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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: EMEA/H/C/001109/P46/058

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**	**Need for discussion**
☐	Start of procedure	21/06/2022	21/06/2022	☐
☐	CHMP Rapporteur Assessment Report	25/07/2022	25/07/2022	☐
☐	CHMP members comments	08/08/2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	11/08/2022	n/a	☐
☒	CHMP adoption of conclusions	19/08/2022	19/08/2022	☐

Table of contents

1. Introduction

On 02 May 2022, the MAH submitted a completed paediatric study 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 CACZ885D1401, Drug Use Investigation of ILARIS for s.c. injection 150 mg and ILARIS solution for s.c. injection 150 mg, is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

ILARIS for s.c. injection 150 mg and ILARIS solution for s.c. injection 150 mg

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CACZ885D1401, Drug Use Investigation of ILARIS for s.c. injection 150 mg and ILARIS solution for s.c. injection 150 mg

2.3.2. Clinical study

CACZ885D1401-Drug Use Investigation of ILARIS for s.c. injection 150 mg and ILARIS solution for s.c. injection 150 mg

Description

Study ACZ885D1401 was an observational study conducted in, which aimed to evaluate post-marketing safety and efficacy on the long-term clinical use of ILARIS in cryopyrin-associated periodic syndromes (CAPS) patients. Study ACZ885D1401 enrolled 41 pediatric subjects (aged <18 years) and concluded on 15-Nov-2021 (final database lock).

ILARIS for s.c. injection 150 mg was approved in for the treatment of cryopyrin-associated periodic syndrome (CAPS) on September 26, 2011, under the condition that "Because of the extremely limited number of patients included in clinical studies in, post-marketing surveillance for safety and efficacy should be conducted by registering all patients treated with this drug during the re-examination period or until data from a certain number of patients are accumulated. In the post marketing surveillance, the safety and efficacy of long-term treatment, including the occurrence of infections, should be thoroughly investigated."

This was a single-group, multicenter, observational study (drug use investigation) with no control group that is conducted in accordance with the GPSP Ordinance.

The study included an observation period of 2 years and a follow-up period of up to 5 years.

Methods

All-case surveillance was conducted by the central registration method.

The observation period was 2 years from the start of treatment with ILARIS (for patients who discontinued or dropped out of treatment, until discontinuation or dropout of treatment). For patients who entered from the Japanese clinical trial D2308 (hereinafter, the clinical trial) to the post marketing clinical study after approval of ILARIS and switched from the investigational product to the marketed product, the observation period was 2 years from the switch (for patients who discontinued or dropped out of treatment, until discontinuation or dropout of treatment) with the day of switch as the start date of treatment.

Study participants

The investigation included all patients who used ILARIS in daily medical practice for a certain period of time after marketing for CAPS, including familial cold auto inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), or neonatal onset multi-system inflammatory disease (NOMID). Patients who entered from a clinical trial to a post marketing clinical study after approval of ILARIS and then switched from the investigational product to the marketed product were also subject to registration. Although the investigation was to be started on or after the date of conclusion of the contract for the investigation, patients who started treatment with ILARIS before the date of conclusion of the contract were also enrolled in the investigation and the case report form was completed for them.

Treatments

ILARIS for s.c. injection 150 mg and ILARIS solution for s.c. injection 150 mg. This investigation is non-interventional and does not specify a treatment plan, treatment procedures, or visit schedule.

Objective(s)

The objective of this investigation was to collect and evaluate the following information under the long-term clinical use in CAPS patients who used ILARIS for s.c. injection 150 mg and ILARIS solution for s.c. injection 150 mg.

1. Unknown adverse reactions (particularly important adverse reactions)
2. Understanding of the occurrence status of adverse reactions under the actual use status of the drug
3. Factors that may affect the safety, efficacy, etc.
4. Understanding of safety (occurrence of infections and malignant tumors) and efficacy (severity of symptoms that may affect physical function and life prognosis) in long-term use
5. Priority investigation items:
    - Occurrence of infections
    - Occurrence of tuberculosis
    - Occurrence of severe injection site reactions
    - Occurrence of malignant tumors
    - Occurrence of demyelinating disorders
    - Occurrence of neutropenia
    - Occurrence of hypercholesterolaemia
    - Occurrence of hepatic function disorder

Outcomes/endpoints

Patient demographics, history of prior treatment (biologics, non-biologics, and non-drug therapies), status of administration of ILARIS, status of drug suspension, status of use of concomitant medications, status of implementation of concomitant therapies, clinical evaluations (auto inflammatory symptoms, treatment response, and symptoms considered to have a significant impact on physical function and life prognosis), laboratory tests (hematology general tests), discontinuation/dropout of treatment with ILARIS, adverse events (presence/absence of adverse events specified as priority investigation items, presence/absence of other adverse events, and details of adverse events), and follow-up.

Efficacy endpoints

The following analyses were performed for the efficacy endpoints.

- Proportion (%) of patients who did not relapse at Week 24 and thereafter (including patients in whom the dose was increased)
- Response to treatment (proportion of patients with complete remission) by Day 15 after the start of treatment in patients without dose increase and by Day 29 after the start of treatment in patients with dose increase
- Physician's global assessment of auto inflammatory symptoms at Week 24 and thereafter
- Mean CRP and SAA at Week 24 and thereafter
- Efficacy evaluation by patient characteristics
- Physician's assessment of clinical symptoms that may significantly affect the physical function and life prognosis of CAPS patients

Randomisation and blinding (masking)

N/A

Statistical Methods

Details of the statistical analyses are described in "Statistical Analysis Plan Ver. 20.0."

Results

Participant flow and recruitment

In total, 43 pediatric patients were enrolled in the study. The safety analysis set includes 41 patients, of which 39 patients (95.12%) completed the 2-year observation period and 2 patients (4.88%) prematurely discontinued from the study. The reasons for discontinuation were occurrence of adverse events and inadequate response (1 patient, 2.44% each). During the reexamination period, ILARIS was used for in 2 patients for the treatment of hyper-IgD syndrome (mevalonate kinase deficiency), which was not approved at the start of treatment with ILARIS, after consultation with the regulatory authorities. The safety analysis set therefore excludes these 2 patients with off-label use.

Baseline data

Among the 41 patients in the safety analysis set, the proportion of new patients was 73.17% (30 patients) and the proportion of continued patients was 26.83% (11 patients). The median age (minimum to maximum) at the start of treatment with ILARIS was 5.5 (0 to 17) years in new patients and 10.0 (4 to 17) years in continuing patients. Only new patients had those aged < 2 years (8

patients, 26.67%) included. The median body weight (minimum to maximum) at the start of treatment with ILARIS was 17.35 (2.1 to 53.9) kg in new patients and 23.33 (15.0 to 46.7) kg in continuing patients. Among new patients, the most common phenotypes included were MWS (16 patients, 53.33%) and NOMID (8 patients, 26.67%). A similar trend was observed for continuing patients where the most common phenotypes were NOMID (6 patients 54.55%) and MWS (5 patients, 45.45%).

Table 2-3 Demographics characteristics and other baseline values (patients aged <18 years), Safety analysis set

Item	Category	Number of patients (%)					
		All patients		New patients		Continuing patients	
Patients included in safety analysis		41	(100.00)	30	(73.17)	11	(26.83)
CAPS phenotype	FCAS patients	6	(14.63)	6	(20.00)	0	(0.00)
	MWS patients	21	(51.22)	16	(53.33)	5	(45.45)
	NOMID patients	14	(34.15)	8	(26.67)	6	(54.55)
Sex	Male	21	(51.22)	15	(50.00)	6	(54.55)
	Female	20	(48.78)	15	(50.00)	5	(45.45)
Presence/absence of pregnancy during the observation period in this investigation (Denominator is female)	Absent	19	(95.00)	15	(100.00)	4	(80.00)
	Present	0	(0.00)	0	(0.00)	0	(0.00)
	Unknown/ not specified	1	(5.00)	0	(0.00)	1	(20.00)
Age at the start of treatment with ILARIS [years]	< 2 years	8	(19.51)	8	(26.67)	0	(0.00)
	2 to < 15 years	27	(65.85)	19	(63.33)	8	(72.73)
	≥15 years	6	(14.63)	3	(10.00)	3	(27.27)
	Number of patients	41		30		11	
	Mean ± standard deviation	7.7 ± 5.66		6.7 ± 5.77		10.3 ± 4.61	
	Median [minimum to maximum]	7.0 [0 to 17]		5.5 [0 to 17]		10.0 [4 to 17]	
Duration of CAPS [years]	< 5 years	16	(39.02)	15	(50.00)	1	(9.09)
	5 to < 10 years	10	(24.39)	4	(13.33)	6	(54.55)
	≥ 10 years	14	(34.15)	10	(33.33)	4	(36.36)
	Unknown/ not specified	1	(2.44)	1	(3.33)	0	(0.00)
	Number of patients	40		29		11	
	Mean ± standard deviation	6.5 ± 5.25		5.3 ± 5.15		9.5 ± 4.46	
	Median [minimum to maximum]	6.5 [0 to 17]		4.0 [0 to 16]		8.0 [3 to 17]	
Body weight at the start of treatment with ILARIS [kg]	≤ 40 kg	33	(80.49)	24	(80.00)	9	(81.82)
	> 40 kg	8	(19.51)	6	(20.00)	2	(18.18)
	Number of patients	40		30		10	
	Mean ± standard deviation	23.01 ± 14.131		22.03 ± 15.163		25.94 ± 10.572	
	Median [minimum to maximum]	20.25 [2.1 to 53.9]		17.35 [2.1 to 53.9]		23.33 [15.0 to 46.7]	
Presence/absence of *NALP3* gene mutation	Absent	6	(14.63)	5	(16.67)	1	(9.09)
	Present	35	(85.37)	25	(83.33)	10	(90.91)
	None	11	(26.83)	3	(10.00)	8	(72.73)
	Minimal	4	(9.76)	2	(6.67)	2	(18.18)

Physician's global assessment of autoinflammatory disease activity (at the start of treatment with ILARIS)	Mild	13	(31.71)	12	(40.00)	1	(9.09)
	Moderate	13	(31.71)	13	(43.33)	0	(0.00)
	Severe	0	(0.00)	0	(0.00)	0	(0.00)
Skin disease assessment (at the start of treatment with ILARIS)	None	14	(34.15)	6	(20.00)	8	(72.73)
	Minimal	6	(14.63)	3	(10.00)	3	(27.27)
	Mild	6	(14.63)	6	(20.00)	0	(0.00)
	Moderate	12	(29.27)	12	(40.00)	0	(0.00)
	Severe	3	(7.32)	3	(10.00)	0	(0.00)
CRP [mg/dL] (at the start of treatment with ILARIS)	Number of patients	40		29		11	
	Mean ± standard deviation	2.78 ± 2.994		3.51 ± 3.170		0.86 ± 1.119	
	Median [minimum to maximum]	1.38 [0.0 to 9.8]		3.53 [0.0 to 9.8]		0.43 [0.0 to 3.6]	
SAA [µg/mL] (at the start of treatment with ILARIS)	Number of patients	30		24		6	
	Mean ± standard deviation	149.77 ± 172.661		179.96 ± 180.665		29.04 ± 30.014	
	Median [minimum to maximum]	65.50 [1.3 to 590.7]		91.15 [1.3 to 590.7]		18.00 [1.3 to 80.00]	
Presence/absence of allergy history	Absent	32	(78.05)	24	(80.00)	8	(72.73)
	Present	4	(9.76)	3	(10.00)	1	(9.09)
	Unknown/ not specified	5	(12.20)	3	(10.00)	2	(18.18)
Presence/absence of past medical history	Absent	28	(68.29)	22	(73.33)	6	(54.55)
	Present	8	(19.51)	5	(16.67)	3	(27.27)
	Unknown/not specified	5	(12.20)	3	(10.00)	2	(18.18)
Presence/absence of complications	Absent	22	(53.66)	15	(50.00)	7	(63.64)
	Present	17	(41.46)	14	(46.67)	3	(27.27)
	Unknown/ not specified	2	(4.88)	1	(3.33)	1	(9.09)
Presence/absence of complications (renal impairment)	Absent	38	(92.68)	29	(96.67)	9	(81.82)
	Present	1	(2.44)	0	(0.00)	1	(9.09)
	Unknown/ not specified	2	(4.88)	1	(3.33)	1	(9.09)
Presence/absence of complications (hepatic function disorder)	Absent	36	(87.80)	26	(86.67)	10	(90.91)
	Present	3	(7.32)	3	(10.00)	0	(0.00)
	Unknown/ not specified	2	(4.88)	1	(3.33)	1	(9.09)

Number analysed

Table 2-2 Disposition of discontinuations/dropouts (patients aged <18 years), Safety analysis set

Reason for discontinuation/dropout	Number of patients (%)	
Patients included in safety analysis	41	
Completion of 2-year observation period	39	(95.12)
Discontinuation/dropout	2	(4.88)
Reason for discontinuation/dropout		
Occurrence of adverse events	1	(2.44)
Inadequate response	1	(2.44)

Source: DS_T001_E

Efficacy results

Complete remission and relapse

New patients

The proportions of patients with complete remission and with no relapse after complete remission at each evaluation time point per physician's assessment in new patients aged < 18 years are shown in Table 2-4.

The response rate in patients aged < 18 years was 72.41% (21/29 patients). The proportion of patients with no relapse after complete remission was 100.00% (21/21 patients) at Week 24, 90.91% (20/22 patients) at Week 48, 84.21% (16/19 patients) at Week 74, and 95.00% (19/20 patients) at Week 104.

Table 2-4 Complete remission and relapse at each evaluation time point assessed by the physician in EU pediatrics (<18 years) (new patients/efficacy analysis set)

		Evaluation time point							
		Week 24 m = 29 n (%)		Week 48 m = 27 n (%)		Week 74 m = 23 n (%)		Week 104 m = 23 n (%)	
Patients who achieved complete remission by the time of evaluation		21	(72.41)	22	(81.48)	19	(82.61)	20	(86.96)
Presence/absence of relapse at each evaluation time point	Present	0	(0.00)	2	(9.09)	1	(5.26)	0	(0.00)
	Absent	21	(100.0)	20	(90.91)	16	(84.21)	19	(95.00)
No relapse after complete remission		19	(90.48)	18	(81.82)	16	(84.21)	17	(85.00)

m: Number of patients evaluated in each applicable period (Week 24, 168 ± 28 days; Week 48, 336 ± 28 days; Week 74, 518 ± 28 days; Week 104, 728 ± 28 days)

Patients who achieved complete remission by each evaluation time point: Patients who achieved complete remission at least once by the applicable evaluation time point

The denominator for the proportion of patients who achieved complete remission by each evaluation time point was m.

The proportion of patients who experienced relapse is the proportion of patients who achieved complete remission by each evaluation time point.

The presence/absence of relapse was unknown/not specified in 2 patients at Week 74 and in 1 patient at Week 104.

Source: REM_T001n_E

Continuing patients

The proportions of patients with complete remission and with no relapse after complete remission at each evaluation time point per physician's assessment in continuing patients aged < 18 years are shown in Table 2-5.

The response rate in patients aged < 18 years was 81.82 (9/11 patients). The proportion of patients with no relapse after complete remission was 100.00% (9/9 patients) at Week 24, 100.00% (9/9 patients) at Week 48, 100.00% (8/8 patients) at Week 74, and 100.00% (9/9 patients) at Week 104.

Table 2-5 Complete remission and relapse at each evaluation time point assessed by the physician in EU pediatrics (<18 years) (continuing patients/efficacy analysis set)

		Evaluation time point			
		Week 24 m = 11 n (%)	Week 48 m = 10 n (%)	Week 74 m = 9 n (%)	Week 104 m = 9 n (%)
Patients who achieved complete remission by the time of evaluation		9 (81.82)	9 (90.00)	8 (88.89)	9 (100.00)
Presence/absence of relapse at each evaluation time point	Present	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Absent	9 (100.00)	9 (100.00)	8 (100.00)	9 (100.00)
No relapse after complete remission		9 (100.00)	9 (100.00)	7 (87.50)	8 (88.89)

m: Number of patients evaluated in each applicable period (Week 24, 168 ± 28 days; Week 48, 336 ± 28 days; Week 74, 518 ± 28 days; Week 104, 728 ± 28 days)

Patients who achieved complete remission by each evaluation time point: Patients who achieved complete remission at least once by the applicable evaluation time point

The denominator for the proportion of patients who achieved complete remission by each evaluation time point was m.

The proportion of patients who experienced relapse is the proportion of patients who achieved complete remission by each evaluation time point.

Source: [CSR – Table 10-27]

Safety results

The occurrence of adverse events and serious adverse events in patients aged < 18 years is shown in Table 2-6. The incidence of adverse events in patients aged < 18 years was 92.68% (38 patients), and common adverse events by SOC were "infections and infestations" in 73.17% (30 patients) and "gastrointestinal disorders" in 31.71% (13 patients). Common adverse events by PT were bronchitis in 36.59% (15 patients) and upper respiratory tract infection in 31.71% (13 patients). The incidence of serious adverse events in patients aged < 18 years was 19.51% (8 patients). Common serious adverse events by SOC were "infections and infestations" in 12.20% (5 patients) and "respiratory, thoracic and mediastinal disorders" in 9.76% (4 patients). By PT, serious adverse events that occurred in ≥ 2 patients were bronchitis, pneumonia, and asthma in 7.32% (3 patients) each, and neutropenia in 4.88% (2 patients), and the outcomes were all "resolved" or "resolving." The outcomes of all other serious adverse events observed in 1 patient each were either "resolved" or "resolving," except for papilloedema (with sequelae), circulatory collapse and sepsis (fatal), and rhabdomyosarcoma (unknown). Overall, canakinumab was also well tolerated over longer term treatment in this study population, with no new safety signal detected and no change in frequency of known safety signals.

Table 2-6 Occurrence of adverse events and serious adverse events in EU pediatrics (< 18 years) (by SOC and PT) (safety analysis set)

		Adverse events		Serious adverse events	
Patients included in safety analysis		41		41	
Number of patients with adverse events		38		8	
Proportion of patients with adverse events (%)		92.68		19.51	
Type of adverse events		Number of patients with events (%)			
Infections and infestations		30	(73.17)	5	(12.20)
	Bronchitis	15	(36.59)	3	(7.32)
	Upper respiratory tract infection	13	(31.71)	-	
	Gastroenteritis	9	(21.95)	1	(2.44)
	Pharyngitis	8	(19.51)	-	
	Nasopharyngitis	5	(12.20)	-	
	Pneumonia	5	(12.20)	3	(7.32)
	Impetigo	4	(9.76)	-	
	Influenza	4	(9.76)	-	
	Otitis media	3	(7.32)	1	(2.44)
	Conjunctivitis	2	(4.88)	-	
	Hand-foot-and-mouth disease	2	(4.88)	1	(2.44)
	Rhinitis	2	(4.88)	-	

	Sinusitis	2	(4.88)	-	
	Tonsillitis	2	(4.88)	-	
	Viral infection	2	(4.88)	-	
	Adenovirus infection	2	(4.88)	1	(2.44)
	Streptococcal infection	2	(4.88)	-	
	Oral herpes	2	(4.88)	-	
	Bronchiolitis	1	(2.44)	1	(2.44)
	Bronchopulmonary aspergillosis	1	(2.44)	1	(2.44)
	Chronic sinusitis	1	(2.44)	-	
	Chronic tonsillitis	1	(2.44)	-	
	Cystitis	1	(2.44)	-	
	Exanthema subitum	1	(2.44)	1	(2.44)
	Gastroenteritis viral	1	(2.44)	-	
	Genital herpes	1	(2.44)	-	
	Infection	1	(2.44)	1	(2.44)
	Meningitis	1	(2.44)	-	
	Molluscum contagiosum	1	(2.44)	-	
	Oral candidiasis	1	(2.44)	-	
	Otitis media acute	1	(2.44)	-	
	Pericoronitis	1	(2.44)	-	
	Pneumonia mycoplasmal	1	(2.44)	-	
	Respiratory syncytial virus bronchiolitis	1	(2.44)	1	(2.44)
	Sepsis	1	(2.44)	1	(2.44)
	Subcutaneous abscess	1	(2.44)	-	
	Tinea capitis	1	(2.44)	-	
	Varicella	1	(2.44)	-	
	Viral pharyngitis	1	(2.44)	-	
	Vulvovaginal candidiasis	1	(2.44)	-	
	Beta haemolytic streptococcal infection	1	(2.44)	-	
	Perichondritis	1	(2.44)	-	
	Tonsillitis bacterial	1	(2.44)	-	
	Gastroenteritis norovirus	1	(2.44)	-	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		1	(2.44)	1	(2.44)
	Rhabdomyosarcoma	1	(2.44)	1	(2.44)

Blood and lymphatic system disorders		7	(17.07)	3	(7.32)
	Iron deficiency anaemia	3	(7.32)	-	
	Anaemia	2	(4.88)	-	
	Neutropenia	2	(4.88)	2	(4.88)
	Lymphadenitis	1	(2.44)	1	(2.44)
Immune system disorders		1	(2.44)	1	(2.44)
	Haemophagocytic lymphohistiocytosis	1	(2.44)	1	(2.44)
Metabolism and nutrition disorders		5	(12.20)	1	(2.44)
	Hypertriglyceridaemia	2	(4.88)	-	
	Dehydration	1	(2.44)	-	
	Hypercholesterolaemia	1	(2.44)	-	
	Hyperphagia	1	(2.44)	-	
	Hypocholesterolaemia	1	(2.44)	-	
	Carnitine deficiency	1	(2.44)	1	(2.44)
	Decreased appetite	1	(2.44)	-	
	Hyperlipidaemia	1	(2.44)	-	
Psychiatric disorders		2	(4.88)	-	
	Eating disorder	1	(2.44)	-	
	Enuresis	1	(2.44)	-	
Nervous system disorders		2	(4.88)	-	
	Asterixis	1	(2.44)	-	
	Cerebral atrophy	1	(2.44)	-	
	Dizziness	1	(2.44)	-	
	Headache	1	(2.44)	-	
	Subdural hygroma	1	(2.44)	-	
	Benign enlargement of the subarachnoid spaces	1	(2.44)	-	
Eye disorders		5	(12.20)	2	(4.88)
	Astigmatism	1	(2.44)	-	
	Blepharitis	1	(2.44)	-	
	Eyelid oedema	1	(2.44)	-	
	Glaucoma	1	(2.44)	1	(2.44)
	Papilloedema	1	(2.44)	1	(2.44)
	Periorbital swelling	1	(2.44)	-	
Ear and labyrinth disorders		2	(4.88)	-	
	Deafness transitory	1	(2.44)	-	

	Tinnitus	1	(2.44)	-	
	Vertigo	1	(2.44)	-	
Cardiac disorders		1	(2.44)	1	(2.44)
	Cardiac ventricular thrombosis	1	(2.44)	1	(2.44)
Vascular disorders		1	(2.44)	1	(2.44)
	Circulatory collapse	1	(2.44)	1	(2.44)
Respiratory, thoracic and mediastinal disorders		8	(19.51)	4	(9.76)
	Asthma	3	(7.32)	3	(7.32)
	Rhinitis allergic	2	(4.88)	-	
	Aspiration	1	(2.44)	-	
	Atelectasis	1	(2.44)	1	(2.44)
	Epistaxis	1	(2.44)	-	
	Pneumonia aspiration	1	(2.44)	1	(2.44)
	Rhinorrhoea	1	(2.44)	-	
	Oropharyngeal pain	1	(2.44)	-	
Gastrointestinal disorders		13	(31.71)	-	
	Stomatitis	4	(9.76)	-	
	Diarrhoea	3	(7.32)	-	
	Constipation	2	(4.88)	-	
	Nausea	2	(4.88)	-	
	Anal fissure	1	(2.44)	-	
	Enterocolitis	1	(2.44)	-	
	Irritable bowel syndrome	1	(2.44)	-	
	Ranula	1	(2.44)	-	
	Acetonaemic vomiting	1	(2.44)	-	
Hepatobiliary disorders		6	(14.63)	1	(2.44)
	Hepatic function abnormal	5	(12.20)	1	(2.44)
	Hepatic steatosis	1	(2.44)	-	
	Liver disorder	1	(2.44)	-	
Skin and subcutaneous tissue disorders		11	(26.83)	-	
	Eczema	4	(9.76)	-	
	Dry skin	2	(4.88)	-	
	Miliaria	2	(4.88)	-	
	Rash	2	(4.88)	-	
	Asteatosis	2	(4.88)	-	
	Dermatitis	1	(2.44)	-	
	Dermatitis diaper	1	(2.44)	-	

	Drug eruption	1	(2.44)	-	
	Eczema asteatotic	1	(2.44)	-	
	Erythema	1	(2.44)	-	
	Pruritus	1	(2.44)	-	
	Urticaria	1	(2.44)	-	
Musculoskeletal and connective tissue disorders		4	(9.76)	-	
	Arthralgia	1	(2.44)	-	
	Pain in extremity	1	(2.44)	-	
	Musculoskeletal stiffness	1	(2.44)	-	
	Knee deformity	1	(2.44)	-	
Renal and urinary disorders		1	(2.44)	-	
	Pollakiuria	1	(2.44)	-	
Congenital, familial and genetic disorders		4	(9.76)	-	
	Muckle-Wells syndrome	3	(7.32)	-	
	Chronic infantile neurological cutaneous and articular syndrome	1	(2.44)	-	
General disorders and administration site conditions		6	(14.63)	1	(2.44)
	Pyrexia	4	(9.76)	1	(2.44)
	Pain	1	(2.44)	-	
	Injection site swelling	1	(2.44)	-	
Investigations		8	(19.51)	1	(2.44)
	C-reactive protein increased	2	(4.88)	-	
	White blood cell count increased	2	(4.88)	-	
	Haemoglobin decreased	1	(2.44)	1	(2.44)
	Platelet count decreased	1	(2.44)	1	(2.44)
	Blood alkaline phosphatase increased	1	(2.44)	-	
	Hepatic enzyme increased	1	(2.44)	-	
	Occult blood positive	1	(2.44)	-	
	Serum amyloid A protein increased	1	(2.44)	1	(2.44)
	Streptococcus test positive	1	(2.44)	-	
Injury, poisoning and procedural complications		4	(9.76)	1	(2.44)
	Arthropod sting	1	(2.44)	-	
	Femur fracture	1	(2.44)	-	
	Road traffic accident	1	(2.44)	-	
	Subdural haematoma	1	(2.44)	1	(2.44)

MedDRA/J version (23.1)

A patient with multiple episodes of the same event (PT) was counted only once. The order of adverse events is as follows: SOC is shown in ascending order of international consensus; PT is shown in descending order of the incidence in the adverse event column and then in ascending order of PT code. Source: AE_T001_E, AE_L001_E

Adverse events in patients excluded from the safety analysis set

In the 2 patients excluded from the safety analysis set, 24 adverse events were observed, and all of which were not related to ILARIS (Source: AE_L003_E). In the first excluded patient, 22 adverse events occurred. Nine events were considered serious by the investigator, including 2 events of vomiting and 1 event each of dehydration, gastroenteritis, tibia fracture, pharyngitis, gastroenteritis

viral, headache, and nasopharyngitis. The outcomes of all 9 serious adverse events were "resolved." The outcomes of the 13 nonserious adverse events were "not resolved" for 1 event of inflammation and "resolved" or "resolving" for the other events. Two adverse events occurred in the second excluded patient. One event of gastroenteritis norovirus was considered serious and 1 event of upper respiratory tract infection was considered non-serious. The outcomes of both events were "resolved."

Death

There was one fatal case.

The events with fatal outcome were circulatory collapse and sepsis, which were both assessed as serious events and assessed as not related to ILARIS. Factors other than ILARIS were the underlying disease or complications. All other adverse events reported in this patient were assessed as not related to ILARIS.

2.3.3. Discussion on clinical aspects

The results of the finalized study CACZ885D1401, Drug Use Investigation, showed the efficacy of canakinumab in maintaining a treatment response and symptom control in the evaluated patients. Results showed a high proportion of complete and long term responders and patients in complete remission without relapse events. The efficacy of long-term treatment with ILARIS in CAPS patients in the routine clinical setting in was therefore consistent with that observed in global clinical studies.

The overall safety profile of canakinumab in this study was consistent with previous global studies without any new safety signals observed and no change in frequency of known safety signals. Infections were the most frequently reported events during the observation. Infections and infestations are already described in the SmPC of canakinumab. The safety data presented showed no new safety findings compared to the known safety profile of canakinumab.

3. CHMP overall conclusion and recommendation

The efficacy and safety results of the presented investigational post approval study in in paediatric and adult subjects do not alter the benefit risk balance.

Overall, the described safety findings are in line with the already known profile reflected in the SmPC.

☒ Fulfilled:

No regulatory action required.