26 March 2015
EMA/334385/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

ILARIS

International non-proprietary name: CANAKINUMAB

Procedure No. EMA/H/C/001109/P46 040

Note

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

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1. Introduction

On 15 December 2014, the MAH submitted a completed paediatric study for Ilaris, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study

An open-label, multicenter, efficacy and safety study of 4-month canakinumab treatment with 5-month follow-up and long-term treatment period in patients with active recurrent or chronic TNF-receptor associated periodic syndrome (TRAPS) - CACZ885D2203

is part of a clinical development program. A line listing of all the concerned studies is annexed.

Canakinumab was first registered under the trade name ILARIS® for the treatment of CAPS in the United States (US) on 17 Jun 2009. Novartis is currently Marketing Authorization Holder in 72 countries worldwide for 150 mg powder for injection and 36 countries worldwide for the 150 mg powder and solvent for injection (convenience kit).

ILARIS® is also approved for the treatment of acute gouty arthritis (GA) attacks in the EU, Russia, Ecuador, Argentina, Mexico, Peru and Israel. Lastly ILARIS® is also approved for the treatment of systemic idiopathic arthritis (SJIA) in the EU, United States, Switzerland, Philippines, Russia, Chile, Argentina, Peru, Hong Kong, Singapore, Canada, Israel, Australia, Morocco and Malaysia. Submissions are either pending or in progress worldwide.

2.2. Information on the pharmaceutical formulation used in the study

Canakinumab was administered subcutaneously (subcutaneous injections) at a dose of 2 mg/kg for patients ≤ 40 kg or 150 mg for patients ≥ 40 kg. One dose escalation at Day 8 was incorporated into the design for patients in whom the 2 mg/kg or 150 mg dose was not sufficient to resolve the qualifying TRAPS flare. Batch and formulation numbers are provided in below table:

Study drug and strength	Formulation control number	Batch number
ACZ885 150 mg	7004942.009	Y034 0308
ACZ885 150 mg	7004942.009	U002 0409

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **Study number**: CACZ885D2203

An open-label, multicenter, efficacy and safety study of 4-month canakinumab treatment with 5-month follow-up and long-term treatment period in patients with active recurrent or chronic TNF-receptor associated periodic syndrome (TRAPS)

2.3.2. Clinical study

CACZ885D2203: An open-label, multicenter, efficacy and safety study of 4-month canakinumab treatment with 5-month follow-up and long-term treatment period in patients with active recurrent or chronic TNF-receptor associated periodic syndrome (TRAPS)

Methods

Objective(s)

Primary objectives: To assess if canakinumab induces complete or almost complete response in patients with active TRAPS at Day 15 (defined as 15 days after the first dose).

Secondary objectives:

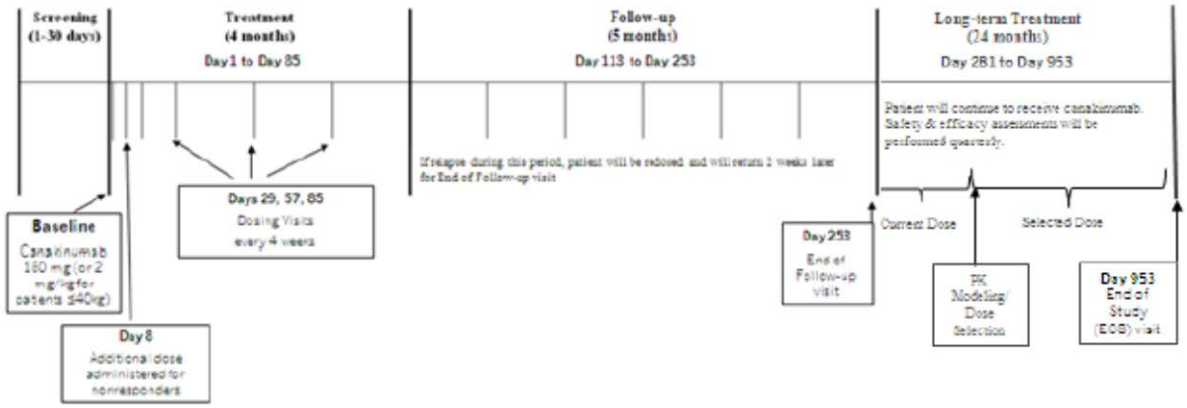
- To assess if canakinumab can induce complete or almost complete response in patients with active TRAPS at Day 8.
- To assess the percentage of patients with complete clinical remission (Physician's Global Assessment score ≤ 1) at Day 8 and Day 15.
- To assess the percentage of patients with C-reactive protein (CRP) < 10mg/L and serum amyloid A (SAA) < 10mg/L at Day 8 and Day 15.
- To assess if canakinumab can induce complete or almost complete response at Day 15 for patients who received an additional dose on Day 8.
- To assess time to patient's assessed clinical remission (Patient's Global Assessment score ≤ 1) after initial canakinumab treatment.
- To assess time to physician's assessed clinical remission (Physician's Global Assessment score ≤ 1) after initial canakinumab treatment.
- To assess the profile over time in CRP and SAA from baseline to end of study.
- To assess the profile over time in each of the 4 key TRAPS signs and symptoms (skin rash, eye manifestations, extremity pain, and abdominal pain) from baseline to end of study.
- To assess the profile over time in physician's global assessment score from baseline to end of study.
- To assess the profile over time in patient's global assessment of TRAPS activity from baseline to end of study.
- To assess percentage of patients who relapse during the 4-month treatment and long-term treatment periods.
- To assess the time to relapse after last canakinumab dose in the 4-month treatment period.
- To assess percentage of patients who relapse and require corticosteroid rescue treatment during the 4-month treatment and long-term treatment periods.
- To assess percentage of patients who relapse and require only NSAID rescue treatment during the 4-month treatment and long-term treatment periods.
- To assess percentage of patients who are able to reduce their corticosteroid maintenance dose during the 4-month treatment and long-term treatment periods.
- To assess the pharmacokinetics/pharmacodynamics of canakinumab in patients with TRAPS.
- To assess pharmacokinetic (PK)/ pharmacodynamic (PD) relationships in order to derive a dose regimen (dose and dosing frequency) required to treat signs and symptoms of active TRAPS and to prevent recurrence/relapse of TRAPS.

- To assess the immunogenicity of canakinumab in patients with TRAPS.

Study design

This was an open-label, single treatment arm, multicentre study of monthly canakinumab 150 mg (2 mg/kg for patient ≤ 40 kg) subcutaneous injections in patients with active recurrent or chronic TRAPS. There was the potential for a single dose up-titration at Day 8 to 300 mg (4 mg/kg for patient ≤ 40 kg), dependent on response. The overall study duration was up to 33 months (4-month treatment period with a maximum 5-month follow-up period following withdrawal plus a maximum 24-month long-term treatment period).

Figure 2-1 Study design



Study population /Sample size

The study population consisted of male and female patients aged ≥ 4 years with clinically and genetically confirmed diagnosis of TRAPS.

The study was planned to recruit 20 patients. A total of 29 patients screened for the study, of which 20 were allocated to treatment and analysed.

Inclusion criteria:

- Patient's written informed consent for ≥ 18 years of age before any assessment was performed. Parent or legal guardian's written informed consent and child's assent, if appropriate, were required before any assessment was performed for patients < 18 years of age.
- Male and female patients at least 4 years of age at the time of the screening visit.
- Patients with a clinical diagnosis of TRAPS and a mutation of TNFRSF1A gene. Patients with low penetrance mutations, such as R92Q or P46L, can be included with mutual agreement between the investigator and Novartis.
- Patients with a diagnosis of *recurrent* TRAPS must have experienced more than 6 episodes/year prior to receiving an effective biologic therapy and the duration of each episode was to have at least 8 days. For patients receiving biologic therapy, this criterion applied to the disease state prior to receiving the biologic therapy.
- Patients who had been treated with anakinra must have demonstrated a partial or complete clinical response with an associated decrease in their inflammation markers (CRP and SAA).

- Active TRAPS as evidenced by clinical signs and symptoms of active TRAPS (Physician's Global Assessment ≥ 2) and an elevated CRP > 10 mg/L (Normal CRP range ≤ 10 mg/L) and/or SAA > 10 mg/L (Normal SAA range ≤ 10 mg/L) at time of first canakinumab treatment.

Important exclusion criteria:

- Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
- History of being immunocompromised, including a positive HIV at screening (enzyme linked immunosorbent assay, ELISA and Western blot) test result.
- Positive QuantiFERON (QFT-TB G In-Tube) test or positive Purified Protein Derivative (PPD) test (≥ 5 mm induration) at screening or within 2 month prior to the screening visit, according to the national guidelines. Patients with a positive PPD test (≥ 5 mm induration) at screening could be enrolled only if they had either a negative chest x-ray or a negative QuantiFERON test.
- History of recurrent and/or evidence of active bacterial, fungal, or viral infection(s).
- Live vaccinations within 3 months prior to the start of the trial, during the trial, and up to 3 months following the last dose.
- History of known hypersensitivity to canakinumab.
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases.

Treatments

Canakinumab was administered subcutaneously (subcutaneous injections) at a dose of 2 mg/kg for patients ≤ 40 kg or 150 mg for patients ≥ 40 kg. One dose escalation at Day 8 was incorporated into the design for patients in whom the 2 mg/kg or 150 mg dose was not sufficient to resolve the qualifying TRAPS flare.

Duration of treatment: 33 months (4 months of treatment period + maximum of 5 months of followup period following study drug withdrawal + maximum of 24 months long-term treatment period). Those patients who were dosed upon relapse in the follow-up period entered a country-specific program prior to the implementation of Protocol Amendment 2 (17 patients).

There was no reference therapy.

Outcomes/endpoints

Efficacy assessment was mainly based on:

- Physician's Global Assessment of TRAPS activity
- Physician's severity assessment of key TRAPS signs and symptoms
- Response to treatment criteria
- Inflammation markers (CRP and SAA)
- Relapse
- Patient's Global Assessment of TRAPS activity
- Corticosteroid and NSAID Use

Response to treatment criteria

Response to treatment was defined as follows:

Complete response

Complete response was defined as follows (all criteria to be fulfilled on the same day):

- Clinical remission: Physician's Global Assessment score ≤ 1

AND

- Serologic remission: CRP < 10 mg/L and /or SAA < 10 mg/L.

Almost complete response

Almost complete response was defined as follows:

- Clinical remission: Physician's Global Assessment score ≤ 1

AND

- Partial serologic remission*: ≥ 70% reduction of baseline CRP and/or ≥ 70% reduction of baseline SAA.

*The aforementioned percent reduction was applicable only if the baseline serologic values were significantly above the normal range.

Non-response

Non-response was defined as follows (all criteria to be fulfilled on the same day):

- No change or worsening from baseline Physician's Global Assessment score

AND/OR

- Increased or < 50% reduction from baseline CRP and/or SAA value(s).

Partial response

Partial response was defined as all other cases not meeting the definition of Complete response, Almost complete response and Non-response.

Relapse

Relapse at a given study visit was defined as follows:

- Clinical relapse: Physician's Global Assessment ≥ 2 AND Physician's Global Assessment score increases by at least 1 point from Day 15.

AND

- Serologic relapse: CRP and/or SAA ≥ 30 mg/L without other explanation for cause AND represent a 30% increase from Day 15, unless according to the Investigator's judgment, serological relapse was a result of other factors (e.g. concurrent infection) and not due to relapse of disease activity.

Safety:

Safety assessments included collecting all AEs, serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They also included the regular monitoring of hematology, blood chemistry and urine and regular assessments of vital signs, physical condition and body weight.

Bioanalytics:

Pharmacokinetic assessments: Canakinumab concentrations were analyzed in serum.
Pharmacodynamic assessments: Total IL-1β (sum of free and bound canakinumab) concentrations were determined in serum by means of a competitive ELISA assay.

Statistical Methods

Categorical variables were summarized by absolute frequencies and percentages. Continuous variables were summarized by mean, standard deviation, median, minimum, maximum, and number of non-missing data points. All tables were presented for the single treatment group and all listings were presented by country, center and patient number.

Analysis sets

- Full Analysis Set (FAS): all patients who received at least one dose of study treatment and had at least one post-baseline assessment for primary efficacy. No data are excluded from the FAS analyses because of protocol deviations.
- Safety Set (SAF): all patients who received at least one application of study treatment and had least one post-baseline safety assessment. The statement that a patient had no AEs also constitutes a safety assessment

Analysis of the primary variable

The primary objective of the study was to provide a first estimate of the ability of canakinumab to induce Complete or Almost complete response in patients with active TRAPS at Day 15. Analysis focused on estimation (point estimate together with 95% confidence interval [CI]).

The proportion of subjects with Complete or Almost complete response at Day 15 was estimated using an exact (Clopper-Pearson) 95% CI. No statistical hypothesis testing was performed. The primary analysis was performed on the FAS.

Analysis of secondary variables

Proportions were analyzed using the same method as for the primary variable. Time to event data were analyzed using Kaplan-Meier estimates. Analysis of all secondary variables was based on the FAS.

Pharmacokinetic/Pharmcodynamic evaluations

Data relating to PK/PD evaluations were summarized by presenting descriptive statistics by visit.

Safety

Treatment-emergent adverse events (the onset date is on or after the date of first study treatment) are summarized. Adverse events which occurred during the country-specific program were collected in the patient's source documents and later transcribed in the clinical database. These events have been pooled and summarized with all treatment-emergent adverse events. Vital signs were analyzed descriptively including defined notable vital signs abnormalities. Laboratory data were analyzed descriptively and information summarized on newly occurring selected notable laboratory abnormalities.

Other

Health-related Quality of Life (patient ≥ 18 years at baseline completed the SF-36 and patients who were 5-17 years old at baseline completed the CHQ-PF50) was analyzed descriptively as exploratory analyses.

Determination of sample size

From prior experience with anakinra it was expected that 80-90% of subjects would respond favorably to canakinumab. In this proof of concept study, for a sample size of 20 completed patients, when the observed proportion of subjects with complete or almost complete response at Day 15 is 80% an exact

(Clopper Pearson) 95% confidence interval (CI) would extend from 56.3% to 94.3%. For an observed response rate of 90%, the 95% CI would extend from 68.3% to 98.8%. Sample size calculations were done using StatXact-8®.

Interim analyses

Although the overall study duration was up to 33 months, the primary efficacy endpoint occurred at 15 days. The main purpose of the study was to establish the efficacy and safety of canakinumab treatment and provide PK/PD data to help determine optimal dosing to support further development in this rare, very symptomatic condition. Therefore the primary analysis at Day 15 was done prior to all patients completing the maximal 33-month study period. This was in order to allow the assessment of initial efficacy of canakinumab in TRAPS patients and to determine if development should move forward to Phase III. The analyses at the end of the active treatment period (4 months) and follow-up period (5 months) were also done prior to patients completing the maximal 33-month study period. In each case, the analyses were carried out when all patients had completed all the appropriate visits (up to Day 15 for the primary efficacy analysis, up to 4 months for the secondary efficacy analysis at the end of the 4-month active treatment period and up to the completion of the 5-month follow-up period to assess PK/PD data). The analyses conducted at these time points were based on data cleaned and locked at the respective time points and focused on the primary efficacy variable and available secondary variables.

As the study is open-label with a single treatment group and the primary and other efficacy variables were examined only when data for all patients were cleaned and locked to the appropriate time point, no statistical adjustments were required.

Results

Recruitment/ Number analysed

In this multicenter open label study, a total of 29 patients were screened, of whom 9 failed screening and 20 were enrolled, exposed to study medication and included in all analyses. The mean age of patients was 34.6 years, with the youngest patient being 7 years old and oldest being 77 years. The majority of patients (65%) were male, Caucasian (95%), and referred through the Investigator's own practice.

Baseline data

The mean duration of TRAPS prior to enrollment was 4.6 years, all patients had a confirmed mutation of the TNFRS1A gene, and 11 patients had chronic TRAPS. The mean number of TRAPS episodes per year for those patients (9) with relapsing TRAPS, was 9.9, with mean duration of 11.9 days.

At baseline, patients had a median body temperature within the normal range, but elevated median CRP and SAA levels. The Physician's Global Assessment of TRAPS Activity was mild to moderate.

Individual components of TRAPS activity showed absent to severe manifestations, predominantly absent to moderate.

Six pediatric patients (<18 years of age) were included in the study. Two children were between 4 and 12 years old (1 boy 7 and 1 boy 13 years old) and 4 children were between 12 and 18 years old (1 boy 13, 1 girl 14, 1 girl16 and 1 boy 17 years old). Two pediatric patients had chronic TRAPS. Of the four patients with identifiable relapses, two patients had seven episodes per year, one patient had 10

episodes per year and one patient had 12 episodes per year. The duration of episodes ranged from 10 to 20 days. The duration of TRAPS diagnosis was 0.0-7.5 years.

Efficacy results

Canakinumab at protocol recommended dose levels demonstrated rapid disease control for both, clinical signs and symptoms, as well as serologic response in patients with active TRAPS:

- The primary objective of the study was to determine whether canakinumab induces complete or almost complete response in patients with active TRAPS at Day 15. A total of 19 patients, 95.0% (95% CI: 75.1, 99.9), achieved a complete or almost complete response at Day 15.
- Sixteen patients (80.0%) had achieved a complete or almost complete response, defined as both clinical and serologic remission at Day 8. The one patient who at Day 15 did not have a complete or almost complete response, was in clinical remission at that time, but lost the serologic remission from Day 8 due to a concomitant infection.
- At Day 8, 18 patients (90.0%) had achieved a complete clinical remission, and at Day 15, all patients had achieved complete clinical remission. The KM estimate of median time to remission (Physician-assessed clinical remission) was 4.0 days.
- By Day 3, no patients had severe disease activity, and by Day 8, all patients had either absent (11 patients, 55.0%), minimal (seven patients, 35.0%) or mild (two patients, 10.0%) disease activity. At Day 15, all patients had absent (16 patients, 80.0%), or minimal (four patients, 20.0%) disease activity.
- Pediatric patients responded the same way than adult patients to 2 mg/kg (150 mg) canakinumab, and all six achieved a complete or almost complete response at Day 15.
- Successful administration of ACZ885 as well as binding of IL-1β to canakinumab was evident from the increase in total IL-1β concentrations following the first dose on Day 1.

Biomarker of inflammation rapidly declined after canakinumab treatment:

- At Day 3, the CRP level had changed from baseline by a median of -36.83% and the SAA by -42.51% (Day 1 median levels were 124.78 mg/L and 198.00 mg/L, respectively). By Day 8 the median CRP and SAA levels were nearly within normal range (11.11 mg/L and 10.30 mg/L respectively). Both CRP and SAA median levels were within normal range at Day 15 and remained there for the duration of the treatment period. At the end of the follow-up period the median CRP and SAA values were 4.80 mg/L and 2.20 mg/L.
- Throughout the long-term treatment period, median values of both CRP and SAA remained within normal range (≤ 10 mg/L). At the end of study visit, median CRP and SAA levels were noted at 4.00 mg/L and 4.85 mg/L.
- At Day 8, seven patients (35%) had both normal CRP and SAA levels, which increased to 12 patients (60%) at Day 15.

Relapse episodes decreased during the follow up period after the canakinumab treatment:

- All the 20 patients relapsed during the follow-up period (upon discontinuing canakinumab). The KM estimated median time to relapse was 91.5 days (95% CI: 65, 117) after the last canakinumab dose. Two weeks after re-treatment following relapse, clinical and serological markers were similar to those seen during remission indicating a rapid response to retreatment with canakinumab.

- Seven patients experienced relapse during the long-term treatment period, out of which four patients had more than one relapse episodes.

Safety results

All patients experienced at least one AE. The most common AEs were nasopharyngitis, headache, abdominal pain, oropharyngeal pain, pyrexia, diarrhea and vomiting. The majority of patients had AEs with 55% of patients having a worst severity of moderate and 30% of patients experiencing severe AEs. Six patients experienced eight severe AEs: abdominal pain (in four patients), foot deformity, dental caries, condition aggravated and intestinal obstruction. Except for one episode of abdominal pain in patient 0001-00001 and the dental caries AE, all the other severe AE cases were reported as SAEs. A total of 60.0% of patients experienced AEs suspected of being study drug related by the investigator.

The most commonly reported AE suspected to be study drug related was nasopharyngitis. No patients died during the study. Seven patients (35.0%) experienced SAEs, none of them were suspected to be related to study drug by the investigator. There were no AEs leading to discontinuation. Two patients experienced an AE (condition aggravated and respiratory tract infection) resulting in dose adjustment or temporary interruption. These 2 events were regarded as being of moderate severity. The event respiratory tract infection was suspected to be related to the study drug, whereas the event condition aggravated was not suspected to be related to the study drug by the Investigator. There were no meaningful changes in hematology, clinical chemistry or vital signs parameters during the course of the study.

Bioanalytical results

Successful administration of ACZ885 as well as binding of IL-1β to canakinumab was evident from the increase in total IL-1β concentrations following the first dose on Day 1.

2.3.3. Discussion on clinical aspects

Canakinumab at protocol recommended dose levels demonstrated rapid disease control for clinical signs and symptoms as well as serologic response in patients with active TRAPS. There was a rapid improvement in the Physician's Global Assessment of TRAPS activity following treatment with canakinumab; by Day 8; 16 patients (80%) had a complete or almost complete response; 18 patients (90.0%) had a clinical remission. At Day 8, the two patients without a clinical remission (2 adults) received an additional dose of canakinumab. At Day 15, 19 of 20 patients (95.0%) had a complete or almost complete response. All patients had clinical remission, with one patient (an adult) (5.0%) not achieving a serological remission. Both patients who were up-titrated achieved a complete or almost complete response at Day 15, as did the two patients (among them 1 child) without a response at Day 8 who were not up-titrated. The Kaplan-Meier (KM) estimate of time to physician assessed clinical remission was 4.0 days, whereas KM estimate of time to patient's assessed clinical remission was 3.0 days.
All patients had absent, minimal or mild symptoms for each disease area, as assessed by the Physician's Global Assessment of TRAPS disease activity from Day 15 until the end of the treatment period. Following retreatment upon relapse, all patients experienced again absence to mild symptoms. The data collected in the long-term treatment period was in line with what was observed in the initial treatment period; i.e., during this period the majority of patients experienced absent, minimal or mild disease activity and none of the patients had severe disease activity. The patient reported assessment of TRAPS disease activity showed similar results.

Serological response to both CRP and SAA was achieved by all but one patient at Day 15. This patient had a serological response at Day 8, but then contracted an infection, and the inflammatory markers increased as well. In spite of the fact that the patient was in clinical remission at Day 15, the patient was classified as a non-responder.
By Day 15, median CRP and SAA levels were within the normal ranges, and remained so throughout the course of the treatment period and long-term treatment period. Following re-treatment after relapse, both inflammatory markers showed a rapid decrease. The persistent decrease in SAA might help to reduce amyloidosis in patients with TRAPS.
Response in pediatric patients was not different from response in adult patients; all pediatric patients had a complete or almost complete response at Day 15.
Canakinumab was well tolerated with no unexpected safety findings. No deaths occurred in the study. There were seven patients with SAEs reported during the study, one of them in a child, and none of them were suspected to be related to the study drug by the Investigator.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

Canakinumab was effective in improving clinical signs and symptoms of TRAPS. After administration of Ilaris, a normalisation of serological inflammatory markers occurred and a prolonged disease control with only few relapses during the conduct of the study could be demonstrated.

The safety profile showed no remarkable changes compared to previous canakinumab studies in other indications.

The report does not provide any evidence that further actions are required.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Ilaris

Active substance: Canakinumab

Not applicable for the TNF-receptor associated periodic syndrome (TRAPS) development program. Ilaris has been registered for more than 5 years in the European Union. It is currently registered for the treatment of patients of 2 years of old and above with Cryopyrin-Associated Periodic Syndromes (CAPS) and Systemic Juvenile Idiopathic Arthritis (SJIA) and in adults for the treatment of gouty arthritis attacks.

Clinical studies

Product Name: Ilaris

Active substance: Canakinumab

Study title	Study number	Date of completion	Date of submission of final study report
An open-label, multicenter, efficacy and safety study of 4-month canakinumab treatment with 5- month follow-up and long-term treatment period in patients with active recurrent or chronic TNFreceptor associated periodic syndrome (TRAPS)	CACZ885D2203	June 2014	December 2014
A randomized, double-blind, placebo controlled study of canakinumab in patients with Hereditary Periodic Fevers (TRAPS, HIDS, or crFMF), with subsequent randomized withdrawal/ dosing frequency reduction and open-label long term treatment epochs	CACZ885N2301	May 2017	November 2017