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Clinical Development & Medical Affairs

ILARIS® (canakinumab)

Non-interventional Final Study Report

β-Confident - Clinical Outcomes and Safety: A registry Study of Ilaris® (canakinumab) Patients

An open-label, long-term, prospective, observational study to monitor the safety and effectiveness of Ilaris® in CAPS patients

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Marketing authorization holder	Novartis Europharm Ltd
Joint PASS	No
Research question and objectives	The purpose of this observational study was to gather additional information with respect to long-term safety and effectiveness of Ilaris used to treat patients with Cryopyrin-Associated Periodic Syndromes (CAPS) in routine clinical practice. The primary objective of the β-CONFIDENT Registry was to monitor the overall safety of Ilaris in CAPS through the incidence of serious infections,

	malignancies, hypersensitivity reactions, and other selected events. The secondary objectives were: to describe the long-term impact of Ilaris on disease progression; to explore growth and development patterns of children aged ≥2 or ≥4 (depending on local label) to ≤17 years of age exposed to Ilaris; to identify previously unrecognized serious adverse drug reactions; and to describe the usage and patterns of dosing of Ilaris in routine clinical practice.
Countries of study	Austria, Belgium, Denmark, France, Germany, Greece, Hungary, Netherlands, Norway, Spain, Switzerland, the United Kingdom, the United States.
Author	See [Appendix 16.1.5]

Marketing authorization holder

Marketing authorization holder(s)	Novartis Europharm Ltd
MAH contact person	Not available

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1 Abstract

Title

β-CONFIDENT – Clinical Outcomes and Safety: A Registry Study of Ilaris® (canakinumab) Patients

Keywords

Cryopyrin-Associated Periodic Syndromes, Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, Neonatal Onset Multisystem Inflammatory Disease, Ilaris (canakinumab)

Rationale and background

Cryopyrin-Associated Periodic Syndromes (CAPS), specifically Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), are a group of rare hereditary autoinflammatory diseases. These conditions are part of a spectrum of diseases with overlapping traits and differences in severity. As with all very rare diseases, the original clinical development program of Ilaris (canakinumab) for treatment of these autoinflammatory diseases included a very limited number of patients; therefore, the β-CONFIDENT Registry, initiated in 2009 during the post-approval period, was a critical step to gather more knowledge regarding the short- and long-term safety, effectiveness, and treatment patterns associated with use of the product in routine clinical practice.

Research question and objectives

The primary objective of the β-CONFIDENT Registry was to monitor and further explore the overall safety of Ilaris in patients with CAPS focusing on infections, malignancies, hypersensitivity reactions, vertigo and other selected events.

The secondary objectives were: to describe the long-term impact of Ilaris on disease progression (including systemic Amyloid A [AA] amyloidosis as evidenced by renal function, neurologic and ophthalmologic symptoms, and sensorineural deafness); explore the growth and development patterns in children aged ≥2 or ≥4 (depending on local label) to ≤17 years of age exposed to Ilaris; identify previously unrecognized serious adverse drug reactions in the treated population; and describe the usage and patterns of dosing of Ilaris in routine clinical practice.

Study design

The β-CONFIDENT Registry was a multicenter, long-term, prospective, observational study conducted in compliance with Volume 9a of the Rules Governing Medicinal Products in the European Union (EudraLex Volume 12a, version September 2008). The design of the study was intended to allow assessment of safety and effectiveness in patients with CAPS who were exposed to Ilaris in routine clinical practice. There was no internal comparator; however, descriptive analyses for relevant subgroups were performed (e.g., by indication, age).

Setting

Participants were recruited from 38 sites in a total of 12 countries in Europe and the United States (US).

Subjects and study size, including dropouts

This study was descriptive in nature and no formal hypothesis testing or statistical significance testing was conducted. Therefore, no formal sample size estimation was performed. Among the 38 sites involved in the study, 288 patients were enrolled and data were available for 285 patients.

Variables and data sources

The following data elements were collected, if available: demographics, vital signs, duration of CAPS, indication for treatment with Ilaris, autoinflammatory disease activity, and safety. Data collected by the treating physician, including data collected from the medical record or directly from patients or their parents/legal representative, were entered into a validated database, at baseline and every 6 months thereafter.

Results

Among the 285 patients who contributed data to the analyses, 243 (85.3%) were classified as CAPS patients, 18 (6.3%) as atypical CAPS, and 24 (8.4%) as "Other" indications. Patients were predominately adults (62.5%) and less than 10% were below 6 years of age.

A considerable number of registry patients (58.9%) were rollover patients, defined as those previously exposed to Ilaris in a clinical trial and/or received IL-1 inhibitor medication, other than Ilaris, with an exposure duration prior to the start of Ilaris at baseline slightly higher in patients <18 years old (47.5 weeks) compared to ≥18 years old (37.6 weeks).

The mean duration of exposure to Ilaris during the course of this Registry was 3.6 years (SD 1.6 years) in the overall registry population, with a slightly lower duration in children aged 6-<12 years and in elderly patients (mean of 2.8 and 2.7 years, respectively).

A total of 1114 adverse events (AEs) were reported in 223 patients (78.2%) and 155 serious AEs (SAEs) were reported in 83 patients (29.1%) during the course of the Registry among all registry patients. Focusing on CAPS patients only (n=243), 187 (76.9%) reported 914 AEs and 68 (28.0%) reported 128 SAEs. Serious infections were the most frequent SAEs, with 43 events in 32 patients (13.2%). A total of 11 CAPS patients (4.5%) reported 14 events of malignancies, 3 CAPS patients (1.2%) reported 4 hypersensitivity events and 21 CAPS patients (8.6%) reported 31 vertigo episodes.

Regarding AEs suspected to be related to Ilaris during the course of this Registry among CAPS patients, 109 patients (44.9%) reported 305 events suspected to be related to Ilaris. Infections and Infestations were the most common event suspected to be related to Ilaris (126 events in 68 patients).

There was an increase in the proportion of patients having no disease activity over the course of the Registry, in both rollover (from 49.4% at baseline to 64.1% at 12 months) and non-rollover patients (from 31.6% at baseline to 59.1% at 12 months). At 48 months after baseline,

87.5% of patients (n/N= 126/144) were considered to be stable since last visit, representing a considerable improvement from the 60.9% of patients (n/N= 131/215) who were recorded as stable at 6 months after baseline.

Among the 83 registry patients aged 6 to <18 years, a delay in sexual maturation was reported in 2 patients at last assessment and who had no sexual maturation delay or unknown status at baseline. Conversely, 4 patients with a delay in sexual maturation at baseline registered no delay at last assessment. Change in sexual maturation was not available for 45 patients (54.2%).

More than half of patients (56.6%) with evaluable data had no delay of cognitive function at baseline and at the last assessment. Change in delay from baseline to last assessment was not available for 30 patients (36.1%).

Mean levels of CRP and SAA remained low and tended to further decrease over the course of the Registry.

More than one-third of registry patients (38.9%) received 2 to <3 mg/kg of Ilaris on average since baseline and approximately one-fifth (22.5%) received 1 to <2 mg/kg on average. The majority of registry patients received Ilaris every 7 to 9 weeks during follow-up; with one-third of registry patients receiving Ilaris every 8 weeks (35.0%). Although almost 25% of all patients (predominantly pediatrics) required a dose change at some point because of a lack of therapeutic effect, only 2.5% of patients in total permanently discontinued Ilaris due to a lack of therapeutic effect.

Of the 285 registry patients, 87 (30.5%) reported having received at least 1 vaccine of any type and 74 of these were CAPS patients. The remaining patients did not receive a vaccine or had missing or unknown information on vaccination. Of the 87 registry patients who received at least 1 vaccine, reactions were reported for 19 patients (21.8%, n=19/87). Pneumococcal vaccine registered the highest proportion of patients reporting at least 1 reaction, with pain, redness, and swelling being the most frequently reported reactions.

Discussion

While patients were followed-up for approximately 4 years in this observational study, total exposure was longer for over 40% of CAPS patients exposed to Ilaris in previous CAPS clinical studies.

Results of this study showed that efficacy was preserved long-term (up to 4 years of follow-up) and there were no new safety concerns. There was a low rate of discontinuation due to lack of therapeutic response, indicating that the treatment is effective and dose adjustments as per labelling in case of insufficient efficacy are appropriate and effective. Disease activity, as measured by PGA, CRP and SAA, improved or remained stable for a majority of patients. Ilaris does not appear to impact sexual maturation or development of the cognitive function based on limited data in patients aged 6 to <18 years. The profile of AEs and SAEs, including infections and other events of interest, reported during the course of this long-term registry study was consistent with the known safety profile for Ilaris. No new or unexpected safety concerns, or previously unrecognized serious adverse drug reactions were identified.

The cumulative long-term data from this non-interventional registry study confirm the safety of Ilaris treatment in pediatric and adult patients in routine clinical practice. As the efficacy and safety data were both consistent with those of prior clinical studies, the favorable benefit-risk profile of Ilaris remains unchanged.

Marketing Authorization Holder(s)

Not applicable

Name(s) and Affiliation(s) of Principal Investigator(s)

Prof. Dr. med. [redacted], Universitätsklinikum Tübingen

2 List of abbreviations

AA	Amyloid A
AE	Adverse event
ANA	Antinuclear antibody
CAPS	Cryopyrin-associated periodic syndromes
CIAS1/NLRP-3	Cold-induced autoinflammatory 1/NOD-like receptor protein 3 gene
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CINCA	Chronic Infantile Neurologic Cutaneous Articular
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
DILI	Drug-induced liver injury
dsDNA	Double-stranded deoxyribonucleic acid
eCRF	electronic Case Report Form
EDC	Electronic data capture
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
FCAS	Familial cold autoinflammatory syndrome
GPA	Granulomatosis polyangiitis
GVP	Good Pharmacovigilance Practices
HiB	Haemophilus influenza B
HPV	Human papillomavirus
ICF	Informed consent form
IEC	Independent Ethics Committee
IL-1β	Interleukin 1β
IRB	Institutional review board
MASAC	Macrophage Activation Syndrome Adjudication Committee
MMR	Measles, mumps & rubella
MRI	Magnetic resonance imaging
MWS	Muckle-Wells syndrome
NOD	Nucleotide-binding oligomerization domain
NOMID	Neonatal onset multisystem inflammatory disease
NSAID	Non-steroid anti-inflammatory drug
PASS	Post-authorization safety study
PGA	Physician’s global assessment
PT	Preferred term
REB	Research ethics board
RMP	Risk management plan
SAA	Serum amyloid A
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of product characteristics
TNF	Tumor necrosis factor
US	United States

3 Investigators

A list of investigators, their affiliations and qualifications, plus that of other important staff, as well as members of the safety committee, is provided in Appendix 16.1.4.

4 Other responsible parties

This study was performed by Quintiles, a contract research organization (CRO), with guidance, input, review, and approval of Novartis. Activities included development of materials, recruitment, training and management of sites, electronic data capture (EDC) and data management and analysis. Additionally, Quintiles wrote this clinical study report, which included the appendices and the narratives, with guidance from Novartis.

5 Milestones

Refer to Table 5-1 for planned and actual dates for study milestones.

Table 5-1 Study milestones

Table	Planned date	Actual date
Date of first IEC/IRB approval		16 November 2009 (Germany)
Date of last IEC/IRB approval		07 July 2012 (Belgium)
Start of data collection	05 October 2009	04 December 2009
End of data collection		18 December 2015
Final report of study results	19 April 2016	27 May 2016

6 Rationale and background

Cryopyrin-Associated Periodic Syndromes (CAPS), specifically Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), are a group of rare hereditary autoinflammatory diseases. These syndromes are typically a result of an autosomal dominant or de novo mutation of the cold-induced autoinflammatory 1/nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 (*CIAS1/NLRP3*) gene on chromosome 1 (Neven, et al., 2008). Although it remains poorly understood precisely how *CIAS1/NLRP-3* mutations cause inflammatory diseases, it is known that the protein encoded by this gene, NALP3 or cryopyrin, interacts with other intracellular proteins to form an intracellular complex called the inflammasome. This complex is important for innate immunity as it detects intracellular pathogens and other danger signals. Mutations in the *CIAS1/NLRP-3* gene cause up-regulation of NALP3 and activation of the inflammasome, resulting in an overproduction of interleukin 1β (IL-1β), a proinflammatory cytokine (Neven, et al., 2008; Hawkins, et al., 2004).

These conditions, part of a spectrum of disease with overlapping traits and differences in severity, may be generally described as life-long, recurrent fever episodes accompanied by differing degrees of neutrophil-mediated systemic inflammation. Intermittent, disruptive exacerbations or flares can be triggered at any time by exposure to cool temperatures, stress, exercise, or other stimuli. Flares can include fever, fatigue, rashes, arthralgia, myalgia

headaches, and in more severe cases, lead to severe complications such as hearing loss, blindness, and amyloidosis resulting in kidney failure.

Until recently, treatment has been limited to non-specific symptomatic anti-inflammatory therapy with limited success. With the identification of the genetic basis for the disease and the common pathway of IL-1β, new approaches to treating these conditions have been identified, among them canakinumab, the active principle of Ilaris, a fully human monoclonal antibody that acts on the selective blockade of IL-1β. Canakinumab has shown remarkable efficacy in CAPS patients in a multicenter, multinational, 3-part, 48-week, double-blind, placebo-controlled, randomized withdrawal study (CACZ885D2304) (Lachmann, 2009). In Part I (single-dose, open-label treatment period), 97% of the 35 CAPS patients attained complete response to canakinumab and in Part II (double-blind withdrawal period), all 15 patients (100%) who continued to receive canakinumab remained in remission, whereas 81% of the 16 patients randomized to placebo experienced disease flare ($p<0.001$). The 28 (90%) of the 31 patients who entered Part III (open-label treatment period), completed the study in complete remission.

In spite of its pivotal role in the treatment and management of CAPS patients, the use of Ilaris is not devoid of risks. The inhibition of the inflammatory response mediated by IL-1 may result in an increased susceptibility to infections. Similarly, the use of monoclonal antibodies within humans more generally has demonstrated that hypersensitivity reactions are also a potential risk. Additionally, IL-1 is up-regulated in many tumor types and thus may play a role in tumor progression and cell proliferation; however, the effects of long-term immunosuppression via blockade of IL-1 on the overall balance of its systemic effects is not known.

No deaths or life-threatening adverse events (AEs) were reported in the pivotal trial, CACZ885D2304, which had 84 patients. Of the 2 patients who experienced a serious adverse event (SAE), 1 was hospitalized with a lower urinary tract infection, and the other withdrew from the study due to unsatisfactory therapeutic effect after being diagnosed with an episode of vertigo accompanied by acute closed-angle glaucoma related to CAPS. The majority of patients (>91%) included in Parts I and II did not report injection-site reactions; only 4 patients had a mild reaction. Over the 48 weeks of the study, no anti-canakinumab antibodies were detected, and no hematologic safety issues surfaced. The most frequently affected organ class was infections and infestations (77.1%), followed by gastrointestinal disorders (51.4%). All other organ classes had AEs reported by fewer than 50% of patients. Thus, despite the favorable benefit/risk balance, it was considered that long-term safety was not well established and more information was required. Also, the assessment concerning sub-populations was not considered meaningful, and further investigations would need to be performed, especially in children and the impact of childhood vaccinations.

As with all very rare (orphan) diseases, the original clinical development program for Ilaris (canakinumab) included a very limited number of patients; therefore, the post-approval period is a critical phase in which to gather more knowledge regarding the short- and long-term safety, effectiveness, and treatment patterns associated with use of the product by clinicians and patients. Unlike other IL-1 agents like anakinra or rilonacept, canakinumab specifically blocks only IL-1β, the form of the IL-1 that causes disease flares in these autoinflammatory diseases.

The ß-Confident Registry (Study CACZ885D2401) was initiated in 2009 to provide data during the post-approval period on the long-term safety and effectiveness of Ilaris treatment in pediatric and adult patients in routine clinical practice.

After clinical submission (while the β-CONFIDENT Registry was ongoing), additional safety and efficacy information for canakinumab in this indication was obtained from other clinical studies: multicenter, open-label, 24-month treatment study to establish the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of canakinumab (anti-IL-1 beta antibody) in patients with NOMID/Chronic Infantile Neurologic Cutaneous Articular (CINCA) syndrome (CACZ885D2201; Sibley, 2015); an open-label study to evaluate the efficacy and safety in Japanese CAPS patients for 24 weeks, with an extension phase up to 48 weeks (CACZ885D2308; T. Imagawa, 2013); and an open-label, multicenter trial to assess efficacy, safety and tolerability of canakinumab and the efficacy and safety of childhood vaccinations in patients aged 4 years or younger with CAPS (CACZ885D2307 and CACZ885D2307E1).

The present study is part of the Risk Management Plan (RMP) for Ilaris submitted to, and approved by, the Committee for Medicinal Products for Human Use (CHMP). The CHMP considered the measures outlined in the RMP to adequately address the safety concerns associated with the long-term use of Ilaris in CAPS patients. The results presented in this report are intended to complement the information currently available and thus provide more insight into the risks associated with the use of Ilaris in routine clinical practice.

7 Research question and objectives

The β-CONFIDENT Registry was designed to provide additional information regarding the long-term safety of Ilaris use in pediatric and adult patients, as well as information regarding the long-term effectiveness and use of Ilaris in routine clinical practice.

Primary objective

The primary objective was to monitor and further explore the overall safety of Ilaris in patients with CAPS focusing on serious infections, malignancies, hypersensitivity reactions, vertigo, and other selected events.

Secondary objectives

The secondary objectives were to:

- Describe the long-term impact of Ilaris on disease progression (including systemic Amyloid A [AA] amyloidosis as evidenced by renal function, neurologic and ophthalmologic symptoms, and sensorineural deafness);
- Explore the growth and development patterns in children aged ≥2 or ≥4 (depending on local label) to ≤17 years of age exposed to Ilaris;
- Identify previously unrecognized serious adverse drug reactions in the treated population;
- Describe the usage and patterns of dosing of Ilaris in routine clinical practice.

Other selected events

Other selected events mentioned in the primary objective were defined and analyzed according to identified/potential risks from the latest RMP version 9.0 including neutropenia, opportunistic infections, immunogenicity/allergenicity, effect on growth, autoimmunity reactions, drug-induced liver injuries (DILI), disorders of lipoprotein metabolism, canakinumab– immunosuppressants combination therapy toxicity, interactions with vaccines, pregnancy and lactation, and long term effect on kidney function.

8 Amendments and updates to the protocol

Refer to Table 8-1 Protocol amendment summary for a summary of the amendments to the protocol and reasons why these amendments were required.

Table 8-1 Protocol amendment summary

Number	Date	Section of study protocol	Amendment or update	Reason
1	22 July 2010	Section 5 Section 6.1 Section 6.3	Section 5: The study population is updated to state that patients treated with Ilaris for autoinflammatory conditions other than CAPS are eligible except in countries where only CAPS patients are eligible. Section 6.1: Clarification is made for the data collection schedule. It is recommended that data entry be performed at baseline and every 6 months. During follow-up, however, the time of data entry should be retrospective to the previous data collection time point. Table 6-1 was edited to include 1 column for “follow-up” (previously 3 separate columns: “first 6 months”, “Year 1 thru 5” and “end of registry”). Changes to Table 6-1 do not appear in track changes. Section 6.3: Addition of vaccination record and outcome to data collection plan.	To fulfill a request by the Health Authority in Spain to only include patients using Ilaris as per label in order for the study design to comply with being a prospective observational study. Therefore, this amendment allowed only CAPS patients above the age of 4 to be included in the study in Spain and in other countries with a similar Health Authority request.
2	24 April 2013	Synopsis Section 1 Section 4 Section 5 Section 5.2 Section 6.1	Synopsis: Clarified population and study design Section 1: Background updated with new literature and specifics. Section 4: Additional information added regarding patients, data collection, and follow-up Section 5: New inclusion information Section 5.2: New exclusion criteria Section 6.1: Additional details on data collection.	Addressed low pediatric patients enrollment in comparison to adult patients and clarified that follow-up of all patients in this registry study will continue until one year after the last of a total of 260 expected patients have been recruited. Adverse event collecting and reporting was adapted to meet the requirement of EMA guideline on good pharmacovigilance practices (GVP) and 3 independent

Number	Date	Section of study protocol	Amendment or update	Reason
				adjudication committees (Macrophage Activation Syndrome Adjudication Committee (MASAC), Infection Adjudication Committee (IAC) and a Malignancy Adjudication Committee (MAC)) are added to comply with the current Ilaris (canakinumab) Risk Management Plan (RMP).
3	25 November 2013	Synopsis Section 7.1	Synopsis: Tense changed to past. Section 7.1: Additional circumstances were added as AEs regardless if a clinical event occurred.	The purpose of this amendment was to include special scenarios which should be reported as AEs to comply with EMA Guideline on Good Pharmacovigilance Practices (GVP), GVP Module VI regulations for non-interventional studies (EMA GVP Module VI).

CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; GVP: Guideline on Good Pharmacovigilance Practices

9 Research methods

9.1 Study design

The β-CONFIDENT Registry was a multicenter, long-term, prospective, observational study conducted in compliance with Volume 9a of the Rules Governing Medicinal Products in the European Union (EudraLex Volume 12a, version September 2008). The design was intended to allow assessment of safety and effectiveness in patients with CAPS who were exposed to Ilaris in routine clinical practice. There was no internal comparator; however, descriptive analyses included relevant subgroups (e.g., by indication, age group).

The registry enrolled patients for 5 years, with first patient first visit in December 2009 and last patient last visit in December 2015, during which time patients were enrolled and followed up for a minimum period of 1 year. Patients receiving Ilaris as part of their routine medical care and presented for routine clinic visit during the enrollment period were eligible and invited to participate.

There were no protocol-mandated visits or procedures associated with the registry. Data collection was aligned with standard medical practice and resulted from routine medical assessments performed during the initiation and follow-up of Ilaris treatment, including safety and other clinical outcomes. Any treatment and evaluation decisions regarding the patient's disease were determined by the treating physician according to standard of care and local clinical practice.

In order to focus on patients receiving Ilaris as part of their routine medical care for CAPS and adjust the proportion of pediatric patients in the study, the recruitment of adult patients and those with other autoimmune diseases were terminated after implementation of Amendment 2. Only pediatric CAPS patients aged ≥2 or ≥4 (depending on local label) to ≤17 years continued to be enrolled into the study thereafter.

Where required by local regulations, an Independent Ethics Committee (IEC), Institutional Review Board (IRB) or Research Ethics Board (REB) reviewed and approved the study protocol and amendments to the protocol, informed consent forms (ICF), and pediatric assent forms before any patient was consented.

9.2 Setting

Physicians routinely involved in the care and treatment of patients with CAPS were targeted for recruitment in Europe (see Abstract for a detailed list of countries) and the United States (US). Site selection criteria included projected availability of eligible patients in a 12-month period and the availability of physician (and other site staff) time to complete the case report forms (CRFs). To the extent possible, representative sites reflective of the treatment patterns within each country were recruited. Selection criteria and basic site information (e.g., site size, investigator specialty, site type) were collected via a site qualification survey.

9.3 Patients

Inclusion criteria

All patients fulfilling the following criteria were included:

- CAPS patients aged ≥2 or ≥4 (depending on local label) to ≤17 years of age receiving Ilaris treatment at enrollment as part of their routine clinical care (specified in Amendment 2);
- Adult patients receiving Ilaris enrolled before the implementation of Amendment 2 were allowed to remain in the study until the study was completed;
- Patients or parent(s)/legal representative of the patient willing and able to provide written informed consent.

Exclusion

- Patients receiving Ilaris for autoimmune diseases other than CAPS were excluded from the study after Amendment 2.

9.3.1 Patient enrollment

Eligible patients were enrolled at the time of presentation for a routine clinic visit, but no clinic visits were required as part of participation in this study. In addition, eligible patients could have rolled over from a previous Ilaris clinical trial, prescribed an IL-1 inhibitor other than Ilaris prior to study start, or enter the registry as newly treated patients (i.e., naïve patient who did not participate in any Ilaris clinical trial and has not been treated with any IL-1 inhibitor).

All patients presenting during the enrollment period were assessed for eligibility according to the defined selection criteria and all eligible patients were consecutively proposed to be enrolled in the study. A screening log was maintained by each site to record the disposition of consecutive patients potentially eligible for study participation in order to better assess the representativeness of the sampled population.

Patients could withdraw consent and discontinue participation from the study at any time, without prejudice. This did not imply the removal of the patient from the registry. If a patient was withdrawn prior to completing the study follow-up period, any known reason for withdrawal was documented in the database. All information already collected as part of the study was retained for analysis, and whenever possible, patients exposed to Ilaris continued to be followed for safety-related outcomes.

9.4 Variables

9.4.1 Patient demographics/other baseline characteristics

The following data elements were collected at baseline, if available:

- Demographics, including age (date of birth; years); gender (Male, Female), and race (White/Caucasian, Black, Asian, Native American, Pacific Islander, Unknown and "Other") (where permitted by local regulations, which did not include France)
- Vital signs [current height (cm), weight (kg), blood pressure (mmHg)]

- Estimated duration of symptomatic CAPS at time of registry enrollment (months)
- Indication for treatment with Ilaris (FCAS, FCAS/MWS, MWS, MWS/NOMID, NOMID, Atypical CAPS)
- CAPS genotype (*NLRP*-3 mutation)
- Clinical assessment of autoinflammatory disease activity (Absent, Mild/Moderate, Severe, Not Assessed): (historical and current assessments were collected, respectively see Protocol Table 6-1)
- CAPS-related clinical evaluations, if performed:
  1. Audiograms
  2. Neurological assessments
  3. Ophthalmologic assessments
- CAPS and Non-CAPS medical history:
  1. Cardiovascular
  2. Immune
  3. Malignancy (Past, Current)
  4. Other relevant history (Past, Current)
- Previous Ilaris dosing (date of administration and dose)
- Local clinical laboratory tests (Protocol Table 6-1)
- Previous therapy types taken for treatment of the autoinflammatory disease
- Cerebrospinal fluid analysis results, if evaluated (Normal, Abnormal, Unknown)
- Pediatric patients aged 6 to ≤17 years only (delay in sexual development status, delay in cognitive function, menarche status, grade level in school)

9.4.2 Clinical outcomes

The following data elements were collected as part of clinical follow-up:

- Date of assessment
- Treatment status:
  1. Permanent discontinuation
  2. Temporary interruption or changes in Ilaris dosing
  3. Primary reason for discontinuation, interruption or change
- Ilaris dosing (total exposure since last follow-up time point)
- Other treatments for CAPS (any changes to therapies (other than Ilaris) for treatment of the patient's autoinflammatory disease since last data collection)
- Vital signs:
  1. Current height
  2. Weight
  3. Blood pressure

- Changes in medical status, including disease progression:
  1. Systemic AA amyloidosis and C-reactive protein (CRP)
  2. Change in brain magnetic resonance imaging (MRI), audiogram and ophthalmologic examination
- Clinical assessment of autoinflammatory disease activity (symptom presence/intensity)
- Overall results of CAPS-related clinical testing, if performed:
  1. Audiogram
  2. Ophthalmologic examination
  3. Brain MRI
- Local clinical laboratory testing
- Physician's overall global assessment since last registry visit (Much Improved, Slightly Improved, Stable, Slightly Worsened, Much Worsened)
- Cerebrospinal fluid analysis (if collected)
- Pediatric patients age 6 to <18 years only:
  1. Sexual development status (if evaluated)
  2. Menarche status
  3. Neurocognitive development status (if evaluated)
  4. In a grade level in school appropriate for their age
- AEs and serious adverse reactions
- Vaccination record and outcome: including vaccinations within 3 months of baseline and throughout follow-up

9.4.3 Treatment exposure

Although it was expected that most patients would receive treatment every 8 weeks per local labeling, it was recognized that in the clinical setting, dosing may be delayed or interrupted due to personal reasons, physical condition, or co-morbidities. In addition to prescribed treatment schedule, actual treatment dates were recorded, when available.

As an observational registry of real-world treatment practices in this patient population, this study did not provide or recommend the use of any therapy and no restrictions on concomitant treatments were imposed.

Additional information on treatment exposure can be found in Section 10.3.

9.4.4 Safety

To ensure patient safety, all SAEs, regardless of relationship to Ilaris occurring after the patient had provided informed consent and until 30 days after the patient had stopped registry participation were reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 30-day period were reported to Novartis at the physician's discretion and in accordance with the physician's normal post-marketing AE spontaneous reporting practices.

Adverse events occurring in rollover patients from previous studies were not collected as part of the registry. Medical conditions/diseases present before starting Ilaris were only considered to be AEs if they worsened after starting Ilaris. Abnormal laboratory values or test results constituted AEs only if they induced clinical signs or symptoms, were considered to be clinically meaningful, or required therapy. All selected events (as listed in Section 7) and other SAEs were recorded regardless of whether considered related to Ilaris. Results on the safety of Ilaris can be found in Section 10.6.

Each pregnancy in patients exposed to Ilaris was reported to Novartis within 24 hours of learning of its occurrence. The pregnancy was followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any congenital abnormalities or maternal and/or newborn complications. A Pregnancy Form was used to record any pregnancy; pregnancy follow-up was recorded on the same form and included an assessment of the possible relationship to Ilaris of any pregnancy outcome. Any SAE(s) experienced during pregnancy was reported on an SAE Report Form.

9.4.5 Effectiveness/disease progression

Information regarding the following aspects of long-term effectiveness (disease progression) were collected:

- AA amyloidosis
- Renal dysfunction
- Sensorineural deafness
- Blindness/vision loss
- Neurologic symptoms
- Growth and development (for children)

The results of disease progression can be found in Section 10.4.2.1.

9.5 Data sources and measurement

Data collected by the treating physician, including data collected from the medical record or directly from patients or their parents/legal representative were entered into a validated database at baseline and at every medical visit during routine clinical care.

The schedule of data collection performed is presented in Table 9-1.

Table 9-1 Schedule of data collection

Period	Baseline	Follow-up (until study ended or premature discontinuation)[1]
Timing	**Enrollment**	**Every 6 months**
Informed consent	X	
CAPS indication	X	
CAPS genotype (NLRP-3 mutation),if available	X	
Non-CAPS medical history	X	

Period	Baseline	Follow-up (until study ended or premature discontinuation)[1]
Timing	**Enrollment**	**Every 6 months**
Vital signs (height, weight, blood pressure)	X	X
Ilaris dosing/status	X	X
Historical and concomitant medications for autoinflammatory disease[1]	X	X
Selected AEs[2]		X
Other serious AEs and non-serious AEs[1]		X
CAPS clinical assessment[1]	X	X
CAPS-related clinical testing results, if performed	X	X
Selected local laboratory testing[3]	X	X
Sexual development status (pediatric only)	X	X
Neurocognitive status (pediatric only)	X	X
Cerebrospinal fluid analysis	X	X
Vaccination record and outcome	X	X
Pregnancy status (females of child-bearing potential only)		X
Registry disposition		X

[1]When possible, these assessments were also conducted during follow-up for patients who discontinued Ilaris but remained in the registry.

[2]Selected AEs were defined as neutropenia-infections, autoimmunity reactions, DILI, disorders of lipoprotein metabolism, canakinumab – immunosuppressants combination therapy toxicity, interactions with vaccines, pregnancy and lactation, and long term effect on kidney function.

[3]Tests included cerebrospinal fluid analysis, CRP, SAA, ESR, ANA, and dsDNA.

Enrollment/baseline

Baseline data were collected from medical records, physician examinations, and from patients/legal guardians. These data included informed consent/pediatric assent, demographics, medical history, CAPS genotype, vital signs, medications (historical and concomitant), Ilaris treatment details (indication, dosing), assessment of autoinflammatory disease activity, sexual development and neurocognitive status (for pediatrics only), and vaccinations.

Follow-up

During the follow-up period, the treating physician or other staff collected data during routine clinical visits. Although it was expected that during routine clinical care most patients would receive treatment approximately every 8 weeks at their physician's office, the timing of each visit depended on the individual patient's healthcare management.

Discontinuation

The following data were collected for all discontinued patients:

- Date of discontinuation
- Reason for discontinuation

Adjudication committee

An independent adjudication committee reviewed and adjudicated information on all suspected cases of macrophage activation syndrome. Information on the members, mission and procedures of the adjudication committee can be consulted in the charter.

Action was required solely from the Macrophage Activation Syndrome Adjudication Committee (MASAC) for 2 patients. The first case of adjudication occurred on 27 June 2013 and the second on 29 July 2015. In both cases, the event was reported as histocytosis haematophafic and the MASAC concluded the information available was not sufficient for adjudication. There were not enough clinical and laboratory features of MAS specifically.

Safety-related measurements

Data regarding the occurrence of the following selected AEs were specifically solicited:

- Serious infections
- Malignancies
- Hypersensitivity reactions to Ilaris
- Development of autoantibodies (antinuclear antibody [ANA], double-stranded deoxyribonucleic acid [dsDNA])
- Clinical manifestations of an autoimmune disease (e.g., lupus, vasculitis, and rheumatoid arthritis)
- Vertigo
- Any other SAEs
- Pregnancy status (female patients of child-bearing potential only)
- Other selected events such as neutropenia-infections, autoimmunity reactions, DILI, disorders of lipoprotein metabolism, canakinumab – immunosuppressants combination therapy toxicity, interactions with vaccines, pregnancy and lactation, and long term effect on kidney function

Details of any other serious and non-serious AEs that were reported during follow-up were also collected.

Information on AE severity (mild, moderate, severe), relationship to Ilaris by investigator, duration, whether it constituted an SAE, and any treatment received was recorded on the AE CRF.

9.6 Bias

While clinical trials provide crucial information regarding the efficacy and safety of the drug, observational data can extend and augment what is known, including identifying optimal regimens and optimal therapies for special populations of patients who are unlikely to be adequately represented in clinical trials such as those with rare hereditary autoinflammatory diseases. However, it should be noted that there are some limitations associated with observational study designs and this study in particular.

Enrollment bias. In order to evaluate the potential for enrollment bias, differences in the enrollment and selection of patients were compared with the broader population of CAPS patients treated with Ilaris. Sites were instructed to approach all available CAPS patients being treated with Ilaris and were required to maintain a screening log of eligible patients, including their age and sex. The enrollment and eligibility log documented all eligible patients that were included or excluded from the Post-Authorization Safety Study (PASS), in order to assess the potential for selection bias. To the extent possible, consecutive eligible patients were included, and reasons for non-participation were documented.

Information bias can result from differences in collected data (e.g., accuracy or completeness) that misclassify patients in terms of exposure or outcomes. Systematic site training and standardized CRFs and other guidance documentation were utilized to ensure consistent data collection. Definitions of the main outcomes of interest were provided for further consistency across sites. Along with manual data review, programmable data edit checks for missing, illogical, or out-of-range values were built into the EDC system to ensure data quality for all sites.

Follow-up bias may occur when differences exist between study participants and patients lost to follow-up or who discontinued. To address this bias, the reason for discontinuation was collected for patients not completing the study to ensure that they did not withdraw for a reason associated with a study outcome or AE. In addition, baseline demographic and medical history characteristics were compared for enrolled patients and patients lost to follow-up or discontinued to allow for assessment of the bias.

9.7 Study size

No formal sample size calculation was used to manage enrollment in the registry since the goal was to obtain participation by all eligible patients. The estimate over the 5 years of enrollment was a minimum of 260 patients. This study was descriptive in nature and no formal hypothesis testing or statistical significance testing was conducted.

9.8 Data transformation

Indication

Indication for treatment with Ilaris was grouped into 3 mutually exclusive indication categories: CAPS, atypical CAPS, and “Other” non-CAPS diagnoses. CAPS includes those patients with FCAS, FCAS/MWS, MWS, MWS/NOMID, NOMID, and CINCA indications. “Other” indication includes Systemic Juvenile Idiopathic Arthritis, unspecified autoinflammatory syndromes, Familial Mediterranean Fever, Mevalonate Kinase Deficiency,

Adult-onset Still's Disease, tumor necrosis factor (TNF)-Receptor Associated Periodic Syndrome, Erdheim-Chester Disease, Blau's Syndrome, and granulomatosis polyangiitis (GPA).

Results in this study report are presented using all registry patients, CAPS patients only, atypical CAPS, and "Other" as shown in Table 9-2.

Table 9-2 Ilaris indications

Indication for treatment with Ilaris as entered on the CRF:	Indication used for analyses:
CAPS	**CAPS**
FCAS	FCAS
FCAS/MWS	MWS
MWS	
MWS/NOMID	NOMID
NOMID	
CINCA	
Atypical CAPS	**Atypical CAPS**
Other	**Other**

Refer to Section 9.9.1.2, Section 9.9.1.3, Section 9.9.1.3, and Section 9.9.1.4 for further information on data categorization.

9.9 Statistical methods

All data collected were analyzed by Quintiles, under the supervision of the Sponsor, and displayed in the patient data listings.

All computations and generation of tables, listings, and data for figures were performed using SAS version 9.2 (or higher) (SAS Institute, North Carolina, US).

9.9.1 Main summary measures

Descriptive analyses were performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables were reported as mean (and standard deviation [SD]) or median, range (minimum and maximum), and interquartile range (IQR) where appropriate. Categorical variables were summarized as number (n) and proportion (%) with 95% confidence intervals (CI) of the total study population, or by subgroups where appropriate.

9.9.1.1 Patient demographics/other baseline characteristics

All demographic and disease baseline characteristics (i.e., indication for treatment) were presented using descriptive statistics, as described in Section 9.9.1. Those patients described as children or adolescent in the protocol (2 to ≤17 years) were defined as non-adults (<18 years) throughout the statistical analysis. For analysis purposes, infants were defined as <4 years, children as 4 to <6 years and 6 to <12 years, adolescents as 12 to <18 years and adults as ≥18 years.

9.9.1.2 Exposure

Dosing characteristics, including dose at baseline, dose at each treatment date, and changes in treatment patterns over time were presented using descriptive statistics.

9.9.1.3 Primary measures

The primary measures of interest were occurrence of serious infections, malignancies, hypersensitivity reactions, vertigo, and other selected events (Section 7) after initial treatment with Ilaris. Each measure was also stratified by indication and age category and the cumulative frequencies were summarized.

9.9.1.4 Secondary measures

The secondary measures of interest were:

- Disease progression: summarized by frequency (proportion and percentage) of patients who had evidence of any disease progression symptoms, including: systemic AA amyloidosis as evidenced by renal function, neurologic and ophthalmic symptoms, and sensorineural deafness, stratified by children (0 to <18 years old) and adults (≥18 years old), at each visit. Changes from baseline were provided.
- Growth and sexual maturation: summary statistics and changes from baseline were presented showing how heights of children and adolescents (6 to <18 years of age) changed over the course of the study. For the subgroup of patients from ages 6 to <18 years, frequency tables were presented for number and percentage of patients who had a delay in sexual development. For females, summary statistics for age to menarche were presented.
- Occurrence of any new, previously unrecognized serious adverse drug reactions: summarized by the number of patients and percentage of unrecognized serious adverse drug reactions.

9.9.1.5 Main statistical methods

The primary analyses included summarizing the frequencies (proportions or incidence rates and 95% CI) of serious infections, malignancies, hypersensitivity reactions, vertigo, and other selected events (Section 7) after the initial treatment with Ilaris. Each of these AEs was also stratified by indication and age category.

9.9.2 Missing values

Weight was imputed for baseline and follow-up visits where actual weight was not available in order to calculate mg/kg dose values. No other missing value imputation techniques were applied in this registry.

Reasonable attempts were made to limit the amount of missing data related to safety and patient outcomes to ensure that important information related to the primary objective of the Registry and evaluation of the long-term safety of Ilaris were captured.

9.9.3 Sensitivity analyses

Not applicable.

9.9.4 Amendments to the statistical analysis plan (SAP)

Table 9-3 summarizes all the amendments to the SAP.

Table 9-3 History of amendments to the statistical analysis plan

Version	Date	Change
Version 1.0	11 December 2009	First version
Version 2.0	04 February 2013	Updated to reflect changes to the CRFs. Final report analyses, and publications analyses.
Version 3.0	29 April 2016	Updated to reflect need for imputation of weight in final analyses.

9.10 Quality control

All data were collected and entered by the sites directly into the EDC system. All sites were fully trained for using the online data capture system, including electronic case report form (eCRF) completion guidelines.

It was the treating physician's responsibility to ensure the accuracy of the data provided to the Registry by any site staff who were trained for registry data collection.

Initiation and selective monitoring of the participating sites was performed by Quintiles. Patient confidentiality was strictly maintained. Quintiles followed their own internal standard operating procedures that were reviewed and approved by Novartis. Further information regarding quality control can be found in the study protocol.

10 Results

10.1 Participants

A total of 288 patients from 38 sites within 12 countries in Europe and the US were enrolled ([Appendix 16.1.4]).

Three patients were excluded from the final analysis due to protocol deviations regarding informed consent (Section 10.1.1). As a result, data for 285 patients were included in the final analysis population ("All Registry Patients" population in the results presented below).

10.1.1 Protocol deviations

Forty-six percent of all patients had at least 1 protocol deviation. The most frequent deviations were issues regarding collection of informed consent (e.g., failure to sign the ICF before first injection; failure to re-consent patients as they became adults), and issues surrounding reporting of SAEs (e.g., late and un-reported SAEs). A protocol deviation was reported for 1 patient who was misdiagnosed with CAPS. This patient's indication was correctly updated to "Other" during the Registry and data collection was immediately stopped with the patient remaining in the Registry through study close-out.

ICFs at the site were missing for 3 patients and therefore these 3 patients were excluded from all analyses. Seven patients signed an ICF after the site had entered data into the database. As

a result, baseline clinical assessment and physical examination data were removed from analyses for these 7 patients since they were conducted at baseline and not considered historical data collected at baseline. One of these 7 patients also completed 2 follow-up visits before providing informed consent, therefore, all data collected from those visits, including adverse event data, were not included in the analysis results.

Please see Appendix 16.2.2 for more details.

10.1.2 Pregnancy and lactation

There were 8 pregnancies reported in 7 patients during the course of the study (5 MWS patients, 2 FCAS patients). One pregnancy event was reported with exposure to Ilaris at week 8 of gestation by which time the patient switched from Ilaris to Anakinra. Outcome of the pregnancy was not reported.

There were 3 abortions reported in the same patient, 2 of which reported as serious (as they were considered medically significant) and occurred after the patient discontinued treatment with Ilaris due to an unspecified reason.

10.1.3 Disposition of patients

The 285 registry patients in the final analysis population included 243 CAPS patients, 18 atypical CAPS patients, and 24 patients with "Other" indications (including Systemic Juvenile Idiopathic Arthritis [n=8], unspecified autoinflammatory syndromes [n=5], Familial Mediterranean Fever [n=3], Mevalonate Kinase Deficiency [n=2], Adult-onset Still's Disease [n=2], TNF-Receptor Associated Periodic Syndrome [n=1], Erdheim-Chester Disease [n=1], Blau's Syndrome [n=1], and GPA [n=1]) ([Listing 16.2.1-1.2]). The majority of enrolled CAPS patients were MWS patients (69.5%), followed by FCAS patients (17.3%), and NOMID patients (13.2%).

Table 10-1 summarizes patient disposition including reasons for early discontinuation, for all registry patients and by indication. Completion of the study was defined as not discontinuing the study prior to last visit. Of all registry patients, 60 (21.1%) discontinued the study prior to completion with the most common reasons for discontinuation cited as lost to follow-up, request of study close-out by the site, and changed physician.

Table 10-1 Disposition of patients

Disposition	Indication[1]						
	FCAS N=42	MWS N=169	NOMID N=32	Atypical CAPS N=18	Other N=24	All CAPS Patients N=243	All Registry Patients N=285
Completed, n (%)	28 (66.7)	142 (84.0)	25 (78.1)	15 (83.3)	15 (62.5)	195 (80.2)	225 (78.9)
Discontinued prior to completion, n (%)	14 (33.3)	27 (16.0)	7 (21.9)	3 (16.7)	9 (37.5)	48 (19.8)	60 (21.1)
Primary reason for discontinuation, n (%)[2]							
Patient withdrew consent	0 (0.0)	1 (3.7)	1 (14.3)	0 (0.0)	0 (0.0)	2 (4.2)	2 (3.3)
Loss to follow-up	6 (42.9)	12 (44.4)	2 (28.6)	1 (33.3)	0 (0.0)	20 (41.7)	21 (35.0)
Changed physician	0 (0.0)	1 (3.7)	3 (42.9)	0 (0.0)	2 (22.2)	4 (8.3)	6 (10.0)
Death	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	1 (1.7)
Changed therapy	0 (0.0)	2 (7.4)	0 (0.0)	0 (0.0)	1 (11.1)	2 (4.2)	3 (5.0)
Clinical remission	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	3 (5.0)
Desired pregnancy	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	1 (1.7)
Discontinued Ilaris per patient preference	0 (0.0)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.2)	2 (3.3)
Lack of efficacy	0 (0.0)	1 (3.7)	0 (0.0)	1 (33.3)	1 (11.1)	1 (2.1)	3 (5.0)
Patient in home for elderly	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	1 (1.7)
Patient moved	0 (0.0)	3 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.3)	3 (5.0)
Adverse events	0 (0.0)	2 (7.4)	1 (14.3)	1 (33.3)	2 (22.2)	3 (6.3)	6 (10.0)
Site requested study close-out	8 (57.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (16.7)	8 (13.3)

Source: Table 14.1-1.1

[1]MWS indication includes diagnoses of MWS and FCAS/MWS, NOMID indication includes diagnoses of NOMID and MWS/NOMID, Other indication includes non-CAPS diagnoses.
[2]Percentages are calculated out of the number of patients discontinued.

Approximately 20% of all the 243 CAPS patients discontinued the study early, with the main reasons for discontinuation cited as lost to follow-up (41.7%). Only 1 patient (2.1%) discontinued due to loss of efficacy and 3 (6.3%) patients due to AEs. Among CAPS-specific indications, FCAS patients had the highest proportion of early discontinuation (33.3%), followed by NOMID patients (21.9%) and MWS patients (16.0%).

A considerably higher percentage of patients with "Other" indication discontinued prior to study completion (n=9, 37.5%), however, 3 out of 9 discontinued due to clinical remission. Three patients with atypical CAPS discontinued the study.

10.2 Descriptive data

Baseline characteristics

Table 10-2 summarizes key demographic and baseline characteristics for all registry patients and by indication. Patients were predominately ≥18 years old (62.5%) with an average age of 30.4 years (SD 19.98). In terms of race distribution, the majority of all registry patients were classified as 'White/Caucasian" (73.0%). For 20.7% of the registry patients, race was classified as not applicable due to country-specific regulations not permitting race to be collected. There was a higher percentage of females enrolled than males (53.7% v 46.3%, respectively).

Table 10-2 Demographics and other baseline characteristics

Variable	Indication[1] FCAS N=42	MWS N=169	NOMID N=32	Atypical CAPS N=18	Other N=24	All CAPS Patients N=243	All Registry Patients N=285
Age group, n (%)							
Infant: <4 years	1 (2.4)	6 (3.6)	0 (0.0)	1 (5.6)	1 (4.2)	7 (2.9)	9 (3.2)
Child: 4 to <6 years	2 (4.8)	6 (3.6)	4 (12.5)	1 5.6)	2 (8.3)	12 (4.9)	15 (5.3)
Child: 6 to <12 years	5 (11.9)	19 (11.2)	7 (21.9)	3 (16.7)	4 (16.7)	31 (12.8)	38 (13.3)
Adolescent: 12 to<18 years	3 (7.1)	25 (14.8)	7 (21.9)	2 (11.1)	8 (33.3)	35 (14.4)	45 (15.8)
Adult: ≥18 years	31 (73.8)	113 (66.9)	14 (43.8)	11 (61.1)	9 (37.5)	158 (65.0)	178 (62.5)
Age (years)							
n	42	169	32	18	24	243	285
Mean	36.5	32.1	19.1	32.1	21.9	31.2	30.4
SD	20.96	19.47	13.71	24.77	17.99	19.66	19.98
Median	35.2	33.5	17.2	20.5	14.1	28.6	26.6
Range	2.6, 71.8	1.7, 78.3	4.7, 54.9	3.9, 78.0	3.6, 61.4	1.7, 78.3	1.7, 78.3
Sex, n (%)							
n	42	169	32	18	24	243	285
Male	14 (33.3)	87 (51.5)	15 (46.9)	9 (50.0)	7 (29.2)	116 (47.7)	132 (46.3)
Female	28 (66.7)	82 (48.5)	17 (53.1)	9 (50.0)	17 (70.8)	127 (52.3)	153 (53.7)
Predominant race, n (%)							
n	42	169	32	18	24	243	285
White/Caucasian	27 (64.3)	132 (78.1)	25 (78.1)	14 (77.8)	10 (41.7)	184 (75.7)	208 (73.0)
Black	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Asian	0 (0.0)	4 (2.4)	0 (0.0)	0 (0.0)	1 (4.2)	4 (1.6)	5 (1.8)
Other	0 (0.0)	2 (1.2)	2 (6.3)	0 (0.0)	0 (0.0)	4 (1.6)	4 (1.4)
Unknown	2 (4.8)	3 (1.8)	0 (0.0)	3 (16.7)	0 (0.0)	5 (2.1)	8 (2.8)
Not collected	13 (31.0)	27 (16.0)	5 (15.6)	1 (5.6)	13 (54.2)	45 (18.5)	59 (20.7)
Diagnosed with NLRP3 mutation, n (%)							
n	42	169	32	18	24	243	285
Yes	39 (92.9)	158 (93.5)	30 (93.8)	10 (55.6)	0 (0.0)	227 (93.4)	237 (83.2)

Variable	Indication[1]						
	FCAS N=42	MWS N=169	NOMID N=32	Atypical CAPS N=18	Other N=24	All CAPS Patients N=243	All Registry Patients N=285
No	2 (4.8)	8 (4.7)	2 (6.3)	6 (33.3)	16 (66.7)	12 (4.9)	34 (11.9)
Unknown	1 (2.4)	3 (1.8)	0 (0.0)	2 (11.1)	0 (0.0)	4 (1.6)	6 (2.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (33.3)	0 (0.0)	8 (2.8)
Previous exposure to Ilaris in CAPS studies, n (%)							
n	42	169	32	18	24	243	285
Yes	24 (57.1)	71 (42.0)	9 (28.1)	0 (0.0)	0 (0.0)	104 (42.8)	104 (36.5)
No	18 (42.9)	95 (56.2)	23 (71.9)	18 (100.0)	24 (100.0)	136 (56.0)	178 (62.5)
Unknown	0 (0.0)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	3 (1.1)
If Yes, Cohort, n (%)							
n	24	71	9	0	0	104	104
CACZ885 D2304	0 (0.0)	9 (12.7)	0 (0.0)	0 (0.0)	0 (0.0)	9 (8.7)	9 (8.7)
CACZ885 D2306	24 (100.0)	47 (66.2)	8 (88.9)	0 (0.0)	0 (0.0)	79 (76.0)	79 (76.0)
CACZ885 D2201	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.0)
CACZ885 A2102	0 (0.0)	15 (21.1)	0 (0.0)	0 (0.0)	0 (0.0)	15 (14.4)	15 (14.4)
Estimated duration of symptomatic CAPS at time of Registry enrollment (months)							
n	42	158	31	17	3	231	251
Mean	371.3	286.1	178.3	219.1	384.0	287.1	283.7
SD	268.29	224.08	129.37	172.05	264.82	228.43	225.56
Median	342.0	210.0	168.0	132.0	360.0	216.0	216.0
Range	13.0, 852.0	3.0, 900.0	24.0, 588.0	4.0, 504.0	132.0, 660.0	3.0, 900.0	3.0, 900.0
Missing	0 (0.0)	11 (6.5)	1 (3.1)	1 (5.6)	21 (87.5)	12 (4.9)	34 (11.9)

Source: Table 14.1-2.1

SD: standard deviation

[1]MWS indication includes diagnoses of MWS and FCAS/MWS, NOMID indication includes diagnoses of NOMID and MWS/NOMID, Other indication includes non-CAPS diagnoses.

The proportion of patients within each age group was slightly different between CAPS indications with more infants diagnosed with MWS and a larger proportion of children and adolescents diagnosed with MWS and NOMID compared to FCAS. FCAS had the largest proportion of adult patients ≥18 years old (73.8%) within CAPS patients. For age groups <18 years at baseline, the largest group (14.4%) was the adolescents aged 12-<18 years, followed by children aged 6-<12 (12.8%) and children aged 4-<6 (4.9%), the lowest group being infants <4 years (4.9%).

One patient was enrolled at 1.7 years old at baseline prior to the implementation of Amendment 2, which defined the age range for patient inclusion in the study.

Regarding the history of mutation and disease duration in CAPS patients since diagnosis, 93.4% were diagnosed with *NLRP3* mutation while 4.9% were not and 1.6% reported an unknown diagnosis. A total of 43% of CAPS patients (n=104/243) had previous exposure to Ilaris in a clinical trial (CACZ885D2304, CACZ885D2306, CACZ885D2201, or CACZ885A2102). On average, CAPS patients had an estimated duration of symptomatic CAPS at time of registry enrollment of 24 years (287.1 months). There was a variation in the average number of months of active disease across different CAPS indications, ranging from 178.2 months to 371.3 with the well represented MWS population having an average of 286.1 months of active disease.

Baseline clinical evaluations and laboratory testing

Table 10-3 summarizes CAPS-related clinical evaluations for all registry patients and by indication. Of all registry patients who reported results for each assessment, 51.8% (n=88/170) had an abnormal audiogram assessment for their age at baseline, 25.4% (n=34/134) had an abnormal ophthalmologic assessment at baseline, and 19.0% (n=15/79) had an abnormal brain MRI assessment at baseline. Similar patterns were seen for all CAPS patients. Twelve registry patients (4.2%) reported a history of vertigo at baseline.

Table 10-3 Baseline CAPS-related clinical evaluations

Variable	Indication[1]						
	FCAS N=42	MWS N=169	NOMID N=32	Atypical CAPS N=18	Other N=24	All CAPS Patients N=243	All Registry Patients N=285
History of sensorineural hearing loss, n (%)							
n	42	169	32	18	24	243	285
Yes	3 (7.1)	96 (56.8)	20 (62.5)	6 (33.3)	1 (4.2)	119 (49.0)	126 (44.2)
No	36 (85.7)	71 (42.0)	10 (31.3)	10 (55.6)	20 (83.3)	117 (48.1)	147 (51.6)
Unknown	3 (7.1)	2 (1.2)	2 (6.3)	2 (11.1)	3 (12.5)	7 (2.9)	12 (4.2)
Audiogram assessment, n (%)							
n	42	169	32	18	24	243	285
Yes	22 (52.4)	123 (72.8)	21 (65.6)	4 (22.2)	0 (0.0)	166 (68.3)	170 (59.6)
Normal for age	18 (81.8)	52 (42.3)	7 (33.3)	2 (50.0)	0 (0.0)	77 (46.4)	79 (46.5)
Abnormal for age	3 (13.6)	69 (56.1)	14 (66.7)	2 (50.0)	0 (0.0)	86 (51.8)	88 (51.8)
Unknown	1 (4.5)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	3 (1.8)
No	20 (47.6)	46 (27.2)	11 (34.4)	14 (77.8)	24 (100.0)	77 (31.7)	115 (40.4)
History of nystagmus, n (%)							
n	42	169	32	18	24	243	285
Yes	0 (0.0)	3 (1.8)	1 (3.1)	0 (0.0)	0 (0.0)	4 (1.6)	4 (1.4)
No	33 (78.6)	143 (84.6)	20 (62.5)	14 (77.8)	19 (79.2)	196 (80.7)	229 (80.4)
Unknown	9 (21.4)	23 (13.6)	11 (34.4)	4 (22.2)	5 (20.8)	43 (17.7)	52 (18.2)
History of uveitis, n (%)							
n	42	169	32	18	24	243	285
Yes	3 (7.1)	16 (9.5)	11 (34.4)	3 (16.7)	1 (4.2)	30 (12.3)	34 (11.9)
No	33 (78.6)	131 (77.5)	13 (40.6)	10 (55.6)	18 (75.0)	177 (72.8)	205 (71.9)
Unknown	6 (14.3)	22 (13.0)	8 (25.0)	5 (27.8)	5 (20.8)	36 (14.8)	46 (16.1)

Variable	Indication[1]						
	FCAS N=42	MWS N=169	NOMID N=32	Atypical CAPS N=18	Other N=24	All CAPS Patients N=243	All Registry Patients N=285
History of papillitis/ papilledema, n (%)							
n	42	169	32	18	24	243	285
Yes	0 (0.0)	14 (8.3)	18 (56.3)	1 (5.6)	0 (0.0)	32 (13.2)	33 (11.6)
No	33 (78.6)	132 (78.1)	3 (9.4)	13 (72.2)	19 (79.2)	168 (69.1)	200 (70.2)
Unknown	9 (21.4)	23 (13.6)	11 (34.4)	4 (22.2)	5 (20.8)	43 (17.7)	52 (18.2)
Ophthalmologic assessment, n (%)							
n	42	169	32	18	24	243	285
Yes	18 (42.9)	87 (51.5)	20 (62.5)	5 (27.8)	4 (16.7)	125 (51.4)	134 (47.0)
Normal for age	16 (88.9)	61 (70.1)	10 (50.0)	2 (40.0)	4 (100.0)	87 (69.6)	93 (69.4)
Abnormal for age	2 (11.1)	20 (23.0)	10 (50.0)	2 (40.0)	0 (0.0)	32 (25.6)	34 (25.4)
Unknown	0 (0.0)	6 (6.9)	0 (0.0)	1 (20.0)	0 (0.0)	6 (4.8)	7 (5.2)
No	24 (57.1)	82 (48.5)	12 (37.5)	13 (72.2)	20 (83.3)	118 (48.6)	151 (53.0)
History of chronic meningitis, n (%)							
n	42	169	32	18	24	243	285
Yes	2 (4.8)	10 (5.9)	15 (46.9)	1 (5.6)	0 (0.0)	27 (11.1)	28 (9.8)
No	37 (88.1)	143 (84.6)	11 (34.4)	12 (66.7)	22 (91.7)	191 (78.6)	225 (78.9)
Unknown	3 (7.1)	16 (9.5)	6 (18.8)	5 (27.8)	2 (8.3)	25 (10.3)	32 (11.2)
History of headaches, n (%)							
n	42	169	32	18	24	243	285
Yes	13 (31.0)	101 (59.8)	29 (90.6)	8 (44.4)	3 (12.5)	143 (58.8)	154 (54.0)
No	27 (64.3)	61 (36.1)	3 (9.4)	7 (38.9)	19 (79.2)	91 (37.4)	117 (41.1)
Unknown	2 (4.8)	7 (4.1)	0 (0.0)	3 (16.7)	2 (8.3)	9 (3.7)	14 (4.9)

Variable	Indication[1]						
	FCAS N=42	MWS N=169	NOMID N=32	Atypical CAPS N=18	Other N=24	All CAPS Patients N=243	All Registry Patients N=285
If yes, frequency of headaches, n (%)							
n	13	101	29	8	3	143	154
Daily	3 (23.1)	27 (26.7)	19 (65.5)	4 (50.0)	1 (33.3)	49 (34.3)	54 (35.1)
Weekly	0 (0.0)	33 (32.7)	2 (6.9)	2 (25.0)	0 (0.0)	35 (24.5)	37 (24.0)
Unknown	10 (76.9)	41 (40.6)	8 (27.6)	2 (25.0)	2 (66.7)	59 (41.3)	63 (40.9)
If yes, headaches related to meningitis, n (%)							
n	13	101	29	8	3	143	154
Yes	1 (7.7)	8 (7.9)	13 (44.8)	1 (12.5)	0 (0.0)	22 (15.4)	23 (14.9)
No	8 (61.5)	68 (67.3)	7 (24.1)	2 (25.0)	3 (100.0)	83 (58.0)	88 (57.1)
Unknown	4 (30.8)	25 (24.8)	9 (31.0)	5 (62.5)	0 (0.0)	38 (26.6)	43 (27.9)
History of vertigo, n (%)							
n	42	169	32	18	24	243	285
Yes	0 (0.0)	6 (3.6)	3 (9.4)	2 (11.1)	1 (4.2)	9 (3.7)	12 (4.2)
No	40 (95.2)	152 (89.9)	23 (71.9)	12 (66.7)	21 (87.5)	215 (88.5)	248 (87.0)
Unknown	2 (4.8)	11 (6.5)	6 (18.8)	4 (22.2)	2 (8.3)	19 (7.8)	25 (8.8)
Brain MRI assessment, n (%)							
n	42	169	32	18	24	243	285
Yes	15 (35.7)	45 (26.6)	17 (53.1)	2 (11.1)	0 (0.0)	77 (31.7)	79 (27.7)
Normal for age	12 (80.0)	37 (82.2)	10 (58.8)	2 (100.0)	0 (0.0)	59 (76.6)	61 (77.2)
Abnormal for age	3 (20.0)	6 (13.3)	6 (35.3)	0 (0.0)	0 (0.0)	15 (19.5)	15 (19.0)
Unknown	0 (0.0)	2 (4.4)	1 (5.9)	0 (0.0)	0 (0.0)	3 (3.9)	3 (3.8)
No	27 (64.3)	124 (73.4)	15 (46.9)	16 (88.9)	24 (100.0)	166 (68.3)	206 (72.3)

Variable	Indication[1]						
	FCAS N=42	MWS N=169	NOMID N=32	Atypical CAPS N=18	Other N=24	All CAPS Patients N=243	All Registry Patients N=285
History of anemia, n (%)							
n	42	169	32	18	24	243	285
Yes	5 (11.9)	20 (11.8)	17 (53.1)	3 (16.7)	6 (25.0)	42 (17.3)	51 (17.9)
No	31 (73.8)	135 (79.9)	9 (28.1)	12 (66.7)	18 (75.0)	175 (72.0)	205 (71.9)
Unknown	6 (14.3)	14 (8.3)	6 (18.8)	3 (16.7)	0 (0.0)	26 (10.7)	29 (10.2)
History of neutropenia, n (%)							
n	42	169	32	18	24	243	285
Yes	1 (2.4)	2 (1.2)	1 (3.1)	0 (0.0)	0 (0.0)	4 (1.6)	4 (1.4)
No	33 (78.6)	153 (90.5)	26 (81.3)	16 (88.9)	24 (100.0)	212 (87.2)	252 (88.4)
Unknown	8 (19.0)	14 (8.3)	5 (15.6)	2 (11.1)	0 (0.0)	27 (11.1)	29 (10.2)
History of hyperlipidemia, n (%)							
n	42	169	32	18	24	243	285
Yes	0 (0.0)	13 (7.7)	0 (0.0)	2 (11.1)	1 (4.2)	13 (5.3)	16 (5.6)
No	30 (71.4)	129 (76.3)	26 (81.3)	13 (72.2)	16 (66.7)	185 (76.1)	214 (75.1)
Unknown	12 (28.6)	27 (16.0)	6 (18.8)	3 (16.7)	7 (29.2)	45 (18.5)	55 (19.3)

[1] MWS indication includes diagnoses of MWS and FCAS/MWS, NOMID indication includes diagnoses of NOMID and MWS/NOMID, Other indication includes non-CAPS diagnoses.

In regard to the clinical evaluation results by CAPS indication, 13.6% of FCAS patients reported an abnormal audiogram assessment with MWS and NOMID reporting 56.1% and 66.7%, respectively. Ophthalmologic assessment results at baseline varied across CAPS indications with 11.1% of FCAS patients, 23.0% of MWS patients, and 50.0% of NOMID patients reporting abnormal results. Variation by indication was also seen in the brain MRI results where 20.0% of FCAS patients, 13.3% of MWS patients, and 35.3% of NOMID patients reported abnormal results at baseline.

The majority of patients (58.8%) presented with headaches at baseline, with headache in 22 (15.4%) patients related to meningitis. Twenty-seven (11.1%) patients from the all CAPS population presented with chronic meningitis at baseline.

The majority of atypical CAPS and "Other" indication patients did not report results for the audiogram assessment, ophthalmologic assessment, or brain MRI assessment at baseline.

Table 10-4 Baseline CAPS-related laboratory testing

Variable	Indication[1]						
	FCAS N=42	MWS N=169	NOMID N=32	Atypical CAPS N=18	Other N=24	All CAPS Patients N=243	All Registry Patients N=285
Most recent C-reactive protein (CRP) (mg/L)							
n	30	152	30	12	21	212	245
Mean	7.0	9.1	18.1	7.4	36.8	10.1	12.3
SD	9.80	14.30	32.18	12.29	58.29	17.70	24.76
Median	1.5	4.2	5.4	4.6	7.0	4.0	4.9
Range	0.2, 40.0	0.0, 81.0	0.1, 149.0	0.0, 45.0	0.1, 219.0	0.0, 149.0	0.0, 219.0
Q1-Q3	1.0 - 8.0	1.0 - 9.0	2.0 - 13.0	1.0 - 6.5	3.0 - 64.0	1.0 - 9.4	1.0 - 10.0
Not Tested	12 (28.6)	17 (10.1)	2 (6.3)	6 (33.3)	3 (12.5)	31 (12.8)	40 (14.0)
Most recent serum amyloid A (SAA) (mg/L)							
n	19	127	23	9	7	169	185
Mean	22.1	32.5	50.2	13.9	11.1	33.7	31.9
SD	38.56	67.32	73.99	19.76	17.61	65.79	63.36
Median	3.0	7.0	12.0	5.0	5.0	6.0	6.0
Range	1.0, 150.0	1.0, 500.0	1.0, 264.0	3.0, 59.0	2.0, 51.0	1.0, 500.0	1.0, 500.0
Q1-Q3	2.0 - 37.0	3.0 - 22.0	5.0 - 77.0	3.0 - 7.0	5.0 - 5.0	3.0 - 34.0	3.0 - 23.0
Not Tested	23 (54.8)	42 (24.9)	9 (28.1)	9 (50.0)	17 (70.8)	74 (30.5)	100 (35.1)
Most recent erythrocyte sedimentation rate (ESR) (mm/hr)							
n	10	93	19	5	14	122	141
Mean	13.9	15.7	12.7	6.6	22.9	15.1	15.6
SD	13.03	14.67	11.10	3.05	23.34	13.99	15.12
Median	8.0	9.0	7.0	8.0	12.5	9.0	9.0
Range	2.0, 40.0	1.0, 79.0	1.0, 42.0	2.0, 9.0	4.0, 81.0	1.0, 79.0	1.0, 81.0
Q1-Q3	5.0 - 24.0	6.0 - 22.0	5.0 - 17.0	5.0 - 9.0	6.0 - 38.0	5.0 - 22.0	5.0 - 21.0
Not Tested	32 (76.2)	76 (45.0)	13 (40.6)	13 (72.2)	10 (41.7)	121 (49.8)	144 (50.5)

Variable	Indication[1]						
	FCAS N=42	MWS N=169	NOMID N=32	Atypical CAPS N=18	Other N=24	All CAPS Patients N=243	All Registry Patients N=285
Cerebrospinal fluid analysis, n (%)							
n	42	169	32	18	24	243	285
Normal	0 (0.0)	3 (1.8)	3 (9.4)	0 (0.0)	0 (0.0)	6 (2.5)	6 (2.1)
Abnormal	0 (0.0)	7 (4.1)	11 (34.4)	1 (5.6)	0 (0.0)	18 (7.4)	19 (6.7)
Unknown	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Not Tested	35 (83.3)	105 (62.1)	13 (40.6)	14 (77.8)	21 (87.5)	153 (63.0)	188 (66.0)
Missing	7 (16.7)	53 (31.4)	5 (15.6)	3 (16.7)	3 (12.5)	65 (26.7)	71 (24.9)
If abnormal, increased intracranial pressure, n (%)							
n	0	7	11	1	0	18	19
Yes	0 (0.0)	4 (57.1)	7 (63.6)	1 (100.0)	0 (0.0)	11 (61.1)	12 (63.2)
No	0 (0.0)	1 (14.3)	1 (9.1)	0 (0.0)	0 (0.0)	2 (11.1)	2 (10.5)
Unknown	0 (0.0)	2 (28.6)	3 (27.3)	0 (0.0)	0 (0.0)	5 (27.8)	5 (26.3)
Pleocytosis, n (%)							
n	0	7	11	1	0	18	19
Yes	0 (0.0)	5 (71.4)	7 (63.6)	1 (100.0)	0 (0.0)	12 (66.7)	13 (68.4)
No	0 (0.0)	2 (28.6)	1 (9.1)	0 (0.0)	0 (0.0)	3 (16.7)	3 (15.8)
Unknown	0 (0.0)	0 (0.0)	3 (27.3)	0 (0.0)	0 (0.0)	3 (16.7)	3 (15.8)
Elevated protein, n (%)							
n	0	7	11	1	0	18	19
Yes	0 (0.0)	3 (42.9)	5 (45.5)	0 (0.0)	0 (0.0)	8 (44.4)	8 (42.1)
No	0 (0.0)	3 (42.9)	4 (36.4)	0 (0.0)	0 (0.0)	7 (38.9)	7 (36.8)
Unknown	0 (0.0)	1 (14.3)	2 (18.2)	1 (100.0)	0 (0.0)	3 (16.7)	4 (21.1)

Source: Table 14.2-3.4

[1]MWS indication includes diagnoses of MWS and FCAS/MWS, NOMID indication includes diagnoses of NOMID and MWS/NOMID, Other indication includes non-CAPS diagnoses.

Laboratory test results related to disease activity such as CRP, serum amyloid A (SAA), erythrocyte sedimentation rate (ESR), and cerebrospinal fluid analysis were reported at baseline with the following results of interest based on number of patients reporting results and abnormal values in Table 10-4. CRP results at baseline were available for 86% of registry patients. Among CAPS patients, the mean CRP level was 10.1 mg/L (SD 17.70). Higher levels of CRP were found in NOMID patients with a mean CRP value of 18.1 mg/L (SD 32.18) and "Other" indications (mean CRP of 36.8 mg/L, SD 58.29). FCAS, MWS, and atypical CAPS patients reported an average CRP value <10 mg/L.

Of the 65% (185/285) of registry patients with SAA results at baseline, the highest mean SAA levels were in NOMID patients (50.2 mg/L) followed by MWS patients (32.5 mg/L), and FCAS patients (22.1 mg/L). Atypical CAPS patients and "Other" indication patients reported values of 13.9 mg/L and 11.1 mg/L, respectively.

Only 25 (8.8%) of the 285 registry patients reported cerebrospinal fluid analysis results at baseline, with 19 out of 25 patients (76.0%) reporting abnormal results. Of the patients reporting abnormal results, 42.1% had elevated protein levels.

Previous treatments and Ilaris dosing information at baseline

Table 10-5 summarizes medications for autoinflammatory disease before the start of Ilaris for all registry patients. There were 138 patients (48.4%) who reported receiving at least one autoinflammatory disease medication before starting Ilaris. A total of 58.9% (n=168/285) of registry patients were rollover patients, defined as those previously exposed to Ilaris in a clinical trial and/or received IL-1 inhibitor medication, excluding Ilaris, prior to the start of Ilaris in the study. Specifically, 57 patients were only previously exposed to Ilaris in a clinical trial, 64 patients only received IL-1 inhibitor medication, excluding Ilaris, prior to the start of Ilaris in the study, and 47 patients were exposed to both Ilaris in a clinical trial and IL-1 inhibitor medication prior to the start of Ilaris in the study.

Table 10-5 Medications for autoinflammatory disease prior to and ended before the start of Ilaris

Medication Category[2]	Indication[1]						
	FCAS N=42	MWS N=169	NOMID N=32	Atypical CAPS N=18	Other N=24	All CAPS Patients N=243	All Registry Patients N=285
Number of patients reporting at least one auto-inflammatory disease medication (excluding Ilaris)	17	76	19	7	19	112	138
Biologics, n (%)							
Anti-TNF	0	6 (7.9)	5 (26.3)	1 (14.3)	8 (42.1)	12 (10.7)	20 (14.5)
IL-1 inhibitor	15 (88.2)	60 (78.9)	18 (94.7)	7 (100.0)	11 (57.9)	100 (89.3)	111 (80.4)
IL-6 inhibitor	0	1 (1.3)	0	0	1 (5.3)	1 (0.9)	2 (1.4)
Other medications, n (%)							
Corticosteroids	7 (41.2)	40 (52.6)	15 (78.9)	5 (71.4)	14 (73.7)	67 (59.8)	81 (58.7)
Cytotoxic agents	1 (5.9)	15 (19.7)	8 (42.1)	1 (14.3)	13 (68.4)	25 (22.3)	38 (27.5)
NSAIDs	10 (58.8)	48 (63.2)	9 (47.4)	4 (57.1)	10 (52.6)	71 (63.4)	81 (58.7)
Other inflammatory inhibitors	3 (17.6)	9 (11.8)	1 (5.3)	2 (28.6)	10 (52.6)	15 (13.4)	25 (18.1)
Number of patients previously exposed to Ilaris in a clinical trial and/or received IL-1 inhibitor medication prior to/ended before the start of Ilaris in study (rollover patients)	28	102	20	7	11	150	168

Source: Table 14.2-3.4

[1] MWS indication includes diagnoses of MWS and FCAS/MWS, NOMID indication includes diagnoses of NOMID and MWS/NOMID, Other indication includes non-CAPS diagnoses.

[2]Subjects can report more than 1 type of medication. Biologics = any patient who reported an anti-TNF, IL-1 inhibitor, and/or an IL-6 inhibitor (excluding Ilaris). Other medications = any patient who reported a corticosteroid, cytotoxic agent, NSAID and/or other inflammatory inhibitor.

Table 10-6 reviews Ilaris treatment at baseline for all registry patients and by age groups of <18 years old and ≥18 years old. As this study started enrolling patients after Ilaris was approved, exposure and dosing characteristics include all registry patients, not just those defined as rollover. There were 91.6% of registry patients with date of first dose of Ilaris available at baseline with a mean duration since first dose of 41.3 weeks mainly due to the fact that 104 patients were previously exposed to Ilaris in a clinical trial. Only 8.4% of registry patients either did not have a first date of Ilaris available (n=10) or had a date of first dose of Ilaris after baseline (n=14) and were not included in this calculation. The mean exposure duration since first dose at baseline was slightly higher in registry patients <18 years old (47.5 weeks) compared to ≥18 years old (37.6 weeks).

Table 10-6 Summary statistics of Ilaris treatment at baseline

Treatment Exposure	Statistics	All CAPS Patients		All Registry Patients		
		Age: <18 Years	Age: ≥18 Years	Age: <18 Years	Age: ≥18 Years	All Patients
Duration of exposure to Ilaris (weeks)	n (# patients)[1]	77	146	98	163	261
	Mean	48.1	38.6	47.5	37.6	41.3
	SD	52.75	30.36	50.80	31.37	39.98
	Median	43.1	38.9	41.6	37.7	38.3
	Range	0.1-247.6	0.0-157.3	0.1-247.6	0.0-157.3	0.0-247.6
	Q1 - Q3	2.1-60.1	8.1-59.3	3.0-61.1	8.1-58.4	7.7-59.4
	At baseline n (%)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)	1 (0.4)
	<4 weeks	21 (27.3)	21 (14.4)	25 (25.5)	28 (17.2)	53 (20.3)
	4 to <12 weeks	5 (6.5)	20 (13.7)	6 (6.1)	20 (12.3)	26 (10.0)
	12 to <24 weeks	3 (3.9)	10 (6.8)	3 (3.1)	14 (8.6)	17 (6.5)
	24 to <36 weeks	6 (7.8)	17 (11.6)	11 (11.2)	18 (11.0)	29 (11.1)
	36 to <48 weeks	8 (10.4)	21 (14.4)	13 (13.3)	21 (12.9)	34 (13.0)
	48 to <60 weeks	14 (18.2)	21 (14.4)	14 (14.3)	23 (14.1)	37 (14.2)
	60 to <72 weeks	6 (7.8)	20 (13.7)	8 (8.2)	20 (12.3)	28 (10.7)
	72 to <84 weeks	4 (5.2)	7 (4.8)	5 (5.1)	9 (5.5)	14 (5.4)
	84 to <96 weeks	1 (1.3)	3 (2.1)	2 (2.0)	3 (1.8)	5 (1.9)
	96 to <144 weeks	3 (3.9)	4 (2.7)	4 (4.1)	5 (3.1)	9 (3.4)
	≥144 weeks	6 (7.8)	1 (0.7)	7 (7.1)	1 (0.6)	8 (3.1)
Total dose per patient at baseline (mg/kg)	n (# patients)[2]	75	138	96	153	249
	0 to < 1 mg/kg	3 (4.0)	9 (6.5)	3 (3.1)	9 (5.9)	12 (4.7)
	1 to <2 mg/kg	13 (17.3)	38 (27.5)	16 (16.7)	44 (28.8)	60 (24.1)
	2 to <3 mg/kg	29 (38.7)	64 (46.4)	36 (37.5)	73 (47.7)	109 (43.8)
	3 to <4 mg/kg	20 (26.7)	21 (15.2)	30 (31.3)	21 (13.7)	51 (20.5)
	4 to <5 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	5 to <6 mg/kg	3 (4.0)	3 (2.2)	4 (4.2)	3 (2.0)	7 (2.8)
	6 to <7 mg/kg	3 (4.0)	2 (1.4)	3 (3.1)	2 (1.3)	5 (2.0)
	7 to <8 mg/kg	1 (1.3)	1 (0.7)	1 (1.0)	1 (0.7)	2 (0.8)

Treatment Exposure	Statistics	All CAPS Patients		All Registry Patients		
		Age: <18 Years	Age: ≥18 Years	Age: <18 Years	Age: ≥18 Years	All Patients
	8 to <9 mg/kg	2 (2.7)	0 (0.0)	2 (2.1)	0 (0.0)	2 (0.8)
	9 to <10 mg/kg	1 (1.3)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.4)
Average time elapsed between dose dates per patient at baseline (weeks) n (%)	n (# patients)[3]	79	149	100	166	266
	Only one dose date available	25 (31.6)	37 (24.8)	30 (30.0)	44 (26.5)	74 (27.8)
	2 weeks	1 (1.3)	2 (1.3)	1 (1.0)	2 (1.2)	3 (1.1)
	3 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4 weeks	4 (5.1)	1 (0.7)	11 (11.0)	2 (1.2)	13 (4.9)
	5 weeks	1 (1.3)	2 (1.3)	2 (2.0)	3 (1.8)	5 (1.9)
	6 weeks	2 (2.5)	7 (4.7)	2 (2.0)	7 (4.2)	9 (3.4)
	7 weeks	11 (13.9)	15 (10.1)	13 (13.0)	17 (10.2)	30 (11.3)
	8 weeks	21 (26.6)	52 (34.9)	23 (23.0)	54 (32.5)	77 (28.9)
	9 weeks	7 (8.9)	8 (5.4)	8 (8.0)	8 (4.8)	16 (6.0)
	10 weeks	1 (1.3)	6 (4.0)	3 (3.0)	7 (4.2)	10 (3.8)
	>10 weeks	6 (7.6)	19 (12.8)	7 (7.0)	22 (13.3)	29 (10.9)

Source: Table 14.1-5.1f; Table 14.1-5.1g.
[1] n = number of patients with date of first dose of Ilaris; mean = average weeks since first dose of Ilaris.
[2] n = number of patients with date of baseline dose of Ilaris and weight available at baseline.
[3] n = number of patients with dosing history at baseline.

The total dose administered per patient at baseline was recorded for 249 registry patients, ranging between 0 to <10 mg/kg, with 93.2% receiving <4 mg/kg. In general, registry patients <18 years old received a higher dose per patient at baseline compared to patients ≥18 years old.

The average time that elapsed between dose dates at baseline was calculated for 192 registry patients who had at least 2 dose dates available prior to baseline. The most common interval between dose dates was 8 weeks (40.1%). A total of 15.1% of registry patients <18 years old received Ilaris every 4 weeks prior to baseline compared to 1.6% of registry patients.

Similar trends were seen in all CAPS patients and between both age groups within CAPS patients for duration since first dose of Ilaris, total dose at baseline, and average time elapsed between dose dates.

Baseline developmental status – patients 6-18 years

Table 10-7 summarizes baseline developmental status for registry patients 6-18 years only. Overall, 4.8% of registry patients age 6-<18 years old reported a delay in sexual development; 16.9% reported not being in the appropriate age-related grade level, and 7.2% had a delay in cognitive function at baseline.

Table 10-7 Baseline developmental status - patients 6-18 years only

Variable	Indication[1]						
	FCAS N=8	MWS N=44	NOMID N=14	Atypical CAPS N=5	Other N=12	All CAPS Patients N=66	All Registry Patients N=83
Delay in sexual development, n (%)							
n	8	44	14	5	12	66	83
Yes	0 (0.0)	1 (2.3)	1 (7.1)	0 (0.0)	2 (16.7)	2 (3.0)	4 (4.8)
No	6 (75.0)	33 (75.0)	7 (50.0)	1 (20.0)	9 (75.0)	46 (69.7)	56 (67.5)
Unknown	2 (25.0)	10 (22.7)	6 (42.9)	4 (80.0)	1 (8.3)	18 (27.3)	23 (27.7)
Menarche status[2], n (%)							
n	7	18	7	2	8	32	42
Yes	5 (71.4)	5 (27.8)	4 (57.1)	0 (0.0)	3 (37.5)	14 (43.8)	17 (40.5)
No	2 (28.6)	10 (55.6)	2 (28.6)	1 (50.0)	3 (37.5)	14 (43.8)	18 (42.9)
Missing	0 (0.0)	3 (16.7)	1 (14.3)	1 (50.0)	2 (25.0)	4 (12.5)	7 (16.7)
Appropriate age-related grade level, n (%)							
n	8	44	14	5	12	66	83
Yes	6 (75.0)	30 (68.2)	8 (57.1)	3 (60.0)	12 (100.0)	44 (66.7)	59 (71.1)
No	0 (0.0)	10 (22.7)	4 (28.6)	0 (0.0)	0 (0.0)	14 (21.2)	14 (16.9)
Unknown	2 (25.0)	4 (9.1)	2 (14.3)	2 (40.0)	0 (0.0)	8 (12.1)	10 (12.0)
Delay in cognitive function, n (%)							
n	8	44	14	5	12	66	83
Yes	0 (0.0)	1 (2.3)	5 (35.7)	0 (0.0)	0 (0.0)	6 (9.1)	6 (7.2)
No	7 (87.5)	40 (90.9)	6 (42.9)	3 (60.0)	12 (100.0)	53 (80.3)	68 (81.9)
Unknown	1 (12.5)	3 (6.8)	3 (21.4)	2 (40.0)	0 (0.0)	7 (10.6)	9 (10.8)

Source: Table 14.1-4.1

[1]MWS indication includes diagnoses of MWS and FCAS/MWS, NOMID indication includes diagnoses of NOMID and MWS/NOMID, Other indication includes non-CAPS diagnoses.

[2]Menarche status only includes female patients.

When comparing developmental status by CAPS indication, only 2 patients (n=1 MWS, n=1 NOMID) reported a delay in sexual development and only MWS and NOMID patients reported not being in the appropriate age-related grade level (22.7% and 28.6%, respectively). Of note, 5 of the 6 patients who reported a delay in cognitive function at baseline were in the NOMID population (35.7%).

A total of 40.5% of female registry patients between 6-<18 years old had gone through menarche by baseline. There was variation across CAPS indications with the highest proportion FCAS population (n=5, 71.4%).

10.3 Outcome data

Total exposure to Ilaris during study

Table 10-8 summarizes duration of exposure to Ilaris during the study in years, stratified by age and indication. The mean duration of exposure to Ilaris in this study was 3.6 years (SD 1.6 years) for patients with available data.

Table 10-8 Duration of Ilaris exposure in years during study

Indication	Statistics	Infant <4 (n=9)	Child 4-<6 (n=15)	Child 6-<12 (n=38)	Adolescent 12-<18 (n=45)	Adult 18-<65 (n=164)	Elderly >=65 (n=14)
FCAS	n (nmiss)	1 (0)	2 (0)	5 (0)	2 (1)	25 (2)	4 (0)
(n=42)	Mean (SD)	1.2 (n.a.)	2.8 (2.2)	3.5 (1.3)	4.1 (0.1)	3.9 (1.1)	3.5 (1.1)
	Median	1.2	2.8	4.0	4.1	4.0	3.7
	Q1-Q3	1.2-1.2	1.3-4.4	3.9-4.0	4.0-4.1	3.9-4.5	2.8-4.2
MWS	n (nmiss)	6 (0)	6 (0)	18 (1)	25 (0)	100 (5)	8 (0)
(n=169)	Mean (SD)	3.4 (2.0)	3.1 (1.4)	2.8 (1.8)	4.2 (1.3)	4.2 (1.3)	2.7 (1.9)
	Median	2.6	3.3	2.4	4.5	4.6	2.0
	Q1-Q3	1.9-5.9	1.9-4.4	1.2-4.5	4.2-5.2	3.7-5.1	1.2-4.7
NOMID	n (nmiss)	0	4 (0)	7 (0)	7 (0)	14 (0)	0
(n=32)	Mean (SD)	n.a.	4.0 (2.0)	2.6 (1.8)	3.4 (1.8)	3.7 (1.5)	n.a.
	Median	n.a.	4.4	2.9	4.1	4.2	n.a.
	Q1-Q3	n.a.	2.5-5.5	0.8-4.2	2.4-4.3	2.8-4.6	n.a.
Atypical CAPS	n (nmiss)	1 (0)	1 (0)	3 (0)	2 (0)	9 (0)	2 (0)
(n=18)	Mean (SD)	5.7 (n.a.)	5.8 (n.a.)	1.1 (0.2)	2.9 (2.4)	2.5 (1.9)	1.4 (1.7)
	Median	5.7	5.8	1.2	2.9	2.7	1.4
	Q1-Q3	5.7-5.7	5.8-5.8	0.9-1.2	1.2-4.6	1.0-4.0	0.2-2.6
Other	n (nmiss)	1 (0)	2 (0)	4 (0)	8 (0)	9 (0)	0
(n=24)	Mean (SD)	4.1 (n.a.)	2.4 (0.2)	3.6 (2.0)	2.8 (1.7)	3.1 (2.4)	n.a.
	Median	4.1	2.4	4.4	2.9	4.2	n.a.
	Q1-Q3	4.1-4.1	2.3-2.6	2.4-4.8	1.6-4.4	0.6-5.1	n.a.
All CAPS Patients	n (nmiss)	7 (0)	12 (0)	30 (1)	34 (1)	139 (7)	12 (0)
(n=243)	Mean (SD)	3.1 (2.0)	3.4 (1.7)	2.9 (1.7)	4.0 (1.4)	4.1 (1.3)	2.9 (1.7)
	Median	2.4	3.9	3.4	4.3	4.5	3.1
	Q1-Q3	1.6-5.9	1.6-4.5	1.2-4.4	3.6-4.9	3.6-4.8	1.3-4.6
All Registry Patients	n (nmiss)	9 (0)	15 (0)	37 (1)	44 (1)	157 (7)	14 (0)
(n=285)	Mean (SD)	3.5 (1.9)	3.4 (1.6)	2.8 (1.7)	3.8 (1.5)	3.9 (1.5)	2.7 (1.7)
	Median	2.8	3.6	2.9	4.3	4.5	2.6
	Q1-Q3	1.9-5.7	1.9-4.5	1.2-4.4	2.8-4.7	3.0-4.8	1.2-4.5

Source: Table 14.2-3.7
nmiss = number of patients with unknown duration of Ilaris exposure.
SD = standard deviation.

There was some variation with regards to the mean duration of exposure to Ilaris between age groups with children and adolescents between 6 and 12 years of age and the elderly falling short by approximately 1 year in exposure (mean exposure 2.8 years and 2.7 years, respectively) as compared to adults between 18 and 65 years old (mean exposure 3.9 years). Similar trends were seen in CAPS patients. The likely explanation for the difference is due to the fact that children were not enrolled until implementation of Amendment 2.

10.4 Main result

10.4.1 Primary Objective

The overall safety of Ilaris in patients with CAPS focused on specific events including serious infections, malignancies, hypersensitivity reactions, and vertigo, as described in this section.

Other selected events, analyzed according to the most recent RMP v9.0, included neutropenia opportunistic infections, immunogenicity/allergenicity, effect on growth, autoimmunity reactions, DILI, disorders of lipoprotein metabolism, canakinumab – immunosuppressants combination therapy toxicity, interactions with vaccines, pregnancy and lactation, and long term effect on kidney function. This analysis is described in Section 10.5.

Among all registry patients, there were a total of 1114 AEs reported in 223 patients with an incidence rate of 110.71 per 100 person-years (95% CI 104.30-116.49). There were a total of 155 SAEs reported in 83 registry patients with an incidence rate of 15.40 per 100 person-years (95%, CI13.07-17.67). For the 243 CAPS patients specifically, a total of 187 patients reported 914 AEs, with an incidence rate of 103.16 per 100 person-years (95% CI 96.58-110.07) and a total of 68 patients reported 128 SAEs, with an incidence rate of 14.45 (95% CI 12.05-17.18) SAEs per 100-person-years. Further details regarding AEs and SAEs by CAPS indication and by age groups for all registry patients can be found in Section 10.6.

Table 10-9 summarizes serious infections for all CAPS patients and by indication. There were a total of 43 serious infections reported by 32 CAPS patients with an incidence rate of 4.85 per 100 person-years (95% CI 3.51-6.54). Of the 43 serious infections, the most common events included pneumonia (n=5 events), urinary tract infection (n=4 events), bronchitis (n=3 events), tonsillitis (n=3 events), and 2 events each of abscess, cellulitis, lower respiratory tract infection, meningitis, and perirectal abscess.

NOMID patients had a slightly higher incidence rate of 6.38 serious infections per 100 person-years (95% CI 2.57-13.15) compared to MWS patients who had an incidence rate of 5.53 per 100 patients-years (95% CI 3.85-7.69). On the contrary, only 1 FCAS patient only reported a serious infection (tonsillitis). These trends are similar to the total number of SAEs reported for each indication.

Table 10-9 Serious infections regardless of study drug relationship for CAPS patients

Primary System Organ Class/ Preferred Term	Indication[1]															
	FCAS N = 42				MWS N = 169				NOMID N = 32				CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Any SAE	**3 (7.1)**	**4**	**2.79**	**(0.76, 7.15)**	**56 (33.1)**	**100**	**15.80**	**(12.85, 19.21)**	**9 (28.1)**	**24**	**21.88**	**(14.02, 32.55)**	**68 (28.0)**	**128**	**14.45**	**(12.05, 17.18)**
Infections and Infestations	**1 (2.4)**	**1**	**0.70**	**(0.02, 3.89)**	**26 (15.4)**	**35**	**5.53**	**(3.85, 7.69)**	**5 (15.6)**	**7**	**6.38**	**(2.57, 13.15)**	**32 (13.2)**	**43**	**4.85**	**(3.51, 6.54)**
Abscess	0 (0.0)	0	0.00	(0.00, 0.00)	2 (1.2)	2	0.32	(0.04, 1.14)	0 (0.0)	0	0.00	(0.00, 0.00)	2 (0.8)	2	0.23	(0.03, 0.82)
Bronchitis	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	3	0.47	(0.10, 1.39)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	3	0.34	(0.07, 0.99)
Cellulitis	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.16	(0.00, 0.88)	1 (3.1)	1	0.91	(0.02, 5.08)	2 (0.8)	2	0.23	(0.03, 0.82)
Lower respiratory tract infection	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.16	(0.00, 0.88)	1 (3.1)	1	0.91	(0.02, 5.08)	2 (0.8)	2	0.23	(0.03, 0.82)
Meningitis	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (3.1)	2	1.82	(0.22, 6.59)	1 (0.4)	2	0.23	(0.03, 0.82)
Perirectal abscess	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	2	0.32	(0.04, 1.14)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	2	0.23	(0.03, 0.82)
Pneumonia	0 (0.0)	0	0.00	(0.00, 0.00)	4 (2.4)	5	0.79	(0.26, 1.84)	0 (0.0)	0	0.00	(0.00, 0.00)	4 (1.6)	5	0.56	(0.18, 1.32)
Tonsillitis	1 (2.4)	1	0.70	(0.02, 3.89)	2 (1.2)	2	0.32	(0.04, 1.14)	0 (0.0)	0	0.00	(0.00, 0.00)	3 (1.2)	3	0.34	(0.07, 0.99)
Urinary tract infection	0 (0.0)	0	0.00	(0.00, 0.00)	3 (1.8)	3	0.47	(0.10, 1.39)	1 (3.1)	1	0.91	(0.02, 5.08)	4 (1.6)	4	0.45	(0.12, 1.16)

Source: Table 14.3.1-1.2a, Table 14.3.1-1.2b, Table 14.3.1-1.4a, Table 14.3.1-1.4b

IR: incidence rate per 100-person-years; CI: confidence interval.

[1]MWS indication includes diagnoses of MWS and FCAS/MWS, NOMID indication includes diagnoses of NOMID and MWS/NOMID.

Table 10-10 shows serious infections by age group for all registry patients. There were a total of 52 serious infections reported by 38 registry patients (IR 5.17, 95% 3.86-6.55). The types of serious infections among all registry patients was similar to that of all CAPS patients with 1 more patient reporting pneumonia and 1 more patient reporting tonsillitis.

Differences were seen among age groups with the highest incidence rate of serious infections in <12 years old (IR: 8.07, 95% CI 4.52-13.31) followed by 12 to <18 years old and ≥18 years old.

Table 10-10 Serious infections regardless of study drug relationship by age group for all registry patients

Primary System Organ Class/ Preferred Term	Age Group															
	Age: <12 years N = 62				Age: 12 to <18 years N = 45				Patients ≥18 years N = 178				All Registry Patients N = 285			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Any SAE	**16 (25.8)**	**26**	**13.99**	**(9.14, 20.50)**	**15 (33.3)**	**28**	**16.87**	**(11.21, 24.38)**	**52 (29.2)**	**101**	**15.43**	**(12.57, 18.75)**	**83 (29.1)**	**155**	**15.40**	**(13.07, 17.67)**
Infections and Infestations	**13 (21.0)**	**15**	**8.07**	**(4.52, 13.31)**	**8 (17.8)**	**11**	**6.63**	**(3.31, 11.86)**	**17 (9.6)**	**26**	**3.97**	**(2.60, 5.82)**	**38 (13.3)**	**52**	**5.17**	**(3.86, 6.55)**
Abscess	1 (1.6)	1	0.54	(0.01, 3.00)	0 (0.0)	0	0.00	0	1 (0.6)	1	0.15	(0.00, 0.85)	2 (0.7)	2	0.20	(0.02, 0.64)
Bronchitis	0 (0.0)	0	0.00	0	0 (0.0)	0	0.00	0	1 (0.6)	3	0.46	(0.09, 1.34)	1 (0.4)	3	0.30	(0.06, 0.79)
Cellulitis	0 (0.0)	0	0.00	0	0 (0.0)	0	0.00	0	2 (1.1)	2	0.31	(0.04, 1.10)	2 (0.7)	2	0.20	(0.02, 0.64)
Lower respiratory tract infection	1 (1.6)	1	0.54	(0.01, 3.00)	0 (0.0)	0	0.00	0	1 (0.6)	1	0.15	(0.00, 0.85)	2 (0.7)	2	0.20	(0.02, 0.64)
Meningitis	0 (0.0)	0	0.00	0	1 (2.2)	2	1.20	(0.15, 4.35)	0 (0.0)	0	0.00	0	1 (0.4)	2	0.20	(0.02, 0.64)
Perirectal abscess	0 (0.0)	0	0.00	0	0 (0.0)	0	0.00	0	1 (0.6)	2	0.31	(0.04, 1.10)	1 (0.4)	2	0.20	(0.02, 0.64)
Pneumonia	2 (3.2)	3	1.61	(0.33, 4.72)	0 (0.0)	0	0.00	0	3 (1.7)	4	0.61	(0.17, 1.57)	5 (1.8)	7	0.70	(0.28, 1.33)
Tonsillitis	0 (0.0)	0	0.00	0	2 (4.4)	2	1.20	(0.15, 4.35)	2 (1.1)	2	0.31	(0.04, 1.10)	4 (1.4)	4	0.40	(0.11, 0.93)
Urinary tract infection	1 (1.6)	1	0.54	(0.01, 3.00)	1 (2.2)	1	0.60	(0.02, 3.36)	2 (1.1)	2	0.31	(0.04, 1.10)	4 (1.4)	4	0.40	(0.11, 0.93)

Source: Table 14.3.1-1.2b, Table 14.3.1-1.4b, Table 14.3.1-1.7b, Table 14.3.1-1.8b, Table 14.3.1-1.9b, Table 14.3.1-1.10b

IR: incidence rate per 100-person-years; CI: confidence interval.

Table 10-11 summarizes malignancies, hypersensitivity reactions, and vertigo AEs for all CAPS patients and by indication. There were 31 episodes of vertigo that occurred among 21 CAPS patients (incidence rate 3.50 per 100 person-years [95% CI 2.38-4.97]). While the majority of vertigo events among CAPS patients specifically occurred among MWS patients (n=21/31 events), NOMID patients had the highest incidence rate (8.20 per 100 person-years [95% CI 3.75-15.57]).

There were 14 events of malignant and benign neoplasms among 11 CAPS patients (4.5%), 8 events of which were considered serious by the Investigator. Malignancies were reported for 6 CAPS patients all of which were adults and/or elderly.

Three events were reported in 1 elderly patient 76 years old with end stage metastatic rectal cancer (including lungs, lymph nodes, and central nervous system) who died 6 months later after being diagnosed ([Patient 0109-0015]). The event was not suspected to be related to Ilaris by the treating Investigator ([Listing 16.2-1.1. 1]).

One event of adenocarcinoma of left axillary lymph node in a female patient 44 years old with a history of breast cancer was reported as not being related to Ilaris by the Investigator. One event of metastatic gastrointestinal adenocarcinoma in a female patient 45 years old was reported as not being related to Ilaris by the Investigator.

A prostate cancer event was reported in a 72 years old man who remained on treatment with Ilaris for about 3 year after being diagnosed with cancer. No relation to Ilaris was considered by the treating physician.

One event of neurilemmoma benign and 1 event of uterine leiomyoma reported were both considered as not related to Ilaris by the treating Investigator.

Table 10-11 Malignancies, hypersensitivity reactions, and vertigo adverse events regardless of study drug relationship for CAPS patients

Primary System Organ Class/ Preferred Term	Indication[1] FCAS N = 42 Patients n (%)	Events n	Events IR	Events 95% CI	MWS N = 169 Patients n (%)	Events n	Events IR	Events 95% CI	NOMID N = 32 Patients n (%)	Events n	Events IR	Events 95% CI	CAPS Patients N = 243 Patients n (%)	Events n	Events IR	Events 95% CI
Any AE	**26 (61.9)**	**114**	**79.54**	**(65.61, 95.55)**	**134 (79.3)**	**681**	**107.58**	**(99.65, 115.97)**	**27 (84.4)**	**119**	**108.48**	**(89.87, 129.81)**	**187 (77.0)**	**914**	**103.16**	**(96.58, 110.07)**
Ear and Labyrinth Disorders	**2 (4.8)**	**2**	**1.40**	**(0.17, 5.04)**	**23 (13.6)**	**28**	**4.42**	**(2.94, 6.39)**	**5 (15.6)**	**12**	**10.94**	**(5.65, 19.11)**	**30 (12.3)**	**42**	**4.74**	**(3.42, 6.41)**
Vertigo	1 (2.4)	1	0.70	(0.02, 3.89)	17 (10.1)	21	3.32	(2.05, 5.07)	3 (9.4)	9	8.20	(3.75, 15.57)	21 (8.6)	31	3.50	(2.38, 4.97)
Immune System Disorders	**1 (2.4)**	**1**	**0.70**	**(0.02, 3.89)**	**3 (1.8)**	**4**	**0.63**	**(0.17, 1.62)**	**1 (3.1)**	**1**	**0.91**	**(0.02, 5.08)**	**5 (2.1)**	**6**	**0.68**	**(0.25, 1.47)**
Drug hypersensitivity	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)
Hypersensitivity	0 (0.0)	0	0.00	(0.00, 0.00)	2 (1.2)	3	0.47	(0.10, 1.39)	1 (3.1)	1	0.91	(0.02, 5.08)	3 (1.2)	4	0.45	(0.12, 1.16)
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	**1 (2.4)**	**1**	**0.70**	**(0.02, 3.89)**	**10 (5.9)**	**13**	**2.05**	**(1.09, 3.51)**	**0 (0.0)**	**0**	**0.00**	**(0.00, 0.00)**	**11 (4.5)**	**14**	**1.58**	**(0.86, 2.65)**
Adenocarcinoma	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.16	(0.00, 0.88)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	1	1.58	(0.86, 2.65)
Basal cell carcinoma	1 (2.4)	1	0.70	(0.02, 3.89)	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	1	0.11	(0.00, 0.63)
Gastrointestinal neoplasm	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.16	(0.00, 0.88)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	1	0.11	(0.00, 0.63)
Lipoma	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.16	(0.00, 0.88)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	1	0.11	(0.00, 0.63)
Melanocytic naevus	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.16	(0.00, 0.88)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	1	0.11	(0.00, 0.63)
Meningioma	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.16	(0.00, 0.88)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	1	0.11	(0.00, 0.63)
Neurilemmoma benign	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.16	(0.00, 0.88)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	1	0.11	(0.00, 0.63)

Primary System Organ Class/ Preferred Term	Indication[1]															
	FCAS N = 42				MWS N = 169				NOMID N = 32				CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Neurofibroma	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.16	(0.00, 0.88)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	1	0.11	(0.00, 0.63)
Prostate cancer	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.16	(0.00, 0.88)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	1	0.11	(0.00, 0.63)
Rectal cancer	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	3	0.47	(0.10, 1.39)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	3	0.34	(0.07, 0.99)
Uterine leiomyoma	0 (0.0)	0	0.00	(0.00, 0.00)	1(0.6)	2	0.32	(0.04, 1.14)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.4)	2	0.23	(0.03, 0.82)

Source: Table 14.3.1-1.1a, Table 14.3.1-1.1b, Table 14.3.1-1.3a, Table 14.3.1-1.3b

IR: incidence rate per 100-person-years; CI: confidence interval.

[1]MWS indication includes diagnoses of MWS and FCAS/MWS, NOMID indication includes diagnoses of NOMID and MWS/NOMID.

Table 10-12 shows malignancies, hypersensitivity reactions, and vertigo by age group for all registry patients. These AEs accounted for 4.1% (46/1114) of all AEs reported by the registry patients. Within each age category (<12 years, 12 to <18 years, and ≥18 years), over 70% of the patients experienced any AE.

Vertigo had the highest incidence rate of 3.38 per 100-person-years (95% CI 2.34-4.53) across all registry patients (34 events in 24 patients) with higher incidence rate in patients ≥18 years.

Three of the 4 hypersensitivity reactions occurred in patients <12 years. There was 1 event recorded for drug hypersensitivity which was not related to Ilaris and occurred in a patient 12 to <18 years.

There were 15 events of malignant and benign neoplasms reported among 12 registry patients (4.2%). No cases were observed in patients <18 years except one case of melanocytic naevus reported in a patient aged 12 to <18 years.

One death was reported during the course of the study for an MWS patient [Patient 0109-0015]. The patient was diagnosed with end stage metastatic rectal cancer with metastasis to the lung, lymph nodes, and central nervous system. This death was not suspected to be related to the study drug [Listing 16.2-1.1. 1].

Table 10-12 Malignancies, hypersensitivity reactions, and vertigo adverse events regardless of study drug relationship by age group for all registry patients

Primary System Organ Class/ Preferred Term	Age Groups															
	Age: <12 years N = 62				Age: 12 to <18 years N = 45				Patients ≥18 years N = 178				All Registry Patients N = 285			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Any AE	**44 (71.0)**	**218**	**117.30**	**(102.24,133.94)**	**37 (82.2)**	**220**	**132.52**	**(115.58,151.23)**	**142 (79.8)**	**676**	**103.30**	**(95.66,111.39)**	**223 (78.2)**	**1114**	**110.71**	**(104.30, 116.49)**
Ear and Labyrinth Disorders	**2 (3.2)**	**3**	**1.61**	**(0.33,4.72)**	**4 (8.9)**	**4**	**2.41**	**(0.66,6.17)**	**28 (15.7)**	**39**	**5.96**	**(4.24, 8.15)**	**34 (11.9)**	**46**	**4.57**	**(3.35, 5.88)**
Vertigo	1 (1.6)	1	0.54	(0.01,3.00)	1 (2.2)	1	0.60	(0.02,3.36)	22 (12.4)	32	4.89	(3.34, 6.90)	24 (8.4)	34	3.38	(2.34, 4.53)
Immune System Disorders	**3 (4.8)**	**4**	**2.15**	**(0.59,5.51)**	**1 (2.2)**	**1**	**0.60**	**(0.02,3.36)**	**4 (2.2)**	**4**	**0.61**	**(0.17, 1.57)**	**8 (2.8)**	**9**	**0.89**	**(0.41, 1.58)**
Drug hypersensitivity	0 (0.0)	0	0.00	(0.00, 0.00)	1 (2,2)	1	0.60	(0.02,3.36)	0 (0.0)	0	0	(0.00, 0.00)	1 (0.4)	1	0.10	(0.00, 0.48)
Hypersensitivity	2 (3.2)	3	1.61	(0.33,4.72)	0 (0.0)	0	0.00	(0.00,0.00)	1 (0.6)	1	0.15	(0.00, 0.85)	3 (1.1)	4	0.40	(0.11, 0.93)
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	**0 (0.0)**	**0**	**0.00**	**(0.00,0.00)**	**1 (2.2)**	**1**	**0.60**	**(0.02,3.36)**	**11 (6.2)**	**14**	**2.14**	**(1.17, 3.59)**	**12 (4.2)**	**15**	**1.49**	**(0.83, 2.32)**
Adenocarcinoma	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.15	(0.00, 0.85)	1 (0.4)	1	0.10	(0.00, 0.48)
Basal cell carcinoma	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.15	(0.00, 0.85)	1 (0.4)	1	0.10	(0.00, 0.48)
Gastrointestinal neoplasm	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1(0.6)	1	0.15	(0.00,0.85)	1(0.4)	1	0.10	(0.00, 0.48)
Lipoma	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1(0.6)	1	0.15	(0.00,0.85)	1(0.4)	1	0.10	(0.00, 0.48)
Melanocytic naevus	0(0.0)	0	0.00	(0.00, 0.00)	1(2.2)	1	0.60	(0.02,3.36)	1(0.6)	1	0.15	(0.00,0.85)	2(0.7)	2	0.10	(0.02, 0.64)
Meningioma	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1(0.6)	1	0.15	(0.00,0.85)	1(0.4)	1	0.20	(0.00, 0.48)
Neurilemmoma	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1(0.6)	1	0.15	(0.00,0.85)	1(0.4)	1	0.10	(0.00, 0.48)

Primary System Organ Class/ Preferred Term	Age Groups															
	Age: <12 years N = 62				Age: 12 to <18 years N = 45				Patients ≥18 years N = 178				All Registry Patients N = 285			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
benign																
Neurofibroma	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1(0.6)	1	0.15	(0.00,0.85)	1(0.4)	1	0.10	(0.00, 0.48)
Prostate cancer	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	1	0.15	(0.00, 0.85)	1 (0.4)	1	0.10	(0.00, 0.48)
Rectal cancer	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1 (0.6)	3	0.46	(0.09, 1.34)	1 (0.4)	3	0.30	(0.06, 0.79)
Uterine leiomyoma	0 (0.0)	0	0.00	(0.00, 0.00)	0 (0.0)	0	0.00	(0.00, 0.00)	1(0.6)	2	0.31	(0.04,1.10)	1(0.4)	2	0.20	(0.02, 0.64)

Source: Table 14.3.1-1.1b, Table 14.3.1-1.3b, Table 14.3.1-1.7a, Table 14.3.1-1.8a, Table 14.3.1-1.9a, Table 14.3.1-1.10a

IR: incidence rate per 100-person-years; CI: confidence interval.

10.4.2 Secondary Objectives

10.4.2.1 Long-term impact of Ilaris on disease progression

The long-term impact of Ilaris on disease progression was reported through CAPS-related evaluations by utilizing the physician's overall global assessment (PGA) for each follow-up visit and local laboratory testing (CRP and SAA testing), when available.

Table 10-13 summarizes the results from the PGA of autoinflammatory disease activity measured at baseline and at each follow-up visit. Physician's global assessment of autoinflammatory disease activity was available for 89.1% (n=254/285) of registry patients at baseline, with 3.9% (n=11/285) of patients reporting severe disease activity, 43.2% (n=123/285) of patients reporting mild or moderate disease activity and 42.1% (n=120/285) of patients reporting no disease activity.

It should be noted that the number of patients contributing PGA data decreased after 48 months in this long-term registry study. The analysis of PGA up to 48 months showed stable or improved disease activity for a majority of patients (Table 10-13). The proportion of patients having no disease activity increased from 42.1% at baseline to 46.7% at 48 months. Similarly, the proportion of patients presenting mild/moderate disease activity increased from 43.2% at baseline to 52.6% at 48 months, while the proportion of patients with severe disease activity decreased from 3.9% at baseline to 0% at 48 months. As patients were already receiving Ilaris prior to enrolment in this registry study, these results show the sustained long-term effectiveness of Ilaris in the study population.

Table 10-13 Physician's global assessment of autoinflammatory disease activity over time

	Baseline N=285	3 M N=86	6 M N=198	12 M N=216	18 M N=191	24 M N=190	30 M N=167	36 M N=159	42 M N=139	48 M N=135	54 M N=55	60 M N=38	66 M N=14	72 M N=1
Absent, n (%)	120/285 (42.1)	34/86 (39.5)	119/198 (60.1)	134/216 (62.0)	110/191 (57.6)	100/190 (52.6)	93/167 (55.7)	88/159 (55.3)	72/139 (51.8)	63/135 (46.7)	16/55 (29.1)	16/38 (42.1)	13/14 (92.9)	1/1 (100.0)
Mild/ Moderate, n (%)	123/285 (43.2)	46/86 (53.5)	73/198 (36.9)	85/216 (39.4)	77/191 (40.3)	85/190 (44.7)	72/167 (43.1)	69/159 (43.4)	63/139 (45.3)	71/135 (52.6)	34/55 (61.8)	20/38 (52.6)	1/14 (7.1)	0/1 (0.0)
Severe, n (%)	11/285 (3.9)	3/86 (3.5)	1/198 (0.5)	2/216 (0.9)	2/191 (1.0)	2/190 (1.1)	1/167 (0.6)	0/159 (0.0)	0/139 (0.0)	0/135 (0.0)	3/55 (5.5)	1/38 (2.6)	0/14 (0.0)	0/1 (0.0)
Not assessed, n (%)	14/285 (4.9)	3/86 (3.5)	5/198 (2.5)	3/216 (1.4)	2/191 (1.0)	4/190 (2.1)	1/167 (0.6)	3/159 (1.9)	4/139 (2.9)	1/135 (0.7)	2/55 (3.6)	1/38 (2.6)	0/14 (0.0)	0/1 (0.0)
Missing, n (%)	17/285 (6.0)	0/86 (0.0)	0/198 (0.0)	0/216 (0.0)	0/191 (0.0)	0/190 (0.0)	0/167 (0.0)	0/159 (0.0)	0/139 (0.0)	0/135 (0.0)	0/55 (0.0)	0/38 (0.0)	0/14 (0.0)	0/1 (0.0)

Source: 14.2-1.1b1

M: Months

Table 10-14 shows the PGA over time for all registry patients which was completed at each follow-up visit comparing a patient's condition to the previous clinical visit. Stable disease increased over time from 55.6% reported at baseline to 87.5% (126 out of 144 patients) reported at 48 months among patients with data available. The proportion of patients who presented with a much improved disease activity was highest at 3-6 months (18.1%-15.8%) and decreased over time, although this result may reflect the increasing proportion of patients with stable disease rather than a worsening over time. Indeed, the proportion of patients with slightly worsened or much worsened disease declined over time. No patient was considered much worsened (0.0%) and fewer patients were reported as slightly worsened (from 13.9% to 4.9%) at 48 months. Throughout the registry study, less than 2% of patients assessed at any time point presented a much worsened disease activity and the majority had stable disease activity (range 50.0%-87.5%). Results were similar in patients who required a dose or regimen change ([Table 14.2-6.4.1]).

In Table 10-15 and Table 10-16 the PGA of all registry patients is provided for both rollover and non-rollover patients throughout the course of the Registry. Rollover patients reported fewer cases of severe disease compared to non-rollover patients at baseline (2.4% and 6.0%, respectively), most probably reflecting the beneficial effect from previous exposure to Ilaris maintained over time. The percentage of patients with severe disease decreased during follow-up with no patient reporting severe disease at 48 months in both groups. A similar increase in the absence of disease was observed with non-rollover patients going from 31.6% at baseline to 59.1% at 12 months and rollover patients increasing from 49.4% at baseline to 64.1% at 12 months.

Table 10-14 Physician's overall global assessment

	3 M N=72	6 M N=215	12 M N=231	18 M N=199	24 M N=195	30 M N=180	36 M N=164	42 M N=147	48 M N=144	54 M N=68	60 M N=43	66 M N=16	72 M N=2
Much Improved, n (%)	13 (18.1)	34 (15.8)	29 (12.6)	14 (7.0)	13 (6.7)	9 (5.0)	11 (6.7)	9 (6.1)	3 (2.1)	1 (1.5)	1 (2.3)	0 (0.0)	0 (0.0)
Slightly Improved, n (%)	7 (9.7)	32 (14.9)	30 (13.0)	20 (10.1)	14 (7.2)	10 (5.6)	10 (6.1)	10 (6.8)	6 (4.2)	3 (4.4)	2 (4.7)	2 (12.5)	0 (0.0)
Stable, n (%)	40 (55.6)	131 (60.9)	147 (63.6)	153 (76.9)	150 (76.9)	146 (81.1)	133 (81.1)	113 (76.9)	126 (87.5)	52 (76.5)	34 (79.1)	11 (68.8)	1 (50.0)
Slightly Worsened, n (%)	10 (13.9)	10 (4.7)	18 (7.8)	11 (5.5)	18 (9.2)	12 (6.7)	9 (5.5)	12 (8.2)	7 (4.9)	10 (14.7)	4 (9.3)	1 (6.3)	0 (0.0)
Much Worsened, n (%)	1 (1.4)	1 (0.5)	3 (1.3)	1 (0.5)	0 (0.0)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Missing, n (%)	1 (1.4)	7 (3.3)	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	3 (2.0)	2 (1.4)	1 (1.5)	2 (4.7)	2 (12.5)	1 (50.0)

Source: Table 14.2-6.4
M: Months

Table 10-15 Physician's overall global assessment for rollover patients (all registry patients)

	Baseline N=168	3 M N=38	6 M N=120	12 M N=128	18 M N=118	24 M N=120	30 M N=102	36 M N=107	42 M N=90	48 M N=91	54 M N=38	60 M N=24	66 M N=10	72 M N=1
Absent, n (%)	83 (49.4)	16 (42.1)	72 (60.0)	82 (64.1)	65 (55.1)	63 (52.5)	54 (52.9)	58 (54.2)	44 (48.9)	45 (49.5)	11 (28.9)	11 (45.8)	9 (90.0)	1 (100.0)
Mild/ Moderate, n (%)	63 (37.5)	18 (47.4)	45 (37.5)	47 (36.7)	50 (42.4)	54 (45.0)	46 (45.1	47 (43.9)	44 (48.9)	46 (50.5)	24 (63.2)	12 (50.0)	1 (10.0)	0
Severe, n (%)	4 (2.4)	1 (2.6)	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.7)	1 (1.0)	0 (0.0)	0	0	2 (5.3)	0)	0	0
Not assessed, n (%)	12 (7.1)	3 (7.9)	2 (1.7)	1 (0.8)	2 (1.7)	2 (1.7)	1 (1.0)	3 (2.8)	2 (2.2)	0	1 (2.6)	1 (4.2)	0	0
Missing, n (%)	6 (3.6)	0	0	0	0	0	0	0	0	0	0	0	0	

	Baseline N=168	3 M N=38	6 M N=120	12 M N=128	18 M N=118	24 M N=120	30 M N=102	36 M N=107	42 M N=90	48 M N=91	54 M N=38	60 M N=24	66 M N=10	72 M N=1

Source: Table 14.2-1.1b2
M: Months

Table 10-16 Physician's overall global assessment for non-rollover patients (all registry patients)

	Baseline N=117	3 M N=48	6 M N=78	12 M N=88	18 M N=73	24 M N=70	30 M N=65	36 M N=52	42 M N=49	48 M N=44	54 M N=17	60 M N=14	66 M N=4	72 M N=0
Absent, n (%)	37 (31.6)	18 (37.5)	47 (60.3)	52 (59.1)	45 (61.6)	37 (52.9)	39 (60.0)	30 (57.7)	28 (57.1)	18 (40.9)	5 (29.4)	5 (35.7)	4 (100.0)	0
Mild/ Moderate, n (%)	60 (51.3)	28 (58.3)	28 (35.9)	38 (43.2)	27 (37.0)	31 (44.3)	26 (40.0)	22 (42.3)	19 (38.8)	25 (56.8)	10 (58.8)	8 (57.1)	0	0
Severe, n (%)	7 (6.0)	2 (4.2)	0	1 (1.1)	1 (1.4)	0 (0.0)	0	0	0	0	1 (5.9)	1 (7.1)	0	0
Not assessed, n (%)	2 (1.7)	0	3 (3.8)	2 (2.3)	0	2 (2.9)	0	0	2 (4.1)	1 (2.3)	1 (5.9)	0	0	0
Missing, n (%)	11 (9.4)	0	0	0	0	0	0	0	0	0	0	0	0	0

Source: Table 14.2-1.1b3
M: Months

Table 10-17 and Table 10-18 display results over time for the inflammation markers CRP and SAA, respectively, for all registry patients. The baseline median level of CRP was 4.9 mg/L (range 0.0-219.0 mg/L). Over time, the median CRP was consistently within normal range at all visits and slightly decreased to 3.0 mg/L at 48 months.

Similarly, median SAA levels decreased from baseline at 6.0 mg/L to 5.0 mg/L at 48 months, remaining at normal level over time.

Table 10-17 CRP (mg/L): summary statistics over time

	Baseline N=245	3 M N= 95	6 M N= 177	12 M N= 192	18 M N= 185	24 M N= 176	30 M N= 158	36 M N= 137	42 M N= 128	48 M N= 112	54 M N=48	60 M N=36	66 M N=8	72 M N=1
Mean, mg/L	12.3	16.3	7.0	7.1	6.1	7.2	7.3	6.9	7.2	6.8	8.5	4.4	9.5	6.0
SD	24.76	46.63	10.05	11.14	9.99	13.78	18.19	18.82	15.17	16.94	21.59	10.90	14.25	n.a.
Median, mg/L	4.9	5.0	4.2	4.0	3.0	3.0	3.0	3.0	4.1	3.0	5.0	2.0	3.8	6.0
Range	0.0, 219.0	0.0, 308.0	0.0, 57.0	0.0, 76.0	0.0, 74.0	0.0, 81.2	0.0, 123.0	0.0, 182.0	0.0, 131.0	0.0, 147.0	0.0, 119.0	0.0, 65.0	1.5, 44.0	6.0, 6.0

Source: 14.2-2.1
M: Months; SD: Standard Deviation

Table 10-18 SAA (mg/L): summary statistics over time

	Baseline N=185	3 M N= 63	6 M N= 141	12 M N= 142	18 M N= 121	24 M N= 124	30 M N= 130	36 M N= 106	42 M N= 102	48 M N= 93	54 M N=39	60 M N=25	66 M N=5	72 M N=0
Mean, mg/L	31.9	34.1	19.4	18.1	16.2	28.3	17.9	18.3	15.8	10.2	10.7	14.4	8.7	0
SD	63.36	102.1	52.00	40.39	41.12	79.17	52.57	45.09	51.31	19.10	23.04	44.34	4.34	n.a.
Median, mg/L	6.0	5.0	5.0	4.0	5.0	4.8	5.0	5.0	5.0	5.0	4.4	4.5	7.1	n.a.
Range	1.0, 500.0	0.9, 521.0	0.0, 461.0	0.0, 280.0	0.0, 337.0	0.0, 486.0	0.0, 408.0	0.0, 300.0	1.0, 465.0	0.0, 130.0	1.6,138.0	0.0,226.0	4.8,16.1	n.a.

	Baseline	3 M	6 M	12 M	18 M	24 M	30 M	36 M	42 M	48 M	54 M	60 M	66 M	72 M
	N=185	N= 63	N= 141	N= 142	N= 121	N= 124	N= 130	N= 106	N= 102	N= 93	N=39	N=25	N=5	N=0

Source: Table 14.2-2.2
M: Months; SD: Standard Deviation

Audiogram, ophthalmologic, and brain MRI assessments were also recorded at baseline and for each follow-up visit, when available. Table 10-17 summarizes changes from baseline assessment to last assessment for all registry patients. Please reference Table 10-3 for baseline assessment results.

Table 10-19 CAPS-related testing results in all registry patients: changes from baseline to last assessment

Test Results N=285	Last Assessment, n (%)			
	Normal	Abnormal	Unknown	Missing
Audiogram Assessment				
Baseline, n (%)				
Normal	15 (5.3)	3 (1.1)	1 (0.4)	60 (21.1)
Abnormal	7 (2.5)	27 (9.5)	0 (0.0)	54 (18.9)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)
Missing / No Results Available	5 (1.8)	7 (2.5)	0 (0.0)	103 (36.1)
Ophthalmological Assessment				
Baseline, n (%)				
Normal	14 (4.9)	6 (2.1)	2 (0.7)	71 (24.9)
Abnormal	2 (0.7)	3 (1.1)	0 (0.0)	29 (10.2)
Unknown	1 (0.4)	0 (0.0)	0 (0.0)	6 (2.1)
Missing / No Results Available	13 (4.6)	5 (1.8)	0 (0.0)	133 (46.7)
Brain MRI Assessment				
Baseline, n (%)				
Normal	1 (0.4)	2 (0.7)	0 (0.0)	58 (20.4)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	15 (5.3)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)
Missing / No Results Available	7 (2.5)	0 (0.0)	0 (0.0)	199 (69.8)

Source: Table 14.2-6.1g, Table 14.2-6.2g, Table 14.2-6.3g

Overall, audiogram results at last assessment were abnormal for 37 registry patients (3.0%), including 3 patients (1.1%) with normal assessment at baseline. A total of 7 patients (2.5%) changed from abnormal results at baseline to normal at last assessment. Change in audiogram results was not available for 77.2% of patients which limited the ability to assess the long term impact of Ilaris on hearing acuity.

Change in ophthalmological test results was only available for 46 registry patients (16.1%) which, similar to audiogram results, limited the power of the assessment. Results at last assessment were abnormal for 4.9% of registry patients, including 6 patients (2.1%) with

normal assessment at baseline. A total of 2 patients (0.7%) reported a change in abnormal baseline results to normal at last assessment.

Brain MRI results at last assessment were abnormal for 2 patients (0.7%), who both had normal results at baseline. Change in MRI results was not available 96.5% of patients.

10.4.2.2 Long-term impact of Ilaris on sexual maturation and neurocognitive development

Data on the sexual maturation and neurocognitive development were collected for 41 males and 42 females aged 6 to <18 years, including 34 male and 32 female CAPS patients.

Sexual maturation

Among all 6 to <18 year old registry patients, 2 patients reported a delay in sexual maturation at last assessment: 1 male (2.4%) with an assessment of no delay at baseline, and 1 female (2.4%) with unknown status at baseline. Three males (7.3%) and 1 female (2.4%) diagnosed with delay in sexual maturation at baseline registered no delay at last assessment. Fourteen males (34.1%) and 19 females (45.2%) recorded no delay in sexual maturation at baseline and at last assessment. Change in sexual maturation was not available for 23 males (56.1%) and 22 females (52.4%). Table 10-20 summarizes the change in sexual maturation from baseline to last assessment, for registry patients aged 6 to <18 years and by sex.

Table 10-20 Sexual Maturation: change from baseline to last assessment overall

		Last Assessment			
Sex	**Baseline, n (%)**	**Delay**	**No Delay**	**Unknown**	**Missing**
Male (N=41)	Delay	0	3 (7.3)	0	0
	No Delay	1 (2.4)	14 (34.1)	5 (12.2)	5 (12.2)
	Unknown	0	4 (9.8)	6 (14.6)	3 (7.3)
Female (N=42)	Delay	0	1 (2.4)	0	0
	No Delay	0	19 (45.2)	4 (9.5)	8 (19.0)
	Unknown	1 (2.4)	4 (9.5)	3 (7.1)	2 (4.8)

Source: Table 14.2-7.1g

Among CAPS patients, none aged 6 to <18 years experienced a delay in sexual maturation at last assessment. Two males within this group (5.9%) did experience a delay in sexual maturation at baseline; however, they then reported no delay at the last assessment. Change in sexual maturation among CAPS patients was not available for 20 males (58.8%) and 20 females (62.5%) (Table 14.2-7.1f).

Two patients with "Other" indication reported delay in sexual maturation at last assessment: 1 male (25.0%) registering no delay at baseline, and 1 female (12.5%) whose baseline status was not known (Table 14.2-7.1b, Table 14.2-7.1c, Table 14.2- 7.1e).

Neurocognitive development

Among the 83 registry patients aged 6 to <18 years, 5 (6.0%) presented with delay in cognitive function at last assessment with 1 patient having no delay initially recorded at baseline. One patient (1.2%) initially diagnosed with delay in cognitive function at baseline

changed to no delay at last assessment. More than half of the patients (56.6%) maintained the baseline assessment of no delay at last assessment. Change in delay of cognitive function from baseline to last assessment was not available for 30 (36.1%) patients. Table 10-21 summarizes the change in the cognitive function from baseline to last assessment for patients 6 to <18 years old.

Fifty-one patients (61.4%) aged 6 to <18 year old were considered to have a grade level in school appropriate for age at last assessment (Table 14.2-8.1g). Of the 10 patients (12.0%) with a grade level in school not appropriate for age, 5 had been recorded as having an appropriate grade level for their age at baseline. Conversely, another 5 patients (6.0%) with a grade level in school not appropriate for age at baseline were considered to have an appropriate grade level at last assessment. Change in grade level in school from baseline to last assessment was not available for 22 patients (26.5%).

Table 10-21 Delay in cognitive function: change from baseline to last assessment overall

	Last Assessment			
Baseline, N= 83	**Yes**	**No**	**Unknown**	**Missing**
Yes, n (%)	4 (4.8)	1 (1.2)	0 (0.0)	1 (1.2)
No, n (%)	1 (1.2)	47 (56.6)	6 (7.2)	14 (16.9)
Unknown, n (%)	0 (0.0)	7 (8.4)	2 (2.4)	0 (0.0)

Source: Table 14.2-8.2g

Among CAPS patients aged 6 to <18 years, 5 recorded delay in cognitive function at last assessment and all were in the more severe phenotypes of MWS and NOMID. One of these 5 cases had no delay at baseline (Table 14.2-8.2f). One patient changed from delay at baseline to no delay at last assessment. Change in cognitive function from baseline to last assessment was not available for 28 CAPS patients (42.4%).

Of the 5 patients who recorded a delay in cognitive function at last assessment, only 1 MWS patient (2.3%) presented no delay at baseline (Table 14.2-8.2b). One other MWS patient and 3 NOMID (21.4%) patients maintained the baseline status of delay (Table 14.2-8.2c). There were no cases of delay in cognitive function at last assessment among FCAS patients, atypical CAPS, and patients with "Other" indication (Table 14.2-8.2a, Table 14.2-8.2d, Table 14.2-8.2e).

10.4.2.3 Adverse drug reactions among CAPS patients

Adverse drug reactions are defined as adverse events suspected to be related to Ilaris and are summarized in Table 10-22. Only those PTs with 3 or more events among all CAPS patients, and all PTs related to injection and/or vaccination are included in the table.

Table 10-22 Adverse events suspected to be related to Ilaris exposure - all CAPS patients

Primary System Organ Class/ Preferred Term	Patients <18 years N = 85				Patients ≥18 years N = 158				All CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
All AEs Suspected to be Related to Ilaris	**38 (44.7)**	**128**	**44.87**	**(37.43,53.35)**	**71 (44.9)**	**177**	**29.46**	**(25.28,34.14)**	**109 (44.9)**	**305**	**34.42**	**(30.67,38.51)**
Blood and lymphatic system disorders	**1 (1.2)**	**1**	**0.35**	**(0.01,1.95)**	**2 (1.3)**	**2**	**0.33**	**(0.04,1.20)**	**3 (1.2)**	**3**	**0.34**	**(0.07,0.99)**
Cardiac disorders	**1 (1.2)**	**1**	**0.35**	**(0.01,1.95)**	**1 (0.6)**	**1**	**0.17**	**(0.00,0.93)**	**2 (0.8)**	**2**	**0.23**	**(0.03,0.82)**
Congenital, familial and genetic disorders	**0 (0.0)**	**0**	**0.00**	**(0.00,0.00)**	**1 (0.6)**	**1**	**0.17**	**(0.00,0.93)**	**1 (0.4)**	**1**	**0.11**	**(0.00,0.63)**
Ear and labyrinth disorders	**1 (1.2)**	**2**	**0.70**	**(0.08,2.53)**	**13 (8.2)**	**18**	**3.00**	**(1.78,4.74)**	**14 (5.8)**	**20**	**2.26**	**(1.38,3.49)**
Vertigo	0 (0.0)	0	0.00	(0.00,0.00)	11 (7.0)	16	2.66	(1.52,4.32)	11 (4.5)	16	1.81	(1.03,2.93)
Endocrine disorders	**0(0.0)**	**0**	**0.00**	**(0.00,0.00)**	**1 (0.6)**	**1**	**0.17**	**(0.00,0.93)**	**1 (0.4)**	**1**	**0.11**	**(0.00,0.63)**
Eye disorders	**3 (3.5)**	**3**	**1.05**	**(0.22,3.07)**	**3 (1.9)**	**4**	**0.67**	**(0.18,1.70)**	**6 (2.5)**	**7**	**0.79**	**(0.32,1.63)**

Primary System Organ Class/ Preferred Term	Patients <18 years N = 85				Patients ≥18 years N = 158				All CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Gastrointestinal disorders	**4 (4.7)**	**9**	**3.15**	**(1.44,5.99)**	**7 (4.4)**	**9**	**1.50**	**(0.69,2.84)**	**11 (4.5)**	**18**	**2.03**	**(1.20,3.21)**
Abdominal pain	1 (1.2)	1	0.35	(0.01,1.95)	2 (1.3)	2	0.33	(0.04,1.20)	3 (1.2)	3	0.34	(0.07,0.99)
Abdominal pain upper	2 (2.4)	4	1.40	(0.38,3.59)	1 (0.6)	1	0.17	(0.00,0.93)	3 (1.2)	5	0.56	(0.18,1.32)
Diarrhoea	1 (1.2)	1	0.35	(0.01,1.95)	2 (1.3)	3	0.50	(0.10,1.46)	3 (1.2)	4	0.45	(0.12,1.16)
General disorders and administration site conditions	**12 (14.1)**	**17**	**5.96**	**(3.47,9.54)**	**10 (6.3)**	**16**	**2.66**	**(1.52,4.32)**	**22 (9.1)**	**33**	**3.72**	**(2.56,5.23)**
Condition aggravated	1 (1.2)	1	0.35	(0.01,1.95)	2 (1.3)	2	0.33	(0.04,1.20)	3 (1.2)	3	0.34	(0.07,0.99)
Fatigue	2 (2.4)	4	1.40	(0.38,3.59)	1 (0.6)	1	0.17	(0.00,0.93)	3(1.2)	5	0.56	(0.18,1.32)
Immediate post-injection reaction	1(1.2)	1	0.35	(0.01,1.95)	0(0.0)	0	0.00	(0.00,0.00)	1(0.4)	1	0.11	(0.00,0.63)
Injection site haematoma	0(0.0)	0	0.00	(0.00,0.00)	1(0.6)	1	0.17	(0.00,0.93)	1(0.4)	1	0.11	(0.00,0.63)
Injection site irritation	1(1.2)	1	0.35	(0.01,1.95)	0(0.0)	0	0.00	(0.00,0.00)	1(0.4)	1	0.11	(0.00,0.63)
Injection site pain	0(0.0)	0	0.00	(0.00,0.00)	1(0.6)	1	0.17	(0.00,0.93)	1(0.4)	1	0.11	(0.00,0.63)
Injection site reaction	1 (1.2)	1	0.35	(0.01,1.95)	2 (1.3)	2	0.33	(0.04,1.20)	3 (1.2)	3	0.34	(0.07,0.99)
Pyrexia	3 (3.5)	5	1.75	(0.57,4.09)	0 (0.0)	0	0.00	(0.00,0.00)	3 (1.2)	5	0.56	(0.18,1.32)
Vaccination site erythema	0(0.0)	0	0.00	(0.00,0.00)	1(0.6)	1	0.17	(0.00,0.93)	1(0.4)	1	0.11	(0.00,0.63)
Vaccination site inflammation	2 (2.4)	2	0.70	(0.08,2.53)	2 (1.3)	2	0.33	(0.04,1.20)	4 (1.6)	4	0.45	(0.12,1.16)
Vaccination site reaction	0(0.0)	0	0.00	(0.00,0.00)	2(1.3)	2	0.33	(0.04,1.20)	2(0.8)	2	0.23	(0.03,0.82)

Primary System Organ Class/ Preferred Term	Patients <18 years N = 85				Patients ≥18 years N = 158				All CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Immune system disorders	**1 (1.2)**	**1**	**0.35**	**(0.01,1.95)**	**1 (0.6)**	**1**	**0.17**	**(0.00,0.93)**	**2 (0.8)**	**2**	**0.23**	**(0.03,0.82)**
Infections and infestations	**28 (32.9)**	**55**	**19.28**	**(14.52,25.09)**	**40 (25.3)**	**71**	**11.82**	**(9.23,14.91)**	**68 (28.0)**	**126**	**14.22**	**(11.85,16.93)**
Bronchitis	1 (1.2)	1	0.35	(0.01,1.95)	4 (2.5)	7	1.17	(0.47,2.40)	5 (2.1)	8	0.90	(0.39,1.78)
Cellulitis	0 (0.0)	0	0.00	(0.00,0.00)	3 (1.9)	3	0.50	(0.10,1.46)	3(1.2)	3	0.34	(0.07,0.99)
Ear infection	3 (3.5)	4	1.40	(0.38,3.59)	0 (0.0)	0	0.00	(0.00,0.00)	3 (1.2)	4	0.45	(0.12,1.16)
Gastroenteritis	3 (3.5)	4	1.40	(0.38,3.59)	0 (0.0)	0	0.00	(0.00,0.00)	3 (1.2)	4	0.45	(0.12,1.16)
Herpes zoster	0 (0.0)	0	0.00	(0.00,0.00)	2 (1.3)	3	0.50	(0.10,1.46)	2 (0.8)	3	0.34	(0.07,0.99)
Hordeolum	0 (0.0)	0	0.00	(0.00,0.00)	1 (0.6)	3	0.50	(0.10,1.46)	1 (0.4)	3	0.34	(0.07,0.99)
Influenza	2 (2.4)	2	0.70	(0.08,2.53)	4 (2.5)	7	1.17	(0.47,2.40)	6 (2.5)	9	1.02	(0.46,1.93)
Laryngitis	3 (3.5)	3	1.05	(0.22,3.07)	0 (0.0)	0	0.00	(0.00,0.00)	3 (1.2)	3	0.34	(0.07,0.99)
Lower respiratory tract infection	3 (3.5)	4	1.40	(0.38,3.59)	8 (5.1)	9	1.50	(0.69,2.84)	11 (4.5)	13	1.47	(0.78,2.51)
Nasopharyngitis	5 (5.9)	6	2.10	(0.77,4.58)	8 (5.1)	9	1.50	(0.69,2.84)	13 (5.3)	15	1.69	(0.95,2.79)
Pneumonia	1 (1.2)	1	0.35	(0.01,1.95)	2 (1.3)	3	0.50	(0.10,1.46)	3 (1.2)	4	0.45	(0.12,1.16)
Rhinitis	1 (1.2)	2	0.70	(0.08,2.53)	2 (1.3)	2	0.33	(0.04,1.20)	3 (1.2)	4	0.45	(0.12,1.16)
Tonsillitis	3 (3.5)	4	1.40	(0.38,3.59)	4 (2.5)	4	0.67	(0.18,1.70)	7 (2.9)	8	0.90	(0.39,1.78)
Urinary tract infection	3 (3.5)	5	1.75	(0.57,4.09)	5 (3.2)	6	1.00	(0.37,2.17)	8 (3.3)	11	1.24	(0.62,2.22)
Vaccination site cellulitis	0(0.0)	0	0.00	(0.00,0.00)	1(0.6)	1	0.17	(0.00,0.93)	1(0.4)	1	0.11	(0.00,0.63)
Injury, poisoning and procedural complications	4(4.7)	6	2.10	(0.77,4.58)	6(3.8)	10	1.66	(0.80,3.06)	10(4.1)	16	1.81	(1.03,2.93)
Procedural headache	1(1.2)	1	0.35	(0.01,1.95)	1(0.6)	2	0.33	(0.04,1.20)	2(0.8)	3	0.34	(0.07,0.99)

Primary System Organ Class/ Preferred Term	Patients <18 years N = 85				Patients ≥18 years N = 158				All CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Procedural nausea	2(2.4)	2	0.70	(0.08,2.53)	1(0.6)	1	0.17	(0.00,0.93)	3(1.2)	3	0.34	(0.07,0.99)
Vaccination complication	2(2.4)	2	0.70	(0.08,2.53)	2(1.3)	2	0.33	(0.04,1.20)	4(1.6)	4	0.45	(0.12,1.16)
Investigations	**4(4.7)**	**5**	**1.75**	**(0.57,4.09)**	**10(6.3)**	**12**	**2.00**	**(1.03,3.49)**	**14(5.8)**	**17**	**1.92**	**(1.12,3.07)**
Weight increased	1(1.2)	1	0.35	(0.01,1.95)	7(4.4)	7	1.17	(0.47,2.40)	8(3.3)	8	0.90	(0.39,1.78)
Metabolism and nutrition disorders	**0(0.0)**	**0**	**0.00**	**(0.00,0.00)**	**1(0.6)**	**1**	**0.17**	**(0.00,0.93)**	**1(0.4)**	**1**	**0.11**	**(0.00,0.63)**
Musculoskeletal and connective tissue disorders	**1(1.2)**	**1**	**0.35**	**(0.01,1.95)**	**1(0.6)**	**2**	**0.33**	**(0.04,1.20)**	**2(0.8)**	**3**	**0.34**	**(0.07,0.99)**
Nervous system disorders	**5(5.9)**	**6**	**2.10**	**(0.77,4.58)**	**9(5.7)**	**10**	**1.66**	**(0.80,3.06)**	**14(5.8)**	**16**	**1.81**	**(1.03,2.93)**
Headache	4(4.7)	5	1.75	(0.57,4.09)	2(1.3)	2	0.33	(0.04,1.20)	6(2.5)	7	0.79	(0.32,1.63)
Syncope	0(0.0)	0	0.00	(0.00,0.00)	2(1.3)	3	0.50	(0.10,1.46)	2(0.8)	3	0.34	(0.07,0.99)
Psychiatric disorders	**0(0.0)**	**0**	**0.00**	**(0.00,0.00)**	**3(1.9)**	**3**	**0.50**	**(0.10,1.46)**	**3(1.2)**	**3**	**0.34**	**(0.07,0.99)**
Renal and urinary disorders	**0(0.0)**	**0**	**0.00**	**(0.00,0.00)**	**1(0.6)**	**1**	**0.17**	**(0.00,0.93)**	**1(0.4)**	**1**	**0.11**	**(0.00,0.63)**
Reproductive system and breast disorders	**1(1.2)**	**2**	**0.70**	**(0.08,2.53)**	**1(0.6)**	**1**	**0.17**	**(0.00,0.93)**	**2(0.8)**	**3**	**0.34**	**(0.07,0.99)**

Primary System Organ Class/ Preferred Term	Patients <18 years N = 85				Patients ≥18 years N = 158				All CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Respiratory, thoracic and mediastinal disorders	**5(5.9)**	**9**	**3.15**	**(1.44,5.99)**	**4(2.5)**	**4**	**0.67**	**(0.18,1.70)**	**9(3.7)**	**13**	**1.47**	**(0.78,2.51)**
Cough	3(3.5)	4	1.40	(0.38,3.59)	1(0.6)	1	0.17	(0.00,0.93)	4(1.6)	5	0.56	(0.18,1.32)
Oropharyngeal pain	3(3.5)	4	1.40	(0.38,3.59)	0(0.0)	0	0.00	(0.00,0.00)	3(1.2)	4	0.45	(0.12,1.16)
Skin and subcutaneous tissue disorders	**7(8.2)**	**9**	**3.15**	**(1.44,5.99)**	**5(3.2)**	**8**	**1.33**	**(0.57,2.62)**	**12(4.9)**	**17**	**1.92**	**(1.12,3.07)**
Rash	1(1.2)	1	0.35	(0.01,1.95)	1(0.6)	2	0.33	(0.04,1.20)	2(0.8)	3	0.34	(0.07,0.99)
Vascular disorders	1(1.2)	1	0.35	(0.01,1.95)	1(0.6)	1	0.17	(0.00,0.93)	2(0.8)	2	0.23	(0.03,0.82)

Source: Table 14.3.1-1.7a, Table 14.3.1-1.8a

Approximately 45% of patients experienced AEs suspected to be related to Ilaris exposure. Infections and Infestations was the most commonly reported SOC, with 14 PTs in this category having ≥3 events suspected to be related to Ilaris. The most common among these were nasopharyngitis (n=15 events), lower respiratory tract infections (n=13 events), urinary tract infections (n=11 events), influenza (n=9 events), bronchitis (n=8 events), and tonsillitis (n=8 events). However, vertigo was the most common PT overall (n=16 events, incidence rate 1.81 per 100 person-years [95% CI 1.03-2.93]). Other common AEs suspected to be related to Ilaris included weight increase, headache, and abdominal pain (including upper abdominal pain).

AEs suspected to be related to Ilaris were balanced across both age groups of <18 years old and ≥18 years old. Common Infections and Infestations noted above occurred in somewhat similar proportions between age groups, with the exception of lower respiratory tract infections and bronchitis where a higher percentage of adult/elderly patients were affected. Similarly, all episodes of vertigo suspected to be related to Ilaris occurred among patients ≥18 years of age.

10.4.2.4 Patterns of dosing of Ilaris

Table 10-23 summarizes Ilaris treatment for all registry patients and for all CAPS patients by age groups of <18 years old and ≥18 years old, respectively. There were 275 registry patients with a date of first dose of Ilaris available. This date coincides with the first dose of Ilaris irrespective of Registry enrollment. For all registry patients, the mean Ilaris duration since first dose of Ilaris was 243.4 weeks. The cumulative number of doses ranged from <1 mg/kg to over 120 mg/kg. Ten patients did not have a first date of Ilaris available and were not included in this calculation.

The mean duration since first exposure to Ilaris was 249.8 weeks in registry patients ≥18 years old and 233.0 weeks in registry patients <18 years old.

Table 10-23 Summary statistics of Ilaris treatment at last visit

	All CAPS Patients		All Registry Patients		
Treatment Exposure Statistics	**Age: <18 Years**	**Age: ≥18 Years**	**Age: <18 Years**	**Age: ≥18 Years**	**All Patients**
Duration of exposure to Ilaris irrespective of Registry enrollment (weeks)					
n (# patients)[1]	83	152	104	171	275
Mean	234.1	253.9	233.0	249.8	243.4
SD	94.95	86.25	95.55	87.05	90.56
Median	282.7	294.1	277.6	290.3	286.3
Range	3.9-355.0	10.7-348.7	3.9-355.0	10.7-352.3	3.9-355.0
Q1 - Q3	143.6-301.3	201.9-319.1	147.6-300.7	182.1-319.1	175.3-316.0
<48 weeks, n (%)	5 (6.0)	4 (2.6)	5 (4.8)	5 (2.9)	10 (3.6)
48-<96 weeks, n (%)	6 (7.2)	8 (5.3)	10 (9.6)	9 (5.3)	19 (6.9)
96-<144 weeks, n (%)	10 (12.0)	9 (5.9)	11 (10.6)	10 (5.8)	21 (7.6)
144-<192 weeks, n (%)	3 (3.6)	15 (9.9)	5 (4.8)	20 (11.7)	25 (9.1)
192-<240 weeks, n (%)	7 (8.4)	15 (9.9)	9 (8.7)	18 (10.5)	27 (9.8)

Treatment Exposure Statistics	All CAPS Patients		All Registry Patients		
	Age: <18 Years	Age: ≥18 Years	Age: <18 Years	Age: ≥18 Years	All Patients
240-<288 weeks, n (%)	15 (18.1)	18 (11.8)	20 (19.2)	20 (11.7)	40 (14.5)
288-<336 weeks, n (%)	33 (39.8)	72 (47.4)	37 (35.6)	77 (45.0)	114 (41.5)
336-<384 weeks, n (%)	4 (4.8)	11 (7.2)	7 (6.7)	12 (7.0)	19 (6.9)
Total dose per patient at last visit (mg/kg)					
n (# patients)[2]	81	137	103	153	256
0 to < 1 mg/kg	2 (2.5)	6 (4.4)	2 (1.9)	6 (3.9)	8 (3.1)
1 to <2 mg/kg	15 (18.5)	37 (27.0)	19 (18.4)	41 (26.8)	60 (23.4)
2 to <3 mg/kg	29 (35.8)	66 (48.2)	36 (35.0)	75 (49.0)	111 (43.4)
3 to <4 mg/kg	24 (29.6)	23 (16.8)	33 (32.0)	26 (17.0)	59 (23.0)
4 to <5 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5 to <6 mg/kg	6 (7.4)	2 (1.5)	7 (6.8)	2 (1.3)	9 (3.5)
6 to <7 mg/kg	3 (3.7)	2 (1.5)	4 (3.9)	2 (1.3)	6 (2.3)
7 to <8 mg/kg	1 (1.2)	1 (0.7)	1 (1.0)	1 (0.7)	2 (0.8)
8 to <9 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
9 to <10 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>= 10 mg/kg	1 (1.2)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.4)
Cumulative number of doses per patient since baseline (mg/kg)					
n (# patients)[3]	85	158	107	178	285
<1 mg/kg, n (%)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.4)
1-<10 mg/kg, n (%)	8 (9.4)	27 (17.1)	8 (7.5)	32 (18.0)	40 (14.0)
10-<20 mg/kg, n (%)	10 (11.8)	9 (5.7)	14 (13.1)	13 (7.3)	27 (9.5)
20-<30 mg/kg, n (%)	5 (5.9)	7 (4.4)	5 (4.7)	7 (3.9)	12 (4.2)
30-<40 mg/kg, n (%)	1 (1.2)	17 (10.8)	2 (1.9)	21 (11.8)	23 (8.1)
40-<50 mg/kg, n (%)	4 (4.7)	12 (7.6)	6 (5.6)	15 (8.4)	21 (7.4)
50-<60 mg/kg, n (%)	14 (16.5)	16 (10.1)	17 (15.9)	17 (9.6)	34 (11.9)
60-<70 mg/kg, n (%)	7 (8.2)	16 (10.1)	10 (9.3)	16 (9.0)	26 (9.1)
70-<80 mg/kg, n (%)	7 (8.2)	11 (7.0)	8 (7.5)	12 (6.7)	20 (7.0)
80-<90 mg/kg, n (%)	3 (3.5)	14 (8.9)	4 (3.7)	15 (8.4)	19 (6.7)
90-<100 mg/kg, n (%)	2 (2.4)	4 (2.5)	2 (1.9)	4 (2.2)	6 (2.1)
100-<110 mg/kg, n (%)	5 (5.9)	4 (2.5)	6 (5.6)	4 (2.2)	10 (3.5)
110-<120 mg/kg, n (%)	1 (1.2)	8 (5.1)	2 (1.9)	8 (4.5)	10 (3.5)
>=120 mg/kg, n (%)	18 (21.2)	12 (7.6)	23 (21.5)	13 (7.3)	36 (12.6)
Average dose per patient since baseline (mg/kg)					
n (# patients)[4]	85	158	107	178	285
<1 mg/kg, n (%)	3 (3.5)	7 (4.4)	5 (4.7)	21 (11.8)	26 (9.1)
1-<2 mg/kg, n (%)	18 (21.2)	51 (32.3)	20 (18.7)	44 (24.7)	64 (22.5)
2-<3 mg/kg, n (%)	25 (29.4)	68 (43.0)	32 (29.9)	79 (44.4)	111 (38.9)
3-<4 mg/kg, n (%)	19 (22.4)	17 (10.8)	25 (23.4)	19 (10.7)	44 (15.4)
4-<5 mg/kg, n (%)	8 (9.4)	11 (7.0)	11 (10.3)	11 (6.2)	22 (7.7)
5-<6 mg/kg, n (%)	4 (4.7)	3 (1.9)	6 (5.6)	3 (1.7)	9 (3.2)
6-<7 mg/kg, n (%)	6 (7.1)	0 (0.0)	6 (5.6)	0 (0.0)	6 (2.1)
7-<8 mg/kg, n (%)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.4)
>=10 mg/kg, n (%)	2 (2.4)	0 (0.0)	2 (1.9)	0 (0.0)	2 (0.7)

Treatment Exposure Statistics	All CAPS Patients		All Registry Patients		
	Age: <18 Years	Age: ≥18 Years	Age: <18 Years	Age: ≥18 Years	All Patients
Average time elapsed between dose dates per patient during follow-up (weeks), n (%)					
n (# patients)[4]	85	156	107	176	283
Only one dose date available	1 (1.2)	1 (0.6)	1 (0.9)	2 (1.1)	3 (1.1)
2 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3 weeks	1 (1.2)	0 (0.0)	1 (0.9)	1 (0.6)	2 (0.7)
4 weeks	5 (5.9)	3 (1.9)	10 (9.3)	5 (2.8)	15 (5.3)
5 weeks	5 (5.9)	3 (1.9)	10 (9.3)	3 (1.7)	13 (4.6)
6 weeks	3 (3.5)	4 (2.6)	3 (2.8)	5 (2.8)	8 (2.8)
7 weeks	14 (16.5)	19 (12.2)	15 (14.0)	22 (12.5)	37 (13.1)
8 weeks	24 (28.2)	62 (39.7)	31 (29.0)	68 (38.6)	99 (35.0)
9 weeks	10 (11.8)	21 (13.5)	10 (9.3)	23 (13.1)	33 (11.7)
10 weeks	4 (4.7)	12 (7.7)	4 (3.7)	15 (8.5)	19 (6.7)
11 weeks	4 (4.7)	5 (3.2)	4 (3.7)	5 (2.8)	9 (3.2)
12 weeks	1 (1.2)	8 (5.1)	2 (1.9)	8 (4.5)	10 (3.5)
>12 weeks	13 (15.3)	18 (11.5)	16 (15.0)	19 (10.8)	35 (12.4)

Source: Table 14.2-3.1f; Table 14.2-3.2g.

[1] n = number of patients with date of first dose of Ilaris; mean = average weeks since first dose of Ilaris.

[2] n = number of patients with date of Ilaris dose and weight available.

[3] n = number of patients with Ilaris dosing history and weight available.

[4] n = number of patients with Ilaris dosing history.

The total dose administered per patient at last visit was recorded for 256 registry patients. Doses at last visit were similar to baseline. Almost half of patients (43.4%) received 2 to <3 mg/kg on average at last visit. About one quarter of registry patients received 1 to <2 mg/kg (23.4%) and another quarter of registry patients (23.0%) received 3 to <4 mg/kg at last visit. In general, registry patients <18 years old received a higher dose per patient. The majority of patients ≥18 years old had an average dose of 1-<3 mg/kg over the duration of the registry whereas the majority of patients <18 years old had an average dose of 2-<4mg.kg. A total of 23.5% of patients in the <18 year old CAPS group had an average dose >4 mg/kg whereas only 9.5% of patients ≥18 years old had an average dose of >4mg/kg. Furthermore, 28.2% of patients <18 years old maintained an average dose with an 8 week interval compared to 39.7% patients ≥18 years old. Patients ≥18 years old deviated more towards every 9 weeks compared to the <18 year old group where more patients deviated towards less than 8 weeks.

The average time that elapsed between dose dates was calculated for 283 registry patients who had at least 2 dose dates available during follow-up. The most common interval between dose dates followed the same trend as intervals between doses prior to baseline with one-thirds of registry patients receiving Ilaris every 8 weeks (35.0%). Registry patients <18 years old had a higher proportion of patients receiving Ilaris every 4 and 5 weeks compared to registry patients ≥18 years old.

Table 10-24 summarizes reasons for dose adjustment and discontinuation.

Table 10-24 Patients who required dose adjustment

Dose Adjustment	Primary Reason	Age: 0-18 Years N = 107 n (%)	Age: >=18 Years N = 178 n (%)	Overall N = 285 n (%)
Dose or regimen changed	n	76	71	147
	Adverse event	4 (3.7)	4 (2.2)	8 (2.8)
	Lack of therapeutic effect	34 (31.8)	35 (19.7)	69 (24.2)
	Patient preference	10 (9.3)	13 (7.3)	23 (8.1)
	Environmental (seasonal) factors	2 (1.9)	7 (3.9)	9 (3.2)
	Other	52 (48.6)	38 (21.3)	90 (31.6)
Permanently discontinued	n	9	14	23
	Adverse event	3 (2.8)	2 (1.1)	5 (1.8)
	Lack of therapeutic effect	2 (1.9)	5 (2.8)	7 (2.5)
	Patient preference	1 (0.9)	4 (2.2)	5 (1.8)
	Environmental (seasonal) factors	0 (0.0)	0 (0.0)	0 (0.0)
	Other	3 (2.8)	3 (1.7)	6 (2.1)
Temporarily interrupted	n	17	35	52
	Adverse event	5 (4.7)	8 (4.5)	13 (4.6)
	Lack of therapeutic effect	1 (0.9)	7 (3.9)	8 (2.8)
	Patient preference	6 (5.6)	10 (5.6)	16 (5.6)
	Environmental (seasonal) factors	0 (0.0)	1 (0.6)	1 (0.4)
	Other	9 (8.4)	16 (9.0)	25 (8.8)

Source: Table 14.2-3.3g

There were 147 (51.6%) registry patients who required a dose adjustment. Fifty-two patients temporarily interrupted their Ilaris treatment (18.2%) and 23 patients (8.1%) permanently discontinued Ilaris treatment. Patients could provide multiple reasons as to why they elected to alter their study medication.

Among the 147 patients who required a dose adjustment, 90 (31.6%) patients listed “Other” as the reason for dose change followed by 69 (24.2%) patients due to lack of therapeutic effect, 23 (8.1%) due to patient preference, 9 (3.2%) due to environmental factors, and 8 (2.8%) changed dose due to an AE.

For patients <18 years old, 31.8% required a dose change due to lack of therapeutic effect whereas 19.7% patients ≥18 years old required a dose change for this reason. However, a smaller proportion of patients <18 years old discontinued Ilaris due to lack of therapeutic effect compared to the patient group ≥18 years old, suggesting that after a dose change patients <18 year old are in general treated with satisfactory therapeutic effect. Lastly, only 15.9% of patients <18 years old interrupted Ilaris for any reason, whereas almost 50% of patients ≥18 years old, interrupted Ilaris at any point.

For the 52 patients who temporarily interrupted Ilaris treatment, 2 reasons were cited most frequently: "Other" (n=25, 8.8%) and patient preference (n=16, 5.2%). Of the 23 patients who permanently discontinued Ilaris treatment, 7 (2.5%) patients discontinued due to lack of

therapeutic effect, 6 (2.1%) patients for “Other” reasons, 5 (1.8%) patients due to AE, and 5 (1.8%) patients due to patient preference (Table 14.2-3.3g).

A total of 119 of the 243 CAPS patients had a dose or regimen change. Of these, 54 (18.9%) reported a dose or regimen change due to lack of therapeutic effect and 21 (7.4%) due to patient preference; an additional 71 (24.9%) patients changed for “Other” reasons. There were 14 patients who chose to permanently discontinue treatment with 4 (1.4%) patients stating due to AE, 4 (1.4%) patients selecting "Other" reasons, 3 (1.1%) patients reporting lack of therapeutic effect, and 3 (1.1%) patients reporting patient preference. There were 43 CAPS patients who reported temporarily interrupting their treatment with "Other" (n=21, 7.4%) being the most common reason (Table 14.2-3.3f, Listing 16.2.5-2.1a-c).

Eight atypical CAPS patients reported a change in their dose or regimen with 6 (2.1%) patients citing a lack of therapeutic effect and 3 (1.1%) patients listing patient preference. Two patients chose to permanently discontinue treatment and both (0.7%) did so out of patient preference. Two patients also chose to temporarily interrupt treatment; both (0.7%) indicated "Other" as their reason (Table 14.2-3.3d).

Among FCAS patients, 9 reported changing their dose or regimen, with 5 (11.9%) patients listing lack of therapeutic effect. Five patients also interrupted their dose with 4 (9.5%) patients citing "Other" reasons and 1 (2.4%) patient stating lack of therapeutic effect. There were no patients with FCAS who discontinued treatment (Table 14.2-3.3a).

There were 94 MWS patients who had a dose or regimen change, including 40 (23.7%) patients citing lack of therapeutic effect and 58 (34.3%) patients listing "Other" as their reason for change in treatment. There were 37 patients who temporarily interrupted treatment with 10 (5.9%) patients reporting due to AEs, 14 (8.3%) patients due to patient preference, and 16 (9.5%) patients stating “Other" reason (Table 14.2-3.3b).

The NOMID population had 23 patients change their dose or regimen with 14 (43.8%) patients reporting due to "Other" reason, 12 (37.5%) patients stating lack of therapeutic effect, 3 (9.4%) patients due to patient preference, and 2 (6.3%) patients due to seasonal factors. Four NOMID patients permanently discontinued Ilaris treatment with 2 (6.3%) patients stating due to AEs and 2 (6.3%) stating due to lack of therapeutic effect. Only 1 (3.1%) patient temporarily interrupted treatment due to an "Other" reason (Table 14.2-3.3c).

Out of the 23 patients who permanently discontinued Ilaris treatment, 7 (30.4%) discontinued treatment due to lack of therapeutic effect (n=1 MWS, n=2 NOMID, n=4 "Other").

Although almost 25% of all patients (predominantly pediatrics) required a dose change at some point because of a lack of therapeutic effect, only 2.5% of patients in total permanently discontinued Ilaris due to a lack of therapeutic effect demonstrating that most patients experience a satisfactory therapeutic effect after dose changes.

In conclusion, the dosing patterns observed in the study reflects the dosing scheme as recommended in the Ilaris Summary of Product Characteristics (section 4.2 Posology and method of administration), in terms of dose levels and frequency.

10.5 Other analyses

Other identified/potential risks as defined in the latest RMP v9.0 were also analyzed including neutropenia opportunistic infections, immunogenicity/allergenicity, effect on growth, autoimmunity reactions, DILI, disorders of lipoprotein metabolism, canakinumab–immunosuppressants combination therapy toxicity, interactions with vaccines, pregnancy and lactation, and long term effect on kidney function.

10.5.1 Neutropenia

There was one case of mild neutropenia (1, 36 $X10^9$ [Listing 16.2.8-1.1]) reported as AE, not associated with infection and not suspected to be related to Ilaris according to the Investigator.

10.5.2 Opportunistic infections

Upon medical review of all infection AEs reported during the Registry, 5 events of herpes zoster, 2 events of varicella, 3 events of herpes virus infection, and 1 event of Epstein Barr infection were reported. None of these events were reported as serious or opportunistic by the Investigator.

10.5.3 Effect on growth

For more information on effect on growth refer to Section 10.4.2.2.

10.5.4 Immunogenicity /allergenicity

There were 7 allergy events reported not related to Ilaris. Four events were classified as seasonal allergy and allergy to arthropod bite, 3 as hypersensitivity reactions and 1 as drug hypersensitivity reaction to amoxicillin, which was reported as serious and resolved in 2 days.

ADA (antidrug antibodies) testing was not performed, due to the observational nature of the study and the lack of availability to perform the test in the real life setting.

10.5.5 Autoimmunity reactions

There was only 1 event of autoimmune hepatitis reported in a patient with JIA diagnosed based on liver biopsy findings along with presence of specific SMA (smooth muscle antibodies). The event was not considered to be related to Ilaris by the treating Investigator and was resolved while the patient was still on treatment with Ilaris.

There were no events of drug induced lupus reported despite 13 patients presenting with ANA after Ilaris initiation lacking any relevant concomitant clinical symptomatology.

10.5.6 Drug-induced liver injuries (DILI)

There were 5 patients with elevated liver enzymes reported among all registry patients, 4 of which were CAPS patients. Elevated liver enzymes and/or bilirubin were likely due to underlying hepatobiliary conditions such as cholestasis (n=1 patient), cholelithiasis (n=3 patients) and hepatic steatosis (n=1 patient). None of the patients were suspected to be related to Ilaris by the Investigator.

10.5.7 Disorders of lipoprotein metabolism

Among all registry patients there were only 6 CAPS patients reporting high blood cholesterol levels (n=4) and high LDL levels (low levels lipoprotein, n=2), none of them considered serious or related to Ilaris by the Investigator.

10.5.8 Canakinumab-immunosuppressants combination therapy toxicity

There were no events of myelotoxicity, hepatotoxicity, or renal toxicity reported among all registry patients related to Ilaris in combination with other cytotoxic agents commonly used for the treatment of autoinflammatory diseases such methotrexate, azathioprine and colchicine (Listing 16.2.5-1.3).

10.5.9 Interactions with vaccines

Of the 285 registry patients, 87 (30.5%) reported having received at least 1 vaccine of any type, information on vaccination was missing or unknown for 44/285 patients (15.4%), and the reminder did not receive a vaccine during the registry study (Table 14.2.6.5g). Of the 87 patients who received at least 1 vaccine, 74 were CAPS patients. In total, 19 patients (21.8%, 19/87) reported at least 1 reaction to vaccine among patients vaccinated (Listing 16.2.5-1.5a). Antibody titers were not measured or information was unknown for all vaccinated patients, with the exception of 2 MWS adult patients, (1 male and 1 female) and 2 NOMID female patients, who were administered pneumococcal vaccine and seroconverted with protective titers.

The percentage of CAPS patients with at least 1 vaccination reaction was the highest among MWS (25.9%) and NOMID (28.6%) indications. Atypical CAPS did not report any reactions to vaccination. Across all indications, local and systemic reactions were reported as pain, redness, swelling, and fever. Four patients reported reactions classified as "Other" (not specified) in association with influenza and pneumococcal vaccines. (Table 10-25) summarizes exposure to, at least, 1 vaccine and reporting of, at least, 1 reaction to vaccination, by indication.

Table 10-25 Exposure and reactions to vaccination by indication

	FCAS N= 42	MWS[3] N= 169	NOMID N= 32	Atypical CAPS N= 18	Other N= 24	All CAPS N= 243	All Registry Patients N=285
Received at least 1 dose of vaccine[1]							
n (%)	13 (31.0)	54 (32.0)	7 (21.9)	5 (27.8)	8 (33.3)	**74 (30.5)**	**87 (30.5)** [4]
Unknown/Missing, n (%)	13 (30.9)	21 (12.5)	3 (9.4)	4 (22.2)	3 (12.5)	**37 (15.2)**	**44 (15.4)**
Reported at least 1 reaction among vaccinated[2]							
n (%)	2 (15.4)	14 (25.9)	2 (28.6)	0 (0.0)	1 (12.5)	**18 (24.3)**	**19 (21.8)**

Source: Table 14.2-6.5a, Table 14.2-6.5b, Table 14.2-6.5c, Table 14.2-6.5d, Table 14.2-6.5e, Table 14.2-6.5g, Listing 16.2.5-1.5a

N: number of patients in each category.

[1] denominator used for % calculation = N

[2] denominator used for % calculated = total patients who received at least 1 vaccine per indication.

[3] includes 2 FCAS/MWS patients.

	FCAS N= 42	MWS[3] N= 169	NOMID N= 32	Atypical CAPS N= 18	Other N= 24	All CAPS N= 243	All Registry Patients N=285

[4] one patients is missing due to having baseline vaccination but not further follow-up vaccination information as no vaccination data were entered by the site

Table 10-26 summarizes the number of patients, by age group, who received at least 1 dose of vaccine of any type and those who reported at least 1 reaction to vaccination. The proportion of patients receiving at least 1 vaccine of any type was similar across age categories, ranging from 22.2% in patients <4 years to 33.3% in patients 12-<18 years. There were no reactions to vaccination reported in patients ≥65 years. Most patients reporting at least 1 reaction to vaccination were >18 years.

Table 10-26 Exposure and reactions to vaccination by age group

	Infant <4 N= 9	Child 4- <6 N= 15	Child 6- <12 N= 38	Adolescent 12- <18 N= 45	Adult 18- <65 N=164	Elderly ≥65 N= 14
Received at least 1 dose of vaccine[1]						
n (%)	2 (22.2)	4 (26.7)	10 (26.3)	15 (33.3)	52 (31.7)	4 (28.6)
Unknown/Missing, n (%)	1 (11.1)	2 (13.4)	13 (34.2)	3 (6.7)	21 (12.8)	4 (28.5)
Reported at least 1 reaction among vaccinated[2]						
n (%)	1 (50.0)	1 (25.0)	1 (10.0)	3 (20.0)	13 (25.0)	0

Source: Table 14.2-6.5g, Listing 16.2.5-1.5a

N: number of patients in each age group.

[1] denominator=N.

[2] denominator=total patients who received at least 1 vaccine in each age group.

Table 10-27 summarizes the patients who were exposed vaccines and the number of doses received per type of vaccine. Patients could receive more than 1 vaccine. Among the 87 patients who received vaccinations, the most frequent vaccine received was the influenza vaccine, followed by the pneumococcal vaccine. The highest number of vaccine doses administered (n=131) was also registered for the influenza vaccine.

Other vaccines were received by 39 patients during the study and included: human papillomavirus (HPV) (n=1, 1.1%); tetanus only (n=7, 8.0%); varicella (n=1, 1.1%); measles, mumps and rubella (MMR) (n=2, 2.3%); hepatitis A (n=6, 6.9%); hepatitis B (n=8, 9.2%); polio (n= 2, 2.3%); Lyme disease (n=1, 1.1%); and typhoid (n= 3, 3.4%) vaccines; another 8 patients (9.2%) received other vaccines not specified.

Table 10-27 Exposure to vaccination by type of vaccine

N= 87 Patients Vaccinated	Influenza	Pneumococcal	Tetanus, diphtheria and pertussis	Other vaccines
Patients exposed, n (%)	65 (74.7)	22 (25.3)	6 (6.9)	39 (44.8)
Doses received, n	131	25	6	42

Source: Table 14.2-6.5g, Table 14.2-6.6g

Patients could be exposed to more than 1 vaccine.

Table 10-28 summarizes the type and frequency of reactions following vaccination. Reactions to vaccination were reported with influenza, pneumococcal, and tetanus, diphtheria and pertussis vaccines. There were no reactions reported with other vaccines.

Overall, 6 patients (n=6/65, 9.2%) vaccinated for influenza,13 patients (n=13/22, 59.1%) vaccinated for pneumococcal vaccination and 2 patients (n=2/6, 33.3%) for tetanus, diphtheria and pertussis vaccination reported at least one site reaction with the most frequent signs being local pain redness and swelling.

The majority of the reactions were noted with pneumococcal vaccination compared to those exposed to influenza, tetanus, diphtheria, pertussis vaccines. Pain, redness and swelling were the most frequently reported reactions followed by fever and other reactions. Neither of the 2 patients exposed to tetanus, diphtheria and pertussis vaccine reported fever or other reactions. Other reactions observed in patients who received influenza or pneumococcal vaccination were headache and nausea (n=1), cellulitis of left arm (n=2), and shingles and burst of original symptoms (n=1) (following influenza vaccination).

Table 10-28 Type and frequency of reaction to vaccination

	Influenza N= 65	Pneumococcal N= 22	Tetanus, diphtheria and pertussis N= 6
Patients with at least one reaction, n (%)	6 (9.2)	13 (59.1)	2 (33.3)
Type of reaction[1]			
Fever	2 (3.1)	7 (31.8)	0 (0.0)
Pain	3 (4.6)	13 (59.1)	2 (33.3)
Redness	4 (6.2)	12 (54.5)	2 (33.3)
Swelling	4 (6.2)	10 (45.5)	2 (33.3)
Other	1 (1.5)	3 (13.6)	0

Source: Table 14.2-6.5g, Table 14.2-6.6g, Listing 16.2.5-1.5a

N: number of patients exposed to the vaccine.

[1]Patients could have experienced more than 1 reaction.

Of note, the CRF was not designed to capture the severity of the vaccinations reactions displayed in Table 10-28. An assessment of the seriousness of vaccination reactions may be provided by evaluation of SAEs related to vaccination. All serious reactions resolved while the patient remained on Ilaris treatment.

Six patients recorded 8 SAEs, all in association with pneumococcal vaccination and suspected to be related to Ilaris (Table 14.3.1-1.5b; Listing 16.2.7-1.1).

One NOMID patient aged 4-6 years had a non-serious AE of erysipelas and this event reoccurred and was reported as serious after the patient received a pneumococcal vaccine. The serious erysipelas resolved while the patient was still on treatment with Ilaris.

One MWS patient aged 18-<65 years reported 1 SAE of vaccination site cellulitis (of the left arm) and 1 SAE of bacterial meningitis; the latter led to hospitalization. Relevant concomitant medication included corticosteroids and interleukin-1 inhibitor. Both events resolved while the patient was still on treatment with Ilaris.

One NOMID patient aged 18- <65 years reported 1 SAE of cellulitis of the left arm. The event resolved while the patient was still on treatment with Ilaris.

Three MWS patients (2 patients 12-<18 years and 1 patient 18-<65 years) reported 3 SAEs of vaccination site inflammation. The patient 18-<65 years also reported an SAE of vaccination complication described as fever. All events resolved while the patient was still on treatment with Ilaris.

10.5.10 Pregnancy and lactation

There were 8 pregnancies reported in 7 patients during the course of the study (5 MWS patients, 2 FCAS patients). One pregnancy event was reported with exposure to Ilaris at week 8 of gestation by which time the patient switched from Ilaris to anakinra. Outcome of the pregnancy was not reported.

There were 3 abortions reported, 2 of which were reported as serious in 1 patient after Ilaris was discontinued due to patient's desire for pregnancy.

10.5.11 Long term effect on kidney function

There were 13 AEs reported in CAPS patients as laboratory findings suggestive of renal function impairment including clearance creatinine decreased (n=1 MWS patient), protein urine presence (n=12 with n=4 FCAS, n=3 MWS, and n=5 NOMID), and urine protein/creatinine ratio increased (n=1 MWS patient). Amongst them, there was only 1 event of renal failure reported in a NOMID patient with medical history of nephropathy, pyelonephritis, proteinuria, and chronic kidney disease that was not considered related to Ilaris by the Investigator.

10.6 Adverse events by indication and age group

Safety data for CAPS patients

Additional safety data are presented below for all CAPS patients. Table 10-29 and Table 10-30 summarize all AEs and SAEs by SOC term by indication, respectively. There were 914 AEs reported in 187 CAPS patients (77.0%, IR 103.16, 95% CI 96.58-110.07) and 128 SAEs reported in 68 CAPS patients (28.0%, IR 14.45, 95% CI 12.05-17.18).

Among all indications, approximately 80% of patients within each indication category reported experiencing an AE, with the exception of FCAS patients (61.9%) (Table 14.3.1-1.3a, Table 14.3.1-1.1a). For FCAS patients there were 114 AEs for 26 patients (61.9%, IR 79.54, 95% CI 65.61-95.55), for MWS patients there were 681 events for 134 patients (79.3%, IR

107.58, 95% CI 99.65-115.97), and for NOMID patients there were 119 events for 27 patients (83.3%, IR 108.48, 95% CI 89.87-129.81).

Infection and Infestation-related AEs were reported most frequently, with nearly half of all CAPS patients experiencing at least 1 event. Infection and Infestation-related AEs also had the highest incidence rate, with approximately 39 AEs occurring per 100 person-years among CAPS patients. Within this SOC, nasopharyngitis had the highest frequency and incidence rate with approximately 10 cases per 100 person-years. Other high frequency Infections and Infestations among CAPS patients included gastroenteritis (20 events for 17 patients with an IR of 2.26, 95% CI 1.38-3.49), influenza (16 events for 12 patients with an IR of 1.81, 95% CI 1.03-2.93), and tonsillitis (14 events for 12 patients with an IR of 1.58, 95% CI 0.86-32.65).

Incidence of Infections and Infestations was similar across all CAPS indications with an approximate IR of 40 events per 100 person-years; nasopharyngitis and gastroenteritis had the highest incidence among all other PTs classified within this SOC.

General Disorders and Administration Site conditions were the next most commonly reported SOC, with 76 total events in 48 (19.8%) of CAPS patient resulting in approximately 9 events per 100 person-years. Within this SOC, fatigue and pyrexia were reported most frequently. The IR of events reported in this SOC for FCAS patients was 2.79 events in 4 patients, 62 events reported in 37 MWS patients (9.79 IR , 95% CI 7.51, 12.56), and 10 events reported in 7 NOMID patients (9.12 IR , 95% CI 4.37, 16.76). No PT under any indication was above the threshold (≥10%) for reporting.

Under the Gastrointestinal Disorder SOC, 17% of CAPS patients reported experiencing at least 1 gastrointestinal disorder event, resulting in an incidence rate of approximately 7 events per 100 person-years. Among Gastrointestinal Disorders, diarrhea events occurred at least twice as often compared to all other PTs (13 events among 11 CAPS patients; IR 1.47 events per 100 person-years). FCAS patients had 8 events among 7 patients (16.7%) with approximately 5.5 events per 100 person-years. MWS patients had 51 events for 31 patients (18.3%) with an IR of 8.06 (95% CI 6.00-10.59) and NOMID patients had 6 events in 3 patients (9.4%). Incidence of events under the Nervous System Disorders SOC was 6.21 for all CAPS patients. The incidence reported among NOMID patients (IR: 15.50 per 100-person-years [9.03-24.81] was approximately 3 times higher than the other CAPS indications; headache events had the highest incidence rate within this SOC among NOMID patients (IR: 9.12 events per 100-person-years [4.37-16.76]).

Under the Investigations SOC, nearly 14% of CAPS patients reported at least 1 investigation event with an IR of 5.19 events per 100 person-years (95% CI 3.80-6.92). There were a total of 9 events in 8 FCAS patients with an IR of 6.28 events per 100 person-years, 30 events in 20 MWS patients with an IR of nearly 5 events per 100 person-years, and 7 events in 5 NOMID patients with an IR of just over 6 events per 100 person-years. Only 1 PT was common for any indication with 5 events of protein urine in 4 NOMID patients.

Among CAPS patients, there were 42 events in 31 patients with a nearly 5 events per 100-person-years for the Skin and Subcutaneous Tissue Disorder SOC. The events were reported in 14% of FCAS, 11% of MWS patients and 22% of NOMID patients (8 events in 7 patients). The only PT that stood out among CAPS patients was 2 events of rash in 2 NOMID patients.

Table 10-29 Adverse events regardless of study drug relationship for CAPS patients - all SOCs reported

	Indication[1]															
	FCAS N = 42				MWS N = 169				NOMID N = 32				CAPS Patients N = 243			
Primary System Organ Class	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Any AE	26(61.9)	114	79.54	(65.61, 95.55)	134(79.3)	681	107.58	(99.65, 115.97)	27(84.4)	119	108.48	(89.87, 129.81)	187(77.0)	914	103.16	(96.58, 110.07)
Blood and lymphatic system disorders	0(0.0)	0	0.00	(0.00, 0.00)	9(5.3)	9	1.42	(0.65, 2.70)	1(3.1)	1	0.91	(0.02, 5.08)	10(4.1)	10	1.13	(0.54, 2.08)
Cardiac disorders	0(0.0)	0	0.00	(0.00, 0.00)	8(4.7)	11	1.74	(0.87, 3.11)	0(0.0)	0	0.00	(0.00, 0.00)	8(3.3)	11	1.24	(0.62, 2.22)
Congenital, familial and genetic disorders	0(0.0)	0	0.00	(0.00, 0.00)	4(2.4)	4	0.63	(0.17, 1.62)	0(0.0)	0	0.00	(0.00, 0.00)	4(1.6)	4	0.45	(0.12, 1.16)
Ear and labyrinth disorders	2(4.8)	2	1.40	(0.17, 5.04)	23(13.6)	28	4.42	(2.94, 6.39)	5(15.6)	12	10.94	(5.65, 19.11)	30(12.3)	42	4.74	(3.42, 6.41)
Endocrine disorders	1(2.4)	1	0.70	(0.02, 3.89)	2(1.2)	2	0.32	(0.04, 1.14)	0(0.0)	0	0.00	(0.00, 0.00)	3(1.2)	3	0.34	(0.07, 0.99)
Eye disorders	3(7.1)	4	2.79	(0.76, 7.15)	14(8.3)	20	3.16	(1.93, 4.88)	4(12.5)	5	4.56	(1.48, 10.64)	21(8.6)	29	3.27	(2.19, 4.70)
Gastrointestinal disorders	7(16.7)	8	5.58	(2.41, 11.00)	31(18.3)	51	8.06	(6.00, 10.59)	3(9.4)	6	5.47	(2.01, 11.90)	41(16.9)	65	7.34	(5.66, 9.35)
General disorders and administration site conditions	4(9.5)	4	2.79	(0.76, 7.15)	37(21.9)	62	9.79	(7.51, 12.56)	7(21.9)	10	9.12	(4.37, 16.76)	48(19.8)	76	8.58	(6.76, 10.74)
Hepatobiliary disorders	0(0.0)	0	0.00	(0.00, 0.00)	4(2.4)	5	0.79	(0.26, 1.84)	0(0.0)	0	0.00	(0.00, 0.00)	4(1.6)	5	0.56	(0.18, 1.32)
Immune system disorders	1(2.4)	1	0.70	(0.02, 3.89)	3(1.8)	4	0.63	(0.17, 1.62)	1(3.1)	1	0.91	(0.02, 5.08)	5(2.1)	6	0.68	(0.25, 1.47)

Primary System Organ Class	Indication[1]															
	FCAS N = 42				MWS N = 169				NOMID N = 32				CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Infections and infestations	21(50.0)	54	37.68	(28.30, 49.16)	84(49.7)	244	38.55	(33.86, 43.70)	16(50.0)	45	41.02	(29.92, 54.89)	121(49.8)	343	38.71	(34.72, 43.03)
Injury, poisoning and procedural complications	4(9.5)	6	4.19	(1.54, 9.11)	20(11.8)	29	4.58	(3.07, 6.58)	0(0.0)	0	0.00	(0.00, 0.00)	24(9.9)	35	3.95	(2.75, 5.49)
Investigations	8(19.0)	9	6.28	(2.87, 11.92)	20(11.8)	30	4.74	(3.20, 6.77)	5(15.6)	7	6.38	(2.57, 13.15)	33(13.6)	46	5.19	(3.80, 6.92)
Metabolism and nutrition disorders	1(2.4)	1	0.70	(0.02, 3.89)	4(2.4)	4	0.63	(0.17, 1.62)	0(0.0)	0	0.00	(0.00, 0.00)	5(2.1)	5	0.56	(0.18, 1.32)
Musculoskeletal and connective tissue disorders	5(11.9)	8	5.58	(2.41, 11.00)	21(12.4)	35	5.53	(3.85, 7.69)	1(3.1)	4	3.65	(0.99, 9.34)	27(11.1)	47	5.30	(3.90, 7.05)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1(2.4)	1	0.70	(0.02, 3.89)	10(5.9)	13	2.05	(1.09, 3.51)	0(0.0)	0	0.00	(0.00, 0.00)	11(4.5)	14	1.58	(0.86, 2.65)
Nervous system disorders	5(11.9)	5	3.49	(1.13, 8.14)	29(17.2)	33	5.21	(3.59, 7.32)	11(34.4)	17	15.50	(9.03, 24.81)	45(18.5)	55	6.21	(4.68, 8.08)
Pregnancy, puerperium and perinatal conditions	0(0.0)	0	0.00	(0.00, 0.00)	4(2.4)	5	0.79	(0.26, 1.84)	0(0.0)	0	0.00	(0.00, 0.00)	4(1.6)	5	0.56	(0.18, 1.32)
Psychiatric disorders	0(0.0)	0	0.00	(0.00, 0.00)	8(4.7)	9	1.42	(0.65, 2.70)	1(3.1)	1	0.91	(0.02, 5.08)	9(3.7)	10	1.13	(0.54, 2.08)
Renal and urinary disorders	0(0.0)	0	0.00	(0.00, 0.00)	4(2.4)	4	0.63	(0.17, 1.62)	0(0.0)	0	0.00	(0.00, 0.00)	4(1.6)	4	0.45	(0.12, 1.16)
Reproductive system and breast disorders	0(0.0)	0	0.00	(0.00, 0.00)	5(3.0)	8	1.26	(0.55, 2.49)	0(0.0)	0	0.00	(0.00, 0.00)	5(2.1)	8	0.90	(0.39, 1.78)
Respiratory, thoracic and	2(4.8)	3	2.09	(0.43, 6.12)	22(13.0)	32	5.06	(3.46, 7.14)	2(6.3)	2	1.82	(0.22, 6.59)	26(10.7)	37	4.18	(2.94, 5.76)

Primary System Organ Class	Indication[1]															
	FCAS N = 42				MWS N = 169				NOMID N = 32				CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
mediastinal disorders																
Skin and subcutaneous tissue disorders	6(14.3)	6	4.19	(1.54, 9.11)	18(10.7)	28	4.42	(2.94, 6.39)	7(21.9)	8	7.29	(3.15, 14.37)	31(12.8)	42	4.74	(3.42, 6.41)
Vascular disorders	1(2.4)	1	0.70	(0.02, 3.89)	8(4.7)	11	1.74	(0.87, 3.11)	0(0.0)	0	0.00	(0.00, 0.00)	9(3.7)	12	1.35	(0.70, 2.37)

Source: Table 14.3.1-1.1a, Table 14.3.1-1.1b, Table 14.3.1-1.3a, Table 14.3.1-1.3b

IR: incidence rate per 100 person-years.

CI: confidence interval.

[1]MWS indication includes diagnoses of MWS and FCAS/MWS, NOMID indication includes diagnoses of NOMID and MWS/NOMID.

The SAEs with the highest incidence rates in CAPS patients were Infections and Infestations (4.85 per 100 person-years), Neoplasms Benign, Malignant, and Unspecified (1.47 per 100 person years), Nervous System Disorders (1.47 per 100 person-years), Gastrointestinal Disorders (1.02 per 100 person-years), and General Disorders and Administration Site Conditions (1.02 per 100 person-years). Within these SOC terms, the most common PT for all CAPS patients included pancreatitis (n=6 events reported in 1 patient), pneumonia (n=5 events reported in 4 patients), headache (n=4 events reported in 3 patients), and vaccination site inflammation (n=3 events reported in 3 patients).

The 6 events of pancreatitis were reported in a MWS patient who was on multiple concomitant medications and the event pancreatitis was considered to be related to underlying cholelithiasis and not suspected to be related to Ilaris by the Investigator. The event was resolved and treatment with Ilaris was ongoing.

Pneumonia was reported in 2 MWS patients, and in 1 NOMID patient in whom the events resolved with continuation of Ilaris. One atypical CAPS patient had 2 episodes of pneumonia which was resolved with treatment. None of the events led to discontinuation of Ilaris.

Headache was reported in 2 NOMID patients: 1 NOMID patient had history of migraine and another NOMID patient with history of glaucoma and increased intracranial pressure developed headache which was resolved without discontinuation of Ilaris. Investigator causality was not suspected with Ilaris in both of these cases. There was 1 MWS patient who experienced worsening of pre-existing headaches which was considered as not suspected to be related to Ilaris by the Investigator and the event was resolved.

Vaccination site inflammation was reported in 3 MWS patients after receiving pneumococcal vaccine and the events resolved in all 3 patients. Investigator causality was suspected to be related to Ilaris in all the 3 cases.

By indication, MWS patients experienced the highest number of SAEs overall and within each of the common SOC terms with the majority of the Infections and Infestation SAEs (n=35) occurring in this population.

Table 10-30 Serious adverse events regardless of study drug relationship for CAPS patients - all SOCs reported

	Indication[1]															
	FCAS N = 42				MWS N = 169				NOMID N = 32				CAPS Patients N = 243			
Primary System Organ Class	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Any SAE	3 (7.1)	4	2.79	(0.76, 7.15)	56 (33.1)	100	15.80	(12.85, 19.21)	9 (28.1)	24	21.88	(14.02, 32.55)	68 (28.0)	128	14.45	(12.05, 17.18)
Blood and lymphatic system disorders	0(0.0)	0	0.00	(0.00, 0.00)	2(1.2)	2	0.32	(0.04, 1.14)	0(0.0)	0	0.00	(0.00, 0.00)	2(0.8)	2	0.23	(0.03, 0.82)
Cardiac disorders	0(0.0)	0	0.00	(0.00, 0.00)	3(1.8)	5	0.79	(0.26, 1.84)	0(0.0)	0	0.00	(0.00, 0.00)	3(1.2)	5	0.56	(0.18, 1.32)
Congenital, familial and genetic disorders	0(0.0)	0	0.00	(0.00, 0.00)	0(0.0)	0	0.00	(0.00, 0.00)	0(0.0)	0	0.00	(0.00, 0.00)	0(0.0)	0	0.00	(0.00, 0.00)
Ear and labyrinth disorders	0(0.0)	0	0.00	(0.00, 0.00)	2(1.2)	2	0.32	(0.04, 1.14)	3(9.4)	3	2.73	(0.56, 7.99)	5(2.1)	5	0.56	(0.18, 1.32)
Eye disorders	0(0.0)	0	0.00	(0.00, 0.00)	2(1.2)	2	0.32	(0.04, 1.14)	1(3.1)	2	1.82	(0.22, 6.59)	3(1.2)	4	0.45	(0.12, 1.16)
Gastrointestinal disorders	0(0.0)	0	0.00	(0.00, 0.00)	4(2.4)	9	1.42	(0.65, 2.70)	0(0.0)	0	0.00	(0.00, 0.00)	4(1.6)	9	1.02	(0.46, 1.93)
General disorders and administration site conditions	0(0.0)	0	0.00	(0.00, 0.00)	6(3.6)	6	0.95	(0.35, 2.06)	3(9.4)	3	2.73	(0.56, 7.99)	9(3.7)	9	1.02	(0.46, 1.93)
Hepatobiliary disorders	0(0.0)	0	0.00	(0.00, 0.00)	3(1.8)	3	0.47	(0.10, 1.39)	0(0.0)	0	0.00	(0.00, 0.00)	3(1.2)	3	0.34	(0.07, 0.99)
Immune system disorders	0(0.0)	0	0.00	(0.00, 0.00)	0(0.0)	0	0.00	(0.00, 0.00)	0(0.0)	0	0.00	(0.00, 0.00)	0(0.0)	0	0.00	(0.00, 0.00)
Infections and infestations	1(2.4)	1	0.70	(0.02, 3.89)	26(15.4)	35	5.53	(3.85, 7.69)	5(15.6)	7	6.38	(2.57, 13.15)	32(13.2)	43	4.85	(3.51, 6.54)

Primary System Organ Class	Indication[1]															
	FCAS N = 42				MWS N = 169				NOMID N = 32				CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Injury, poisoning and procedural complications	2(4.8)	2	1.40	(0.17, 5.04)	4(2.4)	4	0.63	(0.17, 1.62)	0(0.0)	0	0.00	(0.00, 0.00)	6(2.5)	6	0.68	(0.25, 1.47)
Investigations	0(0.0)	0	0.00	(0.00, 0.00)	1(0.6)	1	0.16	(0.00, 0.88)	0(0.0)	0	0.00	(0.00, 0.00)	1(0.4)	1	0.11	(0.00, 0.63)
Metabolism and nutrition disorders	0(0.0)	0	0.00	(0.00, 0.00)	1(0.6)	1	0.16	(0.00, 0.88)	0(0.0)	0	0.00	(0.00, 0.00)	1(0.4)	1	0.11	(0.00, 0.63)
Musculoskeletal and connective tissue disorders	0(0.0)	0	0.00	(0.00, 0.00)	4(2.4)	4	0.63	(0.17, 1.62)	1(3.1)	2	1.82	(0.22, 6.59)	5(2.1)	6	0.68	(0.25, 1.47)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0(0.0)	0	0.00	(0.00, 0.00)	6(3.6)	8	1.26	(0.55, 2.49)	0(0.0)	0	0.00	(0.00, 0.00)	6(2.5)	8	0.90	(0.39, 1.78)
Nervous system disorders	1(2.4)	1	0.70	(0.02, 3.89)	6(3.6)	6	0.95	(0.35, 2.06)	3(9.4)	6	5.47	(2.01, 11.90)	10(4.1)	13	1.47	(0.78, 2.51)
Pregnancy, puerperium and perinatal conditions	0(0.0)	0	0.00	(0.00, 0.00)	2(1.2)	3	0.47	(0.10, 1.39)	0(0.0)	0	0.00	(0.00, 0.00)	2(0.8)	3	0.34	(0.07, 0.99)
Psychiatric disorders	0(0.0)	0	0.00	(0.00, 0.00)	2(1.2)	2	0.32	(0.04, 1.14)	1(3.1)	1	0.91	(0.02, 5.08)	3(1.2)	3	0.34	(0.07, 0.99)
Reproductive system and breast disorders	0(0.0)	0	0.00	(0.00, 0.00)	1(0.6)	1	0.16	(0.00, 0.88)	0(0.0)	0	0.00	(0.00, 0.00)	1(0.4)	1	0.11	(0.00, 0.63)
Respiratory, thoracic and mediastinal disorders	0(0.0)	0	0.00	(0.00, 0.00)	1(0.6)	1	0.16	(0.00, 0.88)	0(0.0)	0	0.00	(0.00, 0.00)	1(0.4)	1	0.11	(0.00, 0.63)

Primary System Organ Class	Indication[1]															
	FCAS N = 42				MWS N = 169				NOMID N = 32				CAPS Patients N = 243			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Skin and subcutaneous tissue disorders	0(0.0)	0	0.00	(0.00, 0.00)	3(1.8)	3	0.47	(0.10, 1.39)	0(0.0)	0	0.00	(0.00, 0.00)	3(1.2)	3	0.34	(0.07, 0.99)
Vascular disorders	0(0.0)	0	0.00	(0.00, 0.00)	2(1.2)	2	0.32	(0.04, 1.14)	0(0.0)	0	0.00	(0.00, 0.00)	2(0.8)	2	0.23	(0.03, 0.82)

Source: Table 14.3.1-1.2a, Table 14.3.1-1.2b, Table 14.3.1-1.4a, Table 14.3.1-1.4b

IR: incidence rate per 100 person-years.

CI: confidence interval.

[1]MWS indication includes diagnoses of MWS and FCAS/MWS, NOMID indication includes diagnoses of NOMID and MWS/NOMID.

Safety data for all registry patients by age group

Table 10-31 and Table 10-32 summarize all AEs and SAEs by SOC term and by age group for all registry patients, respectively. Among all registry patients, a total of 1114 AEs were reported in 223 patients, with an IR of 110.71 per 100 person-years (95% CI 104.30-117.40). This included 44 of 62 (71.0%) patients under 12 years of age, with a total of 218 AEs (Table 14.3.1-1.9a). Among adolescents, 12 to <18 year olds, there were 45 total patients, of whom 37 (82.2%) had 220 AEs and among patients ≥18 years old there were 142 of 178 (79.88%) patients reporting 676 AEs.

The most frequently reported AEs were Infections and Infestations, with more than half of all registry patients (n=146) experiencing 402 events. Among all registry patients, the IR for Infection and Infestation-related AEs was approximately 40 per 100 person-years. The most common events within this SOC included nasopharyngitis (n=100 events), gastroenteritis (n=26 events), influenza (n=20 events), tonsillitis (n=19 events), and urinary tract infection (n=18 events).

The next most commonly reported SOC was General Disorders and Administration Site Conditions with 96 events reported in 58 patients, with a resulting IR of 9.54 events per 100 person-years (95% CI 7.73-11.65). Pyrexia and fatigue were the PTs that occurred most often, with patients reporting 24 events and 23 events, respectively. This was followed closely by Gastrointestinal Disorders SOC, for which the IR was 8.84 events per 100 person-years (95% CI 7.10-10.88). A total of 54 registry patients reported 89 Gastrointestinal Disorders, including 16 diarrhea events and 11 abdominal pain events.

Events related to the Nervous System Disorders SOC were reported in 50 patients (IR: 6.56 events per 100 person-years; 95% CI 5.07-8.34), with 66 events among which the majority were headaches (n=31 events). Almost 14% of all registry patients (n=39) experienced 68 Musculoskeletal and Connective Tissue Disorders, corresponding to an IR of 6.76 events per 100 person-years (95% CI 5.25-8.57). Among Musculoskeletal and Connective Tissue Disorders, arthralgia, back pain, and pain in extremity were the most frequent PTs, with reports of 11 events, 8 events, and 7 events, respectively.

There were 38 patients who experienced 54 events of Respiratory, Thoracic, and Mediastinal Disorders, with an IR of 5.37 events per 100 patient-years (95% CI 4.03-7.00). The majority of these AEs were cough (n=16 events) or oropharyngeal pain (n=12 events). About 46 events related to Skin and Subcutaneous Tissue Disorders occurred in 25 registry patients. The IR for these disorders was 4.57 events per 100 patient-years (95% CI 3.35-6.10), with rash being the most commonly reported PT (n=11 events).

Finally, the events related to SOCs of Investigations and Ear and Labyrinth Disorders each occurred in 34 patients, with 47 and 46 events reported, respectively. The IR for Investigations was 4.67 per 100 person-years (95% CI 3.43-6.21), while the IR for Ear and Labyrinth Disorders was 4.57 per 100 person-years (95% CI 3.35-6.10). The most frequently reported Investigations were the presence of urine protein (n=12 events) and weight gain (n=10 events). Vertigo was the only Ear and Labyrinth Disorder with more than 2 events reported (n=34 events), accounting for almost 75% of all PTs within this SOC.

Across age groups, although the greatest percentage of patients in the adolescent group reported Infections and Infestations as compared to the child and adult age groups (68.9%), patients under 12 years of age had the highest IR, with 46.27 events per 100 person-years (95% CI 37.01-57.14). General Disorders and Administration Site Conditions, as well as Gastrointestinal Disorders, were more frequent in patients under 12 years old and 12 to <18 years old. Conversely, Nervous System Disorders and Musculoskeletal and Connective Tissue Disorders were both less common in children.

Table 10-31 Adverse events regardless of study drug relationship for all registry patients by age group - all SOCs reported

	Age Groups															
	Age: <12 years N = 62				Age: 12 to <18 years N = 45				Patients ≥18 years N = 178				All Registry Patients N = 285			
Primary System Organ Class	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Any AE	44(71.0)	218	117.30	(102.24,133.94)	37(82.2)	220	132.52	(115.58,151.23)	142(79.8)	676	103.30	(95.66,111.39)	223(78.2)	1114	110.71	(104.30,117.40)
Blood and lymphatic system disorders	2(3.2)	2	1.08	(0.13,3.89)	3(6.7)	5	3.01	(0.98,7.03)	8(4.5)	8	1.22	(0.53,2.41)	13(4.6)	15	1.49	(0.83,2.46)
Cardiac disorders	1(1.6)	1	0.54	(0.01,3.00)	0(0.0)	0	0.00	(0.00,0.00)	9(5.1)	13	1.99	(1.06,3.40)	10(3.5)	14	1.39	(0.76,2.33)
Congenital, familial and genetic disorders	2(3.2)	3	1.61	(0.33,4.72)	1(2.2)	1	0.60	(0.02,3.36)	6(3.4)	6	0.92	(0.34,2.00)	9(3.2)	10	0.99	(0.48,1.83)
Ear and labyrinth disorders	2(3.2)	3	1.61	(0.33,4.72)	4(8.9)	4	2.41	(0.66,6.17)	28(15.7)	39	5.96	(4.24,8.15)	34(11.9)	46	4.57	(3.35,6.10)
Endocrine disorders	0(0.0)	0	0.00	(0.00,0.00)	1(2.2)	1	0.60	(0.02,3.36)	3(1.7)	3	0.46	(0.09,1.34)	4(1.4)	4	0.40	(0.11,1.02)
Eye disorders	7(11.3)	8	4.30	(1.86,8.48)	3(6.7)	3	1.81	(0.37,5.28)	16(9.0)	23	3.51	(2.23,5.27)	26(9.1)	34	3.38	(2.34,4.72)
Gastrointestinal disorders	13(21.0)	26	13.99	(9.14,20.50)	12(26.7)	18	10.84	(6.43,17.14)	29(16.3)	45	6.88	(5.02,9.20)	54(18.9)	89	8.84	(7.10,10.88)
General disorders and administration site conditions	14(22.6)	23	12.37	(7.84,18.57)	16(35.6)	29	17.47	(11.70,25.09)	28(15.7)	44	6.72	(4.89,9.03)	58(20.4)	96	9.54	(7.73,11.65)

	Age Groups															
	Age: <12 years N = 62				Age: 12 to <18 years N = 45				Patients ≥18 years N = 178				All Registry Patients N = 285			
Primary System Organ Class	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Hepatobiliary disorders	0(0.0)	0	0.00	(0.00,0.00)	2(4.4)	2	1.20	(0.15,4.35)	5(2.8)	7	1.07	(0.43,2.20)	7(2.5)	9	0.89	(0.41,1.70)
Immune system disorders	3(4.8)	4	2.15	(0.59,5.51)	1(2.2)	1	0.60	(0.02,3.36)	4(2.2)	4	0.61	(0.17,1.57)	8(2.8)	9	0.89	(0.41,1.70)
Infections and infestations	27(43.5)	86	46.27	(37.01,57.14)	31(68.9)	76	45.78	(36.07,57.30)	88(49.4)	240	36.68	(32.18,41.62)	146(51.2)	402	39.95	(36.14,44.05)
Injury, poisoning and procedural complications	3(4.8)	3	1.61	(0.33,4.72)	11(24.4)	17	10.24	(5.97,16.40)	14(7.9)	23	3.51	(2.23,5.27)	28(9.8)	43	4.27	(3.09,5.76)
Investigations	3(4.8)	4	2.15	(0.59,5.51)	6(13.3)	11	6.63	(3.31,11.86)	25(14.0)	32	4.89	(3.34,6.90)	34(11.9)	47	4.67	(3.43,6.21)
Metabolism and nutrition disorders	1(1.6)	1	0.54	(0.01,3.00)	0(0.0)	0	0.00	(0.00,0.00)	4(2.2)	4	0.61	(0.17,1.57)	5(1.8)	5	0.50	(0.16,1.16)
Musculoskeletal and connective tissue disorders	2(3.2)	3	1.61	(0.33,4.72)	9(20.0)	16	9.64	(5.51,15.65)	28(15.7)	49	7.49	(5.54,9.90)	39(13.7)	68	6.76	(5.25,8.57)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0(0.0)	0	0.00	(0.00,0.00)	1(2.2)	1	0.60	(0.02,3.36)	11(6.2)	14	2.14	(1.17,3.59)	12(4.2)	15	1.49	(0.83,2.46)
Nervous system disorders	7(11.3)	11	5.92	(2.95,10.59)	10(22.2)	13	7.83	(4.17,13.39)	33(18.5)	42	6.42	(4.63,8.68)	50(17.5)	66	6.56	(5.07,8.34)
Pregnancy, puerperium and perinatal conditions	0(0.0)	0	0.00	(0.00,0.00)	0(0.0)	0	0.00	(0.00,0.00)	4(2.2)	5	0.76	(0.25,1.78)	4(1.4)	5	0.50	(0.16,1.16)
Psychiatric	2(3.2)	3	1.61	(0.33,4.72)	0(0.0)	0	0.00	(0.00,0.00)	8(4.5)	9	1.38	(0.63,2.61)	10(3.5)	12	1.19	(0.62,2.08)

	Age Groups															
	Age: <12 years N = 62				Age: 12 to <18 years N = 45				Patients ≥18 years N = 178				All Registry Patients N = 285			
Primary System Organ Class	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
disorders																
Renal and urinary disorders	2(3.2)	2	1.08	(0.13,3.89)	0(0.0)	0	0.00	(0.00,0.00)	2(1.1)	2	0.31	(0.04,1.10)	4(1.4)	4	0.40	(0.11,1.02)
Reproductive system and breast disorders	0(0.0)	0	0.00	(0.00,0.00)	1(2.2)	2	1.20	(0.15,4.35)	4(2.2)	6	0.92	(0.34,2.00)	5(1.8)	8	0.80	(0.34,1.57)
Respiratory, thoracic and mediastinal disorders	9(14.5)	16	8.61	(4.92,13.98)	10(22.2)	13	7.83	(4.17,13.39)	19(10.7)	25	3.82	(2.47,5.64)	38(13.3)	54	5.37	(4.03,7.00)
Skin and subcutaneous tissue disorders	13(21.0)	17	9.15	(5.33,14.64)	7(15.6)	7	4.22	(1.70,8.69)	15(8.4)	22	3.36	(2.11,5.09)	35(12.3)	46	4.57	(3.35,6.10)
Vascular disorders	2(3.2)	2	1.08	(0.13,3.89)	0(0.0)	0	0.00	(0.00,0.00)	8(4.5)	11	1.68	(0.84,3.01)	10(3.5)	13	1.29	(0.69,2.21)

Source: Table 14.3.1-1.7a, Table 14.3.1-1.8a, Table 14.3.1-1.9a, Table 14.3.1-1.10a

IR: incidence rate per 100 person-years.

CI: confidence interval.

Among all registry patients, a total of 155 SAEs were reported in 83 (29.1%) patients, giving an IR of 15.40 events per 100 person-years (95% CI 13.07-18.03). There were 31 (29.0%) patients under the age of 18 years who reported a total of 54 SAEs. Patients <12 years old had 26 SAEs among 16 (25.8%) patients and patients 12 to <18 had 28 SAEs among 15 (33.3%) patients. Infections and Infestations occurred most frequently, with 52 SAEs reported in 38 patients. The IR of Infections and Infestations in all registry patients was 5.17 per 100 person-years (95% CI 3.86-6.78), with pneumonia as the most common PT (n=7 events). Regarding the occurrence of Infections and Infestations across the age groups, 13 (21.0%) of the younger patients experienced 15 SAEs, 8 (17.8%) patients in the adolescent group experienced 11 SAEs, and 17 (9.6%) patients in the adult group experienced 26 SAEs. No single type of event occurred in >5% of patients Table 14.3.1-1.9b.

Table 10-32 Serious adverse events regardless of study drug relationship for all registry patients by age group - all SOCs reported

	Age Groups															
	Age: <12 years N = 62				Age: 12 to <18 years N = 45				Patients ≥18 years N = 178				All Registry Patients N = 285			
Primary System Organ Class	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Any SAE	16(25.8)	26	13.99	(9.14,20.50)	15(33.3)	28	16.87	(11.21,24.38)	52(29.2)	101	15.43	(12.57,18.75)	83(29.1)	155	15.40	(13.07,18.03)
Blood and lymphatic system disorders	1(1.6)	1	0.54	(0.01,3.00)	0(0.0)	0	0.00	(0.00,0.00)	1(0.6)	1	0.15	(0.00,0.85)	2(0.7)	2	0.20	(0.02,0.72)
Cardiac disorders	0(0.0)	0	0.00	(0.00,0.00)	0(0.0)	0	0.00	(0.00,0.00)	4(2.2)	7	1.07	(0.43,2.20)	4(1.4)	7	0.70	(0.28,1.43)
Congenital, familial and genetic disorders	1(1.6)	1	0.54	(0.01,3.00)	0(0.0)	0	0.00	(0.00,0.00)	0(0.0)	0	0.00	(0.00,0.00)	1(0.4)	1	0.10	(0.00,0.55)
Ear and labyrinth disorders	0(0.0)	0	0.00	(0.00,0.00)	1(2.2)	1	0.60	(0.02,3.36)	4(2.2)	4	0.61	(0.17,1.57)	5(1.8)	5	0.50	(0.16,1.16)
Eye disorders	0(0.0)	0	0.00	(0.00,0.00)	0(0.0)	0	0.00	(0.00,0.00)	3(1.7)	4	0.61	(0.17,1.57)	3(1.1)	4	0.40	(0.11,1.02)
Gastrointestinal disorders	2(3.2)	2	1.08	(0.13,3.89)	2(4.4)	2	1.20	(0.15,4.35)	4(2.2)	9	1.38	(0.63,2.61)	8(2.8)	13	1.29	(0.69,2.21)
General disorders and administration site conditions	2(3.2)	2	1.08	(0.13,3.89)	4(8.9)	4	2.41	(0.66,6.17)	4(2.2)	4	0.61	(0.17,1.57)	10(3.5)	10	0.99	(0.48,1.83)
Hepatobiliary disorders	0(0.0)	0	0.00	(0.00,0.00)	1(2.2)	1	0.60	(0.02,3.36)	4(2.2)	5	0.76	(0.25,1.78)	5(1.8)	6	0.60	(0.22,1.30)
Immune system	0(0.0)	0	0.00	(0.00,0.00)	1(2.2)	1	0.60	(0.02,3.36)	0(0.0)	0	0.00	(0.00,0.00)	1(0.4)	1	0.10	(0.00,0.55)

	Age Groups															
	Age: <12 years N = 62				Age: 12 to <18 years N = 45				Patients ≥18 years N = 178				All Registry Patients N = 285			
Primary System Organ Class	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
disorders																
Infections and infestations	13(21.0)	15	8.07	(4.52,13.31)	8(17.8)	11	6.63	(3.31,11.86)	17(9.6)	26	3.97	(2.60,5.82)	38(13.3)	52	5.17	(3.86,6.78)
Injury, poisoning and procedural complications	0(0.0)	0	0.00	(0.00,0.00)	3(6.7)	3	1.81	(0.37,5.28)	4(2.2)	4	0.61	(0.17,1.57)	7(2.5)	7	0.70	(0.28,1.43)
Investigations	0(0.0)	0	0.00	(0.00,0.00)	0(0.0)	0	0.00	(0.00,0.00)	1(0.6)	1	0.15	(0.00,0.85)	1(0.4)	1	0.10	(0.00,0.55)
Metabolism and nutrition disorders	0(0.0)	0	0.00	(0.00,0.00)	0(0.0)	0	0.00	(0.00,0.00)	1(0.6)	1	0.15	(0.00,0.85)	1(0.4)	1	0.10	(0.00,0.55)
Musculoskeletal and connective tissue disorders	1(1.6)	1	0.54	(0.01,3.00)	1(2.2)	1	0.60	(0.02,3.36)	5(2.8)	6	0.92	(0.34,2.00)	7(2.5)	8	0.80	(0.34,1.57)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0(0.0)	0	0.00	(0.00,0.00)	0(0.0)	0	0.00	(0.00,0.00)	6(3.4)	8	1.22	(0.53,2.41)	6(2.1)	8	0.80	(0.34,1.57)
Nervous system disorders	1(1.6)	1	0.54	(0.01,3.00)	1(2.2)	1	0.60	(0.02,3.36)	9(5.1)	12	1.83	(0.95,3.20)	11(3.9)	14	1.39	(0.76,2.33)
Pregnancy, puerperium and perinatal conditions	0(0.0)	0	0.00	(0.00,0.00)	0(0.0)	0	0.00	(0.00,0.00)	2(1.1)	3	0.46	(0.09,1.34)	2(0.7)	3	0.30	(0.06,0.87)
Psychiatric disorders	0(0.0)	0	0.00	(0.00,0.00)	0(0.0)	0	0.00	(0.00,0.00)	3(1.7)	3	0.46	(0.09,1.34)	3(1.1)	3	0.30	(0.06,0.87)
Reproductive system and breast disorders	0(0.0)	0	0.00	(0.00,0.00)	0(0.0)	0	0.00	(0.00,0.00)	1(0.6)	1	0.15	(0.00,0.85)	1(0.4)	1	0.10	(0.00,0.55)

Primary System Organ Class	Age Groups															
	Age: <12 years N = 62				Age: 12 to <18 years N = 45				Patients ≥18 years N = 178				All Registry Patients N = 285			
	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI	Patients n (%)	Events n	Events IR	Events 95% CI
Respiratory, thoracic and mediastinal disorders	1(1.6)	1	0.54	(0.01,3.00)	1(2.2)	1	0.60	(0.02,3.36)	1(0.6)	1	0.15	(0.00,0.85)	3(1.1)	3	0.30	(0.06,0.87)
Skin and subcutaneous tissue disorders	1(1.6)	1	0.54	(0.01,3.00)	2(4.4)	2	1.20	(0.15,4.35)	0(0.0)	0	0.00	(0.00,0.00)	3(1.1)	3	0.30	(0.06,0.87)
Vascular disorders	1(1.6)	1	0.54	(0.01,3.00)	0(0.0)	0	0.00	(0.00,0.00)	1(0.6)	1	0.15	(0.00,0.85)	2(0.7)	2	0.20	(0.02,0.72)

Source: Table 14.3.1-1.7b, Table 14.3.1-1.8b, Table 14.3.1-1.9b, Table 14.3.1-1.10b.

IR: incidence rate per 100 person-years.

CI: confidence interval.

11 Discussion

11.1 Key results

The main objective of this Registry was to monitor and assess the long term safety and efficacy of Ilaris in children and adult populations across Europe and the US with particular attention to serious infections, malignancies, hypersensitivity reactions, and vertigo. Among the 285 patients who contributed to the analysis, 243 (85.3%) were classified as CAPS patients, 18 (6.3%) as atypical CAPS patients, and 24 (8.4%) as "Other" indications. Patients were predominately adults (62.5%) and less than 10% was below 6 years of age.

Exposure to Ilaris /other IL1 inhibitor medication before and during the Registry

A considerable number of registry patients (58.9%) were rollover patients, defined as those previously exposed to Ilaris in a clinical trial and/or received IL-1 inhibitor medication, other than Ilaris, with an exposure duration prior to the start of Ilaris at baseline slightly higher in patients <18 years old (47.5 weeks) compared to ≥18 years old (37.6 weeks).

The mean duration of exposure to Ilaris during the course of this Registry was 3.6 years (SD 1.6 years) in the overall registry population, being slightly lower in children aged 6-<12 years and the elderly population (mean of 2.8 and 2.7 years, respectively).

Safety related to /regardless of Ilaris

AEs and SAEs regardless of Ilaris relationship reported during the course of the Registry among all registry patients were a total of 1114 AEs reported in 223 patients (78.2%) and 155 SAEs reported in 83 patients (29.1%). Focusing on CAPS patients (N=243), 187 patients (76.9%) reported 914 AEs and 68 patients (28.0%) reported 128 SAEs. Serious infections were the most frequent types of SAEs, with 43 events in 32 patients (13.2%). A total of 11 CAPS patients (4.5%) had 14 malignancies, 3 CAPS patients (1.2%) had 4 hypersensitivity events, and 21 CAPS patients (8.6%) had 31 vertigo episodes.

Regarding AEs suspected to be related to Ilaris during the course of this Registry among CAPS patients, 109 patients (44.9%) reported 305 events suspected to be related to Ilaris. Infections and Infestations were the most common event reported (126 events in 68 patients) followed by General Disorders and Administration Site Conditions (33 events in 22 patients), which were observed in more children and adolescents compared to adults.

One cancer death was reported which was not suspected to be related to the study drug.

Ilaris long-term efficacy

There was an increase in the proportion of patients having no disease activity over the course of the registry study, in both rollover (from 49.4% at baseline to 64.1% at 12 months) and non-rollover patients (from 31.6% at baseline to 59.1% at 12 months). Similarly there was an increase over time in the proportion of patients presenting with mild/moderate disease activity, while no patients with severe disease activity were reported at 48 months in both groups**.**

At 48 months after baseline, 87.5% of patients (n/N= 126/144) were considered to be stable since last visit; this represented a considerable improvement from the 60.9% of patients (n/N= 131/215) who were recorded as stable at 6 months after baseline. In addition, the proportion of patients reporting any level of improvement was greater than the percentage of those experiencing any level of worsening, at all points in time. There were only 3 registry patients at most during any follow-up visit who presented with a much worsened disease activity.

Among the 83 registry patients aged 6 to <18 years, delay in sexual maturation was reported in 2 patients at last assessment without sexual maturation delay or unknown status at baseline. Conversely, 4 patients diagnosed with delay in sexual maturation at baseline registered no delay at last assessment. Change in sexual maturation was not available for 45 patients (54.2%).

More than half of patients (56.6%) who presented no delay of cognitive function at baseline had no change at last assessment. Change in delay from baseline to last assessment was not available for 30 patients (36.1%).

Mean levels of CRP and SAA tended to decrease over the course of the Registry , though data became scarcer from 54 months of follow-up and beyond.

Altogether, these findings are evidence of the long-term, sustained efficacy of Ilaris.

Ilaris dosing schemes

More than one-third of registry patients (38.9%) received 2 to <3 mg/kg of Ilaris on average since baseline and approximately one-fifth (22.5%) received 1 to <2 mg/kg on average. The majority of registry patients received Ilaris every 7 to 9 weeks during follow-up; with one-third of registry patients receiving Ilaris every 8 weeks (35.0%).

Although almost 25% of all patients (predominantly pediatrics) required a dose change at some point because of a lack of therapeutic effect, only 2.5% of patients in total permanently discontinued Ilaris due to a lack of therapeutic effect, demonstrating that most patients experience a satisfactory therapeutic effect after dose changes.

In conclusion, the dosing patterns observed in the study reflects the dosing scheme as recommended in the Ilaris Summary of Product Characteristics (section 4.2 Posology and method of administration), in terms of dose levels and frequency

Reactions to vaccinations

Of the 285 patients included in the Registry, 87 (30.5%) received at least 1 vaccine of any type, 44 patients (15.4%) had missing or unknown information and the remainder did not receive any vaccines. In total, 19 patients (21.8%, n=19/87) reported at least 1 reaction to vaccine. Reactions to vaccination were reported following influenza, pneumococcal, and tetanus, diphtheria and pertussis vaccination. The highest rate of reactions was observed for the pneumococcal vaccine, with pain, redness, and swelling being the most frequently reported reactions. In addition, 6 patients had 8 SAEs related to pneumococcal vaccination, all of which were suspected to be related to Ilaris and resolved while the patient remained on Ilaris treatment.

The frequency of reporting is, however, in line with that described in Prevenar and Pneumovax 23 SmPC, where swelling, pain, fever and redness reactions were classified as very common (≥1/10) and common (≥1/100), across all age groups (EMA 2016 - update for Pneumovax 23).

11.2 Limitations

One limitation of this study was the small number of patients in the youngest age categories. There were a total of 9 (3.2%) patients <4 years and 15 (5.3%) patients >4 and <6 years old.

Another limitation is that only a fraction of the enrolled population was still available for evaluation from 54 months of follow-up. In addition, missing data led to the inability to assess change from baseline in sexual maturation and neurocognitive development in more than one third of the 6-<18 years age group.

11.3 Interpretation

Adverse events

In the study by Lachmann et al. (Lachmann, 2009), where CAPS patients received Ilaris every 8 weeks for a minimum of 16 weeks for a total study duration of 48 weeks in the last open-label part of the study, a similar proportion of patients reporting AEs (77.4%, n=24/31 patients) was observed compared to this Registry (76.9%). Around twice as many CAPS patients presented SAEs in this Registry (28.0 %) compared to the published study (12.9%, n=4/31 patients). This can be explained by the larger sample size in the Registry (243 versus 31 patients) and by long-term exposure to Ilaris (3.6 years on average versus 5.6 months).

Long-term impact of Ilaris on disease progression

To assess the long-term impact of Ilaris on disease progression, the PGA as well as changes in audiogram, brain MRI and ophthalmological examination were measured at several points in time, after enrollment. Levels of the inflammatory markers SAA and CRP were collected at the same points in time.

Autoinflammatory disease activity was absent or classified as mild/moderate in more than 90% of the patients at all points in time after baseline, as per the PGA. Rollover patients had fewer cases of severe disease compared to non-rollover patients at baseline. Both rollover and non-rollover patients with absent disease activity increased over the course of the study. These results are in line with those reported at the end of part 3 of CACZ885D2304 study, where 97% of patients (n/N= 30/31) were rated as having no or minimal disease activity and the remaining patients reporting mild disease activity, as assessed by the treating physician (Lachmann 2009). The proportion of patients with absent autoinflammatory disease activity was actually higher than the 40% reported at the end of part 2 of the same study, at most points in time. At 48 months after baseline, 87.5% of registry patients (n/N= 126/144) were considered to be stable; this represented an increase of 31.9% from baseline. In addition, the proportion of patients reporting any level of improvement was greater than the percentage of those experiencing any level of worsening, at all points in time. Altogether, these findings are evidence of the long-term, sustained efficacy of Ilaris.

The median level of SAA stabilized at 5.0 mg/L, matching the level found at the end of part 3 CACZ885D2304 study (Lachmann 2009). The theoretical reduction of the long-term risk of AA amyloidosis is, therefore, confirmed in clinical practice.

The median level of CRP at 48 months of follow-up was slightly higher than that reported by Lachmann for the 15 patients who received canakinumab throughout Study CACZ885D2304, 3.0 mg/L versus 1.9 mg/L, respectively, although both values were under the upper limit of normal range for CRP (10 mg/L).

Change in audiogram, brain MRI, and ophthalmological examination results was not possible to assess for 81.8%, 98.9% and 91.2% of patients, respectively. This greatly limits the ability to drawn meaningful conclusions on the impact of Ilaris on these parameters. Overall, 11 patients registered a change from normal results at baseline to abnormal at last assessment, as opposed to 9 patients who reported an improvement from baseline to last assessment.

Long-term impact of Ilaris on sexual maturation and neurocognitive development

Data on the long-term impact of Ilaris on sexual maturation and neurocognitive development was available for 83 patients aged 6 to <18 years included in the Registry.

The very low proportion of patients with delay in sexual maturation at last assessment (2.4%) suggests that Ilaris is not expected to negatively impact the sexual maturation of patients aged 6 to <18 years. Also, there were no meaningful differences between males and females. However, the absence of information on change in sexual maturation in over half of the patients limits the ability to make definitive conclusions on the impact of Ilaris on sexual maturation.

A low proportion of patients presented delay in cognitive development (6.0%), with 12% of patients presenting a grade level in school not appropriate for age at last assessment; thus suggesting minimal impact on those parameters.

Effectiveness of Ilaris

The efficacy of Ilaris was maintained in most patients, as evidenced by the stable or improved autoinflammatory disease activity and good control of inflammatory markers over time.

The very low number of patients who permanently discontinued Ilaris due to lack of therapeutic effect indicates that the treatment was effective and the recommended dose adjustments in cases of insufficient efficacy, as per labeling, were appropriate and effective. The patterns of use of Ilaris reflected the approved label dosing scheme.

Vaccination and reactions to vaccination

The proportion of vaccinated patients who reported at least 1 reaction among those vaccinated (21.8%) did not differ substantially between indications; however, the relatively low number of patients did not allow for a meaningful comparison by indication. Pneumococcal vaccination registered the highest proportion of patients with at least 1 reaction documented (n=14/22, 63.6%). Local and systemic reactions were limited to redness, swelling, pain, and

fever, and have been reported previously in the literature (Kieninger et al 2013; DeStefano et al 2008).

The reactogenicity and safety of inactivated quadrivalent influenza vaccine in comparison to inactivated trivalent vaccine in adults has been evaluated in a Phase III randomized trial; injection site pain was found to be the most commonly reported reaction (59.5% of patients [n/N= 750/1260] in the quadrivalent vaccine group, and 41.2% [n/N= 89/216] to 44.7% [n/N= 93/208] of patients vaccinated with the trivalent vaccine), whereas redness, swelling, and fever were observed in less than 10% of patients in each group (Tinoco et al 2014). A much lower proportion of patients (4.6%) within this study reported pain, and fever, redness, and swelling were equally found in less than 10% of patients.

The reactions associated with pneumococcal vaccination reported in this registry study are consistent with the reactions classified as common (≥1/100) and very common (≥1/10), across all age groups, in Prevenar14 SmPC. The frequencies of reactions following pneumococcal vaccination are in line with those described in Prevenar13 SmPC, with pain and redness for 5 to 6 patients in 10 and fever and swelling for 3 to 5 patients in 10.

The low proportion of vaccinated patients included in this Registry did not allow for a meaningful comparison between the frequency of the reactions recorded during the course of the study and that found in the literature. Nonetheless, the safety profile of vaccines commonly used by the general population is not expected to differ when administered to patients being treated with Ilaris.

11.4 Generalizability

Enrollment in the study was based primarily in Europe and the US. The study population, reflecting the regions involved, was mostly White/Caucasian with few other racial/ethnic groups represented. This may limit generalizability of the results to a broader population worldwide. This same concern can be applied to patients younger than 6 years. While there were a number of older children in the study, there were few young children and therefore safety data in this small sample size should be interpreted with caution. In addition, most of the registry population were CAPS patients thus limiting the generalizability of the results to atypical CAPS forms and “Other” indications.

Considering the current study population and data availability, the observations and conclusions drawn can be representative for CAPS patients.

12 Other information

Not applicable.

13 Conclusion

The benefits and safety of canakinumab treatment in CAPS patients have been demonstrated in a significant number of patients relative to the limited size of the target population. In view of the limited therapeutic options for CAPS patients in Europe, especially in patients 2-12 years of age with NOMID/CINCA, Ilaris addresses a significant unmet medical need.

Study CACZ885D2401 was a 5-year registry study of patients already receiving Ilaris as part of their routine medical care, which included mainly CAPS patients and a substantial proportion of pediatric patients. While patients were followed-up for approximately 4 years in this observational study, total exposure was longer for over 40% of CAPS patients exposed to Ilaris in previous CAPS clinical studies.

Results of Study CACZ885D2401 showed that efficacy was preserved long-term (up to 4 years of follow-up) and there were no new safety concerns. There was a low rate of discontinuation due to lack of therapeutic response, indicating that the treatment is effective and dose adjustments as per labelling in case of insufficient efficacy are appropriate and effective. Disease activity, as measured by PGA, CRP and SAA, improved or remained stable for a majority of patients. The profile of AEs, including infections and other events of interest, reported during the course of this long-term registry study was consistent with the known safety profile for Ilaris.

The cumulative long-term data from this non-interventional registry study confirm the safety of Ilaris treatment in pediatric and adult patients in routine clinical practice. As the efficacy and safety data were both consistent with those of prior clinical studies, the favorable benefit-risk profile of Ilaris remains unchanged.

14 References

Available upon request

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Appendices

Annex 1 – List of stand-alone documents

None

Annex 2 – Additional information

Supportive information provided below.