, and gender, but was found to increase with body weight (in an allometric relationship with a power of approximately 0.7-0.8). This supports the choice of body weight adjusted dosing in children.

Data on dose-proportionality are available from three clinical studies where at least three doses have been studied. In B2101, exposure parameters C_{max} and AUC were not statistically dose proportional over the range of 1-10 mg/kg, but can be considered approximately dose-proportional. In A1101 and A2101, exposure parameters increased in proportion to dose over the range of 0.30 to 10.0 mg/kg i.v. and 150 to 300 mg s.c. Thus, the PK of canakinumab can be considered linear.

Furthermore, there is no evidence for time-dependent change in the pharmacokinetic properties of canakinumab.

A mean value of 5.6 L for the central volume of distribution was calculated from non-compartmental analysis. This value was confirmed by the values Vc/F (about 8 L) obtained from the subcutaneous single dose studies in healthy subjects and CAPS patients when a bioavailability (F) of about 70% is assumed.

The value for Vc/F in psoriasis patients (about 15 L) was approximately twice the corresponding volume in healthy volunteers or other patient groups. In agreement with this, serum clearance (CL/F) was also increased. A greater volume of distribution may indicate that a larger amount of IL-lβ is absorbed in tissues, such as the subcutis. However, since differences in bioavailability between populations cannot be excluded, the increase in Vc/F and Cl/F might also be attributed to reduced subcutaneous bioavailability in psoriasis patients.

From the population PK analysis using a dynamic drug-ligand binding and turnover model which integrates both mAb and IL-1β inputs and elimination (turnover) and binding affinity ("PK binding model"), estimation of the volumes of distribution of the central and peripheral compartments (VD and VP) were 3.30 ± 0.135 and 2.71 ± 0.151 L per 70 kg, with a distribution half-life of 2.2 days. The total volume of distribution during steady state (Vss) in a CAPS patient weighing 70 kg was estimated to be 6.0 L.

It can be concluded that the volume of distribution of canakinumab corresponds to 1-2 times the plasma volume which is in accordance with values obtained for other monoclonal antibodies.

Based on the parameter estimates from the final PK-binding model, the terminal half-life (t1/2) in CAPS patients weighing 70 kg was estimated to be 26.6 days. This is in line with the half-life estimate of approximately 26 days in CAPS patients by non-compartmental analysis.

The single dose PK parameters from CAPS patients were in good agreement to those derived from (Japanese) healthy volunteers. Population PK results support the assumption that the PK parameters between CAPS patients and other study populations (Japanese healthy volunteers, asthma, rheumatoid arthritis, and psoriatic patients) were comparable, except for the non-Japanese healthy volunteers, which differed from CAPS patients in that they had approximately 20% slower clearance (after adjustment for body weight). However, this was not considered to have clinical relevance.

Thorough multiple dose PK data are not available for CAPS patients (or any other subjects). Pharmacokinetics after repeated subcutaneous doses applying the intended multiple dose q8w regimen was assessed in one (pivotal) study. Sparse PK data (Ctrough) from 15 CAPS patients after up to 6 consecutive doses are available. Measured mean Ctrough level from 12 patients after 6 doses of 150 mg sc every 8 weeks is 6.23 ± 2.53 µg/mL (mean SD). There is good agreement between the observed and predicted steady state trough concentrations for the CAPS patients with consistent 150 mg s.c dosing every 8 weeks. Steady state PK data (Ctrough) for children < 40 kg receiving the 2 mg/kg dose are limited to one child only. No measured values reflecting the extent of exposure during steady state (C_{max} or AUC) are available.

The time to achieve steady state based on the observed Ctrough data agrees closely with the estimate from the PK-binding model, which predicts 24 weeks to reach 98.8 percent of the steady-state levels with an 1.3-fold accumulation factor after multiple dosing of 150 mg s.c. every 8 weeks.

Based on the PK binding model, following multiple doses of 150 mg every 8 weeks in CAPS patients, the following steady state values for C_{max}, C_{trough} and AUCτ were simulated for different weight and age groups:

Table: Summary statistics (mean, SD, min, max) of model-simulated steady state pharmacokinetic parameters (C_{max},ss (µg/mL), Ctrough,ss (µg/mL), AUC0-tau,ss (µg*day/mL)) in CAPS patients after 150 mg SC (or 2 mg/kg) q 8 weeks

Parameter	WGT=16 kg AGE=4	WGT=25 kg AGE=8	WGT=41 kg AGE=12	WGT=55 kg AGE=34	WGT=70 kg AGE=21	WGT=70 kg AGE=50	WGT=70 kg AGE=75
Dose	2 mg/kg q 8 wk	2 mg/kg q 8 wk	150 mg q 8 wk	150 mg q 8 wk	150 mg q 8 wk	150 mg q 8 wk	150 mg q 8 wk
$C_{max,ss}$	13.3 ± 3.0	14.3 ± 3.6	31.8 ± 7.5	24.6 ± 6.7	21.2 ± 5.3	19.2 ± 5.6	17.9 ± 4.3
	(7.5,21.6)	(7,23.4)	(17.3,51.7)	(11.2,44)	(12.9,39.8)	(10,34)	(7.8,29.3)
$C_{trough,ss}$	3.1 ± 1.3	3.7 ± 1.9	7.6 ± 2.8	6.8 ± 3.1	5.9 ± 2.4	6 ± 2.8	5.4 ± 2.5
	(1,6.4)	(0.7,9.2)	(3,17.1)	(1.1,18.4)	(1.7,13.8)	(1.4,15)	(1.6,12.2)
$AUC_{0-tau,ss}$	100.6 ± 16.3	106.2 ± 19.5	149.2 ± 14.9	138.7 ± 19.5	131.6 ± 15.8	130 ± 18.9	126.5 ± 16.3
	(60.9,132.6)	(49.6,152)	(114.9,181)	(81.5,182.4)	(92.9,180.3)	(78.3,174.9)	(79,161.7)

The simulations indicate that exposure should be highest in the BW group of 40-70 kg and lowest in children < 40 kg. Thus, there might be a risk of overexposure in patients weighing 40-70 kg and a risk of underexposure in children. Simulated Ctrough levels suggest that children are at higher risk to fall below 1 µg/ml which is considered to be a minimum flare-free level.

Further thorough examination of steady state pharmacokinetics especially in children is needed.

CL/F and C_{max} values in four CAPS patients with moderate to end stage renal insufficiency were close to the mean values in adult CAPS patients (0.228 L/d and 15.9 µg/mL). This is expected as large IgG molecules are not excreted by kidneys and thus impaired renal function is unlikely to have an influence on canakinumab PK.

No formal PK studies in patients with hepatic impairment were performed. Serum albumin was a significant covariate for canakinumab clearance, probably due to competition for the FcRn receptor. A 28% difference in CL is predicted over the range of albumin observed in the patient population, from 35 to 50 g/L, considered not to be clinically significant. However, impaired hepatic function leading to low serum albumin may enhance canakinumab clearance leading to reduced steady state drug exposure.

Based on the population PK analysis in 233 subjects, gender, race and study population had no influence on the PK of canakinumab, apart from a slight decrease in CL in non-Japanese healthy volunteers (see above).

Body weight was a significant covariate for both clearance and the apparent size of the central compartment. Both parameters increase by body weight suggesting that BW adjusted dosing at least in children is justified.

The chosen dosing regimen for the intended indication (150 mg SC flat for adults and 2 mg/kg for children < 40 kg) reduces the risk of overexposure in small children. But the intended regimen leads to a relatively lower dose of 1-2 mg/kg when BW is > 75 kg, and a relatively higher dose of 2-3.75 mg/kg for the BW group between 40 and 75 kg. Therefore, this group (40-75 kg) might be overdosed compared to lower and higher body weight groups. PK data for the BW group between 40 and 70 kg are limited. Whether the intended dosing regimen leads to comparable and sufficient efficacy profile in all BW groups has to be further assessed by the MAH. The MAH is asked to calculate steady state predictions for different weight groups.

Age was found to be a significant covariate on the subcutaneous drug absorption rate (Ka), slowing with age. This may reflect changes in lymphatic drainage, with approximately a 1.5 fold decrease in the absorption rate as age doubles. This could cause lower bioavailability in elderly patients and a possible need for dose adjustment.

It has to be considered that the PK data available from children (total children treated: N=12; thereof only N=1 child receiving more than a single BW-adjusted 2 mg/kg dose) and from elderly patients (> 65y; n=1 CAPS) are very limited. Long term data of (steady state) exposure (C_{max} and C_{trough} levels) in children (and adults) are needed and should be measured in ongoing/further studies in order to validate the BW-adjusted dosing for children < 40 kg BW.

In conclusion, single dose PK of canakinumab is well characterized but there is further need to characterize the steady state PK of canakinumab in the treated population relating to the extent, variability and upper limits of drug exposure, represented by C_{maxss} and AUCss and accumulation ratio (R). A particular focus should be put on these parameters in very low BW patients (children), very high BW patients as well as elderly patients in order to verify or adjust the proposed dosage regimen.

- Dose proportionality and time dependencies

A non-linear mixed effects PK-flare probability model was created to identify a dosing regimen which keeps free IL-1ß production below the threshold associated with clinical evidence of CAPS. The response model was created from the PK data and clinical symptoms of relapse from the first 7 patients enrolled in study A2102. . The model enabled the prediction of the levels of exposure of CAPS patients to canakinumab over time, for both i.v. and s.c. doses, and the probability of relapse at any point in time for a specific dosing regimen and range of bodyweights.

The model was able to fit the data for canakinumab concentration and the binary relapse data.

The model estimated a canakinumab concentration of 1.1 µg/mL at which there is a 50:50 probability of clinical relapse . This concentration corresponds to about 7 times the value of KD of binding between canakinumab and IL-1ß (about 1 nM or 0.15 µg/ml) reflecting about 90% occupancy of IL-1ß in serum at that time. Thus, the probability of relapse increases with the decline of full occupancy of IL-1ß in serum. Therefore,, the failure of dectection of free IL-1ß in serum during the whole treatment is plausible since it will be completely occupied by canakinumab.

Simulations of different dosing regimens and Phase III trial designs were conducted. The simulations suggested that the most realistic dosing regimen should be 150 mg s.c. canakinumab every 8 weeks, or 2 mg/kg if body weight is less than 40 kg. Based on the body weight range observed in these patients this should have a low probability of relapse in the region of 1% after subsequent dose at steady state. These were therefore the doses used in studies (CACZ85D2304) and (CACZ85D2306).

The prediction was validated from study (CACZ85D2304) where all 15 patients in Part II on treatment with canakinumab were free of disease flare. There was good agreement between predicted and observed Ctrough levels. However, validation is not complete since there are no observed values for C_{max},ss and AUCss, and data on children < 40 kg are limited. This has to be completed in further studies.

Since the time to relapse in children during the pivotal study was significantly shorter than in adults this might be explained by a lower exposure in children leading to an earlier decline in serum concentrations of canakinumab. The applicant was requested to perform, after marketing authorisation, further pharmacokinetic studies in paediatric subjects.

- Special populations

Renal impairment: since canakinumab is a human IgG immunoglobulin with large molecular size (~150 kDa), little intact immunoglobulin is expected to be filtered by the kidney. Therefore, impairment of renal function is not likely to have influence on the PK of canakinumab, and this was supported by the clearance and C_{max} values of four patients with renal insufficiency included in one of the studies.

Hepatic impairment: No formal study has been performed with canakinumab in patients with impaired hepatic function. Elimination of protein drugs such as canakinumab is thought to occur via proteolytic catabolism in different tissues. Although liver is known to be a major organ of protein degradation, impaired hepatic function was not expected to be a limiting factor for elimination.

Paediatric patients: Due to the lack of data, Ilaris will not be recommended for use in children below 4 years or 15 kg of weight. Further pharmacokinetic investigations in children have also been requested by the CHMP.

Elderly: Results from the PK-binding model demonstrated that age had an effect on the s.c. absorption rate constant; however, no effect of age was observed on canakinumab clearance, and steady state exposure was not affected by age.

The proposed SPC wording was: "Pharmacokinetic/pharmacodynamic modeling indicates that age has no effect on weight adjusted clearance (see pharmacokinetic properties). However clinical experience in such patients is limited."

- Pharmacokinetic interaction studies

No studies have been performed.

- Pharmacokinetics using human biomaterials

Studies on plasma protein binding, hepatic metabolism and drug interaction, human biomaterials and on extrinsic factors were not performed.

Pharmacodynamics

- Mechanism of action

Canakinumab binds to human IL-1β (not to IL-1α or IL-1ra), and blocks the interaction of this cytokine with its receptors, thereby functionally neutralizing its bioactivity. This results in inhibition of the down-stream events of IL-1 signaling, including IL-1β production, IL-1β pathway related gene activation, elevation of acute phase proteins such as SAA and CRP, and mobilization of neutrophils and platelets from the bone marrow.

The resulting complexes of canakinumab and IL-1β are biologically inactive and are supposed to be eliminated at a much slower rate than free IL-1β, resulting in elevation of total IL-1β (free plus complex) following canakinumab administration. Thus, measurement of free plus complexed IL-1β, i.e. total IL-1β, is considered a relevant biomarker for canakinumab indicative of binding of IL-1β by the antibody.

Members of the IL-1 superfamily form an important part of the inflammatory response of the body against infection. Thus, permanent suppression of IL-1β pathway is associated with known risks of immunoincompetence, including infections and malignancies.

IL-1β/canakinumab complexes mirror the reduction in free IL-1β level. PD studies include some data on the levels of other cytokines, such as IL-1Ra, IL-5, IL-6, IL-8, TNFα, following canakinumab dosing.

- Primary and Secondary pharmacology

Neither healthy subjects nor patients had elevated serum IL-1β levels at baseline. This indicates that IL-1β serum/plasma levels are not useful as a biomarker to classify disease severity. 66% (61/92) of all CAPS patients studied had no detectable levels of IL-1β at baseline (IL-1β as measured by a commercial ELISA kit with a limit of quantification of 0.10 pg/mL). Where it was detectable (in 31/92 patients), it was usually low, within the range 0.16 pg/mL to 3.42 pg/mL.

Practically no free IL-1β was detected throughout the studies with the method chosen. In contrast, small but detectable levels of (total) IL-1β were often detected pre-dose in canakinumab-treated subjects and in placebo-treated subjects.

An increase in total IL-1β (bound to canakinumab) was observed in all studies, in both healthy subjects as well as patient populations, including CAPS patients, after canakinumab dosing.

In study B2101 with healthy volunteers, all three dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg) produced an approximately similar increase in total IL-1β. In study A1101 the increase of total IL-1β was greater with higher doses. In both studies, the duration of higher total IL-1β was increased with increasing dose. These results suggest that the limiting factor for canakinumab binding is the availability of free IL-1β, and the excess canakinumab remains in circulation ready to bind any IL-lβ produced.

Based on the PK-binding model, predicted steady state levels (C_{trough},ss and C_{max},ss) for total IL-1β following 150 mg s.c. doses of canakinumab every 8 weeks are 19.3 and 26.7 pg/mL. Higher levels of total IL1-ß in CAPS patients compared to other populations are consistent with the assumption of a

higher production rate in tissue of these patients. There was a high inter-subject variability in Il-1ß levels between CAPS patients after canakinumab.

There is no clear relationship between increased plasma/serum levels of total IL-1β and response to canakinumab in CAPS patients, although the timing of normalization of clinical inflammatory symptoms appears synchronous with the measured increase in canakinumab–IL-1β complexes and

simulated inhibition of free IL-1β in the interstitium and in the blood, It is apparent that serum is not the relevant compartment for IL-1β accumulation. The Applicant has discussed the recruitment of IL-1β from other compartments. According to literature provided by the Applicant, mast cells may play an important role in IL-1β production in the skin and possibly also in the joints and central nervous system.

The levels of serum cytokines studied (IL-1ra, IL-6 and TNFα) did not show any clinically relevant changes in healthy volunteers. In 4 CAPS patients (study A2102) a decrease in the mean IL-6 and IL-1ra levels was observed.

In D2304, IL-1ra levels in CAPS patients at baseline markedly varied in the range of 120 to 3500 pg/mL. After canakinumab treatment there was a tendency of decrease of the high levels (range at the end of part III: 113 to 628 pg/mL), the median values at baseline and throughout parts I, II, and III remained stable at about 200 pg/mL. In part II there was no significant difference in IL-1ra levels between placebo and treated group. There is a tendency of decrease in IL-6 while the levels of IL-18 remained stable. The data available on MMP-1 and MMP-3 levels are sparse and does not allow any conclusions.

Exploratory genomic studies were conducted in two CAPS studies to identify gene expression patterns of blood cells that are associated with treatment response to canakinumab. A treatment related decrease in the expression of the IL-1β target gene and associated inflammatory pathway genes IL-1R1, IL-1R2, IL-1RN, TL-R2 and TL-R4, but not in the expression of the unrelated inflammation gene TNF-α was observed in CAPS patients. These down-regulations were detectable as early as Day 8 of treatment and persisted throughout the study.

Thus, it appears that a negative feedback system following canakinumab binding to IL-1β results in decrease in the production of IL-1β and associated cytokines.

PD modelling

IL-1β production and clearance were highest in CAPS patients. However, they had clearly lower binding affinity of canakinumab to IL-1β than in the patient with asthma, rheumatoid arthritis or psoriasis. The CAPS patients responded to canakinumab treatment, indicating that the level of IL-1β capture was good enough for a clinical response. In the population modelling analysis, no clear relationships with body weight, age, serum albumin, cell line, or sex were observed in the binding of canakinumab with IL-1β, or in the turnover of IL-1β.

Clinical efficacy

Approximately 830 patients (including 37 children aged ≥4 years) have been receiving canakinumab in completed and ongoing clinical trials on various indications.

Efficacy, safety and tolerability data on canakinumab from CAPS studies (completed or with an interim data cut-off) are available for 104 subjects (including 23 children aged from 4 to 17 years of age). Of these, 20 patients were classified as having FCAS, 72 as MWS, 10 with MWS/NOMID, and 1 with NOMID. Patients were observed for up to 3¾ years, the overall duration of exposure was approximately 96 patient years.

The single pivotal CAPS study used a controlled withdrawal design. Given the severity of the patient population in this trial, a placebo-controlled randomization of canakinumab-naïve patients was deemed unethical, especially in children. Instead, an open-label run-in phase, requiring complete response, gave all patients initial treatment.

Supportive efficacy data were provided in other open -label CAPS studies in which some patients with the most severe phenotype (MWS/NOMID and NOMID) were enrolled.

- Dose response studies

Specific dose-finding studies were not possible due to the scarcity of patients. Thus, modelling and simulation was applied to data obtained from study A2102 (an open-label dose-titration study in 34 CAPS patients with NALP3 mutations) that included assessment of drug levels and disease relapse.

Dose selection was designed to:

1. Achieve a C_{max} allowing for fast and complete clinical and serological response
2. Maintain clinical response for several weeks to permit a convenient dosing regimen
3. Select a subcutaneous injection volume not exceeding 1 ml.

Canakinumab plasma levels and clinical assessments of relapse were collected in patients who received an i.v. dose of canakinumab. A nonlinear mixed effect PK-flare probability model was created to identify a dosing regimen which keeps free IL-1β below the threshold associated with clinical evidence of CAPS. The response model was created from the PK data and clinical symptoms of relapse from the first 7 patients enrolled. All 7 patients achieved complete remission 2-7 days after canakinumab i.v. or s.c.. The time to relapse with the corresponding plasma level data were used to predict the dose of 150 mg s.c. if >40kg and 2 mg/kg s.c. was used when ≤ 40kg, both every 8 weeks.

- Main study (Study D2304)

Study No.	Study objective, population	Treated patients	Treatment duration	Dosage	Efficacy endpoint
D2304	Safety / efficacy in MWS **(Parts I & III:** uncontrolled) **(Part II:** placebo-controlled withdrawal)	35	48 wks in total: Part I: 8 weeks Part II: 24 weeks Part III: 16 weeks	**Part I** 150 mg s.c. single dose (>40kg) or 2 mg/kg s.c. (15 -40kg) **Part II** 150 mg s.c. q 8wk (>40kg) or 2 mg/kg s.c. (15 -40kg) or placebo **Part III** 150 mg s.c. q 8wk (>40kg) or 2 mg/kg s.c. (15 -40kg)	Proportion of patients with disease flare in Part II

METHODS

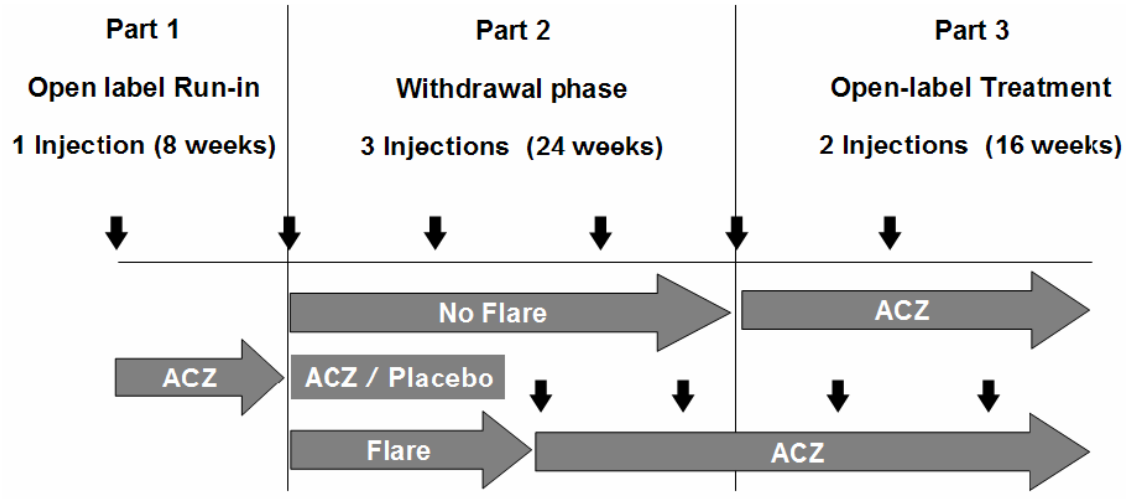
Study Participants

Study D2304 was a multicenter, multinational, 3-part study (Parts I and III uncontrolled, Part II placebo controlled) in adults and children with MWS (NALP3 mutation confirmed).

Treatments

150 mg s.c. if >40kg and 2 mg/kg s.c. when ≤ 40kg, both every 8 weeks.

All patients received 1 injection of canakinumab in Part I (8 weeks) and those who had a complete and sustained response were randomized in Part II to receive a maximum of 3 injections of canakinumab or placebo at 8 week intervals. Patients who finished Part II, or flared beforehand, entered Part III and received canakinumab every 8 weeks until 48 weeks.



Objectives

The primary objective was to assess the efficacy of canakinumab (percentage of patients who experienced disease flare) compared with placebo in Part II as determined by the Physician's global assessment of autoinflammatory disease activity, assessment of skin disease and inflammation markers (CRP and/or SAA).

The secondary objectives were to assess the safety, tolerability and immunogenicity of canakinumab, to assess overall efficacy (response rate) of canakinumab in Part I and Part III as determined by the

Physician's global assessment of autoinflammatory disease activity, assessment of skin disease and inflammation markers, to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of

canakinumab and to assess the effect on disease progression with regards to deafness, kidney function, neurological and ophthalmological symptoms.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of patients with disease flare in Part II (defined as those who experienced a protocol-defined clinical relapse, or discontinued from Part II for any reason) compared to placebo.

Disease relapse was defined as a CRP and/or SAA values greater than 30 mg/L, as well as a physician global assessment of auto-inflammatory disease that was either rated above minimal or, if equal to minimal, accompanied by skin disease activity rated above minimal (assessed on the same day).

This composite score uses a combination of patient reported outcomes, physician global assessment and laboratory values that has not been validated. The prevention of flare activity was considered a meaningful objective as flares are characterised by inflammatory activity that is the cause for long term disease progression and organ damage/amyloidosis.

The following secondary efficacy endpoints were analyzed:

- Proportion of canakinumab treatment responders in Part I
- Proportion of patients without disease relapse in Part III
- Change in inflammatory markers CRP and SAA
- Investigator's clinical assessment of autoinflammatory disease activity
- Patient's assessment of symptoms
- Assessment of skin disease

Health-related Quality of Life was assessed using the following instruments: Medical Outcome Short Form (36) Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F), Health Assessment Questionnaire (HAQ), and Child Health Questionnaire – Parent Form (CHQ-PF87) (in children/adolescent patients).

Sample size

The total sample size was planned to be at least be 20 patients randomized into the withdrawal period (Part II). The sample size was calculated to show superiority of canakinumab relative to placebo for the proportions of patients with disease flare. A sample size of 10 patients per group would give 90% power to detect a treatment difference between disease flare rate of 15% for the active group and of 90% for the placebo group, based on Fisher's exact test with a 0.05 two-sided significance level.

A total of 35 patients were screened and enrolled in Part I, of whom 31 were randomized into Part II (15 canakinumab : 16 placebo). All these 31 patients entered Part III. All patients were included in the safety and intent to treat populations.

Randomisation

There was an imbalance between placebo- and canakinumab-treated groups with regard to gender (93.3% females versus 6.7%). The applicant was requested to critically evaluate the effect of gender in the clinical efficacy of canakinumab. In the answer, no gender effect regarding response to canakinumab could be discerned based on several assessments across canakinumab CAPS studies with regard to response to treatment and duration of response, and this was accepted by CHMP.

Statistical methods

Analysis used the intent-to-treat (ITT) population (all randomized patients receiving at least one dose of study drug). In Parts I, II and III the proportion of patients who responded without disease relapse was calculated. In Part II treatment comparison was performed on common odds ratio by a stratified test procedure. The withdrawal design was found acceptable by CHMP during a scientific advice procedure.

RESULTS

Participant flow

There was an open-label design in Part I for identification of canakinumab responders. Patients with complete response and without disease relapse until Week 8 in Part I entered Part II, which was a double-blind, placebo controlled withdrawal period for up to 24 weeks. Upon disease flare or completion in Part II patients entered Part III, which was open-label, active treatment with canakinumab for 16 weeks.

Patient disposition – n (%) of patients (Safety population)

	Part I	Part II			Part III
Disposition Reason	ACZ885 N=35 n (%)	ACZ885 N=15 n (%)	Placebo N=16 n (%)	Total N=31 n (%)	ACZ885 N=31 n (%)
Completed	31 (88.6)	15 (100)	4 (25.0)	19 (61.3)	29 (93.5)
Discontinued	4 (11.4)	0 (0.0)	12 (75.0)	12 (38.7)	2 (6.5)
Adverse Event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
Unsatisfactory therapeutic effect	4 (11.4)	0 (0.0)	12 (75.0)	12 (38.7)	1 (3.2)

In Part I, one patient (0003) did not achieve the protocol-defined response criteria. After reviewing the patient's PK data, it was concluded that the canakinumab levels were substantially lower possibly due to suboptimal administration of canakinumab (self-administeration was reported on the dosage administration record). Other 3 patients who initially responded in Part I discontinued due to unsatisfactory therapeutic effect. They showed signs of clinical relapse according to the investigators before week 8 completion, but two of them did not meet the protocol defined criteria for flare. The 12 patients discontinued in the placebo group entered into Part III.

Conduct of the study

The majority of protocol deviations were minor, predominantly missing laboratory tests and visits outside of visit windows.

Baseline data

All patients had a molecular diagnosis of NALP3 mutation. Based on investigators' confirmations, the confirmed mutation in NALP3 was R260W for more than half of the patients (18, 51.4%); seven patients had mutation T348M, three patients had D303N, two patients had E311K; the five remaining patients had mutations A439V, D305N, T346N, T346I and M662T.

Baseline disease assessments (Safety population)

	Part I	According to randomization in Part II		
Demographic variable	**ACZ885 N=35**	**ACZ885 N=15**	**Placebo N=16**	**Total N=31**
Molecular diagnosis of NALP3 mutation – n (%)				
Yes	35 (100)	15 (100)	16 (100)	31 (100)
Audiogram assessment – n (%)				
Normal	5 (14.3)	3 (20.0)	1 (6.3)	4 (12.9)
Clinically insignificant abnormality	8 (22.9)	4 (26.7)	3 (18.8)	7 (22.6)
Clinically significant abnormality	22 (62.9)	8 (53.3)	12 (75.0)	20 (64.5)
Neurological assessment – n (%)				
Normal	15 (42.9)	5 (33.3)	7 (43.8)	12 (38.7)
Clinically insignificant abnormality	12 (34.3)	4 (26.7)	7 (43.8)	11 (35.5)
Clinically significant abnormality	8 (22.9)	6 (40.0)	2 (12.5)	8 (25.8)
Ophthalmological assessment – n (%)				
Normal	13 (37.1)	5 (33.3)	8 (50.0)	13 (41.9)
Clinically insignificant abnormality	16 (45.7)	7 (46.7)	7 (43.8)	14 (45.2)
Clinically significant abnormality	5 (14.3)	2 (13.3)	1 (6.3)	3 (9.7)
Missing	1 (2.9)	1 (6.7)	0 (0.0)	1 (3.2)
MRI assessment – n (%)				
Normal	24 (68.6)	8 (53.3)	12 (75.0)	20 (64.5)
Clinically insignificant abnormality	4 (11.4)	2 (13.3)	2 (12.5)	4 (12.9)
Clinically significant abnormality	2 (5.7)	2 (13.3)	0 (0.0)	2 (6.5)
Missing	5 (14.3)	3 (20.0)	2 (12.5)	5 (16.1)

Background and disease characteristics at baseline (Safety population)

	ACZ885 (All patients starting in Part I)	According to randomization in Part II		
	N=35	ACZ885 N=15	Placebo N=16	Total N=31
C-Reactive Protein (mg/L)				
N	35	15	16	31
Mean	30.7	29.2	37.6	33.6
SD	27.07	25.65	29.03	27.32
Median	20.0	19.6	26.0	22.0
Min – Max	2 - 105	2 - 102	8 - 105	2 - 105
Serum Amyloid A (mg/L)				
N	35	15	16	31
Mean	137.3	141.9	162.2	152.4
SD	165.64	178.44	167.57	170.31
Median	48.9	48.2	111.9	84.8
Min – Max	3 – 530	4 – 508	9 – 530	4 - 530
HAQ score				
N	30	12	14	26
Mean	0.4	0.6	0.3	0.4
SD	0.65	0.72	0.52	0.63
Median	0.0	0.4	0.0	0.0
Min – Max	0.0 – 2.3	0.0 – 2.3	0.0 – 1.6	0.0 – 2.3
Physician's Global assessment of auto-inflammatory disease activity – n (%)				
Minimal	2 (5.7)	1 (6.7)	0 (0.0)	1 (3.2)
Mild	7 (20.0)	2 (13.3)	5 (31.3)	7 (22.6)
Moderate	22 (62.9)	10 (66.7)	9 (56.3)	19 (61.3)
Severe	4 (11.4)	2 (13.3)	2 (12.5)	4 (12.9)
Assessment of skin disease – n (%)				
Absent	4 (11.4)	1 (6.7)	2 (12.5)	3 (9.7)
Minimal	6 (17.1)	3 (20.0)	3 (18.8)	6 (19.4)
Mild	9 (25.7)	4 (26.7)	5 (31.3)	9 (29.0)
Moderate	15 (42.9)	7 (46.7)	5 (31.3)	12 (38.7)
Severe	1 (2.9)	0 (0.0)	1 (6.3)	1 (3.2)
Patient's Global assessment of symptoms – n (%)				
Absent	4 (11.4)	2 (13.3)	2 (12.5)	4 (12.9)
Minimal	6 (17.1)	2 (13.3)	2 (12.5)	4 (12.9)
Mild	8 (22.9)	4 (26.7)	3 (18.8)	7 (22.6)
Moderate	9 (25.7)	5 (33.3)	3 (18.8)	8 (25.8)
Severe	4 (11.4)	2 (13.3)	2 (12.5)	4 (12.9)

Numbers analysed

One patient in the canakinumab treatment group was excluded from the per protocol population due to missing primary endpoint assessments.

Analysis populations – n (%) of patients

Total number of patients studied	Part I ACZ885 N=35 n (%)	Part II ACZ885 N=15 n (%)	Part II Placebo N=16 n (%)	Total N=31 n (%)
Enrolled patients	35 (100)			
Randomized Population		15 (100)	16 (100)	31 (100)
Analysis population				
Safety	35 (100)	15 (100)	16 (100)	31 (100)
ITT	35 (100)	15 (100)	16 (100)	31 (100)
Per-protocol	N/A	14 (93.3)	16 (100)	30 (96.8)

Outcomes and estimation

In Part I, 97.1% of patients achieved a complete response, 71.4% by the first scheduled time point (Day 8) the remainder by Day 15, except for 1 patient on Day 29, who had a viral infection interfering with response assessment. Only 1 patient did not achieve the protocol defined complete response criteria. By Day 8, mean CRP levels had decreased from 30.7 to 5.4 mg/L and SAA had decreased from 137.3 to 18.3 mg/L compared to baseline.

The primary efficacy endpoint in Part II was met by demonstrating a statistically significant and clinically relevant difference in the proportion of patients who experienced a disease flare (none on canakinumab, 81% on placebo) as shown in the following table. The median time to disease flare in the placebo treated patients in Part II was 100 days.

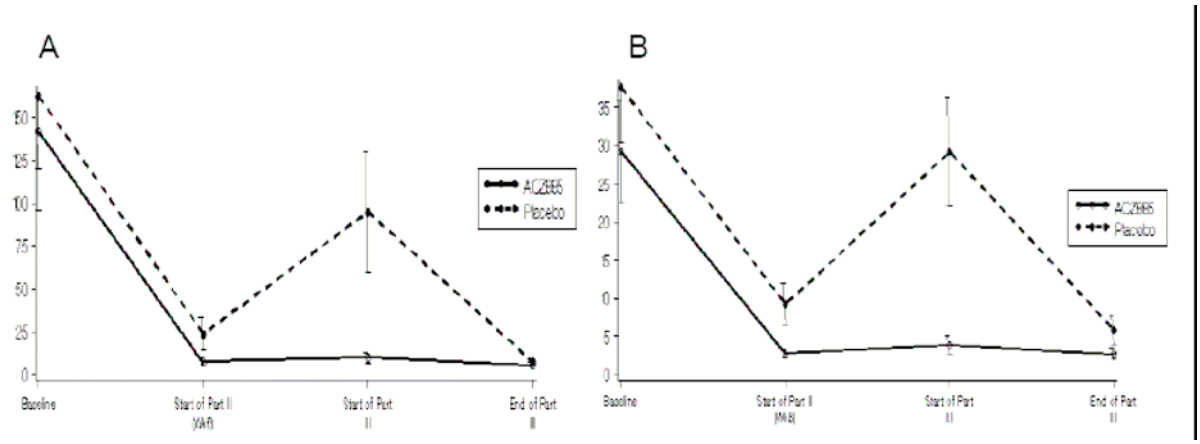
ACZ885 n/N (%)	Placebo n/N (%)	Comparison			
		Odds ratio	95% CI	p-value 1	p-value 2
0/15 (0.0)	13*/16 (81.3)	0.00	[0.00,0.14]	<0.001	1.000

n = number of patients with flare, N = number of patients treated, CI = confidence interval
p-value 1 = test for odds ratio equal to 1, p-value 2 = test for homogeneity of odds ratio

Secondary efficacy variables were change in CRP and SAA levels during Part II.

This showed that the low levels achieved in Part I stayed low in the canakinumab group but rose in the placebo group after active treatment withdrawal in Part II (see following figure)

Figure: Inflammatory markers, SAA (A) and CRP (B), over time in D2304 in mg/L, mean±SEM



Concordant with the re-appearance of disease activity in the opinion of the investigator and the acute phase proteins under placebo at end of Part II, patients also rated their disease activity higher and their symptoms stronger under placebo as compared to canakinumab. The difference was clinically

meaningful and showed a trend towards statistical significance (p=0.07). The missed statistical significance might be explainable by the fact that 3 patients in the canakinumab group rated their disease activity severe at end of Part II while they also reported disease-related and unrelated symptoms including insomnia, vertigo, blurred vision, abdominal pain and diarrhoea. Thus, the occurrence of these AEs may have influenced their assessment of their disease activity.

A complete clinical response in Part I was achieved by 97.1% of patients, all receiving canakinumab. In Part II there was a statistically significant difference ($p<0.001$) in the number of patients with disease flares, with no patients on canakinumab and 13/16 (81.3%) placebo-treated patients meeting the protocol-defined flare criteria. At the end of Part III, 96.8% of patients were without disease relapse. One male patient experienced a disease relapse on Day 336 from baseline. When patients resumed treatment with canakinumab in Part III, levels of serum inflammatory markers decreased to levels seen at the start of Part II.

At the time of the second interim analysis of the uncontrolled long-term safety and efficacy study D2306, a total of 98 patients had received canakinumab treatment. Treatment was shown to be highly effective as 5 (5.9%) of the patients with available assessment data had experienced a disease relapse.

- Uncontrolled studies

Summary of uncontrolled trials

Study No.	Study objective, population	Treated patients	Treatment duration	Dosage	Efficacy endpoint
A2102	Dose ranging / efficacy / tolerability in CAPS (MWS, FCAS, NOMID + MWS)	34	Up to 28 months	(Multiple doses, re-dosing upon relapse) **initially** 10 mg/kg i.v. (first 4 patients only) **then** 1 mg/kg i.v. (first 4 patients only) **next** 150 mg s.c. (age >16) or 2 mg/kg s.c. (age ≤16)	Time to relapse
D2306	Safety / efficacy in CAPS (MWS, FCAS, NOMID + MWS)	57 (at cut-off)	6 months-2 years	150 mg s.c. q 8wk (>40kg) or 2 mg/kg s.c. (15 - 40kg)	Maintenance of response (absence of relapse)

Study A2102 was a dose-titration and efficacy, safety and tolerability study of canakinumab administered s.c. or i.v. to adults or children (≥ 4 years) and included 2 subjects with FCAS (adults), 27 with MWS patients (5 of them children), 4 with MWS/ NOMID (2 adults, 2 adolescents), and 1 with NOMID (adult).

For dose selection, in Stage 1, four patients received 10 mg/kg canakinumab i.v. infusion on Day 1, and upon relapse a second i.v. infusion of canakinumab (1 mg/kg), and upon second relapse, 150 mg canakinumab s.c. In Stage 2, the 4 patients and additional 30 patients received 150 mg canakinumab s.c. injection and another 150 mg upon each relapse. The remaining patients were to provide short and long-term efficacy and safety data with the predicted dose, and received 150 mg canakinumab s.c. or 2 mg/kg s.c. if aged ≤16 years at relapse.

After the first 150 mg dose of canakinumab, 28 of 29 adult/paediatric patients achieved a complete clinical response in 2 to 9 days and 1 patient achieved a partial response. The estimated median time to relapse was 115 days, consistent with the results from the pivotal study.

After the first 2 mg/kg dose, all 5 children (≤16 years, <40 kg) achieved complete clinical response within 2 to 8 days, however 2 children (both with the V198M mutation) relapsed within a week but responded to 'rescue' treatment. The median time to relapse was 48.6 days.

In later periods, 3 patients again achieved complete response and 2 again needed rescue treatment.

Treatment with canakinumab resulted in a rapid onset of efficacy, with disappearance or significant improvement of symptoms within one day after dosing (day 2). Laboratory parameters such as high CRP or SAA normalized within days of canakinumab injection.

Improvements in audiologic tests were noted in 6 patients and quality of life assessments showed general trends for improvement after dosing.

Study D2306 was designed to provide long-term safety and efficacy data for canakinumab administered as an s.c. injection in patients who participated in the A2102 or D2304 studies or newly identified patients with CAPS. An interim analysis was conducted for this study.

The demographics of patients included up to the cut-off date (09-Jan-2009) showed that most of the 57 patients were Caucasian and 18 to 40 years old. Nine patients below 18 years of age were enrolled. All except 2 patients were diagnosed with NALP3 mutations.

Up to the data cut-off (09-Jan-2009), 98 patients were exposed. Of these, 54 were roll-over patients, made up of 24 patients from Study A2102 and 30 patients from Study D2304 respectively. At the time of data cut-off, 44 canakinumab naïve patients had received treatment in this protocol. Overall, there were 19 FCAS patients, 69 patients with MWS, 8 with MWS with overlapping NOMID, and 1 predominant NOMID phenotype patient although this patient from Study A2102 is grouped together with the MWS/NOMID for the purposes of interim analysis). At cut off, there were 54 patients from prior studies and 44 new patients not previously exposed to canakinumab.

The dosing regimen of 150 mg s.c. was effective in treatment of 77 out of 98 CAPS patients (77/88 patients with available response data). 16 (16.3%) patients needed to use an intensified dosing regimen and were treated with an adjusted dose.

For the canakinumab-naïve patients, 41 out of 44 patients for whom response data was available at database lock achieved a complete clinical response. Of the 3 patients without complete response according to physician assessment, 1 was falsely classified as FCAS and subsequently recorded as protocol deviation due to the diagnosis of cold urticaria.

Canakinumab-naïve patients showed a substantial reduction (normalization) of their mean acute phase protein levels, with a decrease mg/L at baseline for CRP

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

Classical subgroup analyses were not performed owing to the small size of each study and the inability to pool across the differently designed studies to obtain reasonable sample sizes.

However, the data were explored for any gross differences between patients with different disease expressions (i.e. FCAS, MWS, MWS/NOMID or NOMID) and were examined for differences between adult and paediatric patients.

Subgroups of MWS patients

As time to relapse data provided more suitable quantitative information, this was used for subgroup exploration in a study of mostly MWS patients.

In Study A2102 there were no significant differences in time to relapse between subgroups with regard to gender, or previous use of canakinumab or anakinra (most patients).

Response in FCAS Patients

In total there were 9 patients with FCAS were included in the studies. All patients responded to therapy (except for one with missing response criteria) regardless of age or previous use of anakinra or canakinumab.

The 2 patients with FCAS from Study 2102 (adults) had among the highest baseline disability scores (HAQ-DI questionnaire) and the highest baseline level of fatigue (FACIT-F questionnaire) in the study, yet both showed complete response to canakinumab. Their baseline CRP/SAA values were 152/618 mg/L and 23.5 /48.9 mg/L, normalizing to <10mg/L by Day 8 and Day 3, respectively.

Response in MWS/NOMID or NOMID Patients

In total there were 5 patients with MWS/NOMID overlap and 1 patient with a predominant phenotype of NOMID. These patients responded similarly to all other CAPS patients to therapy regardless of age or previous use of anakinra or canakinumab.

- Clinical studies in special populations

Response in paediatric patients

Included in the studies, there were 8 children ≤40 kg, who received 2 mg/kg and another 7 adolescents <18 years of age, who received 150 mg. All of the adolescents were responders to the 150 mg dose, given at 8 week intervals, except for 1 patient who showed a partial response. After the first 2 mg/kg dose, all 8 children achieved a complete clinical response in 2 to 8 days and 6 children were kept in remission with the given dose. However 2 children in Study A2102 (both with V198M mutation) rapidly lost response, but responded to a higher dose (rescue), which was needed repeatedly throughout the study.

Clinical safety

- Patient exposure

Safety data overall are rather limited. Safety and tolerability data from completed non-CAPS trials were available from 465 male or female subjects, and trials with an interim analysis were available from 104 male or female CAPS subjects (including 23 children), who were treated with canakinumab, and observed for periods of up to 3½ years at the initial evaluation. In response to the CHMP LoQ the applicant provided an updated report on safety. Extent and duration of exposure is shown in the following table.

Duration of exposure	ACZ885 pediatrics <18 years (N=23)	ACZ885 adults ≥18 years (N=81)	Total ACZ885 N=104
≥ 1 day	23	81	104
≥ 12 weeks	15	66	81
≥ 24 weeks	12	50	62
≥ 36 weeks	11	46	57
≥ 48 weeks	10	46	56
≥ 96 weeks	0	6	6
≥ 144 weeks	0	4	4
Mean duration (days)	261.4	357.1	336.0
Median duration (days)	169.0	396.0	392.0
Min (days)	29	9	9
Max (days)	658	1429	1429
Patient-years	16.5	79.2	95.7

Studies D2304, A2102, D2306 (up to 9-Jan-2009)
Source: Table 1.2-1A and Table 1.2-1A1

The following table shows the available database as regards diagnosis by age group.

	Children (n=23)				Adults (n=81)			
Type	4 - 11 yrs		12 - 17 yrs		18 - 59 yrs		>60 yrs	
	Sep. 12 2008	Jan. 9, 2009	Sep. 12 2008	Jan 9, 2009	Sep. 12 2008	Jan. 9, 2009	Sep. 12 2008	Jan. 9, 2009
FCAS (n=20)	1	2	-	-	8	15	-	3
MWS (n=72)	5	7	6	8	50	53	2	4
MWS/NOMID (n=10)	1	2	2	3	2	5	-	-
NOMID (n=1)	-	-	-	-	1	1	-	-
unspecified (n=1)	-	1	-	-	1	-	-	-

Source: (Appendix-Listing 1.1C) and [SCS-Table 7-3]

- Adverse events

The most commonly observed AE in CAPS trials were nasopharyngitis (31.7%), upper respiratory tract infection (16.3%), headache (16.3%), rhinitis (11.5%), oropharyngeal pain (11.5%), and nausea (10.6%).

Of note, vertigo was experienced by 9 patients (8.7%), of which 7 patients had pre-existing vertigo and 6 of these patients presented with active vertigo at the start of the study.

There was no striking difference in AE between placebo group and verum group in the pivotal trial. This analysis is likely to be conservative as the treatment phase with verum was longer than in patients on placebo that discontinued/switched after shorter treatment duration.

There were no opportunistic infections observed.

Treatment of up to one year was not associated with a different pattern of AE.

- Serious adverse event/deaths/other significant events

No deaths were observed in the CAPS trial. There were 10 serious AE in 8 CAPS patients, one patient with chest infection, one with pyrexia and urinary tract infections, two cases of vertigo (one patient additionally with unilateral blindness, increase intraocular pressure), one patient with flare of MWS, one patient with progression of fibromyalgia and one patient with intra-abdominal abcess following appendectomy.

Out of 612 patients treated (active treatment and placebo) in 10 ongoing studies, 58 SAEs were reported by the cut-off date (12-Sep-2008) for the dossier. These include 16 cases of confirmed infections (urosepsis, lower respiratory tract infection, hand abscess, acute appendicits, diverticultitis, soft tissue injury/infection, pharyngitis, acute adenitis, pneumonia, pericarditis, sinusitis, and exacerbation of COPD.

There was 1 death in the AMD study F2201 5 months after a single dose of 10 mg/kg canakinumab. The death of this patient was not felt by the investigator to be study drug related.

In the ongoing Study B2204, there was 1 death in this COPD study. A 75 year-old man with COPD received 1 dose of blinded study medication (canakinumab 1 mg/kg or placebo) on 11-Oct-07, presented with dyspnoea and pulmonary congestion (21-Oct-07), was then hospitalized (28-Oct 2007) with worsening dyspnoea and a productive cough diagnosed as pneumonia. Despite treatment with moxifloxacin, a tracheotomy and assisted ventilation, the patient died of respiratory failure (28-Nov-07). The investigator reported the death of this patient as due the progression of the underlying disease without relationship to the study drug.

- Immunogenicity

No anti-canakinumab antibodies were detected.

Local tolerability was good, the majority of patients had no injection site reactions.

None of the 192 adult and paediatric subjects treated with canakinumab in the six different clinical studies (thereof 31 with a duration of exposure > 48 weeks) developed anti-canakinumab antibodies, which indicates that the immunogenic potential of canakinumab is low. However, due to methodological insufficiencies (drug interference) underestimation of antibody incidence could not be excluded. An improved assay should be developed.

- Laboratory findings

Overall there were no clinically significant changes in the laboratory parameters observed. There were 3 patients with asymptomatic liver enzyme elevations (transaminases), either present at baseline or transient changes in a patient with positive viral serology.

Haemoglobin values increased, platelet count decreased and lymphocyte count decreased with canakinumab treatment, all consistent with reduced inflammatory activity.

- Safety in special populations

Due to the low number of patients in the CAPS trial the evaluation as regards subpopulations was not considered meaningful at the time of authorisation. Further investigations, particularly in children with respect to the effect on childhood vaccinations, were requested as part of the Risk Management Plan.

- Safety related to drug-drug interactions and other interactions

No formal clinical drug interaction studies between canakinumab and other medicinal products have been performed.

The most common concomitant medications in CAPS patients were paracetamol, nonsteroidal anti-inflammatory drugs, systemic glucocorticosteroids in about 15% of patients, antibiotics (cephalosporin, amoxicillin) and iron supplements. It is not expected that these medications will influence the PK of canakinumab. This is mainly because monoclonal antibodies are not metabolized by the cytochrome P450 system, and their mechanism of elimination could be via catabolism, different from elimination pathways of small molecules.

The concomitant administration of anakinra (IL-1 receptor antagonist) with etanercept did not improve efficacy, but worsened the safety profile compared to each drug alone in RA patients (Genovese, et al. 2004), thus anakinra is not to be used with a TNF-α inhibitor (Kineret Prescribing Information). Consequently, the concomitant use of canakinumab and a TNF-α inhibitor is, although not tested, also not recommended.

Another aspect to be taken into account is that the expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as IL-1 beta. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as canakinumab, is introduced.

The normalisation of inflammatory activity induced by treatment may cause an increase of CYP that could be relevant for CYP substrates. This is reflected in the SPC.

- Discontinuation due to adverse events

Discontinuation in the CAPS population was predominantly caused by unsatisfactory therapeutic response.

- Post marketing experience

Not applicable.

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

Risk Management Plan

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

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
Identified Risks		
Infections	Routine pharmacovigilance activities Targeted follow-up of serious clinical trial and post-marketing cases using a targeted questionnaires/checklist Study CACZ885D2401: Ilaris® Registry Review and adjudication by dedicated Allergy-Infection-Malignancy (AIM) Adjudication Committee	Labeling: **Warnings and precautions (Section 6 of the Core Data Sheet [CDS])** **Interactions (Section 8 of the CDS)** **SmPC-Section 4.4 [Special warnings and precautions for use (serious infections)]** *An alert card for patients to*

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
		highlight the key safety findings and thus further promote safety use of Ilaris are being prepared. This risk comunication/minimization initiative is subject to national laws and thus will be discussed and agreed upon with the national HAs prior to Ilaris launch in each countries. Physicians Educational Program
Potential Risks		
Severe ISR	Routine pharmacovigilance activities including cumulative review in PSUR Dedicated CRF in clinical trial ACZ885D2306 (CAPS indication)	**SmPC-Section 4.8 (Undesirable effects)** There is only one serious injection site reaction reported in A2204 study. Injection site reactions were reported in 8.6% (Part I) and 13.4% (canakinumab, Part II) of patients and predominantly mild in nature. Physicians Educational Program
Immunogenicity/ allergenicity	Routine pharmacovigilance activities including cumulative review in PSUR Targeted follow-up of serious clinical trial and post-marketing cases using a targeted questionnaires/checklist Review and adjudication by dedicated Allergy-Infection-Malignancy (AIM) Adjudication Committee	**SmPC-Section 4.4 [Special warnings and precautions for use (Hypersensitivity reactions)]** There are two serious event reported in A2204 study viz. serious injection site reaction and Lip edema. The majority of the reported AEs were mild in severity and resolved completely. Physicians Educational Program
Opportunistic infections	Routine pharmacovigilance activities including cumulative review in PSUR Targeted follow-up of serious clinical trial and post-marketing cases using a targeted questionnaires/checklist Study CACZ885D2401: Ilaris® Registry	Labeling: **[SmPC-Section 4.4 (Special warnings and precautions for use) serious infections]** '*ILARIS may be associated with an increased incidence of serious infections.* Therefore patients should be monitored carefully for signs and symptoms of infections during and after treatment with Ilaris. *Physicians should exercise caution when administering ILARIS to patients with*

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
		infections, a history of recurring infections or underlying conditions which may predispose them to infections. Treatment with ILARIS should not be continued or initiated in patients with severe infections *predominantly of the upper respiratory tract, in some instances serious, have been reported more frequently with ILARIS than with placebo treatment. Course and response to therapy (including antibiotic therapy) appear normal. Taking ILARIS with tumour necrosis factor (TNF) inhibitors is not recommended because this may increase the risk of serious infections'* **[SmPC-Section 4.5 (interactions)]** '*An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Use of ILARIS with TNF inhibitors is not recommended because this may increase the risk of serious infections*.' Physicians Educational Program
Malignancy	Routine pharmacovigilance activities including cumulative review in PSUR Targeted follow-up of serious clinical trial and post-marketing cases using a targeted questionnaires/checklist Study CACZ885D2401: Ilaris® Registry Review and adjudication by dedicated Allergy-Infection-Malignancy (AIM) Adjudication Committee	This risk is adequately addressed and communicated in the prescribing information and the label. Labeling: **[SmPC-Section 4.4 (Special warnings and precautions for use) malignancies]** '*The risk for the development of malignancies with anti-interleukin (IL)-1 therapy is unknown. A potential risk can not be excluded in patients treated with ILARIS*'. Physicians Educational Program
Lymphoid organ	Routine pharmacovigilance activities	No AEs of lymphoid organ

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
toxicity	including cumulative review in PSUR	toxicity have been reported during the clinical program in CAPS and RA patients so far. Not listed in the CDS.
Neutropenia	Routine pharmacovigilance activities including cumulative review in PSUR Targeted follow-up of serious clinical trial and post-marketing cases using a targeted questionnaires/checklist Study CACZ885D2401: Ilaris® Registry	Labeling: **[SmPC-Section 4.4 (Special warnings and precautions for use) Neutropenia]** "Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) has been observed commonly with another medicinal product that inhibits IL-1 used in a patient population (rheumatoid arthritis) other than CAPS. Neutropenia was observed commonly in patients with rheumatoid arthritis (not an approved use) who were administered Ilaris subcutaneously in clinical studies. None of these patients had serious infections associated with the neutropenia. Although neutropenia was observed uncommonly in CAPS patients, the numbers studied are small. Treatment with Ilaris should not be initiated in patients with neutropenia. It is recommended that neutrophil counts be assessed prior to initiating treatment, after 1 to 2 months, and periodically thereafter while receiving Ilaris. If a patient becomes neutropenic the ANC should be monitored closely and treatment should be discontinued." Additional: Physicians Educational Program
Vertigo	Routine pharmacovigilance activities including cumulative review in PSUR Targeted follow-up of serious clinical trial and post-marketing cases using a targeted questionnaires/checklist Study CACZ885D2401: Ilaris® Registry	Labeling: **Undesirable effects (Section 4.8 of the SmPC)** The ability to drive and operate machines may be impaired by some symptoms associated with CAPS. Patients who experience vertigo during Ilaris treatment should wait for this to resolve completely before driving or operating machines. '*Vertigo has been reported in 6-13% of patients in CAPS and*

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
		rheumatoid arthritis studies, and considered serious in approximately a third of cases. The majority of events occurred in close temporal relation to treatment initiation and responded to symptomatic treatment in all instances. Events resolved despite continuous treatment with Ilaris'.
Hypercholesterolemia	Routine pharmacovigilance activities including cumulative review in PSUR	Not listed in the CDS. In the CAPS dataset, mean changes from baseline to end of study drug treatment were not clinically relevant for biochemistry parameters, except cholesterol and triglycerides where the mean changes seen in canakinumab-treated patients were increases of approximately 10% In RA pooled dataset, mean increases in cholesterol were greater in the canakinumab groups versus placebo. Additional: Physicians Educational Program
Hepatic transaminase and bilirubin elevations	Routine pharmacovigilance activities including cumulative review in PSUR	**[SmPC-Section 4.4 (Special warnings and precautions for use) hepatic function]** Rare, mild, transient and asymptomatic cases of elevations of serum transaminases and bilirubin have been reported patients with confounding factors in clinical trials. This risk is adequately addressed and communicated in the prescribing information and the label.
Combination therapy toxicity	Routine pharmacovigilance activities including cumulative review in PSUR Study CACZ885D2401: Ilaris® Registry	This risk is adequately addressed and communicated in the prescribing information and the label. **[SmPC-Section 4.5 (interactions)]** *'An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF*

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
		inhibitors. Use of ILARIS with TNF inhibitors is not recommended because this may increase the risk of serious infections'
Autoimmunity reactions	Routine pharmacovigilance activities including cumulative review in PSUR	No risk minimization measure is considered necessary at this time. Upon the emergence of new safety findings related to autoimmunity reactions, as reviewed regularly in the PSUR, appropriate updated risk management activities will be considered. The risk of development of autoimmune disorders with anti-IL-1 therapy is unknown. Should symptoms of autoimmune reactions occur, patients should be monitored for presence of anti-nuclear antibodies (ANA) and double-stranded DNA (ds-DNA).
Missing information		
Pregnancy	Routine pharmacovigilance activities including cumulative review in PSUR Study CACZ885D2401: Ilaris® Registry	This risk is adequately addressed and communicated in the prescribing information and the label. (**section 4.6 of SmPC, Pregnancy and lactation**). *There is a limited amount of data from the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). The risk for the foetus/mother is unknown and treatment of women who are pregnant or who desire to become pregnant should therefore only be treated after a thorough benefit-risk evaluation.* Physicians Educational Program
Important potential interactions		
Vaccines	Routine pharmacovigilance activities including cumulative review in PSUR Vaccination study (CACZ885A2106) Additional: post-vaccination antibody titers will be determined as part of the new interventional Vaccination Study.	**SmPC, section 4.4 warning & precautions:** No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
		patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris. It is recommended that, if possible, paediatric and adult patients complete all immunisations in accordance with current immunisation guidelines prior to initiating Ilaris therapy. SmPC, section 4.5: Should vaccination with live vaccines be indicated after initiation of Ilaris treatment, the recommendation is to wait for at least 3 months after the last Ilaris injection and before the next one (see section 4.4). Additional: The Alert Card informs the patients to tell their doctors if they are scheduled to receive any vaccine Physicians Educational Program
Pharmacodynamic interactions	Routine pharmacovigilance activities including cumulative review in PSUR	**SmPC, section 5.1 Pharmacodynamic properties:** In clinical studies, CAPS patients who have uncontrolled overproduction of IL-1 beta show a rapid response to therapy with canakinumab, i.e. C-reactive protein (CRP) and serum amyloid A (SAA) levels, leukocytosis and high platelet count rapidly returned to normal within one week. No antibodies to canakinumab have been detected in CAPS patients treated with canakinumab.
Drugs eliminated by CYP450 enzymes	Routine pharmacovigilance activities including cumulative review in PSUR	**[SmPC] section 4.5:** The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as IL-1 beta. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
		CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. On initiation of canakinumab in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary. No additional risk minimization measure is considered necessary at this time. Upon the emergence of new safety findings related to drug-drug interactions, as reviewed regularly in the PSUR, appropriate updated risk management activities will be considered.

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.

2.6. Overall conclusions, risk/benefit assessment and recommendation

Quality

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The documentation provided with the application demonstrates consistent batch-to-batch production of Canakinumab achieving a consistent quality for the drug substance and the drug product. The fermentation and purification of the drug substance, Canakinumab (ACZ885), are adequately controlled and validated. The drug substance has been adequately characterised with regard to its physicochemical and biological characteristics using state-of the-art methods. The manufacturing process of the drug product has been described and validated in sufficient detail. In addition, the viral safety and the safety concerning other adventitious agents (including TSE) have been sufficiently assured. In general, appropriate drug substance and drug product specifications have been set.

Non-clinical pharmacology and toxicology

The safety profile of canakinumab and a mouse anti-mouse surrogate antibody (01BSUR) were investigated in a series of repeat-dose toxicity studies in mice and marmosets. All pivotal studies were performed according to current regulatory standards and Good Laboratory Practice Regulations.

Genotoxicity and carcinogenicity studies were not conducted. This is in line with the ICH Guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6, 1997).

Immunotoxicity was investigated with the 01BSUR surrogate in mice at doses up to 150 mg/kg. There were no findings that could be unequivocally attributed to the treatment. Lymphoid hyperplasia of spleen and lymphoid depletion that were the most noteworthy immunological findings observed in the

toxicity studies in marmosets, were not observed in this mouse study with the surrogate antibody 01BSUR. This raised a question of the relevance of this mouse model in immunotoxicity evaluation. Consequently, immune toxicity related to canakinumab treatment could not be excluded. This was considered especially important for the paediatric patients since the immune function was not evaluated in the juvenile study. The possibility of differential effect of canakinumab on immune function in children and adult patients should be further investigated by performing a study in juvenile animals.

Efficacy

Demonstrated benefits:

The immediate benefit of treatment of patients with CAPS by 8-weekly injections of canakinumab is the reduction of inflammatory activity caused by neutralisation of excessively secreted IL-1 and reduction of secondary inflammatory mediators, e.g. IL-6. Benefit has been demonstrated by the prevention of relapses in MWS patients in a blinded randomised trial with a withdrawal design. The chosen endpoint was regarded as meaningful for the objective of relapse reduction/flare prevention.

There is currently no approved therapy for CAPS, commonly used treatments involve anakinra, corticosteroids, colchicine and non-steroidals. Anakinra has not been tested in randomised trials but is commonly used because it is the only agent countering pathogenetic events in CAPS.

Uncertain benefits:

Long term benefit is expected to involve the reduction/prevention of amyloidosis and end organ damage caused by the inflammatory process. This endpoint cannot be assessed in clinical studies with a feasible duration. Biomarkers for inflammation have been included as secondary endpoint in the pivotal trial, a meaningful reduction of SAA and CRP has been demonstrated and therefore long term benefit as regards amyloidosis appears possible.

Several phenotypes have been described, all with underlying mutations in the NALP3 gene, the reasons for different phenotypes are unclear at present. The pivotal trial was conducted in MWS patients, other phenotypes were included in open label studies. Induction and maintenance of response showed similarity between the different clinical phenotypes of CAPS ranging from FCAS over MWS to NOMID including overlap syndromes. Considering the known pathogenesis and the fact that patients had confirmed mutation in the NALP3 gene inclusion of these patients in the indication appeared justified. No patients without confirmed genetic mutation were included in the trials. Preliminary data indicated that phenotypically indistinguishable patients may benefit from treatment as well.

Safety

Demonstrated risks:

Infections (upper respiratory tract) are more commonly observed with canakinumab treatment. No opportunistic infections were observed so far.

The available safety data show that therapy with canakinumab appeared to be rather well tolerated.

Uncertain risks:

The safety database was limited at the time of authorisation, 56 patients had been treated for more than 48 weeks, only 6 patients had been treated for more than 96 weeks. Thus long term safety was not well known.

Malignancies are a potential risk for any immunosuppressant.

Drug interactions have not been studied but normalisation of inflammatory activity may cause an increase of CYP that could be relevant for CYP substrates.

The risk of intensified treatment with an increased dose, as used in a 20 patients (7 paediatric and 13 adults) not responding long enough, remains currently unclear, the available data indicate no increased risk.

Immunogenicity is low, however the performance of the assay requires improvement. The good local tolerability is regarded as clinical evidence that immunogenicity could be low.

From the safety database all the adverse reactions reported in clinical trials 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

- User consultation

The readability test was considered acceptable, for a more comprehensive picture the company was requested to provide further information on the demographics of the recruited participants.

Risk-benefit assessment

The benefit/risk balance is considered favourable in adults with MWS, confirmed mutations and inflammatory activity. Extrapolation to less well investigated phenotypes appears reasonable considering the pathogenesis.

Long term safety beyond 1 year is unclear and will be further investigated.

Efficacy has also been demonstrated in children; however duration of treatment response appears to be shorter in some patients, a finding that should be investigated further in combination with further PK/PD studies.

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.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of ILARIS in the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 4 years and older with body weight above 15 kg, including:

– Muckle-Wells Syndrome (MWS),

– Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),

– Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.

Furthermore, the agreed Paediatric Investigation Plan is not fully completed yet as only some of the measures are completed. Already available paediatric data of studies subject to this plan are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.