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Human Medicines Division

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

Ilaris

Canakinumab

Procedure no: EMA/PAM/0000280285

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	25 August 2025	25 August 2025
☐	CHMP comments	8 September 2025	N/A
☐	Updated CHMP Rapporteur AR	11 September 2025	N/A
☒	CHMP outcome	18 September 2025	18 September 2025

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1. Introduction

On 16 June 2025, the MAH submitted a completed paediatric study for Ilaris, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures in Japan.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study Special drug use investigation of Ilaris 150 mg for Subcutaneous Injection, Ilaris 150 mg Solution for Subcutaneous Injection (SJIA, CACZ885G1401) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Ilaris 150 mg for Subcutaneous Injection, Ilaris 150 mg Solution for Subcutaneous Injection/Canakinumab (genetical recombinant)

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

• CACZ885G1401- Special drug use investigation of Ilaris 150 mg for Subcutaneous Injection, Ilaris 150 mg Solution for Subcutaneous Injection (SJIA, CACZ885G1401)

2.3.2. Clinical study

Special drug use investigation of Ilaris 150 mg for Subcutaneous Injection, Ilaris 150 mg Solution for Subcutaneous Injection (SJIA, CACZ885G1401)

Description

This study was a post-marketing surveillance conducted in accordance with a direction by the regulatory authorities at approval to collect the clinical safety and effectiveness data of Ilaris 150 mg for subcutaneous injection and Ilaris 150 mg solution for subcutaneous injection (hereafter called Ilaris) in clinical use in systemic juvenile idiopathic arthritis (hereafter called SJIA) patients for the purpose of submitting at the re-examination application after the approval of the additional indication of SJIA.

Methods

Study participants

Patients diagnosed with SJIA previously treated with canakinumab (investigational drug) in the G1301 study and new patients who have not been treated with canakinumab for SJIA before.

Treatments

The commercial canakinumab medicine was administered to patients diagnosed with SJIA at 4 mg/kg (up to a maximum of 300 mg) every four weeks via subcutaneous injection in accordance with the Japan canakinumab label and in compliance with the Japanese Good Post-Marketing Study Practice ordinance. The maximum observation period was 104 weeks starting from the first dose of commercial canakinumab.

Table 1 - Objective(s)/Outcomes/Endpoints

Primary objective	**Objective(s)** To collect and evaluate the safety of canakinumab single injection for up to 104 weeks	**Endpoint(s)** • Proportion of patients with AEs from the first dose up to 30 days from the last injection • Proportion of suspected related AEs from the first dose up to 30 days from the last injection • Proportion of patients with SAEs from the first dose up to 30 days from the last injection • Proportion of suspected related SAEs from the first dose up to 30 days from last injection • Proportion of patients with AEs of special interest from the first dose up to 30 days from the last injection
Secondary objectives	• **Objective(s)** • To collect and evaluate the efficacy of canakinumab single injection for up to 104 weeks	**Endpoint(s)** • Proportion of patients achieving a corticosteroid dose reduction at Week 28, Week 48 and Week 104 from the start of canakinumab • Corticosteroid dose at Week 28, Week 48 and Week 104 from the start of canakinumab • Proportion of patients achieving SJIA symptoms remission at Week 48 and Week 104 from the start of canakinumab • Proportion of patients diagnosed with SJIA relapse occurring after SJIA symptoms remission at Week 48 and Week 104 from the start of canakinumab • Proportion of patients with no common SJIA disease signs and symptoms at Week 28, Week 48 and Week 104 from the start of canakinumab • Proportion of patients with no disease activity measured by Physician's global assessment (PGA) at Week 28, Week 48 and Week 104 from the start of canakinumab • Proportion of patients with CRP normalization at Week 28, Week 48 and Week 104 from the start of canakinumab

Sample size

A total of 128 patients were enrolled and received at least one dose of canakinumab of which 104 pediatric patients were aged < 18 years old and 24 were aged ≥ 18-year-old at the time of enrollment. Three patients were not diagnosed with SJIA (2 patients < 18 y old and 1 patient > 18 y old) and ten patients transitioned from the CACZ885G1301 trial.

Randomisation and blinding (masking)

This was an open-label non interventional study.

Statistical Methods

There was no formal hypothesis testing. The results of primary and secondary endpoints were presented descriptively. The AEs were collected from the date of the first study drug dose until 30 days post the last dose. The incidence was calculated and presented by System Organ Class (SOC) and Preferred Terms (PTs). The proportion of patients with a successful corticosteroid dose reduction response rate was calculated with 95% confidence intervals.

Results

Participant flow

In this study, CRF data were locked for 128 of 129 patients in the registration-confirmed population (excluding the registration-only patients), excluding 1 patient whose CRF could not be collected, resulting in 125 patients being included in the safety analysis set and 114 patients being included in the effectiveness analysis set.

Demographics

The demographic analysis was presented in the total SJIA population (125 patients). The proportion of men and women was similar (43.20 % and 56.80 %). Most of the patients were aged less than 20 years old with 26 patients aged < 6 years, 47 patients aged ≥ 6 to < 12 years old, and 41 patients aged ≥ 12 to < 20 years old. The proportion of patients less than 18 years old accounted for 81.60% (102 patients).

Baseline data

In the total SJIA population (125 patients), the median disease duration was 48.03 months (range: 0.4 to 410.2 months). Almost all the patients (94.40%) had received prior medications for their condition. The level of SJIA disease activity at the start of the study was measured by the PGA scale. 55 patients reported no signs or minor signs and symptoms (PGA score 0-1), 49 patients mild and moderate signs and symptoms (PGA score 2 and 3) and 6 patients severe signs and symptoms (PGA score 4) [Study G1401 CSR - Table 10-2].

A total of 34 patients (27.20%) reported a concomitant medical history. History of MAS within 6 months before the start of canakinumab treatment was reported for 9 patients (7.20%) of which 6 were pediatric patients. In addition, hepatic impairment was reported for 6 pediatric patients, and renal impairment for 2 pediatric patients. One patient aged ≥12 years old entered the study with malignancy and hepatic impairment medical condition. No patient reported a history of active or recurrent infections [Study G1401 CSR - Table 10-2], [G1401 Supplement CSR - Listing DM]. Almost all the patients (94.40%) had

received prior treatment for the SJIA disease and 88.80 % were receiving concomitant drugs at the start of the study including oral steroids (71.20%), other DMARDs (56.00%) and Methotrexate (29.60%) [Study G1401 CSR - Table 10-2].

Number analysed

A total of 128 patients were enrolled and received at least one dose of canakinumab of which 104 pediatric patients were aged < 18 years old and 24 were aged ≥ 18-year-old at the time of enrollment. Three patients were not diagnosed with SJIA (2 patients < 18 y old and 1 patient > 18 y old) and ten patients transitioned from the CACZ885G1301 trial.

Efficacy results

The efficacy analysis set included 114 pediatric and adult patients diagnosed with SJIA. From the total treated population (128 patients), 14 patients were excluded, of which 10 patients transitioning from the study CACZ885G1301, 1 patient was previously treated with canakinumab for a different indication and 3 patients not diagnosed with SJIA [Study G1401 CSR - Table 10-1].

- The proportion of patients with a successful corticosteroid dose reduction (response rate) increased over time, being 55.00% (44/80 patients) at 28 weeks, 63.51% (47/74 patients) at 48 weeks, and 67.19% (43/64 patients) at 104 weeks. The mean (standard deviation) daily corticosteroid dose (oral prednisolone equivalent) also decreased over time after the start of Ilaris.

- The proportion of patients without common signs/symptoms characteristic to SJIA was 75.96% (79/104 patients) at the start of Ilaris and remained at 90% or higher after 28 weeks throughout the observation period.

- The proportion of patients with SJIA symptom remission increased over time, being 38.60% (44/114 patients) at 48 weeks and 50.88% (58/114 patients) at 104 weeks. The proportion of patients with relapse after SJIA symptom remission was 3.51% (4/114 patients) at 48 weeks and 7.02% (8/114 patients) at 104 weeks, being less than 10% throughout the observation period.

- The proportion of patients with PGA of “0 or 1 (no disease activity)” increased from 46.53% (47/101 patients) at the start of Ilaris to 80.22% (73/91 patients) at 28 weeks and then remained at approximately 90% until 104 weeks. Correspondingly, the proportion of patients rated as “2 (mild signs and symptoms)” or “3 (moderate signs and symptoms)” decreased throughout the observation period after the start of Ilaris. The percentage of patients rated as “4 (severe signs and symptoms)” remained at close to 0% throughout the observation period after the start of Ilaris.

- The proportion of patients with CRP levels within the normal range (≤ 1 mg/dL) was 83.49% (91/109 patients) at the start of Ilaris. It then remained at 90% or more at each evaluation time point, and CRP levels were within the normal range in all patients at 104 weeks. While the median CRP level remained unchanged throughout the observation period, suggesting a possible effect of data variation at each evaluation time point, the mean (standard deviation) CRP level decreased over time.

- In the effectiveness analysis by patient characteristics, the response rate in patients with PGA of “Moderate signs and symptoms or severe signs and symptoms” was 42.86% (6/14 patients) and

tended to be lower than that in patients with PGA of "No signs and symptoms" [92.31% (12/13 patients)] (odds ratio: 0.063; 95% confidence interval: 0.006, 0.622). Although the small sample size requires caution in interpretation, it was suggested that the response rate might be lower in SJIA patients with "Moderate signs and symptoms or severe signs and symptoms."

- Among patients with special characteristics, the response rate at 104 weeks tended to be lower in pediatric patients aged < 15 years [64.15% (34/53 patients)], pediatric patients aged < 18 years [65.45% (36/55 patients)], and patients with hepatic impairment [57.14% (4/7 patients)] than in the corresponding subgroups [patients aged ≥ 15 years: 81.82% (9/11 patients), patients aged ≥ 18 years: 77.78% (7/9 patients), and patients without hepatic impairment: 68.42% (39/57 patients)]. However, Ilaris was also effective in a certain proportion of patients in these subgroups.

Safety results

In the safety analysis set, the median (range) age at the start of Ilaris was 10.0 (1 to 51) years, and patients aged ≥ 6 to < 12 years (37.60%) and ≥ 12 to < 20 years (32.80%) accounted for approximately 70%. The proportion of male patients was 43.20% (54/125 patients), and the proportion of female patients was 56.80% (71/125 patients). The proportion of patients by PGA was 4.80% for severe, 13.60% for moderate, 25.60% for mild, and 20.00% for slight. The median (range) duration of treatment with Ilaris (including interruption) was 710.0 (1 to 729) days, and the median (range) total number of doses of Ilaris was 25.0 (1 to 29).

- The incidence of related adverse events was 28.00% (35/125 patients). The most common related adverse event by PT was haemophagocytic lymphohistiocytosis (4.00%), followed by upper respiratory tract inflammation (3.20%) and Still's disease (2.40%).

- An analysis of the occurrence of related adverse events by time to first occurrence in patients with prior use of canakinumab (patients treated with canakinumab continuously from a previous clinical trial or patients previously treated with canakinumab for non-SJIA indications) showed no particular trend in related adverse events by time to first occurrence or by the type of PT. Among newly treated patients, related adverse events most frequently occurred at an early time after the start of Ilaris. By PT, related adverse events that occurred in 2 or more patients were white blood cell count decreased (2/114 patients) at < 4 weeks and tonsillitis and upper respiratory tract inflammation (2/111 patients each) at ≥ 24 to < 36 weeks.

- The incidence of serious related adverse events was 17.60% (22/125 patients). The most common serious related adverse event by PT was haemophagocytic lymphohistiocytosis (4.00%), followed by bacteraemia, infectious mononucleosis, Crohn's disease, and Still's disease (1.60% each). The outcome of serious related adverse events was mostly reported as resolved or resolving, and the events were manageable.

- The incidence of related adverse events leading to discontinuation of Ilaris was 7.20% (9/125 patients). By PT, Crohn's disease was reported in 1.60% (2 patients), and all other events were reported only in 1 patient each.

- One death considered related to Ilaris was reported. This was a < 6 years old patient who developed Epstein-Barr virus infection on the day of the sixth dose of Ilaris (139 days after the first dose) and died 176 days after the first dose [38 days after the last (sixth) dose].

- The incidence of related adverse events by safety consideration was 11.20% for “Infections (including opportunistic infections),” 4.00% for “MAS” (all events were haemophagocytic lymphohistiocytosis), 2.40% for “Hepatic impairment,” and 1.60% for “Neutropenia.” No events of “Shock, anaphylaxis” or “Malignancies” were reported. The outcome of all events of haemophagocytic lymphohistiocytosis was reported as resolved or resolving.

- The safety analysis by patient demographics identified no factors that might possibly affect the safety.

- Among patients with special characteristics, the incidence of related adverse events in patients with hepatic impairment and patients with prior use of canakinumab was 44.44% (4/9 patients) and 36.36% (4/11 patients), respectively, and this was higher than that in the corresponding subgroups [patients without hepatic impairment (26.72%, 31/116 patients) and newly treated patients (27.19%, 31/114 patients), respectively]. The outcome of related adverse events observed in these subgroups was all reported as resolved or resolving, and there was no particular trend in the type of related adverse events by PT compared with the corresponding subgroups.

- As an exploratory safety assessment, the effect of Ilaris administration on body height and weight was examined. No abnormal changes were observed in either of the variables throughout the observation period, suggesting no concerns associated with Ilaris.

- As an exploratory safety assessment, the hospitalization status and the outpatient visit status were examined, and this assessment did not suggest any effects of concern of Ilaris on hospitalization and outpatient visit.

2.3.3. Discussion on clinical aspects

The finalized non-interventional open label study enrolled 128 patients of which 104 were aged <18 years. 97.66% of patients treated in compliance with the canakinumab approved drug label. The study population was balanced and homogeneous in terms of gender, age group, and disease activity.

Half of the patients achieved successful corticosteroid dose reduction and disease remission at week 104. The proportion of patients achieving these goals increased steadily over time. The study results were consistent with the known efficacy profile of canakinumab, confirming its effectiveness. The efficacy profile of the pediatric population is highly equivalent to the total treated population.

The median treatment duration was 710 days, with a high compliance rate (9.60% interruption rate). The overall incidence of adverse events (73.53%) was lower than in a comparable Japanese study (CACZ885G1301). The most common AEs (≥ 10%,) by preferred terms were Upper respiratory tract inflammation and Still's disease representing Still's disease exacerbation, worsening or relapse of the underlying disease.

SAEs were reported in 41 pediatric patients (40.20%). The overall incidence of SAEs that were suspected to be study drug related was 17.65% (18/102 patients) amongst them 6.86% under the Infections and infestations SOC and 4.90% under Immune system disorders SOC (all PTs HLH). The number of Macrophage Activation Syndrome (MAS) cases was comparable to previous studies (8.82%)

Therefore, the safety profile was consistent with the known profile of canakinumab, with no increased rate of infections, hepatic impairment, or malignancy.

3. CHMP's overall conclusion and recommendation

Study G1401 demonstrated the efficacy and safety of canakinumab in Japanese pediatric patients with SJIA, consistent with the overall population and post-authorization experience.
Considering the results of Study G1401, no changes to the current Ilaris Core Data Sheet and/or to the approved EU Product Information are proposed which can be agreed.

Fulfilled:

No regulatory action required.