PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrILARIS®

canakinumab injection

150 mg/1 mL solution for subcutaneous injection

Immunomodulatory Agent, a selective interleukin-1 beta (IL-1β) inhibitor

ATC Code: L04AC08

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, Drug reaction with eosinophilia and systemic symptoms (DRESS)	[06/2025]

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ILARIS® (canakinumab) is an interleukin-1 beta (IL-1β) inhibitor indicated for the treatment of the following autoinflammatory Periodic Fever Syndromes.

Cryopyrin-Associated Periodic Syndromes (CAPS)

ILARIS is indicated for the ongoing management of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children aged 2 years and older, including:

- Familial Cold Autoinflammatory Syndrome (FCAS)/ Familial Cold Urticaria (FCU),
- Muckle-Wells Syndrome (MWS)

ILARIS may also be used in Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/ Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA). Clinical data have not confirmed improvement in CNS symptoms in patients with this phenotype.

Tumor Necrosis Factor receptor Associated Periodic Syndrome (TRAPS)

ILARIS is indicated for the treatment of Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients.

Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)

ILARIS is indicated for the treatment of Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adult and pediatric patients.

Familial Mediterranean Fever (FMF)

ILARIS is indicated for the treatment of Familial Mediterranean Fever (FMF) in adult and pediatric patients.

ILARIS can be given as monotherapy or in combination with colchicine.

ILARIS is also indicated for the treatment of:

Still's Disease

ILARIS is indicated for the treatment of active Still's disease including Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older, and Adult-Onset Still's Disease (AOSD).

1.1 Pediatrics

Pediatrics (<18 years of age):
CAPS, TRAPS, HIDS/MKD, and FMF: Ilaris is not recommended for use in children below the age of 2 years due to the lack of clinical data.
SJIA: The safety and efficacy of Ilaris in patients below the age of 2 years and with a body weight under 9 kg have not been established.

1.2 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of Ilaris did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to canakinumab or to any ingredient in the formulation of Ilaris or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING. A risk for hypersensitivity reactions, which is not uncommon for injectable proteins, cannot be excluded.
- Patients who have active, severe infections (see 8 ADVERSE REACTIONS, Serious Infections).

4 DOSAGE AND ADMINISTRATION

Continued treatment with Ilaris in patients without clinical improvement should be reconsidered by the treating health professional.

4.1 Dosing Considerations

Special populations:

- Renal impairment: No dose adjustment is required in patients with renal impairment. However, clinical experience in such patients is limited.
- Hepatic impairment: Ilaris has not been studied in patients with hepatic impairment.
- Pediatric patients (<18 years of age):

  CAPS, TRAPS, HIDS/MKD, and FMF: Ilaris is not recommended for use in children below the age of 2 years.

  SJIA: The safety and efficacy of Ilaris in SJIA patients under 2 years of age and with a body weight < 9 kg have not been established.
- Geriatric patients (> 65 years of age): No dose adjustment is required in geriatric patients. However, clinical experience in such patients is limited.

4.2 Recommended Dose and Dosage Adjustment

Dosage for CAPS

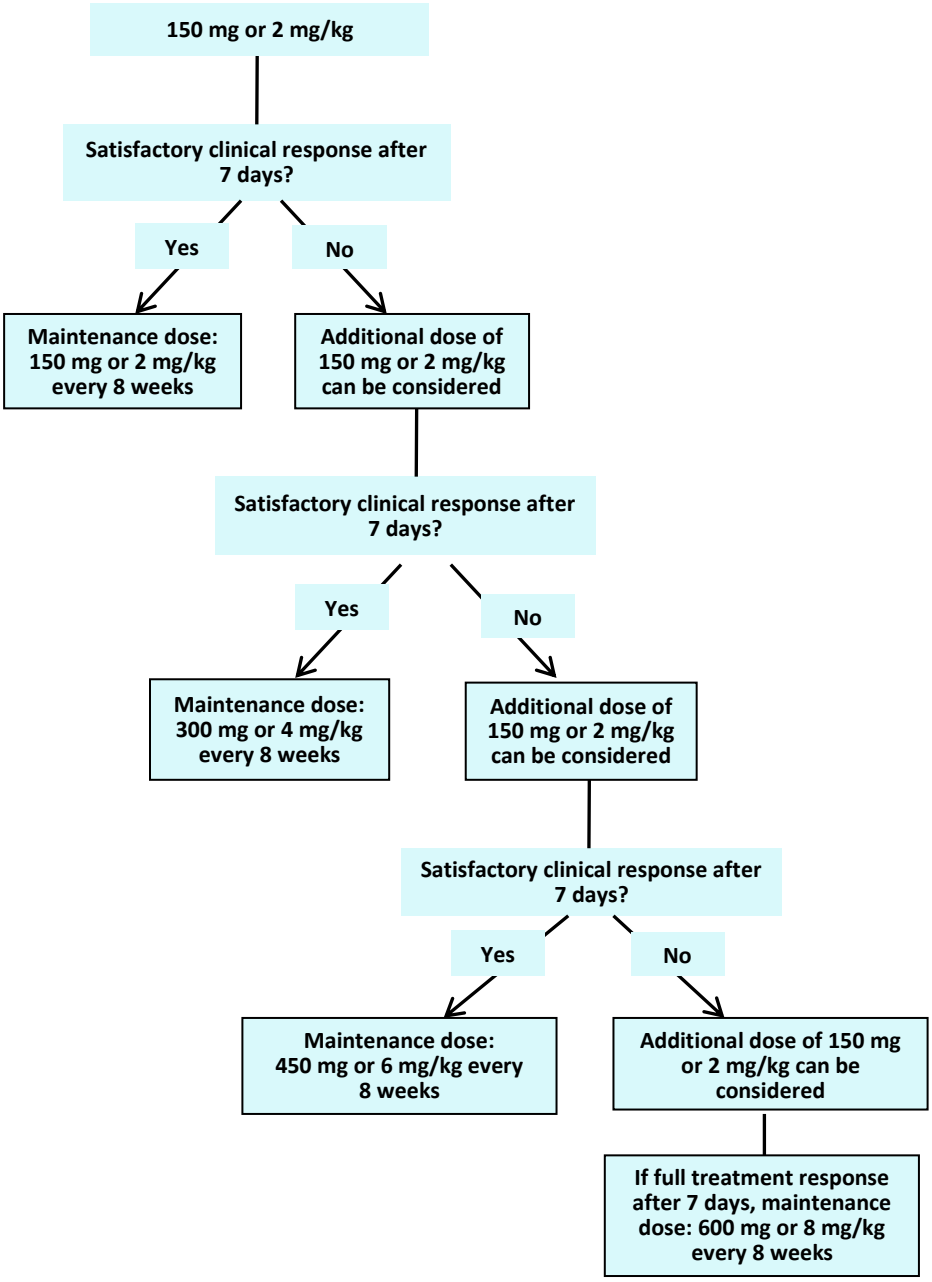
The recommended starting dose of Ilaris for CAPS patients is:

- 150 mg with body weight >40 kg
- 2 mg/kg with body weight ≥15 kg and ≤40 kg

If a satisfactory clinical response (resolution of rash and other generalized inflammatory symptoms) has not been achieved 7 days after the first dose, the dose can be individually adjusted in 150 mg or 2 mg/kg increments **with a minimum of 1 week** observation period for satisfactory treatment response between increases, **to a maximum of 600 mg (body weight > 40 kg) or 8 mg/kg (body weight 15 - 40 kg)**.

If a full treatment response is subsequently achieved, the intensified dose should be maintained and administered every 8 weeks.

Adults and children ≥ 2 years of age ≥ 15 kg



Discontinuation of drug should be considered if an unsatisfactory therapeutic effect persists.

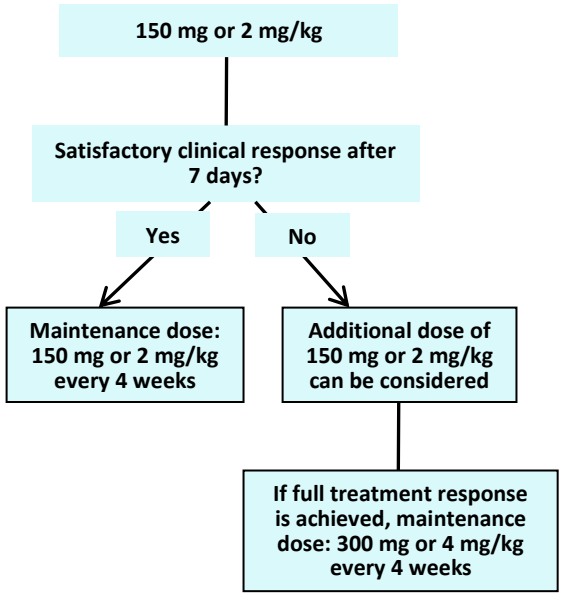
Dosage for TRAPS, HIDS/MKD and FMF

The recommended starting dose of Ilaris for TRAPS, HIDS/MKD and FMF patients is:

- 150 mg with body weight >40 kg
- 2 mg/kg with body weight ≤40 kg

This is administered every four weeks as a single dose via subcutaneous injection.

If a satisfactory clinical response has not been achieved 7 days after the first dose, a second dose of Ilaris at 150 mg or 2 mg/kg can be administered. If a full treatment response (no or minimal disease activity) is subsequently achieved, the intensified dosing regimen of 300 mg or 4 mg/kg every 4 weeks should be maintained.



Dosage for Still's disease (SJIA and AOSD)

The recommended dose of Ilaris for patients with Still's disease with a body weight >9 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection.

4.4 Administration

Treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of CAPS, TRAPS, HIDS/MKD, FMF & / or Still's disease (SJIA and AOSD).

After proper training in injection technique, patients or caregivers may inject Ilaris if their health professional determines that it is appropriate and with medical follow-up as necessary.

Ilaris 150 mg/1 mL solution for injection is supplied in a single-use vial for individual use.

Any unused product or waste material should be disposed of in accordance with local requirements.

Prior to the injection, the vial containing the solution for injection should be left unopened to allow the content to reach room temperature. The vial must not be exposed to heat. The solution should be practically free of visible particles and clear to opalescent. The solution should be colorless or may have a slight brownish-yellow tint. The solution should not be used if particles are present.

Carefully withdraw the required volume depending on the dose to be administered using an appropriate size needle and a 1 mL syringe and subcutaneously inject using a 27 G x 0.5" needle. Once the vial is pierced, use the solution immediately.

Injection into scar-tissue should be avoided as this may result in insufficient exposure to Ilaris.

5 OVERDOSAGE

There is limited experience with overdosage. In early clinical trials, patients and healthy volunteers received doses as high as 10mg/kg administered intravenously or subcutaneously without evidence of acute toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted as necessary.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	150 mg / 1 mL canakinumab solution for injection	Mannitol, L-histidine, L-histidine HCl monohydrate, polysorbate 80, water for injection. No preservatives are present.

Ilaris is supplied in sterile, single-use, colorless 2 mL glass vial closed with a grey stopper, covered with an aluminium crimp seal with plastic flip-off cap. Each vial contains 150 mg/ 1 mL of canakinumab as a clear to opalescent, colorless to slightly brownish yellow solution. A volume of up to 1.0 mL can be withdrawn, which is designed to deliver 150 mg for subcutaneous administration only.

Description

Ilaris (canakinumab) is a genetically engineered high-affinity human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It is expressed in a murine Sp2/0-Ag14 cell line and comprised of two 447- (or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145 kDa. The mechanism of action of canakinumab is to bind to and inactivate IL-1β and thus to inhibit the downstream events of IL-1β signalling.

7 WARNINGS AND PRECAUTIONS

General

Serious infections

Ilaris is associated with an increased incidence of serious infections. Therefore patients should be monitored carefully for signs and symptoms of infections during and after treatment with Ilaris. Health professionals should exercise caution when administering Ilaris to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections. Treatment with Ilaris should not be initiated or continued in patients with active infection requiring medical intervention.

Serious infections were observed in 28.6% of the 2-3 years age group and in 21.4% of the 4-11 year old age group vs. 2.7% in adult CAPS patients. The severe phenotype and disease severity in young children may have played a role in this difference.

Concomitant use of Ilaris with tumour necrosis factor (TNF) inhibitors is not recommended because this may increase the risk of serious infections (see 9 DRUG INTERACTIONS).

Isolated cases of unusual or opportunistic infections (including aspergillosis, atypical mycobacterial infections, herpes zoster) have been reported during Ilaris treatment however no cases have been confirmed to be opportunistic in CAPS patients. A causal relationship of Ilaris to these events cannot be excluded.

Tuberculosis screening

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as Ilaris that block IL-1 increases the risk of TB or other atypical or opportunistic infections.

Prior to initiating immunomodulatory therapies, including Ilaris, patients should be tested for latent tuberculosis infection. Ilaris has not been studied in patients with a positive tuberculosis screen, and the safety of Ilaris in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with Ilaris.

In approximately 12% of CAPS patients tested with a PPD skin test in clinical trials, follow-up testing yielded a positive test result while treated with Ilaris without clinical evidence of a latent or active tuberculosis infection. Before initiation of therapy, all patients must be evaluated for both active and latent tuberculosis infection. Particularly in adult patients, this evaluation should include a detailed medical history and appropriate screening tests. Patients must be monitored closely for signs and symptoms of tuberculosis during and after treatment with Ilaris. In the event of conversion from a negative to a positive PPD test, especially in high-risk patients, alternative means of screening for a tuberculosis infection should be considered.

Cardiovascular

In clinical trials for CAPS, notable changes from baseline in systolic and diastolic blood pressure values were more frequently seen in patients in the canakinumab group than in patients in the placebo group. Blood pressure should be monitored in patients on Ilaris treatment (see 8 ADVERSE REACTIONS, Vital Signs and Physical Findings).

Hepatic/Biliary/Pancreatic

Hepatic function: Rare, mild, transient and asymptomatic cases of elevations of serum transaminases or bilirubin have been reported in clinical trials for CAPS (see 8 ADVERSE REACTIONS, Hepatobiliary Events, and 8.4 Abnormal Laboratory findings: Hematologic and Clinical Chemistry Findings).

Hypersensitivity reactions

Hypersensitivity reactions with Ilaris therapy have been reported. The majority of these events were mild in severity. During clinical trials, no anaphylactoid or anaphylactic reactions attributable to treatment with canakinumab have been reported. However, the risk for severe hypersensitivity reactions, which is not uncommon for injectable proteins, cannot be excluded (see 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS).

Lymphoid organ toxicity

Minimal to slight lymphoid hyperplasia of the spleen and lymph nodes has been infrequently observed in animal studies. Enlargement of lymphoid organs (lymph nodes, spleen), in patients treated with Ilaris, should be assessed for their etiology.

Macrophage activation syndrome in patients with Still's disease (SJIA and AOSD)

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular Still's disease, and should be aggressively treated. Health professionals should be attentive to symptoms of infection or worsening of Still's disease, as these are known triggers for MAS. Eleven cases of MAS were observed in 201 SJIA patients treated with Ilaris in clinical trials. Based on clinical trial experience, Ilaris does not appear to increase the incidence of MAS in Still's disease patients, but no definitive conclusion can be made.

Malignancies

Malignancy events have been reported in patients treated with Ilaris. The risk for the development of malignancies with anti-interleukin (IL)-1 therapy is unknown.

Monitoring and Laboratory Tests (CAPS)

Annual monitoring for changes in lipid profile is recommended.

Neutropenia

Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) has been observed with medicinal products that inhibit IL-1, including Ilaris. Treatment with Ilaris should not be initiated in patients with neutropenia. It is recommended that neutrophil counts be assessed prior to initiating treatment, after 1 to 2 months, and periodically thereafter while receiving Ilaris. If a patient becomes neutropenic the ANC should be monitored closely and treatment discontinuation should be considered.

Vaccinations

Live vaccines should not be given concurrently with Ilaris (see 9 DRUG INTERACTIONS).

Since Ilaris may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving Ilaris. No data are available on the effectiveness of vaccinations with inactivated (killed) antigens in patients receiving Ilaris.

Prior to initiation of Ilaris therapy, adult and pediatric patients should receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. In a dedicated study in healthy volunteers, a normal antibody-response to vaccination with meningococcal and influenza antigen was observed.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has rarely been reported in patients treated with Ilaris, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Patients with DRESS may require hospitalization, as this condition may be fatal. If signs and symptoms of DRESS

are present and an alternative etiology cannot be established, Ilaris should not be readministered and a different treatment considered.

7.1 Special Populations

Patients with Renal Impairment: No formal studies have been conducted to examine the pharmacokinetics of Ilaris administered subcutaneously in patients with renal impairment.

Patients with Hepatic Impairment: No formal studies have been conducted to examine the pharmacokinetics of Ilaris administered subcutaneously in patients with hepatic impairment (see 10 CLINICAL PHARMACOLOGY).

7.1.1 Pregnant Women

Pregnant Women and Women of Child-Bearing Potential: There are no adequate and well-controlled studies of Ilaris in pregnant women or women of child-bearing potential. There is a limited amount of data from the use of Ilaris in this population. Women should use effective contraceptives during treatment with Ilaris and for up to 3 months after the last dose.

A significant shift in the litter size was observed in marmosets treated with 150 mg/kg of canakinumab. Singlet pregnancy that was seen in 0% of animals in the control group, increased to 21% in the treated group and triplet pregnancy in control vs. treated group was down from 45% to 7%. This shift could be an indication of impaired fertility. Delayed ossification was seen in study 0680148 in a mouse model. Because animal reproduction studies are not always predictive of the human response, the risk for the foetus/mother is unknown, therefore, Ilaris should not be given to pregnant women or women who desire to become pregnant, unless clearly needed (see 16 NON-CLINICAL TOXICOLOGY).

Animal studies indicate that canakinumab crosses the placenta and is detectable in the foetus. No human data are available, but as canakinumab is an immunoglobulin of the G class (IgG1), human transplacental transfer is expected. The clinical impact of this is unknown. However, administration of live vaccines to infants exposed to canakinumab in utero is not recommended for 16 weeks following the mother's last dose of Ilaris before childbirth. Women who received Ilaris during pregnancy should be instructed to inform the baby's healthcare professional before any vaccinations are given to their infant.

7.1.2 Breast-feeding

It is not known whether canakinumab is excreted in human milk. Animal studies have shown that a murine anti-murine IL-1 beta antibody had no undesirable effects on development in nursing mouse pups and that the antibody was transferred to them (see 16 NON-CLINICAL TOXICOLOGY).

Breast-feeding is not recommended during Ilaris therapy.

7.1.3 Pediatrics

Pediatrics (<18 years of age):

CAPS, TRAPS, HIDS/MKD, and FMF: Ilaris is not recommended for use in children below the age of 2 years due to the lack of clinical data.

SJIA: The safety and efficacy of Ilaris in patients below the age of 2 years and with a body weight < 9 kg

have not been established.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of Ilaris did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Periodic Fever Syndromes

Cryopyrin-Associated Periodic Syndromes (CAPS)

The data described herein reflect exposure to Ilaris in 194 adult and pediatric CAPS patients (31 FCAS, 110 MWS, 52 NOMID, and 1 miss-classified with cold-induced urticaria) in placebo-controlled and uncontrolled studies. One hundred and seventy-seven (177) patients were exposed to Ilaris for at least 24 weeks, 127 for at least 48 weeks and 8 for at least 144 weeks. A total of 16 patients reported serious adverse drug reactions during the clinical trial program in CAPS, including vertigo (2 patients), increased transaminases (1 patient) and infection (13 patients). The infections included 3 cases of pneumonia considered to be typical and successfully treated, one case of abdominal abscess following appendectomy, bronchitis, cellulitis, chronic tonsillitis, lower respiratory tract infection, sepsis and tonsillitis. Serious infections were observed in 2 (28.6%) of the 2-3 years age group and in 7 (25%) of the 4-11 year old age group vs. 2.7% in adult CAPS patients. The severe phenotype and disease severity in young children may have played a role in this difference. The following were identified as the infectious agents and none were reported more than once: Epstein-Barr virus, H1N1 influenza virus, mumps virus, parvovirus and Staphylococcus. The most commonly reported adverse reaction associated with Ilaris treatment in the CAPS patients were upper respiratory tract infections and nasopharyngitis. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment. One (1) patient discontinued treatment due to infection.

Tumor Necrosis Factor receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF)

A total of 169 adult and pediatric TRAPS, HIDS/MKD, and FMF patients have received Ilaris in one pivotal phase III clinical trial (N2301) that consisted of a 12-week screening period (Part I), and a 16-week, randomized, double-blind, placebo-controlled treatment period (Part II). Ilaris patients were treated with 150 mg subcutaneous or 2 mg/kg if body weight was ≤40 kg. The safety of Ilaris compared to placebo treated patients from the 16-week treatment period (Part II) is shown in Table 1.

In Part II, the most commonly reported adverse reactions (greater than or equal to 10%) associated with Ilaris treatment in TRAPS, HIDS/MKD, and FMF patients were injection site reactions and nasopharyngitis. The reported adverse reactions (greater than or equal to 3%) associated with Ilaris treatment in TRAPS, HIDS/MKD, and FMF patients were injection site reactions (10.1%), and infections including nasopharyngitis (10.7%), upper respiratory tract infection (7.1%), rhinitis (5.3%), gastroenteritis (3.0%), and pharyngitis (3.0%). Serious infections (e.g., conjunctivitis, pneumonia, pharyngitis, pharyngotonsillitis) were observed in approximately 2.4% (0.03 per 100 patient-days) of patients receiving Ilaris in Part II of the TRAPS, HIDS/MKD, and FMF Study N2301.

Overall, there were 43 TRAPS, 68 HIDS/MKD, and 58 FMF patients in the Safety set with a cumulative canakinumab exposure of 47.61 patient-years. The cumulative exposure in the placebo group was 8.03 patient-years.

Table1: Tabulated summary of reported adverse drug reactions from pivotal Periodic Fever Syndromes (TRAPS, HIDS/MKD, FMF) clinical trial

Adverse drug reactions (SOC)	TRAPS, HIDS/MKD, FMF combined	
	Ilaris N=169 n (%)	Placebo N=91 n (%)
Infections and infestations		
Infection (e.g. nasopharyngitis, sinusitis, upper respiratory tract infection, tonsillitis, rhinitis, bronchitis, urinary tract infection, ear infection, gastroenteritis, pharyngitis, pneumonia, vulvovaginal candidiasis, etc.)	72 (42.6%)	14 (15.4%)
General disorders and administration site conditions		
Injection site reactions[1]	17 (10.1%)	2 (2.2%)
Investigations		
Neutrophil count decreased (≥ Grade 2)[2]	11 (6.5%)	3 (3.8%)
Platelet count decreased (≥ Grade 2)[3]	1 (0.6%)	0 (0.0%)

[1] No injection site reaction led to study discontinuation

[2] Based on 168 Ilaris and 79 placebo patients. One patient had an associated mild upper respiratory tract infection.

[3] Based on 169 Ilaris and 80 placebo patients. There was no associated bleeding.

Infections and infestations: Upper respiratory tract infections (24.9%) made up more than half of the reported events, followed by ear infections and lower respiratory tract and lung infections (4.1% respectively).

Abnormal Hematologic and Clinical Chemistry Findings: Most of the newly occurring or worsening hematology abnormalities in Part II in the FMF, HIDS/MKD, and TRAPS cohorts were CTCAE (Common Terminology Criteria for Adverse Events) grade 1 or 2. Most of these hematology abnormalities were decreases in neutrophils, leukocytes and platelets in patients receiving canakinumab. One HIDS/MKD patient and 1 TRAPS patient had a grade 3 neutropenia, and 1 HIDS/MKD patient had a grade 3 thrombocytopenia.

Still's disease (SJIA and AOSD)

The most frequently reported adverse drug reactions were infections predominantly of the upper respiratory tract. The majority of the events were mild to moderate although serious infections were observed.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Periodic Fever Syndromes

Cryopyrin-Associated Periodic Syndromes (CAPS)

To date, 211 patients with CAPS have received Ilaris, including 86 children (aged 28 days to 17 years) in completed clinical trials.

The safety of Ilaris compared with placebo was investigated in a pivotal phase III trial (Study D2304) that consisted of an 8-week, open-label period (Part I), followed by a 24-week, randomized, double-blind and placebo-controlled withdrawal period (Part II), followed by a 16-week open-label period (Part III). All patients were treated with Ilaris 150 mg subcutaneously or 2 mg/kg if body weight was ≥15 kg and ≤40 kg (see Table 2).

In placebo-controlled period in Part II of Study D2304 (canakinumab; n=15 vs. placebo; n=16), with a mean duration of 168.4 days (mean 3 doses) in Ilaris patients and 109.9 days (mean 2.3 doses) in placebo patients, there were more patients in the canakinumab treatment group reporting adverse events in the immune system disorders (13.3% vs. 0), infections and infestations (80% vs. 56.3%), injury, poisoning and procedural complications (26.7% vs. 12.5%), nervous system disorders (26.7% vs. 0), psychiatric disorders (20.0% vs. 6.3%) and respiratory, thoracic and mediastinal disorders (33.3% vs. 6.3%) in system organ classes than in the placebo group.

In all 5 CAPS clinical trials (**Study D2304, A2102, D2306, D2308, and D2201**), a total of 194 unique CAPS patients analysed for safety included 31 FCAS, 110 MWS, 52 NOMID and 1 mis-diagnosed patient with an overall exposure of 269.46 patient-years and a treatment duration of greater than 4 years, with age ranging from 2 to 91 years of age at time of treatment-start with canakinumab. This includes 69 pediatric (2 to 17 years of age; median: 11 years) patients.

Adverse events (AEs) were reported in 88.2% in Study A2102, and in 82.9% (Part I), 100% in canakinumab group and 87.5% in placebo group (Part II) and 77.4% (Part III) of Study D2304. A total of 11 patients reported serious adverse drug reactions during the clinical trial program in CAPS, including vertigo (2 patients), nasopharyngitis (3 patients), upper respiratory tract infection (4 patients), and viral infection (3 patients). The most commonly reported adverse events associated with Ilaris treatment in the CAPS patients were upper respiratory tract infections and nasopharyngitis. There were no deaths reported in any of the 5 clinical trials for CAPS.

Table 2: Number (%) of patients with AEs by primary system organ class and preferred terms, in Parts I, II and III and the entire study D2304 (Safety population)

	Part I	Part II		Part III	Entire Study
Primary system organ class affected	**ACZ885**	**ACZ885**	**Placebo**	**ACZ885**	**ACZ885**
	N=35	**N=15**	**N=16**	**N=31**	**N=35**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
n % of patients with AEs	**29 (82.9)**	**15 (100)**	**14 (87.5)**	**24 (77.4)**	**35 (100)**
Ear and labyrinth disorders	2 (5.7)	1 (6.7)	0 (0.0)	6 (19.4)	8 (22.9)
Tinnitus	0 (0.0)	1 (6.7)	0 (0.0)	1 (3.2)	2 (5.7)
Vertigo	1 (2.9)	0 (0.0)	0 (0.0)	3 (9.7)	4 (11.4)
Gastrointestinal disorders	6 (17.1)	6 (40.0)	5 (31.3)	8 (25.8)	18 (51.4)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)	2 (5.7)

Abdominal pain upper	2 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.7)
Aphthous stomatitis	0 (0.0)	1 (6.7)	1 (6.3)	1 (3.2)	3 (8.6)
Diarrhea	0 (0.0)	1 (6.7)	2 (12.5)	5 (16.1)	7 (20.0)
Mouth ulceration	0 (0.0)	1 (6.7)	0 (0.0)	1 (3.2)	2 (5.7)
Nausea	3 (8.6)	1 (6.7)	1 (6.3)	1 (3.2)	5 (14.3)
Stomach discomfort	1 (2.9)	1 (6.7)	0 (0.0)	0 (0.0)	2 (5.7)
General disorders and administration site conditions	7 (20.0)	3 (20.0)	3 (18.8)	4 (12.9)	14 (40.0)
Asthenia	2 (5.7)	1 (6.7)	0 (0.0)	0 (0.0)	2 (5.7)
Influenza like illness	1 (2.9)	0 (0.0)	0 (0.0)	1 (3.2)	2 (5.7)
Infections and infestations	12 (34.3)	12 (80.0)	9 (56.3)	10 (32.3)	27 (77.1)
Bronchitis	3 (8.6)	1 (6.7)	1 (6.3)	0 (0.0)	4 (11.4)
Gastroenteritis	0 (0.0)	2 (13.3)	1 (6.3)	2 (6.5)	4 (11.4)
Influenza	1 (2.9)	2 (13.3)	3 (18.8)	0 (0.0)	6 (17.1)
Nasopharyngitis	4 (11.4)	4 (26.7)	2 (12.5)	4 (12.9)	12 (34.3)
Oral herpes	1 (2.9)	0 (0.0)	2 (12.5)	0 (0.0)	3 (8.6)
Pharyngitis	0 (0.0)	1 (6.7)	1 (6.3)	2 (6.5)	4 (11.4)
Rhinitis	4 (11.4)	1 (6.7)	2 (12.5)	0 (0.0)	6 (17.1)
Upper respiratory tract infection	0 (0.0)	1 (6.7)	1 (6.3)	1 (3.2)	3 (8.6)
Urinary tract infection	0 (0.0)	2 (13.3)	0 (0.0)	1 (3.2)	2 (5.7)
Viral infection	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)	2 (5.7)
Injury, poisoning and procedural complications	1 (2.9)	4 (26.7)	2 (12.5)	3 (9.7)	9 (25.7)
Joint sprain	0 (0.0)	2 (13.3)	1 (6.3)	0 (0.0)	3 (8.6)
Investigations	3 (8.6)	0 (0.0)	1 (6.3)	2 (6.5)	6 (17.1)
Weight increased	3 (8.6)	0 (0.0)	0 (0.0)	1 (3.2)	4 (11.4)
Musculoskeletal and connective tissue disorders	6 (17.1)	3 (20.0)	2 (12.5)	6 (19.4)	13 (37.1)
Back pain	1 (2.9)	0 (0.0)	0 (0.0)	2 (6.5)	3 (8.6)
Muscle contracture	0 (0.0)	0 (0.0)	1 (6.3)	1 (3.2)	2 (5.7)
Muscle spasms	2 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.7)
Musculoskeletal pain	0 (0.0)	1 (6.7)	1 (6.3)	2 (6.5)	4 (11.4)
Pain in extremity	1 (2.9)	0 (0.0)	0 (0.0)	2 (6.5)	3 (8.6)
Nervous system disorders	4 (11.4)	4 (26.7)	0 (0.0)	9 (29.0)	13 (37.1)
Headache	0 (0.0)	2 (13.3)	0 (0.0)	3 (9.7)	5 (14.3)
Memory impairment	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)	2 (5.7)
Nystagmus	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)	2 (5.7)
Sciatica	1 (2.9)	1 (6.7)	0 (0.0)	2 (6.5)	2 (5.7)

Tension headache	1 (2.9)	0 (0.0)	0 (0.0)	1 (3.2)	2 (5.7)
Psychiatric disorders	1 (2.9)	3 (20.0)	1 (6.3)	2 (6.5)	6 (17.1)
Anxiety	0 (0.0)	1 (6.7)	1 (6.3)	0 (0.0)	2 (5.7)
Depression	0 (0.0)	1 (6.7)	0 (0.0)	1 (3.2)	2 (5.7)
Respiratory, thoracic and mediastinal disorders	5 (14.3)	5 (33.3)	1 (6.3)	5 (16.1)	12 (34.3)
Cough	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)	2 (5.7)
Epistaxis	1 (2.9)	0 (0.0)	1 (6.3)	1 (3.2)	3 (8.6)
Oropharyngeal pain	1 (2.9)	1 (6.7)	0 (0.0)	1 (3.2)	3 (8.6)
Respiratory tract congestion	1 (2.9)	0 (0.0)	0 (0.0)	1 (3.2)	2 (5.7)
Skin and subcutaneous tissue disorders	4 (11.4)	1 (6.7)	0 (0.0)	7 (22.6)	10 (28.6)
Acne	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)	2 (5.7)
Erythema	1 (2.9)	0 (0.0)	0 (0.0)	2 (6.5)	3 (8.6)
Hyperhidrosis	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)	2 (5.7)
Pruritus	1 (2.9)	1 (6.7)	0 (0.0)	1 (3.2)	3 (8.6)
Vascular disorders	2 (5.7)	2 (13.3)	1 (6.3)	0 (0.0)	5 (14.3)
Haematoma	1 (2.9)	0 (0.0)	1 (6.3)	0 (0.0)	2 (5.7)
Hot flush	1 (2.9)	1 (6.7)	0 (0.0)	0 (0.0)	2 (5.7)

Part I: AEs occurring from baseline up to Week 8.

Part II: AEs occurring from Week 8 up to the end of part II.

Part III: AEs occurring from Visit 11 up to the end of study. Entire study: AEs occurring from baseline up to the end of study. AEs preferred terms in each primary system organ class are presented alphabetically.

In the CAPS studies which included a total of 194 adult and pediatric patients with a mean exposure of 507.3 days and which included dose escalations, events of infections (89.3%) (gastroenteritis 21.4%, respiratory tract infection 10.7%, and upper respiratory tract infection 32.1%), vomiting (21.4%) and dizziness (17.9%) were more frequently reported in the 600 mg or 8 mg/kg dose group than in other dose groups. Overall, the adverse events were comparable among the different cohorts by phenotype and by age.

There were seven 2-3 year old patients (six patients had the NOMID phenotype, one patient had MWS). Six of the seven received a dose escalation (two to 300 mg or 4 mg/kg, and four to 600 mg or 8 mg/kg). All patients in this age group experienced infections. The infection events that were more common in these patients represented infections typical of this age group: ear infection (28.6%), gastroenteritis (28.6%), nasopharyngitis (57.1%) and rhinitis (42.9%). None were serious or led to discontinuation and all resolved with no intervention or with standard therapy.

Vertigo: Vertigo AEs were reported for 20 patients (10.3%) in the CAPS population, eight patients (15.4%) in the NOMID group, 11 patients (10.0%) in the MWS group and one patient (3.2%) in the FCAS group.

Hematology: In clinical trials in CAPS, thrombocytopenia AEs were reported for 28 patients (14.4%); one patient in the 2-3 years age group experienced thrombocytopenia-related AEs (see 8 ADVERSE REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative

Data).

Injection Site Reactions: In Study D2304, subcutaneous injection site reactions were observed in 9% of patients in Part I with mild tolerability reactions; in Part II, one patient each (7%) had a mild or a moderate tolerability reaction and, in Part III, one patient had a mild local tolerability reaction. No severe injection-site reactions were reported and none led to discontinuation of treatment. In the 1 clinical study with a controlled portion and 4 uncontrolled clinical studies for CAPS, no patients experienced severe injection site reactions.

Immunogenicity: A specific biosensor binding assay was used to detect antibodies directed against canakinumab in patients who received Ilaris.

Antibodies against Ilaris were observed in approximately 1.5% of the patients treated with Ilaris. One hundred and twenty-seven (127) of 194 CAPS patients had duration of exposure to canakinumab for at least 48 weeks. The data obtained in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, underlying disease, and the number of patients tested. For these reasons, comparison of the incidence of antibodies to canakinumab with the incidence of antibodies to other products may be misleading.

Hepatobiliary Events: In 1 patient a transient and reversible elevation of liver function test (LFT) was reported as "toxic hepatitis" (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Vital Signs and Physical Findings

Overall in the D2304, A2102, D2306 and D2308 studies, isolated elevations in blood pressure and heart rate were recorded in several patients, however, there were no sustained changes, or evidence of a clear pattern of higher blood pressure or changes in heart rate in any patient. Seven patients (3.6%) reported an adverse event associated with hypertension and 4 of those patients required starting or adjustment of anti-hypertensive medications.

Tumor Necrosis Factor receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF)

In the canakinumab group in Study N2301 Part II, the incidence rate of AEs was comparable across the cohorts, with a slightly higher incidence in HIDS/MKD patients: 81.0% in FMF patients, 86.8% in HIDS/MKD patients, and 76.7% in TRAPS patients.

In Part II, the most commonly reported AEs associated with Ilaris treatment in FMF patients were injection site reaction (13.8%), and diarrhea (12.1%). The most commonly reported AEs in HIDS/MKD patients were pyrexia (23.5%), headache (17.6%), and diarrhea and oropharyngeal pain (each 11.8%). The most commonly reported AEs in TRAPS patients were pyrexia (14.0%), and abdominal pain, injection site reaction, and nasopharyngitis (each 11.6%). All injection site reactions were mild and none were SAEs or AEs that led to discontinuation.

In Table 3, the "Total ACZ" group includes all events that occurred from randomization (for those patients randomized to canakinumab) or the day of each patient's first dose of canakinumab (for those patients randomized to placebo who switched to canakinumab) for all cohorts (FMF, TRAPS, or HIDS/MKD) combined for Part II (AEs of special interest only) and Parts II-IV (all safety events).

Table 3: Adverse Events (AEs) with incidence rate ≥ 1% in Total ACZ (canakinumab) group, by primary system organ class and preferred terms, in study N2301 (Safety population)

	TRAPS		HIDS		FMF		Total	
Primary system organ class affected	**ACZ885**	**Placebo**	**ACZ885**	**Placebo**	**ACZ885**	**Placebo**	**ACZ885**	**Placebo**
	N=43	**N=24**	**N=68**	**N=35**	**N=58**	**N=32**	**N=169**	**N=91**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
n % of patients with at least one AEs	34 (79.1)	10 (41.7)	58 (85.3)	24 (68.6)	49 (84.5)	21 (65.6)	141 (83.4)	55 (60.4)
Blood and lymphatic system disorders	4 (9.3)	0 (0.0)	10 (14.7)	5 (14.3)	2 (3.4)	1 (3.1)	16 (9.5)	6 (6.6)
Lymphadenopathy	3 (7.0)	0 (0.0)	6 (8.8)	1 (2.9)	1 (1.7)	0 (0.0)	10 (5.9)	1 (1.1)
Neutropenia	2 (4.7)	0 (0.0)	0 (0.0)	2 (5.7)	1 (1.7)	0 (0.0)	3 (1.8)	2 (2.2)
Ear and labyrinth disorders	2 (4.7)	0 (0.0)	4 (5.9)	1 (2.9)	3 (5.2)	1 (3.1)	9 (5.3)	2 (2.2)
Ear pain	1 (2.3)	0 (0.0)	3 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	0 (0.0)
Tinnitus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (1.2)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)	1 (1.5)	1 (2.9)	1 (1.7)	1 (3.1)	2 (1.2)	0 (0.0)
Eye disorders	4 (9.3)	0 (0.0)	5 (7.4)	0 (0.0)	1 (1.7)	0 (0.0)	10 (5.9)	0 (0.0)
Conjunctivitis allergic	1 (2.3)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Eye pain	1 (2.3)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Ocular hyperaemia	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Gastrointestinal disorders	16 (37.2)	4 (16.7)	21 (30.9)	6 (17.1)	26 (44.8)	3 (9.4)	63 (37.3)	13 (14.3)
Abdominal pain	5 (11.6)	1 (4.2)	7 (10.3)	4 (11.4)	9 (15.5)	2 (6.3)	21 (12.4)	7 (7.7)
Abdominal pain upper	4 (9.3)	1 (4.2)	5 (7.4)	1 (2.9)	3 (5.2)	0 (0.0)	12 (7.1)	2 (2.2)
Aphthous ulcer	0 (0.0)	0 (0.0)	5 (7.4)	0 (0.0)	1 (1.7)	0 (0.0)	6 (3.6)	0 (0.0)
Constipation	0 (0.0)	1 (4.2)	2 (2.9)	0 (0.0)	3 (5.2)	0 (0.0)	5 (3.0)	1 (1.1)
Diarrhea	4 (9.3)	1 (4.2)	9 (13.2)	2 (5.7)	9 (15.5)	1 (3.1)	22 (13.0)	4 (4.4)
Gastritis	3 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	4 (2.4)	0 (0.0)
Gingival swelling	1 (2.3)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Mouth ulceration	1 (2.3)	0 (0.0)	2 (2.9)	1 (2.9)	0 (0.0)	0 (0.0)	3 (1.8)	1 (1.1)
Nausea	2 (4.7)	0 (0.0)	3 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.0)	0 (0.0)
Oesophagitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (1.2)	0 (0.0)
Toothache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (1.2)	0 (0.0)
Umbilical hernia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (1.2)	0 (0.0)
Vomiting	5 (11.6)	1 (4.2)	7 (10.3)	1 (2.9)	3 (5.2)	2 (6.3)	15 (8.9)	4 (4.4)
General disorders and administration site conditions	15 (34.9)	2 (8.3)	34 (50.0)	9 (25.7)	20 (34.5)	4 (12.5)	69 (40.8)	15 (16.5)
Asthenia	2 (4.7)	0 (0.0)	3 (4.4)	0 (0.0)	2 (3.4)	0 (0.0)	7 (4.1)	0 (0.0)
Chills	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.2)	0 (0.0)
Fatigue	2 (4.7)	1 (4.2)	3 (4.4)	0 (0.0)	1 (1.7)	0 (0.0)	6 (3.6)	1 (1.1)

Influenza like illness	2 (4.7)	0 (0.0)	1 (1.5)	0 (0.0)	3 (5.2)	3 (9.4)	6 (3.6)	3 (3.3)
Injection site reaction	5 (11.6)	0 (0.0)	5 (7.4)	1 (2.9)	11 (19.0)	0 (0.0)	21 (12.4)	1 (1.1)
Non-cardiac chest pain	2 (4.7)	0 (0.0)	2 (2.9)	0 (0.0)	3 (5.2)	0 (0.0)	7 (4.1)	0 (0.0)
Oedema peripheral	1 (2.3)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Pyrexia	6 (14.0)	1 (4.2)	25 (36.8)	6 (17.1)	5 (8.6)	2 (6.3)	36 (21.3)	9 (9.9)
Immune system disorders	0 (0.0)	1 (4.2)	2 (2.9)	0 (0.0)	1 (1.7)	0 (0.0)	3 (1.8)	1 (1.1)
Infections and infestations	18 (41.9)	3 (12.5)	46 (67.6)	6 (17.1)	36 (62.1)	5 (15.6)	100 (59.2)	14 (15.4)
Bronchitis	1 (2.3)	0 (0.0)	5 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.6)	0 (0.0)
Conjunctivitis	2 (4.7)	0 (0.0)	2 (2.9)	0 (0.0)	2 (3.4)	0 (0.0)	6 (3.6)	0 (0.0)
Cystitis	1 (2.3)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)
Fungal skin infection	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.2))	0 (0.0
Gastroenteritis	1 (2.3)	0 (0.0)	5 (7.4)	0 (0.0)	2 (3.4)	0 (0.0)	8 (4.7)	0 (0.0)
Impetigo	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Influenza	2 (4.7)	0 (0.0)	4 (5.9)	0 (0.0)	5 (8.6)	1 (3.1)	11 (6.5)	1 (1.1)
Lymphangitis	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Nasopharyngitis	5 (11.6)	0 (0.0)	7 (10.3)	1 (2.9)	6 (10.3)	0 (0.0)	18 (10.7)	1 (1.1)
Oral candidiasis	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Oral herpes	1 (2.3)	0 (0.0)	1 (1.5)	0 (0.0)	2 (3.4)	2 (6.3)	4 (2.4)	2 (2.2)
Otitis externa	0 (0.0)	0 (0.0)	3 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)
Otitis media	2 (4.7)	0 (0.0)	5 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.1)	0 (0.0)
Pharyngitis	1 (2.3)	0 (0.0)	3 (4.4)	0 (0.0)	2 (3.4)	0 (0.0)	6 (3.6)	0 (0.0)
Pharyngotonsillitis	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (3.4)	0 (0.0)	3 (1.8)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	4 (5.9)	0 (0.0)	1 (1.7)	0 (0.0)	5 (3.0)	0 (0.0)
Respiratory tract infection	1 (2.3)	0 (0.0)	3 (4.4)	1 (2.9)	0 (0.0)	0 (0.0)	4 (2.4)	1 (1.1)
Rhinitis	4 (9.3)	0 (0.0)	6 (8.8)	0 (0.0)	2 (3.4)	1 (3.1)	12 (7.1)	1 (1.1)
Sinusitis	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	3 (1.8)	0 (0.0)
Tonsillitis	1 (2.3)	0 (0.0)	2 (2.9)	0 (0.0)	5 (8.6)	0 (0.0)	8 (4.7)	0 (0.0)
Upper respiratory tract infection	4 (9.3)	1 (4.2)	5 (7.4)	2 (5.7)	8 (13.8)	0 (0.0)	17 (10.1)	3 (3.3)
Urinary tract infection	1 (2.3)	1 (4.2)	1 (1.5)	0 (0.0)	4 (6.9)	0 (0.0)	6 (3.6)	1 (1.1)
Viral infection	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	3 (5.2)	0 (0.0)	5 (3.0)	0 (0.0)
Viral upper respiratory tract infection	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Vulvovaginal candidiasis	0 (0.0)	0 (0.0)	4 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	0 (0.0)
Injury, poisoning and procedural complications	3 (7.0)	1 (4.2)	7 (10.3)	2 (5.7)	6 (10.3)	1 (3.1)	16 (9.5)	4 (4.4)

Ligament sprain	0 (0.0)	0 (0.0)	3 (4.4)	0 (0.0)	1 (1.7)	0 (0.0)	4 (2.4)	0 (0.0)
Road traffic accident	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.2)	0 (0.0)
Investigations	4 (9.3)	0 (0.0)	7 (10.3)	2 (5.7)	4 (6.9)	2 (6.3)	15 (8.9)	4 (4.4)
Alanine aminotransferase increased	1 (2.3)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Blood creatine phosphokinase increased	1 (2.3)	0 (0.0)	3 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	0 (0.0)
Serum amyloid A protein increased	1 (2.3)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Metabolism and nutrition disorders	1 (2.3)	0 (0.0)	1 (1.5)	0 (0.0)	5 (8.6)	1 (3.1)	7 (4.1)	1 (1.1)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (1.2)	0 (0.0)
Obesity	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (3.4)	0 (0.0)	3 (1.8)	0 (0.0)
Musculoskeletal and connective tissue disorders	14 (32.6)	1 (4.2)	16 (23.5)	1 (2.9)	15 (25.9)	3 (9.4)	45 (26.6)	5 (5.5)
Arthralgia	3 (7.0)	1 (4.2)	9 (13.2)	0 (0.0)	5 (8.6)	1 (3.1)	17 (10.1)	2 (2.2)
Back pain	3 (7.0)	0 (0.0)	5 (7.4)	0 (0.0)	2 (3.4)	0 (0.0)	10 (5.9)	0 (0.0)
Musculoskeletal pain	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.7)	1 (3.1)	2 (1.2)	1 (1.1)
Myalgia	2 (4.7)	0 (0.0)	4 (5.9)	0 (0.0)	4 (6.9)	1 (3.1)	10 (5.9)	1 (1.1)
Neck pain	2 (4.7)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)
Pain in extremity	1 (2.3)	1 (4.2)	0 (0.0)	0 (0.0)	5 (8.6)	2 (6.3)	6 (3.6)	3 (3.3)
Nervous system disorders	6 (14.0)	2 (8.3)	18 (26.5)	4 (11.4)	15 (25.9)	2 (6.3)	39 (23.1)	8 (8.8)
Dizziness	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.2)	0 (0.0)
Headache	4 (9.3)	2 (8.3)	15 (22.1)	3 (8.6)	11 (19.0)	2 (6.3)	30 (17.8)	7 (7.7)
Psychiatric disorders	0 (0.0)	0 (0.0)	3 (4.4)	0 (0.0)	5 (8.6)	0 (0.0)	8 (4.7)	0 (0.0)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (1.2)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (1.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	10 (23.3)	0 (0.0)	22 (32.4)	5 (14.3)	9 (15.5)	2 (6.3)	41 (24.3)	7 (7.7)
Asthma	1 (2.3)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Cough	3 (7.0)	0 (0.0)	10 (14.7)	3 (8.6)	2 (3.4)	1 (3.1)	15 (8.9)	4 (4.4)
Epistaxis	2 (4.7)	0 (0.0)	2 (2.9)	0 (0.0)	1 (1.7)	0 (0.0)	5 (3.0)	0 (0.0)
Nasal congestion	0 (0.0)	0 (0.0)	3 (4.4)	1 (2.9)	0 (0.0)	0 (0.0)	3 (1.8)	1 (1.1)
Oropharyngeal pain	4 (9.3)	0 (0.0)	11 (16.2)	1 (2.9)	3 (5.2)	1 (3.1)	18 (10.7)	2 (2.2)
Rhinorrhoea	2 (4.7)	0 (0.0)	2 (2.9)	1 (2.9)	0 (0.0)	0 (0.0)	4 (2.4)	1 (1.1)
Skin and subcutaneous tissue disorders	11 (25.6)	2 (8.3)	11 (16.2)	3 (8.6)	9 (15.5)	1 (3.1)	31 (18.3)	6 (6.6)
Eczema	2 (4.7)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	0 (0.0)

Erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.9)	0 (0.0)	4 (2.4)	0 (0.0)
Hidradenitis	1 (2.3)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)
Petechiae	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.2)	0 (0.0)
Psoriasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (1.2)	0 (0.0)
Rash	3 (7.0)	1 (4.2)	1 (1.5)	1 (2.9)	1 (1.7)	1 (3.1)	5 (3.0)	3 (3.3)
Rash macular	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Urticaria	3 (7.0)	1 (4.2)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.0)	1 (1.1)

Systemic Juvenile Idiopathic Arthritis (SJIA)

A total of 201 SJIA patients aged 2 to <20 years have received Ilaris in clinical trials. The safety of Ilaris compared to placebo was investigated in two pivotal phase III studies (G2305 and G2301). The only reason for discontinuation in Study G2305 was unsatisfactory therapeutic effect (14% for Ilaris and 90% for placebo). In the placebo-controlled portion of Study G2301, the most common reason for discontinuation was unsatisfactory therapeutic effect (22% for Ilaris and 40% of placebo), followed by adverse event (8%, placebo group only). In both trials, infections were the most common type of adverse event reported followed by abdominal pain (upper). In Study G2305, 30% of Ilaris treated patients reported an infection adverse event. Serious infections were reported for two canakinumab treated patients (bronchopneumonia and varicella) as compared to one patient (gastroenteritis) in the placebo group. No serious infections led to discontinuation from the study in any of the treatment groups. In Study G2301, 55% of canakinumab treated patients in Part I and 54% in Part II reported an infection adverse event. In the placebo-controlled portion of Study G2301, serious infections were reported for two (4%) patients in each treatment group. Serious infections reported in the canakinumab group included respiratory tract infection (n=1) and otitis media (n=1), in both cases requiring hospitalization. None of the canakinumab treated patients discontinued the study due to serious infection. Two patients reporting a total of four serious infections in the placebo group discontinued the study (n=1 septic shock, sepsis and n=1 measles, pneumonia). The following were identified as the infectious agents in these two pivotal trials: herpes virus; adenovirus, coxsackie virus; Epstein-Barr virus; molluscum contagiosum; varicella virus; Enterobiasis; and varicella. All but herpes virus (n=8) and varicella virus (n=3) were reported in only one patient. No confirmed opportunistic infections were reported in any SJIA clinical trial (see 14 CLINICAL TRIALS).

Adult-Onset Still's Disease (AOSD)

The safety profile of Ilaris in AOSD patients in a randomized, double blind placebo-controlled study (GDE01T) in 36 adult patients (aged 22 to 70 years) was similar to what was observed in SJIA patients.

Table 4: Tabulated summary of adverse drug reactions from pivotal SJIA clinical trials

	G2301			G2305	
	Part I	Part II			
	Ilaris N=177 n (%)	Ilaris N=50 n (%)	Placebo N=50 n (%)	Ilaris N=43 n (%)	Placebo N=41 n (%)
Infections and infestations					
Infection (e.g. nasopharyngitis, (viral) upper respiratory tract infection, pneumonia, rhinitis, pharyngitis, tonsillitis, sinusitis, urinary tract infection, gastroenteritis, viral infection)	97 (54.8%)	27 (54%)	19 (38%)	13 (30.2%)	5 (12.2%)
Gastrointestinal disorders					
Abdominal pain (upper)	25 (14.1%)	8 (16%)	6 (12%)	3 (7%)	1 (2.4%)
General disorders and administration site conditions					
Injection site reaction[1]					
mild	19 (10.7%)	6 (12.0%)	2 (4.0%)	0	3 (7.3%)
moderate	2 (1.1%)	1 (2.0%)	0	0	0

[1] No injection site reaction led to study discontinuation

Table 5: Number (%) of patients with AEs by primary system organ class and preferred terms, in Parts I, II in study G2301 and study G2305 (Safety population)

	Study G2305		Study G2301		
			Part I	Part II	
Primary system organ class affected	**ACZ885**	**Placebo**	**ACZ885**	**ACZ885**	**Placebo**
	N=43	**N=41**	**N=177**	**N=50**	**N=50**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
n % of patients with AEs	**24 (55.8)**	**16 (39.0)**	**138 (78.0)**	**40 (80.0)**	**35 (70.0)**
Blood and lymphatic system disorders	1 (2.3)	1 (2.4)	8 (4.5)	3 (6.0)	4 (8.0)
Lymphadenopathy	0	0	0	2 (4.0)	2 (4.0)
Anemia	0	0	2 (1.1)	1 (2.0)	0
Neutropenia	1 (2.3)	0	2 (1.1)	0	0
Leukopenia	1 (2.3)	0	1 (0.6)	0	0
Ear and labyrinth disorders	1 (2.3)	1 (2.4)	6 (3.4)	4 (8.0)	0
Ear pain	0	0	4 (2.3)	2 (4.0)	0
Tinnitus	1 (2.3)	1 (2.4)	0	0	0
Middle ear effusion	0	0	0	1 (2.0)	0
Otorrhoea	0	0	0	1 (2.0)	0
Eye disorders	0	1 (2.4)	11 (6.2)	4 (8.0)	5 (10.0)
Conjunctivitis	0	0	2 (1.1)	2 (4.0)	1 (2.0)
Conjunctivitis allergic	0	0	0	2 (4.0)	0

	Study G2305		Study G2301		
			Part I	Part II	
Primary system organ class affected	**ACZ885**	**Placebo**	**ACZ885**	**ACZ885**	**Placebo**
	N=43	**N=41**	**N=177**	**N=50**	**N=50**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
n % of patients with AEs	**24 (55.8)**	**16 (39.0)**	**138 (78.0)**	**40 (80.0)**	**35 (70.0)**
Astigmatism	0	0	0	1 (2.0)	0
Excessive eye blinking	0	0	0	1 (2.0)	0
Myopia	0	0	0	1 (2.0)	1 (2.0)
Gastrointestinal disorders	7 (16.3)	2 (4.9)	52 (29.4)	15 (30.0)	15 (30.0)
Abdominal pain	2 (4.7)	0	17 (9.6)	6 (12.0)	4 (8.0)
Nausea	1 (2.3)	0	9 (5.1)	3 (6.0)	1 (2.0)
Abdominal pain upper	1 (2.3)	1 (2.4)	9 (5.1)	2 (4.0)	2 (4.0)
Aphthous stomatitis	0	0	0	1 (2.0)	0
Cheilitis	0	0	0	1 (2.0)	0
Colitis	0	0	1 (0.6)	1 (2.0)	0
Constipation	1 (2.3)	0	6 (3.4)	1 (2.0)	0
Diarrhoea	3 (7.0)	1 (2.4)	17 (9.6)	1 (2.0)	3 (6.0)
Gastritis	0	0	0	1 (2.0)	1 (2.0)
Gastrointestinal disorder	0	0	0	1 (2.0)	0
Mouth ulceration	0	0	0	1 (2.0)	1 (2.0)
Odynophagia	0	0	0	1 (2.0)	1 (2.0)
Toothache	0	0	4 (2.3)	1 (2.0)	2 (4.0)
Vomiting	1 (2.3)	1 (2.4)	18 (10.2)	1 (2.0)	4 (8.0)
Anal fissure	0	0	2 (1.1)	0	0
General disorders and administration site conditions	2 (4.7)	1 (2.4)	28 (15.8)	10 (20.0)	7 (14.0)
Pyrexia	2 (4.7)	0	18 (10.2)	7 (14.0)	5 (10.0)
Asthenia	0	0	2 (1.1)	1 (2.0)	1 (2.0)
Chest pain	0	0	1 (0.6)	1 (2.0)	0
Cyst	0	0	0	1 (2.0)	0
Fatigue	0	1 (2.4)	2 (1.1)	1 (2.0)	1 (2.0)
Mucosal inflammation	0	0	0	1 (2.0)	0
Influenza like illness	0	0	2 (1.1)	0	0
Thirst	0	1 (2.4)	2 (1.1)	0	0
Hepatobiliary disorders	1 (2.3)	1 (2.4)	4 (2.3)	1 (2.0)	1 (2.0)
Hepatomegaly	0	1 (2.4)	1 (0.6)	1 (2.0)	1 (2.0)

	Study G2305		Study G2301		
			Part I	Part II	
Primary system organ class affected	**ACZ885**	**Placebo**	**ACZ885**	**ACZ885**	**Placebo**
	N=43	**N=41**	**N=177**	**N=50**	**N=50**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
n % of patients with AEs	**24 (55.8)**	**16 (39.0)**	**138 (78.0)**	**40 (80.0)**	**35 (70.0)**
Hepatitis	1 (2.3)	0	1 (0.6)	0	0
Immune system disorders	1 (2.3)	0	1 (0.6)	2 (4.0)	4 (8.0)
Seasonal allergy	0	0	0	2 (4.0)	4 (8.0)
Allergic oedema	1 (2.3)	0	0	0	0
Infections and infestations	13 (30.2)	5 (12.2)	97 (54.8)	27 (54.0)	19 (38.0)
Nasopharyngitis	3 (7.0)	1 (2.4)	27 (15.3)	7 (14.0)	7 (14.0)
Upper respiratory tract infection	3 (7.0)	0	18 (10.2)	6 (12.0)	5 (10.0)
Rhinitis	1 (2.3)	0	17 (9.6)	5 (10.0)	7 (14.0)
Oral herpes	0	1 (2.4)	3 (1.7)	4 (8.0)	0
Tinea pedis	0	0	0	3 (6.0)	0
Otitis media	0	0	1 (0.6)	2 (4.0)	0
Sinusitis	0	0	4 (2.3)	2 (4.0)	0
Urinary tract infection	1 (2.3)	0	3 (1.7)	2 (4.0)	1 (2.0)
Varicella	1 (2.3)	0	1 (0.6)	2 (4.0)	0
Abscess limb	0	0	0	1 (2.0)	0
Acarodermatitis	0	0	0	1 (2.0)	0
Acute tonsillitis	0	0	0	1 (2.0)	0
Bronchitis	2 (4.7)	0	6 (3.4)	1 (2.0)	0
Ear infection	0	0	1 (0.6)	1 (2.0)	0
Enterobiasis	0	0	0	1 (2.0)	0
Folliculitis	0	0	4 (2.3)	1 (2.0)	0
Fungal skin infection	0	0	1 (0.6)	1 (2.0)	0
Gastroenteritis	1 (2.3)	2 (4.9)	14 (7.9)	1 (2.0)	1 (2.0)
Gastroenteritis viral	0	0	2 (1.1)	1 (2.0)	0
Influenza	0	0	2 (1.1)	1 (2.0)	0
Lice infestation	0	0	0	1 (2.0)	0
Lower respiratory tract infection	0	0	0	1 (2.0)	0
Pharyngitis	0	0	9 (5.1)	1 (2.0)	2 (4.0)
Pharyngotonsillitis	0	0	0	1 (2.0)	0
Post viral fatigue syndrome	0	0	0	1 (2.0)	0
Rash pustular	0	0	0	1 (2.0)	0

	Study G2305		Study G2301		
			Part I	Part II	
Primary system organ class affected	**ACZ885**	**Placebo**	**ACZ885**	**ACZ885**	**Placebo**
	N=43	**N=41**	**N=177**	**N=50**	**N=50**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
n % of patients with AEs	**24 (55.8)**	**16 (39.0)**	**138 (78.0)**	**40 (80.0)**	**35 (70.0)**
Respiratory tract infection	0	0	2 (1.1)	1 (2.0)	1 (2.0)
Respiratory tract infection viral	0	0	0	1 (2.0)	0
Rhinotracheitis	0	0	2 (1.1)	1 (2.0)	0
Tonsillitis	0	0	0	1 (2.0)	0
Tooth abscess	0	0	0	1 (2.0)	0
Viral infection	0	0	2 (1.1)	1 (2.0)	0
Viral upper respiratory tract infection	0	0	5 (2.8)	1 (2.0)	0
Febrile infection	0	0	3 (1.7)	0	0
Pneumonia	0	0	3 (1.7)	0	0
Gastrointestinal infection	0	0	2 (1.1)	0	0
Impetigo	0	0	2 (1.1)	0	0
Oral candidiasis	0	1 (2.4)	2 (1.1)	0	0
Otitis media acute	1 (2.3)	0	0	0	0
Bronchopneumonia	1 (2.3)	0	0	0	0
Tracheitis	1 (2.3)	0	0	0	0
Acute sinusitis	0	1 (2.4)	1 (0.6)	0	1 (2.0)
Injury, poisoning and procedural complications	0	1 (2.4)	10 (5.6)	8 (16.0)	8 (16.0)
Post-traumatic pain	0	0	0	2 (4.0)	0
Excoriation	0	0	0	1 (2.0)	1 (2.0)
Femur fracture	0	0	0	1 (2.0)	0
Joint sprain	0	0	3 (1.7)	1 (2.0)	0
Laceration	0	0	0	1 (2.0)	0
Limb injury	0	0	0	1 (2.0)	1 (2.0)
Post procedural haemorrhage	0	0	0	1 (2.0)	0
Road traffic accident	0	0	0	1 (2.0)	0
Sunburn	0	0	0	1 (2.0)	0
Traumatic fracture	0	0	0	1 (2.0)	1 (2.0)
Arthropod bite	0	0	2 (1.1)	0	0
Contusion	0	0	2 (1.1)	0	0
Fall	0	0	2 (1.1)	0	0

	Study G2305		Study G2301		
			Part I	Part II	
Primary system organ class affected	**ACZ885**	**Placebo**	**ACZ885**	**ACZ885**	**Placebo**
	N=43	**N=41**	**N=177**	**N=50**	**N=50**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
n % of patients with AEs	**24 (55.8)**	**16 (39.0)**	**138 (78.0)**	**40 (80.0)**	**35 (70.0)**
Investigations	1 (2.3)	2 (4.9)	17 (9.6)	5 (10.0)	8 (16.0)
Alanine aminotransferase increased	0	0	3 (1.7)	1 (2.0)	2 (4.0)
Aspartate aminotransferase increased	0	0	2 (1.1)	1 (2.0)	0
Blood bilirubin increased	0	0	1 (0.6)	1 (2.0)	0
Haemoglobin decreased	0	0	2 (1.1)	1 (2.0)	0
Haptoglobin decreased	0	0	0	1 (2.0)	0
Hepatic enzyme increased	0	0	3 (1.7)	1 (2.0)	0
Platelet count decreased	0	0	1 (0.6)	1 (2.0)	0
Weight decreased	0	0	2 (1.1)	1 (2.0)	0
White blood cell count decreased	0	0	1 (0.6)	1 (2.0)	0
Blood triglycerides increased	0	0	3 (1.7)	0	1 (2.0)
Platelet count increased	0	0	2 (1.1)	1 (2.0)	0
Serum ferritin increased	0	0	2 (1.1)	0	1 (2.0)
Weight increased	1 (2.3)	0	0	0	1 (2.0)
Musculoskeletal and connective tissue disorders	2 (4.7)	2 (4.9)	29 (16.4)	17 (34.0)	10 (20.0)
Arthralgia	0	0	10 (5.6)	12 (24.0)	5 (10.0)
Pain in extremity	1 (2.3)	1 (2.4)	7 (4.0)	6 (12.0)	4 (8.0)
Musculoskeletal pain	0	0	2 (1.1)	4 (8.0)	0
Back pain	1 (2.3)	1 (2.4)	2 (1.1)	2 (4.0)	0
Torticollis	0	0	0	2 (4.0)	0
Musculoskeletal chest pain	0	0	0	1 (2.0)	0
Myalgia	0	0	2 (1.1)	1 (2.0)	2 (4.0)
Neck pain	0	0	4 (2.3)	1 (2.0)	1 (2.0)
Osteochondrosis	0	0	0	1 (2.0)	0
Pain in jaw	0	0	0	1 (2.0)	0
Joint stiffness	0	0	2 (1.1)	0	0
Joint swelling	0	0	2 (1.1)	0	0
Juvenile arthritis	0	0	2 (1.1)	0	2 (4.0)
Musculoskeletal stiffness	0	0	2 (1.1)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2.3)	1 (2.4)	5 (2.8)	2 (4.0)	3 (6.0)

	Study G2305		Study G2301		
			Part I	Part II	
Primary system organ class affected	**ACZ885**	**Placebo**	**ACZ885**	**ACZ885**	**Placebo**
	N=43	**N=41**	**N=177**	**N=50**	**N=50**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
n % of patients with AEs	**24 (55.8)**	**16 (39.0)**	**138 (78.0)**	**40 (80.0)**	**35 (70.0)**
Skin papilloma	0	0	1 (0.6)	1 (2.0)	2 (4.0)
Splenic neoplasm malignancy unspecified	0	0	0	1 (2.0)	0
Histiocytosis haematophagic	1 (2.3)	1 (2.4)	4 (2.3)	0	1 (2.0)
Nervous system disorders	4 (9.3)	1 (2.4)	28 (15.8)	7 (14.0)	5 (10.0)
Headache	2 (4.7)	1 (2.4)	23 (13.0)	3 (6.0)	3 (6.0)
Exertional headache	0	0	0	1 (2.0)	0
Restless leg syndrome	0	0	0	1 (2.0)	0
Syncope	0	0	0	1 (2.0)	0
Tremor	0	0	0	1 (2.0)	0
Dizziness	1 (2.3)	0	2 (1.1)	0	0
Coordination abnormal	1 (2.3)	0	0	0	0
Psychiatric disorders	0	0	6 (3.4)	3 (6.0)	0
Insomnia	0	0	1 (0.6)	2 (4.0)	0
Depression	0	0	0	1 (2.0)	0
Anxiety	0	0	5 (2.8)	0	0
Renal and urinary disorders	0	0	3 (1.7)	0	2 (4.0)
Pollakiuria	0	0	2 (1.1)	0	0
Reproductive system and breast disorders	0	0	3 (1.7)	2 (4.0)	0
Pelvic pain	0	0	0	1 (2.0)	0
Vulvovaginal pruritus	0	0	0	1 (2.0)	0
Respiratory, thoracic and mediastinal disorders	3 (7.0)	1 (2.4)	37 (20.9)	13 (26.0)	12 (24.0)
Cough	1 (2.3)	0	20 (11.3)	8 (16.0)	6 (12.0)
Epistaxis	0	0	0	2 (4.0)	2 (4.0)
Oropharyngeal pain	1 (2.3)	0	6 (3.4)	2 (4.0)	2 (4.0)
Adenoidal hypertrophy	0	0	0	1 (2.0)	0
Pharyngeal erythema	0	0	0	1 (2.0)	0
Rales	0	0	0	1 (2.0)	0
Rhinitis allergic	0	0	0	1 (2.0)	0
Rhinorrhoea	0	1 (2.4)	6 (3.4)	1 (2.0)	1 (2.0)
Dyspnoea	0	0	2 (1.1)	0	0

	Study G2305		Study G2301		
			Part I	Part II	
Primary system organ class affected	**ACZ885**	**Placebo**	**ACZ885**	**ACZ885**	**Placebo**
	N=43	**N=41**	**N=177**	**N=50**	**N=50**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
n % of patients with AEs	**24 (55.8)**	**16 (39.0)**	**138 (78.0)**	**40 (80.0)**	**35 (70.0)**
Nasal congestion	0	0	2 (1.1)	0	0
Productive cough	1 (2.3)	0	1 (0.6)	0	1 (2.0)
Skin and subcutaneous tissue disorders	6 (14.0)	1 (2.4)	33 (18.6)	11 (22.0)	13 (26.0)
Urticaria	0	0	1 (0.6)	4 (8.0)	2 (4.0)
Eczema	0	0	9 (5.1)	3 (6.0)	1 (2.0)
Pruritus	1 (2.3)	0	0	2 (4.0)	3 (6.0)
Rash	0	0	4 (2.3)	2 (4.0)	2 (4.0)
Blister	0	0	0	1 (2.0)	0
Dermatitis atopic	0	0	0	1 (2.0)	0
Dry skin	0	1 (2.4)	4 (2.3)	1 (2.0)	1 (2.0)
Granuloma annulare	0	0	0	1 (2.0)	0
Heat rash	0	0	1 (0.6)	1 (2.0)	0
Psoriasis	0	0	0	1 (2.0)	0
Rash erythematous	0	0	0	1 (2.0)	0
Rash papular	0	0	1 (0.6)	1 (2.0)	0
Pruritus generalized	0	0	5 (2.8)	0	1 (2.0)
Dermatitis allergic	1 (2.3)	0	3 (1.7)	0	0
Acne	0	0	2 (1.1)	0	1 (2.0)
Rash maculo-papular	2 (4.7)	0	1 (0.6)	0	1 (2.0)
Erythema	1 (2.3)	0	1 (0.6)	0	2 (4.0)
Petechiae	1 (2.3)	1 (2.4)	1 (0.6)	0	0
Vascular disorders	1 (2.3)	1 (2.4)	3 (1.7)	0	2 (4.0)
Hypertension	0	0	2 (1.1)	0	1 (2.0)
Haematoma	1 (2.3)	0	0	0	0

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Periodic Fever Syndromes

Cryopyrin-Associated Periodic Syndromes (CAPS)

There are 69 pediatric CAPS patients (2 to 17 years of age) in 5 CAPS clinical trials (Study D2304, A2102, D2306, D2308 and D2201). Overall, there were no clinically meaningful differences for the safety and

tolerability profile of Ilaris in pediatric patients compared to the overall CAPS population (comprised of adult and pediatric patients, N=194) including, the overall frequency and severity of infectious episodes. Infections of the upper respiratory tract (nasopharyngitis 36.2%, rhinitis 20.3% and upper respiratory tract infection 20.3%) were the most frequently reported infection events.

In addition, study D2307 was a 56-week open-label clinical study in 17 pediatric CAPS patients ≤ 4 years of age, (including 6 patients under the age of 2 years). In patients < 2 years of age the adverse reaction profile was comparable overall to that observed in patients 2 – 4 years of age; however, pyrexia and diarrhea were reported more frequently in patients < 2 years of age, including one serious event of diarrhea. There was one serious infection reported in a patient < 2 years of age (post-surgical staphylococcal wound infection).

Tumor Necrosis Factor receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF)

There were 102 pediatric Ilaris patients with an age range from 2 to 17 years. Overall, there were no clinically meaningful differences in the safety and tolerability profile of Ilaris in pediatric patients compared to the overall population.

8.3 Less Common Clinical Trial Adverse Reactions

Other AE reported <1% in controlled clinical trials:

- **Blood and lymphatic system disorders**: Iron deficiency anemia, lymphadenitis, lymph node pain, lymphopenia, splenomegaly, thrombocytopenia;
- **Cardiac disorders**: Cyanosis, left ventricular hypertrophy, pericarditis, ventricular extrasystoles, wandering pacemaker;
- **Ear and labyrinth disorders**: Deafness, ear congestion, sudden ear loss;
- **Eye disorders**: Amblyopia, blepharitis, cataract, chalazion, eczema eyelids, eye allergy, eye pruritus, eyelid oedema, keratitis, eye discharge, eyelid pain, visual acuity reduced;
- **Gastrointestinal disorders**: Abdominal discomfort, abdominal pain lower, anal fistula, anal haemorrhage, ascites, breath odour, colitis, dental caries, dyspepsia, dysphagia, enteritis, enterocolitis, faeces discoloured, gastric ulcer, gastroesophageal reflux disease, diarrhea hemorrhagic, haematochezia, hemorrhagic erosive gastritis, haemorrhoids, inguinal hernia, injection site pain, lumbar hernia, non-infective gingivitis, salivary gland enlargement, teething, stomatitis;
- **General disorders and administration site conditions**: Axillary pain, chest discomfort, chest pain, drug intolerance, face oedema, inflammation, injection site erythema, injection site pruritus, injection site swelling, malaise, medical device complication, pain, peripheral swelling, polyserositis, serositis, vaccination site reaction;
- **Hepatobiliary disorders**: Hepatic failure, hepatitis cholestatic, bile duct stone, biliary colic, granulomatous liver disease, hepatic cirrhosis;
- **Immune system disorders**: Allergy to arthropod sting, house dust allergy, drug hypersensitivity;
- **Infections and infestations**: Adenoiditis, adenovirus infection, anogenital warts, atypical pneumonia, bronchitis viral, candidiasis, cellulitis, coxsackie viral infection, dermatitis infected, dermatophytosis, diarrhea infectious, encephalitis, Epstein-Barr virus infection, eye infection, fungal infection, furuncle, gastritis viral, gastroenteritis rotavirus, gastrointestinal viral infection, genital candidiasis, genital infection fungal, herpes simplex, hordeolum, labyrinthitis, lobar pneumonia, lymph node abscess, molluscum contagiosum, oesophageal candidiasis, paronychia,

pelvic abscess, periodontitis, pseudocroup, pyelonephritis, scarlet fever, sialoadenitis, skin infection, subcutaneous abscess, tinea infection, tonsillitis streptococcal, tooth infection, upper respiratory tract infection bacterial, vulvitis, vulvovaginal mycotic infection, wound infection;

- **Injury, poisoning and procedural complications:** Ankle fracture, bone contusion, concussion, face injury, hand fracture, injury, joint dislocation, joint injury, muscle strain, post-procedural complication, procedural pain, seroma, thermal burn, tooth fracture, vaccination complication, wrist fracture;
- **Investigations**: Blood calcium decreased, blood cholesterol increased, blood fibrinogen increased, blood iron decreased, blood lactate dehydrogenase increased, blood pressure diastolic increased, blood pressure increased, blood sodium decreased, blood triglycerides abnormal, blood urine present, body temperature increased, C-reactive protein increased, coagulation test abnormal, Gamma-glutamyltransferase increased, haematocrit decreased, neutrophil count decreased, neutrophil count increased, serum ferritin decreased, sinus rhythm, transaminases increased, white blood cell count increased, white blood cells urine positive;
- **Metabolism and nutrition disorders**: Dehydration, hyperinsulinism, hyperglycaemia, hyperuricaemia, hypoalbuminaemia, hypokalaemia;
- **Musculoskeletal and connective tissue disorders**: Arthritis, bone pain, intervertebral disc protrusion, foot deformity, groin pain, muscle spasm, muscle tightness, muscular weakness, musculoskeletal discomfort, osteoporosis, polyarthritis, synovitis, temporomandibular joint syndrome;
- **Neoplasms benign, malignant and unspecified (including cysts and polyps):** Benign neoplasm of thyroid gland;
- **Nervous system disorders**: Amnesia, disturbance in attention, hypersomnia, intercostal neuralgia, memory impairment, migraine, paraesthesia, parosmia, posterior reversible encephalopathy syndrome, seizure, somnolence, trigeminal neuralgia, VIIth nerve paralysis, visual field defect;
- **Psychiatric disorders**: Aggression, depressed mood, self injurious behaviour, sleep disorder, sleep terror, suicide attempt;
- **Renal and urinary disorders**: Dysuria, haematuria, renal cyst, renal pain;
- Reproductive system and breast disorders: Breast swelling, dysmenorrhoea, menorrhagia, menstruation irregular, premenstrual pain, pruritus genital, testicular pain, vulvovaginal erythema;
- **Respiratory, thoracic and mediastinal disorders**: Bronchitis chronic, catarrh, dysphonia, dyspnoea exertional, hyperventilation, interstitial lung disease, laryngeal stenosis, lung consolidation, nasal ulcer, pleurisy, pulmonary hypertension, rhinalgia, sneezing, upper respiratory tract irritation, wheezing;
- **Skin and subcutaneous tissue disorders**: Alopecia, dermatitis, dermatitis contact, dermatomyositis, dermatitis exfoliative, dermatosis, granulomatous rosacea, heat rash, livedo reticularis, night sweats, rash macular, skin fissures, skin striae, urticaria;
- **Vascular disorders**: Vasculitis

Hypersensitivity reactions: Hypersensitivity reactions with Ilaris therapy have been reported in patients treated with canakinumab. The majority of these events were mild in severity. During clinical development of Ilaris in over 2500 patients, no anaphylactoid or anaphylactic reactions have been reported (see 7 WARNINGS AND PRECAUTIONS, Hypersensitivity reactions).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Periodic Fever Syndromes

Cryopyrin-Associated Periodic Syndromes (CAPS)

Hematology: During clinical trials with canakinumab in CAPS patients mean values for hemoglobin increased and for white blood cell, neutrophils and platelets decreased.

Hepatic transaminases: Elevations of transaminases have been observed rarely in CAPS patients.

Bilirubin: Asymptomatic and mild elevations of serum bilirubin have been observed in CAPS patients treated with canakinumab without concomitant elevations of transaminases.

Table 6: Proportion of patients with post-baseline AST/ALT and Bilirubin elevations in 2-<4 years age group and all CAPS population

	Age group: 2-<4 years ACZ885 N=7		All CAPS ACZ885 N=194	
	Total*	n (%)	Total*	n (%)
SGPT (ALT)				
> 1 to < 3 x ULN	7	1 (14.3)	193	26 (13.5)
> 3 x ULN	7	0 (0.0)	193	7 (3.6)
> 5 x ULN	7	0 (0.0)	193	4 (2.1)
SGOT (AST)				
> ULN	7	1 (14.3)	193	25 (13.0)
> 3 x ULN	7	0 (0.0)	193	5 (2.6)
> 5 x ULN	7	0 (0.0)	193	4 (2.1)
Bilirubin (total)				
> ULN	7	0 (0.0)	193	9 (4.7)
> 1.5 x ULN	7	0 (0.0)	193	0 (0.0)
> 2 x ULN	7	0 (0.0)	193	0 (0.0)
> 2 x ULN and ALT or AST > 3 x ULN	7	0 (0.0)	193	0 (0.0)

*Number of patients with post-treatment values

ULN = Upper Limit of Normal

Some patients experienced increased ALT and AST values in Part I of the Study D2304 after one dose of Ilaris. Two (2) patients had decreased values in Part II with placebo, 1 of them increased up to 5X ULN in Part III after re-treatment with Ilaris (see 7 WARNINGS AND PRECAUTIONS).

Tumor Necrosis Factor receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF)

In all N2301 cohorts in Part II and in Parts II-IV, all newly occurring or worsening notable post-baseline abnormalities in biochemistry and urinalysis parameters were mild or CTCAE grade 1. In Parts II-IV in the Total ACZ group, 0 patients showed changes in creatinine clearance, gamma glutamyl transferase, cholesterol, or triglycerides. The most commonly observed change was a creatinine increase ≥ 25%

from baseline, which occurred in 28.4% of patients. No patients in the Total ACZ group had a creatinine increase ≥ 3 times the ULN. Overall, clinical chemistry and urinalysis changes were comparable across the FMF, HIDS/MKD, and TRAPS cohorts.

Systemic Juvenile Idiopathic Arthritis (SJIA)
Hematology: Decreased white blood cell counts (WBC) ≤0.8× lower limit of normal (LLN) were reported in 5 patients (10.4%) in the Ilaris group compared to 2 (4.0%) in the placebo group.

Transient decreases in absolute neutrophils counts (ANC) to less than $1x10^9$/L were reported in 3 patients (6.0%) in the Ilaris group compared to 1 patient (2.0%) in the placebo group. One case of ANC counts $<0.5x10^9$/L was observed in the Ilaris group and none in the placebo group (see 7 WARNINGS AND PRECAUTIONS).

Mild (<LLN and $>75x10^9$/L) and transient decreases in platelet counts were observed in 3 (6.3%) Ilaris treated patients versus 1 (2.0%) placebo-treated patient.

ALT/AST: High ALT and/or AST >3× upper limit of normal (ULN) were reported in 2 (4.1%) Ilaris-treated patients and 1 (2.0%) placebo patient. All patients had normal values at the next visit.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interactions between Ilaris and other medicinal products have not been investigated in formal studies.

9.3 Drug-Behavioural Interactions

Specific drug-lifestyle interaction studies have not been conducted with canakinumab.

9.4 Drug-Drug Interactions

Immunization: No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris. It is recommended that, if possible, pediatric and adult patients should complete all immunizations in accordance with current immunization guidelines prior to initiating Ilaris therapy (see 7 WARNINGS AND PRECAUTIONS, Vaccinations).

The results of a 56-week, open label study in CAPS patients demonstrated that all 7 patients aged 4 years and younger who received non-live, standard of care childhood vaccinations developed protective levels of antibody.

Cytochrome P450 Substrates: The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as IL-1 beta. Thus, CYP450 expression may be normalised when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). On initiation of canakinumab, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

TNF-Blocker and IL-1 Blocking Agent: The concomitant administration of Ilaris with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacological interactions between Ilaris and a recombinant IL-1ra, concomitant administration of Ilaris and other agents that block IL-1 or its receptors is not recommended.

An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Use of Ilaris with TNF inhibitors is not recommended because this may increase the risk of serious infections.

9.5 Drug-Food Interactions

Since canakinumab is given as a subcutaneous injection no studies on oral food effects were performed.

9.6 Drug-Herb Interactions

The interaction of canakinumab with herbal medications or supplements has not been studied.

9.7 Drug-Laboratory Test Interactions

No evidence suggests that canakinumab interferes with laboratory tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1β) antibody of the IgG1/ κ isotype. Canakinumab binds with high affinity specifically to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors, and thereby, prevents IL-1β-induced gene activation and the production of inflammatory mediators, such as interleukin-6 or cyclooxygenase-2.

10.2 Pharmacodynamics

CAPS

Excess production of IL-1β in inflammatory diseases leads to local or systemic inflammation, increased production of the acute phase response markers such as C-reactive protein (CRP) or serum amyloid A (SAA), and fever. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. The pharmacodynamic (PD) action of canakinumab is to bind to and inactivate IL-1β and thus to inhibit the down-stream events of IL-1 signaling, including IL-1β production, IL-1β pathway related gene activation, elevation of acute phase proteins such as SAA and CRP, and the mobilization of neutrophils and platelets from bone marrow.

CAPS patients who have an uncontrolled overproduction of IL-1β manifesting as fever, rash, fatigue, skin rash, arthritis, leukocytosis, high platelets counts, and acute phase protein response, show a rapid response to Ilaris therapy. Following Ilaris treatment, CRP and SAA levels, leukocytosis and high platelet count rapidly returned to normal within 8 days.

Still's disease (SJIA and AOSD)

Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult Onset Still's Disease (AOSD) are severe

autoinflammatory diseases, driven by innate immunity by means of pro-inflammatory cytokines, a key one being interleukin 1β (IL-1β).

10.3 Pharmacokinetics

Absorption

The peak serum canakinumab concentration (C_{max}) of 16±3.5 mcg/mL occurred approximately 7 days following single subcutaneous administration of 150 mg in adult CAPS patients. The mean terminal half-life was 26 days.

The absolute bioavailability of subcutaneous canakinumab in the CAPS population including children from 2 years of age was estimated to be 66%. Exposure parameters (such as AUC and C_{max}) increased in proportion to dose over the dose range of 0.30 to 10.0 mg/kg given as intravenous infusion or from 150 to 600 mg as subcutaneous injection.

Distribution

Canakinumab binds to serum IL-1 beta. The volume of distribution (Vss) of canakinumab varied according to body weight and was estimated to be 6.2 L in a typical CAPS patient of body weight 70 kg, 5.0 litres in a Periodic Fever Syndrome patient (TRAPS, HIDS/MKD, FMF) of body weight 55 kg and 3.2 litres in a SJIA patient of body weight 33 kg. The expected accumulation ratio was 1.3-fold for CAPS patients and 1.6-fold for SJIA patients following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks and 4 mg/kg every 4 weeks, respectively (see 4 DOSAGE AND ADMINISTRATION).

Elimination

Clearance (CL) of canakinumab varied according to body weight and was estimated to be 0.17 L/day in a typical CAPS patient weighing 70 kg, 0.14 L/day in a Periodic Fever Syndrome patient (TRAPS, HIDS/MKD, FMF) of body weight 55 kg and 0.11 L/day in a SJIA patient of body weight 33 kg. After accounting for body weight differences, no clinically significant differences in the pharmacokinetic properties of canakinumab were observed between CAPS, TRAPS, HIDS/MKD, FMF and SJIA.

There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. No gender or age-related pharmacokinetic differences were observed after correction for body weight.

Special Populations and Conditions

- **Pediatrics:** Pharmacokinetic properties are similar in Periodic Fever Syndrome (CAPS, TRAPS, HIDS/MKD, FMF) and SJIA pediatric populations.

  In CAPS patients, peak concentrations of canakinumab occurred between 2 to 7 days following single subcutaneous administration of canakinumab 150 mg or 2 mg/kg in pediatric patients 4 years of age and older. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults. Based on the population PK modeling analysis, the pharmacokinetics of canakinumab in children 2 to <4 years of age were similar to patients 4 years of age and older.

  In Periodic Fever Syndromes (TRAPS, HIDS/MKD, FMF), exposure parameters (trough concentrations) were comparable across age groups from 2 to <18 years following subcutaneous administration of canakinumab 2 mg/kg (body weight ≤ 40 kg) or 150 mg (body weight > 40 kg) every 4 weeks.

In SJIA, exposure parameters (such as AUC and C_{max}) were comparable across age groups from 2 to <20 years following subcutaneous administration of canakinumab 4 mg/kg every 4 weeks.

In AOSD patients, canakinumab exposure was similar to that observed in SJIA patients, based on population pharmacokinetic analysis using sparse sampling data from 26 AOSD patients.

- **Geriatrics:** Based on the pharmacokinetic-binding model, subject's age did not impact the key pharmacokinetic parameters (canakinumab clearance, volumes of distribution) after correction for the subject's body weight. It should also be noted that the number of patients aged 65 and over is not sufficient to determine whether the pharmacokinetics of canakinumab is truly different in elderly patients compared to the adult patients.
- **Ethnic Origin:** Based on the population pharmacokinetic binding model, which included 175 Caucasians, 54 Asians (of which 48 were healthy Japanese and 6 non-Japanese Asians), 1 black, 1 Native American, and 2 coded as "other", the pharmacokinetic parameters were comparable between CAPS patients who were predominantly Caucasians and the Japanese healthy volunteers. Ethnicity (Japanese vs non-Japanese) showed no trends once the other covariates (age, weight) were taken into account.
- **Hepatic Insufficiency:** No formal studies have been conducted to examine the pharmacokinetics of Ilaris administered subcutaneously in patients with hepatic impairment.
- **Renal Insufficiency** No formal studies have been conducted to examine the pharmacokinetics of Ilaris administered subcutaneously in patients with renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Ilaris unopened vial must be stored under refrigerated conditions, between 2°C and 8°C. Do not freeze. Store in the original package in order to protect from light.

Prior to the injection, the vial containing the solution for injection should be left unopened to allow the content to reach room temperature. The vial must not be exposed to heat. Once the vial is pierced, the solution should be used immediately.

Ilaris must be kept out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Ilaris 150 mg/1 mL solution for injection is supplied in a single-use vial for individual use. Any unused product or waste material should be disposed of in accordance with local requirements.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be free of particles and should be colorless or may have a slight brownish yellow tint.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Canakinumab

Chemical name:

- Immunoglobulin G1, anti-(human interleukin 1β) (human clone canakinumab heavy chain V region)
- Immunoglobulin G1, anti-(human interleukin-1 beta (IL-1β)) human monoclonal canakinumab; (1Glu>Glp)-γ1 heavy chain (221-214')-disulfide with kappa light chain, dimer (227-227":230-230")-bisdisulfide

Molecular formula and molecular mass: $C_{6452}H_{9958}N_{1722}O_{2010}S_{42}$

Mr=145157 daltons.

Structural formula:

Ala	A	68	Gly	G	86	Pro	P	92
Arg	R	40	His	H	26	Ser	S	166
Asn	N	52	Ile	I	30	Thr	T	100
Asp	D	58	Leu	L	98	Trp	W	22
Cys	C	32	Lys	K	90	Tyr	Y	56
Gln	Q	64	Met	M	10	Val	V	122
Glu	E	64	Phe	F	48			

Physicochemical properties:

The pH of the aqueous solution of canakinumab is in the range of 6.2 to 6.8.

The isoelectric points (pI) of the main canakinumab variants determined by gel isoelectric focusing are in a range between 8.4 and 8.9.

The calculated extinction coefficient (Gill and von Hippel 1989) at 280 nm of canakinumab based on the amino acid composition is 1.369×103 mL/(g · cm).

Product Characteristics:

Canakinumab is a genetically engineered high-affinity human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It is expressed in a murine Sp2/0-Ag14 cell line and comprised of two 447- (or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145157 Daltons. Both heavy chains of canakinumab contain oligosaccharide chains linked to the protein backbone at Asn (298).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Cryopyrin-Associated Periodic Syndromes (CAPS)

In 1 placebo-controlled and 4 uncontrolled clinical studies for CAPS, a total of 194 unique CAPS patients included 31 FCAS, 110 MWS and 52 NOMID patients, with an overall exposure of 269.46 patient-years and a treatment duration of up to 5½ years, with age ranging from 2 to 91 years of age at time of treatment-start with canakinumab. This includes 69 pediatric (2 to 17 years of age) patients. Description of the study designs are provided in Table 7.

Table 7: Summary of clinical trials supporting the efficacy and safety in patients with CAPS

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
A2102	Non-randomized, open-label, Phase II study to investigate the clinical efficacy, safety, PK and PD of different doses of canakinumab administered i.v. and s.c., in patients with NALP3 mutations and a clinical picture characteristic of MWS, NOMID overlapping with MWS, and FCAS	Stage 1: single dose of 10 mg/kg i.v., single dose of 1 mg/kg i.v. upon relapse, single dose of 150 mg s.c. upon second relapse. Stage 2: repeat single dose of 150 mg s.c. upon each relapse (in children from 4 to 16 years an equivalent of 2 mg/kg s.c.). If needed: rescue dose of 5 or 10 mg/kg i.v. infusion (i.v.) and/or injection (s.c.) Duration: Up to 28 months, median of 46 weeks. Redosing upon each relapse, until roll-over to Phase III studies CACZ885D2304 or CACZ885D2306, or until study discontinuation	34	4 years to 51 years	Male and female

D2304	Placebo-controlled double-blind, multicenter, 3-part trial (Parts I and III uncontrolled, Part II placebo controlled) in adults and children (4 years – 75 years of age) with Muckle-Wells Syndrome (MWS)	Part I (single dose of 8-wks duration) 150 mg s.c. every 8wk (>40 kg), 2 mg/kg s.c (15-40 kg) Part II (multiple doses, duration up to 24 wks) 150 mg s.c. every 8 wk (>40 kg), 2 mg/kg s.c (15- 40 kg) placebo (part II only) Part III (duration of 16 wks if part II 24 wk period completed, or longer) 150 mg s.c. every 8wk (>40 kg), 2 mg/kg s.c. (15-40 kg)	35 31 31	9 years to 74 years	Male and female
D2306	Open-label long-term safety and efficacy trial in CAPS patients at least 4 years of age and older	150 mg s.c every 8 wks (>40 kg), 2 mg/kg (15-40 kg). Step-wise dose escalation allowed up to 600 mg or 8 mg/kg Duration: 6 months- 2 years	166	3 years to 91 years	Male and female
D2308	Open-label long-term safety and efficacy trial in Japanese CAPS patients with FCAS, MWS or NOMID	150 mg s.c. q8wk (>40 kg) or 2 mg/kg s.c. q8wk (≤40 kg) Step-wise dose-escalation: 300 mg s.c. or 4 mg/kg (15 – 40 kg), 450 mg s.c. or 6 mg/kg (15 – 40 kg), and up to 600 mg s.c. or 8 mg/kg (15 – 40 kg) Duration: 48 weeks at IA	19	2 years to 48 years	Male and female
D2201	Open-label, 24-month treatment study to establish safety, tolerability, efficacy and PK/PD in NOMID/CINCA patients	Variable dosing regimen: Starting dose of canakinumab q8wk 150 mg (or 2 mg/kg for patients with body weight ≤ 40 kg) for the first 3 patients enrolled or 300 mg (or 4 mg/kg for patients with body weight ≤ 40 kg) Duration: 6 months (+ ext to 2 years)	6	11 years to 34 years	Male and female

s.c : subcutaneous

The efficacy and safety of Ilaris for the treatment of CAPS was demonstrated in Study D2304, a 3-part

trial in patients 9 to 74 years of age with the MWS phenotype of CAPS. Throughout the trial, patients weighing more than 40 kg received Ilaris 150 mg and patients weighing 15 to 40 kg received 2mg/kg. Part I was an 8-week open-label, single-dose period where all patients received Ilaris. Patients who achieved a complete clinical response and did not relapse by Week 8 were randomized into Part II, a 24-week randomized, double-blind, placebo-controlled withdrawal period. Patients who completed Part II or experienced a disease flare entered Part III, a 16-week open-label active treatment phase. A complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and had serum levels of C-Reactive Protein (CRP) and Serum Amyloid A (SAA) less than 10 mg/L. A disease flare was defined as a CRP and/or SAA values greater than 30 mg/L and either a score of mild or worse for PHY or a score of minimal or worse for PHY and SKD.

Baseline demographic characteristics are shown in Table 8 below. Patients were predominantly at least 17 years old, and had an active disease status as evidenced by elevated CRP and SAA values.

Five (5) patients below 18 years were enrolled into the study (in the canakinumab treatment group: 9, 15 and 17 years old, in the placebo treatment group: 14 and 16 years old).

Table 8: Baseline demographic characteristics and disease assessments (Safety population)* of Study D2304

Demographic variable	Part I	According to randomization in Part II		
	ACZ885	ACZ885	Placebo	Total
	N=35	N=15	N=16	N=31
Baseline Age – n (%)				
≥4 - <17	4 (11.4)	2 (13.3)	2 (12.5)	4 (12.9)
≥17 - <41	17 (48.6)	6 (40.0)	9 (56.3)	15 (48.4)
≥41 - <75	14 (40.0)	7 (46.7)	5 (31.3)	12 (38.7)
Sex – n (%)				
Female	25 (71.4)	14 (93.3)	7 (43.8)	21 (67.7)
Male	10 (28.6)	1 (6.7)	9 (56.3)	10 (32.3)
Cohort – n (%)				
Patients from CACZ885A2102	9 (25.7)	4 (26.7)	3 (18.8)	7 (22.6)
ACZ885 naive patients	26 (74.3)	11 (73.3)	13 (81.3)	24 (77.4)
Race – n (%)				
Asian	1 (2.9)	0 (0.0)	1 (6.3)	1 (3.2)
Caucasian	33 (94.3)	15 (100)	14 (87.5)	29 (93.5)
Other	1 (2.9)	0 (0.0)	1 (6.3)	1 (3.2)
C-Reactive Protein (mg/L)				
n	35	15	16	31
Mean	30.7	29.2	37.6	33.6
SD	27.07	25.65	29.03	27.32
Median	20.0	19.6	26.0	22.0
Serum Amyloid A (mg/L)				
n	35	15	16	31
Mean	137.3	141.9	162.2	152.4
SD	165.64	178.44	167.57	170.31

Median	48.9	48.2	111.9	84.8

*All patients had MWS except 2 who had MWS/NOMID.

The pivotal study D2304 consisted of a 48-week three-part multicenter study, i.e., an 8-week open-label period (Part I), a 24-week randomized, double-blind, placebo-controlled withdrawal period (Part II), followed by a 16-week open-label period (Part III). The aim of the study was to assess efficacy, safety, and tolerability of Ilaris in patients with MWS.

- Part I: A complete clinical and biomarker response (defined as composite of: Physician's Global Assessment on autoinflammatory and on skin disease ≤ "minimal" and CRP or SAA values <10 mg/L) to Ilaris was observed in 97% of patients and in 71% of these patients a complete response appeared within 7 days of initiation of treatment (see Figure 1 and Table 9).
- Part II: In the withdrawal period of the pivotal study, the primary endpoint was defined as disease relapse/ flare: none (0%) of the patients randomized to Ilaris flared, compared with 81% of the patients randomized to placebo. The 95% confidence interval for treatment difference in the proportion of flares was 53% to 96%; p <0.001 (see Table 7).
- Part III: Patients treated with placebo in Part II who entered the open-label extension on Ilaris, again showed a significant clinical and serologic improvement of disease activity, comparable to patients continuously treated with Ilaris. Laboratory parameters such as high CRP and SAA, high neutrophils and platelet counts normalised rapidly within days of canakinumab injection.

Table 9 describes the physician's assessment of auto-inflammatory disease and the assessment of skin disease in Study D2304, Part I, II and III.

Table 9: Physician's Global Assessment of Auto-Inflammatory Disease Activity and Assessment of Skin Disease: Frequency Table and Treatment Comparison in Part I, II and III (Using LOCF, ITT Population)

	Start Part I		Start of Part II		End of Part II		End of Part III	
	Ilaris (N=15)	Placebo (N=16)	Ilaris (N=15)	Placebo (N=16)	Ilaris (N=15)	Placebo (N=16)	Ilaris (n=15)	Placebo (N=16)
Physician's Global Assessment of Auto-Inflammatory Disease Activity – n (%)								
Absent	0	0	9 (60)	8 (50)	8 (53)	0	10 (67)	10 (63)
Minimal	1 (7)	0	4 (27)	8 (50)	7 (47)	4 (25)	5 (33)	5 (31)
Mild	2 (13)	5 (31)	2 (13)	0	0	8 (50)	0	1 (6)
Moderate	10 (67)	9 (56)	0	0	0	4 (25)	0	0
Severe	2 (13)	2 (12)	0	0	0	0	0	0
Assessment of Skin Disease – n (%)								

Absent	1 (7)	2 (12)	13 (87)	13 (81)	14 (93)	5 (31)	15 (100)	14 (88)
Minimal	3 (20)	3 (19)	2 (13)	3 (19)	1 (7)	3 (19)	0	2 (13)
Mild	4 (27)	5 (31)	0	0	0	5 (31)	0	0
Moderate	7 (47)	5 (31)	0	0	0	3 (19)	0	0
Severe	0	1 (16)	0	0	0	0	0	0

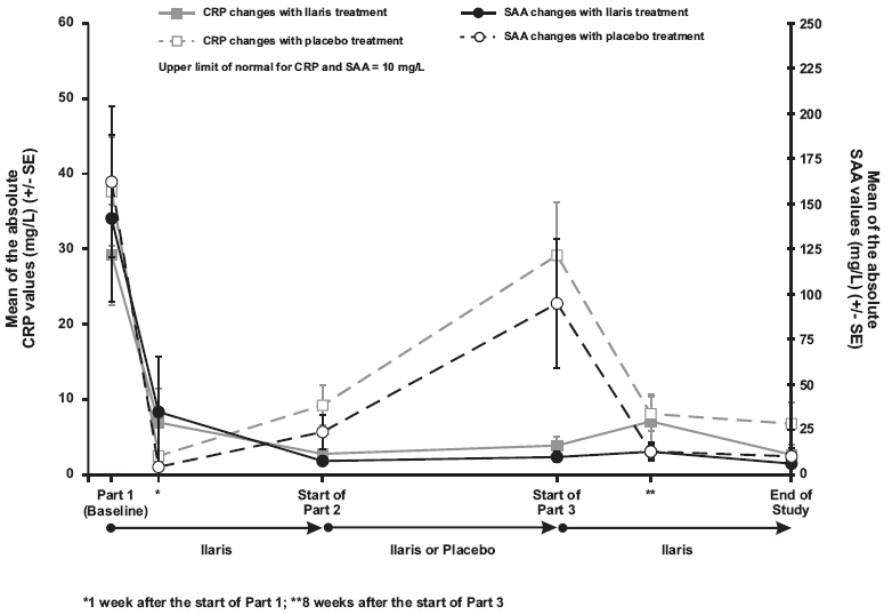
At the start of Part II (Week 8), 13.3% of patients in the canakinumab treatment group had a physician's global assessment of auto-inflammatory disease activity of mild and none had an assessment worse than mild. None of the patients in the placebo group had an assessment worse than minimal. By the end of Part II, all patients in the canakinumab treatment group had no or minimal auto-inflammatory disease activity according to the Physician's Global Assessment, compared with 4 patients (25%) in the placebo group.

The assessment of skin disease was absent or minimal for both treatment groups at Week 8. By the end of Part II, 14 patients (93%) in the canakinumab had absent of skin disease, compared to 5 patients in the placebo group (Table 9).

Inflammatory markers: CRP and SAA, normalized within 8 days of treatment in the majority of patients. Normal mean CRP and SAA values were sustained throughout study D2304 in patients continuously treated with canakinumab, but rose in the placebo group. After withdrawal of canakinumab in Part II, CRP and SAA values again returned to abnormal values and subsequently normalized after

reintroduction of canakinumab in Part III. The pattern of normalization of CRP and SAA was similar (Figure 1).

Figure 1: Mean C–Reactive Protein Levels and Serum Amyloid A at the End of Parts I, II and III of Study D2304



*1 week after the start of Part 1; **8 weeks after the start of Part 3

Five (5) NOMID/CINCA patients (4 presenting with symptoms of both MWS and NOMID/CINCA) were treated in a phase II study. All patients achieved a complete response by day 8. The median time to relapse was shorter in NOMID/CINCA patients (95 days) compared with MWS (120 days).

Two open-label, uncontrolled, long-term phase III studies were performed. One was a safety, tolerability, and efficacy study of canakinumab in patients with CAPS. The total treatment duration ranged from 6 months to 2 years. The other was an open-label study with canakinumab to evaluate the efficacy and safety in Japanese CAPS patients for 24 weeks with an extension phase up to 48 weeks. The primary objective was to assess the proportion of patients who were free of relapse at week 24 including those patients whose dose was increased.

In the pooled efficacy analysis for these two studies, 65.6% of patients who had not previously been treated with canakinumab achieved complete response at 150 mg or 2 mg/kg, while 85.2% of patients achieved complete response at any dose. Of the patients treated with 600 mg or 8 mg/kg (or even higher), 43.8% achieved complete response. Of the patients who achieved complete response, 20.3% experienced a relapse. Relapse was defined as having: 1) CRP and/or SAA >30 mg/L and 2) Physician's Global Assessment of auto-inflammatory disease >minimal or Physician's Global Assessment of auto-inflammatory disease ≥minimal and assessment of skin disease >minimal. Additionally, patients who did not have complete information to determine relapse were considered as having a relapse. Patients (n=10, 7.8%) who did not achieve complete response at any dose were excluded from the relapse calculation. The percentage of patients who had a relapse were highest with NOMID (34.4%), followed by MWS (17.5%) and FCAS (10.3%) phenotype respectively. Relapse occurred more often in pediatric

patients (26.1%), especially those < 4 years old (50%), although the more severe phenotype and disease severity in the youngest patients may have been a more important factor.

Experience from individual patients who achieved a complete response following dose escalation to 600 mg (8 mg/kg) every eight weeks suggests that a higher dose may be beneficial in patients not achieving complete response or not maintaining complete response with the recommended doses (150 mg or 2 mg/kg for patients ≥15 kg and ≤40 kg).

An increased dose was administered more frequently to patients aged 2 to <4 years and patients with NOMID/CINCA symptoms compared with FCAS or MWS.

Pediatric population

The CAPS trials with canakinumab included a total of 69 pediatric patients with an age range from 2 to 17 years. Overall, a lower percent of pediatric patients (75%) achieved a complete response than did adults (92%), although more severe phenotype and disease severity in the youngest patients may have been a more important factor.

Patients aged 2-3 years old had the lowest rate of complete response and required more dose escalations than other age groups. Six of the 7 patients in this age group had the NOMID phenotype and 3 of them achieved complete response and 1 subsequently relapsed.

Table 10: Pediatric CAPS patients by phenotype and age group

	Children (n=69)		
Type	**2-3 yrs**	**4 – 11 yrs**	**12 – 17 yrs**
FCAS	0	3	2
MWS	1	16	13
NOMID	6	8	19

Limitations of the clinical trial results

There was no specific guidance for how an investigator should perform their clinical assessment. The global assessment was driven by the physician's clinical judgement and the knowledge of patient's medical history.

There was no pre-specified guidance regarding the assessment of skin disease. Evaluation of the patient's skin disease severity was driven by the physician's judgement and the knowledge of patients' medical history.

The agreement between the physician's global assessment and patient's global assessment is moderate: 33.3% for the Ilaris group and 60.0% for the placebo group based on Cohen's Kappa Statistics.

Due to the limited number of patients in the program, the pooled efficacy analysis was conducted using studies of similar design and with slightly differing dose escalation algorithms to enable evaluation of the largest number of patients possible.

Treatment of TRAPS, HIDS/MKD and FMF

The efficacy and safety of Ilaris for the treatment of TRAPS, HIDS/MKD and FMF was demonstrated in a single, pivotal, 4-part study (N2301) consisting of three separate disease cohorts which enrolled 185

patients aged >28 days. In Part I, patients in each disease cohort aged 2 years and older entered a 12-week screening period during which they were evaluated for the onset of disease flare. In Part II, patients at flare onset were then randomized into a 16-week double-blind, placebo-controlled treatment period where they received either 150 mg Ilaris (2 mg/kg for patients ≤40 kg) subcutaneous (s.c.) or placebo every 4 weeks. Patients who completed 16 weeks of treatment, and were classified as responders, were then re-randomized into a 24-week, double-blind withdrawal period (Part III) where they received Ilaris 150 mg (2 mg/kg for patients ≤40 kg) s.c. or placebo every 8 weeks. All patients treated with Ilaris 150 mg (2 mg/kg for patients ≤ 40 kg) every 8 weeks without flare were then entered into a 72-week open-label treatment extension period (Part IV).

In Part II, patients treated with Ilaris whose disease flare did not resolve, or who had persistent disease activity from Day 8 up to Day 14 (PGA ≥2 or CRP >10 mg/L and no reduction by at least 40% from baseline) received an additional dose of 150 mg (or 2 mg/kg for patients less than or equal to 40 kg). Patients treated with Ilaris whose disease flare did not resolve, or who had persistent disease activity from Day 15 up to Day 28 (PGA ≥2 or CRP >10 mg/L and no reduction by at least 70% from baseline), also received an additional dose of 150 mg (or 2 mg/kg for patients less than or equal to 40 kg). On or after Day 29, patients treated with Ilaris in Part II with PGA ≥2 and CRP ≥30 mg/L were also up-titrated. All up-titrated patients remained at the increased dose of 300 mg (or 4 mg/kg for patients less than or equal to 40 kg) every 4 weeks.

Patients randomized in the TRAPS cohort (N=46) were aged 2 to 76 years (median age at baseline: 15.5 years) and of this population, 57.8% did not have fever at baseline. Randomized TRAPS patients were those with chronic or recurrent disease activity defined as 6 flares per year (median number of flares per year: 9.0) with PGA greater than or equal to 2 and CRP greater than 10 mg/L (median CRP at baseline: 112.5 mg/L). In the TRAPS cohort, 11/22 (50.0%) patients randomized to Ilaris 150 mg q4w received up-titration to 300 mg q4w during the 16-week treatment period, while 21/24 (87.5%) patients randomized to placebo crossed over to Ilaris.

Patients randomized in the HIDS/MKD cohort (N=72) were aged 2 to 47 years (median age at baseline: 11.0 years) and of this population, 41.7% did not have fever at baseline. Randomized HIDS/MKD patients were those with a confirmed diagnosis of HIDS according to known genetic MVK/enzymatic (MKD) findings, and documented prior history of greater than or equal to 3 febrile acute flares within a 6 month period (median number of flares per year: 12.0) when not receiving prophylactic treatment and during the study, had active HIDS flares defined as PGA greater than or equal to 2 and CRP greater than 10 mg/L (median CRP at baseline: 113.5 mg/L). In the HIDS/MKD cohort, 19/37 (51.4%) patients randomized to Ilaris 150 mg q4w received up-titration to 300 mg q4w during the 16-week treatment period, while 31/35 (88.6%) patients randomized to placebo crossed over to Ilaris.

Patients randomized in the FMF cohort (N=63) were aged 2 to 69 years (median age at baseline: 18.0 years) and of this population, 76.2% did not have fever at baseline. Randomized FMF patients were those with documented active disease despite colchicine therapy or documented intolerance to effective doses of colchicine. Patients had active disease defined as at least one flare per month (median number of flares per year: 18.0) and CRP greater than 10 mg/L (median CRP at baseline: 94.0 mg/L). Patients were allowed to continue their stable dose of colchicine without change. Of the 63 randomized patients, 55 (87.3%) were taking concomitant colchicine therapy on or after randomization. In the FMF cohort, 10/31 (32.3%) patients randomized to Ilaris 150 mg q4w received up-titration to 300 mg q4w during the 16-week treatment period, while 27/32 (84.4%) patients randomized to placebo crossed over to Ilaris.

The primary efficacy endpoint of the randomized treatment period (Part II) was the proportion of responders within each cohort who had resolution of their index disease flare at Day 15, and did not experience a new flare during the remainder of the 16-week treatment period. Resolution of the index disease flare was defined as having a Physician's Global Assessment (PGA) Disease Activity score <2 ("minimal or no disease") and CRP within normal range (≤10 mg/L) or reduction ≥70% from baseline. A new flare was defined as a PGA score ≥2 ("mild, moderate, or severe disease") and CRP ≥30 mg/L. Secondary endpoints, all based on Week 16 results (end of Part II), included the proportion of patients who achieved a PGA score of <2, the proportion of patients with serologic remission (defined as CRP ≤10 mg/L), and the proportion of patients with a normalized SAA level (defined as SAA ≤10 mg/L). In the 16-week treatment period, patients who needed dose escalation, who crossed over from placebo to canakinumab, or patients who discontinued from the study due to any reason prior to the Week 16 were considered as non-responders.

For the primary efficacy endpoint, Ilaris was superior to placebo for all 3 disease cohorts in the proportion of patients who resolved their index disease flare at Day 15 and had no new flare during the remainder of the 16-week treatment period.

Table 11 Comparison between treatment groups for patients who responded at Week 16 by cohort (Full analysis set)

Cohort	Ilaris 150 mg n/N (%)	Placebo n/N (%)	Treatment Comparison RD (%) (95 % CI)*	p-value
TRAPS	10/22 (45.5)	2/24 (8.3)	37.1 (8.2, 61.2)	0.0050**
HIDS/MKD	13/37 (35.1)	2/35 (5.7)	29.4 (6.1, 49.9)	0.0020**
FMF	19/31 (61.3)	2/32 (6.3)	55.0 (31.0, 73.0)	<0.0001**

n=number of responders; N=number of evaluable patients; RD=risk difference; CI=confidence Interval.
*Exact method was used to obtain the risk differences and the corresponding 95% confidence intervals.
** indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test.

Table 12 Comparison between treatment groups for patients who had PGA <2, CRP ≤ 10 mg/L, and SAA ≤ 10 mg/L at Week 16 by cohort (Full Analysis Set)

	TRAPS			HIDS/MKD			FMF		
Variable	Ilaris 150 mg n/N (%)	Placebo n/N (%)	Treatment Comparison RD (%) (95% CI)*	Ilaris 150 mg n/N (%)	Placebo n/N (%)	Treatment Comparison RD (%) (95% CI)*	Ilaris 150 mg n/N (%)	Placebo n/N (%)	Treatment Comparison RD (%) (95% CI)*
PGA < 2	10/22 (45.5)	1/24 (4.2)	41.3 (12.8, 64.8)	17/37 (45.9)	2/35 (5.7)	40.2 (17.7, 59.7)	20/31 (64.5)	3/32 (9.4)	55.1 (31.0, 73.3)
CRP ≤10 mg/L	8/22 (36.4)	2/24 (8.3)	28.0 (-0.8, 53.8)	15/37 (40.5)	2/35 (5.7)	34.8 (11.9, 54.8)	21/31 (67.7)	2/32 (6.3)	61.5 (38.1, 78.4)
SAA ≤10 mg/L	6/22 (27.3)	0/24 (0.0)	27.3 (-1.1, 53.7)	5/37 (13.5)	1/35 (2.9)	10.7 (-13.1, 32.9)	8/31 (25.8)	0/32 (0.0)	25.8 (0.8, 47.8)

n=number of responders; N=number of evaluable patients; RD=risk difference; CI=confidence Interval.
*Exact method was used to obtain the risk differences and the corresponding 95% confidence intervals.

Pediatric patients

A total of 169 patients were randomized and treated with canakinumab in the TRAPS, HIDS/MKD, and FMF trial in which 102 pediatric patients (TRAPS, HIDS/MKD and FMF patients) were within an age range from 2 to 17 years. This total included 9 patients between the age of 2 and 4 years. Pediatric patients <18 years comprised 59% of the TRAPS cohort, 75% of the HIDS/MKD cohort and 46% of the FMF cohort. The proportion of responders in this age group at Week 16 in TRAPS, HIDS/MKD and FMF pediatric patients was 35.7%, 32.1% and 71.4% for Ilaris treated patients respectively, vs. 7.6%, 7.6% and 6.6% in TRAPS, HIDS/MKD and FMF pediatric patients treated with placebo.

Treatment of Still's disease (SJIA and AOSD)

SJIA

The efficacy of Ilaris for the treatment of active SJIA was assessed in two pivotal phase III studies (G2305 and G2301). Patients enrolled were aged 2 to < 20 years (mean age at baseline: 8.5 years) with a confirmed diagnosis of SJIA at least 2 months before enrollment (mean disease duration at baseline: 3.5 years). Patients had active disease defined as ≥ 2 joints with active arthritis (mean number of active joints at baseline: 15.4), documented spiking, intermittent fever (body temperature > 38°C) for at least 1 day within 1 week before study drug administration, and CRP >30 mg/L (normal range < 10 mg/L) (mean CRP at baseline: 200.5 mg/L). Patients were allowed to continue their stable dose of methotrexate, corticosteroids, and/or NSAIDs without change, except for tapering of the corticosteroid dose as per study design in Study G2301 (see below).

Table 13 Baseline demographic and disease characteristics (Safety population) of Study G2305 and Study G2301

	Study G2305		Study G2301			
Demographic variable	**Ilaris**	**Placebo**	**Part I**	**According to randomization in Part II**		
	N=43	**N=41**	**Ilaris**	**Ilaris**	**Placebo**	**Total**
			N=177	**N=50**	**N=50**	**N=100**
Age – n (%)						
2- < 4 years	9 (20.9)	0 (0.0)	21 (12)	5 (10)	5 (10)	10 (10)
4 - < 6 years	8 (18.6)	7 (17.1)	32 (18)	5 (10)	11 (22)	16 (16)
6 - < 12 years	14 (32.6)	22 (53.7)	76 (43)	24 (48)	18 (36)	42 (42)
12 - < 20 years	12 (27.9)	12 (29.3)	48 (27)	16 (32)	16 (32)	32 (32)
Sex – n (%)						
Male	16 (37.2)	18 (43.9)	79 (45)	22 (44)	23 (46)	45 (45)
Female	27 (62.8)	23 (56.1)	98 (55)	28 (56)	27 (54)	55 (55)
Race – n (%)						
Caucasian	40 (93)	37 (90)	151 (85)	41 (82)	42 (84)	83 (83)
Asian	0 (0)	1 (2)	6 (3)	3 (6)	2 (4)	5 (5)

Black	2 (5)	0 (0)	7 (4)	2 (4)	1 (2)	3 (3)
Other	1 (2)	3 (7)	13 (7)	4 (8)	5 (10)	9 (9)
C-Reactive Protein (mg/L), median (min, max)	142 (21, 800)	137 (1, 657)	160 (3.3, 1865)	121 (6, 651)	149 (6, 742)	138 (6, 742)
Steroid – n (%) -	31 (69)	28 (68)	128 (72)	32 (64)	30 (60)	62 (62)
Methotrexate – n (%)	29 (67)	24 (59)	93 (53)	28 (56)	26 (52)	54 (54)
Number Active Joints– median (min, max)	10.0 (2, 58)	7.0 (2, 55)	10.0 (0, 66)	7.0 (2, 48)	7.5 (0, 43)	7.0 (0, 45)
Physician Global Assessment disease activity (VAS, 0-100mm) median (min, max)	67 (25, 100)	66 (21, 99)	70 (5, 100)	60 (12, 100)	66 (25, 100)	63 (12, 100)
CHAQ score, median (min, max)	1.63 (0, 3)	1.50 (0.125, 3)	1.75 (0, 3)	1.625 (0, 3)	1.500 (0.125, 3)	1.563 (0, 3)

CHAQ: Childhood Health Assessment Questionnaire; VAS, visual analog scale

Table 14 Summary of clinical trials supporting the efficacy and safety in patients with SJIA

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Sex
G2305	A randomized, double-blind, placebo controlled, single-dose study to assess the initial efficacy of Ilaris in patients with SJIA	Ilaris, 4mg/kg (300mg max) sc; duration 28 days	Ilaris: n=43 Placebo: n=41	8.0 yrs (2-19)	Males and females
G2301	A randomized, double-blind, placebo controlled withdrawal study of flare prevention of Ilaris in patients with SJIA	Ilaris 4mg/kg (300mg max), every 4 weeks for up to 9 months (median 113 weeks) in the open label part and until 37 flares reported in the treatment withdrawal part (median 164 weeks)	Open label: n=177 Treatment withdrawal: Ilaris, n=50; placebo, n=50	8.7 yrs (2-19)	Males and females
G2301E1	An open-label extension study of Ilaris in patients with SJIA	Ilaris 4mg/kg (300mg max) or 2mg/kg (150mg max)[1], every 4 weeks	N=147	9.5 yrs (2-20)	Males and females

[1]Ilaris dose was reduced for patients with strong response. Please see clinical trial section for details

Study G2305

Study G2305 was a randomized, double-blind, placebo-controlled, single-dose 4-week study assessing the short-term efficacy of Ilaris in 84 patients randomized to receive a single subcutaneous (s.c.) dose of 4 mg/kg Ilaris or placebo (43 patients received Ilaris and 41 patients received placebo). The primary objective of this study was to demonstrate the superiority of Ilaris versus placebo in the proportion of

patients who achieved at least 30% improvement in an adapted pediatric American College of Rheumatology (ACR) response criterion which included both the pediatric ACR core set (ACR30 response) and absence of fever (temperature ≤38°C in the preceding 7 days) at Day 15. Additionally, "inactive disease" (defined as no active arthritis, no fever, no rash, no serositis, no hepatomegaly or lymphadenopathy attributable to SJIA, normal CRP, and physician global assessment indicating no disease activity) was evaluated. However, it was not an endpoint of the study.

Pediatric ACR responses are defined as the percentage improvement (30%, 50%, 70%, 90%, and 100%) from baseline in 3 of any 6 core outcome variables, with worsening of ≥30% in no more than one of the remaining variables. Core outcome variables included a physician global assessment of disease activity, parent or patient global assessment of wellbeing, number of joints with active arthritis, number of joints with limited range of motion, CRP and functional ability (Childhood Health Assessment Questionnaire - CHAQ).

Percentage of patients by pediatric ACR response are presented in Table 15.

Table 15: Pediatric ACR response at Day 15 and Day 29

	Day 15			Day 29		
	Ilaris N=43	Placebo N=41	Weighted Difference[1] (95% CI)[2]	Ilaris N=43	Placebo N=41	Weighted Difference[1] (95% CI)[2]
ACR30	84%**	10%	70% (56%, 84%)	81%	10%	70% (56%, 84%)
ACR50	67%	5%	68% (50%, 80%)	79%	5%	76% (63%, 88%)
ACR70	61%	2%	64% (49%, 79%)	67%	2%	67% (52%, 81%)
ACR100	33%	0%	35% (21%, 49%)	33%	2%	35% (19%, 50%)

**p≤0.0001

[1]Weighted difference is the difference between the Ilaris and placebo response rates, adjusted for the stratification factors (number of active joints, previous response to anakinra, and level of oral corticosteroid use)

[2]CI: confidence interval for the weighted difference

Ilaris treatment improved components of pediatric ACR core set as compared to placebo at Days 15 and 29. All patients treated with Ilaris had no fever at Day 3 compared to 86.8% of patients treated with placebo.

Results for the components of the adapted pediatric ACR which included systemic and arthritic components were consistent with the overall ACR response results. At day 15, the median change from baseline in the number of joints with active arthritis and limited range of motion were 67% and 73% for Ilaris (N=43), respectively, compared to a median change of 0% and 0% for placebo (N=41). The mean change in patient pain score (0-100 mm visual analogue scale) at day 15 was -50.0 mm for Ilaris (N=43), as compared to +4.5 mm for placebo (N=25). The mean change in pain score among Ilaris treated patients was consistent at day 29.

Study G2301

Study G2301 was a randomized, double-blind, placebo-controlled withdrawal study of flare prevention by Ilaris in patients with active SJIA. The study consisted of two major parts with two independent primary endpoints. One hundred and seventy-seven (177) patients were enrolled in the study and

received Ilaris 4mg/kg subcutaneously every 4 weeks in Part I and either Ilaris subcutaneously 4mg/kg or placebo every 4 weeks in Part II.

Corticosteroid dose tapering
Part I had an open-label design to assess whether Ilaris allowed successful tapering of corticosteroids in at least 25% of the patients entering the study using a corticosteroid. Of the 128 patients who entered the study taking corticosteroids, 57 (45%) successfully tapered the corticosteroid dose ($p<0.0001$) and 42 (33%) discontinued their corticosteroids. Of the 92 patients who attempted corticosteroid tapering, 57 (62%) successfully tapered the corticosteroid dose, 42 (46%) discontinued corticosteroids. The mean baseline corticosteroid prednisone equivalent dose was 0.34 (range: 0.02-1.00) mg/kg/day.

Time to flare
Part II was a withdrawal design to demonstrate that the time to flare was longer with Ilaris than with placebo. The probability of experiencing a flare in Part II was statistically lower for the Ilaris treatment group than for the placebo group. The median time to flare was 236 days for the placebo group and could not be determined for the Ilaris group because less than 50% of the patients treated with Ilaris experienced a flare event over the observation period (maximum of 560 days). This corresponded to a statistically significant 64% relative reduced risk for patients in the Ilaris group to experience a flare event as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032).

Health-related outcomes
Treatment with Ilaris resulted in improvements in patients' daily functioning as assessed by the Childhood Health Assessment Questionnaire (CHAQ).

In Study G2305, improvement from baseline in the CHAQ score for patients treated with Ilaris versus placebo was observed, with a difference in mean improvement of 0.9 vs. 0.2 [minimal clinically important difference (MCID) equals a change of 0.19].

Long-term data
147 patients entered a long-term extension trial and received 4 mg/kg open label Ilaris every 4 weeks. The main objective of this study is to assess the safety and tolerability of canakinumab.

AOSD
The efficacy of Ilaris 4 mg/kg (up to maximum 300 mg) administered every 4 weeks for the treatment of active AOSD is based on pharmacokinetic exposure and extrapolation of the established efficacy of Ilaris in SJIA patients. Efficacy of Ilaris was also assessed in a randomized, double-blind, placebo-controlled study (GDE01T) that enrolled 36 AOSD patients 22 to 70 years of age. The efficacy response (e.g. continuous adapted ACR response, adapted ACR30 response, and reduced number of active joints), as well as improvement in the systemic inflammatory manifestations (e.g. lower serum CRP level and reduced fever) were generally consistent with the results of a pooled efficacy analysis of SJIA patients based on a Bayesian analysis.

14.3 Immunogenicity

Antibodies against Ilaris were observed in approximately 1.5% and 3%, of the patients treated with Ilaris for CAPS and SJIA respectively. Most of the SJIA clinical studies employed a higher sensitive

bridging assay. No neutralizing antibodies were detected. No apparent correlation of antibody development to clinical response or adverse events was observed.

There were no antibodies against Ilaris observed in TRAPS, HIDS/MKD and FMF patients treated with doses of 150 mg and 300 mg over 16 weeks of treatment.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Detailed Pharmacology

Canakinumab binds to human and marmoset IL-1β with a dissociation binding constant (K_D) of about 40 pM, and does not cross-react with human IL-1α, IL-1Ra, or any other member of the IL-1 family including IL-18 and IL-33. Also, canakinumab does not interact with recombinant IL-1β from other mammalian species, including mouse, rat, rabbit and cynomolgus monkey and rhesus monkeys, due to differences in the amino acid position 64 of IL-1β, which consists of glutamic acid in humans and marmosets, and alanine in the other species.

Canakinumab prevents the interaction of human recombinant IL-1β with both the signaling receptor IL-1 type I receptor (IL-1RI) and the decoy IL-1 type II receptor (IL-1RII). This experimental finding is supported by the X-ray structure of the molecular complex between canakinumab Fab and human IL-1β, which predicts steric inhibition of binding of the canakinumab:human IL-1β complex to IL-1RI. As a consequence, canakinumab inhibits downstream gene expression induced by human IL-1β in an appropriate cell-based assay with an IC_{50} of about 40 pM.

Canakinumab prevents joint swelling and neutrophil migration induced by human IL-1β in pharmacodynamic mouse models *in vivo* with an ED_{50} between 0.06 and 0.65 mg/kg IP, respectively.

Canakinumab does not inhibit T-cell proliferation in the human mixed lymphocyte reaction *in vitro*, suggesting that it is not acutely T-cell immunosuppressive. Canakinumab does elicit antibody dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) as IL-1β is a soluble antigen which does not bind to cell surface receptor in the presence of canakinumab.

Toxicology

Non-clinical data reveal no special hazard for humans based on cross-reactivity, repeated dose, immunotoxicity, reproductive and juvenile toxicity studies performed with canakinumab or a murine anti-murine IL-1 beta antibody.

Since canakinumab binds to marmoset (C. jacchus) and human IL-1 beta with a similar affinity, the safety of canakinumab has been studied in the marmoset. No undesirable effects of canakinumab were seen following twice weekly administration to marmosets for up to 26 weeks or in an embryofoetal developmental toxicity study in pregnant marmosets.

Plasma concentrations, that are well tolerated in animals are in excess of at least 42-fold (C_{max}) and 78-fold (C_{avg}) the plasma concentrations in pediatric CAPS patients, treated with clinical doses of canakinumab up to 8 mg/kg subcutaneously every eight weeks and are in excess of 62-fold (C_{max}) and 104-fold (C_{avg}) the plasma concentrations in pediatric SJIA patients treated with up to 4 mg/kg of canakinumab subcutaneously every 4 weeks. In addition, no antibodies to canakinumab were detected

in these studies. No non-specific tissue cross-reactivity was demonstrated when canakinumab was applied to normal human tissues.

In an embryofoetal development study in marmosets canakinumab showed no maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis. In addition, canakinumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery and nursing (see 7 WARNINGS AND PRECAUTIONS, Special populations). Canakinumab had no effect on male fertility parameters in marmoset (C. jacchus).

No long-term animal studies have been performed to establish the carcinogenic potential of canakinumab. Formal carcinogenicity and mutagenicity studies have not been conducted with canakinumab.

No undesirable effects of a murine anti-murine IL-1 beta antibody were seen in a complete set of reproductive and juvenile studies in mice. The high dose used in these studies was in excess of the maximally effective dose in terms of IL-1 beta suppression and activity.

An immunotoxicology study in mice with a murine anti-murine IL-1 beta antibody showed that neutralising IL-1 beta has no effects on immune parameters and caused no impairment of immune function in mice.

Canakinumab has been shown to produce delays in fetal skeletal development when evaluated in marmoset monkeys using doses 23-fold the maximum recommended human dose (MRHD) and greater (based on a plasma area under the time-concentration curve [AUC] comparison). Doses producing exposures within the clinical exposure range at the MHRD were not evaluated. Similar delays in fetal skeletal development were observed in mice administered a murine analog of canakinumab. There are no adequate and well-controlled studies of Ilaris in pregnant women.

Embryofetal developmental toxicity studies were performed in marmoset monkeys and mice. Pregnant marmoset monkeys were administered canakinumab subcutaneously twice weekly at doses of 15, 50 or 150 mg/kg (representing 23 to 230-fold the human dose based on a plasma AUC comparison at the MRHD) from gestation days 25 to 109 which revealed no evidence of embryotoxicity or fetal malformations. There were increases in the incidence of incomplete ossification of the terminal caudal vertebra and misaligned and/or bipartite vertebra in fetuses at all dose levels when compared to concurrent controls suggestive of delay in skeletal development in the marmoset. Since canakinumab does not cross-react with mouse or rat IL-1, pregnant mice were subcutaneously administered a murine analog of canakinumab at doses of 15, 50, or 150 mg/kg on gestation days 6, 11 and 17. The incidence of incomplete ossification of the parietal and frontal skull bones of fetuses was increased in a dose-dependent manner at all dose levels tested. There are, however, no adequate and well-controlled studies in pregnant women.

Table 16: Nonclinical Toxicology Studies with ACZ885

Study Reports/ Compound administered/ Species	Duration/ Route of Administration/ Dose (mg/kg)/ Dosage and/or Concentration	Results/ Findings
1. Study no. 0370163: Subcutaneous tolerability study in female marmosets with toxicokinetics/ Canakinumab / Process A (made from the early development cell line)	s.c/ 0, 5, 50, 150 once on Day 1 and Day 43	One marmoset in 50 mg/kg group experienced an anemia on day 44 (decreased RBC, Hgb, HCT) and had an inflammatory leukocytosis, with increases in lymphocytes, monocytes, and eosinophils. This change was not drug-related because not found in high dose group. The following incidences were noted after microscopic examination: - Jejunum: marked lymphocytic infiltrate, slight (epithelial and Peyer's patch) hyperplasia and minimal abscess in 1/4 high dose group. -Gall Bladder: slight leukocytic infiltrate in 1/4 mid dose and 1/4 high dose groups. -Liver: minimal (1/4 high dose groups), slight (1/2 control, 2/4 Low dose, 1/4 mid dose and 1/4 high dose groups) and moderate (1/4 Low dose, 1/4 mid dose and 1/4 high dose groups) hepatocellular vacuolation. - Bone marrow: Minimal cellularity decrease observed in all treated groups (1/4 LD, 3/4MD and 1/4 HD). - Inguinal lymph node: Minimal (1/4 HD) chronic adventitia inflammation and slight (1/4 MD) chronic hematoma in high dose (150 mg/kg/day) group. - Mandibular lymph node: Minimal multinucleated giant cell in 1/4 mid and 1/4 high dose groups. Minimal lymphoid hyperplasia observed in all treated groups (1/4 LD, 2/4 MD and 2/4 HD). - Mesenteric lymph node: Minimal lymphangiectasis (1/4), minimal lymphoid depletion (1/4) and minimal lymphoid hyperplasia (2/4) in high dose group. - Thymus: Minimal cyst was observed in (2/4) high dose group. - Lung: Minimal osseous metaplasia (1/4) and minimal leukocytic infiltrate (1/4) were observed in high dose group. However, since these findings were not observed in the long-term s.c. and i.v. toxicity studies, they are considered not to be treatment-related.
2. Study no. 0470033: 13-week subcutaneous toxicity study in marmosets (♀ and ♂) with an 8-week recovery period/ Canakinumab/ Process A	13-week + 8-week recovery period/ s.c/ 0 (vehicle control), 15 (LD), 50 (MD), and 150 (HD) mg/kg/twice weekly	Minimal leukocytic or mononuclear infiltrates at the site of injection without a relationship to dose because observed in all genders in control group of recovery animals and not observed in treated female animals. Histopathology examination also indicated a dose-related increase in minimal lymphoid hyperplasia of the spleen in all treated groups (1/4 in 15 mg/kg, 2/4 in 50 mg/kg & 2/4 in 150 mg/kg) and recovery (1/2) males, observed in the absence of treatment-related effects on phenotyping of splenic suspensions and blood samples, anti-drug antibody levels, and treatment-related findings in the spleen in the female animals as presented in review. There were no significant in-life or post-mortem findings in response to ACZ885 and exposure was confirmed. There was no evidence of production of anti-ACZ885 antibodies, therefore, under the conditions of this study the no-observed adverse effect level (NOAEL) was 150 mg/kg.

3. Study No. 0770370: 13-week, twice weekly subcutaneous batch comparison study in marmosets (♀ and ♂) Process A and liquid formulation from process C (made from the final cell line)	13-week/ s.c/0 (vehicle control), 150 mg/kg/twice weekly	Based on the pathology report submitted, the following findings were observed: - Females: The final body weights were slightly reduced compared to the control group. The organ weights (kidney, heart, liver, pituitary gland and uterus) of all treated female animals were lower than in control group. In addition, the spleen and thyroid gland weights of female animals treated with ACZ885 formulation A (pre-filled syringes), made from the final cell line, were higher than those of the control group and the animals treated with ACZ885 formulation B (lyophilisate vials) made from the early development cell line. - In males, the majority of male animals treated with ACZ885 formulation B showed a distinct body weight reduction compared to the control group and those treated with ACZ885 formulation A. Heart, kidneys, liver, prostate, pituitary gland weights of animals treated with ACZ885 formulation A were higher than in control and in group ACZ885 formulation B. The toxicokinetic data were similar between the two batches. But, the safety profile of the two formulations cannot be performed because of the wide variability observed in background microscopic lesions, in-life observations, and clinical pathology.
4. Study no. 0280160: 28-Day Intravenous Administration Toxicity Study with a 2-Month Recovery Period in the marmoset (♀ and ♂)/ Canakinumab / Process A	i.v. slow bolus injection/ 0, 10, 30 and 100 mg/kg/dose twice weekly to 3 animals per sex and dose group	Based on the lack of systemic test substance toxicity at high dose and due to the fact that no treatment-related effects were observed in anti-drug antibody, lymphocyte subpopulations and monocytes in marmoset administered ACZ885 at dose levels up to 100 mg/kg twice weekly intravenously for 28 days (8 applications), the no-effect level (NOEL) is established at the dose of 100 mg/kg/twice weekly.
5. Study no. 0380070: 26-Week I.V. Administration Toxicity Study with a 6-Week Recovery Period in the marmoset (♀ and ♂)/ Canakinumab/ Process A	i.v. slow bolus injection/ 0, 10, 30 and 100 mg/kg/dose twice weekly to 6 animals per sex and dose group for 26 weeks	Considering that, there was no evidence of treatment-related effects on the male reproduction system, there were no findings concerning lymphocyte subpopulations and monocytes and no anti- ACZ885 antibodies were detected in marmoset administered ACZ885 at dose levels of 10-100 mg/kg twice weekly intravenously for 26 weeks, the no-effect level (NOEL) is established at the dose of 100 mg/kg/twice weekly intravenously.
Reproductive and Development Toxicity		
1. Study No. 0680149: A once weekly subcutaneous injection fertility study in the mouse/ 01BSUR/ Mice (♀ and ♂)	s.c/ 0, 15, 50 and 150 mg/kg/day	One female at 150 mg/kg/day was found dead on the second day of mating (study day 17); this was not attributed to treatment based upon the clinical and pathological findings and lack of any other mortality. There were no effects on the clinical condition of males and females. Body weights, body weight gains and food consumption were unaffected by 01BSUR. There were no 01BSUR-related effects on the oestrous cycles (including the number of days in oestrus, the number of cycles seen and the average cycle length of observed cycles). The mean day to mating, mating and fertility indices and conception rate were unaffected.

		The uterine parameters assessed (*i.e.*, number of corpora lutea, implantation sites, live and dead foetuses, resorptions, and the pre- and post implantation losses) in each treated group were unaffected. There were no 01BSUR-related effects on the absolute and relative organ weights nor any gross pathological findings attributed to 01BSUR. The administration of the 01BSUR did not induce changes on the sperm motility, spermatozoa counts or spermatozoa morphology. Analysis of blood samples collected from selected animals at 15, 50 and 150 mg/kg/day and tested for ACZ885 surrogate (01BSUR) determination confirmed that animals had been exposed to the compound, with levels measured being dose proportional in males and females. **Macroscopic observations:** An enlargement of the spleen was observed at each dose level in females, including the controls. As the incidence of this finding in treated groups was comparable to the controls (*i.e.*, 6/22 affected females in the control group *versus* 9/22, 5/22 and 9/22 at 15, 50 and 150 mg/kg/day, respectively), and in the absence of a dose related trend, these changes were considered to be possibly an effect of the vehicle but not of the test material. Among the males only one mouse (No. 7003. 50 mg/kg/day) had splenic enlargement. However, as for the ACZ885 Study no. 0470033 in marmoset, the spleen enlargement was seen in some females from all groups, including the vehicle control group.
2. Study no. 0480152: A subcutaneous embryo-fetal development study in the marmoset monkey (♀) / Canakinumab/ Process A	s.c/ 0, 15, 50 and 150 mg/kg/ twice weekly	There were no unscheduled deaths observed during the course of the study. The maternal animals did not show compound-related clinical signs. Body weight development was comparable in all study groups and did not show any compound-related effect. Estimation of food intake did not reveal any effect of ACZ885. However, the mean placental weights were reduced all treated animals compared to the controls, representing 15%, 6% and 22% in 15, 50 and 150 mg/kg, respectively but did not elicit any maternal adverse effects. The fetal examination indicated that the number of fetuses per litter was slightly (4%) lower in Group 4 (150 mg/kg) than in control group. The numbers of fetuses with kinked (7% in MD &14% in HD) and bent (3% in MD &5% in HD) tail end were slightly increased in mid and high dose groups compared to the control group. The skeletal examination revealed a slight increase in misaligned and/or unossified vertebrae in treated groups (4 in LD, 10 in MD and 2 in HD) representing 13%, 31 % and 8% respectively compared to control group (1) representing 4%. Misaligned and/or bipartite vertebrae (5, 17, 16, and 12 in the control, LD, MD, and HD groups respectively, representing 19%, 57%, 50%, and 46% the numbers of fetuses examined in each group, respectively). Toxicokinetics showed that all treated animals were exposed to ACZ885 and placental transfer was confirmed by detection of ACZ885 in fetal serum and amniotic fluid. None of the animals tested for anti-ACZ885 antibody formation showed a positive response. Based on the lack of maternal toxicity and major malformations or teratoxicity, the NOAEL is established at 150mg/kg twice weekly. However, based in the numbers of fetuses with kinked in high dose tail end and increased incidence of incomplete vertebral ossification in all treated groups, the NOAEL for minor embryotoxicity was not established.
3. Study no. 0680148: A weekly subcutaneous injection embryo-fetal	s.c/ 0, 15, 50 and 150 mg/kg/day	Following the incidence of necropsy findings by organ/group, the enlargement of the spleen was observed in one female mouse in high dose group (150 mg/kg).

development study in the mouse (♀)/ACZ885 Surrogate (01BSUR)		Fetal weights were unaffected by 01BSUR. The incidence of malformations and minor external and visceral anomalies in fetuses and litters at each dose level was comparable to controls. The overall incidence of fetuses and litters with minor skeletal anomalies was comparable between the treated and control groups. However, considering the individual anomalies, there was a significantly increased incidence of litters and fetuses with incomplete ossification of the parietal bones at 50 and 150 mg/kg/day and increased incidence of fetuses with incomplete ossification of frontal bones at 150 mg/kg/day. These findings were considered indicative of a developmental delay in ossification. Based on the lack of maternal toxicity in this study, the no observed adverse effect level (NOAEL) for maternal toxicity and teratogenicity by 01BSUR was established at 150 mg/kg/day. However, based to a developmental delay in ossification (significantly increased incidence of litters and fetuses with incomplete ossification of the parietal bones at 50 and 150 mg/kg/day and increased incidence of fetuses with incomplete ossification of frontal bones at 150 mg/kg/day), the NOAEL for embryo fetal development was established at 15 mg/kg/day.
Prenatal and postnatal development		
1. Study no. 0680150: A weekly subcutaneous injection pre and postnatal study in the mouse (♀)/ACZ885 Surrogate (01BSUR)	s.c/ 0, 15, 50 and 150 mg/kg/day	**In F_0 generation:** Two females at 150 mg/kg/day (female nos. 451 and 463) were found dead on days 13 and 17 *post partum*, respectively with possible relationship to treatment. At necropsy, a gross and histopathologic examination showed a splenic enlargement and pale discoloration of the spleen in animal no. 451, and an enlargement of the liver and area dark in the lungs of animal no. 463. Both animals (female nos. 451 and 463) had splenic lymphoid hyperplasia and one (no. 463) also had increased extramedullary hematopoiesis. **F_1 generation:** At microscopic examination, there was a treatment-related increased degree of histiocytosis in mandibular and the mesenteric lymph nodes in males at 50 (3/9 and 2/10, respectively, vs. 0/10 in control group) and 150 (4/9 and 3/10, respectively, vs. 2/10 in the controls) mg/kg/day. This finding was not considered toxicologically significant because there were no 01BSUR-related effects on immune function as assessed by blood, spleen and thymus immunophenotyping, no microscopic findings in other lymphoid organs. **F_2 generation pups:** There were no toxic effects on the development of the pups and their survival, physical development, behaviour and reproductive performance. Based on these results, the no observed adverse effect level (NOAEL) for the F_0, F_1 and F_2 generations was established at150 mg/kg/day.
Juvenile Toxicity		

1. Study no. 0770274: A once weekly subcutaneous injection juvenile toxicology study in the mouse (♀ and ♂) /ACZ885 Surrogate (01BSUR)	s.c/ 0, 15, 50 and 150 mg/kg/day	The administration of 01BSUR at 0, 15, 50 and 150 mg/kg/day, by subcutaneous injection, to male and female mouse pups once weekly for 9 consecutive weeks from day 7 *post partum* resulted, at each dose level, in local histopathological changes generally graded as minimal at the injection sites. Such changes were reversible over a 4-week recovery period. Thus, the no-observable-adverse-effect level (NOAEL) for juvenile 01BSUR toxicity in mouse was established at 150 mg/kg/day.
Local Tolerance		
ACZ885 Study no 0670425: Single dose intra-articular administration study in the marmoset (♀)/ Process B (made from the final cell line)	Intra-articular/ 10 mg/kg	Single dose intra-articular administration of canakinumab at a dose level of 10 mg/kg was very well tolerated. Only a slight decrease in lymphocytes and a slight increase in neutrophils were observed. These findings are considered toxicologically non-relevant due to the absence of similar findings in the other toxicology studies using more frequent dosing and for longer durations of exposure.
Cross-reactivity Studies		
Study no. 0180142: Cross reactivity of ACZ885, a human monoclonal IgG1/k antibody against human IL-1beta, with normal human tissues and normal marmoset tissues/ Process A	*in vitro*	The cross-reactivity profile in the marmoset tissues was qualitatively similar to, but quantitatively less than, the cross-reactivity profile observed in human tissues in term of cell types, stain intensity, frequency and subcellular localization that are consistent with known distribution of IL-1β expressing cells. Minor differences observed, included ACZ885 staining in marmoset but not in human follicular and germinal cells in the ovary and in Leydig Sertoli and gametogenic precursors in the testis. There were several differences noted in distribution of low-grade cytoplasmic staining in epithelial tissues at high concentrations of ACZ885-FITC, with staining observed in human but not marmoset prostate and thyroid, and in marmoset but not human parathyroid and vas deferens. Overall, the results of the cross-reactivity studies support the biocomparability of ACZ885 binding and IL-1β bioactivity by drug substance produced using the processes A, B, C, and comparability of marmoset and human responses supporting the selection marmoset for evaluation in the toxicology studies. The marmoset was characterized as an appropriate model to predict human safety.
Study no. 0680267: Cross-reactivity study of ACZ885-FITC with normal human and marmoset tissues Process B	*in vitro*	
Study no. 0770362: Cross-reactivity study of FITC-labeled ACZ885 (HSA-) with normal human and marmoset tissues /Process C	*in vitro*	
Immunotoxicity		

Study no. 0670570: A 28-day (weekly dosing) subcutaneous injection immunotoxicity study in the albino mouse (♀ and ♂) with a 28-day recovery period/ ACZ885 Surrogate (01BSUR)	Sc/ 0, 10, 50 and 150 mg/kg/dose for 5 doses	A slight increase was noted in both absolute and relative thymus weights in females from the main immunophenotyping, immunogenicity and toxicokinetics study phase at 50 mg/kg/dose, however, no correlate was identified macroscopically or microscopically for this change. Because this organ weight change was not statistically significant and there was no macroscopic or microscopic correlate, it was considered unlikely that this organ weight change was related to test-article administration. Blood, spleen and thymus immunophenotyping data from main and recovery study phase demonstrated no effects considered to be related to the administration of 01BSUR. The anti-KLH IgM and anti-KLH IgG response during main and recovery study were not considered to be affected by the administration of 01BSUR. Based on the immunology end points assessed, the NOAEL of 01BSUR was considered to be 150 mg/kg/dose.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrILARIS®

[illARRiss]

canakinumab injection

Read this carefully before you start taking **Ilaris®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Ilaris**.

What is Ilaris used for?

Cryopyrin-Associated Periodic Syndrome (CAPS)

Ilaris is used in adults and children aged 2 years and older for the ongoing management of the following auto-inflammatory diseases which are collectively known as Cryopyrin-Associated Periodic Syndromes (CAPS), including:

- Familial Cold Autoinflammatory Syndrome (FCAS) also called Familial Cold Urticaria (FCU), presenting with signs and symptoms of cold-induced urticarial rash
- Muckle-Wells Syndrome (MWS)

Ilaris may also be used in Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/ Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA). It is not known if Ilaris improves nervous system problems in patients with NOMID, such as inflammatory meningitis, hearing loss or pressure on the brain.

Tumor Necrosis Factor receptor Associated Periodic Syndrome (TRAPS)

Ilaris is used to treat Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients.

Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)

Ilaris is used to treat Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adult and pediatric patients.

Familial Mediterranean Fever (FMF)

Ilaris is used to treat Familial Mediterranean Fever (FMF) in adult and pediatric patients. Ilaris can be used alone or together with colchicine.

Ilaris is also used for the treatment of:

Still's disease including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult Onset Still's Disease (AOSD)

Ilaris is used in adults, adolescents and children to treat active Still's disease including Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older, and Adult-Onset Still's Disease (AOSD).

How does Ilaris work?

CAPS, TRAPS, HIDS/MKD and FMF

In patients with CAPS, TRAPS, HIDS/MKD and FMF, the body produces excessive amounts of a chemical messenger called interleukin-1 beta (IL-1 beta). This may lead to symptoms such as fever, headache, fatigue, skin rash, painful joints and muscles. In some patients, more severe outcomes such as hearing loss are observed.

Still's disease

Still's disease including SJIA and AOSD is an autoinflammatory disorder which can be caused by high levels of certain proteins in the blood such as interleukin-1 beta (IL-1 beta), and can cause fever, rash, headache, tiredness, or painful joints and muscles.

Ilaris belongs to a group of medicines called interleukin-1 (IL-1) inhibitors. The active substance in Ilaris is canakinumab, a human monoclonal antibody. It selectively binds to IL-1 beta, blocking its activity and leading to an improvement in symptoms.

What are the ingredients in Ilaris?

Medicinal ingredient: canakinumab

Non-medicinal ingredients: L-histidine, L-histidine HCl monohydrate, mannitol, polysorbate 80, water for injection.

Ilaris comes in the following dosage form:

Ilaris is supplied as a solution for injection. It is provided in a single-use vial. One vial of solution contains 150 mg/ 1 mL canakinumab.

Do not use Ilaris if:

- you are allergic to canakinumab or to any nonmedicinal ingredients of Ilaris (see list of nonmedicinal ingredients).
- you think you may be allergic to Ilaris solution, ask your healthcare professional for advice. You may need a skin test before you start your treatment.
- you think you may have an infection, ask your healthcare professional for advice.

BEFORE starting Ilaris, your healthcare professional should test you for tuberculosis (TB); monitor you closely for symptoms of TB during treatment with Ilaris; and check you for symptoms of any type of infection before, during and after your treatment with Ilaris.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Ilaris. Talk about any health conditions or problems you may have, including if you:

- currently have an infection or if you have a history of recurring infections or a condition such as low level of white blood cells, which makes you more likely to get infections.
- require vaccinations. You must not be given a certain type of vaccination known as "live vaccines" while being treated with Ilaris.

Other warnings you should know about:

DURING the treatment with Ilaris, tell your healthcare professional immediately if you experience any of the following symptoms:

- Fever higher than 38°C/100°F, Fever lasting longer than 3 days or any other symptoms possibly related to an infection (including serious infection), such as prolonged cough, phlegm, chest pain, difficulty breathing, ear pain, prolonged headache or redness, warmth or swelling of your skin.
- Signs of an allergic reaction such as difficulty breathing or swallowing, nausea, dizziness, skin rash, itching, hives, palpitations (irregular heartbeat) or low blood pressure.
- The serious skin reaction, DRESS (drug reaction with eosinophilia and systemic symptoms), has rarely been reported in association with Ilaris treatment, predominantly in patients with Systemic Juvenile Idiopathic Arthritis (sJIA). Seek medical attention immediately if you notice an atypical, widespread rash, which may occur in conjunction with high body temperature and enlarged lymph nodes.
- Patients with Still's disease may develop a serious condition called macrophage (a type of white blood cell) activation syndrome (MAS), which can cause death. Tell your healthcare professional right away if your Still's disease symptoms become worse, or if you have any symptoms of an infection such as fever, cough, or redness, warmth, or swelling of your skin.

Ilaris is not recommended for children younger than 2 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Ilaris:

You must not be given a certain type of vaccination known as a "live vaccines" while being treated with Ilaris. Your healthcare professional may want to check your vaccination history and give you any vaccinations that you have missed before you start treatment with Ilaris.

You should not take medicines that increase the risk of infection while taking Ilaris such as:

- Other blockers of interleukin-1, such as anakinra (Kineret*).
- Blockers of tumour necrosis factor (TNF), such as etanercept, (Enbrel*), adalimumab (Humira*) or infliximab (Remicade*) should not be used with Ilaris because this may increase the risk of infections. TNF blockers are used mainly in rheumatic and autoimmune diseases.

Proper use of Ilaris:

Driving and using machines

Some symptoms associated with CAPS or with Ilaris treatment, such as a spinning sensation (known as vertigo), may affect your ability to drive or use machines. If you feel a spinning sensation, do not drive or operate any tools or machines until you are feeling normal again.

Ask your healthcare professional, nurse or pharmacist for advice before taking any medicine.

Use in pregnancy and breast feeding

Ilaris has not been studied in pregnant women. It is important to tell your healthcare professional if you are pregnant or could be pregnant, or if you plan to get pregnant. Your healthcare professional will discuss with you the potential risks of taking Ilaris during pregnancy. It is advised you avoid becoming

pregnant, and that you use adequate birth control before starting Ilaris, while using Ilaris and for at least 3 months after the last Ilaris treatment.

If you received Ilaris while you were pregnant, it is important that you inform the baby's healthcare professional or nurse before any vaccinations are given to your baby. Your baby should not receive live vaccines until at least 16 weeks after you received your last dose of Ilaris before giving birth.

It is not known if Ilaris is expressed in human breast milk, or what effects Ilaris could have on the baby. Breast-feeding is therefore not recommended in women who are being treated with Ilaris. It is important to tell your healthcare professional if you are considering breast-feeding during or after treatment with Ilaris.

Use in children

Ilaris can be used in children aged 2 years of age and older.

How to take Ilaris:

After proper training in injection technique, you may inject Ilaris yourself.

- You and your healthcare professional should decide together whether or not you will inject Ilaris yourself.
- Your healthcare professional or nurse will show you how to inject yourself.
- Do not try to inject yourself if you have not been properly trained or if you are not sure how to do it.

Before beginning

- Find a clean, comfortable area.
- Wash your hands with soap and water.
- After removing the vial from the refrigerator, check the expiry dates on the vial. Do not use if the expiry date has passed (last day of the month stamped on the vial).
- Let the vial stand unopened for 10 minutes to allow the contents to reach room temperature. Do not expose the vial to heat.
- Always use new, unopened needles and syringes. Avoid touching the needles and the top of the vial.

Read these instructions all the way through before beginning.

Gather together the necessary items

Included in the pack

A. one vial of Ilaris solution for injection (keep refrigerated)

Not included in the pack

B. one 1mL syringe

C. one appropriate size needle (e.g. 21G or larger) with appropriate length for withdrawing the solution (“withdrawal needle”)

D. one 27 G x 0.5” needle for injecting (“injection needle”)

E. alcohol swabs

F. clean, dry cotton swabs

G. an adhesive bandage

H. a proper disposal container for used needles, syringe and vials (sharps container)

Preparing the injection

1. Remove the protective cap from the vial (A). Do not touch the vial stopper. Clean the stopper with the alcohol swab (E).
2. Open the wrappers containing the syringe (B) and the withdrawal needle (C) (bigger one) and attach the needle to the syringe.
3. Carefully remove the cap from the withdrawal needle and set the cap aside. Insert the syringe needle into the vial of Ilaris solution through the centre of the rubber stopper (Fig. 1).

Figure 1

4. **Do not** invert the vial and syringe assembly. Insert the needle all the way into the vial until it reaches the bottom edge.
5. Tip the vial to ensure that the required amount of solution can be drawn into the syringe (Fig. 2).

Figure 2

6. Slowly pull the syringe plunger up to the correct mark, filling the syringe with Ilaris solution. If there are air bubbles in the syringe, remove bubbles as instructed by your healthcare professional. Ensure that the correct amount of solution is in the syringe.

NOTE: The required amount depends on the dose to be administered. Your healthcare professional will instruct you on the right amount for you.

7. Remove the needle and syringe from the vial and recap the withdrawal needle. Remove the withdrawal needle from the syringe and place in sharps container (H).
8. Open the wrapper containing the injection needle (D) and attach the needle to the syringe. Immediately proceed to administering the injection.

Giving the injection

1. Choose an injection site on the upper arm, upper thigh, abdomen or buttocks. Do not use an area that has a rash or broken skin, or is bruised or lumpy. Avoid injecting into scar-tissue as this may lead to insufficient exposure to canakinumab. Avoid injecting into a vein.
2. Clean the injection site with a new alcohol swab. Allow the area to dry. Uncap the injection needle.
3. Gently pinch the skin up at the injection site. Hold the syringe at a 90-degree angle and in a single, smooth motion, push the needle straight down completely into the skin (Fig. 3).

Figure 3

4. Keep the needle all the way in the skin while slowly pushing the syringe plunger down until the barrel is empty (Fig. 4). Release the pinched skin and pull the needle straight out. Safely dispose of needles and syringe without recapping or removing the needle in the sharps container or as directed by your healthcare provider or pharmacist. Never reuse syringes or needles.

Figure 4

After the injection

1. Do not rub the injection area. If bleeding occurs, apply a clean, dry cotton swab over the area, and press gently for 1 to 2 minutes, or until bleeding stops. Then apply an adhesive bandage (G).

Ilaris 150 mg / 1 mL solution for injection is for individual use only.

Never re-use left-over solution.

Keep the sharps container out of reach of children. Dispose of it as directed by your healthcare professional or pharmacist.

Usual dose:

CAPS

The recommended starting dose of Ilaris for CAPS patients is:

Adults and children aged 2 years and above

- 150 mg for patients with body weight of more than 40 kg.
- 2 mg/kg for patients with body weight between 15 kg and 40 kg (example: a 25 kg child should receive a 50 mg injection).

Every 8 weeks a single dose of Ilaris is injected under the skin.

Do not exceed the recommended dose.

TRAPS, HIDS/MKD and FMF

The recommended starting dose of Ilaris for TRAPS, HIDS/MKD and FMF patients is:

- 150 mg for patients with body weight of more than 40 kg
- 2 mg/kg with body weight ≤40 kg.

With a starting dose of 150 mg or 2 mg/kg, if a satisfactory treatment response has not been achieved 7 days after treatment start, a second dose of 150 mg or 2 mg/kg may be considered by your healthcare professional. If a full treatment response is then achieved, the higher dosing regimen of 300 mg or 4 mg/kg every 4 weeks should be maintained.

Do not exceed the recommended dose.

Still's disease (SJIA and AOSD)

The recommended dose of Ilaris for patients with Still's disease 2 years and older is 4 mg/kg (up to a maximum of 300 mg).

Ilaris is injected every 4 weeks under the skin.

Do not exceed the dose.

Do not use more Ilaris than your healthcare professional has recommended for you (see OVERDOSE below).

How long to use Ilaris

You should continue using Ilaris for as long as your healthcare professional tells you.

Overdose:

If you have CAPS, you should not inject Ilaris earlier than 8 weeks after the previous dose, unless your healthcare professional tells you to. If you have TRAPS, HIDS/MKD or FMF, you should not inject Ilaris earlier than 4 weeks after the last dose, unless your healthcare professional tells you to. If you have Still's disease (SJIA or AOSD), you should not inject Ilaris earlier than 4 weeks after the last dose. If you accidentally inject more Ilaris or sooner than you should, inform your healthcare professional, nurse or pharmacist, as soon as possible.

If you think you, or a person you are caring for, have accidentally injected more Ilaris than the recommended dose, or sooner than they / you should, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take a dose of Ilaris, inject the dose as soon as you remember then contact your healthcare professional to discuss when you should take the next dose. You should then continue with injections at recommended intervals, or as recommended by your healthcare professional.

If you have any further questions on the use of this product, ask your healthcare professional, nurse or pharmacist.

What are possible side effects from using Ilaris?

These are not all the possible side effects you may have when taking Ilaris. If you experience any side effects not listed here, tell your healthcare professional.

As with all medicines, patients treated with Ilaris may experience side effects, although not everybody gets them. Most of the side effects are mild to moderate and will generally disappear a few days to a few weeks after treatment, but some side effects may be serious with medicines such as Ilaris and require your special attention to seek the care of your healthcare professional.

Call your healthcare professional right away if you have any of these signs of an infection:

- a fever lasting longer than 3 days
- a cough that does not go away
- redness in one part of your body
- warm feeling or swelling of your skin
- sudden bleeding or easy bruising

Other possible side effects include:

Very common (affects more than 1 user in 10):

- sore throat with runny nose, blocked nose, sneezing, feeling of pressure or pain in the cheeks and/or forehead with or without fever (nasopharyngitis, pharyngitis, rhinitis)
- painful or frequent urination with or without fever (bladder or kidney infection)
- abdominal pain
- cold symptoms
- diarrhea
- stomach pain and feeling sick (gastroenteritis)

- flu (influenza)
- injection site reaction (such as redness, swelling, warmth, itching)
- headache

Common (affects 1 to 10 users in 100):

- nausea
- being sick (vomiting)
- abnormal levels of triglycerides in the blood (lipid metabolism disorder)
- feeling weak, fatigued (asthenia) or tired
- back pain
- combination of sore throat, fever, swollen or red tonsils, cough, difficulty to swallow and headache (tonsillitis)

Uncommon (affects 1 to 10 users in 1,000):

- heartburn (gastroesophageal reflux)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Cellulitis: Fever lasting longer than 3 days or any other symptoms that might be due to an infection (for example, viral infection, bronchitis and ear infection) and serious infection (including chronic tonsillitis, lower respiratory tract infection, sepsis and other serious infections of the skin, lungs and blood). These include shivering, chills, malaise, loss of appetite, body aches, typically in connection with a sudden onset of illness, prolonged cough, phlegm, chest pain, difficulty breathing, ear pain, prolonged headache or localized redness, warmth or swelling of your skin or inflammation of connective tissues			√
Thrombocytopenia: Sudden bleeding or easy bruising, which could be linked to low levels of blood platelets			√
Sore throat	√		

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Vertigo: Feeling dizzy, spinning sensation	√		
Leucopenia, neutropenia: Fever, sore throat or mouth ulcers due to infections, which could be symptoms of low levels of white blood cells			√
Increase in liver enzymes (transaminases) from a blood test		√	
Signs of hepatitis; increase of bilirubin in CAPS patients: Yellow skin and eyes, dark urine			√
Pneumonia: Fever, cough, difficulty or painful breathing, wheezing, pain in chest when breathing			√
Vaginal yeast infection	√		
RARE			
Signs of an allergic reaction: Trouble breathing or swallowing, nausea, dizziness, skin rash, itching, hives, palpitations (irregular heartbeat) or low blood pressure			√
Signs of a tuberculosis infection: Persistent cough, weight loss or low fever		√	
Fever lasting longer than 3 days or any other symptoms that may be due to an infection, such as prolonged cough, phlegm, chest pain, blood in sputum, difficulty breathing, ear pain, prolonged headache or localized redness, warmth or swelling of your skin (may be symptoms of a typical infection or one that may be more serious (opportunistic infections))			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children.

Do not use Ilaris after the expiry date. The expiry date can be found on the label and carton. The expiry date refers to the last day of that month.

Store Ilaris vials in a refrigerator (2°C to 8°C). Do not freeze. Store in the original package in order to protect from light.

Do not use Ilaris if you notice that the solution is not clear or contains particles. The solution should be clear and free of visible particles.

Ilaris is available as a single use vial. Any unused solution should be discarded.

If you want more information about Ilaris:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.novartis.ca, or by calling 1-800-363-8833.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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