26 March 2015
EMA/334374/2015
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 041

Note

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

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1. Introduction

On 14 January 2015, 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 pilot study of 6-month canakinumab treatment with up to 6-month follow-up in patients with active Hyper-Igd Syndrome (HIDS) - CACZ885D2402

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 powder and solvent for solution for injection were supplied to the investigators at a dose strength of 150 mg. The powder is white and the solvent should be clear and colourless. Both were provided in 6 mL glass vials. Neither active comparator nor placebo was used. All test materials were supplied by Novartis Drug Supply Management (DSM). The batch and formulation numbers of the test drug are presented in Table 9-1.

Table 9-1 Study medication formulation and batch numbers

Study drug and strength	Formulation control number	Batch number
Canakinumab 150 mg	Powder and solvent for solution for injection	S0010[a] S0011[b, c] S0011D[d] S0013[e] S0035[f]

a Seven patients (0102, 0103, 0301-0305) received batch S0010 at all visits during the 6-month treatment and the follow-up periods.

b Patient 0401 received batch S0010 at baseline (flare) and at visits 2, 5 and 6. Then received batch S0011 at visit 7.

c Patient 0402 received batch S0010 at baseline (flare) and at visits 2 and 5. Then received both batch S0010 and batch S0011 (one vial each) at visit 7.

d Batch number S0011D was received for patient 0102 from visit 19 to 25, patient 0103 from visit 21 to 28, patient 0301 from visit 18 to 26, patient 0302 from visit 17 to 25 (except visit 22 which received S0011 / S0011D), patient 0303 from visit 19 to 26, patient 0304 at visit 17, patient 0305 from visit 17 to 23, patient 0401 from visit 20 to 24 and patient 0402 from visit 16 to 22.

e Batch number S0013 was received for patient 0102 from visit 26 to 30, patient 0103 from visit 29 to 30, patient 0301 from visit 27 to 30 the batch, patient 0302 from visit 26 to 30, patient 0303 from visit 27 to 30, patient 0305 from visit 24 to 30, patient 0401 from visit 25 to 30 and patient 0402 from visit 23 to 26.

f Patient 0402 received the batch S0035 from visit 27 to visit 30.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **Study number**: CACZ885D2402

An open-label, multicenter, efficacy and safety pilot study of 6-month canakinumab treatment with up to 6 months follow-up and a 24-month long-term treatment in patients with active Hyper-IgD Syndrome (HIDS)

2.3.2. Clinical study

CACZ885D2402: An open-label, multicenter, efficacy and safety pilot study of 6-month canakinumab treatment with up to 6 months follow-up and a 24-month long-term treatment in patients with active Hyper-IgD Syndrome (HIDS)

Methods

Objective(s)

Primary objectives: To assess if canakinumab reduces the flare frequency in patients with active HIDS during the 6-month treatment period compared to a historical period (defined as the most recent 6 months in which the patient did not receive drugs other than symptomatic treatment with NSAIDs and/or steroids).

Secondary objectives:

- To assess occurrence of flares during the 6-month treatment period and the 24- month long-term treatment period.
- To assess the change in flare severity over time as assessed by the physician's global assessment of HIDS flare severity score.
- To assess the change in flare severity over time as assessed by patient's global assessment of HIDS flare severity score.
- To assess the change in HIDS signs and symptoms over time as assessed by physician assessment of 4 key signs and symptoms severity score.
- To assess the change in HIDS signs and symptoms over time as assessed by the patient assessment of 4 key signs and symptoms severity score.
- To assess the time to resolution of initial flare after first canakinumab treatment.
- To assess the profile over time in CRP and/or SAA from baseline to EOS.
- To assess the number/percentage of patients who received dose up-titration during the 6-month treatment period.
- To assess HIDS control by physician.
- To assess HIDS control by patient.
- To assess the change from baseline in the Childhood Health Assessment Questionnaire (CHAQ) in children and in the Health Assessment Questionnaire (HAQ) in adults.
- To assess changes in the flare duration (mean/median days) during the trial as compared to the historical period.
- To assess the adverse events (AE) reported during the trial.
- To assess percentage of patients who experience a flare requiring rescue treatment.
- To assess/describe flare rescue treatments.
- To assess the time to flare after the last dose of canakinumab during the followup period.
- To assess the pharmacokinetics/pharmacodynamics of canakinumab in patients with HIDS during the trial.
- To assess the immunogenicity of canakinumab in patients with HIDS during the trial.
- To analyze the genetic expression (EG).

Study design

This was an open-label, single treatment arm, efficacy and safety pilot study of canakinumab 300 mg (4 mg/kg for patient ≤ 40 kg) subcutaneous injections every 6 weeks for 6 months in patients with active HIDS. Patients who experienced a new HIDS flare between baseline and Week 4 should receive an additional 150 mg (2mg/kg for patients ≤40 kg) dose at the moment of flare, and they would receive 450 mg (6 mg/kg for patients ≤40 kg) every 6 weeks thereafter starting at Week 6. However, if the flare occurred between Weeks 5-6, the patient should receive rescue medication with NSAIDs or corticosteroids and wait until Week 6 to receive a total of 450 mg every 6 weeks thereafter.

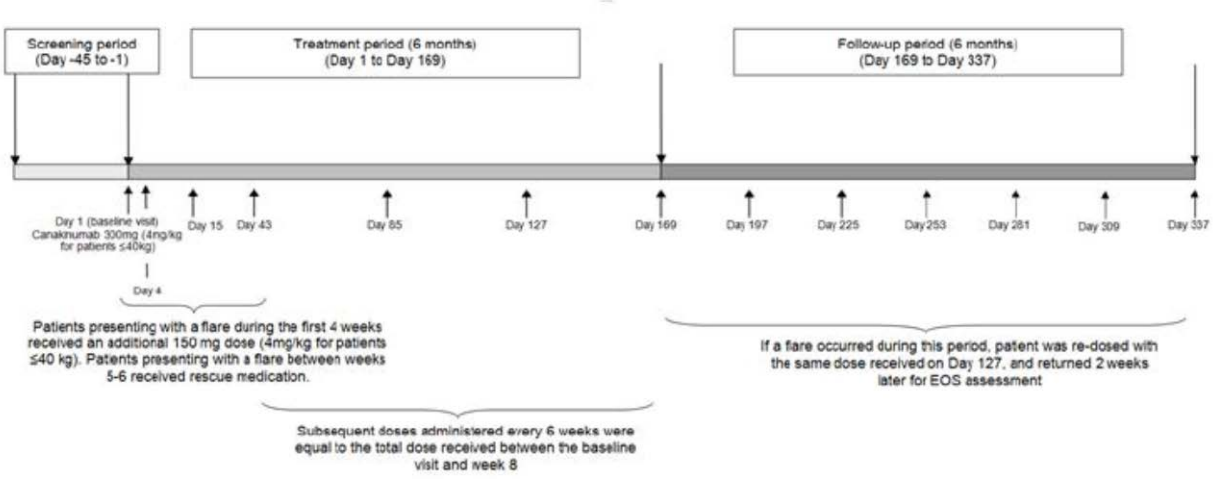
All patients who completed the 6-month treatment period entered into a follow-up period of 6 months maximum duration. Patients remained in the follow-up period until either they completed the full 6-month period or they experienced a HIDS flare. If a flare occurred at the end or prior to completion of the 6-month follow-up period, then the patient was re-dosed with the same dose administered at Day 127. After the 6-month follow-up period all patients entered into a long-term period treatment of 24 months.

While in the long-term treatment period, patients received the same dose administered at Day 127, every 6 weeks. Serum concentrations of canakinumab to evaluate PK, and of total IL-1β (sum of free and bind canakinumab) to evaluate PD, were determined at Baseline (before administration of the first dose of canakinumab), on Days 4, 15, 43, 85, 127, and 169, and on follow-up visits until a flare

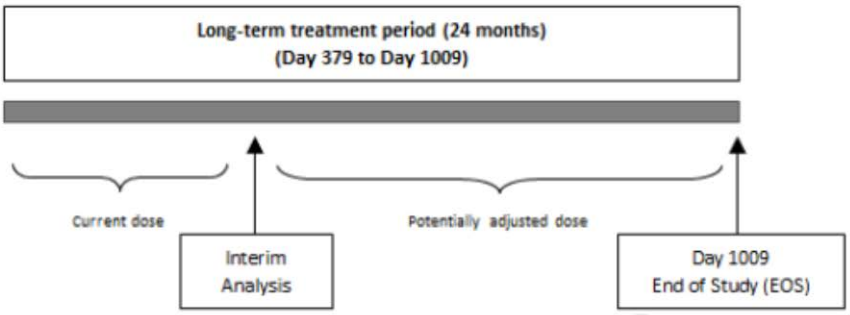
occurred. Serum concentrations were also determined annually during the 24-month long-term treatment period, at the end of study visit, and in all scheduled visits where a flare was confirmed.

Figure 9-1 Overall Study Design

A. Selection, treatment and follow-up periods



B. Long-term treatment period



Study population /Sample size

The study population consisted of patients who were either male or female, aged 2 years or more, with a previous diagnosis of HIDS proven by DNA or enzymatic tests, and active HIDS, were included in the study.

A total of 10 patients were screened for the study, of which 9 were treated and analysed.

Inclusion criteria:

- Male and female patients at least 24 months of age at the time of the screening visit.
- Patients with a diagnosis of HIDS proven by DNA analysis and/or enzymatic studies.
- At time of start of drug treatment: active HIDS as evidenced by a physician global assessment of HIDS flare severity ≥2 and CRP values >10 mg/L (normal CRP ≤10 mg/L).
- Patients who have a history of ≥3 febrile acute HIDS flares in a 6-month period when not receiving prophylaxis treatment (e.g., anakinra daily treatment) with a duration of each flare lasting ≥4 days and limiting the normal daily activities.

- Patients eligible for the 24-month long-term treatment period are those who completed the follow-up period after the implementation of Amendment 5 or completed the follow-up period prior to the implementation of Amendment 5 and continued to receive uninterrupted canakinumab.
- Parent's or legal guardian's written informed consent and child assent, if appropriate or patient's informed consent for patients ≥18 years of age before any assessment is performed.
- Able to communicate with the investigator and comply with the requirements of the study (for children the parent can assist when necessary).

Exclusion criteria:

- Pregnant or nursing (lactating) women.
- History of being immunocompromised, including a positive HIV at screening (ELISA and Western blot) test result.
- Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody positive.
- Live vaccinations within 3 months prior to the start of the trial, during the trial, and up to 3 months following the last study dose.
- History of significant medical conditions, which in the Investigator's opinion would exclude the patient from participating in this trial.
- History of recurrent and/or evidence of active bacterial, fungal, or viral infections.
- 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 may have been enrolled only if they had either a negative chest x-ray or a negative QuantiFERON test. Patients with indeterminate QuantiFERON test result could be considered eligible for the Investigator's opinion.
- Use of the following therapies:
    - NSAIDs for HIDS symptom control/treatment within 2 days prior to baseline visit.
    - Corticosteriods [oral prednisone (or equivalent)] used to treat HIDS within 1 week prior to baseline visit.
    - Anakinra within 24 hours prior to Baseline visit.
    - Rilonacept within 1 week prior to Baseline visit.
    - Etanercept within 2 weeks prior to Baseline visit.
    - Infliximab within 12 weeks prior to the Baseline visit.
    - Adalimumab within 8 weeks prior to the Baseline visit.
    - Any other investigational biologic agent within 8 weeks or 5 half-lives prior to the Baseline visit, whichever is longer.

Patients included in the screening should have stopped previous biologic treatment and other drugs (NSAID, corticosteroids). No patients should have received first dose of canakinumab medication without complying with the described timelines.

- History of malignancy of any organ system (other than treated localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Patients who receive or have received any investigational drug during the 30 days before the enrolment into the study.

Treatments

Dosage form: Canakinumab powder for solution for injection (strength: 150 mg per vial).

Mode of administration: Subcutaneous injection after reconstitution of each vial.

Dosage: All patients received dosing every 6 weeks for 6 months, starting at Day 1 with 300 mg (4mg/kg for patient ≤ 40 kg). In addition, patients who experience a new HIDS flare between Baseline and Week 4 received an additional 150 mg (2mg/kg for patient ≤ 40 kg) at that episode and 450 mg every 6 weeks thereafter starting at Week 6. But if it occurs during weeks 5 and 6, the patient received rescue medication with NSAIDS or corticosteroids and waited until Week 6 to receive a total of 450mg. Subsequent doses (on Weeks 12, and 18) were equal to the total dose received at Week 6. Patients who relapsed during the follow-up period were re-dosed with the same dose administered at Day 127.

Duration of treatment: All patients completed the 6-month treatment period. After the 6-month follow-up period, patients entered in a long-term period treatment of 24 months.

There was no reference therapy.

Outcomes/endpoints

Efficacy:
Assessments for the primary endpoint:

- Occurrence of flare during the 6-month treatment period: a flare was defined as a Physician Global Assessment of HIDS flare severity score of ≥2 and a CRP value >10mg/L.
- Occurrence of flare during a historical period (most recent 6 months in which the patient did not receive treatment for HIDS other than symptomatic treatment with NSAIDs and/or corticosteroids).
- A comparison was made between assessments of these 2 periods in order to achieve the primary objective (assess if canakinumab reduces the flare frequency in patients with active HIDS during the 6-month treatment period compared to a historical period).

Other assessments:

- Physician (as well as patient) global assessment of HIDS flare severity: collected after each flare and based on a 5-point scale: 0 = *Absent signs/symptoms*; 1 = *Minimal signs/symptoms*; 2 = *Mild*; 3= *Moderate*; 4 = *Severe*.
- Physician's (as well as patient's) severity assessment of key HIDS symptoms: the severity of each of 4 key signs and symptoms of HIDS (fever, lymphadenopathy, aphtous ulcers, abdominal pain) was assessed after each flare by the investigator using the following 5- point scale: 0 = *Absent signs/symptoms*; 1 = *Minimal signs/symptoms*; 2 = *Mild*; 3 = *Moderate*; 4 = *Severe*.
- Physician (as well as patient) global assessment of HIDS control based on a 5-point scale: 0 = No control; 1 = Poor control of HIDS associated signs and symptoms since the last visit; 2 = Somewhat control of HIDS associated signs and symptoms since the last visit; 3 = Good control of HIDS associated signs and symptoms since the last visit; 4= Excellent control of HIDS associated clinical signs and symptoms since the last visit.
- Inflammation markers CRP and/or SAA.

Patient reported outcomes about flares were collected through the patient's diary.

Safety:

Safety assessments consisted on the control and collection of all adverse events (AEs) and serious adverse events (SAEs); the regular monitoring of hematology, blood chemistry and urine; regular assessments of vital signs; and physical examinations.

Statistical Methods

In general, categorical data were summarized using counts and percentages, while continuous data were reported using number of subjects, median, minimum and maximum.

The primary efficacy variable (number of flares per patient observed during the 6-month treatment period) was analyzed descriptively for the FAS population.

Time to flare after the last dose of canakinumab during the follow-period was summarized descriptively and analyzed with Kaplan-Meier curves.

Results

Recruitment / Number analysed

A total of 10 subjects with HIDS, from three medical centers, were eligible and entered the screening period, 9 of which were entered in the treatment period of the study. One patient did not have a qualifying flare during the screening period and was therefore discontinued early from the study. Among the 9 patients included in the study, all completed the 6-month treatment period, and the 6-month follow-up period. During the 24-month long-treatment period, 1 patient discontinued the study due to lack of protocol compliance.

Baseline data

Four patients were below 16 years of age, 6 were below 18 years of age, 3 were 18 years or older. The majority were female (66,66%). Median time since HIDS diagnosis was 4.1 years. All patients were Caucasian.

Efficacy results

The median number of flares per patient decreased from 5 (3-12) during the 6-month historical period to 0 (0-2) flares during the 6-month treatment period (Table 4-1).

Table 4-1 Flare rate for historical and canakinumab 6-month treatment period (Safety population)

		Canakinumab N=9
Historical period	Range	3, 12
	Median	5.0
Six-month treatment period	Range	0, 2
	Median	0.0

In the historical period a total of 59 flares (range 3 to 12 flares per patient) were reported. During the 6-month treatment period, only 2 patients had flares (1 patient had one flare; the other patient had two flares). One of the 2 patients received rescue medication because the flare occurred between week

5 and 6, and then received an escalated dose of canakinumab (450 mg) at week 6. In the patient with 2 flares, one flare occurred at week 6 and the patient received an escalated dose of canakinumab (450 mg). The second flare occurred 39 days later for which he did not receive rescue medication.

HIDS flare severity over time

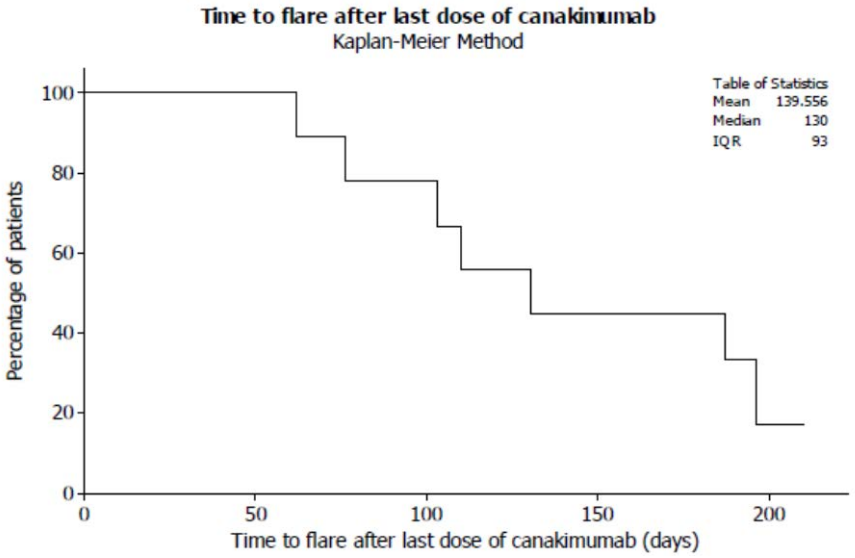
During the treatment withdrawal period, 7 out of 9 patients had a flare. During the first 12-month of the long-term treatment period, 4 patients had 6 flares and during the second year of the long-term follow-up treatment period, 2 patients presented 2 flares.

The severity of the flares decreased under treatment with canakinumab. At baseline, 4 patients had had a PGA of HIDS flare severity score of *moderate* and 5, of *mild signs/symptoms.* In the treatment withdrawal period, 7 out of 9 patients had a flare of which 3 were rated *moderate and 4 mild.* Six flares occurred during the first 12-month follow-up in 4 patients, 4 of which were *mild* and 2 of *minimal* signs/symptoms. In the 2nd year of the long-term follow-up, two flares occurred, one *mild* and one *without signs/symptoms*.

The median time to resolution of the initial flare from the time of the first canakinumab treatment was 3 days (1 to 5 days), which meant that the total duration of the initial flare had a median of 5.0 (3-9) days duration. The median flare duration during the first 6-month treatment period was 3.0 (2-4) days, during the withdrawal period 4.0 days (2-10 days), during the first 12-month long-term treatment period 3.5 (2-8) days and during the second year of the long-term treatment period 8.5 (6-11) days.

For the 7 patients who experienced a flare during the 6-month treatment withdrawal follow-up period, the median time to flare after the last canakinumab dose was 110 (62-196) days (Figure 4-1). Two patients did not flare during the withdrawal period.

Figure 4-1 Time to flare after last dose of canakinumab (KM method)



At baseline, the physician's assessment of HIDS disease control is rated as *no* disease control or *poor* disease control in 6 and 3 patients, respectively. At Day 4, all patients had a score of *good* or *excellent* disease control, and these scores remained such until the end of the study. The patients' assessments of disease control provided similar results.

The inflammation biomarkers were elevated at baseline with median levels of CRP and SAA of 117.7 mg/L and 688.5 mg/L, respectively. Median levels for both had normalized by Day 15 and remained normal for the remainder of the trial. Transient elevations were only observed during acute flares.

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. Pharmacokinetic parameters such as CL/F, Ka and V/F and their associated variability were estimated, as well as parameters describing the kinetics of IL-1β, such as rate of production, clearance, and its binding affinity to canakinumab. The data from this study will be pooled with data from recently completed phase 2 studies in related disease conditions (crFMF, TRAPS, and HIDS).

No blood sample showed positive immunogenicity.

Safety results

All nine patients had at least one AE. The most commonly affected primary SOC were infections-infestations, followed by gastrointestinal disorders and general disorders and administration site conditions. Pyrexia and pharyngo-tonsillitis were the most common AEs in patients who received active treatment and occurred in 44% and 33% of patients, respectively.

Almost all the AEs described were of mild severity, three AEs were reported as severe: anemia, gastrointestinal hemorrhage and cellulitis. According to the causality assessed by the investigator only one of the AEs (vulvovaginal mycotic infection) was considered related to the study drug medication.

No deaths occurred in this study and no patient experienced an adverse event leading to study discontinuation.

Two patients received 450 mg doses of canakinumab every 6 weeks. No differences in terms of AEs and SAEs were observed in those 2 patients as compared with those treated with lower doses of canakinumab.

A total of 14 SAEs were reported in four patients. These 4 patients were between 16 and 20 years old. The youngest patient reported three SAEs. One SAE was due to a temporomandibular dysfunction and required concomitant medication, the second one was a HIDS flare and the last one was chronic headache. All three SAEs required hospitalization. A second patient had one SAE, a hidradenitis suppurativa, which required hospitalization and concomitant medication. Another patient had arm cellulitis which required concomitant medication. Finally, there was a patient who reported 8 SAEs. This patient had a medical history of systemic AA amyloidosis, kidney transplantation, chronic anemia, digestive hemorrhage and hypertension, which appear to be responsible of the SAEs reported by this patient (acute peritonitis, anemia, bacteremia, gastrointestinal bleeding, pneumonia, hypertensive crisis and volume overload). None of these SAEs was considered to be related to study treatment by the investigator.

No clinically significant abnormalities in hematology, clinical chemistry, vital signs, physical findings and/or other observations related to safety were reported. Overall the safety profile of canakinumab did not differ in the pediatric population with HIDS as compared to the adults with HIDS in this study.

2.3.3. Discussion on clinical aspects

The median number of flares was reduced from 5 during the 6-month historical period to 0 during the 6-month canakinumab treatment period.
Two of 9 patients experienced a flare in the treatment period. One patient had a flare between week 5-6 and received rescue medication according to the protocol and waited until week 6 to receive

escalated dose (450 mg). The other patient had two flares, one occurred at week 6 and the patient received escalated dose (6 mg/kg) and the second flare occurred 39 days later, but according to the medical criteria no recue medication was taken.
Seven of the 9 patients had a flare during the 6-month treatment withdrawal follow up period.
Three of the 9 patients had one flare and 1 patient had 3 flares during the first 12- month long-term treatment period, and 2 of the 8 patients had a flare during the second year of the long-term treatment period.
One patient discontinued the study in the first 12-month long-term treatment period due to lack of protocol commitment. The median time to flare after the last dose of canakinumab during the follow-up period was 110 days (62-196 days). Flare severity was of mild to moderate severity at baseline and remained thus during the 6-month treatment withdrawal follow-up period, then changed to mild or minimal signs/symptoms during the 12-month long-term treatment period and to mild or without signs/symptoms during the second year of the long-term treatment period.
Each of the 4 key signs and symptoms of HIDS (fever, lymphadenopathy, aphtous ulcers, abdominal pain) was of mild to moderate severity at baseline in most of the cases, and remained absent from Day 4 until the end of the study in most of the cases.
HIDS control assessment by patient and physician improved from no control disease or poor control at baseline, to good or excellent control from Day 4 until the end of the study. Elevated baseline median CRP and SAA levels normalized from Day 15 until the end of the study. 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.
There were no patient discontinuations due to safety reasons during the study and no deaths were observed. No clinically significant abnormalities in haematology, clinical chemistry, vital signs, physical findings and/or other observations related to safety were reported. The most frequent AEs were infections-infestations, followed by gastrointestinal disorders and general disorders and administration site conditions. During the study, four patients had SAEs, none was considered related to canakinumab. There was only one AE (non SAE) related to canakinumab, a vulvovaginal mycotic infection.

3. Rapporteur’s overall conclusion and recommendation

Overall conclusion

Canakinumab treatment was able to reduce the HIDS flare rate as well as to reduce flare severity. Results of secondary objectives showed that the disease was well control during treatment. There were no patient discontinuations due to safety reasons during the study and no deaths were observed.

Canakinumab was effective in improving signs and symptoms of HIDS, whilst normalizing serological inflammatory markers and providing maintained disease control with only few relapses during the conduct of the study.

The safety profile was consistent with 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 Hyper-Immunoglobuline-D Syndrome (HIDS) 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 pilot study of 6-month canakinumab treatment with up to 6-month follow-up in patients with active Hyper-IgD Syndrome (HIDS)	CACZ885D2402	July 2014	January 2015
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